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J. Barrish, Program Chair

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Challenges in Phenotypic Whole Cell High Throughput Screening and Medicinal Chemistry Optimization of Hits: Strategies to Discover Novel Antiparasitic and Antimycobacterial Agents
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MEDI 1

Phenotypic vs. target based hit discovery approaches for antiparasitic agents

***Paul G Wyatt**, p.g.wyatt@dundee.ac.uk. Drug Discovery Unit, University of Dundee, Dundee, United Kingdom*

The pros and cons of phenotypic and target based screening strategies to find starting points for drug discovery projects in neglected diseases will be discussed. Although, target based screening is a mainstream approach, target selection suffers from many issues, often potent inhibition of targets does not translate into anti- parasitic activity and the rapid resistance development can occur.

In general, phenotypic screening brings the benefits of an increased chance of identifying antiparasitic agents and potentially slowed development of resistance. Conversely, the lack of knowledge of the molecular target can make the optimisation process more challenging, as protein structure based, compound design approaches cannot be used.

Recent advances in technologies have greatly increased the throughput of parasite phenotypic screening. I will discuss the advances in this arena, concluding that a drug discovery portfolio can be achieved by phenotypic screening alone, but for these diseases should include both phenotypic and target-based approaches.

MEDI 2

Whole cell HTS for African trypanosomiasis and malaria: What troubles therein lies for the chemist

***Vicky M Avery**, v.avery@griffith.edu.au. Discovery Biology, Griffith University, Nathan, Queensland 4111, Australia*

The utilisation of whole cell assays for identifying anti-parasitic agents has become increasingly popular in recent years, and as with target based screening, has both positive and negative aspects to contend with. These need to be considered at hit identification (HI) and subsequent Hit-to-Lead (HtL) and Lead Optimisation (LO) stages.

This presentation will review those challenges with respect to whole cell screening to identify hits for Human African Trypanosomiasis and Malaria.

Although elucidation of the biological target requires deconvolution with whole cell assays, active compounds are usually discovered under conditions more physiologically relevant than target based studies. Actives identified through this approach generally have favourable properties, such as high membrane permeability and high aqueous solubility.

However, whole cell HTS does pose a number of considerations for both biologist and chemist at HtL and LO. Collectively, the advantages and limitations of this approach to anti-parasitic drug discovery will be discussed.

MEDI 3

Antimalarial lead discovery: Unraveling the black box

***Francisco-Javier Gamo**, francisco-javier.b.gamo@gsk.com. Diseases of the Developing World, GlaxoSmithKline, Tres Cantos, Madrid 28760, Spain*

Malaria is still one of the most significant causes of mortality and morbidity by infectious diseases in the world. Due to the increasingly problem of resistance to current drug treatments, discovery of new antimalarial classes has become an urgent task. Phenotypic screening is one of the preferred approaches the antimalarial community is pursuing during the last years for the identification of novel drugs. Thousands of compounds with potent activity against the parasite *Plasmodium falciparum* have been described very recently and information about inhibitor structure, molecular descriptors, antiplasmodial potency and cytotoxicity has been made publicly available. With this huge amount of antimalarial hits, the challenge is how to identify the most promising chemotypes and how to progress these compounds through a lead optimization program to render preclinical candidates.

In this presentation we will show the different approaches GSK is following to characterize a collection of 13,500 compounds named TCAMs (**T** res **C** antos **A** nti**M** alarial **s** et) resulting from the screening of 2 million compounds. Functional screening of already validated antimalarial pathways and novel assays we have developed, including determination of the parasite killing rates for the inhibitors and *in vivo* screening, are some of the tools we have using to prioritize this set of compounds and select the most promising molecules to identify preclinical candidates.

MEDI 4

Hit to lead and lead optimization of antimalarial whole cell hits from a SoftFocus library

***Kelly Chibale**[1], Kelly.Chibale@uct.ac.za, Vicky Avery[2], Yassir Younis[1], Diego González Cabrera[1], Frederic Douelle[1], Tzu-Shean Feng[1], Aloysius T Nchinda[1], Claire le Manach[1], Karen L White[3], Jeremy N Burrows[4], David Waterson[4], Michael J Witty[4], Sergio Wittlin[5], Susan A Charman[3]. (1) Department of Chemistry, University of Cape Town, Cape Town, Western Cape 7701, South Africa (2) Eskitis Institute, Griffith University, Brisbane, Queensland QLD 4111, Australia (3) Centre for Drug Candidate Optimisation, Monash University, Parkville/Melbourne, Victoria VIC 3052, Australia (4) Medicines for Malaria Venture, Geneva, Switzerland (5) Parasite Chemotherapy Unit, Swiss Tropical and Public Health Institute, Basel, Switzerland*

Phenotypic whole cell screening of a BioFocus DPI SoftFocus library of 40,000 compounds identified more than 200 hits with greater than 80% inhibition at an average primary and retest concentration of 1.82 uM against the malaria parasite *Plasmodium falciparum* sensitive (3D7) or resistant (Dd2) strains, and which also showed no cytotoxicity at that concentration. The library of 40,000 compounds represented more than 200 scaffolds that had primarily been designed as potential kinase inhibitors, G-Protein Coupled Receptor (GPCR) antagonists or ion channel modulators. Representatives of active series were selected for resynthesis and/or confirmatory testing of the actives against *Plasmodia* and cytotoxicity. Several of these series offered the combination of novelty, potential clean pharmacology, *in vitro* antiplasmodial potency, ADME/physicochemical properties and *in vivo* activity to yield potential lead compounds.

Hit triage, hit to lead and lead optimization campaigns will be described.

MEDI 5

Experiences, successes, and challenges in developing mycobacterium tuberculosis whole cell screening hits as potential antituberculosis agents

***Christopher Cooper**, christopher.cooper@tballiance.org.Global Alliance for TB Drug Development, United States*

Tuberculosis (TB) remains a devastating infectious disease worldwide. It is estimated that over one third of the world's population is infected with TB, with 9.2 million new cases, and nearly three million people succumbing to TB every year. The rise in HIV/TB co-morbidity and mortality as well as MDR- and XDR-TB strains has reaffirmed the global threat of TB in both the developing as well as developed world. New safer TB drug regimens are desperately needed to decrease patient treatment time and complexity, combat the rise of resistant bacilli, and enhance overall quality of life. This presentation will attempt to: (i) describe the current pipeline of discovery and development programs at the TB Alliance, (ii) elaborate on the global TB communities successes/challenges with target- vs. phenotypic screening-based approaches to novel anti-TB agents, and (iii) present the TB Alliance's strategic focus on the identification and interrogation of combined genetically and pharmacologically-validated *M.tb* biochemical targets and pathways of interest. Specific examples of recent efforts in these areas will be presented.

MEDI 6

Phenotypic screening of malaria hepatic stages

***Elizabeth A Winzeler**[1,2], jillcrow@scripps.edu, Stephan Meister[2], David Plouffe[1], Ghislain Bonamy[1]. (1) Department of Infectious Diseases, Genomics Institute of the Novartis Research Foundation, San Diego, CA 92121, United States (2) Department of Genetics, The Scripps Research Institute, La Jolla, CA 92037, United States*

Although several large scale screens for blood stages have been recently described (Plouffe, Brinker et al. 2008; Gamo, Sanz et al. 2010; Guiguemde, Shelat et al. 2010), information on which of the hits from these screens have activity against liver stages is currently lacking. The hepatic forms of Plasmodium species represent a potentially persistent form of malaria parasite infections in humans and a barrier to eradication. We have developed an automated high content screen to identify and characterize compounds with activity against malaria exoerythocytic forms. A "malaria box" of 5697 commercially available compounds with activity (<2 µM) against P. falciparum blood stages was screened for those with hepatic activity. This resulted in 275 compounds with IC50s of less than 10 µM which could be further classified based on potency, structure class and time of action within hepatocyte development. Altogether 62 different scaffold families, comprised of 934 distinct compounds were over or under-enriched in the set ($p<0.05$). Among these we found correlated activity between time of action and scaffold class. Our data highlights the substantial physiological differences between blood and hepatic stages and also offers the malaria community a variety of open-source chemical starting points for drugs that will kill both erythrocytic and pre-erythrocytic malaria parasites, as well as chemical tools that can be used to understand pre-erythrocytic stages.

MEDI 7

Cell-based optimization of novel antiparasitics

Arnab K. Chatterjee*, akc@gnf.org.Genomics Institute of Novartis Research Foundation, La Jolla, CA 92121, United States*

We have employed high-throughput whole-organism screening to discover novel anti-parasitic chemotypes. For Plasmodium falciparum, we previously disclosed a more extensive screening campaign on a library of about 2 million compounds using a cell-based proliferation assay of Plasmodium falciparum. Five thousand of the reconfirmed hits have subsequently disclosed in a public malaria database. The purpose of this work was to optimize hits from this collection to preclinical candidates by employing systematic structure-activity analysis. We analyzed the public hitlist with the following criteria: 1) good potency – IC50s were less than one micromolar against wild type as well as drug resistant strain 2) good safety index - greater than 20 fold in a 6-cell line toxicity panel and 3) easy of synthesis and preferably, with multiple active hits within the scaffold. We used systematic cell-based medicinal chemistry optimization to arrive at a potent compound with good in vivo efficacy, physiochemical properties and in vivo pharmacokinetics in a series of imidazolopiperazines, starting with compound GNF-Pf-5069 from the EBI list. In addition to this work, we have used a similar cell-based approach to find novel compounds fort the related kinetoplastid parasites, including Leishmania, African Sleeping Sickness and Chagas disease. The key challenges to finding novel preclinical candidates from these large hit-lists will be discussed.

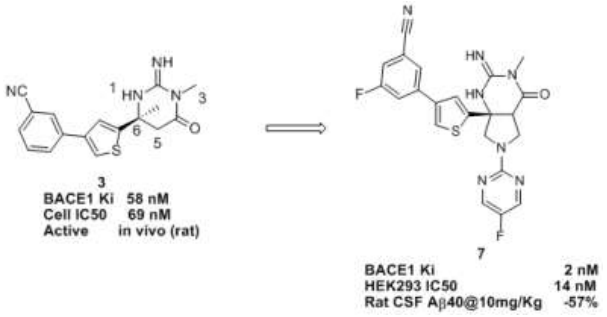
MEDI 8

Discovery and development of pyrrolidinoiminopyrimidinones as potent and selective BACE1 inhibitors

***Zhaoning Zhu**, johnnyzzhu@msn.com. Medicinal Chemistry, Merck Research Laboratories, Kenilworth, NJ 07033, United States*

Alzheimer's disease is caused by widespread neuronal dysfunction and cell death that is believed to be initiated by synaptic deposition of Ab42 oligomers related to their overproduction, decreased clearance or enhanced aggregation. Ab42 is generated from the membrane bound Amyloid Precursor protein (APP) via sequential cleavages first by b-secretase-1 (BACE1) followed by g-secretase. BACE inhibition has been viewed as an attractive path for potential treatment of Alzheimer's disease through reduction of Ab42 production

A unique structural class of cyclic acylguanidine BACE inhibitors has been designed and validated as highly potent and selective and CNS penetrant BACE inhibitors, starting from a fragment based protein NMR screening lead with extensive use of X-ray crystallography and CADD technologies. Here we will briefly discuss the in vivo rat efficacy guided SAR work evolving from iminopyrimidinone **3** to **7** through rational design based on conformational analysis.



MEDI 9

Bicyclic triazoles as modulators of γ-secretase for the treatment of Alzheimer's disease

***Lawrence R Marcin**[1], lawrence.marcin@bms.com, Mendi A Higgins[1], Kimberley A Lentz[3], James E Grace[3], Jeremy H Toyn[2], Richard E Olson[1], Charlie F Albright[2], John E Macor[1], Lorin A Thompson[1]. (1) Department of Medicinal Chemistry, Bristol-Myers Squibb, Wallingford, CT 06492, United States (2) Department of Neuroscience Biology, Bristol-Myers Squibb, Wallingford, CT 06492, United States (3) Department of Metabolism and Pharmacokinetics, Bristol-Myers Squibb, Wallingford, CT 06492, United States*

β-Amyloid (Aβ) is comprised of various peptide fragments ranging from 37-42 amino acids in length which are excised from amyloid precursor protein (APP) by the sequential action of β-secretase (BACE-1) and γ-secretase. The aberrant production and/or clearance of the longer fragment, Aβ42, has been implicated in the underlying cause of Alzheimer's Disease (AD). The inhibition or modulation of γ-secretase activity decreases the production of Aβ42 and may provide a method to treat or delay the progression of AD. γ-Secretase modulators (GSMs) do not inhibit the activity of γ-secretase, but shift the production of Aβ42 and Aβ40 to smaller peptide fragments including Aβ38 and Aβ37. These smaller framents do not demonstrate the same propensity as Aβ42 to form neurotoxic oligomers. In this presentation we disclose the discovery of potent, orally bioavailable, and brain-penetrant bicyclic aminotriazole GSMs that resulted from extensive optimization of an HTS screening hit

MEDI 10

Novel KCNQ2/3 openers for the treatment of pain

Brian S. Brown*, brian.s.brown@abbott.com, Tongmei Li, David J. Anderson, Rama Thimmapaya, Di Zhang, John L. Baranowski, Xu-Feng Zhang, Charles D. Mills, Kathy Kohlhass, Flobert Tanga, Trang Nguyen, Katherine Salte, Yan Pang, Cecilia E. Van Handel, Carol S. Surowy, David A. DeGoey, William A. Carroll, Betty B. Yao.Global Pharmaceutical Research and Development, Abbott Laboratories, Abbott Park, IL 60064, United States*

KCNQ (Kv7) channels are voltage-gated potassium channels composed of homo- or heteromeric tetramers of five different KCNQ subunits (Kv7.1-5). These channels play a key role in the regulation of neuronal excitability through their effects on resting membrane potential, action potential firing, and neurotransmitter release. Because KCNQ2/3 (Kv7.2/7.3) channels are expressed at all levels of the pain pathway, they represent a promising target for the treatment of pain. Both the analgesic Katadolon™ (flupirtine) and the anti-epileptic Potiga™ (retigabine) function as non-selective KCNQ channel openers, but their use is associated with mild to moderate side effects of somnolence, dizziness, nausea, dry mouth and heartburn. The side effects of these compounds may be attributable to activities at other targets, or to their relatively poor selectivity at KCNQ subtypes. KCNQ2, KCNQ3, and KCNQ5 are broadly expressed in the nervous system, while KCNQ1, KCNQ4, and KCNQ5 are expressed in smooth muscle cells. Mutations in KCNQ4 have also been linked to deafness, indicating the potential importance of isoform selectivity in the search for acceptable therapeutic agents. Selective KCNQ2/3 openers were therefore prepared in search of an analgesic agent with a therapeutic index superior to flupirtine. The results of SAR studies will be described, focusing on KCNQ subtype selectivity, PK-ADME and physiochemical properties. Lead compounds were characterized *in vivo* in pain and side-effect models.

MEDI 11

Selective EP2 antagonists for the treatment of Alzheimer's disease

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The EP2 receptor plays an important role in microglial stimulation, and studies have suggested it contributes to neurodegeneration. EP2 knockout mice show an increase in microglial Aβ phagocytosis and a reduction in amyloid plaques is observed in APP overexpressing mice with EP2 deletion.

We have discovered EP2 antagonists that dramatically increase phagocytosis of Aβ plaques in a dose dependent manner using Aβ-containing brain slices and mouse macrophages. We optimized an HTS lead with moderate EP2 potency and poor pharmacokinetic properties to provide an extremely potent and selective human EP2 antagonist (K_i = 8 nM, > 1500-fold selectivity over EP1, EP3, EP4, IP and DP) with good pharmacokinetic properties and excellent CNS permeability.

MEDI 12

CDK9-selective kinase inhibitors as a treatment of inflammatory diseases

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The S/T kinase CDK9 is part of the P-TEFb complex which promotes the productive transcriptional elongation via phosphorylation of serine-2 residues within the RNA polymerase II C-terminal repeat domain. P-TEFb, recruited to responsive promoters via binding to transcription factors or chromatin associated proteins (e.g. NF-kB), is specifically required for the expression of highly inducible genes controlled by extracellular stimuli such as inflammatory processes. Consequently, the selective inhibition of CDK9 leads to a reduced expression of pro-inflammatory mediators, thereby avoiding the interference with processes of the normal cell homeostasis.

Selective CDK9 inhibitors, resulting from our lead development program, have shown to be effective in various acute as well as chronic inflammation models, thereby confirming the proposed mode of action. The lead optimization process resulted in a CDK9 inhibitor, effective and well tolerated in two mouse models of arthritis under prophylactic as well as therapeutic treatment, now entering drug the development phase.

MEDI 13

Target identification of novel anti-inflammatory compound: Orally available small molecule PIKfyve kinase inhibitors by suppressing IL-12/23 production

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IL-12 and IL-23 are pro-inflammatory cytokines which induce serious pathological conditions in diverse of inflammatory diseases such as inflammatory bowel disease (IBD), psoriasis and rheumatoid arthritis. The therapeutic potential of IL-12/23 inhibition has been validated in clinical by Ustekinumab which is an approved monoclonal antibody neutralizing IL-12/23.

Through the cell-based phenotypic screening and extensive medicinal chemistry campaign, we generated APY0201 as a potent and unique inhibitor for IL-12/23 production from activated macrophages, possessing significant selectivity over other cytokines including TNF-α. As a result of chemical proteomics approach and comprehensive analysis of compound-protein binding using highly sensitive direct nano-flow liquid chromatography/tandem mass spectrometry system, PIKfyve kinase was identified as a biological target of our promising IL-12/23 production inhibitor. APY0201 is a potent, highly selective and ATP-competitive PIKfyve kinase inhibitor, which ameliorated inflammation in experimental model of colitis. We will disclose the SAR, biological evaluations both in vitro and in vivo, strategy of target identification and unique character of this novel drug target, to treat autoimmune and inflammatory diseases.

MEDI 14

Discovery of *N*-aryl piperidin-3-yl ureas as potent and selective 11β-HSD-1 inhibitors

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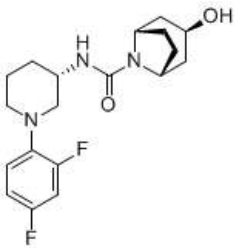
11β-Hydroxysteroid dehydrogenase type 1 (11β-HSD-1) catalyzes intracellular regenration of active cortisol from inactive cortisone. 11β-HSD-1 plays a central role in regulating intracellular cortisol concentration to facilitate the glucocorticoid-mediated functional antagonism of insulin action in adipose tissue. Selective inhibition of 11β-

HSD-1 was therefore hypothesized to be of therapeutic benefit in type-2 diabetes and metabolic syndrome by reducing intracellular cortisol levels within insulin-sensitive tissues. An intense interest has been sparked in the discovery and development of 11β-HSD-1 as novel therapeutic agents. Herein we report the design, syntheses and SAR of novel *N*-aryl 3-aminopiperidine based ureas as potent and selective 11β-HSD-1 inhibitors.



11ß-HSD-1 IC_{50} 3 nM
h-PBMC IC_{50} 1.3 nM

MEDI 15

4-Bicyclic heteroaryl 1, 2, 3, 4-tetrahydroisoquinoline derivatives as novel triple reuptake inhibitors

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Nearly all antidepressants currently prescribed are selective serotonin or dual serotonin - norepinephrine reuptake inhibitors (SSRIs and SNRIs respectively), working through blocking SERT (serotonin transporter) or both SERT and NET (norepinephrine transporter) in the brain. However, about 30-40% of patients do not adequately respond to treatment with SSRIs or SNRIs. Adding a DAT (dopamine transporter) component can potentially improve the efficacy of SSRIs and SNRIs based on clinical evidence from combination studies. Triple reuptake inhibitors (TRIs) block SERT, NET and DAT simultaneously and hold promise as a new therapy for inadequately-treated depression. Here, we report a series of novel 4-bicyclic heteroaryl 1, 2, 3, 4-tetrahydroisoquinoline derivatives as TRIs. The synthesis and the Structure-Activity Relationship of this series will be presented. An advanced compound from this series, ALB 109780 (AMR-000002), exhibited substantial occupancy levels at the three transporters in both rat and mouse brain. It also demonstrated efficacy in rodent models of depression.

MEDI 16

Orally efficacious, selective FLT3 inhibitor for the treatment of acute myeloid leukemia

***Kevin Kreutter**, KKREUTTE@its.jnj.com, Nand Baindur, Guozhang Xu, Alexander J. Kim, Christian A. Baumann, Robert W. Tuman, Dana L. Johnson, Micheal D. Gaul.Janssen Pharmaceutical Companies of J&J, United States*

Acute myeloid leukemia (AML) is the second most common leukemia in the U.S., with an estimated 13,000 new cases and 9,000 deaths in 2011. Approximately 25-30% of AML patients harbor an internal tandem duplication (ITD) mutation in the FLT3 receptor tyrosine kinase, and this mutation constitutively activates FLT3 and correlates with a poor disease outcome. Inhibitors of ITD-mutated FLT3 may therefore be useful in the treatment of AML.

Our starting point, compound **1** , had a > 100-fold selectivity for FLT3 [IC_{50} = 23 nM, fluorescence polarization (FP)] over the closely related c-fms and PDGFRβ kinases (IC_{50} > 3 uM; FP). Optimization of four regions of the molecule focused on improving the rodent PK and the cell-based potency in the presence of plasma. This effort culminated in the discovery of compound **2** , a dual FLT3/cKit inhibitor (IC_{50} = 3 nM/40 nM; FP) that prevents ITD-mutated FLT3-driven cell proliferation in the absence (IC_{50} = 38 nM) and presence of 50% plasma (IC_{50} = 148 nM), and maintains ~100- >1000-fold selectivity over ~70 kinases tested (c-fms IC_{50} = 3.8 uM, PDGFRβ IC_{50} > 20 uM; FP). In an MV4-11 ITD-FLT3-driven mouse xenograft model, compound **2** at 30 and 100 mpk b.i.d. regresses tumor weight by 85% and 99%, respectively. The design, synthesis, and in vitro and in vivo SAR of this novel series will be presented.

MEDI 17

Identification of selective Rho kinase inhibitors as suitable tool compounds for proof of concept studies

***Helmut Mack**, helmut.mack@abbott.com, Bernhard K. Mueller, Reinhold Mueller. Departement of Neuroscience Discovery Research (GPRD), Abbott Gmbh & Co. KG, Ludwigshafen, Germany D67061, Germany*

HTS campaigns for kinase inhibitors often result in numerous hits. The selection of the most promising hits and the identification of potential lead series can be challenging regarding kinome selectivity and also in terms of unfavorable physicochemical parameters. In a HTS campaign for Rho kinase inhibitors more than 3000 hits were obtained. Tools and criteria used to identify and prioritize chemical matter will be discussed including a heat-map tool for visualization of kinase selectivity. Our efforts to optimize a promising single hit using parallel synthesis resulted in tool compounds suitable for proof of concept studies. Examples include enhancement of neurite

outgrowth on inhibitory substrates in vitro and regeneration of axons after crushing the optic nerve in vivo.

MEDI 18

Discovery of novel aspartyl protease inhibitors: The path from BACE to renin

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The development of renin inhibitors with good oral PK has been a considerable challenge for the industry over the past 25 years. As part of our work to identify inhibitors of the aspartyl protease, BACE1, we developed novel cyclic acylguanidines that interact with the catalytic aspartic acids in the active site. This talk will focus on optimization of this pharmacophore for inhibition of renin and the important role of structure based drug design in the discovery of potent, selective and orally active renin inhibitors.

MEDI 19

Discovery and development of LX4211, a dual inhibitor of SGLT1 and SGLT2 for the treatment of type 2 diabetes mellitus

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Sodium glucose transporter 1 (SGLT1) is the primary transporter for glucose absorption in the gastrointestinal tract while SGLT2 is responsible for the reabsorption of glucose in the kidney. These two transporters provide attractive targets for glycemic control in diabetes patients. LX4211 is a small molecule, dual inhibitor of SGLT1 and SGLT2 that increases urinary glucose excretion and triggers release of gastrointestinal peptides GLP-1 and PYY, important mediators of glucose homeostasis and appetite control. In a Phase 2 clinical trial, LX4211 produced rapid, large decreases in fasting and postprandial blood glucose and significant HbA1c reductions after only 4 weeks of treatment. We will present the discovery and early development of LX4211 for the treatment of diabetes mellitus.

MEDI 20

Discovery and development of BMS-927711, a potent oral CGRP antagonist for migraine

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Denton[3], Richard Schartman[3], Yu Fan[4], David Leahy[4], Gary Tong[5], John G Houston[6], John E Macor[1]. (1) Department of Neuroscience Chemistry, Research and Development, Bristol-Myers Squibb Co., Wallingford, CT 06492, United States (2) Department of Neuroscience Biology, Research and Development, Bristol-Myers Squibb Co., Wallingford, CT 06492, United States (3) Department of Pharmaceutical Candidate Optimization, Research and Development, Bristol-Myers Squibb Co., Wallingford, CT 06492, United States (4) Department of Chemical Development, Research and Development, Bristol-Myers Squibb Co., New Brunswick, NJ 08903, United States (5) Department of DM-Immunology, Research and Development, Bristol-Myers Squibb Co., Princeton, NJ 08543, United States (6) Disease Sciences and Biologics, Research and Development, Bristol-Myers Squibb Co., Wallingford, CT 06492, United States

Elevated levels of calcitonin gene-related peptide (CGRP) have been shown to be an early critical part of migraine pathophysiology. A number of CGRP receptor antagonists have been effective in clinical trials as novel anti-migraine agents, and there has been a decade long effort to discover orally available CGRP receptor antagonists. Overall, it has been a tremendously difficult challenge to incorporate all the required structural features in one molecule that can qualify for clinical development. Presently, the only oral CGRP receptor antagonist in clinical trials is BMS-927711. In this presentation, we will present the discovery of BMS-927711 and some initial human pharmacokinetics.

MEDI 21

Identification of GSK2636771, a potent and selective, orally bioavailable inhibitor of phosphoinositide 3-kinase-beta (PI3Kb) for the treatment of PTEN deficient tumors

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Dysregulation of the PI3K pathway is one of the most common causes of tumorigenesis and aberrant pathway activation occurs frequently through loss of the tumor suppressor protein, PTEN. Preclinical studies have shown that selective depletion of the PI3Kβ isoform inhibits tumorigenesis and reduces downstream PI3K signaling in PTEN deficient tumors. This data presents an opportunity for a clear patient selection strategy based on the presence or absence of PTEN. During an extensive knowledge-based lead identification and optimization effort starting from the reported PI3K beta-selective compound TGX-221, we identified several unique series of potent and selective inhibitors with less than desirable pharmacokinetic properties. Through a combination of

structure-based and knowledge-based design, we ultimately identified substituted benzimidazole GSK2636771 as a potent, orally bioavailable, PI3K beta-selective inhibitor. The evolution of our selective inhibitors, leading to the discovery, design, and optimization of GSK2636771 and related analogs, will be described.

MEDI 22

Discovery of GS-9620, an oral agonist of Toll-like receptor 7 for the treatment of chronic hepatitis B and C infection

***Randall L Halcomb**, randall.halcomb@gilead.com, Paul Roethle, Hong Yang, Ryan McFadden, Paul Hrvatin, Hon Hui, Michael Graupe, Daniel Tumas, Xubin Zheng, Bing Lu, Jason Perry, Paul Duatschek, Joseph Hesselgesser, Doris Graupe, Bei Li.Gilead Sciences, Foster City, CA 94404, United States*

Toll-like receptors (TLRs) recognize fragments of invading pathogens and subsequently initiate an immune response. TLR-7 is predominantly localized in endosomes and lysosomes of immune cells, particularly plasmacytoid dendritic cells and B lymphocytes, where it recognizes viral single-stranded RNA as its native ligand. Signaling from the receptor in dendritic cells leads to the secretion of high levels of interferon-alpha, with subsequent activation of these cells for antigen presentation. Substantial published data suggests that TLR-7 agonists could be used for the treatment of chronic infection with hepatitis B and C viruses. The SAR leading to the discovery of GS-9620, an orally available small-molecule TLR-7 agonist, will be described. Additionally, a summary of in vivo animal pharmacodynamics and efficacy models as well as Phase 1 clinical data will be presented.

MEDI 23

Discovery of BMS-791325, an allosteric NS5B replicase inhibitor for the treatment of Hepatitis C

***John F. Kadow**[1], john.kadow@bms.com, Robert Gentles[2], Min Ding[2], John Bender[1], Carl Bergstrom[2], Katherine Grant-Young[1], Piyasena Hewawasam[1], Thomas Hudyma[2], Scott Martin[2], Andrew Nickel[1], Alicia Regueiro-Ren[1], Yong Tu[1], Zhong Yang[1], Kap-Sun Yeung[1], Xiaofan Zheng[2], Bang-Chi Chen[3], Sam Chao[3], Jung-Hui Sun[3], Jianqing Li[3], Arvind Mathur[3], Daniel Smith[3], Dauh-Rurng Wu[3], Brett Beno[4], Umesh Hanumegowda[5], Jay Knipe[5], Dawn D. Parker[5], Xiaoliang Zhuo[5], Julie Lemm[6], Mengping Liu[6], Lenore Pelosi[6], Karen Rigat[6], Stacey Voss[6], Yi Wang[6], Ying-Kai Wang[6], Richard Colonno[6], Min Gao[6], Susan B. Roberts[6], Nicholas A. Meanwell[1]. (1) Virology Chemistry, Bristol-Myers Squibb, United States (2) Early Discovery Chemistry, Bristol-Myers Squibb, United States (3) Department of Chemical Synthesis, Bristol-Myers Squibb, United States (4) Computer Aided Drug Design, Bristol-Myers Squibb, United States (5) Molecular Science Candidate Optimization, Bristol-Myers Squibb, United States (6) Infectious Disease Biology, Bristol-Myers Squibb, United States*

Approximately 3% (170 million) of the world's population are infected with hepatitis C virus (HCV). Greater than 350,000 deaths per year are attributed to HCV related illnesses. The current optimal therapy consists of pegylated interferon (IFN), ribavirin and one of two approved small molecule, direct acting antiviral (DAA), HCV protease inhibitors. A considerable amount of preclinical and clinical research aimed at achieving shorter duration of treatment, improved tolerability, or Peg-IFN alfa free combination regimens is ongoing in the rapidly evolving, global effort to address this disease. This presentation will describe the discovery and preclinical profile of BMS-791325, an allosteric inhibitor of HCV NS5B replicase, which is currently in Phase II clinical trials designed to explore its use in combination therapy against HCV. BMS-791325 is a potent inhibitor of both 1a and 1b HCV virus in replicon studies and displayed pharmacokinetics in three species which supported advancement to clinical studies.

MEDI 24

Discovery and SAR exploration of quinazoline and cyanoisoquinoline inhibitors of Phosphodiesterase 10A (PDE10A)

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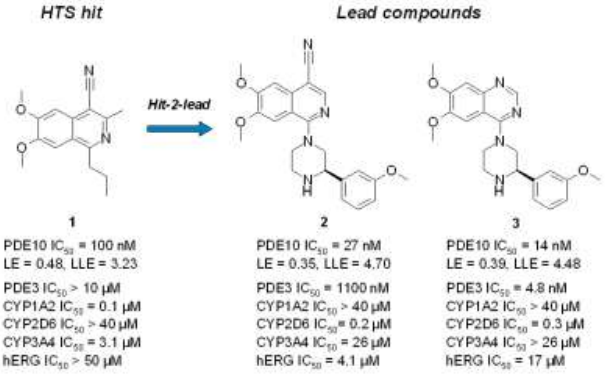
The phosphodiesterases (PDEs) are a superfamily of 11 enzymes that inactivate the second messengers cAMP and cGMP by hydrolysis of the 3'-ester bond, forming the inactive 5'-monophosphate thereby terminating the signaling. PDE10A is a phosphodiesterase with a distinct brain localisation with predominant expression in the medium spiny neurons of the striatal complex. Research has focused on using PDE10A modulators as therapeutics for diseases characterized by dysfunction of the basal ganglia circuit. Such disorders include Parkinson's disease, Huntington's disease, schizophrenia, addiction and obsessive compulsive disorder. In particular, preclinical evidence from animal models suggests that a PDE10A inhibitor could provide anti-psychotic, pro-cognitive and negative symptom efficacy in schizophrenia, which would set a new standard for the pharmacological treatment of this debilitating disease.

Compound **1** was identified in a HTS as a relatively potent inhibitor with excellent ligand efficiency. The SAR exploration and structure-based drug design project ultimately producing the leads **2** and **3** will be presented. Interestingly, the binding mode as determined by X-ray crystallography changed dramatically during this campaign, and the consequences of this variability of the ligand-protein interaction as a function of the substitution pattern will be discussed. Subtype selectivity, in particular with respect to PDE3, was achieved in the cyanoisoquinoline series represented by compound **2** , but not in the closely related quinazoline series exemplified by compound **3** .



MEDI 25

Identification of allosteric agonists of mGlu5: A mechanism for adverse effect liability and implications for potentiator scaffold selection and design

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Allosteric modulators for G-protein-coupled receptors (GPCRs) provide numerous advantages over orthosteric ligands, including greater sub-type selectivity, reduced receptor desensitization, and enhanced therapeutic index. Positive allosteric modulators (PAMs) of the group I metabotropic glutamate receptor mGlu5 are being pursued as a novel approach to treat all three symptom domains of schizophrenia. Interestingly, mGlu5 PAMs can demonstrate a range of in vitro profiles, including robust agonistic activity, and thus the advantages of an allosteric approach could be compromised. In an effort to more fully understand the impact of allosteric agonist activity at mGlu5 we have identified both allosteric agonists (ago-PAMs) and pure positive allosteric modulators (pure-PAMs) of mGluR5 within a single acetylenic biaryl series that are suitable for determining the effects of these profiles in native systems and in behavior models. SAR and strategies to mitigate agonist activity of mGlu5 PAMs will be discussed.

MEDI 26

Discovery of stable protein motifs from dynamic combinatorial libraries

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Biologicals are the fastest growing class of pharmaceuticals. The vast majority of biologicals are antibodies. Antibodies do not cross cell membranes, which limits their therapeutic potential. We are developing protein motifs that marry the exquisite binding specificity of antibodies with the cell-penetrating ability of small molecules. The biggest challenge we face is to stabilize small protein motifs to increase their resistance to intra-

and extracellular proteolysis. To this end, a method has been developed to rigorously explore the dependence of protein folding stability on the identity of hydrophobic amino acids in the protein core. Recursively enriched dynamic combinatorial libraries (REDCLs) have been used to discover the optimal hydrophobic core packing in a triple helical protein. This is the first strategy for probing protein packing that screens directly for thermodynamic stability.

Self-selection of stable proteins from conformationally restricted peptide libraries is achieved using template-assisted assembly: the template is a metal ion and the peptide fragments are augmented with a metal-binding moiety as shown schematically in Figure 1a. Large (>60,000 member) DCLs return native-like proteins with unusual sets of hydrophobic amino acids (Figure 1b).

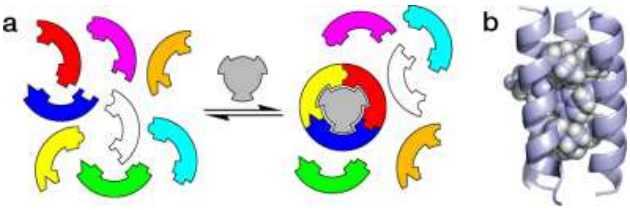

Figure 1 (a) The principle of template-assembled DCLs. (b) Packing of the most stable protein selected from over 1.7 million candidates

Roy, L.; **Case, M. A** . *J. Phys. Chem. B* **2011** , *115*, 2454-2464

Roy, L.; **Case, M. A** . *J. Am. Chem. Soc.* **2010,** *132*, 8894-8896

MEDI 27

WITHDRAWN

MEDI 28

Synthesis and anticonvulsant activity of 4-aryl-2-hydroxytetronimides

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4-Aryl-2-hydroxytetronimides, like the related 4-aryl-2-hydroxytetronic acids, are antioxidants that have potent reactive oxygen species (ROS) quenching activities. However, despite the synthesis and biological evaluation of many 4-aryl-2-

hydroxytetronic acids, biological characterization of 4-aryl-2-hydroxytetronimides have been neglected. In the development of modular pharmaceutical agents, 2-hydroxytetronimides have greater theoretical potential relative to 2-hydroxytetronic acids, because 2-hydroxytetronic acids can only be incorporated in terminal modules, whereas 2-hydroxytetronimides can be incorporated into both terminal and internal modules due to the ability to attach functional groups to the hydroxytetronimide nitrogen. Here, we report the synthesis of 4(fluorophenyl)-2-hydroxytetronimides, and for the first time describe the anticonvulsant activity of these antioxidants. Despite the modest anticonvulsant activity of the 4(fluorophenyl)-2-hydroxytetronimides described, these molecules may be elaborated into more complex, potent antiepileptogenic agents.

MEDI 29

Novel TEMPO-PEG-RGDs conjugates remediate tissue damage induced by acute limb ischemia/reperfusion

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We have recently developed new TEMPO-PEG-RGDs conjugates, and have quantitatively examined their antithrombotic and antioxidant capabilities. These compounds were therapeutically beneficial when characterized in both *in vitro* platelet aggregation assays and a rat model of arterial thrombosis. Moreover, these compounds demonstrated significant protection from organ damage in a rat model of ischemia/reperfusion. Our data indicate that TEMPO-PEG-RGDs represent a new class of adjuvants with therapeutic efficacy in acute and transient ischemic damage.

MEDI 30

Discovery of potent and selective free fatty acid receptor 1 (FFA1/GPR40) agonists

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The free fatty acid receptor 1 (FFA1 /GPR40) is highly expressed in pancreatic beta-cells and responds to long-chain free fatty acids to enhance glucose-stimulated insulin secretion. The receptor has therefore the potential of increasing insulin secretion only at elevated plasma glucose concentrations, and has received considerable attention as a new target for development of safe oral therapeutics of type 2 diabetes with lower risk of hypogycemia. Several series of FFA1 agonists are already known, but many of these are relatively lipophilic, most likely a consequence of the lipophilic nature of the receptor

binding site and free fatty acids serving as leads. Initially starting with free fatty acids as leads, we discovered compounds series that we have been able to optimize to potent FFA1 agonists while at the same time reducing lipophilicity, maintaining a small molecular sized and creating favorable ADME properties. The discovery, optimization and structure-activity relationships will be described.

MEDI 31

Synthesis of unsymmetrical cyclotriazadisulfonamide (CADA) compounds as anti-HIV and human CD4 receptor down-modulating agents

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Cyclotriazadisulfonamide (CADA) potently inhibits human immunodeficiency virus (HIV) entry and replication by specifically down-modulating the main HIV receptor, CD4. The specific biomolecular target of CADA compounds is unknown, but previous studies led to an unsymmetrical binding model. To evaluate this model, methods were developed for effective synthesis of diverse, unsymmetrical CADA compounds. A total of 13 new, unsymmetrical target compounds were synthesized, as well as one symmetrical analog. The new compounds display a wide range of potency for CD4 receptor down-modulation in CD4-transfected cells, CHO.CD4-YFP cells. VGD020 (IC_{50} 46 nM) is the most potent CADA analog discovered to date, and VGD029 (IC_{50} 730 nM) is the most potent fluorescent analog. Structure-activity relationships are analyzed from the standpoint of additive or non-additive energy effects of different substituents. They appear to be consistent with the zipper-type mechanism in which entropy costs are reduced for additional stabilizing interactions between the small molecule and its cellular protein target.

MEDI 32

Evaluation of cyclopentane-1,3-dione as isostere of the carboxylic acid functional group

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Cyclopentane-1,3-diones are known to be relatively strong acids with pK_a values typically in the range of carboxylic acids. To explore the potential of the cyclopentane-1,3-dione unit as an isosteric replacement of the carboxylic acid moiety, the physical

chemical properties of representative mono- and di-substituted cyclopentane-1,3-diones were examined and compared with similar derivatives bearing carboxylic acid or tetrazole residues. The ability of cyclopentane-1,3-diones to form salts with amidines was evaluated by NMR and mass spectrometry. The structure of the dione–amidine complex was also estimated by molecular modeling. These studies reveal that cyclopentane-1,3-diones, in the enol-ketone tautomeric forms, can generate 1:1 complexes with amidines, suggesting that these fragments can substitute for the carboxylic acid functional group in the formation of salt-bridges (J. Med. Chem. 2011, 54, 6969–83). Examples of the use of the cyclopentane-1,3-dione isostere in drug-design will be presented.

MEDI 33

Discovery of a glutathione peroxidase inhibitor that reverses resistance to anticancer drugs in human B-cell lymphoma lines

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The development of resistance to chemotherapy in the treatment of cancer is one of the main causes for therapy failure. Growing evidence indicates that cancer cells can become resistant to chemotherapeutics by increasing their ability to handle oxidative stress, which is often activated by anticancer agents. Drugs that could resensitize resistant cancer cells to the detrimental effects of oxidative stress might be useful in reversing resistance to anticancer drugs when given in combination. For use as a model system of acquired drug resistance in B-cell lymphoma, we established several human cell lines isolated from patients with malignant non-Hodgkin lymphomas that became resistant to chemotherapy during clinical treatment. The cell lines have now been made >3-fold resistant in culture to various anticancer drugs used in the treatment of B-cell lymphoma, including cisplatin, etoposide, methotrexate and bortezomib. In most of the resistant lines the key antioxidative enzyme glutathione peroxidase 1 (GPx-1) was found to be significantly increased in expression, as determined by Western blotting, relative to the native lines. Thus, GPx-1 may be a potential target for inhibitor development. In silico screening by automated docking of a large library of diverse substances to the active site of the X-ray crystal structure of bovine GPx-1 yielded a number of compounds that could potentially block the enzyme. Screening of these compounds with an enzyme assay that used bovine erythrocyte GPx-1 identified a hydrazone heterocyclic that fulfilled Lipinski's rules and had satisfactory enzyme inhibitory activity. When this compound was combined with the anticancer drugs listed above in cytotoxicity experiments, reversal of resistance to varying degrees was achieved in the chemotherapy resistant lymphoma cell lines. Thus, the compound would appear to be a useful lead in the development of more potent GPx-1 inhibitors to help reverse cancer drug resistance.

MEDI 34

Nitrophenylphosphate substrate screening and oxime-based ligation for the development of nanomolar affinity inhibitors of the *Yersinia pestis* protein tyrosine phosphatase YopH

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Effector protein YopH represents an attractive drug target due to the potential use of *Y. pestis* as a bioterrorism agent. The first KM optimization of a library of nitrophenylphosphate-containing substrates was used for generating an inhibitor lead against YopH. A high activity substrate identified by this method (KM = 80 μM) was converted from a substrate into an inhibitor by replacement of its phosphate group with difluoromethylphosphonic acid and by attachment of an aminooxy handle for structural optimization by oxime ligation. A cocrystal structure of this aminooxy-containing platform in complex with YopH allowed the in silico docking studies and furanyl-based oxime derivatives were identified as providing favorable interactions with target residues. By this process, a potent (IC50 = 190 nM) and selective YopH inhibitor was developed. The inhibitor showed significant inhibition of intracellular Y. pestis replication at a noncytotoxic concentration. The approach may afford significant utility beyond its immediate target.

MEDI 35

Mitochondria-targeted gold nanoparticles for combined photothermal and chemotherapy

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The ability of nanoparticles (NPs) to accumulate in tumors as a result of the enhanced permeability and retention effect (EPR) is an advantageous feature for delivery of therapeutics. However, efficient drug delivery is dependent on the ability of NPs to mediate specific delivery to the subcellular site of action. Lipophilic cationic complexes, such as triphenyl phosphine (TPP) have shown to accumulate inside the mitochondria. We have initiated an engineering approach to combine the organelle-targeting property of TPP with EPR effect of NPs by functionalizing the surface of gold NPs with a dendron conjugated to three TPPs and an inhibitor of mitochondrial hexokinase, 3-bromopyruvate. The efficiency in targeting mitochondria by the NPs carrying multivalent TPP will be compared with the NPs with monovalent ligands. The utility of these constructs in the mitochondria-targeted combination therapy will be discussed. These

results will provide guidance for the development of targeted NPs with multivalent ligands.

MEDI 36

Hit validation of ERK5 inhibitors: Expectations and challenges

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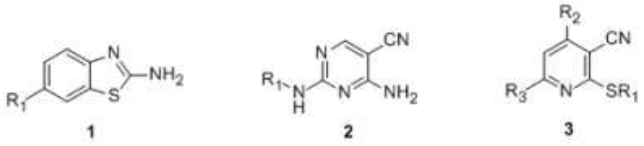
Extracellular signal-regulated kinase 5 (ERK5) plays a key role in the transduction of extracellular signals to intracellular effectors. Activation of the ERK5 signalling pathway is associated with cell survival and proliferation, and thus ERK5 over-expression has implications in carcinogenesis. Inhibiting ERK5 is therefore an effective approach for anti-cancer therapy.



Following a high throughput screening campaign, three chemical series (**1** -**3**) were selected for validation. The syntheses and biological evaluation of novel benzo[*d*]thiazoles (**1**), 4-aminopyrimidine-5-carbonitriles (**2**) and 3-cyanopyridines (**3**) will be discussed.

MEDI 37

Design, synthesis and anticancer activity of artemisinin-combretastatin hybrids

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Combination anticancer therapies are more effective than monotherapies, as they improve therapeutic effect and modulate drug resistance. Artemisinin possesses selective superior anticancer activity in numerous cell-lines. CA-4, a potent tubulin inhibitor is active in several cancer cells including MDR positive cells. In consideration of

developing potent, selective and bi-functional artemisinin based agents, artemisinin-CA-4 hybrids “artcombs” were synthesised. We will show the design and synthesis of series of novel artcombs and their anticancer effect on both drug sensitive and MDR cells.

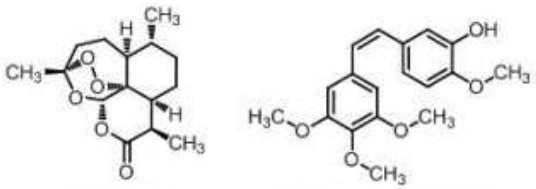

Figure: Chemical structures of artemisinin and CA-4

MEDI 38

Heteroaryl hydroxamic acid derivatives as novel histone deacetylase inhibitors

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Histone deacetylase (HDAC) regulates gene expression and chromatin remodeling by acetylation/ deacetylation of histone. We previously found histone deacetylase inhibitors showed the potential ability to inhibit IL-2 gene expression and possess immunosuppressive activity. This finding prompted us to discover a new class of immunosuppressants for transplantation. We selected a cinnamyl hydroxamic acid derivative FR276457, our original HDAC inhibitor reported previously, as a lead compound. Modification of this compound produced novel heteroaryl hydroxamic acid derivatives as potent HDAC inhibitors with nanomolar IC_{50}s. We also discovered that several compounds prolonged the median survival time of the transplanted grafts in a rat heterotopic cardiac transplant model (ACI to LEW), when orally administered as a monotherapy or in combination with Tacrolimus. We will report the synthesis , the SAR and the pharmacological properties of these compounds.

MEDI 39

Discovery of isozyme-selective histone deacetylase inhibitors by click chemistry

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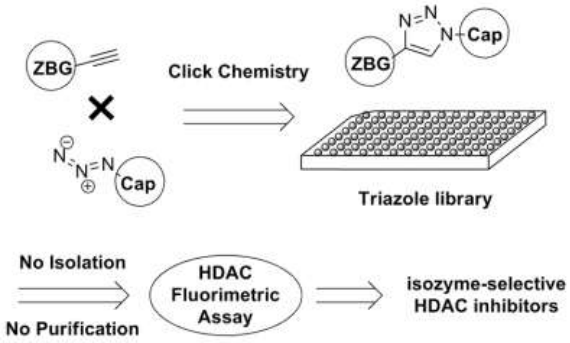
Some of the histone deacetylase (HDAC) isozymes have been suggested to be associated with several disease states. Therefore, isozyme-selective HDAC inhibitors are of interest as therapeutic agents.

The pharmacophore of HDAC inhibitors consists of a zinc-binding group (ZBG), a capping group, and a linker group. To find isozyme-selective inhibitors, we prepared a triazole-based library using click chemistry by reacting alkynes bearing a ZBG with various azides. Screening of the library led to the identification of isozyme-selective HDAC inhibitors.



MEDI 40

Design and synthesis of Duocarmycins and Anthramycin-related DNA minor groove alkylaors

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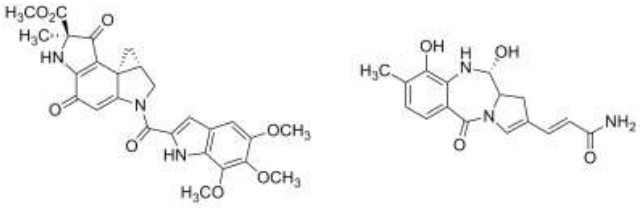
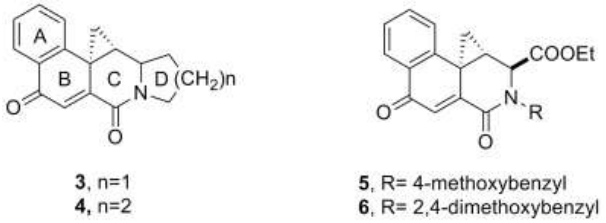
Cancer is ranked as the second leading cause of death accounting for 13% of all mortalities worldwide. Duocarmycin A **1** and Anthramycin **2** represent classes of exceedingly potent antitumors with selective DNA-minor groove binding activities in the AT and GC rich regions respectively.



1, (+)Duocarmycin A **2**, Anthramycin

[Figure 1]

Key structural features of **1** and **2** were used to create hybrid structures **3** and **4** which showed promising antineoplastic activity in the NCI 60 panel screen. To investigate the importance of ring D and to allow for attachment of additional DNA-sequence-selective functionalities, compounds **5** and **6** were prepared. The target compounds were synthesized using an imine-anhydride cycloaddition and Winstein spirocyclization as key steps.



3, n=1
4, n=2

5, R= 4-methoxybenzyl
6, R= 2,4-dimethoxybenzyl

[Figure 2]

MEDI 41

1,2,3-Triazole-4-carboxamide as a nucleobase analog

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The purpose of a nucleobase in a nucleoside is to hold Watson-Crick base pairing groups and a ribose in the correct relative orientation. Several nucleoside analogues containing a 1,2,3-triazole-4-carboxamide in place of a purine ring have been prepared. The anticancer and antiviral activity of some compounds will be presented.

MEDI 42

Discovery of imidazopyridine and imidazopyridazine inhibitors of PI3K

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PI3 kinases are a family of lipid kinases mediating numerous cell processes such as proliferation, migration and differentiation. The PI3 kinase pathway is often de-regulated in cancer through PI3Ka overexpression, gene amplification, mutations and PTEN phosphatase deletion. PI3K inhibitors represent therefore an attractive therapeutic modality for cancer treatment. We herein describe the discovery of a series of 2-acetamido-6-heterocyclyl imidazopyridines/imidazopyridazines as potent, selective pan-PI3 kinase inhibitors. These scaffolds were identified via scaffold hopping from a 6-heterocyclyl-2-acetamidobenzothiazole hit series. The structure-activity relationship study within these scaffolds identified 5-amino-6-substituted pyrazin-2-yl group and 6-amino-5-substituted pyridin-3-yl group as preferred heterocyclyl groups on the 6-position of 2-acetamido-imidazopyridines/imidazopyridazines. Alkoxy substituents led to analogues showing potent activity against class I PI3K in the biochemical assay and pAKT modulation in the cell based assay and good selectivity against protein kinase panels.

MEDI 43

Structure guided optimization of a fragment hit to a series of imidazopyridine inhibitors of PI3K

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PI3 Kinases are a family of lipid kinases mediating numerous cell processes such as proliferation, migration and differentiation. The PI3 Kinase pathway is often de-regulated in cancer through PI3K alpha overexpression, gene amplification, mutation and PTEN phosphatase deletion. PI3K inhibition represents therefore an attractive therapeutic modality for cancer treatment. Herein we describe how the potency of a 2-acetamido benzothiazole fragment hit was quickly improved based on structural information and how this early chemotype was further optimized through scaffold hopping. This effort led to a series of 2-acetamido-6-heterocyclyl imidazopyridines showing potent *in vitro* activity against class I PI3Ks.

MEDI 44

Optically pure apogossypolone derivative as potent pan-active inhibitor of anti-apoptotic Bcl-2 family proteins

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Our focus in the past several years has been on the identification of novel and effective pan-Bcl-2 antagonists. We have recently reported a series of Apogossypolone (ApoG2) derivatives, resulting in the chiral compound (+/-) BI97D6. We report here the synthesis and evaluation on its optically pure (-) and (+) atropisomers. Compound (-) BI97D6 potently inhibits the binding of BH3 peptides to Bcl-X_L, Bcl-2, Mcl-1 and Bfl-1 with IC_{50} values of 76, 31, 25 and 122 nM, respectively. In a cellular assay, compound (-) BI97D6 effectively inhibits cell growth in the PC-3 human prostate cancer and H23 human lung cancer cell lines with EC_{50} values of 0.22 and 0.14 μM, respectively. The compound also shows little cytotoxicity against *bax*$^{-/-}$/*bak*$^{-/-}$ cells, suggesting that it kills cancers cells predominantly via a Bcl-2 pathway. Moreover, compound (-) BI97D6 displays *in vivo* efficacy in both a Bcl-2 transgenic mouse model and in a prostate cancer xenograft model in mice. Therefore, compound (-) BI97D6 represents a promising drug lead for the development of novel apoptosis-based therapies for cancer.

MEDI 45

Design and synthesis of pyrrolo[3,2-*d*]pyrimidine HER2/EGFR dual inhibitors: Exploration of novel back-pocket binders

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In order to develop novel HER2/EGFR kinase inhibitors, we explored pyrrolo[3,2-*d*]pyrimidine derivatives bearing bicyclic-fused lactam rings designed to fit the back pocket of the HER2/EGFR proteins. Among the prepared derivatives, the 1,3-dihydro-2*H*-indol-2-one compound showed both potent HER2/EGFR and cell growth inhibitory (GI) activities related to its pseudo-irreversibility (PI). Furthermore, with the aim of improving the oral bioavailability (BA) without loss of PI, we designed and selected a 1,2-benzisothiazole ring as a suitable back pocket binder for further optimization, because of its strong GI and PI as well as good BA. The representative compound **A** showed both potent HER2/EGFR inhibitory activity (IC_{50} 0.98/2.5 nM) and GI activity in breast cancer BT-474 cell (GI_{50} 2.0 nM). Reflecting these strong *in vitro* activities, compound **A** exhibited potent tumor regressive efficacy against both HER2- and EGFR-

overexpressing tumor (4-1ST and CAL27) xenograft models in mice at an oral dose of 100 mg/kg.

MEDI 46

Design, synthesis, and biological evaluation of cyclopropylamine-based LSD1 inhibitors

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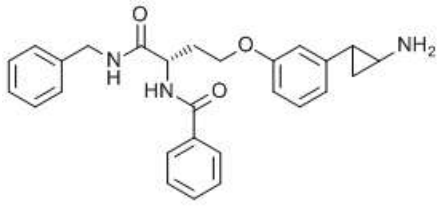
Lysine-specific demethylase 1 (LSD1) has been suggested to be associated with certain disease states including cancer. Therefore, LSD1 inhibitors are of interest as potential therapeutic agents.

To identify potent LSD1-selective inhibitors, we designed several analogues of *trans*-2-phenylcyclopropylamine, a non-selective LSD1 and monoamine oxidase inhibitor. Some of the designed compounds such as NCL1 (**Figure**) were found to be potent and selective LSD1 inhibitors. Furthermore, these showed in vivo histone lysine-methylating activity and antiproliferative activity. Thus, we have identified cell-active LSD1-selective inhibitors.



NCL1

IC_{50} = 2.5μM

Figure Structure of NCL1.

MEDI 47

Design, synthesis, and biological activity of JMJD2 histone demethylase inhibitors

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Jumonji domain-containing protein 2 histone demethylase (JMJD2) is associated with cancer. Therefore, selective inhibitors of JMJD2 can be candidate anticancer agents as well as potential tools for elucidating its biological function. To find potent JMJD2-selective inhibitors, we designed and synthesized hydroxamate analogues on the basis of the crystal structure of JMJD2A. Among these, several compounds including NCDM-32 showed 500-fold greater JMJD2C-inhibitory activity and more than 9100-fold greater JMJD2C-selectivity compared with the lead compound *N*-oxalylglycine (NOG).

NOG	NCDM-32
JMJD2C IC_{50} = 500 μM	JMJD2C IC_{50} = 1.0 μM
JMJD2A IC_{50} = 250 μM	JMJD2A IC_{50} = 2.5 μM
PHD1 IC_{50} = 2.1 μM	PHD1 IC_{50} > 100 μM
PHD2 IC_{50} = 5.6 μM	PHD2 IC_{50} > 100 μM

MEDI 48

Design, synthesis, and SAR studies of duel FLT-3 and Aurora kinase inhibitors

***Hsing-Pang Hsieh**, hphsieh@nhri.org.tw, Hui-Yi Shiao, Wen-Hsing Lin, John Tsu-An Hsu, Yu-Sheng Chao. Institute of Biotechnology and Pharmaceutical Research, National Health Research Institutes, Miaoli, Taiwan Republic of China*

Aurora kinase and FMS-like Tyrosine Receptor 3 (FLT3) was found to associate with various cancers, including breast cancers, colorectal cancers, AML and so on. There are several Aurora kinase inhibitors and FLT3 inhibitors was developed and under clinical investigation. And no Aurora kinase inhibitors or FLT3 inhibitors currently approved for the treatment of cancers still.

We synthesized more than 1000 compounds mainly targeted at Aurora kinase. BPR1K871, a novel, potent, small-molecule inhibitor of multiple kinase showed potent in vitro activities for Aurora kinase A (IC50: 50 nM), FLT-3 (IC50: 29 nM) and at least other 17 kinases with low IC50 activities (nano molar range). In cell-based assay, BPR1K871also demonstrated its excellent anticancer activities (HCT116: 117 nM, MOLM-13: 2 nM, MIA Paca-2: 9 nM, Colo205: 33 nM). In the MOLM-13 xenograft animal studies, BPR1K871 suppressed tumor growth up to 98% at 3 mg/kg once a day for 10-day treatment by IV administration. The body weight loss is less than 5% during the dosing period. This non-clinical profile of BPR1K871 supports the further pre-clinical development.

MEDI 49

In silico test battery for rapid evaluation of genotoxic and carcinogenic potential of chemicals

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This work is an extension of our previous study focusing on computational assessment of genotoxic impurities in drug products. Our new approach relies on a battery of probabilistic QSAR models supplemented by a knowledge-based expert system that identifies structural fragments potentially responsible for hazardous activity. The analysis was based on experimental data obtained from FDA, and involved 21 endpoints corresponding to different mechanisms of toxic action: mutagenicity, clastogenicity, carcinogenicity, etc. Probabilistic models were derived using GALAS (Global, Adjusted Locally According to Similarity) modeling methodology developed in our group. The updated list of alerting groups contained 70 distinct substructures. The expert system was highly sensitive, recognizing >90% of potent carcinogens, as classified by FDA. Sensitivity of probabilistic GALAS models ranged from 60% to 93%, whilst maintaining high (>80%) specificity of predictions. These results show that the described computational platform ensures sufficient prediction accuracy for rapid genotoxicity/carcinogenicity profiling of various chemicals.

MEDI 50

Novel amino acid derivatives of naproxen for colon cancer chemoprevention

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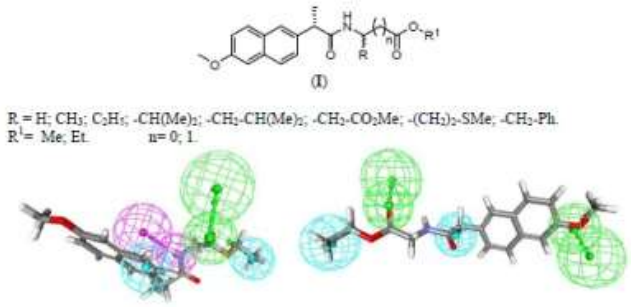
Nonsteroidal anti-inflammatory drugs (NSAID) display promising cancer chemopreventive efficacy, especially for colorectal cancer. Epidemiologic studies have shown that long-term use of NSAIDs is associated with reduced incidence of colorectal cancer in the general population by about 30% to 50%. Accordingly, a series of naproxen amides of amino acid esters (**I**) were synthesized and their potential for cancer chemoprevention were investigated using human colon tumor cell lines. All amide derivatives were found to lack COX-1 and COX-2 inhibitory activity and most displayed improved tumor cell growth inhibitory activity compared with naproxen, one of

which (R=H; R^1=Me; n=0), displayed high potency with IC_{50} values 14.6 µM. Interestingly, the modification also appeared to improve selectivity for colon tumor cell. These effect suggest potential safety and efficacy of this class of compounds for colorectal cancer chemoprevention. A pharmacophore model was developed to further optimize the activity among this series of novel compounds.



MEDI 51

Novel 4-*N*-modified gemcitabine analogs

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Gemcitabine (2',2'-difluoro-2'-deoxycytidine, dFdC) is an effective chemotherapeutic agent used in the treatment of solid tumors in various cancers. However, dFdC is therapeutically restricted by enzymatic deamination by deoxycytidine deaminase (dCDA). Conversion of the exocyclic 4-*N* amino group to an amide function is known to preserve anticancer activity of dFdC (*JMC* **2009** , *52*, 6958). We have synthesized 4-*N*-acyl and 4-*N*-alkyl gemcitabine analogues with alkyl chains of varying lengths (8 to 12 carbons), bearing halo, hydroxyl or olefin functionalities. Cytotoxic and proliferative properties of 4-*N*-acyl and 4-*N*-alkyl analogues were assessed in breast adenocarcinoma cell lines (MCF-7, MDA-MB-231) by SRB and BrdU assays and demonstrated comparable activity to dFdC.

MEDI 52

Biomedical research at core synthesis facility of North Dakota State University

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The Core Synthesis Facility was established North Dakota State University as a part of the Center for Protease Research by a NCRR-NIH-COBRE grant in April 2008, so as to facilitate principal investigators in accomplishing their research targets. The research in this facility is primarily focused on organic synthesis of small molecules for biomedical applications and analytical characterization of substrates of interest. The chemistry involves fluorescent tagging of peptides/amino acids, developing a library of HDAC inhibitors and building an anti-cancer drug delivery model system. We would like to present some research examples in Core Synthesis Facility by cooperating with PIs of Center for Protease Research and researchers nationwide. The presentation will include design of the molecules, organic syntheses and bioactivity tests.

MEDI 53

Discovery of OSI-027: An imidazotriazine-based orally efficacious dual inhibitor of mTORC1 and mTORC2

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The mammalian target of rapamycin (mTOR) protein complexes, mTORC1 and mTORC2, play a central role in regulating cell proliferation and survival, and the PI3K/AKT signaling pathway that activates them is frequently altered in human cancers. Through medicinal and computational chemistry-based design efforts, we optimized our early imidazo[1,5-*a*]pyrazine leads through to the imidazo[5,1-*f*][1,2,4]triazine derivative OSI-027. This agent is a potent and selective dual inhibitor of mTORC1 and mTORC2 that exhibits good oral exposure, pharmacodynamic effects and broad spectrum antitumor efficacy *in vivo* including in rapamycin-insensitive xenografts. OSI-027 is currently in Phase I clinical trials.

MEDI 54

New diarylureas and diarylamides possessing 1*H*-pyrrolo[3,2-*c*]pyridine scaffold: Design, synthesis, and anticancer evaluation

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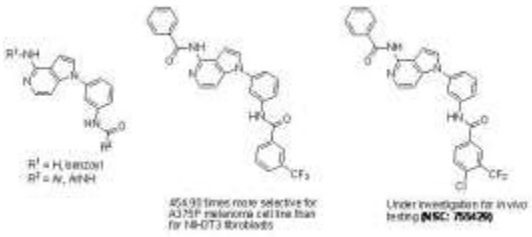
A new series of diarylureas and diarylamides having 1*H*-pyrrolo[3,2-*c*]pyridine scaffold was designed and synthesized. Their *in vitro* antiproliferative activity against A375P

human melanoma cell line was tested. Most of the newly synthesized compounds demonstrated superior activity against A375P to Sorafenib. Ten derivatives showed high potency against A375P with IC_{50} in nanomolar scale. Another three compounds were more potent than Sorafenib against A375P but with IC_{50} in micromolar scale.

We further tested seven compounds, which showed the highest potencies over A375P, against NIH3T3 fibroblasts in order to investigate their selectivity towards melanoma cells over normal cells. One target compound was 454.90 times more selective. Its IC_{50} values were 15.3 nM and 6.96 μM over A375P and NIH3T3, respectively. The selectivity of another three compounds; 4.13, 7.50, and 3.37 times, were comparable to that of Sorafenib (4.42 times).

The target compounds were subjected to *in vitro* anticancer assay against a full panel of 60 cancer cell lines taken from nine different tissues at the NCI. They showed highly potent and broad-spectrum antitumor activity against all the cancer types. One of the target compounds is currently under investigation for *in vivo* anticancer testing at the NCI.



Acknowledgment

This work was supported by Seoul R&BD program (grant number PA100015).

MEDI 55

Design and synthesis of benzylamine and benzyl ether derivatives as Wnt mimetics to promote stem cell pluripotency: Comparison of carbonyl and oxime or oxime ether functionality

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A series of different benzylamine and benzyl ethers analogs with carbonyl and oxime or oxime ether moieties were synthesized and tested as small molecule drugs to promote pluripotency in mouse embryonic stem cells via the canonical Wnt pathway. The compounds contained an aromatic core that was essential to “anchor” the molecule on the main protein. Furthermore, a hydrophobic “tail” was necessary to block the docking interaction with the second protein. The compounds were methodically synthesized to test if structural changes that reflect steric and electronic effects will induce any positive activity in our primary reporter assay. The design, synthesis, and purification of these small molecule drugs as well as the results from some biological studies will be presented with special emphasis on a comparison of the efficiency of the drug as a function of the change in functional group.

MEDI 56

Synthesis and biological evaluation of aminosteroid inhibitors of the inositol phosphatase SHIP1

Dennis R Viernes[1]*, drviernes@yahoo.com, Robert Brooks*[2]*, Sonya Iyer*[2]*, Sandra Fernandes*[2]*, William G Kerr*[2]*, John D Chisholm*[1]*. (1) Department of Chemistry, Syracuse University, Syracuse, NY 13244, United States (2) Department of Microbiology and Immunology, State University of New York Upstate Medical University, Syracuse, NY 13210, United States*

SH2-containing inositol phosphatase (SHIP), a 145 kDa protein, is involved in regulating the formation of new blood cells. Primarily this enzyme has been studies with genetic tools to explore its function, however recently small molecule inhibitors have begun to be explored. High throughput screening of molecules from chemical libraries identified several SHIP inhibitors which includes NSC23922, a mixture of 3α and 3β-aminocholestane. Synthesis and biological evaluation of 3α and 3β-aminocholestane showed that the former was more active probably because of it's much higher solubility in polar solvents. Synthetic studies have been undertaken to determine which portions of the aminosteroid SHIP1 inhibitor are important for biological activity. In addition, modifications to the molecule which improve solubility in water and water/DMSO mixtures have also been explored in order to facilitate the eveluation of these inhibitors in other biological assays.

MEDI 57

Mimicking a protein to inhibit protein-protein interactions: Design and synthesis of peptide-containing drugs to promote pluripotency in stem cells

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A series of small molecule drugs consisting of an acetophenone or a benzaldehyde core with small peptide (2-3 amino acids) tails were prepared and purified in an attempt to generate efficient protein-protein inhibitors. The peptide tails were designed on the basis of one of the proteins itself, hoping to create a large affinity with the other protein. Inhibiting the protein-protein interactions was a major goal in developing small drugs that can be used to promote stem cell pluripotency. The efficiency of the drugs was tested in an assay that determines the amount of accumulated β-catenin. There is an established connection between β-catenin concentration and pluripotency and therefore it is reasonable to assume that use of drugs that lead to high concentrations of β-catenin, are promising leads for maintaining stem cells in a pluripotent state. The synthetic methodologies for the preparation of core molecules with mono-, di-, and tripeptide tails as well as the results from the biological assays will be discussed.

MEDI 58

Development of novel metalloenzyme proinhibitors

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Conventional matrix metalloproteinase (MMP) and histone deacetylase (HDAC) inhibitors utilize a metal-binding group (MBG) that chelates to the catalytic zinc(II) ion to inhibit activity. This work details the development of metalloenzyme inhibitor prodrugs, whose metal binding ability can be controlled based on the surrounding chemical environment. In the presence of appropriate stimuli, such as reactive oxygen species (ROS) or nucleophilic cellular reductants (glutathione), the protecting group appended to the MBG is cleaved, releasing the active inhibitor. This prodrug approach can be applied to MMPs, where the inflammatory response induced by ischemia initiates the formation of ROS, leading to the misregulation of MMPs. HDAC inhibition, leading to cell cycle inhibition and apoptosis in cancer cells, is an additional target for localized metalloenzyme inhibition. The correlation of HDAC activity and cancer, along with the observed upregulation of glutathione in cancer tissues prompted the development of HDAC proinhibitors activated by thiols.

MEDI 59

Use of chalcones and its oxime and oxime ether derivatives as drugs for maintaining stem cell pluripotency

***Brenda Hinh**[1], brendaphinh@csu.fullerton.edu, Kavita Amin[1], Elizabeth Shuman[1], Mikiko Satoh[1], Tyler Routledge[2], Nilay Patel[2], Peter de Lijser[1]. (1) Department of Chemistry and Biochemistry, California State University, Fullerton, Fullerton, CA 92834, United States (2) Department of Biological Science, California State University, Fullerton, Fullerton, CA 92834, United States*

Maintaining the pluripotency of stem cells is of interest for the potential treatment of numerous diseases. We have chosen to study the use of chalcones and their oxime and oxime ether derivatives as small molecule drugs for (a) maintaining stem cells in a pluripotent state, and (b) the directed differentiation of stem cells. Chalcones are a class of biologically active molecules that have found use in a number of applications, including as anti-tumor agents, anti AIDS agents, as well as antimalarial and anti-inflammatory agents. They are easily prepared by reaction commercially available ketones and aldehydes under basic conditions. The variety of substituted ketones and aldehydes that are available makes chalcones a desirable target for drug testing. Oximes and oxime ethers have also found use as drugs in the treatment of a variety of diseases. A variety of substituted chalcones and their oxime and oxime ether derivatives were prepared and purified, and then tested in a biological assay geared at measuring levels of β-catenin in cells. It has been shown previously that pluripotency can be correlated to built-up levels of β-catenin and therefore if treatment of cells with a drug leads to higher levels of β-catenin, it can be taken as a sign of pluripotency. Initial results from our studies suggest that when comparing the chalcones, nonpolar compounds showed a more promising effect. Comparison of all the substrates suggests that oxime derivatives often give better results. The design, synthesis, and biological results of the chalcones will be presented.

MEDI 60

Design and synthesis of mono- and diamides as potential drugs for maintaining stem cell pluripotency

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A set of mono- and diamides were prepared and tested as potential drugs for maintaining the pluripotency of stem cells. The drugs were designed to act as a competitive inhibitor of the docking domain of the protein of interest and block specific protein-protein interactions. The small organic molecule drugs were then tested in an assay that determines the amount of accumulated β -catenin. There is an established connection between β-catenin concentration and pluripotency and therefore it is reasonable to assume that use of drugs that lead to high concentrations of β -catenin, are promising leads for maintaining stem cells in a pluripotent state. The studies show that certain monamides have interesting, yet unexpected results in the biological studies. Some of the drugs were also tested in controlled differentiation experiments, giving promising results. The design, synthesis, and purification of the small molecule drugs as well as the results from some biological studies will be presented.

MEDI 61

Development of point-of-care biosensor: A step forward toward breast cancer diagnosis

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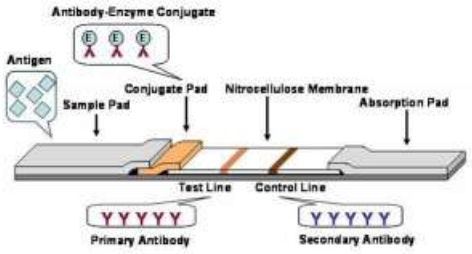
A noninvasive blood test for screening, detecting and diagnosing of cancers has been seen crucial by clinicians with an interest in cancer, and its delivery as a quest for many researchers. For this reason, detection of cancer biomarkers (e.g. circulating proteins) in the plasma and serum of cancer patients is of great interest. For the demonstration of proof-of-concept of the present point-of-care biosensor, enzyme-based immunochromatographic assay was used as a model. We report here the development of a high sensitive, specific, high positive and negative predictive value (>90%); short assay time (~15 min); low-cost, simple, easy-to-use without complex and expensive instrumentation, and disposable dry biosensor that can be used for protein detection. These features make such biosensor ideal for applications such as breast cancer early diagnosis, rapid screening, point-of-care (POC) detection in hospital laboratories, and even for near-patient or home testing.



Schematic representation of the point-of-care enzyme-based immunosensor

MEDI 62

Synthesis and biological investigation of pegylated adenosine A_{2A} receptor antagonist

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Istradefylline (KW-06002) is one of many xanthines that act as antagonists of the A_{2A} adenosine receptor. While this molecule has been recently involved in Phase III clinical trials as a target therapeutic for Parkinson's disease, its' target pathway has also been implicated in tumorigenesis.

Our current interest is in developing prodrugs of KW-6002 that retain selectivity for the A_{2A} receptor, but achieve decreased blood brain barrier permeability, as potential therapeutics for hypoxic tumors. Specific prodrugs of KW-6002 have the capability of not only targeting hypoxic tumors, but also combating existing issues of aqueous solubility and lipophilicity. Utilizing molecular modeling, functional derivatives have been designed and developed, including polyethylene glycol(PEG) and nanoparticle conjugates. Two of these compounds have been synthesized and have shown promising *in vitro* testing as potential therapeutics. Synthetic methodology and preliminary bioanalysis will be presented.

MEDI 63

Design and synthesis of benzimidazole for DNA intercalation

***Alisha J Fisher**, afisher4@scmail.spelman.edu, Leyte Winfield. Department of Chemistry, Spelman College, Atlanta, Georgia 30314, United States*

Benzimidazoles are organic compounds that have been highly suggested to inhibit growth in cancerous cells by binding to DNA in between its base pairs to cause buckling or unraveling of the substrate via a process known as DNA intercalation. Based on this statement, it is hypothesized that a Benzimidazole-based molecule can be used to develop drugs that prevent survival in breast cancer cells by acting as DNA intercalators. The specific goal of this project is to develop a synthesis for such compounds. One critical step in the synthesis of benzimidazole products is the ring forming reaction. Four traditional and microwave reactions were explored for this step. The results and conditions will be presented.

MEDI 64

Sythesis and evaluation of novel isothiocyanates

***Ruthellen H Tornberg**, rhtornberg10@ole.augie.edu, Jared R. Mays, Cody Lensing. Department of Chemistry, Augustana College, Sioux Falls, SD 57197, United States*

Evidence suggests isothiocyanates (ITCs) are responsible for the chemoprevention associated with diets rich in cruciferous vegetables. Non-natural ITCs have previously demonstrated enhanced antiproliferation activity versus the natural ITC L-sulforaphane. To elucidate structure-activity trends, a panel of novel ITCs have been synthesized and tested against MCF-7 human breast cancer cells. Preliminary results have identified several key structure-activity relationships that will be useful in developing improved agents.

MEDI 65

High content screening for the development of novel photosensitizers

***Mathias O. Senge**, sengem@tcd.ie, Gisela M. Vaz, Anthony Davies. Institute of Molecular Medicine, Medicinal Chemistry, Trinity College Dublin, Dublin, Ireland*

Photodynamic cancer therapy (PDT) is increasingly used for treatment of malignancies and is based on the light-activated generation of singlet oxygen from tetrapyrrolic dyes. In order to developing a systematic method of assessing the efficacy of a range of newly synthesized PDT compounds a high content screening approach was developed using the photosensitizer Foscan and esophageal squamous cell carcinoma cell lines. The analysis of multi-parametric cellular data identified several robust sensitive cellular markers that strongly indicate the efficacy of Foscan and other photocytotoxic agents. Markers include nuclear and cellular morphology and cellular proliferation and could be verified with MTT assays. This method allows the quantitative evaluation of potential photosensitizing agents with high content imaging and analysis platform technologies. This approach offers a contextual information rich output that permits a deeper understanding of the mechanistic events during the action of these compounds drug in an intact physiological context.

MEDI 66

Design, synthesis and insight into the structure-activity relationship of 1,3-disubstituted indazoles as novel HIF-1 inhibitors

*Hongchan An[1], Nam-Jung Kim[1], Jong-Wha Jung[1], Hannah Jang[1], **Kyeojin Kim**[1], kyeojin01@snu.ac.kr, Young Taek Han[1], Hyunyoung Moon[1], Jong-Wan Park[2], Young-Ger Suh[1]. (1) College of Pharmacy, Seoul National University, Seoul, Republic of Korea (2) College of Medicine, Seoul National University, Seoul, Republic of Korea*

Hypoxia-inducible factor 1 (HIF-1) is heterodimer consisting of a constitutively expressed HIF-1β and an O_2-regulated HIF-1α as subunits. Under aerobic conditions, HIF-1α is polyubiquitinated and then degraded by proteasomes, leading to HIF-1 suppression. However, HIF-1α under hypoxia is not degraded and intact HIF-1α dimerizes with HIF-1β leading to activation of HIF-1, which play key roles in physiological processes of cell survival and cancer development.

YC-1, 3-(5'-hydroxymethyl-2'-furyl)-1-benzyl indazole, has been considered as one of the most attractive drug candidates due to its potent inhibitory activity against HIF-1α and a novel privileged indazole structure, which was found in a variety of chemotherapeutics with diverse pharmacological effects. Herein, we report design, synthesis and insight into the structure-activity relationship of the 1, 3-disubstituted indazoles based on YC-1 as novel HIF-1α inhibitors. In particular, the substituted furan moiety on indazole skeleton as well as its substitution pattern turns out crucial for the high HIF-1α inhibition.

MEDI 67

Synthesis and RP-HPLC monitored hydrolysis of non-natural glucosinolates

***Kayla Vastenhout**, kjv_2008@yahoo.com, Jared Mays. Department of Chemistry, Augustana College, Sioux Falls, SD 57197, United States*

Studies have shown that diets rich in the Brassica vegetables are associated with reduced risks of cancer. These vegetables contain chemopreventive precursors, called glucosinolates, that undergo a myrosinase-dependent hydrolysis when digested in the body. The goal of this project was to synthesize two non-natural glucosinolates and monitor their hydrolysis to isothiocyanates using RP-HPLC. Both glucosinolates were successfully synthesized in 11% and 19% yields over five steps. A RP-HPLC assay was developed as a method to compare the ability of synthetic glucosinolates to serve as myrosinase substrates and extract the kinetic parameters of the transformation. Using this method, Km and kcat were determined for both glucosinolates by monitoring multiple wavelengths.

MEDI 68

New selective nonsteroidal aromatase inhibitors: Synthesis and inhibitory activity of 3-phenylchroman-4-ones

***Erica Amato**, amatoe1@mymail.nku.edu, Kevin Bonfield, Audrey Rivet, Adam McCallum, Stefan Paula, Lili Ma. Department of Chemistry, Northern Kentucky University, Highland Heights, KY 41076, United States*

Thirteen 3-phenylchroman-4-ones (isoflavanones) with various substituents at the C6 position or with fluorine modification were synthesized utilizing the gold catalyzed annulation reaction. These compounds were characterized by ^{1}H NMR, ^{13}C NMR and HRMS. The purity of each compound was established by HPLC analysis. The inhibitory potencies against aromatase by these isoflavanones were tested using a fluorescence assay. Docking poses of active isoflavanone inhibitors were predicted by computer modeling.

MEDI 69

Development of a new class of aromatase inhibitors: Design, synthesis, and biological activity of 3-phenylchroman-4-one (isoflavanone) derivatives

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The enzyme aromatase (CYP19) is responsible for converting androgens to estrogens, the main stimulant in the development of breast cancer tumors. Inhibiting aromatase is an auspicious strategy for treating hormone-dependent breast cancer. Here, the design and synthesis of isoflavanone derivatives as potential aromatase inhibitors is reported,

in which various functional groups were coupled to the aromatic rings of the isoflavanone scaffold. These structural modifications were implemented via an enhancement to the reaction scheme: a newly-adopted microwave-assisted gold-catalyzed annulation reaction using hydroxyaldehyde and phenylacetylene as precursors to the isoflavanone derivatives. Inhibition of aromatase was performed using fluorescence-based assays *in vitro*, and computerized docking simulations were availed to explore the various hydrogen bonding, hydrophobic interactions, and heme chelation between the isoflavanone derivatives and the enzyme binding pocket. Compounds **1h, 2a** and **3b** exhibited the most potent inhibitory effects against aromatase with IC_{50} values of 2.4 µM, 0.26 µM and 5.8 µM, respectively.

MEDI 70

Discovery of 6-arylsulfonyl pyridopyrimidinones as potent and selective PLK2 inhibitors

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Several families of protein kinases have been shown to play a critical role in the regulation of cell cycle progression, especially progression through mitosis. These kinase families include the Aurora kinases, the Mps1 gene product and the Polo family of protein kinases. Polo like kinases play key roles in mitosis. While the up-regulation of PLK1 in cancers is well documented and PLK3 has been demonstrated to be a tumor suppressor, little is known about the oncogenic significance of PLK2. PLK2 kinase activity is essential for centriole duplication and is also believed to play a regulatory role in the survival pathway by physically stabilizing the TSC1/2 complex in tumor cells under hypoxic conditions.

As a part of our research program, we have developed a library of novel ATP mimetic chemotypes that are cytotoxic against a panel of cancer cell lines. One of these chemotypes, 6-arylsulfonyl pyridopyrimidinones has shown cytotoxicity in nanomolar concentration in most of the cancer cells. The most potent of these compounds, ON 1231320 was found to be specific PLK2 inhibitor when profiled against a panel of 288 wild type, 55 mutant and 12 specific kinases.

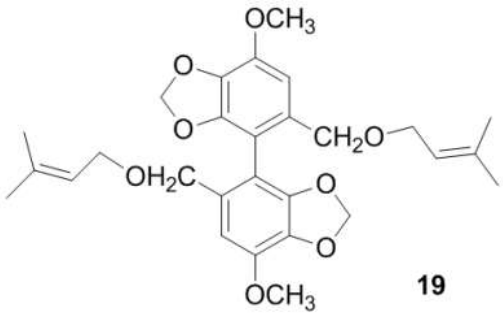
In this presentation we describe the synthesis, structure activity relationship (SAR), in vitro kinase specificity and biological activity of the lead compound ON1231320

MEDI 71

Novel dimethyl dicarboxylate biphenyl (DDB) analogs as potent cancer chemopreventive agents

Hsin-Yi Hung[1]*, hhung@email.unc.edu, Kyoko Nakagawa-Goto*[1]*, Harukuni Tokuda*[2]*, Akira Iida*[3]*, Nobutaka Suzuki*[2]*, Susan L Morris-Natschke*[1]*, Kuo-Hsiung Lee*[1,4]*. (1) Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, United States (2) Department of Complementary of Alternative Medicine, Kanazawa University, Kanazawa, Japan (3) Department of Agriculture, Kinki University, Nara, Japan (4) Chinese Medical Research and Development Center, China Medical University and Hospital, Taichung, Taiwan Republic of China*

Sixteen new analogues of DDB were synthesized and evaluated for their cancer preventive activity by an *in vitro* EBA-EA activation assay and an *in vivo* mouse-skin carcinogenesis test. Compound **19** exhibited remarkable cancer preventive effect *in vitro* and *in vivo*, which suggested that **19** is likely to be a valuable candidate as a cancer preventive agent or as a lead for the development of new antitumor promoter drugs.



19

MEDI 72

Development of S-trityl L-cysteine based inhibitors of the mitotic kinesin Eg5 with in vivo antitumor activity

James AD Good[1]*, j.good@beatson.gla.ac.uk, Fang Wang*[1]*, Oliver Rath*[1]*, Hung Yi Kristal Kaan*[1]*, Dawid Podgórski*[1]*, Oliver B. Sutcliffe*[2]*, Simon P Mackay*[2]*, Frank Kozielski*[1]*. (1) The Beatson Institute For Cancer Research, Glasgow, Lanarkshire G61 1BD, United Kingdom (2) Strathclyde Institute for Pharmacy & Biomedical Sciences, University of Strathclyde, Glasgow, Lanarkshire G20 6UN, United Kingdom*

The mitotic kinesin Eg5 is an important target for the development of new antimitotic chemotherapy therapies. Its primary role is the separation of the duplicated spindle poles in early prometaphase to form the bipolar spindle during mitosis. Small molecule inhibition results in mitotic arrest as the centrosomes fail to separate, activation of the mitotic checkpoint, and subsequent apoptosis in certain tumor cell lines. S-Trityl L-cysteine (STLC) is a selective allosteric inhibitor of the mitotic kinesin Eg5 with GI_{50} values in the region of 1.2 μM. We herein report on the development of STLC analogues with GI_{50} values ≤ 50 nM. Crystallographic studies of the compounds complexed with Eg5 demonstrate that the same allosteric binding mechanism as STLC

is adopted. Compounds from the lead series demonstrate *in vivo* antitumor efficacy in nude-mice xenograft studies, and evaluation of their drug-like properties reveals promising profiles which warrant continuing development.

MEDI 73

Synthesis and biological evaluation of Z-isomer of Rigosertib™ (ON 01910.Na) − a clinical stage (Phase III) multi kinase anticancer agent

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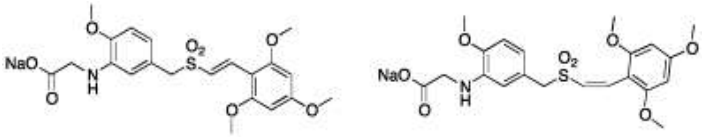
ON 01910.Na is a novel non-ATP competitive anticancer agent that inhibits mitotic progression, promotes G2/M arrest and induces apoptosis in a number of cancer cells while leaving nonmalignant cells virtually unaffected. ON 01910.Na has exhibited both antitumor activity and antiangiogenic activity with a low toxicity profile in various preclinical tumor xenograft models. Unlike other hypomethylating agents, ON 01910.Na exerts potent antitumor activity against Mantle Cell Lymphoma (MCL) cells by inhibition of PI-3K/Akt/mTOR pathway and down regulation of Cyclin D1 translation. The fact that MDS patient's bone marrow over expresses cyclin D1 (particularly trisomy 8) and targeted deletion of this gene was selectively toxic to trisomy 8 cells. A pivotal phase III trial of ON 01910.Na in MDS patients is now underway. Additional blood cancer and solid tumor indications are being developed, both as a single agent and in combination therapy.

The structure activity studies of ON 01910.Na confirmed that the nature, number, and position of substituents on both aromatic rings of the molecule are critical for it's activity. As geometry of a molecule is known to play a critical role in SAR, we have undertaken the synthesis of (Z)- isomer (ON 02180.Na) of ON 01910.Na, which is an active (E)-isomer. In this presentation, we describe the total synthesis, configurational assignment and compare the biological profile of ON 02180.Na with that of ON 01910.Na.



MEDI 74

Design, synthesis and biological study of novel epidermal growth factor receptor kinase (EGFRK) inhibitors

Venkata Subbaiah[1]*, venkata.dandu@mssm.edu, Venkat R Pallela*[2]*, Stephen C Cosenza*[1]*, Gayathri Panda*[1]*, Muralidhar M Mallireddigari*[2]*, E. Premkumar Reddy*[1]*, M. V. Ramana Reddy*[1]*. (1) Department of Oncological Sciences, Mount Sinai School of Medicine, New York, NY 10029, United States (2) Department of Medicinal Chemistry, Onconova Therapeutics Inc., Newtown, PA 18940, United States*

Epidermal growth factor receptor (EGFR/ErbB-1) and Her-2 (ErbB-2), members of the Type 1 receptor tyrosine kinase family, are frequently disregulated in human epithelial tumors, via autocrine stimulation, overexpression, or mutation and play a key role in cell proliferation and differentiation. Overexpression of these receptors is found in a variety of cancers such as breast, ovarian, colon, head and neck and prostate cancers. The ErbB receptors can be activated through homo or heterodimerization with other receptors resulting in phosphorylation events and downstream signaling that produces excessive growth by inducing cell proliferation and inhibiting apoptotic pathways.

In an attempt to identify most potent kinase inhibitors, we developed a library of small molecules containing a backbone of pyrimidines, quinolines, quinazolines and benzothiazinones. While screening these compounds in cytotoxicity assay, we found that 4-aryl/benzylthio quinazolines are found to be very effective in killing $EGFR^+$ cancer cells. The kinase profiling study of this chemotype showed that ON128030 and ON128060 are found to be selectively inhibiting EGFRK unlike Iressa® which inhibits both EGFR and ErbB2 (Her-2) receptor kinases.

In this presentation, we describe the synthesis, characterization, structure activity relationship (SAR), in vitro cytotoxicity and kinase profile of the lead molecule.

MEDI 75

Novel cyano pyridopyrimidines as potent and selective inhibitors of CDK4 and Ark5 kinases

Balaiah Akula[2]*, BAkula@onconova.us, Saikrishna Athuluri*[1]*, Stephen C Cosenza*[1]*, Vinay Kumar*[1]*, E. Premkumar Reddy*[1]*, M. V. Ramana Reddy*[1]*. (1) Department of Oncological Sciences, Mount Sinai School of Medicine, New York, New York 10029, United States (2) Department of Medicinal Chemistry, Onconova Therapeutics Inc, Newtown, PA 18940, United States*

The mammalian cell cycle is regulated by protein complexes that are activated in an ordered fashion to trigger the initiation of specific events such as DNA replication, nuclear envelope breakdown, spindle formation, chromosome segregation and cytokinesis. Cell cycle progression is orchestrated by Cyclin/CDK complexes that are formed at specific stages of the cell cycle, and their activities are required for progression through S phase and mitosis.

As a part of this research program, we undertook development of a novel ATP mimetic chemotype, the cyano pyridopyrimidines. We have synthesized approximately 150

compounds and tested them in tissue culture growth inhibitory (GI_{50}) assays against a panel of sixteen different cancer cell lines. Of these, one compound, ON123300 was found to be most active, being able to arrest the cancer cells at a concentration of approximately 30-100nM. Because of its excellent potency, ON123300 was subsequently tested against a series of 285 functional kinases. Interestingly, this kinase profiling study revealed that ON123300 is a highly specific and a potent inhibitor of CDK4/cyclinD1 and Ark5 kinases.

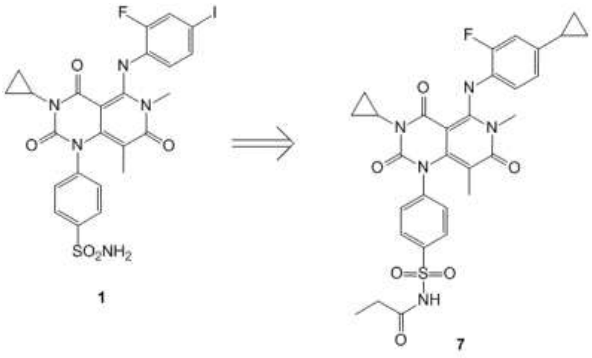
In this presentation, we will focus on the synthesis, structure activity relationship (SAR), kinase inhibitory profile and cytotoxicity of the lead compound 123300 on cancer cells.

MEDI 76

Evaluation of N-acyl sulfonamide prodrug inhibitors of MEK kinase

Jeffrey Ralph*, Jeffrey.m.ralph@gsk.com, Jerry Adams, Domingos Silva, Yanhong Feng, Peter Martin, Swarupa Kulkarni, Katherine Moss, Cynthia Rominger, Maureen Bleam, Sylvie Laquerre. Oncology R&D, Protein Dynamics DPU, GlaxoSmithKline, Collegeville, PA 19426, United States*

A series of novel N-acylsulfonamide prodrugs were evaluated and profiled as inhibitors of MEK kinase. Our pursuit of MEK inhibitors led us to compound **1** , which displayed highly potent and selective inhibition of MEK enzymatic and cellular activities. However, compound 1 had poor solubility and no oral exposure in rats. Using a prodrug approach, solubility and pharmacokinetic parameters of a series of MEK inhibitors were improved, culminating in the discovery of the propionyl sulphonamide **7** . Optimization led to the discovery of compound **7** , which showed improved solubility and PK. This poster describes the SAR leading to compound 7 and the multi-species in vitro and in vivo PK to support compound **7** as a potential candidate.

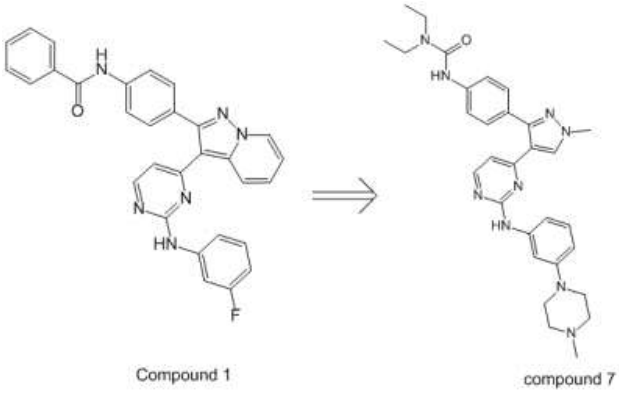


MEDI 77

N-Alkylated diaryl pyrazoles: Selective Aurora kinase inhibitors

***Jeffrey Ralph**, Jeffrey.m.ralph@gsk.com, Yanhong Feng, Domingos Silva, Jerry Adams, Thomas Faitg, Mary Ann Hardwicke, Jamin Wang, Catherine Oleykowski, Melody Diamond, David Sutton, Leo Faucette, Ramona Plant. Oncology R&D, Protein Dynamics Dpu, Glaxosmithkline, Collegeville, PA 19426, United States*

A series of N-alkylated diaryl pyrazoles has been prepared as inhibitors of Aurora B. Originally pursued as ErbB+ kinase inhibitors, pyrazolopyridines such as compound 1 were identified as early leads for the Aurora effort. These compounds displayed good activity against Aurora B in enzymatic and cellular assays. However, the series suffered from poor developability, which we attributed to high molecular weight and clogP. In an effort to identify more developable Aurora inhibitors, we have investigated the corresponding pyrazoles, derived from the pyrazolopyridines by removal of the central phenyl ring. The pyrazoles proved to be excellent Aurora inhibitors, with potent enzymatic and cellular activities, good kinase selectivity and improved developability properties.



This poster will present the various synthetic routes that allowed us to explore the SAR around the pyrazole scaffold. We will also present the work that allowed us to generate the desired N1-alkyl pyrazole in a regioselective manner on multigram scale. The *in vitro* and *in vivo* data about compound **7** will be presented.

MEDI 78

New inhibitors of cathepsin D containing hydroxyethylamine isosteres

***Prashanth Akula**, pg-akula@wiu.edu, Bharat Guda, Durga Yeramala, Franklin Rahman, Ryan Keefer, Naveen Reddy Kadasala, Lisa Wen, Rose McConnell. Department of Chemistry, Western Illinois University, Macomb, IL 61455, United States*

Cathepsin D is an aspartyl lysosomal protease that catalyzes protein cleavage. It is involved in the process of tumor invasion and metastasis. The cathepsin D enzyme has been considered as a potential target for cancer therapy. Cathepsin D from human liver purchased from Sigma was used to develop an activity assay. The synthetic

compounds have been evaluated for their inhibition of human cathepsin D and have also been tested on MCF-7 breast cancer cells. Data analysis of the effectiveness of these synthetic inhibitors will be used to foster development of newer effective inhibitors that may be used for cancer therapy. Supported by National Cancer Institute at NIH (Grant No. 3R15CA086933-04 and 3R15CA086933-04A2S1) and Western Illinois University.

MEDI 79

New cathepsin B inhibitors containing argininal thiosemicarbazones

***Bharat Guda**, b-guda@wiu.edu, Durga Yeramala, Prashanth Akula, Keegan Steele, Franklin Rahman, Naveen Reddy Kadasala, Karthik D. Malayala, Jin Jin, Shaozhong Zhang, Lisa Wen, Jenq-Kuen Huang, Rose M. McConnell. Department of Chemistry, Western Illinois University, Macomb, IL 61455, United States*

Cathepsin B, a lysosomal protease, has been proposed to be involved in the progression and metastatic spread of breast cancer. Associations have been made between high concentrations of cathepsin B and poor patient prognosis in primary breast cancer. Active cathepsin B localized to the plasma membrane has been shown in invasive bladder tumor cells whereas non-invasive tumor cells have cathepsin B confined to the lysosomes. This suggests that membrane associated cathepsins may participate in tumor invasion. Specific proteinase inhibitors could lead to the development of theraputic agents for treatment of many types of carcinomas. Described is the design and synthesis of inhibitors containing C-terminal argininal thiosemicarbazones. Inhibition data for these cathepsin B inhibitors is reported using N-Carbobenzoxy-L-Phenylalanyl-Arginine-4-nitroanilide hydrochloride as the substrate. Supported by National Cancer Institute at NIH (Grant No. 3R15CA086933-04 and 3R15CA086933-04A2S1) and Western Illinois University.

MEDI 80

Design and synthesis of novel DFG-out RAF/VEGFR2 inhibitors: Synthesis and characterization of a novel imide-type prodrug for improving oral absorption

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To develop RAF/VEGFR2 inhibitors that bind to the inactive DFG-out conformation, we conducted structure-based drug design using the BRAF cocrystal structure. Exploration of various [5,6]-fused bicyclic scaffolds resulted in the creation of [1,3]thiazolo[5,4-

b]pyridine derivative **A** which showed potent inhibitory activity against both RAF and VEGFR2. To improve the oral absorption and the solubility, we designed a novel *N*-acyl imide prodrug of compound **A** . *N*-*tert*-butoxycarbonyl (Boc)-introduced imide **P** was a promising prodrug, which was effectively converted to the active compound **A** after its oral administration in animals. Cocrystals of **P** with AcOH possessed good physicochemical properties, and showed *in vivo* antitumor regressive efficacy (T/C = -6.4%) in the A375 human melanoma rat xenograft model. Design, synthesis and characterization of **P** will be discussed in detail.

MEDI 81

Synthesis of azanovobiocin derivatives using Cu(I)/Pd(II)-catalyzed C-N bond formation

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The inhibition of HSP90 by drugs such as novobiocin has recently shown to be a potential cancer treatment pathway. Formation of a novel azanovobiocin derivative with better inhibitory properties seemed possible through metal-catalyzed C-N bond formation with the use of the (cis)-N-(1-(2-bromophenyl)-3-(methylamino)-3-oxoprop-1-en-2-yl)benzamide starting material. Both the CuTC-mediated, MW-assisted lactamization reactions and the Pd-catalyzed reflux lactamization reactions were performed with varying results. Neither was successfully able to produce the azanovobiocin derivative, but major products that were formed from the CuTC reaction included novobiocin, the indo formation of the product with C-N bond formation, and an oxazoquinolone. Products from the Pd-catalyzed reactions produced both a brominated and nonbrominated product that was either an azlactam formation or an isoquinoline formation. Although neither reaction synthesized the expected products, future experiments should focus on CuTC in light of its more promising results.

MEDI 82

Synthesis of novel nitrogenous tetracyclic compounds as potential anticancer agents

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Tetracyclic backbones with hetero atoms are important scaffolds for different biological targets. These compounds have been used as anti-microbial or anti- cancer agents. One important target for cancer therapy is the topoisomerase enzyme. In this study we aimed to synthesize a series of novel tetracyclic indenoquinoline derivatives and evaluate their biological activity through in vitro cytotoxicity studies on cancer cells.

Preliminary results have shown that indenoquinoline backbone posses anticancer activity that prompted us to further examine this backbone for cancer therapy. To this end, we have synthesized a series of tetracyclic indenoquinoline derivatives and analyzed them using NMR, mass and infrared spectroscopy. Anticancer activity of these compounds is currently being investigated in cells. Through rational design based synthesis and characterization of tetracyclic indenoquinoline derivatives we hope to develop novel therapeutic interventions for cancer.

MEDI 83

Discovery, design and synthesis of a novel series of non-peptidomimetic inhibitors of XIAP-caspase 9 interactions

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The interaction between XIAP and caspase 9 has recently been shown to be a promising target for anticancer therapy. We set out to discover novel non-peptidomimetic inhibitors of XIAP by using an *in silico* pharmacophore model to identify a set of 450 commercial structures. These structures were assessed for qualitative docking fit to a crystal structure of XIAP BIR3. This led
to a targeted library of 140 compounds which were purchased and screened using an *in vitro* fluorescence polarization assay against isolated XIAP BIR3 protein, revealing a hydroxypyrrolone hit with an IC_{50} of 15 μM.
The synthesis of this molecule was achieved in 3 linear steps, including a one-pot, three-component cyclisation. Structure-activity relationships of the hit compound have been probed by means of analogue synthesis. This has enabled rational design of more potent inhibitors; a process which is currently ongoing in our laboratory.

MEDI 84

Citotoxic process for clinical evidence of the use of *Cimicifuga racemosa*

Nelvin Acevedo-Valle*, nelvin.acevedo@upr.edu, Nilka M. Rivera-Portalatín. Department of Chemistry, University of Puerto Rico-Mayagüez, Mayagüez, Puerto Rico 00676, Puerto Rico*

The research aims to evaluate the medicinal plant *Cimicifuga racemosa (Black cohosh)* in order to verify if it contains any anti-cancer activity. This plant, native from North

America,contains flavonoids, and has begun to emerge as a drug therapy against cancer. During the investigation, an extraction was made to obtain the essential oils of the plant using dichloromethane as a solvent. Then, the extracts were incubated with HT-29 cells (a colon cancer cell line) in order to determine its citotoxicity against the cancer cells. After incubation, the MTT assay was used to determine the cells viability. Citotoxic effects were observed in the cells incubated with the black cohosh essential oils. For future research, the concentration of the extracts will be increased in order to measure the IC50's. Also, the components of the extract will be isolated and characterized by HPLC to identify the component with the anti-cancer activity

MEDI 85

Design and synthesis of quinazoline derivatives as potentially of novel PI-3K inhibitors

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A new series of quinazolines has been synthesized and evaluated in biochemical assay format for the ability to target the PI3K/AKT/mTOR signaling pathway, which has been of particular interest in cancer drug discovery. Interestingly, a select group of compounds identified from this series were low micromolar inhibitors of crucial components of the cascade targeting PI3K. In the present work we particularly explored PI3K kinase which is preferentially inhibited by the compounds and molecular modeling studies against the most oncogenic mutant of p110a isoform (H1047R), allowed us to draw interesting SAR among the analogs.

MEDI 86

Two modular peptide substrates to identify substrate selective MAPK inhibitors

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ERK2 primarily recognizes substrates through two recruitment sites, which lie outside the
active site cleft of the kinase. These recruitment sites bind modular-docking sequences called docking sites and are potentially attractive sites for the development of non-ATP competitive inhibitors. The D-recruitment site (DRS) and the F-recruitment site (FRS) bind D-sites and F-sites, respectively. To facilitate the design of ERK2 inhibitors it is important to understand how tightly recruitment sites are energetically coupled to other

ligand recognition sites within ERK2. Energetic coupling within ERK2 was investigated using two new modular peptide substrates for ERK2. Modeling shows that one peptide (Sub-D) recognizes the DRS, while the other peptide (Sub-F) binds the FRS. A steady-state kinetic analysis reveals little evidence of thermodynamic linkage between peptide substrate and ATP. Both peptides are phosphorylated through a random-order sequential mechanism with a k_{cat}/K_m comparable to Ets-1, a *bona fide* ERK2 substrate. Occupancy of the FRS with a peptide containing a modular docking sequence has no effect on the intrinsic ability of ERK2 to phosphorylate Sub-D. Occupancy of the DRS with a peptide containing a modular docking sequence has a slight effect on the intrinsic ability of ERK2 to phosphorylate Sub-F. These data suggest that while docking interactions at the DRS and the FRS are energetically uncoupled, the DRS can exhibit weak communication to the active site. In addition, they suggest that peptides bound to the FRS inhibit the phosphorylation of protein substrates through a steric mechanism. The modeling and kinetic data suggest that the recruitment of ERK2 to cellular locations via its DRS may facilitate the formation of F-site selective ERK2 signaling complexes, while recruitment via the FRS will likely inhibit ERK2 through a steric mechanism of inhibition. Such recruitment may serve as an additional level of ERK2 regulation.

MEDI 87

Discovery and characterization of Kevetrin™: A small molecule with potent anticancer activity

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Many small molecules possess anti-cancer activity but frequently display high levels of toxicity. Kevetrin™, a small molecule with broad spectrum anti-cancer activity in xenograft tumor models (lung, breast, colon, prostate, squamous cell, and leukemia), was well tolerated with low toxicity. Cytotoxicity assays revealed a relatively low potency in vitro and yet Kevetrin™ was efficacious against multi-drug resistant tumors. Kevetrin™ inhibits tumor growth by arresting cells in the G2/M stage of cell division together with increased apoptosis. Cell cycle arrest was associated with a change in levels of G2/M proteins (CDK1, cdc25B and WEE1) and cell death was promoted by pro-apoptotic signaling (p53, MDM2, p21 and PUMA) that together affect the metabolic pathways in cancer cells. This presentation will discuss the SAR, mechanism of action, anti-tumor activity, pre-clinical pharmacology, and safety profiles that led to the advancement of Kevetrin™ into Phase I clinical trials.

MEDI 88

Synthesis, spectroscopic characterization and in vitro cytotoxic activities of novel mononuclear Ru(II)
complexes

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In the search for antitumor active metal complexes several ruthenium complexes have been reported to be promising as anticancer drugs. A series of mononuclear Ru(II) complexes of the type $[Ru(T)_2(L)]^{2+}$, where T= 2,2'-bipyridine/1,10-phenanthroline and L= 3-phenyl-5-(3,4,5-trimethoxyphenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide, 3-phenyl-5-p-tolyl-4,5-dihydro-1H-pyrazole-1-carbothioamide,5-(4-(dimethylamino)phenyl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide,N-benzyl isatin thiosemicarbazone, pyrrole isonicotinyl hydrazones have been prepared and characterized by UV-Vis, IR, ^{1}H-NMR,^{13}C-NMR and Mass spectroscopy. The title compounds were subjected to in vitro cytotoxic activity against human cancer cell line Molt 4/C8, CEM and murine tumor cell line L1210. In vitro evaluation of these ruthenium complexes revealed cytotoxic activity from 0.36 to 1.7 µM against Molt 4/C8, 0.24 to 1.4 µM against CEM, and 0.28 to 1.5 µM against L1210.

Graphical abstract:

Where L= 3,4,5-tri-OCH_3-DPC, 4-CH_3-DPC,
4-N-$(CH_3)_2$-DPC, NBITSZ, PINH

T=
2,2'-bipyridine/1,10-phenanthroline.

Keywords:
Ruthenium complexes; Isonicotiny lhydrazones,
Cytotoxicity

MEDI 89

Predicting DNA-intercalator binding: An application of a new arene-arene stacking parameter

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Stacking interactions between nucleic acid bases help stabilize nucleic acid structure. Also, stacking interactions between DNA bases and intercalators are important because intercalators have been shown to be valuable anti-cancer agents. In order to help understand substituent-substituent interactions in DNA/RNA-intercalator binding, multiple duplexes were melted in the presence of naphthalimides with various

substituents at the 3-position. A traditional QSAR analysis was performed using an electronic parameter and a dispersion/polarizability parameter to generate a theoretical ΔT_M value. This was then compared to a QSAR analysis utilizing a novel arene-arene parameter. The results show that the novel arene-arene parameter correlates equally well or better than the traditional two parameter QSAR analysis.

MEDI 90

Small molecule Mcl-1 pathway inhibitor and ABT-737 synergistically inhibit growth and induce apoptosis

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An intricate network of protein-protein interactions between pro-apoptotic and anti-apoptotic Bcl-2 family proteins maintains a balance between cell survival and cell death. The sequestration of pro-apoptotic proteins by the anti-apoptotic Bcl-2 family proteins suppresses mitochondrial damage and ensures cell survival. Increased levels of anti-apoptotic proteins (Bcl-2, Bcl-xL or Mcl-1) are associated with maintenance of malignant diseases, resistance to chemotherapy and poor clinical outcome. Modulating the function of anti-apoptotic proteins using small molecules as a therapeutic strategy has attracted much attention in recent years. ABT-737, a small molecule Bcl-2/Bcl-xL inhibitor suppresses tumor growth and sensitizes cancers to chemotherapeutic agents in preclinical models. However, cancer cells that express high levels of Mcl-1 are refractory to ABT-737 treatment. Down regulation of Mcl-1 sensitizes cells to ABT-737.

To identify small molecules with anti-proliferative activity we screened focused libraries of privileged scaffolds. This resulted in the identification of quinoxaline analogs with low-micromolar potency in growth inhibition assays. To determine the mechanistic basis for the observed growth inhibition a subset of compounds were evaluated for Mcl-1 dependent caspase activation. The best compound, identified from the screen was validated as a specific Mcl-1 modulator. We also show that best compound with ABT-737 synergistically inhibited growth and induced apoptosis. A second iteration of synthesis and screening identified critical functional groups on the quinoxaline core that are required for biological activity. This also led to the identification two additional analogs as Mcl-1 modulators. These are currently being explored in preclinical models.

MEDI 91

Human farnesyl pyrophosphate synthase: New opportunities for a challenging therapeutic target

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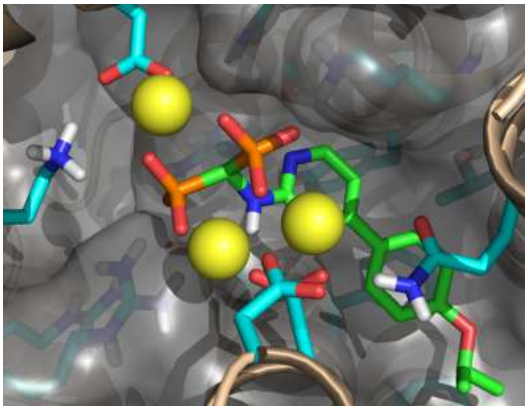
Nitrogen-containing bisphosphonates (*N*-BPs) are the only class of clinically validated drugs that inhibit the human FPPS. They are widely used for the treatment of osteolytic metastases and other bone-related diseases. Clinical data provides evidence that *N*-BPs are also disease modifying therapeutics that improve survival in patients with multiple myeloma *via* mechanisms unrelated to their skeletal effects. However, the current drugs bind so avidly to bone and have such poor cell-membrane permeability that their affects in non-skeletal tissues is seriously compromised. We pursued a structure-based approach to design novel, selective and potent inhibitors of hFPPS. The synthesis and SAR of these inhibitors will be presented. The binding interactions of these analogs with hFPPS were investigated by NMR, X-ray crystallography and Differential Scanning Calorimetry. Furthermore, preliminary biological evaluation of key compounds in anti-proliferation and apoptosis assays using multiple myeloma cells will also be presented.



MEDI 92

Design, synthesis and biological activity of urea derivatives as anaplastic lymphoma kinase inhibitors

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In anaplastic large cell lymphomas, chromosomal translocations involving the kinase domain of anaplastic lymphoma kinase (ALK), generally fused to the 5' part of the nucleophosmin gene, produce highly oncogenic ALK fusion proteins that deregulate cell cycle, apoptosis, and differentiation in these cells. Other fusion oncoproteins involving ALK kinase, such as echinoderm microtubule-associated protein-like 4-ALK, have recently been found in patients with non-small cell lung cancer, breast, and colorectal patients. Research has focused on developing inhibitors for targeted therapy of these ALK-positive tumours. Because kinase inhibitors that target the inactive conformation are thought to be more specific than ATP-targeted inhibitors, we therefore investigated the possibility of using two known inhibitors targeting inactive kinases, doramapimod and sorafenib, to design new urea derivatives as ALK inhibitors. A homology model of ALK in its inactive conformation complexed to doramapimod or sorafenib was generated and it explained why doramapimod is a weak inhibitor and why sorafenib is not inhibiting ALK. Virtual screening of commercially available compounds using the homology model of ALK yielded hit compounds, which were tested using biochemical assays. The preliminary results from the assays were applied in the design and synthesis of a novel series of urea derivatives, which were tested for inhibitory potency on ALK. Structure-activity relationship results showed positions on the core structure that were enhancing or reducing the activity both for the isolated enzyme and in the cellular assays. Some compounds showed inhibition of purified ALK in the high nanomolar range and selective antiproliferative activity on ALK-positive cells.

MEDI 93

Novel anti-inflammatory and pro-resolving aspirin-triggered protectin pathway

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The beneficial health effects of docosahexaenoic acid (DHA) and other omega-3 fatty acids are well documented. The detailed mechanisms of action of these lipids, however, have remained largely unknown until the recent discovery of several new lipid mediators derived from these omega-3 fatty acids, that were shown to exhibit potent anti-inflammatory properties and to serve as promoters of the resolution of inflammation. Herein we will report the stereocontrolled total synthesis and actions of novel oxygenated polyunsaturated metabolites derived from DHA in the presence of aspirin, and use a series of stereochemical pure synthetic isomers to unambiguously establish the stereochemistry. We will also discuss the anti-inflammatory and proresolving actions of these molecules.

MEDI 94

Design and synthesis of novel anticancer agents targeting uracil-DNA repair

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For decades the standard of care for cancer treatment, especially colon cancer, has been 5-fluorouracil (5-FU). 5-FU, the fluorinated derivative of the RNA base uracil, induces cell death by acting as an irreversible inhibitor of thymidylate synthase (TS), a key enzyme in DNA synthesis and cell division. Cancer cells are able to survive TS inhibition by over expressing dUTPase, a non-redundant enzyme responsible for the conversion of the deoxyuridine triphosphate (dUTP) to deoxyuridine monophosphate (dUMP). By over-expressing dUTPase, resistant cells are able to reduce the dUTP levels and prevent concentration-dependent uracil incorporation into DNA. Herein, we report the structure-based design and synthesis of novel dUTPase inhibitors that act as a new class of anticancer agents that are suitable for cancers resistant to 5-FU and other TS inhibitors.

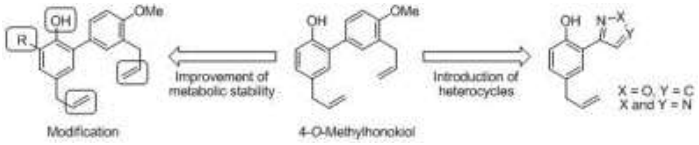
MEDI 95

Synthesis and biological evaluation of 4-*O*-methylhonokiol analogs

Da Young Kim[1], *dy0735@hanmail.net, Bit Lee[2], Hyeju Jo[1], Min Ho Choi[1], Sri Hari Galla[1], Jae-Hwan Kwak[1], Young-Shin Kwak[3], Heesoon Lee[1], Seung-Yong Seo[2], Jae-Kyung Jung[1]. (1) Chungbuk National University, College of Pharmacy and Medical Research Center (MRC), CBITRC, Cheongju, Republic of Korea (2) Woosuk University, College of Pharmacy, Wanju, Jeonbuk 565-701, Republic of Korea (3) Korea Research Institute of Bioscience and Biotechnology, Ochang, Republic of Korea*

Biphenyl-neolignans, such as honokiol, magnolol, obovatol and 4-*O*-methylhonokiol, was isolated from *Magnolia* species and exhibits various biological activities, involved in anti-inflammatory, anti-allergic, anti-bacterial, and anti-depressant activities. Among these biphenyl-neolignans, 4-*O*-methylhonokiol has the higher anti-inflammatory activity (e.g., IC_{50} of 0.06 μM for COX-2) than honokiol and a variety of honokiol analogs. Moreover, 4-*O*-methylhonokiol was recently found to exhibit neurotropic and memory improving activity. However, it was shown to be metabolized rapidly by rat and human liver microsomes in the presence of NADPH and UDPGA, indicating cytochrome P450- and UDP-glucuronosyltransferase-mediated metabolism.

Therefore, 4-*O*-methylhonokiol analogs were designed and prepared to modify the potential metabolic soft spot of 4-*O*-methylhonokiol and to increase the polar surface area for the future assessment of structure-property relationship. In addition, their anti-inflammatory activities were evaluated through inhibition assay of NO production, cyclooxygenase-2 (COX-2) enzyme and PGF_1 production.

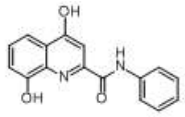


MEDI 96

Amides of xanthurenic acid as zinc-dependent inhibitors of Lp-PLA$_2$

Yi Hu[1]*, yih@activx.com, Emme C. K. Lin*[1]*, Christopher M. Amantea*[1]*, Lan M. Pham*[1]*, Julia Cajica*[1]*, Eric Okerberg*[1]*, Heidi E. Brown*[1]*, Allister Fraser*[1]*, Lingling Du*[1]*, Yasushi Kohno*[2]*, Junichi Ishiyama*[2]*, John W. Kozarich*[1]*, Kevin R. Shreder*[1]*. (1) ActivX Biosciences, Inc., La Jolla, CA 92037, United States (2) Discovery Research Laboratories, Kyorin Pharmaceutical Co. Ltd., 2399-1, Nogi, Nogi-machi, Shimotsuga-gun, Tochigi, Japan*

AX10185 , the phenyl amide of xanthurenic acid, was found to be a sub-100 nM inhibitor of Lp-PLA$_2$. However, in the presence of EDTA the inhibitory activity of **AX10185** was extinguished while the enzymatic activity of Lp-PLA$_2$ did not change. Subsequent metal screening experiments determined the inhibition to be Zn^{2+} dependent. Structure-activity relationship studies indicated the presence of the 4-hydroxy group to be critical and selected substituted phenyl, polycyclic, and cycloaliphatic amides of xanthurenic acid to be well tolerated.



AX10185
human plasma Lp-PLA$_2$ IC_{50} = 27 nM
human plasma Lp-PLA$_2$ (+ 10 mM EDTA) IC_{50} >100000 nM

MEDI 97

Azabenzthiazole inhibitors of leukotriene A$_4$ hydrolase

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Leukotriene A_4 hydrolase (LTA_4H) is a zinc metalloenzyme that converts leukotriene A_4 (LTA_4) to leukotriene B_4 (LTB_4). It is believed that inhibition of LTA_4H will decrease the amount of LTB_4 produced in humans and offers a promising therapy for the treatment of

diseases such as asthma, psoriasis and inflammatory bowel disease. The synthesis of azabenzthiazole inhibitors and the biological trends observed will be discussed.

MEDI 98

Synthesis and activity of folate conjugated didemnin B for potential treatment of inflammatory diseases

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The use of folate as a targeting ligand for the selective delivery of therapeutic agents to folate receptor (FR) expressing activated macrophages has demonstrated potential for the treatment of inflammatory diseases. In this report, a folate receptor targeted didemnin B conjugate was synthesized using a hydrophilic peptide spacer linked to folate via a releasable disulfide carbonate linker. The conjugate displayed a relative affinity compared to free folic acid of 0.18, indicating that the drug moiety did not significantly compromise FR binding. Cytotoxicity and TNF-alpha inhibition in RAW264.7 macrophage-like cells exhibited IC50s of 13 nM and 5 nM, respectively. Folate didemnin B was found to be ~50-100 fold more potent than didemnin B itself. More importantly, activity of the prodrug was blocked by excess folic acid, demonstrating receptor-mediated cellular uptake of the conjugate.

MEDI 99

Design and development of new non steroidal anti-inflammatory drugs that inhibit COX-2 enzyme

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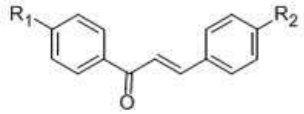
Many non-steroidal anti-inflammatory drugs (NSAIDs) are non-selective towards enzyme inhibition of cyclo-oxygenase COX-1 or COX-2. Adverse effects of NSAIDs result from inhibition of COX-1. Therefore we seek drugs that provide inhibition and selectivity towards COX-2 but not COX-1. Different families of drugs were synthesized to interact with COX-2 pharmachophores to measure their ability to decrease the activity of COX-2 over COX-1 enzyme. Enzyme activity studies and auto docking models include the pharmachophores R_1 SO_2CH_3, SO_2 NH_2, and $SO_2NHCOCH_3$ with various chains R_2 .



$R_1 = SO_2CH_3, SO_2NH_2, SO_2NHCOCH_3$

$R_2 = CH_2CH_3, CH_2CH_2CH_3, CH_2CH_2CH_2CH_3$

MEDI 100

Structure-activity relationship study of isoxazole-derived LPA1 antagonists

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Lysophosphatidic acid (LPA) is a bioactive phospholipid which plays an important role in inflammation, tissue fibrosis and proliferation and migration of various tumor cells. At least five distinct receptors were discovered and designated to LPA1-LPA5, which mediate the cellular signals induced by LPA, leading to various biological and pathological processes. Among these receptors, LPA1 has strong relationship to pathological states of inflammatory diseases by inducing the release of chemokines and lipid mediators, and of fibrotic diseases by chemoattractant activity of fibroblasts. Recently, researchers in Amira pharmaceuticals showed promising anti-fibrotic efficacy of LPA1 antagonists in animal models, to address its potential as a novel drug target, and Amira has completed a Phase 1 clinical study with a novel LPA1 antagonist, in normal, healthy subjects. In this presentation, we will report the synthesis, structure-activity relationship (SAR) study and in vitro and in vivo biological evaluations of isoxazole-derived LPA1 antagonists.

MEDI 101

Discovery and design of 2-phenylindole-based nitric oxide synthesis inhibitors as potential antiinflammatory and chemopreventive agents

Xufen Yu*, xufen@hawaii.edu, Eun-Jung Park, Tamara P Kondratyuk, John M Pezzuto, Dianqing Sun. Department of Pharmaceutical Sciences, University of Hawai'i at Hilo, Hilo, Hawaii 96720, United States*

The indole heterocyclic motif is commonly found in pharmaceutical molecules, and its derivatives have attracted considerable attention due to important biological activities. During the course of evaluating the biologic potential of a commercial compound library, 2-phenylindole was identified as an inhibitor of nitrite production. Nitric oxide (NO) is

formed by nitric oxide synthase (NOS) from L-arginine and is an important cellular signaling molecule. Overproduction of NO can lead to inflammation and cancer. As such, we have undertaken systematic chemical optimization based on this indole lead molecule to develop novel NOS inhibitors. Using one-pot palladium catalyzed Sonogashira-type alkynylation and base-assisted cycloaddition, we synthesized a chemically diversified indole library from an array of substituted 2-iodoanilines and terminal alkynes. Subsequent biological evaluation revealed several of the derivatives (e.g., 3-carboxaldehyde oxime and cyano substituted 2-phenylindoles; IC_{50} values of 4.4±0.5 and 4.8±0.4 μM, respectively) demonstrated improved inhibition in NO production relative to 2-phenylindole (IC_{50} = 38.1±1.8 μM). Synthesis and structure-activity relationship of this novel class of NOS inhibitors will be discussed, as well as their regulation of NFκB.

MEDI 102

Lead optimization of a TYK2 selective scaffold

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Starting with cyclopropyl amide lead **2** , identified through a hit to lead (H2L) effort, we were able to improve TYK2 potency and selectivity against JAK1-3 isoforms. More importantly, improved potency and selectivity was achieved without compromising the excellent ligand efficiency and ADME properties of the original lead **2** . Systematic SAR efforts led to (1*R*, 2*R*)-*cis*-F-cyclopropyl amide **3** , which was cellularly potent, selective, and showed dose-dependent knockdown of IL-12 pathway in a mouse PK/PD model.

MEDI 103

Chemical and biological properties of nitrogen oxide releasing NSAIDs

***Gaurav Bharadwaj**, gaurav@email.arizona.edu, Debashree Basudhar, Yannon Liang, Katrina M Miranda. Chemistry and Biochemistry, The University of Arizona, Tucson, AZ 85721, United States*

Nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin, ibuprofen and indomethacin are the most widely prescribed drugs to treat pain fever and inflammation. However, NSAIDs are associated with serious side effects, such as gastrotoxicity due to inhibition of cyclooxygenase-2 (responsible for pain and inflammation) as well as cyclooxygenase-1(responsible for protecting the gastric mucosa).

Nitric oxide (NO) is an endogenous signaling molecule that is involved in various physiological functions, such as inhibition of platelet aggregation, protection of the stomach lining and immune regulation. To overcome the side effects of NSAIDs, NO based NSAIDs have been synthesized using different NO donors and have been shown

to retain the anti-inflammatory and antipyretic activity of NSAIDs with reduced gastrointestinal toxicity.

Nitroxyl (HNO) has also emerged as a biologically relevant nitrogen oxide, with promising results in treatment of cardiovascular diseases. We have recently shown the chemotherapeutic potential of HNO releasing asprin adducts. In an effort to establish these class of drug candidate as an alternative to conventional NSAIDs, we have synthesized NO/HNO releasing adducts of other NSAIDs. Their NO/HNO release profile as well as their efficacy as cancer drug was examined.

MEDI 104

Substrate analogs as mechanistic probes of nitric oxide synthase

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Nitric oxide synthase (NOS) catalyzes the conversion of arginine to citrulline through the intermediate N^{ω}-hydroxyarginine (NHA), producing nitric oxide, an important mammalian signaling molecule. The first step of the NOS reaction has been well-studied and is presumed to proceed through a cytochrome P450-like mechanism, through a Compound I heme species. The second step, however, is mechanistically unprecedented and is thought to occur via a ferric peroxy anion. To gain insight into the details of this unique second step, four methylated NHA analogues have been synthesized and their substrate or inhibitor properties were determined for both mammalian NOS and bacterial gsNOS. Crystal structures reveal their binding conformations and EPR studies evidence the formation of various ferric-oxo species of the heme catalytic cycle. Results suggest modifications to the NHA structure cause major changes in the active site hydrogen-bonding network, which dictates the heme species formed during turnover.

MEDI 105

Design, synthesis and biological evaluation of novel thiazole derivatives as vascular adhesion pretein-1 inhibitors

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Vascular adhesion protein-1(VAP-1) is an amine oxidase, also known as semicarbazide sensitive amine oxidase(SSAO), which especially exists in human plasma, and it is thought to be an attractive therapeutic target for various inflammatory diseases including diabetes complications (diabetic nephropathy, retinopathy and so on).
In our VAP-1 inhibitor program, subsequent structural modifications following high-throughput screening of our compound library resulted in the discovery of a novel series of thiazole derivatives showing potent inhibitory activity with <50nM IC_{50} values in rat. Moreover, treatment with selected compounds exhibited significant effects on ocular permeability in STZ induced diabetic rats. Synthesis, SAR and pharmacological properties of the thiazole derivatives will be presented.

MEDI 106

Mechanism of inactivation of inducible nitric oxide synthase by amidines

***Wei Tang**, candydon@u.northwestern.edu, Richard B. Silverman. Department of Chemistry, Northwestern University, Evanston, IL 60208, United States*

Nitric oxide synthase (NOS) isoforms catalyze the conversion of L-arginine to L-citrulline and nitric oxide. N^5-(1-iminoethyl)-L-ornithine (L-NIO), an amidine-containing molecule, is an inactivator of inducible NOS. A mechanism for the formation of α-meso-hydroxyheme during amidine inactivation of inducible NOS has been proposed. This implicates a new and general regulation mechanism for heme-containing enzymes: an irreversible enzyme inactivation without inactivator modification. Herein, we attempt to find support for this previously proposed mechanism through the design and synthesis of a series of L-NIO and *N*-(3-(Aminomethyl)benzyl)acetamidine (1400W) analogues. It was found that L-NIO has dual biological functions as an inactivator and substrate. We disclose the exploration of this proposed dual binding mode of L-NIO by derivative design. Furthermore, this work explores heme regulation, which could be applied to other biologically significant heme enzymes.

MEDI 107

Phosphodiesterase inhibitors: Design, synthesis and structure-activity relationships of dual PDE3/4-inhibitory pyrazolo[1,5-*a*]pyridines with anti-inflammatory and bronchodilatory activity

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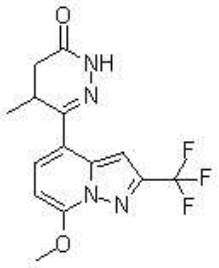
A structural survey of pyrazolopyridine-pyridazinone phosphodiesterase (PDE) inhibitors was made with a view to optimization of their dual PDE3/4-inhibitory activity for respiratory disease applications. These studies identified (–)-6-(7-methoxy-2-

trifluoromethylpyrazolo[1,5-*a*]pyridine-4-yl)-5-methyl-4,5-dihydro-3-(2*H*)-pyridazinone (KCA-1490) as a compound with potent combined bronchodilatory and anti-inflammatory activity and an improved therapeutic window over roflumilast.



KCA-1490 (-)-form

MEDI 108

Design, synthesis, and characterization of a potent and selective subnanomolar bi-dentate JNK inhibitor

Surya K De[1]*, surya@sanfordburnham.org, John L Stebbins*[1]*, Vida Chen*[1]*, Elisa Barile*[1]*, Angela Purves*[1]*, Jason F Cellitti*[1]*, Thomas Machleidt*[2]*, Barbara Becattini*[1]*, Megan Riel-Mehan*[1]*, Li Yang*[1]*, Russell Dahl*[1]*, Maurizio Pellecchia*[1]*. (1) Cancer center, Sanford-Burnham Medical Research Institute, La Jolla, California 92037, United States (2) Discovery services, Life Technologies, Madison, Wisconsin 53719, United States*

The design and synthesis of potent and selective kinase inhibitors is at the center of considerable efforts from both the pharmaceutical sector and academic research. Protein and small molecule kinases also possess binding pockets for substrates and scaffolding proteins that could be equally used to design specific inhibitors. However, these binding surfaces are usually large and shallow hence not particularly suitable for the design of small drug like inhibitors with sufficient potency. Hence, we propose that the design and synthesis of bi-dentate compounds linking the binding energies of weakly interacting ATP and substrate mimetics could result in potent and selective inhibitors. As an application, we describe a bi-dentate molecule, designed against the protein kinase JNK. In view of its favorable inhibition in vitro and in vivo profile, this compound represents a first class of dual ATP- and substrate-competitive kinase inhibitor as well as a promising stepping stone towards the development of a novel class of bi-dentate therapeutics.

MEDI 109

S-Nitrosoglutathione reductase inhibitors for the treatment of diseases

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S-nitrosoglutathione reductase (GSNOR) is a member of alcohol dehydrogenase family of enzymes (ADH), class III, encoded by ADH 5 gene. In the recent years, it was discovered as an efficient enzyme that regulates the levels of *S*-nitrosothiols (SNOs) through catalytic reduction of *S*-nitrosoglutathione (GSNO), a major adduct of endogenous nitric oxide (NO), a form of bioavailable NO. N30's approach is to develop GSNOR inhibitors to modify the diseases characterized by reduced levels of GSNO and bio-available NO, such as asthma, chronic obstructive pulmonary disease (COPD) and inflammatory bowel disease (IBD). In this presentation, we will summarize the discovery and development efforts taken by N30 Pharmaceuticals, discus the structure-activity relationship of three major series of chemical compounds as GSNOR inhibitors and update the development of GSNOR inhibitors as therapeutics for the treatment of these diseases.

MEDI 110

Namalide, a natural cyclic peptide and its analogs as carboxypeptidase A inhibitors

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The synthesis and structure activity relationships of namalide, a marine natural product, are described. Namalide is a cyclic peptide whose macrocycle is formed by three amino acids with an exocyclic ureido phenylalanine moiety at its C-terminus. The configuration of namalide was established and analogs generated through Fmoc-based solid phase peptide synthesis. The synthetic version of natural namalide containing D-Lys and L-Ile was the most potent inhibitor of carboxypeptidase A with an IC_{50} value of 250 nM, where the linear version of it showed an18-fold reduction in activity. Analogs containing L-Lys or L-*allo*-Ile failed to inhibit carboxypeptidase A at the concentrations as high as 30 uM. Analog of Namalide that lacks the C-terminal exocyclic ureido Phe, and the namalide dimer were inactive. Namalide represents a new anabaenopeptin-type scaffold, and its protease inhibitory activity demonstrates that the 13-membered macrolactam can exhibit similar activity as the more common hexapeptides.

MEDI 111

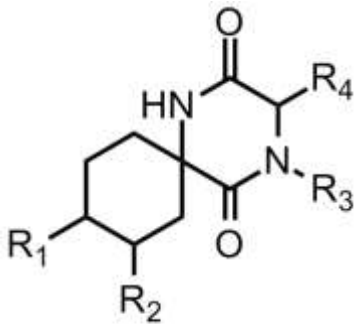
Diketopiperazine-based inhibitors of protein-protein interactions

Mariell Pettersson*, mariell.pettersson@chem.gu.se, Petra Båth, Kristina Luthman, Morten Grøtli. Department of Chemistry, University of Gothenburg, Sweden*

α-Helices are important in controlling protein-protein interactions (PPIs). We are investigating if **1** can be used as an α-helix mimetic and disrupt PPIs. Computational

studies of **1** have revealed that **1** can adopt a helical configuration and place the interacting substituents in the correct orientation.

We will present the design, synthesis and inhibitory activity of diketopiperazine-based inhibitors of PPIs with the general structure **1** .



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MEDI 112

Synthesis and utility of novel peptidomimetics containing hydroxyethyl isostere and imodazolidinone

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Peptidomimetics are important targets in drug discovery, because they can exhibit behavior similar to that of biologically active peptides. The need for new peptidomimetic scaffolds is important for the discovery of new therapeutics.

We describe the synthesis and utility of a new class of peptidomimetics derived from both imidazolidinones and hydroxyethylene isosteres. The key step in the synthesis of this class of peptidomimetics is the ring opening/rearrangement of an α-aminoamide with fused ring aziridines. The opening with an amino amide or a peptide fragment results in an oxazolidinone intermediate, which can rearrange into an imidazolidinone. The resulting diol is converted into an aminoalcohol and then coupled with a second amino acid or peptide fragment. This provides a novel peptidomimetic containing both the well known hydroxyethyl isostere as well as an imidazolidinone. Details regarding the synthesis and utility of these peptidomimetics will be presented.

MEDI 113

Screening vorozole on a series of human liver cytochrome P450s

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Vorozole has been reported to be a potent, long acting and selective non-steroidal aromatase inhibitor. It has the potential to treat estrogen dependent diseases and its carbon-11-analog is currently being tested as a radiotracer for brain aromatase (CYP19). It was found that the carbon-11-vorozole binds tightly to an unknown protein in the liver that is not CYP19. While vorozole is considered selective, this selectivity has only been shown when compared to enzymes involved in steroidogenesis. Since CYP19 is in a superfamily of enzymes called cytochrome P450s (CYPs) and there are many other enzymes in this class that are in high concentration in the liver, it is highly likely that vorozole is binding to a CYP. Screening of vorozole on these CYPs may lead to the identification of this unknown liver enzyme that vorozole is binding to. Our lab uses fluorometric high-throughput screening assays to screen vorozole on these CYPs.

MEDI 114

High throughput determination of glutathione binding ability of small molecules with the use of intrinsically fluorescent probes

Megan M. McCallum*, mccallu7@uwm.edu, Premchendar Nandhikonda, Leggy A. Arnold. Department of Chemistry and Biochemistry, University of Wisconsin - Milwaukee, Milwaukee, WI 53211, United States*

Characterization of hit molecules identified by high throughput screening (HTS) is an essential part of drug discovery. Hundreds to thousands of hit molecules must be characterized by secondary screens, which are not always amendable to a higher throughput format. Herein, we present the development of a HTS assay that enables the identification of reactive electrophilic small molecules. Thiol-containing molecules have an essential role in many biochemical and physiological reactions due to the ease of which they are oxidized. Glutathione is the most abundant non-protein thiol as it is found in the millimolar range in most cells. Therefore, it is important to determine the reactivity of the small molecules with thiols to circumvent compound depletion. Currently, there are no established pre-clinical high throughput assays for the assessment of compound reactivity towards glutathione. With the use of intrinsically fluorescent thiol-containing molecules, the binding ability can be sensitively and selectively determined.

MEDI 115

Highly efficient ^{18}F-fluorination of diaryliodonium salts

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The preparation of ^{18}F-labeled aryl fluorides from diaryliodonium salts has been heavily investigated since 1995. This process is one of only a handful of reported reactions that are capable of direct radiofluorination of electron-rich arenes with [^{18}F]-fluoride under no carrier added (n.c.a.) conditions. Previous work from our laboratory showed that the use of a non-polar solvent system (benzene/or toluene) and/or removal of “inert” electrolyte are the key experimental parameters to achieve high yields of fluoroarenes from diaryliodonium salts. Here we discuss the preparation of a variety of diaryliodonium triflates and use of these compounds in radiofluorination reactions.

MEDI 116

Developing chemical probes for the BET bromodomains

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Bromodomains are acetyl-lysine binding domains found in many chromatin-associated proteins. They play an important role in the epigenetic regulation of gene expression by binding selectively to acetylated lysine residues on histone tails. The BET proteins, a family of dual-bromodomain-containing transcriptional cofactors, are known to play a role in the pathogenesis of several cancers. Chemical probes for the BET bromodomains will enhance our understanding of the therapeutic potential of bromodomain-histone interaction inhibitors.

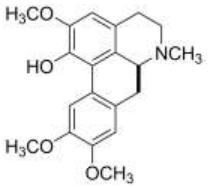
Using a structure-guided design approach, we developed inhibitors of the BET bromodomains based around a 4-phenyl-3,5-dimethylisoxazole scaffold, and evaluated their activity against a panel of bromodomains. The most potent compounds inhibit the binding of BET bromodomains to histone peptides with nanomolar IC_{50} values, and show excellent ligand efficiency. X-ray co-crystal structures illustrated the interactions responsible for the potency and selectivity of these compounds, which represent an important chemotype in the on-going effort to develop chemical probes for epigenetic targets.

MEDI 117

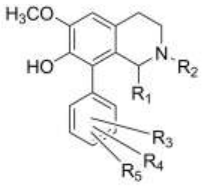
Design and synthesis of 8-phenyl-1,2,3,4-tetrahydroisoquinolines as 5-HT$_7$ receptor ligands

Shiau-Chin Wang, Chia-Ying Yang, ***Ling-Wei Hsin****, lwhsin@ntu.edu.tw. Institute of Pharmaceutical Sciences, National Taiwan University, Taipei, Taiwan 10051, Taiwan Republic of China*

Aporphine and related compounds have demonstrated numerous biological activities, such as antiarrhythmic, hypoglycemic, anti-HIV, anti-inflammatory, and anti-Parkinsonism activities. Our researches have been focused on the pharmacological profiles of thaliporphine derivatives. In preliminary study, thaliporphine exhibited submicromolar binding affinity to 5-HT_7 receptor. Therefore, thaliporphine was chosen as a lead compound for the design and synthesis of novel 5-HT_7 receptor ligands. The core structure of thaliporphine consists of ABCD four rings and therefore concise and efficient preparation of novel thaliporphine derivatives by total synthesis is not feasible. Thus, a series of 8-phenyl-1,2,3,4-tetrahydroisoquinoline, the ABD partial structure of thaliporphine, derivatives was designed and synthesized. The key reaction for the construction of ABD ring system is acid-catalyzed electrophilic aromatic substitution reaction. The 5-HT_7 receptor binding affinity and selectivity to other 5-HT receptor subtypes for these novel ABD derivatives have been determined and several compounds are potent and selective 5-HT_7 receptor ligands.



Thaliporphine



8-Phenyl-1,2,3,4-tetrahydroisoquinoline

MEDI 118

Synthesis and evaluation of novel heteroaromatic substrates of GABA aminotransferase

Dustin D Hawker*, d-hawker@u.northwestern.edu, Richard B Silverman. Department of Chemistry, Northwestern University, Evanston, IL 60208, United States*

Two principal chemicals are involved in the regulation of mammalian neuronal activity: γ-aminobutyric acid (GABA), an inhibitory neurotransmitter, and L-glutamic acid, an excitatory neurotransmitter. Low GABA levels in the brain have been implicated in epilepsy and several other neurological diseases. Due to GABA's inability to cross the blood-brain barrier, a successful strategy in raising brain GABA concentrations is the inhibition or inactivation of GABA aminotransferase (GABA-AT), which degrades GABA to succinic semialdehyde, thus increasing GABA concentration. Vigabatrin, a mechanism-based inactivator of GABA-AT, is currently a successful therapeutic for epilepsy, but has harmful side effects, leaving a need for improved GABA-AT inactivators. Here, we report the synthesis and evaluation of a series of heteroaromatic GABA analogues as substrates of GABA-AT. Compounds identified as substrates will be the basis for the design on novel enzyme inactivators that may lack the side effects exhibited by vigabatrin.

MEDI 119

Rational design and evaluation of substituted-pyrimidines as dual cholinesterase and amyloid aggregation inhibitors

Praveen PN Rao[1]*, praopera@uwaterloo.ca, Tarek Mohamed*[1]*, Jacky CK Yeung*[1]*, Jerry Yang*[2]*. (1) School of Pharmacy, Health Sciences Campus, University of Waterloo, Waterloo, Ontario N2L3G1, Canada (2) Department of Chemistry and Biochemistry, University of California San Diego, La Jolla, California 92093-0358, United States*

We designed and developed a library of over 112 substituted pyrimidines as acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) inhibitors. Substituents of the central pyrimidine ring scaffold was varied to develop suitable pharmacophores to target the peripheral anionic site (PAS) of AChE. The structure activity relationship (SAR) data acquired indicates that a C-2 cyclohexylpiperazine or benzylpiperidine pharmacophores were able to provide dual AChE and BuChE inhibition [eg: 2-(4-cyclohexylpiperazin-1-yl)-*N*-(naphthalene-1-ylmethyl)pyrimidine-4-amine, AChE IC_{50} = 8.0 μM; BuChE IC_{50} = 3.9 μM). A C-4 dimethoxybenzyl substituent was able to prevent AChE-promoted amyloid aggregation indicating its ability to bind to PAS [eg: N^2-(1-benzylpiperidin-4-yl)-N^4-(3,4-dimethoxybenzyl)pyrimidine-2,4-diamine, 59.3% inhibition at 100 μM]. Our rational drug design approach suggests that one can use pyrimidines as suitable ring templates to develop dual cholinesterase and amyloid aggregation inhibitors as disease modifying agents (DMAs) to target multiple pathological routes in Alzheimer's disease (AD).

MEDI 120

Enaminone amides as dual positive allosteric modulators of α7 nACh and $GABA_A$ receptors

Derk J Hogenkamp*, dhogenka@uci.edu, Jin-Cheng Huang, Edward R Whittemore, Wen-Yen Lee, Minhtam Tran, Timothy B Johnstone, Kelvin W. Gee. Department of Pharmacology, University of California, Irvine, Irvine, California 92697, United States*

A series of enaminone amides have been developed as dual positive allosteric modulators (PAMs) of α7 nicotinic acetylcholine (nACh) and γ-aminobutyric $acid_A$ ($GABA_A$) receptors. Structure-activity studies in oocytes expressing human nACh receptors indicate that the compounds have selectivity for α7 over α4β2 and α3β4 receptors. Kinetic studies have shown that the compounds are Type 1 PAMs that do not alter the native kinetics or reverse desensitization of the α7 receptor. In addition, the compounds selectively modulate β2/3- over β1-subunit containing $GABA_A$ receptors that may decrease their sedative liability. The potential for synergistic interaction between these two ligand-gated ion channels in the treatment of schizophrenia will be discussed

MEDI 121

Nootropics for use in schizophrenia: Dual positive allosteric modulation of α7 nAChR & $GABA_AR$

Thomas A Ford-Hutchinson*, tfordhut@uci.edu, Derk Hogenkamp, Ryan Yoshimura, Minhtam Tran, Timothy Johnstone, Edward Whittmore, Hannah Rowlins, Lena Lu, Kelvin Gee. Department of Pharmacology, University of California, Irvine, Irvine, California 92697, United States*

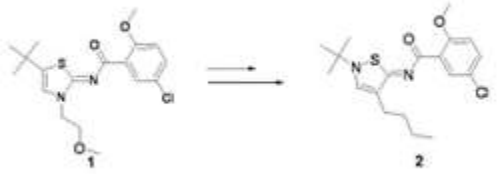
A series of novel pyridine compounds were synthesized and found to be type I positive allosteric modulators (PAMs) of α7 nicotinic receptors (nAChRs) by electrophysiology in Xenopus oocytes expressing human receptors. Type I allosteric modulators do not retard the native kinetics of desensitization of the receptor leaving native signaling intact. In addition some of these compounds were also found to be PAMs of γ-aminobutyric $acid_A$ ($GABA_A$) receptors. Additional modifications were made to achieve selectivity for $GABA_A$ β2/3 over β1 subtype containing receptors to reduce sedative activity as seen with a previous enaminone series. α7 nAChRs have been identified as an important target for nootropics to improve cognitive defects in general. In schizophrenia, both $GABA_A$ receptors and α7 nAChRs are important in regulating sensory gating. Modulation of both targets with one drug can more effectively treat the negative symptoms and cognitive deficits associated with a polygenic disease such as schizophrenia.

MEDI 122

Synthesis and SAR of isothiazolylidene amides as CB_2 agonists

Tongmei Li*, tongmei.li@abbott.com, Arturo Perez-Medrano, Anthony V Daza, George K Grayson, Yihong Fan, Tiffany R Garrison, Betty B Yao, Gin C Hsieh, Prisca Honore, Lanlan Li, Odile El Kouhen, Michael J Dart, Michael D Meyer, William A Carroll. Department of Neuroscience, Abbott Laboratories, Abbott Park, IL 60064, United States*

Activation of cannabinoid CB_1 and/or CB_2 receptors mediates analgesic effects across a broad spectrum of preclinical pain models. Selective modulation of CB_2 receptors may produce analgesia without the undesirable psychotropic side effects associated with activation of CB_1 receptors. Starting from the early thiazolylidene lead compound (**1**) the isothiazolylidene compound (**2**) was developed as a potent and selective CB_2 agonist. Extensive SAR on n-butyl side chain led to potent and selective CB_2 agonist. The synthesis, SAR and pharmacological properties on this series of compounds will be presented.



MEDI 123

6-Position optimization of tricyclic 4-quinolone-based inhibitors of glycogen synthase kinase-3β: Discovery of nitrile derivatives with picomolar potency

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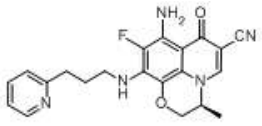
Inhibitors of Glycogen Synthase Kinase 3β (GSK3β), a serine/threonine protein kinase, offer promise as therapeutic agents to treat GSK-3β mediated diseases such as diabetes, Alzheimer's disease, and various CNS disorders. We previously disclosed tricylic, 6-carboxylic acid-bearing 4-quinolones as GSK-3β inhibitors. Herein we discuss the optimization of this series to yield a series of more potent 6-nitrile analogs (e.g., AX9839) with insignificant anti-microbial activity. Finally, KiNativ™ kinase profiling indicated that members of this class were highly specific GSK-3 inhibitors.



AX9839
GSK-3β IC_{50} = 600 pM
anti-bacterial activity MIC (E. coli) > 298 μM

MEDI 124

Benzodiazepine specificity of γ-aminobutyric acid ($GABA_A$) receptor subtypes: High-throughput electrophysiological assay on transiently transfected cells

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$GABA_A$ receptors are ligand-gated ion channels found in the synapses of neurons that conduct chloride ions across neuronal cell membranes. There are at least nineteen different individual $GABA_A$ receptor subunits that assemble the pentameric structure in different combinations to form the native receptor (α1-6, β1-3, γ1-3, δ, ρ1-3, and minor subunits). Of these potential combinations, the receptors containing two of the α1-6, two of any β subunits, and one of the γ2 subunit are the most prevalent in the brain. These receptors are sensitive to benzodiazepine (BDZ) modulation. Over the past decade, there has been an emerging understanding of the specific subunit composition, which mediates the diverse spectrum of BZD pharmacological effects. Due to this, there has been a rising interest in developing subtype-selective drugs. Using a high throughput screening platform (IonFlux), we are able to rapidly study the electrophysiological differences and drug specificities of these different receptor subtypes.

MEDI 125

Discovery of 5-HT4 receptor partial agonist for the treatment of Alzheimer's disease

***Anil Shinde**, anilshinde@suven.com, Ramasastry Kambhampati, Mohammed Abdul Rasheed, Adireddy Dwarampudi, Laxman Kota, Muralimohan Gampa, Padmavathi Kodru, Vinaykumar Tiriveedhi, Sangram Keshri Saraf, Ramkumar Subramanian, Muddukrishna Chillakur, Pradeep Jayarajan, Gopinadh Bhyrapuneni, Ramakrishna Nirogi. Discovery Research, Suven Life Sciences Ltd, Hyderabad, Andhra Pradesh 500034, India*

Dementia is a prevalent disease with estimated 36 million people currently affected. The most common group representing such patient pool is Alzheimer's disease (AD). AD is a progressive neurodegenerative disorder with ageing as the major risk factor. Extracellular beta amyloid deposits and intracellular tau tangles in brain provide the best differentiator of AD from other forms of dementia. Current therapies treat only the disease symptoms and are associated with modest efficacy, offset by dose-limiting side effects. 5-HT4 receptor partial agonist shift the equilibrium of APP processing from amyloidogenic to non-amyloidogenic pathway by activating alpha secretase enzyme and demonstrated excellent pro-cognitive profile in various animal models. Herein, we report our initial findings towards identification of a novel series of 5-HT4 receptor partial agonists. Compounds from this series have shown good selectivity, pharmacokinetic properties, adequate brain penetration and activity in animal models of cognition. Details will be presented in the poster.

MEDI 126

Discovery of novel amides: Highly potent and selective histamine H3 receptor antagonists and their procognitive potential

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Padmavathi Kodru, Vinaykumar Tiriveedhi, Sangram Keshri Saraf, Vishwottam Kandikere, Renny Abraham, Dhanalakshmi Shanmuganathan, Patnala Murthy. Discovery Research, Suven Life Sciences Ltd, Hyderabad, Andhra Pradesh 500034, India

Histamine H3 receptor is widely expressed in the mammalian brain and is believed to be involved in regulating the release of key neurotransmitters that are involved in attention, vigilance, and cognition. Thus, H3R antagonists may have potential utility in addressing a variety of cognitive and sleep disorders. We have identified a novel series of aryl/heteroaryl amide compounds as highly potent and selective H3 receptor antagonists with a favorable pharmacokinetic properties and no hERG liability. The design, synthesis, SAR and pharmacological profile along with neurochemical profile of these novel compounds for potential treatment of cognitive dysfunction will be presented.

MEDI 127

MK-8825: A potent and selective CGRP receptor antagonist with good oral activity in rats

Ian M Bell[1]*, ian_bell@merck.com, Craig A Stump*[1]*, Joseph G Bruno*[3]*, Amy Calamari*[2]*, Christine Fandozzi*[4]*, Steven N Gallicchio*[1]*, Amanda L Kemmerer*[3]*, Eric L Moore*[2]*, Scott D Mosser*[3]*, Nova Sain*[5]*, Donnette D Staas*[1]*, Mark Urban*[5]*, Rebecca B White*[4]*, C Blair Zartman*[1]*, Christopher A Salvatore*[2]*, Stefanie A Kane*[2]*, Samuel L Graham*[1]*, Joseph P Vacca*[1]*, Harold G Selnick*[1]*. (1) Department of Medicinal Chemistry, Merck Research Laboratories, West Point, PA 19486, United States (2) Department of Pain & Migraine, Merck Research Laboratories, West Point, PA 19486, United States (3) Department of In Vitro Pharmacology, Merck Research Laboratories, West Point, PA 19486, United States (4) Department of Pharmacokinetics Pharmacodynamics & Drug Metabolism, Merck Research Laboratories, West Point, PA 19486, United States (5) Department of In Vivo Pharmacology, Merck Research Laboratories, West Point, PA 19486, United States*

Calcitonin gene-related peptide (CGRP) is a 37 amino acid neuropeptide that is widely expressed in the peripheral and central nervous system. CGRP has been implicated as a key player in migraine pathogenesis and clinical studies have demonstrated that small molecule CGRP receptor antagonists are effective for the acute treatment of migraine. The orally bioavailable clinical compounds **telcagepant** and **MK-3207** are both potent antagonists at the human CGRP receptor but they exhibit significantly lower affinity for non-primate CGRP receptors. One consequence of this pronounced species selectivity is that such compounds are unattractive for use in rodent models because the high doses required would be impractical. Nonetheless, the ability to evaluate small molecule CGRP receptor antagonists in rodent models should greatly facilitate efforts to elucidate the complex biology of CGRP. We describe the identification and properties of **MK-8825** , a potent and selective CGRP receptor antagonist with good oral activity in rats.

MEDI 128

Classification of drugs by CNS access: An insight from quantitative blood-brain transport characteristics

*Kiril Lanevskij, **Pranas Japertas**, pranas.japertas@acdlabs.com, Remigijus Didziapetris. ACD/Labs, Inc., Vilnius, Lithuania*

The ultimate goal of QSAR analysis focusing on blood-brain barrier penetration is the ability to discriminate between CNS active and inactive molecules. The objective of the current study was to establish the relationship between quantitative blood-brain transport parameters and qualitative data indicating whether the compound penetrates into the brain efficiently enough to exhibit central action. Two quantitative characteristics were considered: brain/plasma equilibration rate, and the extent of brain/plasma partitioning at equilibrium (logBB). Analysis of a diverse data set consisting of >1500 compounds from World Drug Index database with experimentally assigned brain penetration categories revealed that a linear combination of the above mentioned parameters allowed classifying drugs by CNS access with 94% overall accuracy. Furthermore, the devised classification score well correlated with unbound brain/plasma partitioning coefficient (logKp,uu), which is recognized as an unambiguous determinant of brain exposure. The obtained results confirm the validity of the proposed classification approach.

MEDI 129

Probes for narcotic receptor mediated phenomena: Conceptualization, synthesis and pharmacological evaluation of ring-expanded Phenylmorphans

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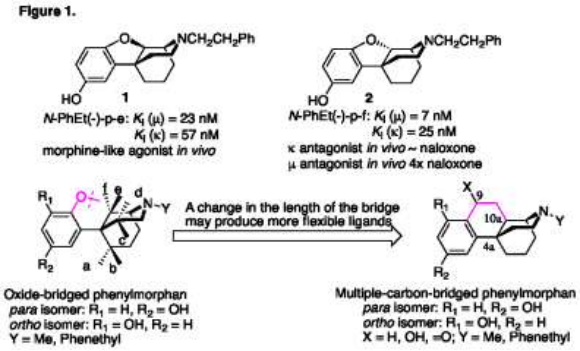
Attempts to understand the ligand-opioid receptor interaction at the molecular level rely heavily on the knowledge of the structure of ligands that can or cannot interact with an opioid receptor, due to the lack of the crystal structure of the opioid receptor and information about the opioid receptor's binding mode. In order to gain greater insight into the ligand-opioid receptor interaction, a series of carbon-bridged phenylmorphan compounds designed to have greater molecular flexibility than the conformationally rigid oxide-bridged phenylmorphan ligands were synthesized. These opioid ligands were pharmacologically evaluated and several interesting compounds were identified to have potent binding affinity to μ-opioid receptor (~0.2 nM).

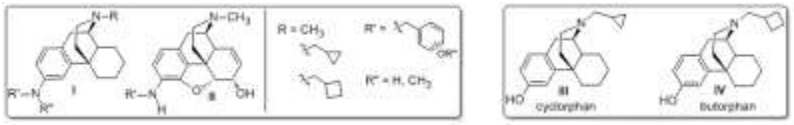


MEDI 130

Synthesis and evaluation of 3-benzylaminomorphinans at the opioid receptors

Anna W. Sromek[1]*, asromek@mclean.harvard.edu, John L. Neumeyer*[1]*, Bin Zhang*[1]*, Tangzhi Zhang*[1]*, Jean M. Bidlack*[2]*. (1) Alcohol and Drug Abuse Research Center, McLean Hospital, Harvard Medical School, Belmont, MA 02478, United States (2) Department of Pharmacology and Physiology, School of Medicine and Dentistry, University of Rochester, Rochester, NY 14642, United States*

A series of 3-benzylamino-3-desoxymorphinan **I** and 3-benzylamino-3-desoxymorphine **II** derivatives were synthesized and evaluated for their binding affinities at MOR, KOR, and DOR. Some of these ligands were found to have high affinity at MOR and KOR and displayed greater selectivity for the MOR over KOR and DOR compared to cyclorphan **III** or butorphan **IV** . Activities for high affinity analogs (K_i ≤ 1 nM) were evaluated using the [^{35}S]GTPγS functional assay. The most mu-selective compound, 3-(3′-hydroxybenzyl)amino-17-methylmorphinan (MCL-725) (24-fold MOR to KOR and 1700-fold MOR to DOR) also had high affinity (K_i = 0.42 nM to the MOR). Although morphine analogs **IV** only had moderate affinities at the MOR, MCL-720, MCL-717, and MCL-721 (K_i = 8.5, 7.0, and 13 nM, respectively) had good selectivity for the MOR. The structure activity relationships of the 3-benzylamino-3-desoxymorphinans **I** and 3-benzylamino-3-desoxymorphines **II** will be presented.



MEDI 131

Insights into the structural features of BACE: Comparison of the isozymes

***Divya Ramamoorthy**, dramamoo@mail.usf.edu, Wayne Guida. Department of Chemistry, University of South Florida, Tampa, Florida 33620, United States*

Alzheimer's disease is the most common form of brain disorder amongst the elderly. In 2006 alone, about 26.6 million people worldwide were affected by this disease and it is predicted to increase by 1 in every 85 people by year 2050. Alzheimer's disease is believed to be caused by the accumulation of amyloid peptides, which are generated by cleavage of the amyloid precursor protein by beta secretase (BACE1) followed by gamma secretase. Since BACE1 cleavage is limiting for the production of amyloid beta,[1] an approach for the treatment of this disease is to generate inhibitors targeting BACE1. BACE2, a homologue of BACE1 is reported to function as an alternate alpha-secretase[2] and thereby prevent the formation of amyloid plaques. Several inhibitors for BACE1 are reported, however their selectivity over BACE2 has not been addressed so far. In order to design selective inhibitors for BACE1, complete structural insight of both enzymes is required. We present a structural study on the isozymes, first of its kind, using MD simulations, which might enable the design of more selective inhibitors.

[1] Stockley JH, O'Neill C., Cell. Mol. Life. Sci. **2008** , 65(20):3265-89.

[2] Yan R, Munzner JB, Shuck ME, Bienkowski MJ., J. Biol. Chem. **2001,** 276(36):34019-27.

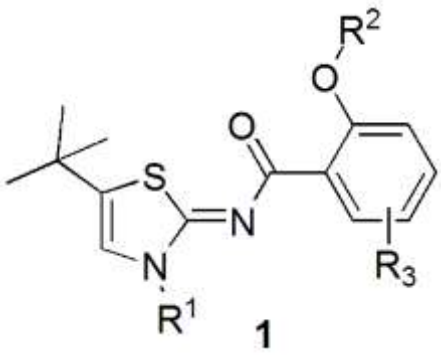
MEDI 132

Amino-containing analogs of N-thiazolylidene arylcarboximide: Potent, selective cannabinoid CB_2-- agonists as novel pain therapeutics

***Xueqing Wang**, xueqing.wang@abbott.com, Bo Liu, Jennifer Frost, Steven Latshaw, Meena Patel, Teodozyj Kolasa, William Carroll, Michael Dart, Anthony Daza, George Grayson, Yihong Fan, Loan Miller, Lanlan Li, Bradley Hooker, Odile El-Kouhen, Prasant Chandran Chandran, Anita Salyers, Madhavi Pai, Gin Hsieh, Betty Yao, Michael Meyer.Neuroscience Research, Abbott Laboratories, Abbott Park, IL 60064, United States*

The CB_1 and CB_2 cannabinoid receptors belong to the class A rhodopsin-like GPCR family. The CB_1 receptor is predominantly found in the CNS and is thought to be responsible for the overt undesired pharmacological effects induced by nonselective cannabinoid receptor agonists. The CB_2 receptor is primarily expressed in peripheral immune tissues. CB_2-selective agonists are analgesic in preclinical models of nociceptive and neuropathic pain without the adverse side effects associated with CB_1 receptor activation. In our research efforts to identify potent and highly selective CB_2 agonists, *N*-thiazol-2(3H)-ylidene carboxamide analogs, generically represented by structure **1** , have been extensively investigated. However, these compounds generally have poor physicochemical properties and CYP induction liabilities. By incorporating amino-containing side-chains at either R^1 or R^2 positions, potent, selective CB_2 agonist properties were retained. Concurrently, these compounds possess significantly

improved physicochemical properties, much attenuated CYP induction potential, and produce robust efficacy in multiple pain models. The structure activity relationships and relevant pharmacological characterization of these compounds will be disclosed.



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MEDI 133

Tetra-alkyl bis-phosphates as bivalent inhibitors of butyrylcholinesterase: Compounds with potential for treatment of Alzheimer's disease

Kim Ngan T Tu*, kim.tu@student.csulb.edu, Elise Van Fossen, Nick Spurlock, Omar Gallegos, Robert Esquivel, Nakayama Kensaku, Roger Acey. Department of Chemistry and Biochemistry, CSU Long Beach, Long Beach, California 92802, United States*

Butyrylcholinesterase (BChE) is a non-specific cholinesterase found in blood plasma with unknown physiological function. It is thought to play a role in growth and development and to act as a scavenger of cholinergic toxins as well as having an auxiliary role in synaptic transmission. BChE, like acetylcholinesterase (AChE), can hydrolyze acetylcholine. Since BChE activity in the brain of Alzheimer's patients is elevated 40-90% above normal, BChE inhibitors can increase acetylcholine concentration in the brain. Therefore, these inhibitors may hold promise in the treatment of cognitive loss due to Alzheimer's disease. Different structural variations of the bivalent inhibitors, tetra-alkyl bis-phosphates, were prepared and evaluated in vitro for their inhibitory activity against BChE to determine the optimal linker chain length between two phosphates and the alkyl groups in order to maximize inhibition. These bivalent inhibitors are thought to interact at two sites of the enzyme and, therefore, their inhibitory properties may be magnified when compared to their monovalent analogs.

MEDI 134

Synthesis and SAR analysis of 1,3-disubstituted isopropanols as novel scaffold for β-secretase inhibition

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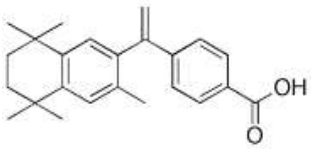
A library of 1,3-disubstituted isopropanols was synthesized and evaluated as novel small molecular scaffold for β-secretase inhibition. By screening a library of 150 1,3-disubstituted isopropanol derivatives against β-secretase, we identified several low micromolar inhibitors. Upon further SAR studies, we optimized these initial hits into nanomolar inhibitory probes for β-secretase.

MEDI 135

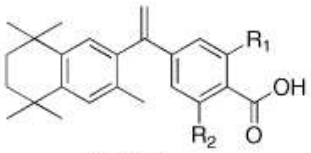
Modeling, synthesis and biological evaluation of Retinoid-X-Receptor (RXR) selective agonists with potential to treat Alzheimer's disease

***Carl E Wagner**[1], Carl.Wagner@asu.edu, Peter W Jurutka[1], Arjan van der Vaart[3], Pamela A Marshall[1], Luis A Montano[1], Gary Landreth[2], Paige E Cramer[2]. (1) Division of Mathematical and Natural Sciences, Arizona State University, Glendale, Arizona 85306, United States (2) Neurosciences, Case Western Reserve University, Cleveland, Ohio 44106, United States (3) Chemistry and Biochemistry, University of South Florida, Tampa, Florida 33620, United States*

Recently, the FDA approved drug Bexarotene (Targretin) to treat cutaneous T cell lymphoma has been found to be effective in reducing the plaque lesions in mouse models of Alzheimer's disease. It has been hypothesized that the drug works by promoting ABCA1 and Apo-E4 gene expression that may be regulated by a Retinoid-X-Receptor (RXR) / Liver-X-Receptor (LXR) heterodimer. Herein, we explore the synthesis, modeling, and biological evaluation of several novel Bexarotene analogs for their ability to serve as selective RXR agonists and their effects in cell culture and Alzheimer's disease models.



Bexarotene



Analog

MEDI 136

Discovery of truncated (N)-methanocarba nucleosides as A_1 adenosine receptor agonists

***Dilip K Tosh**, toshd@niddk.nih.gov, Khai Phan, Francesca Deflorian, Qiang Wei, Zhan-Guo Gao, Kenneth A Jacobson. Laboratory of Bioorganic Chemistry, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD 20892, United States*

A_1 adenosine receptor (AR) agonists are neuroprotective, cardioprotective, and anxiolytic. (N)-Methanocarba adenine nucleosides designed to bind to human A_1AR were truncated to eliminate 5′-CH_2OH. Similar truncation of nucleosides previously converted A_3AR agonists into antagonists, but its effect at A_1AR is unknown. In comparison to ribosides, affinity at A_1AR was less well preserved than at A_3AR, although a few derivatives were moderately A_1AR selective, notably a full agonist N^6-dicyclopropylmethyl derivative. Thus, at the A_1AR, recognition elements for nucleoside binding depend more on 5′ region interactions, and in their absence, A_3AR selectivity predominates. Based on a recently reported agonist-bound AR x-ray structure, this difference between subtypes likely correlates with an essential His residue in transmembrane domain 6 of A_1 but not A_3AR. The derivatives ranged from partial to full agonists in A_1AR-mediated adenylate cyclase inhibition. Truncated derivatives have more drug-like physical properties than other A_1AR agonists; this approach is appealing for preclinical development.

MEDI 137

Synthesis and structure-activity relationship of Tc/Re 2-arylbenzothiazoles as β-amyloid imaging agents

Jinhe Pan[1], N Scott Mason[2], Manik L Debnath[3], Chester A Mathis[2], William E Klunk[3], ***Kuo-Shyan Lin[1]****, klin@bccrc.ca. (1) Centre of Excellence for Functional Cancer Imaging, BC Cancer Agency, Vancouver, BC V5Z 1L3, Canada (2) Department of Radiology, University of Pittsburgh, Pittsburgh, PA 15213, United States (3) Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA 15213, United States*

PET (positron emission tomography) tracers for imaging brain β-amyloid plaque have been developed and successfully applied in clinical studies of Alzheimer's disease. These include 2-arylbenzothiazole derivatives [^{11}C]PIB and [^{18}F]Flutemetamol developed at the University of Pittsburgh. However, the need for a cyclotron and radiochemistry facility for tracer production has limited their widespread applicability. To circumvent these limitations, we aim at exploring Tc-99m labeled 2-arylbenzothiazoles for imaging β-amyloid plaques with the less expensive and more accessible imaging modality SPECT (single photon emission computed tomography). By using Re as a non-radioactive surrogate of Tc, we have synthesized a series of potent, compact and lipophilic Re 2-arylbenzothiazoles and selected the best candidate for labeling with Tc-99m. The design, synthesis, lipophilicity and binding affinities of Re 2-arylbenzothiazoles to aggregated β-amyloid peptides, and the radiolabeling, brain uptake and retention of the Tc-99m 2-arylbenzothiazole analog in mice will be presented.

MEDI 138

Synthesis of trisubstituted-1,2,4-triazoles as somatostatin subtype-4 receptor (sst_4) ligands

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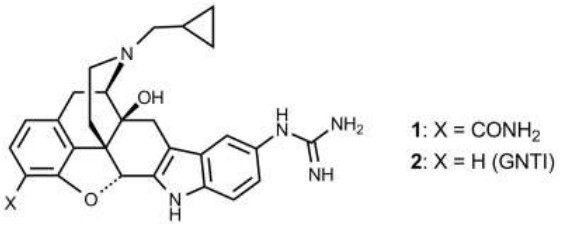
The search for novel nonpeptide somatostatin (SST) agonists has been the focus of our laboratory for over 15 years. SST levels are known to be depressed in the brain cortex and hippocampus of Alzheimer's disease patients. These brain areas contain a high level of expression of sst_4 receptors. Although NNC 26-9100, the first nonpeptide reported, has been shown to increase memory and learning in mice, we have a continued interest in developing new scaffolds with potential therapeutic use in AD. 1,2,4-Triazoles are readily synthesized by a reported method in which thioamides are condensed with hydrazides in the presence of silver benzoate to facilitate ring closure. The resulting derivatives are metabolic stable and diversified at three positions. Although most of the 1,2,4-triazoles showed only weak binding affinity at sst_4, a triazole bearing an (imidazol-4-yl)propyl group at the 1-position of the nucleus demonstrated several fold higher affinity at sst_4 than NNC 26-9100

MEDI 139

Divergent SAR for carboxamido-substituted kappa opioid receptor antagonists

Yigong Bu[1]*, Jean M. Bidlack*[2]*, Dana J. Cohen*[2]*, Qun Lu*[1]*,* ***Mark P. Wentland***[1]*, wentmp@rpi.edu. (1) Department of Chemistry and Chemical Biology, Rensselaer Polytechnic Institute, Troy, NY 12180, United States (2) Department of Pharmacology and Physiology, University of Rochester, Rochester, NY 14642, United States*

We recently reported the synthesis and pharmacological evaluation of an analogue of the kappa opioid receptor antagonist nor-BNI where its two phenolic OH groups were replaced by carboxamido groups ($CONH_2$). As expected from our understanding of the SARs of other carboxamido-substituted natural product-derived opioids, the nor-BNI analogue had very low affinity for kappa and other opioid receptors. We now report our results where the carboxamido analogue **1** of another well know kappa antagonist GNTI (**2**) was made and found to have very high binding affinity [K_i = 0.032 nM] to the kappa receptor. (Supported by NIDA grants R01 DA012180 and K05-DA00360)



1: X = $CONH_2$
2: X = H (GNTI)

MEDI 140

Discovery of fused oxadiazines as gamma secretase modulators

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Alzheimer's disease (AD) is an age related neurodegenerative disorder (cognitive impairment, loss of memory and language ability) that is affecting millions of older people in the United States. It is believed that the accumulation of amyloid-beta (Aβ) peptide plaques and protein tau-derived neurofibrillary tangles contributes to AD progression.

Aβ peptide is formed from a larger amyloid precursor protein (APP) via sequential proteolytic cleavage by β- and γ-secretases. γ-Secretase cleaves APP at multiple sites leading to Aβ peptides of 37-42 amino acids of which Aβ42, the more hydrophobic form, is the most amyloidogenic and neurotoxic. γ-Secretase modulators (GSM) act at an allosteric site to shift the predominant site of γ-secretase cleavage toward shorter, non-amyloidogenic peptides (i.e. Aβ38) by selectively inhibiting Aβ42 formation without blocking overall γ-secretase function. This will offer a potentially better selectivity window over γ-secretase inhibitors – e.g. versus notch processing. In an effort to identify GSMs to treat AD, we have discovered the framework of oxadiazolines (**1**) as selective and orally bioavailable gamma secretase modulators. To further improve the profile of the oxadiazolines, we have chosen to focus on fused oxadiazine series of compounds (**2**). Extensive SAR studies resulted in the identification of lead compounds with excellent *in vitro* and *in vivo* activity and good Aβtotal/Aβ42 selectivity. The SAR development and profile of lead compound will be discussed.

[figure 1]

MEDI 141

Synthesis, characterization, antioxidant and antimicribial activities of some novel pyrazoline derivatives

Rajeshwar Yerra[1], *stsreekanththota@gmail.com, Manasa Udugula*[2], ***Mohammad Imran***[3], *stsreekanththota@gmail.com,* ***Sreekanth Thota***[3], *stsreekanththota@gmail.com. (1) Pharmaceutical Chemistry & Toxicology, S.R. College Of Pharmacy, Warangal, Andhra Pradesh 506371, India (2) Pharmaceutical Chemistry &Toxicology, S.R. College Of Pharmacy, Warangal, Andhra Pradesh 506371, India (3) Department Of Pharmaceutical Chemistry & Toxicology, S.R. College*

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Synthesis of ten 3-phenyl-5(p-tolyl)-4,5,-dihydro-1H-Pyrazole-carbothioamides have been prepared and characterized by UV-Vis, IR, ^{1}H-NMR,^{13}C-NMR and Mass spectroscopy. All the compounds contained a common pyrazoline nucleus. The titled compounds were investigated for their antioxidant, antimicrobial activity against both Gram positive and Gram negative bacteria and antifungal activity aginst fungal spores like Coliobacterium tricum, Aspergillus niger.The significant antibacterial activity was observed most of the compounds against microorganisms like Bacillus Subtilis and Proteus Vulgaris. In case of fungi species like Aspergillus niger and Coliobacterium tricum, more activity shown for few compounds. Antioxidant activity is done by measuring IC_{50} values and it is compared with Ascorbic acid.

MEDI 142

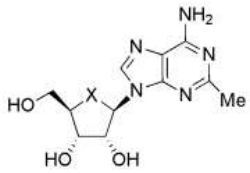
Synthesis and antimycobacterial assessment of 2-methylaristeromycins

***Sherif F Hammad**, sfh0002@auburn.edu, Stewart T Schneller. Department of Chemistry and Biochemistry, Auburn University, Auburn, AL 36849, United States*

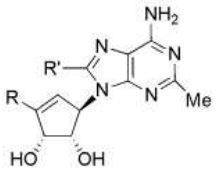
Tuberculosis is currently infecting more than 30% of the global population and accounts for 2 million deaths annually.

Adenosine kinase enzyme is a purine salvage enzyme that catalyzes adenosine phosphorylation to AMP and it has been shown that it leads to the conversion of 2-methyladnosine **1** to compounds with selective anti-mycobacterial activity.

Encouraged by the promising anti-tubercular activity of **1,** our laboratory is seeking analogs with a different mode of action to overcome recently emerging resistant TB strains. In that direction, a series of carbocyclic analogs **2-5** were designed and synthesized for the assessment of their anti-tubercular activity.



1, X=O
3, X=CH_2



2, R=CH_2OH, R'=H
4, R=R'=H
5, R=H, R'=Me

The convergent synthetic procedures conducted for the construction of the target carbocyclic nucleosides include the employment of Grubbs metathesis, Luche's reduction and Mitsunobu coupling reactions.

Compounds **2** and **4** were tested and they did not show a significant activity.

This research has been supported by the Moletter Endowment for Drug Discovery.

MEDI 143

High-throughput screening, virtual screening and rational drug design identify potent inhibitors for Pseudomonas aeruginosa RmlA

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Deoxythimidine diphosphate-L-rhamnose is an important component of the cell wall for many microorganisms, whose biosynthetic pathway does not exist in humans and is, therefore, an important target for antibiotic discovery. The first enzyme in this pathway in *P. aeruginosa*, glucose-1-phosphate thymidylyltransferase (RmlA), was targeted by a combination of high-throughput, *in silico* and rational drug design approaches. High-throughput screening revealed two inhibitors of this enzyme. These were characterised by X-ray crystallography and found to bind the enzyme's allosteric pocket, but display dissimilar binding modes. The two co-crystal structures guided formulation of the pharmacophoric hypotheses. I*n silico* screens were run on our in-house small molecule database, identifying plausible binders, which were confirmed by X-ray crystallography. Furthermore, rational drug design concepts were applied in order to obtain high affinity inhibitors. Herein, we present the current status of this project along with details of the pharmacophore used to identify hits against this enzyme.

MEDI 144

Design and synthesis of anti-trypanosomal drugs based on the 1,4,5,6 tetrahydropyrrolo [3,4-c]pyrazole scaffold via target repurposing

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The realm of drug discovery towards treating neglected tropical diseases (NTDs) such as human African trypanosomiasis (HAT) is still mostly uncharted. HAT is lethal if left untreated and existing therapies are acutely substandard. The work presented herein

focuses on targeting the Aurora kinase 1 enzyme in *Trypanosoma brucei,* the protozoan parasite that causes African sleeping sickness. We are applying a target repurposing strategy, which relies on applying the historical medicinal chemistry knowledge about human Aurora kinase inhibitors, which allows an expedited discovery process for inhibitors of the homologous enzymes in the parasite. Here we describe our results in repurposing the human Aurora kinase inhibitor danusertib, an investigational cancer therapeutic, for treating HAT. New TbAUK1 inhibitors have been designed based on the danusertib chemotype with the guidance of homology modeling of the parasitic enzyme. These compounds are effective in parasite killing *in vitro* and display good selectivity over host cells.

MEDI 145

Identification of small-molecule inhibitors of the trypanosomal kinase TbAUK1 based on comparative modeling

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Human Africa Trypanosomiasis (HAT) is a vector borne disease caused by several species of trypanosomes, affecting thousands of people every year. This disease is fatal if untreated. Current therapeutic interventions are unsatisfactory, all with limited efficacy or life-threatening side effects. The human aurora kinase is an important target for cancer therapies. Its homologue from the pathogenic *Trypanosoma brucei,* Aurora kinase -1 (TbAUK1), is a validated target for therapeutic intervention for trypanosomiasis, providing an opportunity to repurpose human Aurora kinase inhibitors towards the development of TbAUK1 inhibitors. We conducted comparative modeling of TbAUK1 and docking studies to help design and prioritize inhibitors based on a series of analogs of the pyrrolopyrazole inhibitor danusertib, currently in clinical trials for cancer. Ligand binding residues of TbAUK1, computationally predicted by THEMATICS and POOL, provide further structural based insights for design of inhibitor affinity and selectivity. New inhibitors showed low micromolar inhibition in the cell proliferation assay and improved selectivity toward parasite cells over human cells.

MEDI 146

2,4-diaminoquinazolines as anti-leishmanials

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Department of Pharmaceutical Chemistry, University of Kansas, Lawrence, Kansas 66047, United States

Leishmaniasis is a protozoan parasitic disease that puts 350 million people at risk in 88 countries. It is caused by more than 20 species of the genus *Leishmania*. We have synthesized and analyzed the anti-leishmanial properties of a set of 2,4-diaminoquinazoline analogues. These compounds have been found to display single digit micromolar or high nanomolar activity against intracellular *Leishmania donovani* in vitro and also possess selectivity indexes >20 (toxicity against J774 macrophages/activity against intracellular *L. donovani*), making these compounds interesting leads. One 2,4-diaminoquinazoline in this series, KVH14, also displays efficacy in our murine model of visceral leishmaniasis, reducing liver parasitemia by 36% when given by the intraperitoneal route at 15 mg/kg/day for five consecutive days.

MEDI 147

First total synthesis of the (±)-2-methoxy-6-heptadecynoic acid and related 2-methoxylated analogs as effective inhibitors of the leishmania topoisomerase IB enzyme

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The fatty acids (±)-2-methoxy-6*Z*-heptadecenoic acid (**1**), (±)-2-methoxy-6-heptadecynoic acid (**2**) and (±)-2-methoxyheptadecanoic acid (**3**) were synthesized and their inhibitory activity against the *Leishmania* DNA topoisomerase IB enzyme (*Ld*TopIB) determined. Acids **1** and **2** were synthesized from 4-bromo-1-pentanol, the former in ten steps and in 7% overall yield, while the latter in seven steps and in 14% overall yield. Acid **3** was prepared in six steps and in 42% yield from 1-hexadecanol. Acids **1** -**3** inhibited the *Ld*TopIB enzyme following the order **2** > **1** >> **3** , with **2** displaying an EC_{50} = 16.6 ± 1.1 μM and **3** not inhibiting the enzyme at all. Acid **1** preferentially inhibited the *Ld*TopIB enzyme over the human TopIB enzyme. Unsaturation seems to be a prerequisite for effective inhibition, rationalized in terms of weak intermolecular interactions between the active site of *Ld*TopIB and either the double or triple bonds of the fatty acids. Toxicity towards *Leishmania donovani* promastigotes was also investigated resulting in the same order **2** > **1** > **3** , with **2** displaying an EC_{50} = 74.0 ± 17.1 μM. Our results indicate that 2-methoxylation decreases the toxicity of $C_{17:1}$ fatty acids towards *L. donovani* promastigotes, but improves their selectivity index.

MEDI 148

Discovery of new inhibitors of *Trypanosoma cruzi* GAPDH: Protein-based pharmacophore, virtual screening, and biochemical evaluation

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Chagas' disease is a major cause of morbidity and millions of deaths in Latin America. The drugs currently available exhibit poor efficacy and severe side-effects. Therefore, there is an urgent need for new, safe and effective drugs against Chagas' disease. The vital dependence on glycolysis as a source of energy makes the glycolytic enzymes of *Trypanosoma cruzi*, the causative agent of Chagas' disease, attractive targets for drug design. In this work, glyceraldehyde-3-phosphate dehydrogenase (GAPDH) from *T. cruzi* was employed as molecular target for the discovery of new inhibitors as lead candidates. Integrated protein-based pharmacophore and structure-based virtual screening approaches resulted in the identification of 11 hits from three chemical classes with substantial *in vitro* inhibitory activity against GAPDH. The most potent inhibitors showed IC_{50} values in the micromolar range. The new chemotypes are promising lead candidates for future medicinal chemistry efforts aimed at developing new therapeutic alternatives for Chagas' disease.

MEDI 149

3D-QSAR approach on imidazole-dioxolane analogs with anti-plasmodium activity: A strategic design of novel antimalarial agents.

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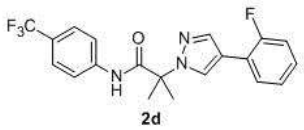
Parasitic diseases are the foremost threat to human health and welfare around the world. Malaria is one of the most lethal parasitic diseases responsible for almost 2 million deaths per year which currently available drugs are limited and not effective. Thus, there is an urgent need for new effective and non-toxic drugs. The imidazole-dioxolane derivatives represent a new class of bioactive compounds with substantial in vitro inhibitory activity against *Plasmodium falciparum* cultures. In the present work, comparative molecular field analysis (CoMFA) and comparative molecular similarity index analysis (CoMSIA) were conducted on a series of 38 imidazole-dioxolane derivatives. Two statistically significant models were obtained ($r^2 > 0.90$ and $q^2 > 0.70$), indicating their predictive ability for untested compounds. The models were then used to predict the potency of an external test set, and the predicted values were in good agreement with the experimental results ($r^2_{pred} > 0.70$).

MEDI 150

Synthesis and structure activity relationship of pyrazole derivatives as anti-tuberculosis agents

***Jinwoo Lee**, jinwoo.lee@nih.gov, Valentina Dona, Helena I. Boshoff, Clifton E. Barry.NIAID/Tuberculosis Research Section, National Institutes of Health, Bethesda, Maryland 20892, United States*

The series of pyrazole derivatives were synthesized and evaluated for anti-tuberculosis activities. Most of compounds exhibited moderate to excellent activities against H37Rv. Among them, compound **2d** showed potent activity against H37Rv with MIC value of 0.78 μM, along with cytotoxicity 85 μM and microomal stability in mice 78% in 30 min.



2d

MEDI 151

Inhibition of adenosylhomocysteine hydrolase of *Trichomonas vaginalis* with 9-(2-deoxy-2-fluoro-β,D-arabinofuranosyl)adenine

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Trichomonas vaginalis is the causative agent of trichomoniasis, a common sexually-transmitted disease in humans. Approximately 5% of cases of trichomoniasis are resistant to treatment with the commonly prescribed metronidazole. The search for alternative new therapies for both nitroimidazole susceptible and resistant cases is imperative. The various purine and pyrimidine nucleoside analogues modified at C2', C3' and C5' of the ribose ring and at position C2 and C6 of the adenine ring were tested against *T. vaginalis* in vitro. The most potent compounds were found to be 2'-modified adenosine derivatives especially ones having *arabino* configuration. Thus, 2'-deoxy-2'-fluoroadenosine, 9-(β,D-arabinofuranosyl)adenine, 9-(2-deoxy-2-fluoro-β,D-arabinofuranosyl)adenine , and 9-(2-chloro-2-deoxy-β,D-arabinofuranosyl)adenine inhibit *T. vaginalis* 100% at 100 μM level. These compounds have an IC_{50} of 2.94 μM, 3.6 μM, 0.09 μM, and 5.93 μM, respectively (Metronidazole's IC_{50} value for the same strain is 0.72 μM).

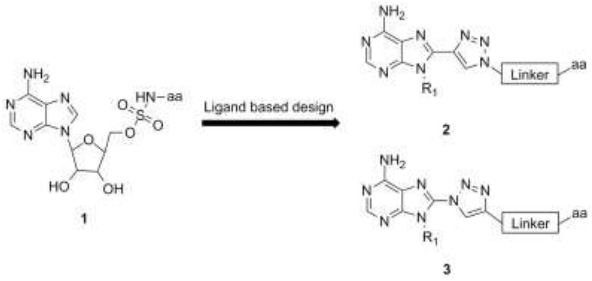
MEDI 152

8-Triazolylpurines as potential t-RNA synthetase inhibitors

***David Bliman**, bliman@chem.gu.se, Itedale Namro Redwan, Morten Grøtli. Department of Chemistry, University of Gothenburg, Gothenburg, Sweden*

Aminoacyl t-RNA synthetases (aaRSs) have been identified as targets for the development of antiinfective drugs due to their essential role in protein synthesis. We are currently developing inhibitors of aaRS based on the 8-triazolylpurine scaffold.

Docking of 8-triazolylpurines (**2** and **3**) in a crystal structure of a tRNAsynthetase protein cocrystallized with known inhibitor **1** revealed a promising structural overlap of **2** and **3** with **1** . The design and synthesis of compounds of general structure **2** and **3** will be presented.

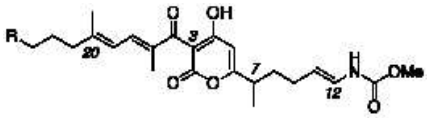


MEDI 153

Design, synthesis and biological evaluation of hybrid–type derivatives of myxopyronin as inhibitors of bacterial RNA polymerase

***Fumika Yakushiji**, fyakushi@toyaku.ac.jp, Reiko Okamoto, Yuki Kunoh, Yuko Miyamoto, Yuri Yamazaki, Yoshio Hayashi. School of Pharmacy, Tokyo University of Pharmacy and Life Sciences, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan*

The polyketide derived naturtal product myxopyronins were isolated from *Myxococcus fulvus* Mx f50 and were found to exhibit selective inhibitory activity against bacterial RNA polymerase (RNAP). The X-ray crystallography of the cocrystal, which was composed of myxopyronin and bacterial RNAP, revealed that myxopyronins possessed novel inhibitory mechanism against bacterial RNAP. Therefore, myxopyronin was expected to be a promising lead compound. However, the high lipophilicity of which were not satisfied with the required value for a drug. In the presentation, we report synthetic studies on novel hybrid–type derivatives of myxopyronins to improve lipophilicity and cell permeability for broad antibacterial spectrums. Synthesized derivatives were evaluated *in vitro* antimicrobial activity and inhibitory activity against bacterial RNAP.



Myxopyronin A: R = H
Myxopyronin B: R = Me

Figure 1. Structures of Myxopyronins

MEDI 154

Design, synthesis, and biological evaluation of new species-selective inhibitors of aspartate semialdehyde dehydrogenase

Amarjit Luniwal[1]*, amarluniwal@gmail.com, Lin Wang*[1]*, Paul W. Erhardt*[2]*, Ronald E Viola*[1]*. (1) Department of Chemistry, University of Toledo, Toledo, OH 43606, United States (2) Center for Drug Design and Development, University of Toledo, Toledo, OH 43606, United States*

Microbes that have gained resistance against previously effective antibiotics pose a major emerging threat to human health. Inhibition of key enzymes responsible for biosynthesis of essential amino acids in uniquely microbial metabolic pathways can be an effective way to deal with this new threat. Aspartate semi-aldehyde dehydrogenases (ASADHs) constitute an early branch point in a microbial biosynthetic pathway for both essential amino acids and quorum sensing molecules. We have focused on the discovery and development of species-selective inhibitors against ASADHs from several species. In the current study we have discovered new inhibitors of ASADH by using structure and fragment-based drug design approaches. These inhibitors show differential inhibitory activity against gram-positive and gram-negative microbial ASADHs. Our molecular docking, synthesis, and biological results will be described. This work is supported by a grant from the NIH (AI077720).

MEDI 155

Design, synthesis and biological evaluation of 2-arylbenzimidazoles targeting intracellular parasites *Chlamydia pneumoniae* and *Leishmania donovani*

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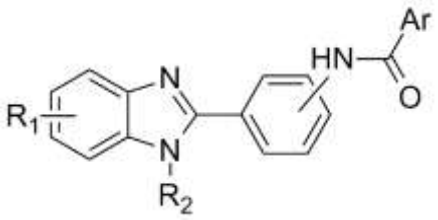
Leishmaniasis is a tropical disease caused by protozoan parasites of the genus *Leishmania*. *Leishmania donovani* and *L. infantum* are primarily responsible for visceral leishmaniasis that is fatal if untreated. Existing drugs suffer from poor compliance, toxicity, cost and parasite resistance. New treatments are urgently needed for this disease that affects millions of people mostly in developing countries. On the other hand, the intracellular bacterium *Chlamydia pneumoniae* causes mild upper and lower respiratory infection and community acquired pneumonia. *C. pneumoniae* infection has ability to turn chronic, and these infections have been linked to for example atherosclerosis. The privileged benzimidazole scaffold is a potential starting point for the new antibiotic compounds. Design and synthesis of 2-arylbenzimidazoles is described. Also the activity results of these compounds against the intracellular parasites, *L. donovani* and *C. pneumoniae* and structure-activity relationships are reviewed. Best compounds show good inhibition activity at micromolar concentrations.



MEDI 156

Identification of cyclic γ-AApeptides with potent and broad-spectrum antimicrobial activity

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Antimicrobial peptides (AMP) have attracted increasing interest because they have the potential to be developed into a new generation of antibiotic agents, which circumvent emerging drug-resistance that occurs with conventional antibiotic treatment. Non-natural antimicrobial oligomeric peptidomimetics hold great promise due to their enhanced potency and *in vivo* stability. Here we report the design, synthesis, and evaluation of γ-AApeptides based cyclic antimicrobial peptidomimetics. These cyclic γ-AApeptides show very potent broad-spectrum activities against fungi, and a series of clinically-relevant Gram-positive and Gram-negative bacteria, including pathogens that are unresponsive to most antibiotics. These results suggest cyclic antimicrobial γ-AApeptides that have the potential to emerge as a new class of novel antibiotic therapeutics. The findings will also shed further light on the design and optimization of other non-natural antimicrobial oligomers in the future.

MEDI 157

Novel and selective inhibitor of bacterial N^5-carboxy-5-aminoimidazole ribonucleotide mutase (N^5-CAIR mutase)

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The increasing frequency of drug-resistant bacterial infections has amplified the need for novel antimicrobial agents. *De novo* purine biosynthesis is one area that has great potential for antibacterial drug development because this pathway is different in microorganisms versus humans. The difference in the pathway is centered on the synthesis and utilization of the purine intermediate N^5-CAIR. N^5-CAIR synthetase makes this intermediate while N^5-CAIR mutase uses N^5-CAIR to produce CAIR. N^5-CAIR mutase has been overlooked as an antibacterial drug target due to the structural and sequence relationship with the human enzyme, AIR carboxylase. In an attempt to identify selective inhibitors of N^5-CAIR mutase, high-throughput screening was conducted using *E. coli* N^5-CAIR mutase with a counterscreen against human AIR carboxylase. These experiments revealed one compound that selectively inhibited bacterial enzyme. Molecular modeling was performed to better understand the binding mode of the inhibitor against N^5-CAIR mutase and AIR carboxylase.

MEDI 158

Discovery of antibacterial leads targeting isoprenoid biosynthesis: A knowledge and structure-based approach

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Here we describe recent efforts aimed at finding new anti-bacterial leads that target enzymes involved in isoprenoid biosynthesis. These enzymes include undecaprenyl diphosphate synthase (UPPS), essential for bacterial cell wall peptidoglycan formation, and dehydrosqualene synthase (CrtM), used in formation of the *Staphylococcus aureus* virulence factor staphyloxanthin, which promotes resistance to oxidant-based host defenses. Several leads were developed based on the observation that most HIV-integrase inhibitors bind to a Mg^{2+}/Asp rich cluster in the active site, and a similar Mg^{2+}/Asp is present in the UPPS and CrtM active sites, while other inhibitors were discovered via *in silico* high throughput screening. We obtained 6 X-ray structures of

several such compounds bound to CrtM and UPPS. These leads can act in a direct manner, killing cells; they can target virulence; plus, they can stimulate innate immunity (via NET formation), and in some cases they have multiple effects.

MEDI 159

2,4-Diaminoquinazolines as antibacterials

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With antibacterial resistance becoming an ever increasing problem, the discovery of new biologically active compounds has become an uphill battle. We have synthesized and analyzed the antimicrobial properties of a set of 2,4-diaminoquinazoline analogues. These compounds have been found to be effective against Methicillin Resistant *Staphylococcus aureus* (MRSA) with the most active compounds having minimum inhibitory concentrations (MIC) < 1 µM. Gene sequencing of the few mutants which were formed using the most active compounds allowed the determination that the mechanism of action for these compounds is not topoisomerase, gyrase, or dihydrofolate reductase inhibition. The synthesis, structure-property relationships and structure-activity relationships are described.

MEDI 160

Design and synthesis of novel antifolates as potent inhibitors of *Bacillus anthracis*

Kishore Viswanathan[1]*, kishore.viswanathan@uconn.edu, Jennifer Beierlin*[2]*, Amy Anderson*[1]*, Dennis Wright*[1]*. (1) School of Pharmacy, University of Connecticut, Storrs, CT 06269, United States (2) Department of Chemistry, Brandeis University, Waltham, MA 02453, United States*

Anthrax, an acute disease caused by the gram positive bacteria *Bacillus anthracis*, has been classified by the NIH as a category A agent on its bioterrorism threat list. Dihydrofolate reductase (DHFR) has long been pursued as a therapeutic target in a large range of diseases. Targeting *Bacillus anthracis* dihydrofolate reductase (BaDHFR), an essential enzyme in the folate biosynthesis pathway, opens up a viable drug discovery path. The studies have shown that BaDHFR is a particularly difficult enzyme to target with novel antifolates. A series of TMP analogs containing an extended propargyl-linker have been synthesized and evaluated against BaDHFR. Using structural and synthetic studies, increasingly potent inhibitors have been designed and synthesized. The most potent of these inhibitors has an IC50 of 180 nM, which represents a 100 fold improvement over TMP, the current standard in antifolate

targeting antibiotics. Work towards synthesizing more potent DHFR inhibitors through rational drug design are on.

MEDI 161

Discovery and development of 4-aminoquinolines as antivisceral leishmaniasis treatments

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Visceral leishmaniasis (VL) is the most deleterious result of infection by the obligate intracellular protozoan parasite of genus *Leishmania*, and is one of several so termed "neglected tropical diseases". As of 2009 there were twelve million reported cases worldwide. Currently, there are few chemotherapies for this disease, and these are prone to acquired resistance by the disease-causing trypanosomes as well as toxic side effects. Until a suitable vaccine is developed, the need for new, cheaply-made anti-VL drugs to treat this condition is great. A novel explant, ex-vivo assay has identified 4-aminoquinolines as compounds with potent anti-VL activity from HTS. Based on these initial hits, five compounds from a synthesized analog library were identified as leads, possessing good anti-VL efficacy as well as high selectivity for parasites vs. host cells, and were subjected to in-vivo testing in Syrian hamsters. Herein, highlights from this anti-VL drug discovery initiative are presented.

MEDI 162

Controlling bacterial behavior by bicyclic brominated furanones with reduced toxicity

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Both naturally occurring and synthetic brominated furanones are known to inhibit biofilm formation by bacteria. However, most of the known structures are toxic to mammalian cells and the growth of bacteria. Here, based on a hypothesis of what the essential structural elements are for biofilm inhibition activities, we designed and synthesized a class of new bicyclic brominated furanones that contained only one bromide group with total control of regiochemistry. This new class of molecules exhibits significant reduction in the cytotoxicity towards bacteria growth and mammalian cells, yet retains the activity for inhibiting the biofilm formation. As biofilm formation is the source of many infectious diseases, health-related problems and industrial settings, these molecules present an

opportunity for controlling biofilm formation without the issue of drug resistance. In this presentation, we will present the synthesis of bicyclic brominated furanones that have 5-, 6-, or 7-memebered rings, and their biological activity studies.

MEDI 163

Discovery and development of highly potent inhibitors of *Mycobacterium tuberculosis* growth in vitro

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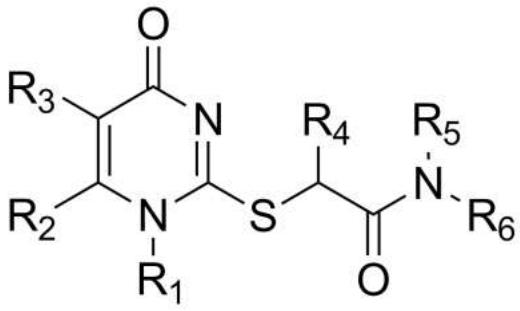

Tuberculosis (TB) is a bacterial disease infecting over 2 billion people and is caused by *Mycobacterium tuberculosis* (*M. tb*). HTS identified a number of novel scaffolds with antitubercular activity. Here we report the medicinal chemistry efforts on a scaffold leading to highly active small molecules with low nanomolar activity against *M. tb* in vitro and very low general cytotoxicity.

MEDI 164

Antibacterial properties of selected herbs on Escherichia coli and Streptococcus aureus

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Herbs may serve as antibacterial agents providing alternatives to the current medications which have a growing tendency towards bacterial resistance. In this study, rotoevaporated filtered, methanol extracts of nine herbs were diluted with dimethyl sulfoxide and used to treat bacteria samples. Quantitative measurements were made on bacteria growing in tryptic soy broth at 37^{o}C. Bacterial growth was determined by measuring decreased percent transmittance at 625nm due to increased turbidity. Catnip, Goldenrod and Kudzu demonstrated the strongest bacterial growth inhibition. Percent inhibition at 50% transmittance of the control sample of Catnip and Goldenrod with *Escherichia coli* and *Streptococcus aureus* were found to be in the range from 24% – 51%. Minimum inhibitory concentrations will be presented for these systems as well as data collected on other herbs. This study indicates that herbs may provide additional antibacterial agents.

MEDI 165

Development of new non-toxic HCV inhibitors with high efficacy and good PK

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Hepatitis C virus (HCV) is a single-stranded positive RNA virus in the Flaviviridae family, which includes several non-structural proteins (NS1, NS2, NS3, NS4a, NS5a, and NS5b). The NS3 protein possesses serine protease activity and is considered essential for viral replication and infectivity. So far, there is about 3-5% of population infected with HCV worldwide. This presentation discloses the toxicity and PK results of some highly potent HCV inhibitors with new macropolycyclic based structure. Currently, several novel macropolycyclic HCV inhibitors have been determined to show not only very potent (IC_{50} and EC_{50} for Ia, Ib, and IIa of NS3-NS4A: 0.1nM-10.0nM) but also non-toxic and competitive or better PK results in comparison with other reported HCV inhibitors such as ITMN-191 (R-7227) and MK-7009 in clinical Phase-II. Furthermore, preclinical study is ongoing and looking forward to discover 2-3 highly competitive HCV inhibitors for further clinical trial.

MEDI 166

Novel HCV NS3/4A protease inhibitors with tetrazoyl P* groups

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Hepatitis C virus (HCV) is a major disease that infects over 170 million people world wide. HCV NS3 protease is essential for cleavage of the viral polypeptide during the viral replication process. In our efforts to identify small molecule inhibitors of HCV NS3 protease, we discovered a novel series of compounds with tetrazoyl P* groups.

Systematic SAR study on both acyclic and P1-P3 macrocyclic compounds led to the discovery of EA-084 with excellent potency in both enzyme (IC_{50} = 0.1 nM) and replicon assays (EC_{50} = 0.8 nM). This compound also has very good bioavailability in rat PK studies. The details of synthetic methods, SAR and PK profile of EA-084 will be presented.

MEDI 167

SAR analysis of a series of acylthiourea derivatives possessing broad-spectrum antiviral activity

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A series of acylthiourea derivatives were designed, synthesized, and evaluated for broad-spectrum antiviral activity with selected viruses from *Poxviridae* (vaccinia virus) and two different genera of the family *Bunyaviridae* (Rift Valley fever and La Crosse viruses). One of the HTS hits, compound **1** , displayed submicromolar antiviral activity against both vaccinia virus (EC_{50} ~ 0.25 µM) and La Crosse virus (EC_{50} ~ 0.27 µM) in cytopathic effect (CPE) assays. SAR analysis was performed to further improve antiviral potency and to optimize drug-like properties of the initial hits. During our analysis, we identified **XX** , which was found to be nearly 4-fold more potent than **1** against both vaccinia and La Crosse viruses. Selected compounds were further tested to more fully characterize the spectrum of antiviral activity. Many of these possessed single digit micromolar and sub-micromolar antiviral activity against a diverse array of targets, including influenza virus (*Orthomyxoviridae*), Tacaribe virus (*Arenaviridae*), and dengue virus (*Flaviviridae*).

MEDI 168

Development of novel small molecule inhibitors of alphavirus replication

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Alphaviruses represent a new and emerging public health threat. These viruses share several characteristics: they infect humans, invade the central nervous system (CNS), are mosquito-borne, and are weaponizable. The focus of our research is the development of novel, indole-based compounds to intervene with infection. Initial HTS screening for inhibitors of alphavirus RNA replication identified the thienopyrrole CCG-

32091 (IC_{50}= 24 µM), which was successfully replaced with the indole analog CCG-102516 (IC_{50}= 15 µM) to avoid predicted metabolic and chemical instability. SAR investigations sought to improve potency, minimize cytotoxicity and bring the physico-chemical properties of CCG-102516 within the range of successful CNS drugs by reducing molecular weight and polar surface area. In addition to antiviral activity, analogs were evaluated for P-glycoprotein (Pgp) interaction and passive membrane permeability in order to assess potential CNS permeability and predicted oral bioavailability. The compounds exhibited high permeability but demonstrated structure-dependent interaction with Pgp.

MEDI 169

Discovery of novel inhibitors of HCV NS5A and proof of concept study in an HCV-infected chimpanzee

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It's estimated that more than 170 million people are chronically infected with HCV worldwide. While the infection is often asymptomatic, chronic infection can lead to liver cirrhosis and cancer. The current standard of care is associated with significant tolerability issues and a lack of efficacy in some patient groups. As a result, current efforts are aimed at developing combinations of direct acting antiviral agents. Along with HCV polymerase and protease inhibiting agents, inhibitors of NS5A have demonstrated clinical efficacy. This work describes a novel series of HCV NS5A inhibitors and selection of a compound suitable for administration in an HCV-infected chimpanzee. Observation of a robust viral load decline provided positive proof of concept for this new series of compounds as inhibitors of HCV infection. The design, synthesis, and structure activity relationships of these compounds will be reported.

MEDI 170

Small molecule anti-virals against western equine encephalitis virus

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Western Equine Encephalitis virus (WEEV), a member of the genus *Alphavirus*, causes a range of ailments from fevers to encephalitis with severe neuronal sequelea. WEEV is

weaponizable and poses a potential bioterrorism agent. Through HTS screening for inhibitors of WEEV RNA replication, CCG-32091 (IC_{50} = 24 µM) was selected for further SAR development. The thienopyrrole core in CCG-32091 was replaced with an indole to minimize metabolic instability. The resulting analog, CCG-102516, has an IC_{50} = 15 µM. Further SAR development around CCG-102516 aims to improve potency, minimize toxicity, and enhance physical chemical properties. Enantiomeric analogs CCG-203926 and CCG-203927 (IC_{50} = 7.1 µM and >100 µM, respectively) were taken into preliminary animal studies. Mice were infected with neuroadapted Sindbis virus and treated at 10 mg/kg and 30 mg/kg IP twice a day. CCG-203926, but not CCG-203927, showed improvements in both severity of disease and survival in a dose dependent manner.

MEDI 171

6,7-Dihydroxy-1-oxoisoindoline-4-sulfonamide-containing HIV-1 integrase inhibitors

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Integrase (IN) is an enzyme encoded by the human immunodeficiency virus type 1 (HIV-1) that is crucial for viral replication. The first FDA-approved HIV-1 IN inhibitor (Merck's Isentress^{TM}; MK-0518 or raltegravir) has several key structural features common to other IN inhibitors. These features typically include a co-planar arrangement of three heteroatoms that efficiently chelate Mg^{2+} ions, which are required cofactors for catalysis, as well as halogen-substituted aromatic functionality that binds in a hydrophobic pocket formed by viral DNA-enzyme complex. Following the emergence of raltegravir-resistant IN mutants, “next-generation” IN inhibitors have been sought, which overcome enzyme resistance. A co-crystal structure of raltegravir bound to the prototype foamy virus (PFV) IN complexed with DNA [Hare, S. et. al. *Nature*, **2010** , *464*, 232-7] provides important insights into possible mechanisms of resistance induced by several mutations. We have previously reported 2,3-dihydro-6,7-dihydroxy-1*H*-isoindol-1-ones as structurally simple compounds that exhibit good IN inhibitory potency and strand transfer selectivity in *in vitro* assays [Zhao, X. Z. et. al. *J. Med. Chem.*, **2008** , *51*, 251-9]. We have recently solved the co-crystal structures of certain of these inhibitors in complex with PFV•DNA, which permit a comparison of their binding interactions with those of raltegravir. Herein, we report a series of 6,7-dihydroxy-1-oxoisoindoline-4-sulfonamide-containing analogues that result from introduction of sulfonamide functionality onto the ring system of the original 2,3-dihydro-6,7-dihydroxy-1*H*-isoindol-1-ones. Many of these analogues exhibit dramatically improved efficacy.

The biological evaluation of these agents, including inhibition data against raltegravir-resistant IN mutants will be presented.

MEDI 172

Synthesis and biological evaluation of West Nile Virus NS2B-NS3 protease inhibitors

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The mosquito borne West Nile Virus (WNV), a member of Flaviviridae family, is one of the major emerging pathogen to humans and animals. This mosquito borne pathogen has spread rapidly across multiple continents during the last decade resulting in significant disease threat to humans and animals including fatalities and severe illness such as encephalitis and meningitis. Despite the growing public health concern associated with WNV infection, till date there have been no successful antiviral therapies and vaccines for human use against WNV. To discover potent inhibitors of WNV NS2B-NS3 serine protease, a library of 110 commercially available compounds with scaffolds that have a history of antimicrobial and antiviral activities were screened using the high-throughput screening (HTS) WNV assay. The most promising 'hit' compound 2-(5-(4-aminophenyl)-4-methyl-4H-1,2,4-triazol-3-ylthio)-N-(2-(2-(benzylamino)-2-oxoethylthio)benzo[d]thiazol-6-yl)acetamide found and its derivatives were subsequently synthesized and evaluated for their inhibitory activities against the WNV NS2B/NS3 protease. The most potent novel inhibitor from this class of compounds showed uncompetitive inhibition against WNV NS2B-NS3 protease with Ki of 2.77 ± 0.13 μM.

MEDI 173

Multiple in silico models for the inhibition of cytochrome P450 (CYP3A4)

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Cytochrome P450 (CYP) is a family of heme-containing enzymes, which are responsible for the metabolism of a variety of drugs. Inhibition of CYP is one of the key factors underlying drug toxicity, loss of therapeutic efficacy, and drug-drug interactions. Computational strategies aimed at generating models for the estimation and prediction of CYP modulation are of great importance. In the present work, we have organized data sets of structurally diverse molecules with known inhibition of CYP3A4 (IC_{50} values ranging from 0.3 to 450.000 nM), and used the data to create predictive QSAR models, employing a specialized fragment-based method (HQSAR). Statistically significant models were obtained showing high predictive ability for molecules not included in the training sets (external validation). The final consensus predictive QSAR models should

be useful for the design of new NCEs with desirable properties. The results of modeling these data sets will be presented and discussed.

MEDI 174

Are top-selling small molecule drugs compliant with state-of-the-art guidelines for current medicinal chemsitry?

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Following the seminal Lipinski paper on the Rule of 5 (1), the current medicinal chemistry literature is rich in guidelines for which properties high quality drug candidates should have in order to minimize attrition during development (for a review see reference 2). Analyses have focussed on predictive compound characteristics such as lipophilicity and topological polar surface area and the like both in terms of drug candidates vs. CNS drugs (3) and in terms of the 'organisational' parameter in drug discovery (4). Inspired by the work of Njardarson (5), we have analyzed the best-selling, orally dosed small molecule drugs from a medicinal chemistry vantage point to explore if the drugs follow the guidelines published over the last decade. The analysis includes the multi-parameter optimization score (MPO; see reference 3), the 'Golden Triangle' analysis (6), and the correlation between lipophilicity, topological polar surface area, and the risk of in vivo toxicological outcomes (7) as well as some of the other rules that have appeared over the last decade in the medicinal chemistry literature.

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MEDI 175

Sequence, structure, and function of GPCRs

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G-protein coupled receptors (GPCRs) encompass a large family of transmembrane receptor proteins that transmit a signal from outside the cell and activate signal transduction pathways inside the cell. Due to their role in a wide variety of signaling pathways, GPCRs are a target of intense pharmacological research. GPCRs are integral membrane proteins having a common architecture with seven transmembrane helices arranged in a barrel-like tertiary structure forming a ligand binding domain within the plasma membrane. Upon binding of the ligand, which can vary in size from small molecules to large peptides, GPCRs undergo a conformational change resulting in the activation of a G protein on the intracellular side. The conformational changes needed to successfully transmit a signal are poorly understood. We have therefore performed a comprehensive analysis of over 4000 primary sequences from multiple species of family A GPCRs and mapped the results onto currently available crystal structures of GPCRs in order to better understand the sequence and structural motifs which may be important to GPCR function. The results show that transmembrane helix-residues on the intracellular half of GPCRs are more highly conserved than those on the extracellular half. Additionally, examination of available X-ray crystal structures reveals a clustering of water molecules around the highly conserved residues on the intracellular half of GPCRs suggesting the all receptors share a common signal transmission mechanism. Grouping of GPCR sequences based on ligand type reveals conserved residues on the extracellular side which may be involved in ligand binding and early receptor conformational changes yielding to receptor activation process.

MEDI 176

Fragment-based drug design towards the advancement of selective and potent metalloenzyme inhibitors

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Drug development from a fragment-based approach is an alternative to traditional methods of drug discovery, such as high-throughput screening. This method begins with screening small, low-affinity fragments probing an active site of interest. Promising fragments can be further developed into molecules that have the potential to be both potent and specific to their target. The focus of this work is to construct inhibitors that are tailored for pathological metalloenzymes of a viral nature such as HIV integrase (HIV-IN). The basis of their design is to selectively chelate to the catalytic metal ions present in the active site of these target enzymes, thus achieving inhibition. The development of fragment hits from a novel metal-chelator library via guidance from computational docking studies has been implemented towards achieving full-length inhibitors with high metalloenzyme specificity. The design, synthesis, and inhibitory activity of these compounds will be discussed.

MEDI 177

Information analysis in biotherapeutics research

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Therapeutics research is undergoing a transformation with the more extensive research on biologics. For chemists it implies that new tools are required to effectively extract and summarize the information being generated. Protein, peptide and nucleic acid biopolymers require the development of tools that bridge the gap between natural and synthetic molecules, that might go beyond the natural amino acids or have substantive modifications not found in nature. We introduce SARvision|Biologics, a software tool to help in the analysis of data in biologics research, which aids in the identification of structure activity relationships (SAR) in biopolymers. The applications of the program are illustrated with biopolymer datasets from the public literature.

MEDI 178

CoMFA and CoMSIA studies of hexahydropyrimidine derivatives

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3D-QSAR models--- of a series of fluorinated hexahydropyrimidine derivatives with cytotoxic activities have been developed using CoMFA and CoMSIA. These models provide a better understanding of the mechanism of action and structure-activity relationship of these compounds. By applying leave-one-out (LOO) cross validation study, the best predictive CoMFA model was achieved with 3 as the optimum number of components, which gave rise to a non-cross-validated r^2 value of 0.978, and standard error of estimate of 0.059, and F value of 144.492. Similarly, the best predictive CoMSIA model was derived with 4 as the number of components, r^2 value of 0.999, F value of 4381.143, and standard error of estimate, 0.011. The above models will inspire the design and synthesis of novel hexahydropyrimidines with enhanced potency and selectivity.

MEDI 179

New approaches to the chemical synthesis of citronellol type componds useful as enzyme inhibitors

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New approaches to the chemical synthesis of citronellol type compounds have been developed. Certain acyclic terpenoid compounds and their derivatives are potent inhibitors of tyrosinase.

MEDI 180

New approaches to chemical syntheses of alkyl and alkenyl phenols

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This paper represents that naturally occurring alkyl or alkenyl phenols can reduce fat and produce a therapeutic benefit. Chemical synthesis of alkyl and alkenyl phenols will be discussed.

MEDI 181

Facile synthesis of sulfonyl fluorides

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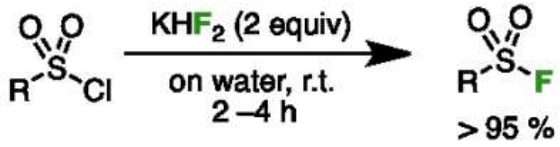
Sulfonyl fluorides are obtained in nearly quantitative yields from diversely substituted alkyl, aryl and heteroaryl sulfonyl chlorides by simply stirring them in water with 2 equivalents of KHF_2. Sulfonyl fluorides are generally shelf-stable reagents and are useful for exquisitely selective modification of complex man-made and biological molecules.



MEDI 182

T3P®: Novel applications of this green reagent

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n-Propanephosphonic Acid Cyclic Anhydride (T3P®) is an exceptional reagent for amide/peptide bond formation. Hazardous additives, such as explosive HOBt, are not required in these amidation reactions. Recent research has documented additional transformations that utilize T3P®, such as: alcohol oxidations under mild (non-cryogenic) conditions, the Lossen rearrangement and the Curtius rearrangement. In addition, the application of this reagent to other condensation reactions, such as esterifications, and the formation of nitriles under mild conditions has been demonstrated. T3P® is very easy to use and provides excellent selectivity, low epimerization and high yields with simple product isolation by liquid/liquid extraction. Additionally, the T3P® reagent is really “green” - nontoxic, non-allergenic/non-sensitizing. In sharp contrast to most other coupling reagents, the by-products are non hazardous and completely water soluble. Numerous examples of these various novel reactions will be presented, wherein the inherent advantages of T3P® will be highlighted.

MEDI 183

Allylic and benzylic oxidations of steroids with pyridinium chlorochromate and pyridinium dichromate

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This paper represents the allylic oxidation of steroids to yield the corresponding α,β-unsaturated ketones. Pyridinium chlorochromate under different reaction conditions and pyridinium dichromate are both effective reagents in argumenting allylic oxidations of steroids.

MEDI 184

Direct synthesis of tetrahydroquinazolines

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Quinazoline derivatives are part of many pharmaceutical drugs having medicinal applications such as sedatives, anti-malarial agents and in cancer treatment. Not many methods for their direct synthesis are available. A new solvent-free methodology using

$Ga(OTf)_3$ as a catalyst has been developed for the direct synthesis of difluoromethylated and trifluormethylated tetrahydroqiunazoline derivatives from the corresponding amines and fluorinated hemiacetals with high yields (40-94%). The green protocol is mild and efficient, useful for the preparation of many novel fluoromethylated tetrahydroquinazolines, which can be screened for potential therapeutic activites.

MEDI 185

Rigid amine-containing pyrrolidinones as CB_1 antagonists

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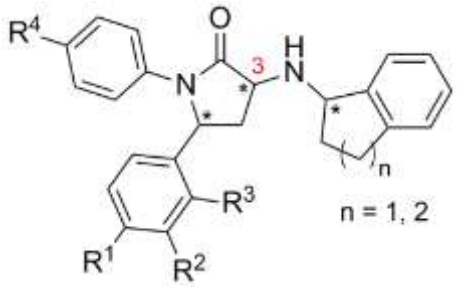
Toward developing safer pharmacotherapeutics for eating disorders, obesity or addiction, a series of rigid amine-containing chiral pyrrolidinones have been developed as CB_1 receptor ligands. To explore the synthetic landscape at C3, rigid amines 1-aminoindane (n=1) and tetrahydro-1-naphthylamine (n=2) have been appended. These novel compounds have shown excellent CB_1 selectivity and affinity (1-30 nm). Ligands will be evaluated *in vitro* and *in vivo* as CB_1-selective inverse agonists or neutral antagonists. The synthetic scheme, stereoisomer characterization and assay results will be discussed.



MEDI 186

Discovery of MK-4256, a subtype selective SSTR antagonist as a potential treatment of type-2 diabetes

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Type 2 diabetes mellitus (T2DM) has become a worldwide epidemic, causing significant morbidity and mortality. We have focused on the development of novel agents that promote glucose-dependent insulin secretion (GDIS) from pancreatic β-cells, thus minimizing hypoglycemia risk. Somatostatin inhibits the release of growth hormone from the anterior pituitary. Somatostain also suppresses the production of the pancreatic hormones (e.g., insulin and glucagon), has a role in central nervous system as a neurotransmitter, is involved in the regulation of gastric secretion, and may regulate cell proliferation. The functions of somatostatin are mediated through five G-protein coupled receptors (SSTR1 to SSTR5). We had found that antagonism of a subtype of SSTR has the potential to be a novel GDIS mechanism for the treatment of T2DM. We will discuss the SAR effort that led to the discovery of MK-4256, a potent subtype selective SSTR antagonist, which demonstrated superior efficacy in a mouse oGTT model.

MEDI 187

Synthesis and evaluation of substituted chroman-4-one and chromone derivatives as SIRT2 selective inhibitors

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Sirtuins are enzymes which function as histone deacetylases requiring NAD^+ as a co-substrate, sirtuins are related to gene silencing. The seven mammalian sirtuins (SIRT1–7) target also non-histone substrates, as they are involved in important cellular processes such as aging and age-related disorders this enzyme class is highly interesting as drug targets. SIRT2 is involved in cell cycle regulation and is related to cancer. Therefore, SIRT2 selective inhibitors would be of specific interest.

Our group has a long-term interest in the chemistry and biological activities of chromone and chroman-4-one derivatives. We have successfully developed methods for the synthesis of 2-alkyl-substituted chroman-4-ones and tetrasubstituted chromone based scaffolds. During our work we have identified a 2-pentyl-substituted chroman-4-one derivative as a highly selective SIRT2 inhibitor with an IC_{50} value of 4.5 μM. A set of chroman-4-ones based on this lead compound has been synthesized to explore the structure-activity relationships.

MEDI 188

Inhibitor of 3-hydroxy-3-methylglutary coenzyme A reductase: Synthesis and activities of 24-ketolanosterol

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This paper represents a simplified chemical synthesis of 24-ketolanosterol, a key intermediate in the synthesis of potential C-24 metabolic regulators, to be a potent inhibitor of HMG-CoA reductase activity in mouse L cells grown in a serum-free medium.

MEDI 189

Discovery of oral AMPK direct activators for the treatment of diabetes

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AMP-activated protein kinase (AMPK) is an evolutionarily conserved fuel-sensing enzyme that is activated in shortage of energy and suppressed in its surfeit. AMPK activation stimulates fatty acid oxidation, enhances insulin sensitivity, alleviates hyperglycemia and hyperlipidemia, and inhibits proinflammatory changes. Thus AMPK is a well-received therapeutic target for type 2 diabetes and other metabolic disorders.

Here, we will report the discovery of pyrrolo derivatives as AMPK direct activators. We will illustrate the synthesis and structure-activity relationships of the series as well as some attempts to improve oral bioavailability. Some compounds exhibited very interesting profiles when evaluated orally in different diabetic and obese animal models.

MEDI 190

Discovery of SIRT2-selective inhibitors

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Sirtuins catalyze the deacetylation of Ac-Lys residues of proteins using NAD^+ as a cofactor. There are seven distinct sirtuin gene products (SIRT1-7). SIRT2 mainly

deacetylates a-tublin regulating cell cycle progression. Recently, it was reported that SIRT2 causes neuron cell death in neurodegenerative diseases. Therefore, SIRT2-selective inhibitors may act as new remedies for neurodegenerative diseases as well as biological reagent to reveal the detailed functions of SIRT2.

We designed and prepared a series of 2-anilinobenzamide analogues based on the homology model of SIRT1 and SIRT2. Enzyme assays using SIRT1 and SIRT2 revealed that several analogues are potent and selective SIRT2 inhibitors. These analogues also caused a dose-dependent selective increase of a-tubulin acetylation in human colon cancer HCT116 cells, indicating selective inhibition of SIRT2 in the cells. Our findings indicate that 2-anilinobenzamide analogues represent an entry into a new class of SIRT2-selective inhibitors.

MEDI 191

Discovery and optimization of 1,5-diarylpyrazole-4-carboxamides as novel CB-1 antagonists

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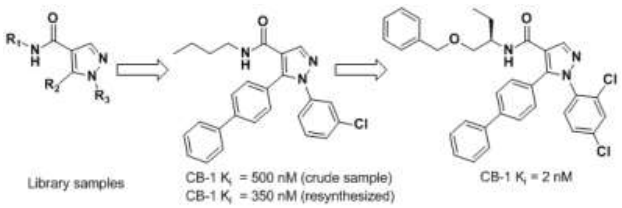
As part of an effort to identify novel G-protein coupled receptor ligands, a GPCR-targeted library of 1,5-diarylpyrazole-4-carboxamides was synthesized using a novel solid-phase synthesis. Screening of the library identified hits that contained a 5-biphenylpyrazole-4-carboxamide motif with promising activity against the cannabinoidreceptor subtype 1 (CB-1). This presentation will describe the initial discovery of the hit series and the subsequent optimization exercise that resulted in the identification of CB-1 antagonists with low nanomolar activity in both binding and functional assays.



MEDI 192

Small molecule inhibitors of Ghrelin O-acyl transferase

***Ryan A Hollibaugh**, rhollib@ucla.edu, HaiXia Liu, Nora Elmajian, Ryan Quiroz, Patrick G Harran. Department of Chemistry and Biochemistry, University of California, Los Angeles, Los Angeles, CA 90095, United States*

Ghrelin is a 28-residue, appetite-stimulating peptide secreted by the stomach. Ghrelin secreting cells acylate the hormone with n-octanoic acid. This atypical lipid modification is essential for ghrelin's endocrine functions. Octanoylated ghrelin is a ligand for the growth hormone secretagogue receptor wherein it stimulates GH release from the pituitary. Its actions have been linked to carbohydrate metabolism, fat storage, and insulin signaling. In 2008, a membrane-bound acyltransferase (GOAT) was discovered that selectively octanoylates serine-3 of ghrelin. This finding provides a special opportunity for chemistry. Ghrelin is the only hormone produced by peripheral tissue known to promote feeding and the one human protein found to be octanoylated. Small molecule inhibitors of the acyltransferase could function with high selectivity. Such compounds could resolve longstanding questions in feeding behavior, help understand ghrelin and/or GOAT knockout phenotypes, and serve as leads for a new class of anti-obesity drugs. Progress towards these goals will be discussed.

MEDI 193

Discovery of novel (−)-Cercosporamide derivatives as selective PPARγ modulators

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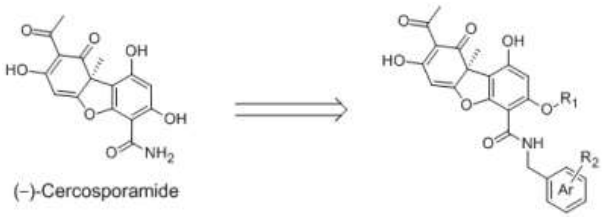
We have discovered that (−)-Cercosporamide, known as an antifungal agent and phytotoxin, showed a glucose lowering effect in hyperglycemic mice. In synthesizing the derivatives and investigating the mechanisms of action, we have noticed that some of the derivatives resulted in a PPARγ partial agonistic effect. We would like to display a detailed SAR study on the PPARγ modulators and *in vivo* efficacies of the most

promising compound, decreasing the plasma glucose level with attenuated PPARγ related adverse effects.



MEDI 194

New cathepsin K inhibitors containing argininal thiosemicarbazones

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Cathepsin K has recently been identified at the major cysteine protease expressed in osteoclasts. The abundance and selective location of cathepsin K in cells responsible for bone resorption has lead to a new interest in design of cathepsin K inhibitors for the treatment of osteoporsis. Increased bone resorption may release factors from the extracellular matrix that contribute to tumor growth. In fact, recent reports indicate that interactions between prostate cancer cells, osteoblasts, osteoclasts, and bone matrix are essential in the formation of bone metastases. The synthesis and evaluation of new synthetic compounds using cathepsin K is reported. Supported by National Cancer Institute at NIH (Grant No. 3R15CA086933-04 and 3R15CA086933-04A2S1) and Western Illinois University.

MEDI 195

WITHDRAWN

MEDI 196

Development of fluorescent probes for the vitamin D receptor and their application as screening tools and the biological probes

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Vitamin D is a pro-hormone, which is metabolized in the liver and kidneys to 1,25-dihydroxyvitamin D_3 (1,25-$(OH)_2D_3$) that in turn binds the transcription factor VDR (vitamin D receptor) with high affinity. Regulation of genes responsible for cell growth, cell differentiation, and calcium homeostasis is mediated by VDR in the presence or absence of 1,25-$(OH)_2D_3$ and is governed by interactions between VDR and coregulators. The development of biochemical assays to quantify molecule interactions with VDR and cell-based assays and *in vivo* studies to determine VDR localization and distribution have been complicated by the fact that the current labeled vitamin D analogs suffer from low affinities, instability and inaccessibility.

Herein, we present the synthesis and characterization of new and fundamentally different fluorescent probes for VDR and their application in biochemical and cell-based assays.

MEDI 197

Discovery of a novel 2-spiro-proline derivative as a novel steroid mimetic scaffold for the potent inhibition of 11β-HSD1

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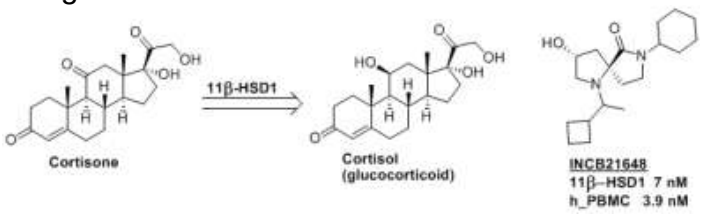
11β-hydroxysteroid dehydrogenase 1 (11β-HSD1) catalyzes the reactivation of inactive cortisone to active cortisol in specific tissues, thereby resulting in the functional antagonism of insulin action. Dysregulation of 11β-HSD1, particularly in adipose tissue, has been associated with the metabolic syndrome and type 2 diabetes. Therefore, inhibition of 11β-HSD1 with a small, non-steroidal molecule is therapeutically desirable. Implementation of a scaffold hopping approach revealed a 3-point pharmacophore for 11β-HSD1 that was utilized to design a 2-spriro-proline derivative as a steroid mimetic scaffold. Reiterative optimization provided valuable insight into the bioactive conformation of our novel scaffold and led to the discovery of INCB21648. Importantly, deleterious hERG inhibition and PXR induction were mitigated through structural design.



MEDI 198

Discovery of amidines as a novel class of potent and selective 11β-hydroxysteroid dehydrogenase Type 1 inhibitors

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Glucocorticoids (GCs) are important regulators of glucose and lipid homeostasis. In humans, GCs circulate in the blood in an active form i.e., cortisol and an inactive form i.e., cortisone. Conversion between the two forms is catalyzed by the enzymes 11β-hydroxysteroid dehydrogenase type 1 and 2. (11β-HSD1 and 11β-HSD2). Excessive glucocorticoid action in liver and adipose tissues leads to insulin resistance, type-2 diabetes, dyslipidemia, increased abdominal obesity, and hypertension. Thus, 11β-HSD1 inhibitors have been recognized as a highly promising therapeutic class.

In our research efforts to design potent and highly selective 11β-HSD1 inhibitors, we investigated the modification of common central amide moiety of lead compounds across multiple series. Replacing the amide moiety with an amidine moiety provided compounds that exhibited excellent 11β-HSD1 potency and selectivity against 11β-HSD2. The synthesis, preliminary SAR and in-vitro metabolism studies of this new class of compounds will be described.

MEDI 199

Progress towards the use of 1,2,4-triazoles as inhibitors of plasminogen activator inhibitor-1

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Plasminogen activator inhibitor-1 (PAI-1) is a mammalian protein and a key regulator of fibrinolysis. Studies have shown that individuals in various disease states experience higher levels of active PAI-1, resulting in an increased risk of thrombosis and embolism. A well-designed synthetic PAI-1 inhibitor will reduce circulating active PAI-1 levels and decrease the risk of thrombosis and embolism. Several synthetic inhibitors of PAI-1 have been reported but none have progressed to the point of late stage human trials. The focus of this research is to develop a novel class of PAI-1 inhibitors that has improved pharmacological potential over previous generations of compounds. Here we present data pertaining to our design, synthesis and pharmacological study of 1,2,4-triazoles as a novel class of PAI-1 inhibitors.

MEDI 200

Boron-based Rho-associated kinase (ROCK) inhibitor: A novel approach to interact with the hinge region and the structure-activity relationships

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Rho-associated kinase (ROCK) is an enzyme involved in control of the actin-myosin cytoskeleton, and thus affects smooth muscle contraction, cell migration, and proliferation. We have found a series of novel benzoxaborole ROCK 1/2 inhibitors including AN3484 that showed IC_{50} values of 7.5 mM and 2.6 mM against ROCK 1 and ROCK 2, respectively. X-ray co-crystal structure of AN3484-ROCK 2 complex revealed that the hydroxy group of the oxaborole ring acting as a hydrogen bond donor and the ring oxygen acting as an acceptor in the hinge region of the enzyme, representing a novel chemical motif of a hydrogen bond donor/acceptor pair. AN3485, a close analog of AN3484, showed better oral bioavailability than AN3484 in mice and oral blood pressure lowering efficacy in spontaneously hypertensive rats. AN3485 also showed potent anti-inflammatory activity both *in vitro* and *in vivo,* suggesting possible applications in lung inflammatory diseases. The SAR will be discussed.

MEDI 201

Cooperativity among hydrogen bonds in ligand-thrombin complexes: Improving from nanomolar to picomolar

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Ligand binding affinity can be significantly enhanced by individual interactions reinforcing each other, so that strong cooperative effects result. Recently we have demonstrated this type of cooperativity within a series of thrombin ligands wherein a hydrophobic interaction and a hydrogen bond mutually reinforce each other. It was shown that these two non-covalent interactions engage each other so that the binding affinity is significantly stronger than would be predicted based upon a formal and artificial additivity of the individual interactions. Herein we demonstrate more pronounced cooperativity among hydrogen bonds and hydrophobic interactions within a new series of thrombin ligands. The addition of one more hydrogen bond interaction to the ligand-thrombin complex increased the binding affinity from the nanomolar to the picomolar range. The demonstration of this level of cooperativity can be instructive for the design of highly potent ligands as a general concept in drug optimization.

MEDI 202

Novel, orally bioavaliable adenosine A_1 receptor agonists with antinociceptive effects in mice

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A_1 adenosine receptor (A_1AR) belongs to a subfamily of four G protein coupled cell surface receptors including A_1, A_{2A}, A_{2B} and A_3. A_1AR is expressed in the highest density in the brain and adipose tissue, kidney and atria and to a lower extent in ventricles, lung, pancreas, liver and GI tract. A_1AR and A_3AR couple to inhibitory G_i/G_o protein, which inhibits adenylate cyclase (AC) activity, thus reducing cellular cAMP levels. On the other hand A_{2A}AR and A_{2B}AR couple to stimulatory G_s protein and stimulate AC activity. Adenosine receptors can also modulate phospholipase C (PLC), influencing inositol triphosphate and Ca^{2+} release from internal stores. In addition, ARs act on both potassium and calcium channels. Many pathophysiological states are associated with changes in adenosine levels, *inter alia,* asthma, neurodegenerative disorders, psychosis, anxiety and chronic inflamatory disease. Thus, A_1AR has been linked to a variety of possible drug targets. Its presence in the brain has been linked to inhibition of synaptic transmission, and its presence in the atrioventicular node of the heart has resulted in clinical development of selective A_1AR agonists to be used as antiarrythmic agents. Although numerous A_1AR agonists have already been developed, few are orally bioavailable. Furthermore, clinical applications of the existing compounds have been greatly hampered by their cardiovascular side effects. Herein we disclose a novel series of compounds possessing marked potency against A_1AR shown in several orthogonal *in vitro* assays. These A_1AR agonists are orally bioavailable and highly efficacious in *in vivo* mouse models in a dose dependant manner. Apparent lack of cardiovascular side effects makes this new series of compounds especially interesting from a therapeutic standpoint.

MEDI 203

Novel synthesis and biological evaluation of indenoindolones as potent anticancer agents that induce major apoptosis in G1 phase

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Cancer is second leading cause of death worldwide. Based on hybridization of chemotypes of some natural product-anticancer drugs/agents, indenoindolones were considered as important scaffold for potential anticancer activity. Towards exploration of their synthesis relevant to medicinal chemistry, we have developed a $ZrCl_4$-mediated regio- and chemoselective Friedel-Crafts acylation of indole[1] and an efficient route of

$ZrCl_4$-mediated Friedel–Crafts 3-acylation of indole with 2-bromobenzoyl chlorides and the intramolecular direct arylation for synthesis of indenoindolones.[2] $ZrCl_4$-catalysis minimizes/eliminates common competing reactions that occur due to high and mutliatom-nucleophilic character of indole. These reactions are feasible for NH-unprotected indoles. Several moieties, which are commonly integrated into bio-active compounds, can be incorporated at ease by this synthesis. Indenoindolone derivatives have shown anticancer activities of higher potency and lower toxicity than clinically used drugs etoposide and 5-fluorouracil. DAPI nuclear staining and FACS analysis have indicated their apoptotic effect majorly in G1 phase of cell cycle.[3]

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MEDI 204

Structure based design, synthesis and biological evaluation of ɣ-lactam based HDAC inhibitors for cancer chemotherapy

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Histone deacetylases (HDACs) and histone acetyltransferases (HATs) are enzymes that related with chromatin remodeling and epigenetic control of gene expression. It is reported that HDACs are associated with carcinogenesis and regulation of HDAC function is considered as anti-cancer agent. HDAC inhibitors are categorized hydroxamic acid, benzamide, short chain fatty acid and cyclic peptide. We designed and synthesized various novel ɣ-lactam based HDAC inhibitors for cancer chemotherapy. Novel ɣ-lactam based HDAC inhibitors are composed with zinc binder, ɣ-lactam core and cap group. In the docking simulation, the big size of core group is difficult to fit in narrow hydrophobic pocket of HDAC active site, a smaller core showed better fit than larger core. ɣ-Lactam core is suggested as a smaller core for HDAC inhibitors. In this study, we prepared the novel ɣ-lactam based HDAC inhibitors with various cap groups for inhibiting profile of HDACs. Most of these analogues showed good HDAC enzyme inhibitory activity and cancer cell growth inhibitory activities. Lipophilic compound usually showed better activity profiles for HDAC inhibitor. Lipophilic analogues provide extra stabilizing interaction with surface of HDAC enzyme, more hydrophobic analogues showed better activity. **8l** , which is the best active compound are posed in tubular hydrophobic pocket and hydroxamic acid was chelated zinc ion in active site. In conclusion, we designed and synthesized ɣ-lactam core HDAC inhibitors which have diverse substituted cap groups. These analogues showed good HDAC inhibitory activity and cancer cell growth inhibitory activity. Based on physicochemical properties and

docking study, we confirmed increasing hydrophobicity lead to increase HDAC enzyme inhibitory activity.

MEDI 205

H2O2-inducible DNA cross-linking agents: Targeted anticancer prodrugs

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The major concern for anticancer chemotherapeutic agents is the host toxicity. The development of anticancer prodrugs targeting the unique biochemical alterations in cancer cells is an attractive approach to achieve therapeutic activity and selectivity. We designed and synthesized a new types of arylboronic ester prodrug that can be activated by high level of reactive oxygen species (ROS) found in cancer cells to form quinone methide (QM) intermediates and release the chemotherapy agent simultaneously. The activation mechanism was determined by NMR analysis. The activity and selectivity of these prodrugs towards ROS was determined by measuring DNA interstrand crosslinks and/or DNA alkylations. To the best of our knowledge, this is the first example of H2O2-activated anticancer prodrugs.

MEDI 206

Synthesis of heterocyclic aryl sulfones and the investigation of their potential therapeutic uses

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Sulfones are compounds that have activity against many diseases such as; malaria, tuberculosis, leprosy, HIV; and consequently are highly desirable lead molecules for research. This laboratory prepared amino aryl sulfones through an acid catalyzed rearrangement of a sulfonanilide to a sulfone. This synthesis method provided an easy access to sulfone products.

High throughput screening with the Shape Signature program have identified three potential targets for the compounds used; antibacterial, antitumor, and anti-pain (analgesic). This program compares lead molecules to a database of therapeutic ligands based on their shape. This program allows the discovery of new candidate molecule leads for ligands that are based on shape instead of structural likeness.

This presentation will involve the synthesis of carbazole, imidostilbene, and imidodibenzyl sulfone and the discovery of new drug targets by Shape Signature. Future work will be to identify, synthesize and assay screening of derivatives of active lead molecules.

MEDI 207

Synthesis and adenosine receptor binding studies of some novel hetero-fused pyrimidines

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The *hetero-fused* thieno/pyrazolo/pyrrolopyrimidines have been identified as new lead compounds in drug discovery for adenosine modulation. To our research interest we have synthesized some novel *hetero-fused* [2-substituted pyrrolo(2,3-*d*)pyrimidines]. The affinity of synthesized compounds towards adenosine A_1 & A_{2a} was evaluated through radioligand binding studies. The compounds have been designed as bioisosters of hetero-fused pyrazolo/ thieno pyrimidines to develop selective adenosine receptor antagonists. Based on reports, fused pyrazolo/ thieno pyrimidines have been found to interact with a variety of P_1 purinergic receptors (adenosine receptors) in the human body, including a number of different subtypes i.e., A_1, A_{2a}, A_{2b}, $A_{3.}$ As a result of their significant potential as therapeutics all the designed compounds were synthesized in good yields following eco-friendly microwave-assisted organic synthesis and screened *in vitro* for their affinity as well as selectivity. All these compounds have affinity towards adenosine A_1 & A_{2a} receptors significantly.

MEDI 208

Accelerating your synthesis screening, optimization and sample preparation work by automated, high-throughput solutions using disposable reactors

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The use of our glass array reactors based automated synthesis platforms has been very successfully proven over more than 10 years in the library synthesis, selective catalysis and optimisation of synthesis sequences. The platform is very modular and can be used for a wide range of different chemistries (from synthesis to work-up and analytical sample preparation). Chemspeed has further developed this platform and now introduces the new ISYNTH concept having the same ability as the former glass array reactors but using flexible disposable formats.

By using selected examples, from library synthesis, catalysis and analytical sample preparation, this presentation will show how various challenging parallel workflows have been successfully automated and how the new ISYNTH concept can be implemented.

Examples will be focusing on:

- Compound library synthesis for protein-protein interaction studies

- Synthesis of oxazolidinone including automated resin dispensing and on-line cleavage

- Automated preparation of a library of potential GLUT 5 carrier inhibitors

- Synthesis and screening (asymmetric hydrogenation) of supramolecular catalysts

- Sample preparation for the determination of relative hepatic gluconeogenisis by

2H-NMR

MEDI 209

Inhibition of COX-2 and ASIC-3 by structural analogs of diclofenac

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Diclofenac is a non-steroidal anti-inflammatory drug (NSAID) whose actions are mediated by inhibition of cyclooxygenase-2 (COX-2, IC50 < 1 µM). Diclofenac has also been shown *in vitro* to inhibit the sustained current of acid-sensing ion channel 3 (ASIC-3), a sodium-conducting ion channel that is thought to be involved in pain signaling, when the channel is activated by acidification to pH 4 (IC50 = 92 µM). Because inhibition of ASIC-3 may represent a new approach to pain pharmacotherapy, we synthesized diclofenac analogues in which modifications were made to the acetic acid group in an attempt to identify a strong ASIC-3 inhibitor with low activity toward COX-2. The synthesis of the diclofenac analogues will be described as well as the results of their use in inhibition assays against COX-2 and ASIC-3.

MEDI 210

Development of novel $P2X_3$ / $P2X_2/_3$ receptor antagonists for the treatment of pain and urinary dysfunction

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We report on the optimisation strategy applied to a tetrahydropyrido[4,3-d]pyrimidine dual $P2X_3$ / $P2X_{2/3}$ receptor antagonist hit, identified from a purinergic focused HTS campaign. SAR and DMPK parameters, including aqueous solubility; protein binding; oral bioavailability and hERG blockade were optimised and the key $P2X_3$ / $P2X_{2/3}$ SAR presented. Several advanced Lead compounds were identified that underwent detailed electrophysiology, DMPK and *in vivo* efficacy testing (inflammatory and neuropathic pain). Here we present the data for one such Lead Compound that warrants further

Early Development Candidate (EDC) profiling and continued evaluation as a potential treatment of pain and urinary dysfunction.

MEDI 211

Development of $GABA_B$ receptor positive modulators for nicotine dependence

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A large body of clinical and experimental studies in humans supports the hypothesis that medications enhancing GABA neurotransmission, may be effective in treating various aspects of drug dependence, including cocaine, alcohol, and nicotine addiction.[1] However, direct agonists of the $GABA_B$ receptor (e.g., baclofen) cause severe side effects, such as sedation, tolerance, and muscle relaxation.[2] We have proposed to develop novel $GABA_B$ positive allosteric modulators as an alternative approach, which should potentiate receptor activity only in presence of endogenous GABA and therefore exclude side effects associated with GABA agonists.

Using techniques of combinatorial chemistry, organic synthesis, and *in situ* click chemistry, we are developing $GABA_B$ positive allosteric modulators based on pyrimidine and triazine scaffolds. *In vitro* pharmacological evaluation of candidate compounds is done by four high throughput functional assays developed at Scripps Florida (using cAMP, Ca^{2+} mobilization, ERK phosphorylation, and cellular impendence as readouts) as well as backscattering interferometry[3] in our laboratory to evaluate interactions with membrane receptors. These sophisticated methods give us an excellent profile of the potency, efficacy, and selectivity of our novel agents against $GABA_B$ receptors. *In vitro* and *in vivo* drug metabolism and pharmacokinetic properties of high priority compounds are then investigated and best candidates are selected for further investigation in animal models of nicotine dependence.

This effort involving three institutions (Scripps La Jolla, Scripps Florida, and UCSD) has resulted in several new lead structures that show excellent properties in functional assays. Further optimization and development of these compounds is ongoing.

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MEDI 212

DMPK driven optimisation of potent histamine H3R antagonists for the treatment of CNS disorders

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We report on a process that has supported the optimisation of highly potent Histamine H3 antagonists using a directed DMPK driven approach. Detailed DMPK experiments were performed; CYP reaction phenotyping studies identified a potential human CYP2D6 liability with one of three Early-Development Candidates (EDC-1). This culminated in a cross-over dog PK study (with / without quinidine, a selective hCYP2D6 / dCYP2D15 inhibitor) to determine the involvement of non-hepatic mechanisms. The DMPK studies support the hypothesis that CYP2D6 is likely to be the major route of clearance for EDC-1 in man.

The seamless integration of DMPK and medicinal chemistry de-risked the H3 program through the timely cessation of EDC-1, and ultimately led to the nomination of two Pre-Development Candidates (PDC).

MEDI 213

Molecular basis of biased signaling in β_2-adrenergic receptor by ^{19}F-NMR

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Extracellular ligand binding to G protein coupled receptors (GPCRs) modulates signaling by changing the conformational states of the G-protein and β-arrestin intracellular binding sites more than 30Å away. Using site specific ^{19}F NMR studies of β_2-adrenergic receptor and its ligand complexes, we observed that the cytoplasmic ends of both helix VI and helix VII can be found in two major conformational states. Changes in NMR spectral line reveal that agonist binding shifts the equilibrium towards an activated state conformation in helix VI and to a lesser extent in helix VII. At the same time, β-arrestin biased ligands predominantly impact the conformational state of helix VII. Such differential changes in equilibrium of helices VI and VII suggests a structural model of biased signaling and partial agonism of pharmacologically relevant ligands. In addition, changes in conformational equilibria of the receptor correlate with the chemical structures of ligands bound. These data provide the first steps to decoding the ways receptor translate chemical space of the ligands to dynamics of intracellular surface.

MEDI 214

Human H1 receptor studies: Homology model validation, docking and mutagenesis

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The human histamine H_1 G-protein coupled receptor (GPCR) is an important drug target for immunological disorders. A homology model of the human H_1 GPCR was developed based on the crystal structure of the human β_2 adrenoceptor (β_2AR). Ligand docking studies and molecular dynamics (MD) simulations at the human H_1 receptor model were undertaken and validated by experimental results from binding studies using wild type as well as novel (Y3.33A, W4.56A, F5.47A, W6.48A, Y6.51A), and known (D3.32A, F6.52A, F6.55A, Y7.43A) point-mutated human H_1 receptors. Differences in ligand binding modes at the human H_1 model correlated to differences in ligand binding affinities at the human H_1 receptor. The β_2AR-based human H_1 homology model was compared to the recently reported crystal structure of the human H_1 receptor at 3.1 Å resolution (PDB code 3RZE): superposition of alpha-carbons in transmembrane domains of the human H_1 model with 3RZE gave RMSD = 2.91 Å, indicating the β_2AR structure is an accurate template for human H_1 GPCR homology modeling.

MEDI 215

Protease activated receptor 2 antagonists

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Protease activated receptor 2 (PAR2) is a GPCR that is activated mainly by serine proteases. It is associated with numerous inflammatory, metabolic and cancer conditions. Since multiple extracellular proteases exert intracellular effects through a common mediator on the cell surface (PAR2), we investigate whether antagonist blockade is an effective therapeutic strategy for disease intervention.

We report the discovery and properties of small molecule ligands that are selective for PAR2, display pathway-specific biased antagonism/agonism, and are orally active. Gene expression and pathway-dependent intracellular protein regulation are used to define PAR2 signaling in human cells. We find that oral administration of PAR2 antagonists and biased agonists to rodents produces activity across a diverse range of inflammatory, metabolic and other disease models. Our focus has been on dissecting influences of molecular components of PAR2 ligands on PAR2 activation, intracellular pathway modulation, and in vivo outcomes relevant to combating disease.

MEDI 216

Being different: Industrial-academic alliances for individual approaches to computer-aided drug design

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Computational tools are nowadays frequently applied at the early stages of medicinal chemistry research. They help to downscale the millions of compounds practically available for screening and to prioritize small compound series by predicting activity and ADME profiles computationally. Although many professional software solutions exist, they often do not meet the individual needs perfectly. Furthermore, software tools applied on similar targets and similar compound data sources may result in similar conclusions in competing pharmaceutical research endeavors. Since the main interest of pharmaceutical companies is new drugs rather than software, the development of novel, innovative and individual computational tools is an ideal field of academic-industrial research alliances. At the same time, the academic partner profits from the extensive application knowledge of the industrial partner. Here, we will report on several successful collaborations with pharma partners that resulted in innovative and effective new computational approaches, some of them now marketed globally.

MEDI 217

Novel tricks for legacy tasks: Probing the reaction mechanism by mass spectrometric identification of supramolecular adducts

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Reactions are the heart and soul of chemistry.[1] Pushing the arrow: understanding the reaction mechanisms is a very tactful task as it offers us insights into how molecules react, enable us to manipulate the course of known reactions, aid us in predicting the course of known reactions using new substrates, and help us to develop new reactions and reagents. In order to understand and write reaction mechanisms, trapping of reactive intermediates and its characterization by various analytical techniques has become routine practice to validate the proposed mechanism. Among various analytical techniques, mass spectrometry (MS) is gaining priority as an analytical tool to analytical/organic/pharmaceutical chemists and biologists due to its appealing features like ease of sample preparation, operational simplicity and ease of spectral interpretation. Mass spectrometric technique holds the place at the crucial stage of analysis such as structural confirmation, purity determination, and conversion. Often interpretation/prediction of the desired product depends upon the understanding of the reaction mechanism. The MS techniques particularly ESIMS is a solution provider towards this end through 'ion fishing' of charged species as reactive intermediates.[2] However, revealing reaction pathways that proceed through noncovalent short lived species remains the challenging task and MALDI and ESI MS techniques are being increasingly used[3-5] for the purpose that adds a new dimension to analytical techniques. This presentation will summarise about a special application of ESI-MS to 'fish' the noncovalent complex/ion directly from solution phase to gas phase that gives insight

into the reaction mechanism and proves it on the basis of trapped reactive intermediate.[6]

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MEDI 218

Hydrogel/calcium phosphate nanocomposites with high mechanical strength: Aiming to bone substitute materials

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In order to improve the mechanical properties of the hybrid material, peroxidized micelles (pMIC) hydrogels with high mechanical strength was chosen as a matrix to make nanocomposites adopting electrophoresis approach. A new type of bone-like nanocomposites based on polyacrylamide (PAAm) and nano-sized hydroxyaptite (HAP) has been developed. Compared with conventional PAAm hydrogels, the nanocomposite hydrogel has higher ultimate elongation, fracture stresses and compressive strengths. Moreover, these nanocomposite hydrogels have excellent shape recoverability as well. It is believed that the mechanical properties are enhanced owing to the interfacial energy of the polymer matrix and the uniformly dispersed nanoparticles. Since HAP and hydrogels are both biologically compatible, these nanocomposite hydrogels would have potential applications in tissue engineering.

MEDI 219

Current and future prospects for novel therapeutics for Alzheimer's disease

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Alzheimer's disease (AD) is the leading cause of dementia worldwide and since age is the most significant risk factor for the disease, the incidence of AD is expected to triple to over 100 million affected by 2050. The amyloid hypothesis of AD states that the accumulation of the toxic amyloid-β peptide (Aβ) induces neuronal dysfunction, leading to brain atrophy, dementia and death. Several therapeutic modalities have been pursued intending to reduce the Aβ burden in AD brain including inhibition of synthesis, acceleration of clearance and disruption or inhibition of aggregation. Recent data from

clinical trials addressing each of these modalities will be reviewed, with a view towards anticipating the results of ongoing clinical studies in order to provide a sense of when the amyloid hypothesis might be fully tested. A brief overview of tau dysfunction in AD will be provided and the current status of tau approaches and therapeutics will be summarized. Finally the status and challenges of symptomatic approaches will be reviewed.

MEDI 220

Microtubule-stabilizing agents as potential treatment for Alzheimer's disease and related tauopathies

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Neurodegenerative tauopathies, which include Alzheimer's disease (AD), are characterized by the presence of insoluble aggregates comprised of hyperphosphorylated
tau proteins. Tau is an endogenous MT-stabilizing agent that is highly expressed in the axons of neurons. The MT-stabilizing function of tau is essential for the axonal transport of proteins, neurotransmitters and other cellular constituents. Under pathological conditions, tau becomes sequestered into insoluble aggregates and no longer can bind to
and stabilize MTs. This phenomenon triggers axonal transport deficits with deleterious consequences for the affected neurons. As a result, one potential strategy for the treatment of AD and related tauopathies is to employ brain-penetrant MT-stabilizing agents that could restore/maintain an effective axonal transport machinery by compensating for the loss of normal tau function. Toward this end, comparative pharmacokinetic studies involving MT-stabilizing agents from different classes of natural products identified epothilone D (EpoD) as a promising candidate. In a preventative study with tau transgenic mice (PS19), weekly doses of EpoD (1 or 3 mg/kg, i.p.) for a period of 3 months resulted in improved MT-density, axonal integrity and cognition in compound-treated animals, without overt signs of side-effects. Equally important, similar outcome was observed in an interventional study in which weekly doses of EpoD (0.3 or 1 mg/kg, i.p.) were administered to aged PS19 mice with existing tau pathology. Collectively, these results suggest that brain-penetrant MT-stabilizing agents hold promise for the treatment of AD and related tauopathies.

MEDI 221

5HT4 partial agonists to improve cognitive dysfunction in learning and memory disorders: Discovery of PF-4995274

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Evidence suggests 5-HT4 receptor agonists act as pro-cognitive agents and may provide therapeutic relief for cognitive impairments associated with Alzheimer's disease (AD). A hallmark of AD is a reduction in acetylcholine levels (ACh) resulting from a loss of cholinergic neurons which contributes to cognitive impairment. 5-HT4 agonists reportedly increase brain ACh levels and reverse memory deficits induced by cholinergic antagonists in behavioral studies. In addition, 5-HT4 receptor agonism is reported to increases hippocampal theta activity; a response that is modulated by ACh and linked to several cognitive, memory and attentional processes. Herein, we report the discovery and characterization of the 5-HT4 receptor agonist PF-04995274.

MEDI 222

Development of 2-aminoquinolines as potent inhibitors of BACE1

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Alzheimer's disease (AD) is a progressive neurological disease of the brain that leads to the irreversible loss of neurons and dementia. The accumulation of the beta-amyloid peptide (Ab) in the brains is a key early initiating event in the pathogenesis of this

disorder. Ab is produced by sequential endoproteolytic cleavage of amyloid precursor protein (APP) by beta-secretase (BACE1) and gamma-secretase. BACE1 is responsible for the initial cleavage of the APP and is believed to be the rate limiting step in Ab production. Thus, BACE1 is considered to be a prime therapeutic target for the development of disease-modifying therapies for AD. There are significant challenges in designing low molecular weight, brain penetrant, and potent BACE1 inhibitors. We used a fragment-based lead generation approach and identified 2-aminoquinoline as an initial fragment hit that displayed potency in the millimolar range with excellent ligand efficiency. Structure guided evolution of this fragment using X-ray crystallography expedited the SAR development for potent inhibitors. Further elaboration on physicochemical properties required for CNS penetration led to potent BACE1 inhibitors that lower CSF Ab levels in rat.

MEDI 223

Central inhibition of Alzheimer's beta-secretase in humans: Proof of concept with LY2811376

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Central deposition of amyloid-β peptide (Aβ) is critical in Alzheimer's disease (AD) pathogenesis. Aβ generation is initiated when β-secretase (BACE1) cleaves the amyloid precursor protein. For more than a decade BACE1 has been a prime target for designing drugs to prevent or treat AD. However, development of such agents has turned out to be extremely challenging with major hurdles in cell penetration, oral bioavailability/metabolic clearance, and brain access. Using a fragment-based chemistry strategy, we have generated LY2811376, the first orally available non-peptidic BACE1 inhibitor that produces profound Aβ-lowering effects in animals, and importantly, translates into strong and long-lasting Aβ reduction in human CNS. Our studies with LY2811376 demonstrate that BACE1 is a tractable small-molecule target with promise for the development of AD therapeutics.

MEDI 224

Discovery and development of a novel class of gamma secretase modulators

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Modulation of gamma secretase to selectively reduce Aβ42 production is a promising approach to disease modifying therapy for AD. Using a targeted screening approach, Satori has discovered a novel structural class of gamma secretase modulators (GSMs). This presentation will focus on the lessons learned during our lead optimization program that have led to the discovery of potent and selective GSMs that exhibit compelling in vitro and in vivo pharmacokinetic profiles.

MEDI 225

Brief history of DGAT1

***Robert V. Farese, Jr.**, bfarese@gladstone.ucsf.edu.Gladstone Institute of Cardiovascular Disease, University of California, San Francisco, California, United States*

The ability to store energy in the form of triacylglycerols is a fundamental process common to eukaryotic cells and organisms. Acyl CoA:diacylglycerol acyltransferase 1 (DGAT1) is one of the two mammalian enzymes that catalyze triacylglycerol synthesis. Dr. Farese will review the basic biology of DGAT1, from its discovery to the most recent studies.

MEDI 226

Discovery of A-970781 as a potent, safe, and orally efficacious inhibitor of acyl CoA: Diacylglycerol acyltransferase 1

***Philip R. Kym**, phil.kym@abbott.com, Vince C.S. Yeh, David W.A. Beno, Sevan Brodjian, Michael E. Brune, Steven C. Cullen, Brian D. Dayton, Madhup K. Dhaon, Hugh D. Falls, Ju Gao, Nelson Grihalde, Philip J. Hajduk, T. Matthew Hansen, Andrew S. Judd, Andrew J. King, Russell C. Klix, Kelly J. Larson, Yau Y. Lau, Kennan C. Marsh, Scott W. Mittelstadt, Dan Plata, Michael J. Rozema, Jason A. Segreti, Eric J. Stoner, Martin J. Voorbach, Xiaojun Wang, Xili Xin, Gang Zhao, Christine A. Collins, Bryan F. Cox, Regina M. Reilly, Andrew J. Souers.Global Pharmaceutical Research and Development, Abbott Laboratories, Abbott Park, IL 60064, United States*

An HTS against human DGAT-1 lead to the identification of a novel pyrazolo[1,5-a]pyramidin-7-amine pharmacophore that was subsequently optimized to afford the potent, selective and orally bioavailable compound A-970781. Oral administration at dose $\geq$ 0.03 mg/kg significantly reduced postprandial triglycerides in mice following an oral lipid challenge. Further assessment in both acute and chronic safety pharmacology abd toxicology studies demonstrated a clean profile up to high plasma levels, thus

culminating in the nomination of A-970781 as a development candidate for the treatment of postprandial hypertriglyceridemia and other metabolic disorders.

MEDI 227

Discovery of a novel class of diacylglycerol acyltransferase 1 (DGAT1) inhibitors

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DGAT 1 is a key enzyme involved in the final step of triglyceride synthesis. Modulation of triglyceride metabolism by inhibiting DGAT1 has been proposed as a therapeutic approach for the treatment of a diverse array of cardiovascular and endocrine disorders. We will discuss the discovery of a novel class of potent DGAT1 inhibitors and their applications toward the treatment of obesity and diabetes.

MEDI 228

Optimisation of a series of pyrazinecarboxamide DGAT1 inhibitors leading to a clinical candidate

***Alan Birch**, Alan.Birch@astrazeneca.com, Linda Buckett, Jan W. Eriksson, Petra Johannesson, Charles O'Donnell, Andrew Turnbull. Alderley Park, AstraZeneca, Cheshire, United Kingdom*

In recent years DGAT1 inhibitors have come to the fore as potential therapeutic agents for the treatment of diabetes, obesity and dyslipidaemia with compounds from several companies entering clinical trials. We will describe the generation and optimisation of a series of pyrazinecarboxamide DGAT1 inhibitors which resulted in the discovery of a clinical candidate molecule.

MEDI 229

Discovery of a potent, orally efficacious DGAT1 inhibitor that improves glucose tolerance and lowers weight in animal models of obesity

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Diacylglycerol acyltransferase-1 (DGAT-1) catalyzes the final step of triglyceride formation by acylation of diacylglycerol with acyl-coenzyme A. DGAT1 (-/-) mice demonstrate resistance to weight gain on high fat diets, enhanced insulin sensitivity and reduced hepatic triglyceride levels and therefore represents a potential approch for the treatment of obesity, dyslipidemia and metabolic syndrome.

We report here, the identification of a high-throughput screening hit and the subsequent lead expansion efforts that developed into the discovery of potent class of carboxylic acid derivatives of 2-phenyl-5-trifluoromethyloxazole-4-carboxamides. Efforts then directed toward improving biopharmaceutical properties, as well as minimizing early *in vitro* safety issues, resulted in the emergence of RO5131723 as a lead candidate. *In vivo*, RO5131723 demonstrated dose dependent inhibition of weight gain in diet induced obese (DIO) rats when dosed for 21 day. Additionally, this compound demonstrated improved glucose tolerance as measured in an oral glucose tolerance test (OGTT) in rats.

MEDI 230

Discovery of a DGAT1 inhibitor with robust suppression of postprandial triglyceride levels in humans

***Michael H Serrano-Wu**, michael.serrano-wu@novartis.com, Youngshin Kwak, Gary Coppola, Cornelia Foster, Tom Gilmore, Yongjin Gong, Guo He, Ying Hou, Aaron Kantor, Jingzhou Li, Wosenu Mergo, Katsumasa Nakajima, Alan Neubert, Branko Radetich, Bryan Stroup, MooJe Sung, Paul Szklennik, Ritesh Tichkule, Lihua Yang, Taeyoung Yoon, Yanyi Zhu, James Wareing, Vinayak Hosagrahara, Monish Jain, Ricardo Chatelain, Renee Commerford, Beatriz Dardik, Dan Meyers, Brian Hubbard.Novartis Institutes for BioMedical Research, Cambridge, MA 02139, United States*

Acyl CoA: diacylglycerol acyltransferase1 (DGAT1) is a ubiquitously-expressed multifunctional enzyme that catalyzes the terminal step of triacylglycerol biosynthesis. One of the signature pharmacodynamic effects of DGAT1 inhibition is the suppression of circulating triglycerides following oral ingestion of lipid, owing to the high intestinal expression of DGAT1 and its role in dietary fat absorption. We describe here medicinal chemistry efforts to identify several unique DGAT1 inhibitor profiles. Preclinical and clinical data which support the development of DGAT1 inhibitors will be presented.

MEDI 231

CETP: At the crossroads of lipoprotein metabolism

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Cholesteryl ester transfer protein (CETP) mediates transfer and exchange of cholesteryl esters (CEs) and triglycerides between plasma lipoproteins and plays an important role in lipoprotein metabolism. Notably, CETP facilitates the transfer of tissue-derived cholesteryl esters from HDL to apoB-containing lipoproteins that are removed from plasma by hepatic receptors. This property suggests that reduction in CETP activity may retard "reverse cholesterol transport" and hence increase cardiovascular disease (CVD) risk. On the other hand, there is also reason to expect that reduction of CETP activity, by raising HDL levels, would lead to reduced CVD by virtue of HDL's capacity to stimulate cholesterol efflux from arterial macrophages, as well as its anti-inflammatory, antioxidative, and antithrombotic properties. Genetic studies have yielded inconsistent evidence for the relation of reduced CETP activity to lower CVD risk. Thus, the potential impact of pharmacological reduction of CETP activity on CVD awaits the outcome of ongoing randomized trials.

MEDI 232

Fluorophilic pharmacophore for cholesteryl ester transfer protein inhibition: Discovery and demise of torcetrapib

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Inhibition of cholesteryl ester transfer protein (CETP) has provided a compelling target for the treatment of cardiovascular diseases given to its promising effects on plasma lipoprotein levels. Events surrounding the discovery, development and discontinuation of torcetrapib will be described.

MEDI 233

Unique properties of dalcetrapib a cholesteryl ester transfer protein (CETP) modulator associated with parameters of HDL functionality: Preclinical and clinical evidence

***Eric J Niesor**, eric_j.niesor@roche.com. Cardiovascular & Metabolic Diseases, F. Hoffmann-La Roche Ltd, Basel, Switzerland*

CETP activity plays a major role in high-density lipoprotein (HDL) remodelling, inhibition of cholesteryl ester (CE) transfer from HDL to low-density lipoprotein (LDL)/Very-low-density lipoprotein (VLDL) and reproducibly increases HDL-cholesterol (HDL-C). Torcetrapib inhibits CE transfer from HDL_3 to LDL/VLDL, from HDL_3 to HDL_2 and pre-β-HDL formation. In contrast dalcetrapib inhibits HDL to LDL/VLDL but not HDL_3 to HDL_2 CE transfer. Dalcetrapib thus preserves CETP-induced pre-β-HDL formation, and promotes ATP-binding cassette transporter A1 (ABCA1)-mediated cholesterol efflux from macrophages *in vitro*. Evaluation of the effect of both compounds on macrophage

to feces reverse cholesterol transport (RCT) in hamsters demonstrated a dose-dependent increase in RCT with dalcetrapib. Plasma pre-β-HDL levels following dalcetrapib treatment and potential biomarkers of ABCA1-mediated pre-β-HDL lipidation were also assessed in hamsters and human.

MEDI 234

Discovery and development of anacetrapib, a potent and orally active CETP inhibitor

***Amjad Ali**, amjad_ali@merck.com. Department of Medicinal Chemistry, Merck Research Laboratories, Rahway, NJ 07065, United States*

Plasma levels of high-density lipoprotein (HDL-C) cholesterol are inversely related to the incidence of coronary heart disease. The beneficial effects of HDL-C are thought to arise in part from its participation in reverse cholesterol transport (RCT), the process by which HDL-C shuttles cholesterol out of the atherosclerotic plaque to the liver for metabolism or elimination.The Merck CETP inhibitor anacetrapib has recently been shown to have robust effects on HDL-C and LDL-C in a Phase III clinical study (DEFINE trial). Sustained effects over 18 months were observed in patients with coronary heart disease and no adverse effects on blood pressure, electrolytes, and aldosterone levels were observed. The long term safety and efficacy of anacetrapib is being evaluated in a 30,000 patient global clinical outcomes study that is currently enrolling (REVEAL trial). The discovery, pre-clinical and clinical evaluation of anacetrapib will be described in detail.

MEDI 235

Discovery and SAR of the benzazepine based cholesteryl ester transfer protein inhibitor, evacetrapib

***Nathan Mantlo**, Mantlo_Nathan@lilly.com, Guoqing Cao, Todd Fields, Xiaodong Wang, Xinchao Chen, Christopher L. Cioffi, Sean R. Dinn, Maria-Carmen Fernandez, Ana I. Mateo, Ana Escribano, Eva M. Martin de la Nava, Saravanan Parthasarathy, Matthew W. Giese, Matthew Carson, Thomas P. Beyer, Sandra L. Cockerham, Karl Kovach, Stephanie Sweetana, Anthony Borel, Timothy M. Jones, Ellen Annette Cannady.Eli Lilly & Co., United States*

Cholesteryl ester transfer protein (CETP) is a plasma glycoprotein that mediates the transfer of cholesteryl ester from high-density lipoprotein (HDL) to low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) with a reciprocal exchange of triglyceride. CETP inhibitors have been shown to raise HDL-cholesterol in humans and slow the progression of atherosclerosis in animal models. As a part of our continued search for therapies targeting HDL-C elevation, we discovered a series of benzazepines as potent CETP inhibitors. This talk will cover the *in vitro* and *in vivo* SAR of this series leading to the discovery of evacetrapib, currently in phase phase II clinical development.

MEDI 236

Metabolic clearance by CYP450 metabolism

***Larry Wienkers**, wienkers@amgen.com. Amgen, United States*

Drug metabolism often represents a major source of inter-individual variability in drug response. A root case for differences in drug metabolism is due to an alteration of cytochrome P450 (CYP) enzymatic activity. Cytochrome P450 enzymes, in particular CYP3A4, are responsible for the bulk of the metabolism of known drugs in humans. As a consequence, changes in the catalytic activity of these enzymes by co-administered drugs can lead to variability in drug exposure. Today the evaluation of the potential of a drug candidate to alter CYP enzyme activity represents an important part of pharmaceutical drug Development process. The goal of these studies are to predict the magnitude of clinical drug-drug interactions (DDI) involving the modulation of the activities of these enzymes. The current presentation will examine ADME activities beyond the common strategies and decision making processes for the assessment of DDI risk in pharmaceutical development.

MEDI 237

Aldehyde oxidase in drug research

***R. Scott Orbach**, r.scott.obach@pfizer.com. Pfizer, Inc., United States*

Aldehyde oxidase (AOX) is a molybdenum cofactor containing enzyme that is capable of oxidizing aldehydes, imines, and aromatic azaheterocyclic compounds. Some basic aspects of its biochemistry will be reviewed. It is different from aldehyde dehydrogenase, a family of enzymes that metabolizes aldehydes. AOX has generally not been a focus in drug research, however, an increase in the prevalence in the use of aromatic azaheterocyclics as substituents in drug design has caused an increase in the importance of AO. But when left unexamined in drug design, an impact of AO on the clearance of a new chemical entity can result in an unexpectedly low exposure in humans. Research we have done in order to improve our understanding of this enzyme and its role in drug disposition will be described. We have developed an in vitro approach whereby human clearance due to AO catalyzed metabolism can be estimated by comparison to known compounds. Additionally, we have recently developed a method wherein the relative contribution of AO to total metabolism can be estimated using human hepatocytes. Finally, strategies to reduce or remove AO mediated clearance will be discussed.

MEDI 238

Roles of transporters in the hepatobiliary and renal elimination of drugs

***Xiaoyan Chu**, xiaoyan_chu@merck.com. Merck & Co., Inc., United States*

Drug transporters can be major determinants in the pharmacokinetic, safety and efficacy profiles of drugs. For example, transporters expressed on liver and kidney play an important role in directional transport of drugs across hepatocytes and renal proximal tubule, therefore, involve in active hepatic and renal elimination. In many cases, transporter-mediated uptake and efflux can be the rate-determining step for the clearance and the exposure of drugs in the liver and kidney. These transporters open the possibility to selectively deliver a drug to the liver or kidney and to control the elimination process. However, genetic polymorphisms in transporters may cause inter-individual variability in drug exposure. Also, inhibition of these transporters may result in clinically significant drug-drug interactions (DDIs). In this presentation, I will focus on recent progress on evaluating the involvement of transporters on hepatic and renal clearance of drugs and predicting transporter related-DDIs.

<h3> </h3>

MEDI 239

Curse and blessings of active metabolites

***Aberra Fura**, aberra.fura@bms.com. Bristol-Myers Squibb, United States*

Active metabolites could have physicochemical, pharmacokinetic, pharmacological and toxicological properties that are different from those of the parent drugs. As a result their contribution to the overall therapeutic and adverse effects of drugs could be significant. With timely recognition of the role of active metabolites one can 1) have better understanding of the mechanism of action of drugs and put nonclinical and clinical pharmacodynamic(PD), pharmacokinetic(PK) and toxicological data in perspectives; 2) extrapolate animal PD data to humans; 3) have appreciation of any potential mechanism based toxicity associated with active metabolites; 4) use the information for optimizing leads, based on structure-activity relationship (potency, metabolic stability, solubility etc.); 5) develop active metabolites as drugs in its own right.

MEDI 240

Dealing with reactive metabolites

***Dominc Williams**, DOM@liverpool.ac.uk. MRC Centre for Drug Safety Science, United Kingdom*

Adverse drug reactions (ADRs) are a complication of drug therapy and impede drug development. Excessive drug accumulation and/or formation of chemically reactive metabolites are implicated in off-target ADRs. Studies with toxicophores, (eg acetaminophen) have helped to define the response of target organs to chemical stress and drug bioactivation with differing biological outcomes, including adaptation, apoptosis, necrosis, inflammation and activation of the innate and adaptive immune systems. Idiosyncratic reactions are rare but can be life-threatening. This can lead to

withdrawal of an otherwise effective therapeutic agent. The fear of such reactions occurring at the post-licensing stage is a major contribution to drug attrition. There are no accepted methods for the identification of drugs which may cause hypersensitivity in man, during preclinical drug evaluation. Predicting such reactions in early drug development requires an integrated understanding of the chemical and biological events underlying adverse drug reactions in patients.

MEDI 241

Oxidative and reductive prodrug activation strategies

***Longqin Hu**, longhu@rutgers.edu. Department of Medicinal Chemistry, Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey, Piscataway, NJ 08854, United States*

Prodrugs can be used to overcome undesirable pharmacokinetic as well as pharmaceutical properties that hinder the further development of pharmacologically active molecules into clinical drugs. While enzyme-catalyzed hydrolysis is a common activation reaction, oxidation and reduction have also been used to activate various prodrugs. This talk will briefly review the design strategies using oxidation and reduction in prodrug activation including an overview of the endogenous and exogenous enzymes and the various reactions and release mechanisms used in the oxidative and reductive activation of prodrugs. There are a number of these prodrugs being used in the clinic including the blockbuster blood thinner clopidogril, the long known anticancer alkylating agents cyclophosphamide and procarbazine, and the colon-targeting anti-inflammatory drugs balsalazine, ipsalazide, olsalazine, and sulfasalazine. Also reviewed are some current research efforts using oxidation and reduction to activate prodrugs as a strategy to improve target selectivity of chemotherapeutic agents for cancer and microbial infections.

MEDI 242

Antibacterial resistance: Recent progress

***Norton P. Peet**, npeet@microbiotix.com, Joseph Guiles, Chester A. Metcalf, Amy Anderson, John D. Williams, Richard Lee. Microbiotix Inc., United States*

Drug resistance is defined as the *reduction in effectiveness of a drug* to cure a disease or improve patient symptoms. Commonly, the term is used in the context of diseases caused by pathogens, e.g., bacteria, fungi, parasites and viruses, where it is an enormous challenge. This symposium will focus on drug resistance as it applies to antibiotics.

In a clinical setting, drug resistance for antibiotics or antibacterial agents is defined as the point at which administration of the drug can no longer safely treat the disease state due to an induced change in the drug target or an inability of the drug to reach the

target. With an antibacterial agent, clinical resistance occurs when the minimum inhibitory concentration (MIC) of the drug, for a given microbial strain, exceeds that concentration of drug that can safely be administered. Resistance to an antibiotic drug can arise by (1) mutation of the gene (or gene cluster); (2) by acquisition of extrachromosomal DNA, or a transposable plasmid, that carries the resistance gene or genes; (3) upregulation of the target; or (4) upregulation of an efflux mechanism. Drug resistance has become a huge problem for clinicians; the challenge is passed to scientists working on new antibacterial agents to find new design approaches.

This symposium will highlight different classes of antibacterial agents that are in various stages of development. Focus will be on medicinal chemistry, the development of structure-activity relationships, and approaches to drug design that lead to agents that are less prone to resistance development.

MEDI 243

Chemical biology of C diff agents - what's new?

Joseph Guiles[1]*, joe.guiles@cedarburghauser.com, Thale Jarvis*[2]*, Urs Ochsner*[2]*, Nebojsa Janjic*[2]*. (1) Cedarburg Hauser, United States (2) Crestone Inc., United States*

Both chemical biology and chemogenomics are strategies being employed for the identification of new lead structures. In particular for clostridium difficile infection (CDI) there is a desire to find agents that work by new modalities (e.g. target specific, systems biology). This lecture will present an update on chemical agents being studied for the treatment of CDI from late stage pre-clinical to commercial stage. Focus will be on presenting a chemical biology and chemogenomics perspective of older and newer agents including Fidaxomicin and CRS3123 (formerly REP3123).

MEDI 244

Discovery of new antibacterial agents targeting gram-positive and gram-negative infections

Chester A. Metcalf*, chester.metcalf@cubist.com, Ed Campanaro, Laurent Chesnel, Jason Cross, Ian Friedland, Yong He, Karen Howland, Timothy Keutzer, Carmela Mascio, Debra Mozill, Hernando Patino, Rob Pawliuk, Jared Silverman, Judith Steenbergen, Grace Thorne, Uschi Stoutenburgh, Ning Yin. Cubist Pharmaceuticals Inc., United States*

Cubist was founded in 1992 and markets CUBICIN® (daptomycin for injection), the first IV antibiotic from a class of antibacterials called lipopeptides. Our overall strategy is to discover, develop, and commercialize products that address unmet medical needs in the acute care environment. This presentation will discuss recent data from two of our clinical pipeline compounds which are being evaluated for treatment of: *Clostridium difficile*-infection (CDI) (CB-183,315) as well as treatment of infections caused by

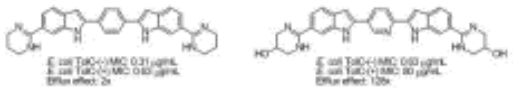
multidrug resistant Gram negative bacteria (CXA-201). CB-183,315 was discovered internally at Cubist as an antibacterial drug candidate, and is a potent, oral, bactericidal lipopeptide. CXA-201 is a novel cephalosporin/tazobactam combination product for the treatment of infections due to drug-resistant *Pseudomonas aeruginosa* and other Gram-negative pathogens. Also presented will be our discovery pipeline strategy and this will include discussion of a recent X-ray co-crystal structure of a clinically important beta-lactamase.

MEDI 245

Antibacterial bisamidines: Features modulating efflux

John D. Williams[1]*, jwilliams@microbiotix.com, Son T. Nguyen*[1]*, Michelle M. Butler*[2]*, Tim J. Opperman*[2]*, Xiaoyuan Ding*[1]*, Tommy Tasjian*[2]*, Norton Peet*[1]*, Terry Bowlin*[1]*. (1) Department of Medicinal Chemistry, Microbiotix Inc., United States (2) Department of Microbiology, Microbiotix Inc, United States*

Drug resistance has been a serious challenge since the discovery of the first antibiotics, as bacteria develop strategies to overcome the mechanism of these critical medications. The importance of developing new, unique antibiotics to combat bacterial infections is universally accepted. We have previously identified a series of bisamidines, based on a heterocyclic framework, that are potent antibacterials. Recent investigations have demonstrated some key features that are responsible for modulating the effect of efflux pumps (one key resistance mechanism) in this series of compounds. We will discuss key features of the molecules and how they influence antibacterial resistance *via* efflux.



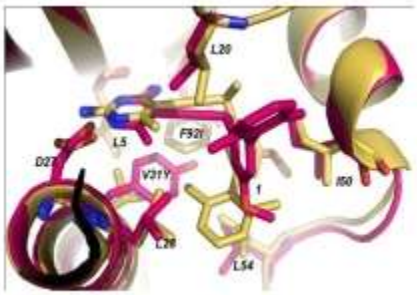
MEDI 246

Toward the prediction of resistance mutations

Amy Anderson[1]*, amy.anderson@uconn.edu, Kathleen Fry*[2]*, Dennis Wright*[2]*, Ivelin Georgiev*[2]*, Pablo Gainza*[2]*, Bruce Donald*[2]*. (1) University of Connecticut, United States (2) Duke University, United States*

Drug resistance resulting from mutations to an enzyme target is a common phenomenon that limits the lifetime of many otherwise successful drugs. Often, these mutations are discovered after clinical exposure, forcing the discovery process to progress through additional cycles. In contrast, it would be useful to be able to predict resistance mutations early in the drug design process and to incorporate that knowledge

to arrive at stronger preclinical drug candidates. Toward this goal, we have applied an ensemble-based protein design algorithm to predict potential resistance mutations toward novel antifolates that target dihydrofolate reductase from *Staphylococcus aureus*. Positive design criteria force the maintenance of catalytic activity; negative design decreases the affinity of a lead compound. We then created and evaluated four predicted enzymes with double mutations. Three of these double mutants maintain activity and exhibit lower affinity for the lead; a crystal structure of the top-ranked mutation reveals the basis for the loss of potency. In a refined strategy, enzymes with single nucleotide polymorphisms (SNPs) were predicted to be resistant to the lead. Of the four mutant enzymes evaluated, all four maintain activity at levels equal to the wild-type enzyme and two exhibit 16-68-fold losses in potency.



MEDI 247

Discovery and development of spectinomycin analogs as antitubercular agents

Richard E. Lee[1]*, Richard.Lee@stjude.org, J. Liu*[1]*, S. Waidyarachchi*[1]*, D. Bruhn*[1]*, Z. Zheng*[1]*, T. Matt*[2]*, M. Scherman*[3]*, A.J. Lenaerts*[3]*, E.C. Boettger*[2]*. (1) Department of Chemical Biology and Therapeutics, St. Jude Children's Research Hospital, United States (2) Institute of Medical Microbiology, University of Zurich, Switzerland (3) Department of Microbiology, Colorado State University, United States*

Spectinomycin was modified using structure based drug design to generate a novel series of 3'-substituted spectinamides. The synthesis of spectinamides was achieved in 4 steps from spectinomycin, their activities were tested against *M. tuberculosis* by microbroth dilution and inhibition of protein synthesis was studied at the ribosomal level in a cell free mycobacterial transcription assay. From the 84 spectinamides synthesized, a clear structure activity relationship has been established with respect to antitubercular activity and protein synthesis inhibition. Analogs with 2-heteroaryl acetic acid substitution displayed the best activities. From this panel, the most potent compounds showed M. tuberculosis MICs that are far superior to the MIC of Spectinomycin and comparable to Streptomycin. Importantly these Spectinamides were not cross resistant to any current tuberculosis therapeutics including other protein synthesis inhibitors. The tight SAR developed was rationalized using molecular modeling and molecular dynamics calculations. Lead spectinamides show low protein binding, excellent solubility, no hepatic metabolism and are excreted unchanged renally. These compounds show good antituberculosis activity in a mouse model of tuberculosis

infection and are undergoing further pre-clinical development as selective and safe tuberculosis therapeutics to treat MDR tuberculosis.

MEDI 248

The chemist as a modeler, the modeler as a chemist: When interfaces disappear

***Martin Stahl**, martin.stahl@roche.com. Department of Medicinal Chemistry, F. Hoffmann-La Roche Ltd., Basel, Switzerland*

A plethora of computational methods and tools seems to exist that support the medicinal chemist in designing better candidate molecules. What information and which tools does a medicinal chemist really need for data analysis and for deciding which compounds to make next? This talk highlights benefits as well as pitfalls of a broader use of computer-aided drug design, ranging from structure-based design to ADMET modeling.

MEDI 249

Exposing QSAR models of in vitro ADMET properties to medicinal chemists

***Andrew M Davis**[1], andy.davis@astrazeneca.com, Scott Boyer[2]. (1) Respiratory and Inflammation Innovative Medicines, AstraZeneca R&D Mölndal, Gothenburg, Sweden (2) Global Safety Assessment, AstraZeneca R&D Mölndal, Gothenburg, Sweden*

In the last 10 years, we have witnessed a growing realization that control of physical properties and ADMET properties of molecules are critical, if we are to improve our success rates in delivering effective new drugs to patients. The concept of compound quality and control at the point of design are the new paradigms. Most medicinal chemist now have access to predictive ADMET software and models that support compound design. But the accuracy and precision of these models limits the control we can exact on compound quality. Improving the models themselves is a current focus for computational chemists, and our recent progress with auto-updating QSAR modelling will be presented. How do medicinal chemists manage the uncertainty implicit in these predictive models? What impact have these models had on compound quality? What limits their use? What are the really successful models and tools that have helped the drug design process?? Some of our current answers to these questions, and useful tools and models will be presented.

MEDI 250

Putting it all together for medicinal chemists: An integrated computational desktop modeling and design environment

***W. Jeffrey Howe**, w.jeffrey.howe@pfizer.com.Worldwide R&D, Pfizer, Inc, Groton, CT 06340, United States*

Small-molecule design for drug discovery makes use of a wide variety of computational tools that shape the molecules toward multiple idealized property endpoints, including primary pharmacology, selectivity, safety, ADME, and physicochemical properties. While many of these computational tools were once the exclusive domain of computational chemists, medicinal chemists now routinely use them in their design work. At Pfizer, this change has been enabled by at least three factors – a cultural change which places greater emphasis on efficient design (designing the right molecules), increased availability of desktop modelling and cheminformatics tools coupled with ample computational power, and integration of the tools in a design environment that recognizes that design is a process requiring multiple methods that need to be invoked in a single design workflow. This presentation will discuss Pfizer's approaches to innovation in all three of these areas, primarily using internally-developed desktop tools that operate within an integrated computational environment.

MEDI 251

Modeling for the masses and the seduction of simplicity: From interfaces to interactions

***Andrew C Good**, andrew.good@genzyme.com. Department of medicinal chemistry, Genzyme, Waltham, MA 02451, United States*

Groups engaged in the business of writing and using CAMD software often buy heavily into the concept of modeling for the masses. Lured by theoretical project impact or potential market size, they are tempted into the creation of software for wide scale deployment within medicinal chemistry. The impacts objectives, personalities, politics and over-simplification have on such efforts are detailed in depth based on experience working within multiple large drug discovery organizations. In addition, modeling tools with the potential for true mass appeal and utility are discussed.

MEDI 252

Representational paradigms: Giving chemists what they want *and* what they need

***Anthony Nicholls**, anthony@eyesopen.com. Department of Chemistry, OpenEye Scientific Software, Inc, Santa Fe, New Mexico 87508, United States*

What singularly seperates modelers and chemists is their use and appreciation for dimensionality. Modelers use and sometimes think in 3D, chemists use and think in 2D, i.e. graph representations of molecules. While there have been many attempts to inculcate 3D into processes used by chemists none have been wildly successful. This talk will consider if perhaps this is because 3D is truly not an effective representational

paradigm for chemists, perhaps not even for modelers, and how a better stategy might be to instead augment 2D representations with information derived from 3D.

MEDI 253

Challenges in the discovery of new antibacterial agents

***Michael Barbachyn**, michael.barbachyn@astrazeneca.com.AstraZeneca R&D Boston, United States*

Bacterial resistance to currently available therapeutic agents continues to grow in scope and magnitude. Nevertheless, there has been a steady decline in the number of new antibacterial agents being approved by the various regulatory agencies. Some of the factors behind this unfortunate situation will be briefly discussed. The principal focus will be on challenges associated with finding novel antibacterial agents, especially those effective against Gram-negative bacteria. The unique physicochemical properties of such agents, as well as the multivariate problem associated with reaching targets essential to the bacteria will be discussed. Finally, some thoughts on screening approaches aimed at identifying new antibacterial scaffolds will be shared.

MEDI 254

Discovery of a novel azaindole class of antibacterial agents targeting the ATPase domains of DNA gyrase and Topoisomerase IV

***John Manchester**, john.manchester@astrazeneca.com.AstraZeneca R&D Boston, United States*

Antibiotic resistance presents a growing problem for the treatment series infections. We present the discovery and optimization of a novel series of bacterial topoisomerase inhibitors. Starting from a virtual screening hit, potency was optimized through a combination of structure-based design and incorporation of substituents established in other series. Synthesis of fewer than a dozen compounds was required to achieve inhibition of the growth of methicillin-resistant *Staphyloccus aureus* (MRSA) at compound concentrations of 1.56 μM. These compounds inhibit both topoisomerase subtypes II and IV at similar nanmolar concentrations, reducing the likelihood of the spontaneous occurrence of target-based resistance.

MEDI 255

Discovery of LFF571 as an investigational agent for c. difficile infection

***Matthew LaMarche**[1], matthew.lamarche@novartis.com, J. Leeds[2], J. Brewer[1], S. Bushell[1], J. Dewhurst[1], J. Ding[1], J. Dzink-Fox[2], G. Gamber[1], K. Lee[1], A. Jain[3], T. Lister[1], S. Mullin[2], C. Osborn[2], M. Patane[1], D. Palestrant[4], E. Rann[1], M. Sachdeva[2], J. Shao[1], S. Tiamfook[2], L. Whitehead[1], A. Yifru[1], D. Yu[2], W. Yan[1], Q. Zhu[1]. (1) Global Discovery*

Chemistry, Novartis Institutes for Biomedical Research, United States (2) Infectious Diseases Area, Novartis Institutes for Biomedical Research, United States (3) Chemical and Pharmaceutical Profiling, Novartis Institutes for Biomedical Research, United States (4) Protein Structure Group, Novartis Institutes for Biomedical Research, United States

Background : Infections of Gram-positive organisms can cause significant morbidity and mortality. New antibacterial chemical templates are needed especially against resistant and recalcitrant infections. A high-throughput screen was performed to identify medicinal chemistry starting points towards identifying unexplored chemical classes of antibacterials. **Methods:** A high-throughput screen identified the natural product GE2270 A and several related fermentation metabolites as active against methicillin and glycopeptide resistant *S. aureus*. Using co-crystal guided medicinal chemistry, semi-synthetic analogs of GE2270 A were designed, synthesized, and evaluated for *in vitro* potency. The goal was to identify novel analogs that were soluble and potent (MIC <1 µg/mL) against MRSA, VRE, group A streptococcus, and *C. difficile*. Potent and soluble compounds were evaluated in mouse sepsis and thigh infection models, and compared with vancomycin, linezolid, and daptomycin. Compounds were also evaluated in the hamster *C. difficile* infection model, and compared with vancomycin. **Results:** Potent *in vitro* antibacterial activities were achieved (MIC <1 µg/mL) against MRSA, VRE, group A streptococcus, and *C. difficile*. Co-crystal studies confirmed the location of binding within EF-Tu and revealed important ligand-protein interactions. Aqueous solubility of the natural product chemical template was significantly improved and the *in vivo* efficacy was enhanced. **Conclusions:** A phenotypic high-throughput screen identified GE2270 A as an antibiotic drug discovery starting point. Medicinal chemistry optimization resulted in the identification of novel and soluble antibacterials with *in vitro* potency and efficacy in animal models. These studies culminated in the selection of LFF571 for further evaluation for the treatment of *C. difficile* infections in humans.

MEDI 256

Discovery of potent, dual targeting pyrrolopyrimidine inhibitors of bacterial DNA gyrase B and topoisomerase IV with broad spectrum antibacterial activity

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To combat antibacterial drug resistance, we are focused on discovering new antibacterial agents that work *via* novel mechanisms of action. To reduce emergence of resistance against these new antibacterial agents, we have used structure-based drug design to discover agents that target two essential bacterial targets: bacterial DNA gyrase B (GyrB) and topoisomerase IV (ParE). While these targets have been utilized in other antibacterial discovery programs, to date, no clinical compounds have emerged

and spectrum of the compounds has been limited mainly to gram-positive bacteria. This presentation will detail our efforts leading to the pyrrolopyrimidine series: the first series of GyrB/ParE antibacterial agents that have an expanded antibacterial spectrum that includes important gram-negative pathogens.

MEDI 257

Novel, non-quinolone inhibitors of DNA gyrase and topoisomerase IV: Antibacterial activity and resistance mechanisms

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We have discovered a structurally novel series of inhibitors of bacterial topoisomerases in Gram-positive organisms. In addition to potent in vitro activity against these precedented targets, the inhibitors possess compelling whole cell activity, with MIC_{90} values of 0.25 mg/mL or lower against critical pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA) and *Streptococcus pyogenes.* In vivo activity against multiple pathogens in both systemic and tissue-based murine models of infection has also been demonstrated. Our studies also included the elucidation of resistance mechanisms to these novel compounds. This understanding was further enhanced using a variety of techniques, including spontaneous mutation frequencies, mutant prevention concentrations (MPCs), and hollow-fiber models aimed at understanding the role of pharmacokinetic/phamacodynamic (PK/PD) relationships in resistance emergence. This talk will provide an overview of chemical, biological, pharmacokinetic, and toxicological properties using data from illustrative examples

MEDI 258

b-Lactam antibiotic-resistance machineries in gram-negative and gram-positive bacteria

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An overview of the elaborate systems that Gram-positive and Gram-negative bacteria have devised in resistance to b-lactam antibiotics will be presented. Acquisition of the *bla* system in Gram-positive bacterium *Staphylococcus aureus* ushered emergence of methicillin-resistant *S. aureus* (MRSA) in 1961, which remains a clinical scourge to the present day. A different system has evolved in Gram-negative bacteria, which links the damage to the cell wall to induction of antibiotic resistance. The knowledge of the details for both these systems has been emerging only recently, revealing an elaborate complexity to these systems that result in inducible antibiotic-resistance mechanisms.

MEDI 259

Discovery and optimization of potent, selective, and orally bioavailable Jak1 inhibitors

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The Janus kinases (Jak1, Jak2, Jak3, and Tyk2) are key regulators of cytokine signaling pathways essential for immune function. We wished to identify Jak1 inhibitors as prospective therapeutics for rheumatoid arthritis (RA) and other immunologic disorders. A central goal of our discovery program was to limit the potential for these agents to cause anemia, an outcome associated with inactivation of Jak2. We used structure-based design to discover a tricyclic scaffold exhibiting potent inhibition of Jak1, yet only limited inhibition of Jak2. Further optimization was carried out using a properties-based approach to produce molecules with desirable characteristics including high aqueous solubility, excellent metabolic stability, and suitable membrane permeability. This work culminated in the identification of a lead compound combining favorable *in vivo* PK properties with high levels of Jak1 potency and selectivity. Details of the design and optimization efforts, as well as the biological characterization and chemical structure of the lead compound will be presented.

MEDI 260

Optimizing triple monoamine reuptake inhibition for depression: The discovery of BMS-820836

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Depressive disorders represent a substantial disability burden to patients and to healthcare systems. Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are employed as first-line treatments. However, a significant proportion of patients show a suboptimal response to treatment, with continued psychosocial and occupational impairment, further healthcare utilization, and relapse. Small clinical trials have demonstrated improved responses after augmentation of SSRI or SNRI therapies with norepinephrine transporter (NET)–dopamine transporter (DAT) inhibitors, suggesting a benefit for combined inhibition of

serotonin transporter (SERT), NET, and DAT. Therefore, a series of 4-aryltetrahydroisoquinoline SERT–NET–DAT inhibitors (triple reuptake inhibitors) has been designed. Optimization has led to BMS-820836, which is currently in Phase II clinical development for patients who have a suboptimal response to current antidepressant treatments. The design, monoamine reuptake profile, and efficacy of BMS-820836 in a preclinical model of depression will be described.

MEDI 261

Discovery of phosphodiesterase-10 (PDE10) inhibitors for the treatment of schizophrenia

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Schizophrenia is a chronic and debilitating neurological disease with onset typically occurring during early adulthood. The disease is characterized by a combination of positive (hallucinations), negative (anhedonia, social withdrawal), and cognitive symptoms, and is estimated to affect 1% of the global population. While currently marketed "typical" and "atypical" therapeutics exist, they are prone to an array of adverse events (AEs), often resulting in discontinuation due to poor efficacy and/or tolerability. As such, alternative pharmacological approaches toward treating schizophrenia represent an unmet medical need.

The phosphodiestereases (PDEs) are a superfamily of 11 enzymes responsible for the hydrolytic degradation of the second messengers cAMP and cGMP. Specifically, PDE10 is highly expressed and localized in the mammalian striatum, and is implicated in the regulation of cyclic nucleotide signalling cascades that intersect both the glutamatergic and dopaminergic pathways regulating behavioral control. As such, inhibition of PDE10 is hypothesized to represent a mechanistically novel approach

toward the treatment of schizophrenia, and recent preclinical results support this hypothesis.

We describe the discovery and development of potent and orally bioavailable tetrahydropyridopyrimidine inhibitors of PDE10 obtained by systematic optimization of a proprietary Merck HTS lead. Leading compounds exhibit sub-nanomolar potencies, excellent pharmacokinetic (PK) properties, and clean off-target profiles. These inhibitors display *in vivo* target engagement as measured by both an *ex vivo* occupancy assay and increased striatal cGMP levels upon oral dosing. They also display dose-dependent efficacy in key pharmacodynamic (PD) assays predictive of anti-psychotic activity, including the psychostimulant-induced rat hyperlocomotion assay and the conditioned avoidance response assay.

MEDI 262

Discovery of triazolopyrimidine-based PDE8 inhibitors: Exceptionally ligand-efficient and lipophilic ligand-efficient compounds

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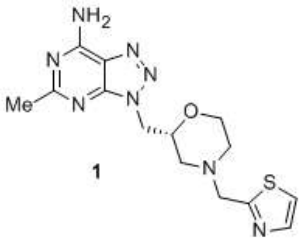
PDE8b is a cAMP-specific isoform of the broader class of phosphosdieserases (PDEs). As no selective PDE8 inhibitors had been reported, a high throughput screen was run with the goal of identifying selective tools for exploring the potential therapeutic utility of PDE8b inhibition. Of the numerous hits, one was particularly attractive since it was amenable to rapid deconstruction leading to inhibitors with very high ligand efficiency (LE) and lipophilic ligand efficiency (LLE). These triazolo pyrimidines were optimized for potency, selectivity and ADME properties ultimately leading to compound **1** . This compound was highly potent and selective with good bioavailability and advanced into pre-clinical development.



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MEDI 263

Discovery and optimization of potent Hepatitis C antiviral agents that target NS4B

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A high-throughput screening campaign aimed at identifying inhibitors of HCV with novel mechanisms-of-action identified a series of imidazopyridine analogs that exhibit potent antiviral activity. Biochemical and genetic evidence suggest the compounds interact directly with NS4B, a viral protein critical for replication and for which few inhibitors have been described. Optimization of the antiviral potency led to GSK337A, a potent inhibitor of both HCV GT1a and 1b replicons (EC_{50}'s of 0.6 and 0.3 nM, respectively). The highly functionalized pyrazolopyridine core and the [3.1.0]-bicyclohexane sidechain with four contiguous chiral centers presented a number of synthetic challenges that were ultimately overcome thereby enabling the preparation of >100 grams of GSK337A.

MEDI 264

Design and synthesis of pyridone inhibitors of non-nucleoside reverse transciptase

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Highly active anti-retroviral therapy (HAART) significantly reduces human immunodificiency virus (HIV) viral load and has led to a dramatic decrease in acquired immunodificiency syndome (AIDS) related mortality. Despite this success, there remains a critical need for new HIV therapies to address the emergence of drug resistent viral strains. Next generation NNRTIs are sought which are effective against these mutant forms of the HIV virus. Pyridones were evaluated as an acyclic conformational constraint to replace the aryl ether core of MK-4965 and the more rigid constraint of MK-6186. The resulting pyridone compounds are potent inhibitors of HIV

RT and have antiviral activity in cell culture that is superior to other next generation NNRTIs. The 4-trifluoromethyl pyridone analog displays adequate pharmacokinetic properties at lower doses but was unable to achieve exposure goals at higher doses. The preparation of prodrugs that were designed to enhance solubility resulted in increased exposures following oral administration to preclinical species.

MEDI 265

AMG 837: A potent, orally bioavailable, partial allosteric agonist of GPR40

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The discovery that certain long chain fatty acids potentiate glucose stimulated insulin secretion through the previously orphaned receptor GPR40 (also known as FFA1) has sparked interest in GPR40 agonists as potential therapeutic agents for the treatment of type II diabetes. We have previously presented a series of beta-substituted phenylpropanoic acids with potent agonistic activity on GPR40. Further exploration of this series led to the identification of a biphenyl-containing analog, designated AMG 837, as a potent GPR40 agonist with a superior pharmacokinetic profile that robustly stimulates glucose dependent insulin secretion in rodent models of type 2 diabetes. Detailed characterization of the pharmacology of AMG 837 revealed that the compound is an allosteric partial agonist capable of amplifying fatty acid signalling through GPR40 in addition to its intrinsic efficacy on the receptor. The favorable preclinical profile of AMG 837 prompted its selection for clinical evaluation for the treatment of type II diabetes.

MEDI 266

Discovery of CEP-32496, a highly potent and orally efficacious inhibitor of V-RAF murine sarcoma viral oncogene homologue B1 (BRAF) V600E

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The Ras/RAF/MEK/ERK mitogen-activated protein kinase (MAPK) signaling pathway plays a central role in the regulation of cell growth, differentiation and survival. Cellular expression of mutant $BRAF^{V600E}$ results in the constitutive activation of the MAPK pathway, which can lead to uncontrolled cellular growth. Approximately 7% of all known human cancers express $BRAF^{V600E}$, being most frequently associated with melanoma, colon, and papillary thyroid carcinomas. In the clinic, the administration of orally available $BRAF^{V600E}$ inhibitors has shown excellent utility in the treatment of mutant BRAF-driven carcinomas. This presentation will describe our own medicinal chemistry efforts toward the identification of orally efficacious inhibitors of $BRAF^{V600E}$. An optimization campaign around an initial 5-*tert*-butyl-isoxazol-3-yl urea containing quinazoline lead will be described. In particular, we describe the targeted replacement of the metabolically sensitive *tert*-butyl moiety with a variety of bioisosteric alkyl fluoride motifs, an effort which led to the identification of a 5-(1,1,1-trifluoro-2-methylpropan-2-yl)isoxazol-3-yl urea-containing quinazoline derivative (CEP-32496). CEP-32496 exhibits high cellular potency against the $BRAF^{V600E}$-dependent A375 and Colo-205 cell lines, and excellent oral exposure in multiple preclinical species. In addition, CEP-32496 proved selective for the RAF kinase members of the MAPK signaling cascade and exhibits selective cytotoxicity for tumor cell lines expressing mutant $BRAF^{V600E}$ versus those containing wild-type BRAF. CEP-32496 also demonstrates significant oral efficacy in a 14-day $BRAF^{V600E}$-dependent human Colo-205 tumor xenograft mouse model when dosed at 30 and 100 mg/kg BID. These observations coupled with excellent drug-like properties led to the selection of CEP-32496 as a clinical candidate.

MEDI 267

Heteromeric G protein-coupled receptors are the principal targets of opioid analgesics

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Opioid agonist ligands have been widely employed in the pharmacotherapy of pain in spite of side effects such as constipation, tolerance, physical dependence, and respiratory depression. Given the burgeoning evidence for heteromeric opioid receptors, it seems likely that many of these side effects are dependent on the activation of specific heteromers. In view of the pharmacologic diversity that may arise from heteromers that contain a combinations of either opioid receptor subtypes or opioid and nonopioid protomers, it is possible that some of these side effects may be due to the activation of specific heteromers. Here we discuss cell-based and in vivo pharmacological evidence for activation of heteromeric opioid receptors by clinically employed analgesics and by selective ligands synthesized in our laboratory in an effort to address this possibility. Since ligands that selectively activate specific heteromers may lead to the development of analgesics devoid of side effects, we have developed mu pharmacophore-containing ligands that are selective for a variety of heteromers for use as pharmacologic tools. The finding that some of our ligands are devoid of tolerance and/or dependence suggests that selective activation of heteromers offers an approach to developing potent analgesics free of side effects.

MEDI 268

Discovery and evaluation of neuropeptide S ligands as potential pharmacotherapies

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The coupling of putative neurotransmitters with orphan receptors using reverse pharmacology has led to the identification of several important ligand-receptor associations that are beginning to demonstrate novel pharmacology in vivo. In particular, this technique has led to the pairing of neuropeptide S (NPS) with its cognate G-protein coupled receptor (NPSR). Neuropeptide S is a 20-amino acid peptide that functions as an agonist through activation of its cognate GPCR receptor system. Importantly, modulation of the Neuropeptide S (NPS) receptor has been associated with a variety of disease states including anxiety, panic disorder, drug abuse, narcolepsy, obesity, and potentially PTSD. Our program has been focused on developing drug-like entities to fill this void using a variety of techniques. This presentation will focus on our efforts to define an NPS pharmacophore using traditional medicinal chemistry as well as our utilization of computational/scaffold hopping approaches to develop compounds that are active in models of anxiolysis and cocaine reinstatement.

MEDI 269

Award Address (Alfred Burger Award in Medicinal Chemistry sponsored by GlaxoSmithKline). Design and development of compounds for substance abuse research

***F. Ivy Carroll**, fic@rti.org. Center for Organic and Medicinal Chemistry, Research Triangle Institute, United States*

Nicotine, cocaine, methamphetamine, opiates, and alcohol abuse have been and still remain major public health problems. This address will highlight our studies directed toward the design and development of potential pharmacotherapies for treating drug abuse and addiction-related behaviors. The main focus will be on the development of the selective dopamine uptake inhibitor RTI-336, the selective kappa opioid receptor antagonist JDTic, and nicotine acetylcholine receptor (nAChR) ligands as well as monoclonal antibodies and vaccines. This address will also provide an overview of the design and development of [^{123}I]RTI-55 (Dopascan, Iometopane) as a single photon emission computed tomography (SPECT) imaging ligand for use as a diagnostic agent for Parkinson's disease

MEDI 270

Targeting protein-protein interactions using fragment-based methods and structure-based design

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Proteins that are involved in protein-protein interactions are generally thought to be undruggable by small organic molecules because protein-protein binding interfaces are large, and the binding surfaces are relatively flat. Yet, protein-protein interactions play a central role in almost all signal transduction processes in a cell. Moreover, many proteins that function by binding to other proteins are highly validated drug targets that could lead to very useful drugs, providing that appropriate methods are used to drug these technically challenging targets. In this presentation, strategies for targeting protein-protein interactions will be described that involve the use of fragment-based methods and structure-based design. In addition, examples will be presented that illustrate these approaches against validated cancer targets.

MEDI 271

Mapping endocannabinoid signaling networks in the mammalian brain

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Endogenous cannabinoids (endocannabinoids) are an important class of signaling lipids that act on both central and peripheral cannabinoid receptors, which also mediate the effects of delta9-tetrahydrocannabinol, the active component of marijuana. The magnitude and duration of endocannabinoid signaling are tightly controlled in vivo by the action of multiple biosynthetic and degradative enzymes. Here, I will discuss our lab's efforts to develop selective genetic and pharmacological tools to perturb the function of individual endocannabinoid metabolic enzymes. These tools have not only confirmed key roles for enzymes, such as fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), in endocannabinoid metabolism, but have also revealed unexpected connectivities between the endocannabinoid system and other lipid signaling pathways, including prostaglandins and lysophospholipids. Such 'systems-level' interactions designate endocannabinoid hydrolases as regulators of larger metabolic networks that may influence diverse physiological and pathological processes, such as cancer, inflammation, and nervous system disorders.

MEDI 272

Award Address (George & Christine Sosnovsky Award for Cancer Research sponsored by the George and Christine Sosnovsky Endowment Fund). Role of inflammation in the cause, detection, and treatment of cancer

***Lawrence J. Marnett**, larry.marnett@vanderbilt.edu. Departments of Biochemistry, Chemistry and Pharmacology, Vanderbilt School of Medicine, United States*

Chronic inflammation has been recognized for nearly 200 years to contribute to the development of cancers in multiple organ sites. The chemical events that contribute to

this linkage are complex and include induction of DNA damage and mutation, release of growth factors that enhance wound-healing and cell proliferation, and production of bioactive lipids that stimulate angiogenesis. Understanding the chemistry responsible for this biology provides strategies for detection, prevention and treatment of inflammation associated cancers. The focal points for this lecture will be the chemistry of inflammation-related DNA damage, the mutagenicity of the damage products, the enzymology of lipid mediator generation, and the synthesis and *in vivo* validation of agents for the detection and prevention of cancer.

MEDI 273

Insights into interactions of the GCPR CCR5 with the HIV viral envelope

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HIV has evolved a target cell entry strategy that utilizes GCPRs CCR5 or CXCR4 as obligatory co-receptors. This process begins with recognition of the HIV viral envelope glycoprotein gp120 with host cell CD4 followed by binding of this CD4-gp120 complex with chemokine receptors CCR5 or CXCR4. In CCR5, the N-terminus (Nt) and extracellular loops, particularly the second extracellular loop (ECL2), play critical roles in mediating HIV entry. While the interactions between sulfated CCR5 Nt and gp120 has been described at the atomic level, little is known about how ECL2 contacts gp120. To gain insight, we employed a medicinal chemistry approach to delineate the regions on ECL2 responsible for gp120 binding. Results from HIV neutralization assays and NMR studies that unveiled ECL2 derived peptides as inhibitors of not only CCR5 using HIV-1 strains but also CXCR4 using strains will be presented. Together they provide evidence that a common structural motif presented by CCR5 ECL2 can mediate viral infectivity, and inhibition, of R5 and X4 strains.

MEDI 274

Structural basis for agonism and inverse agonism in the β_1-adrenoceptor and adenosine A_{2A} receptor

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Structural studies of G protein-coupled receptors are hampered by their lack of stability in detergents and their conformational flexibility. We have developed a mutagenic strategy combined with a radioligand binding assay to isolate thermostable mutants of GPCRs biased towards specific conformations. This led initially to the structure

determination of a thermostabilised avian β_1 adrenoceptor mutant (β36-m23) in complex with the antagonist cyanopindolol at 2.7 Å resolution. Recently we have determined 8 additional structures of β36-m23 bound to different antagonists and agonists and, in addition, the structures of the adenosine A_{2A} receptor bound to the agonists adenosine and NECA. I will discuss the structural basis for the pharmacological profiles of the ligands and how these structures have illuminated the mechanism of GPCR activation upon agonist binding.

MEDI 275

Structure-based design of adenosine receptor ligands

Kenneth A. Jacobson[1]*, kajacobs@helix.nih.gov, Raymond C. Stevens*[3]*, Ruben Abagyan*[2]*, Francesca Deflorian*[1]*, Zhan-Guo Gao*[1]*, Andrei A. Gakh*[1]*, Dilip K. Tosh*[1]*, T. S. Kumar*[1]*, Fei Xu*[3]*, Vsevolod Katritch*[3]*. (1) Laboratory of Bioorganic Chemistry, NIDDK, National Institutes of Health, Bethesda, MD 20892, United States (2) Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California San Diego, San Diego, CA 92063, United States (3) Departments of Molecular Biology & Chemistry, The Scripps Research Institute, San Diego, CA 92037, United States*

Crystal structures of inactive G protein-coupled receptors (GPCRs) have already shown utility in discovery of new antagonists. However, efficiency of virtual screening and rational lead optimization tools in harnessing active-state structures for discovery of novel agonists remains to be assessed. Automatic docking of known potent nucleosides to the agonist-bound A_{2A} adenosine receptor crystallographic structure and to homology models of other subtypes was performed, resulting in new predictions of stabilizing interactions and a structural basis for previous empirical structure activity relationships. We predicted binding of novel C2 terminal and 5' derivatives of adenosine and used these models to interpret effects on measured binding affinity and efficacy of newly-synthesized agonists. Comparison of amino acid conjugates suggested a distal pocket close to EL2 and EL3 on the exofacial surface that could be targeted by chemical derivatization. Virtual fragment screening approaches to optimize the 5'-region improved selectivity for the A_1 subtype. These results suggest utility of molecular modeling in probing determinants of ligand recognition in GPCRs and for rational lead optimization.

MEDI 276

Expanding X-ray structures of GPCRs with predictive models: Opportunities and limitations

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As new high resolution crystal structures of GPCRs bound to different modulators and proteins are being determined, it becomes more important to develop accurate, at least locally, three dimensional models for the remaining 99% of G-protein coupled receptors. The improved modeling techniques promise to expand the scope of proteins as well as the understanding
of how a given protein binds to chemically different agonists, antagonists, inverse or partial agonists, and allosteric modulators. The recent GPCR docking and modeling contest based on crystal structure of chemokine CXCR4 and D3 dopamine receptors with three types of ligands clearly demonstrated both opportunities and limitations of this approach [1].

We demonstrate how the ligand-guided optimization of homology models can improve the initially inaccurate models into an ensemble of highly predictive models (e.g. 2,3). The full atom refinement of the crystallographic structures and further generation of alternative conformations may be a necessary requirement for successful use of the structure based virtual ligand
docking techniques [2,3].

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in Pharmacological Sciences*. *In press.*

MEDI 277

Structure based drug design of Adenosine A_{2A} antagonists

Miles Congreve*, miles.congreve@heptares.com, Stephen P. Andrews, Andrew Dore, James C. Errey, Kaspar Hollenstein, Edward Hurrell, Christopher J. Langmead, Fiona H. Marshall, Jonathan S. Mason, Irene W. Ng, Nathan Robertson, Benjamin Tehan, Malcolm Weir, Andrei Zhukov.Heptares Therapeutics Ltd, Welwyn Garden City, Hertfordshire AL7 3AX, United Kingdom*

Heptares has developed a technology that facilitates the study of GPCRs by dramatically stabilizing these important receptors outside of the cell membrane. The StaR proteins are much more robust than the wild type; they are amenable to crystallography, biophysical/fragment screening and for raising monoclonal antibodies. The process whereby the StaRs are first engineered will be explained. The utility of StaRs for structure-based drug design and biophysical screening of GPCR targets will be presented. A case study of drug discovery for the adenosine A_{2A} receptor will be

described. Adenosine A_{2A} is a validated therapeutic target for treatment of Parkinson's disease and also of interest for other CNS indications. Leads with good ligand efficiency and drug-like properties have been identified from virtual screening and have been progressed to a candidate drug in less than 18 months. Lastly, progress with drug discovery against the muscarinic and orexin GPCR systems will be briefly presented.

MEDI 278

Loop prediction and homology modeling of G-protein coupled receptors

Dahlia A Goldfeld[1]*, dag2115@columbia.edu, Kai Zhu*[2]*, Thijs Beuming*[2]*, Richard A Friesner*[1]*. (1) Department of Chemistry, Columbia University, NY, NY 10027, United States (2) Schrodinger Inc, United States*

We present results of the restoration of all crystallographically available intra and extracellular loops of four G-protein-coupled receptors (GPCRs): bovine rhodopsin, the turkey β-1 adrenergic receptor, and the human β-2 adrenergic and A2A adenosine receptors. We use our Protein Local Optimization Program (PLOP), which samples conformational space to build loop candidates and then discriminates between them using our physics based, all-atom energy function with implicit solvent. We also discuss the use of explicit membrane calculations developed for GPCR loops that interact, either in the native or in low-energy false-positive structures, with the membrane, and thus exist in a multiphase environment not previously incorporated into PLOP. Our results demonstrate a significant advance over previous work reported in the literature. In particular, we are able to accurately restore the extremely long second extracellular loop, which is key for ligand binding. Finally, we discuss current work to develop accurate GPCR homology models.

MEDI 279

Structural insights into the dynamic process of G protein coupled receptor activation

Brian Kobilka*, kobilka@stanford.edu. Molecular and Cellular Physiology, Stanford University, Stanford, CA, United States*

Research in my lab is directed at understanding the structural basis for the functional properties of G protein coupled receptors (GPCRs), which constitute the largest family of membrane proteins in the human genome. GPCRs conduct the majority of transmembrane responses to hormones and neurotransmitters, and mediate the senses of sight, smell and taste. The β_2AR adrenoceptor (β_2AR) is a prototypical Family A GPCR that mediates physiologic responses to adrenaline and noradrenaline. It regulates the activity of several distinct signaling pathways through both G protein dependent and G protein independent mechanisms. Like many GPCRs that respond to hormones and neurotransmitters, the β_2AR exhibits modest basal activity in the absence of an agonist. This activity can be modulated by a spectrum of synthetic

ligands ranging from inverse agonists, which suppress basal activity, to full agonists. We have obtained three-dimensional structures of the β_2AR in inactive and active conformations, as well as a structure of the β_2AR in complex with the G protein Gs. We have also used fluorescence, EPR and NMR spectroscopy to study the dynamic properties of the receptor, and to map ligand-specific conformational changes. I will discuss what we these studies have taught us about the structural basis of β_2AR function.

MEDI 280

What do (medicinal) chemists do all day? (And what does it mean for our molecules?)

Allan M Jordan[1]*, ajordan@picr.man.ac.uk, Stephen D Roughley*[2]*. (1) Cancer Research UK Drug Discovery Unit, Paterson Institute for Cancer Research, Manchester, United Kingdom (2) Medicinal Chemistry, Vernalis (R&D) Ltd, Cambridge, United Kingdom*

According to an informal survey of our drug discovery colleagues outside the synthetic community, our syntheses typically consist of six steps, predominantly composed of amine deprotections to facilitate amide formation reactions and Suzuki couplings to produce biaryl derivatives, resulting in large, flat, achiral derivatives destined for screening cascades.

To investigate these pre-conceptions, we have analysed a subset of medicinal chemistry programmes to determine what comprises the “Medicinal Chemist's toolbox”, and whether these pre-conceptions are truly representative of the medicinal chemist's output. This analysis includes the synthesis of more than 3500 final, screened compounds described in 150 high-impact publications.

The analysis reveals some interesting trends, highlights troubling consequences and suggests potential areas for further synthetic development. Importantly, our analysis suggests that to break from the rigid physical property (and possibly off-target toxicity) liabilities these properties often entail, there is a need to employ alternate methodology to prepare more varied compounds.

MEDI 281

Current medicinal chemistry: Is there room for improvement in compound quality?

Paul D Leeson*, paul.d.leeson@gsk.com.GlaxoSmithKline, Medicines Research Centre, Stevenage, Hertfordshire SG1 2NY, United Kingdom*

Drug-like and lead-like concepts were established in the late 1990s and are widely acknowledged. A large volume of data shows that compounds occupying less drug-like

space have poorer drug metabolism, increased toxicity risks, and increased clinical pipeline attrition. Despite these observations, drug design outcomes over the past decade, as assessed by the compounds in patent applications from major pharmaceutical Companies, show significantly inflated drug-like properties relative to recently approved oral drugs. Overall compound quality - an amalgamation of lipophilicity, size, shape, polarity, chirality and aromaticity - can be quantified. A comparison of 18 different companies' patents, taking into account the targets pursued, shows that inter-company variation in compound quality is comparable to the physicochemical differences between the major drug target classes. There is considerable scope in the pharmaceutical industry for improving small molecule drug design capabilities and drug-like compound quality, thereby minimising risks of compound-related clinical pipeline attrition.

MEDI 282

Escape from Flatland: Increasing saturation as an approach to improving clinical success

***Frank Lovering**, frank.lovering@pfizer.com, Jack Bikker, Christine Humblet.World Wide Medicinal Chemistry, Pfizer, Cambridge, MA 02140, United States*

The medicinal chemistry community has become increasingly aware of the value of tracking calculated physical properties. We hypothesized that the shift to high throughput synthetic practices over the past decade may be another factor that has predisposed molecules to fail by steering discovery efforts toward achiral, aromatic compounds. We have proposed two simple measures of the complexity of molecules prepared as potential drug candidates. The first is carbon bond saturation as defined by fraction sp^3 (Fsp^3). The second is simply whether a chiral carbon exists in the molecule. We demonstrate that both complexity (as measured by Fsp^3) and the presence of chiral centers correlate with success as compounds transition from discovery, through clinical testing, to drugs. In an attempt to explain these observations, we further demonstrate that saturation correlates with solubility and melting point, physical properties critical to success in the drug discovery setting.

MEDI 283

Organotrifluoroborates: Novel reagents and reactivities

***Gary Molander**, gmolandr@sas.upenn.edu. Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104-6323, United States*

Cross-coupling reactions have revolutionized the pharma and other industries by providing facile access to biaryl/heteroaryl systems that were previously difficult to synthesize efficiently.
More recently, investigators have turned to extending the scope of transition metal-catalyzed transformations toward sp^3

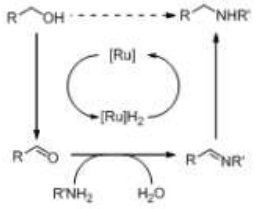
couplings. Such methods permit entry to
substantially less planar derivatives, allowing access to novel areas of
chemical diversity that are not well exemplified in current medicinal chemistry
collections. Emphasis in the talk will
be placed on recent efforts to extend
the scope of palladium-mediated couplings toward processes involving
sp^3-hybridized systems, including aminomethyl and alkoxymethyl
derivatives, allowing access to substantially less planar derivatives and novel
areas of chemical diversity. In
particular, approaches to secondary alkyl, enantioenriched reagents and their
cross-coupling will be outlined.

MEDI 284

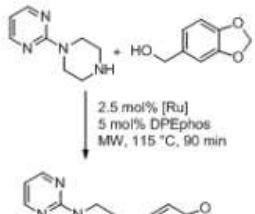
Borrowing hydrogen methodology: Use of alcohols as alkylating agents

***Jonathan MJ Williams**, j.m.j.williams@bath.ac.uk. Department of Chemistry, University of Bath, Bath, United Kingdom*

Medicinal chemists often rely on a limited range of reliable reactions. In an effort to extend this repertoire, there has been considerable interest in metal-catalyzed alkylation reactions using alcohols. Often termed 'Borrowing Hydrogen,' metal catalysts activate alcohols by temporary removal of hydrogen to give a carbonyl compound which is converted into an alkene or imine. The hydrogen is returned to generate a C-C or C-N bond. Examples of the synthesis of APIs will be included using conventional and microwave heating.



Amine alkylation using the Borrowing Hydrogen approach



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MEDI 285

Synthetic challenges in accessing exciting molecular design space

***Dafydd R Owen**, dafydd.owen@pfizer.com.Worldwide Medicinal Chemistry, Pfizer Worldwide R&D, Cambridge, MA 02140, United States*

Many methods to try and enumerate and quantify chemical space have been undertaken. This usually serves as a stark reminder of just how few molecules have

actually ever been made and how futile attempts to 'cover' or 'represent' chemical space through synthesis can seem. Despite the odds, we have discovered many molecules of great utility and function and the need for more, whether they be in pharmaceuticals or not, serves a great rallying call for the science of organic synthesis. The pharmaceutical industry has well curated records of many (generally known) reactions on many (generally unknown) substrates and a good understanding of which molecular sub-units go on to make useful molecules for drug discovery. With this knowledge we are well placed to partner with academia in helping to understand the scope and reliability of known reactions and also collaborate on exciting novel molecular structures that may inspire synthetic methodology towards and new era of target orientated synthesis. In this talk we will share some of our own in house attempts towards these goals through inventing novel methodology to access exciting molecular design space.

MEDI 286

Changing synthetic requirements in medicinal chemistry

***Nathaniel G Martin**, Nathaniel.Martin@astrazeneca.com. Oncology iMed, AstraZeneca R&D, Macclesfield, Cheshire SK10 4TG, United Kingdom*

In an era of dramatic change in the pharmaceutical industry the pressure on discovery synthetic chemistry to deliver target compounds in the shortest possible time and using reduced resources is greater than ever. This is set alongside a greater understanding of medicinally relevant chemical space and a desire to access novel areas within this space. As a consequence of these factors synthetic chemists are being asked to synthesize more complex target structures in a more efficient manner.

Only by changing the way we work presently, seeking to fully embrace new methodologies and develop new ones of our own will we be able to successfully access these complex target structures. The focus of this talk will be to highlight what the synthetic chemistry community in AstraZeneca has done to tackle these issues.

MEDI 287

Beta arrestins: Signal termination and transduction

***Kathryn A DeFea**, kathryn.defea@ucr.edu. Biomedical Sciences Division, University of California, Riverside, Riverside, CA 92521, United States*

Over the last decade β-arrestins have emerged as pleiotropic scaffold proteins, capable of mediating numerous diverse responses to multiple agonists. Most well characterized are the G-protein-coupled receptor (GPCR) stimulated β-arrestin signals, which are sometimes synergistic with, and sometimes independent of, heterotrimeric G-protein signals. Recruitment of β-arrestin to a specific GPCR can promote formation of a select subset of available β-arrestin scaffolds, allowing for a higher level of specificity to given agonists. Emerging evidence suggests that a single GPCR may elicit both beneficial

and pathogenic processes through these independent signaling pathways, which has led to the development of biased agonists and antagonists that activate or inhibit only one. Thus, the **“** wave of the future**”** in terms of targeting GPCRs therapeutically involves an understanding of the molecular mechanisms underlying their signaling bias

MEDI 288

Agonists of the nicotinic acid receptor (HCA_2, GPR109a,)

Graeme Semple*, gsemple@arenapharm.com. Department of Medicinal Chemistry, Arena Pharmaceuticals, San Diego, CA 92121, United States*

Niacin (nicotinic acid) has been used for the prevention and treatment of cardiovascular disease for many years. A resurgence of interest in this area since the discovery of a molecular target for niacin (GPR109a) focused on niacin's ability to increase high density lipoprotein-cholesterol (HDL-C) to a greater extent than other currently available drugs.

The identification of agonist ligands for HCA_2 *via* a classical SAR approach will be described, leading to the discovery of MK-0354. *In vivo*, MK-0354 inhibited lipolysis with comparable efficacy to niacin in acute models and showed a markedly improved therapeutic window between plasma FFA reduction and cutaneous flushing across multiple species. We subsequently showed that the two in vivo effects may be separated on the basis of the compound's differential signaling properties in key cell types. The identification of second generation clinical candidates will also be described.

MEDI 289

Seeking ligand bias: Assessing GPCR coupling to beta arrestins for drug discovery

Laura Bohn*, lbohn@scripps.edu. Department of Molecular Therapeutics, Scripps Research Institute, Jupiter, FL 33458, United States*

In recent years, it has become evident that drug actions at GPCRs is more complex than simply promoting or disrupting the receptors coupling to a cognate G protein. Moreover, it has become evident that GPCRs can signal through multiple G proteins and even independent of G proteins, such as through beta arrestins, to promote biological responses. It is also clear that the chemical nature of the ligand can drive selective coupling between GPCRs and their effectors; a phenomenon which opens a chemistry landscape for potentially fine-tuning of receptor signaling towards preferential effects and away from “side effects”. This presentation will focus on demonstrating functional selectivity of GPCR signaling in vivo and a discussion of certain considerations that must be taken into account when using cell-based systems to model biased agonism for drug discovery.

MEDI 290

Biased ligands as improved therapeutics: Translating theory into drugs

Jonathan D Violin*, jviolin@trevenainc.com. Department of Biology, Trevena Inc, King of Prussia, PA 19406, United States*

Biased GPCR ligands selectively engage or elude distinct receptor signaling mechanisms, and may provide a strategy for designing safer and more efficacious GPCR-targeted drugs. Two examples illustrate how biased ligands can elicit novel pharmacological profiles: TRV027, a beta-arrestin biased ligand of angiotensin II type 1 receptor (AT1R), and TRV002, a G protein-biased ligand of the mu opioid receptor (MOR). Both are examples of how the selective signaling elicited by biased ligands can be targeted and optimized to discover differentiated molecules – either by adding new beneficial effects to the known effects of classical antagonists (in the case of the AT1R), or by reducing “on-target” adverse events (in the case of the MOR).

MEDI 291

Novel neuropharmacologic approaches for the treatment of schizophrenia

Carrie K Jones*, carrie.jones@vanderbilt.edu.Vanderbilt Center for Neuroscience Drug Discovery, Vanderbilty University Medical Center, Nashville, TN 37232, United States*

Schizophrenia is a severe psychiatric illness that affects approximately 1% of the population worldwide and is associated with three broad clusters of symptoms that result in lifelong disability, including positive and negative symptoms and impairments in cognition. Clinical available antipsychotics provide relief for the positive symptoms, but have little to no effect on the negative symptoms or cognitive deficits. Thus, there remains a tremendous unmet need to develop novel therapies to more effectively and safely address the complex symptoms of schizophrenia. While the etiology of schizophrenia is unknown, imbalances in several neurotransmitter systems have been implicated in the pathophysiology of this illness, including the dopaminergic, glutamatergic, and cholinergic systems. Here we will review emerging preclinical and clinical evidence for the potential role of four novel pharmacologic strategies for the treatment of schizophrenia, including mGluR2 positive allosteric modulators, alpha 7 nACh receptor partial agonists, and phosphodiesterase 2A and 10A inhibitors.

MEDI 292

Application of parallel chemistry, structure-based design, and physical property optimization in the identification of potent and brain penetrant phosphodiesterase 2A (PDE2A) inhibitors for the treatment of cognitive impairment associated with schizophrenia (CIAS)

***Christopher Helal**, chris.j.helal@pfizer.com, John Humphrey, Thomas Chappie, Patrick Verhoest, Martin Allen, Zhijun Kang, Robin Kleiman, Christopher Schmidt. Department of Neuroscience Medicinal Chemistry, Pfizer, Groton, CT 06355, United States*

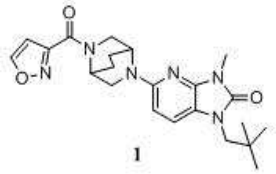
While treatments exist for positive symptoms of schizophrenia in the form of atypical antipsychotics, no approved therapies exist for the concomitant negative symptoms or cognitive impairment associated with schizophrenia (CIAS). The key second messenger molecules cyclic guanosine monophosphate (cGMP) and cyclic adenosine monophosphate (cAMP) have been implicated as playing a major role in cognitive processes. Phosphodiesterase 2A (PDE2A), which hydrolyzes both cGMP and cAMP, has highest levels of expression within limbic and basal ganglia brain circuitry found to be dysfunctional in schizophrenia. Inhibitors of PDE2A would increase cyclic nucleotide levels in these key brain regions and could thus potentially improve cognitive processes. This presentation will detail the identification of a hit series via high-throughput screening and improvement of potency, selectivity, and ADME properties that have allowed for the demonstration of in vivo functional effects. The strategic application of parallel synthesis, structure-based design, and physical property optimization will be highlighted.

MEDI 293

Development of an amino-azabenzimidazolone class of mGluR2 positive allosteric modulators for the treatment of schizophrenia

***Joseph E Pero**[1], joseph_pero@merck.com, Michael A Rossi[1], Hannah D Fiji[1], Kevin J Rodzinak[1], Mark E Layton[1], Alexander J Reif[1], Vadim Y Dudkin[1], Kenneth L Arrington[1], Robert M Garbaccio[1], Marlene A Jacobson[2], Brian C Magliaro[2], Pete H Hutson[2], Julie A O'Brien[3], Jason M Uslaner[4], Sarah L Huszar[4], Kerry L Fillgrove[5], Cuyue Tang[5], Yuhsin Kuo[5], Sylvie M Sur[6]. (1) Department of Medicinal Chemistry, Merck & Co., West Point, PA 19486, United States (2) Department of Psychiatry Research, Merck & Co., West Point, PA 19486, United States (3) Department of In Vitro Sciences, Merck & Co., West Point, PA 19486, United States (4) Department of Central Pharmacology, Merck & Co., West Point, PA 19486, United States (5) Department of Drug Metabolism, Merck & Co., West Point, PA 19486, United States (6) Department of Automated Biotechnology, Merck & Co., West Point, PA 19486, United States*

Up-regulation of glutamatergic transmission in the forebrain has been associated with the symptomology of schizophrenia. Activation of the metabotropic glutamate receptor 2 (mGluR2) regulates glutamate hyperactivity and represents a novel approach toward the treatment of the disease. Clinical proof-of-concept has been demonstrated in a Phase II study with orthosteric mGluR2/3 agonist, LY404039. Alternatively, positive allosteric modulators (potentiators) of mGluR2 may offer distinct advantages over orthosteric mGluR2/3 agonists due to their unique mode of action and selectivity. The discovery of a novel class of azabenzimidazolone-derived mGluR2 potentiators (represented by **1**) is described herein.



1

MEDI 294

Efficacy of novel α7 nicotinic acetylcholine receptor partial agonists in models of schizophrenia

***Dalton King**, kingd@bms.com, Jim Cook, Christiana Iwuagwu, Haiquan Fang, Matthew D. Hill, Robert Mate, Ivar M. McDonald, Kai Xie, F. Christopher Zusi, Amy Easton, Regina Lidge, Kelli Jones, Yu-Wen Li, Rick Pieschl, Digavalli V. Sivarao, Ping Chen, Linda Bristow, Robert Zaczek, Richard E. Olson, John E. Macor. Bristol Myers Squibb, Wallingford, CT 06517, United States*

Despite therapeutic advances made in the treatment of positive symptoms associated with schizophrenia, the treatment of negative symptoms, including cognitive dysfunction, has not been adequately addressed. Preclinical literature indicates that alpha7 nicotinic acetylcholine (α7 nACh) receptor agonists may provide an effective approach to treating cognitive dysfunction in schizophrenia and Alzheimer's Disease. Though several α7 nACh receptor agonists have entered clinical trials in schizophrenia, many have hit developmental roadblocks due to efficacy, safety, or off-target issues. We report herein a series of potent α7 nACh receptor partial agonists, built upon a novel quinuclidine-based scaffold, with high selectivity against other nicotinic receptor subtypes and the 5-HT_{3a} receptor. Optimal members of the series alleviate cognitive impairment and auditory gating deficits in pre-clinical models of schizophrenia.

MEDI 295

Isoquinucline-based GlyT1 inhibitors for schizophrenia: Discovery, optimization, synthesis, and in vivo pharmacology

***Jeffrey S Albert**, jeffrey.albert@astrazeneca.com. Department of Chemistry, AstraZeneca, Montreal, QC H4S1Z9, Canada*

GlyT1 is an emerging key target for the development of a new class of antipsychotics. We explored chemical modifications around compounds related to GlyT1 inhibitor SSR504734 (2-chloro-N-[(S)-phenyl[(2S)-piperidin-2-yl] methyl]-3-trifluoromethyl benzamide with the aim of rapidly and efficiently discovering chemotypes with high solubility, low lipophilicity, and low clearance. We describe synthesis, structures and the properties of the compounds in several in vivo animal models of antipsychotic efficacy and cognitive enhancement. In particular, these compounds elevated glycine levels in

the CSF and were potently active in rodent novel object recognition, conditioned avoidance response, and reversal of MK801-induced elevation of locomotor activity models. In addition, compounds in this series robustly increase glycine in the CSF of monkeys.

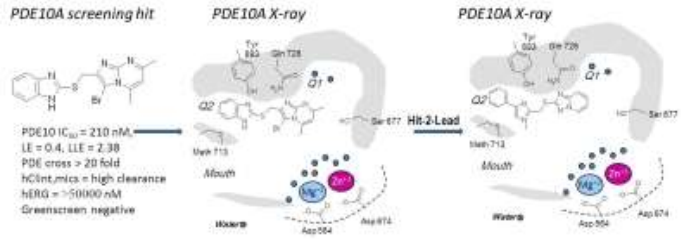
MEDI 296

4-Phenyl imidazoles: A novel class of phosphodiesterase 10A (PDE10A) inhibitors as a potential new generation of antipsychotics

Jan Kehler[1]*, jke@lundbeck.com, Andreas Ritzén*[1]*, Mauro Marigo*[1]*, Ask Püschl*[1]*, John Paul Kilburn*[1]*, Morten Langgård*[1]*, Christoffer Bundgaard*[1]*, Mads Kreilgård*[6]*, Claus Tornby Christoffersen*[2]*, Lise Tøttrup Brennum*[3]*, Anders B. Lassen*[5]*, Björn Steiniger-Brach*[4]*, Jacob Nielsen*[4]*. (1) Discovery Chemistry & DMPK, H. Lundbeck A/S, valby, Denmark (2) Department of Molecular Pharmacology, H. Lundbeck A/S, Ottiliavej 9, DK 2500 valby, Denmark (3) Department of Synaptic Transmission 1, H. Lundbeck A/S, valby, DK 2500, Denmark (4) Department of Synaptic Transmission 2, H. Lundbeck A/S, valby, DK 2500, Denmark (5) Department of Expl. In Vivo Studies, H. Lundbeck A/S, valby, DK 2500, Denmark (6) Faculty of Pharmaceutical Sciences, Dept. Pharmacology & Pharmacotherapy, University of Copenhagen, Oesterbro, DK 2100, Denmark*

Disturbances of implicit planning and execution of cognitive, emotional, and motor repertoires in the basal ganglia is involved in schizophrenia. PDE10A, a BasalGanglia-specific hydrolase, plays an essential role in regulating intracellular signalling via cAMP/PKA and cGMP/PKG cascades. PDE10A inhibition activates cAMP/PKA signalling leading to potentiation of dopamine D_1 and concomitant inhibition of dopamine D_2 signalling. Preclinically, PDE10A inhibitors provide efficacy on positive, cognitive and negative symptoms of schizophrenia.

During Lundbeck-HTS, 2-(1H-Benzoimidazol-2-ylsulfanylmethyl)-3-bromo-5,7-dimethyl-imidazo[1,2-a]pyrimidine was identified as a promising PDE10A-inhibitor. X-ray structure revealed a novel competitive bidentate binding mode to the PDE10A catalytic site and facilitated structure-based design. During hit-to-lead optimization, the benzimidazole moiety was converted to a phenyl imidazole. Solutions were invented to problems with potency, metabolic stability, brain-penetration and hERG issues. The invention of a novel PDE10A radiotracer guided the *in vivo* lead optimization allowing detailed PK-PD assessment. The optimization program delivered a preclinical candidate Lu AE90074, with antipsychotic activity.

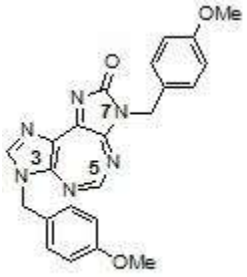


MEDI 297

Design and synthesis of DDX3 inhibitors as anticancer agent

Atul N Kondaskar*, atulk88@yahoo.com, Shilpi Kondaskar, Ramachandra Hosmane, James Fishbein. Department of Chemistry and Biochemistry, University of Maryland Baltimore County, Baltimore, Maryland 21250, United States*

We have recently reported potent antineoplastic activity of **1** in cancers of lung, breast, colon and prostates. It acts by inhibition of DEAD-box enzyme human RNA helicase, called DDX3. We report, herein, our structure-activity relationship (SAR) efforts to increase the efficacy and aqueous solubility of **1** by synthesizing analogues having different substitutions at 3, 5 and 7 positions of heterocycle**.**



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MEDI 298

Surface enhanced Raman spectroscopy for the study of anticarcinogenic activity of different medicinal plants

Zarielys Feliciano-Santiago*, zarielys.feliciano@upr.edu, Nilka M. Rivera-Portalatin. Department of Chemistry, University of Puerto Rico-Mayaguez Campus, Mayaguez, PR 00681, United States*

The research's main goal is to evaluate the anti carcinogenic activity of different medicinal plants. Extractions with the plants' essential oils, followed by incubation with cancer cell lines in order to determine oils' cytotoxic properties is performed. To ensure cell viability, MTT assays are used. Extracts are aggregated to a DNA nitrogenous

base, silver nanoparticles, and diluted aqueous sodium chloride. Nanoassemblies are tested on a Raman microscope for observation and the essential oils interactions with DNA are carefully studied. The full nanoassembly must be achieved in order to obtain defined Raman spectra for oils, which are tested alone, with nanoparticles alone, and with the full aggregate. Comparison between each analyte's aggregate and non-aggregate spectra is used to detect interactions between the oils and DNA. Analysis of all spectra are then collected and used to determine further optimizations needed to obtain accurate spectra. Silver nanoparticles aggregated to oils are previously synthesized from silver nitrate, sodium borohydride, and sodium citrate. For future research, extract components will be isolated and characterized by HPLC for identification of the component that presents anti carcinogenic activity.

MEDI 299

Development and optimization of a cell-based assay to determine intracellular concentrations of bivalent SMAC mimetics

Liu Liu[1]*, liuliull@med.umich.edu, Xiaoqin Li*[2]*, Haiying Sun*[1]*, Jianfeng Lu*[1]*, Duxin Sun*[2]*, Shaomeng Wang*[1]*. (1) Department of Internal Medicine and Comprehensive Cancer Center, University of Michigan, Ann Arbor, MI 48109, United States (2) Department of Pharmaceutical Science, University of Michigan, Ann Arbor, MI 48109, United States*

The inhibitor of apoptosis proteins (IAPs) are a class of key oncogenic proteins which suppress apoptosis by direct binding to and inhibiting caspases and pro-caspases, primarily caspase 3/7. Thus, inhibition of interactions between IAPs and caspases by designing and developing novel small molecular inhibitors has been a promising strategy for novel cancer drug discovery.

Here, we reported the development and optimization of a novel cell-based assay to determine the intracellular concentrations, which represent drug bioavailability closely, of a few bivalent SMAC mimetics reported by our group previously. Compared to the PAMPA assay using artificial membrane to determine drug bioavailability, this assay can produce more straightforward and relevant information beneficial to further drug design and development. Results showed that the intracellular concentrations of our SMAC mimetics correlated well with their molecular hydrophobicities and cellular activities in the MDA-MB-231 cell growth inhibition assay given similar binding affinities of these drugs to IAPs.

MEDI 300

Structure-based design, synthesis and evaluation of a potent, dual inhibitors of Bcl-2 and Bcl- X_L with in vivo activity

Jianfang Chen*, jianfang@umich.edu, Haibin Zhou, Angelo Aguilar, Liu Liu, Longchuan Bai, Chao-Yie Yang, Donna McEachern, Jennifer Meagher, Jeanne Stuckey,*

Shaomeng Wang. Department of Internal medicine, University of michigan, comprehensive cancer center, Ann Arbor, Michigan 48109, United States

Evasion of apoptosis is one of the fundamental hallmarks of most and perhaps all types of cancer. Targeting anti-apoptotic Bcl-2 family proteins which are key apoptotic regulators in the mitochondrial apoptotic pathway with a goal to overcome apoptosis resistance of tumor cells is a promising cancer therapeutic strategy. Starting from the crystal structure of a lead compound which functions as effective antagonist of Bcl-2 and Bcl-X_L in cell-free functional assays in complex with Bcl-X_L, integrating a computational structure-based design strategy, we have successfully designed and synthesized potent small-molecule inhibitors of Bcl-2 and Bcl-X_L proteins. The most promising compound which was identified in this study binds to Bcl-2 and Bcl-X_L with the Ki values <1 nM and shows potent activity in cell growth inhibition in multiple cancer cell lines. Most importantly, this compound strongly induces apoptosis and was capable of achieving complete and long-lasting tumor regression in H146 xenograft tumors. Herein we describe the design, synthesis and *in vtro/vivo* evaluations of this compound.

MEDI 301

Redesign of podophyllotoxin

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The structure of podophyllotoxin has been extensively utilized in drug design leading to important anticancer agents such as etoposide and teniposide. In such efforts many analogues of podophyllotoxin have been synthesized generating substantial SAR data. These SAR data, however, are not systematic and limited by the type of chemistry that podophyllotoxin can undergo. For example, systematic exploration of chemical space occupied by rings A, B and E requires approaches, which do not involve the derivatization of the natural product. Herein, we describe one such approach based on our recently discovered multicomponent reaction (MCR) that permits rapid optimization of this area of chemical space utilizing a mimetic heterocyclic scaffold. Such MCR-based optimized subunits are then incorporated into the structure podophyllotoxin through target-oriented de novo synthesis leading to the redesigned natural product. Synthesis and biological evaluation of one such redesigned podophyllotoxin analogue is presented in this poster.

MEDI 302

Peptide nanorod: A novel drug carrier

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Despite great advances in research and treatment, cancer remains one of the key health concerns in the United States. Efficient drug delivery systems providing therapeutic dose of the drug to the target is a key in development of novel chemotherapy approaches. We present the new type of nanocarrier for hydrophobic and low solubility drugs based on collagen mimetic peptides assembled into triple helix. Triple helix motif lowers enzymatic degradation thus improves bioavailability of the drug. Paclitaxel was use as a model drug conjugated to nanocarrier. The cellular vectors were incorporated into carrier sequence to improve the delivery to nucleus. The effectiveness of the delivery was tested on two cell lines: E6 Jurkats human leukemia cells (FACScan) and NIH-3T3 mice fibroblasts (fluorescent microscopy).

MEDI 303

Synthesis and evaluation of novel inhibitors of MEF2

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Enzymes that play a role in epigenetic modification, such as histone deacetylases (HDACs), provide an attractive target for the treatment of various diseases. Typically, the design of epigenetic modulators involves the direct targeting of the active site of such enzymes. Herein we describe an alternative approach, involving the direct targeting of proteins associated with the function of HDACs. The compounds to be presented target directly the transcription factor Myocyte Enhancer Factor-2 (MEF2), which interacts with Class IIa HDACs and is involved in a number of important diseases, including cardiac hypertrophy, cancer, immune dysfunction, and neurodegenerative disorders. The evaluation of binding of these compounds to MEF2 with several methods, including ^{19}F NMR, and some of their biological properties will also be reported.

MEDI 304

Structural and chemical basis for the antimetastatic properties of a series of migrastatin analogs

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Cancer is a leading cause of death worldwide. The control of metastasis is one of the most important issues in cancer research. The design of novel antimetastatic drugs is of great importance and so is the understanding of the molecular mechanisms and key components driving tumor growth and metastasis. Over-expressed in various cancers, fascin has emerged as a promising target for the treatment of cancer metastasis. Migrastatin, a potent inhibitor of tumor cell migration, has been employed as a lead compound in the development of series of analogs with enhanced tumor cell migration inhibitory properties. The identification of fascin as a macroketone (migrastatin analog) target provided new insights for drug discovery. In the present work, X-ray crystal structural and molecular modeling studies were performed to reveal the molecular and structural basis for the antimetastatic effects of these compounds. The biochemical, structural and molecular modeling results will be presented.

MEDI 305

Analytical and biochemical studies of the DNA damage produced by platinum-acridines and its recognition by the DNA processing enzymes

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Platinum-acridines are a new type of non-crosslinking anticancer drug, which are approximately 500-fold more cytotoxic in non-small-cell lung cancer (NSCLC) than cisplatin. NSCLC resistance to cisplatin regimens has been correlated with high expression levels of nucleotide excision repair (NER) enzymes. The purpose of this study was to compare the molecular and cellular consequences of the damage produced by the hybrid agent and the clinical drug. Drug uptake into H460 NSCLC, nuclear platinum levels, and the type of damage were studied by ICP-MS by enzymatic digestion in conjunction with LC-MS, respectively. The repair efficiency of DNA damaged by platinum-acridine and cisplatin was studied in 143- base-pair DNA fragments containing a single adduct. The role of topoisomerase inhibition in the mechanism of action of platinum-acridines was studied in drug-modified plasmid DNA using gel electrophoresis. Critical differences with respect to adduct formation and recognition are observed between the classical and the hybrid agent.

MEDI 306

Synthesis and biological characterization of a novel platinum-pyrrole hybrid antitumor agent

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Monofunctional platinum complexes have shown great promise as antitumor drugs that trigger cancer cell death by a mechanism at the DNA level different from classical DNA cross-link formation. The non-classical platinum-based drug [PtCl(ethane-1,2-diamine)(N-[2-(acridin-9-ylamino)ethyl]-N-methylpropionamidine] (nitrate salt), a dual platinating/intercalating agent, has been modified by replacing the acridine carrier ligand with a pyrrole-peptide moiety designed to target the DNA minor groove. Here, we report the synthesis of this novel type of hybrid agent ("pyrroliplatin", compound **1**) and its characterization by liquid chromatography-electrospray mass spectrometry. Circular dichroism spectroscopy and gel-based plasmid unwinding assays were used to demonstrate that the target compound induces conformational changes in double-helical DNA distinctly different from those caused by cisplatin. To establish the cytotoxicity profile of the compound, colorimetric cell proliferation assays were performed in cell lines representing several of the most chemoresistant cancers, including NCI-H460 (non-small cell lung), pancreatic (PANC-1), and triple-negative breast (MDA-MB-231) cancer.

MEDI 307

Development and evaluation of novel conjugation chemistries for the targeted delivery and cellular imaging of potent platinum-acridine anticancer agents

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Monofunctional platinum-acridine antitumor agents have shown promising activity in non-small cell lung cancer (NSCLC), however were found to suffer from severe systemic toxicity, which potentially limits their clinical applications. Here, we present novel conjugation strategies based on chemically modified platinum-acridine "warheads" to improve the tumor-targeting ability and extend the anticancer spectrum of this agent. To target estrogen receptor (ER)-positive breast cancer, (Z)-tamoxifen and endoxifen were chosen as the targeting moieties covalently attached to a hydroxyl-modified platinum-acridine analog using a (enzymatically) cleavable carbamate bond. The relative binding affinities (RBA) of the conjugates were determined using a competitive radiometric binding assay. The cell damage was measured using MTS assays in the ER-positive cell line MCF-7 and the triple-negative breast cancer cell line MDA-MB-231. In addition, clickable azide-modified platinum-acridine derivatives were developed as targetable warheads and as fluorescently detectable probes for further mechanistic study of platinum-acridine antitumor agents.

MEDI 308

Design of 3,4,5-trimethoxychalcones as mitotic arresters and cell migration inhibitors

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Inhibition of tubulin polymerization is an important approach for cancer therapy. The design of colchicine site ligands has attracted special interest throughout the last years. Work within our group has led to the development of cytotoxic chalcones that are able to inhibit tubulin polymerization *in vitro* and to provoke cellular mitotic arrest. Considering that the migration of metastatic cancer cells requires remodeling of the cytoskeleton, including the regulation of microtubules, we have evaluated a series of chalcone derivatives for its ability to inhibit cancer cell migration, using the wound healing and Boyden-chamber cell migration assays. Two chalcones inhibited invasive MDA-MB-231 cell migration in a dose-dependent manner similar to that of colchicine (IC_{50} range 475-1095 nM). Together, these findings represent important advances toward the investigation of the anti-metastatic effects of the developed chalcones. The structure-activity relationships and biological data of this series will be presented and discussed.

MEDI 309

Optimization of thiazole analogs of resveratrol for induction of quinone reductase 1 (QR1)

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Quinone reductase 1 (QR1) is a cytoprotective enzymes that exerts its cancer chemoprective activity in two different ways. First, it suppresses formation of intracellular semiquinone radicals. Second, it generates intracellular free radical scavengers such as a-tocopherolhydroquinone. Therefore, it has been proposed that QR1 inducers may act as cancer chemopreventive agents. 3,5-Diphenyl-1,2,4-

thiadiazole provided a new scaffold for novel QR1 inducers. This new scaffold was derived from the natural product resveratrol by replacement of the ethylene linker with five-membered heterocycle. 3,5-Bis(2-fluorophenyl)-1,2,4-thiadiazole has been obtained with a notable improvement in the QR1 induction activity (CD = 1.8 mM) in comparison with resveratrol (CD = 21 mM), where CD is the concentration to double the QR1 activity. Using thiazole as a linker and optimizing the subsitiuent pattern of the two phenyl rings led to a highly potent and selective QR1 inducer with a CD value of 87 nM.

[figure 1]

MEDI 310

Novel 1,4-naphthoquinone derivatives designed as multifunctional small molecules to target non-small cell lung cancer

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A multifunctional strategy using single products that interact simultaneously with many targets either directly or following metabolism has shown significant promise in drug discovery. We have designed novel 1,4-naphthoquinone-based agents that have the potential to induce cancer cell death by a dual mechanism of action involving inhibition of overexpressed epidermal growth factor receptor (EGFR) implicated in the development and progression of non-small cell lung cancer (NSCLC) and bioreduction to DNA-damaging metabolites. The quinone moieties in these agents have the potential to be metabolized by enzymatic reduction under hypoxic conditions by the enzyme DT-diaphorase (DTD)), a reductase overexpressed in NSCLC. The design, molecular docking studies, multistep synthesis and biological evaluation of the target molecules will be presented.

MEDI 311

Synthesis, characterization, and phototoxicity studies of a novel porphyrin series as potential PDT agents

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Certain porphyrins and their derivatives have been shown to be tumor specific and effectively used in Photodynamic Therapy (PDT). Six novel derivatives have been synthesized and characterized by standard techniques. These novel porphyrin derivatives have been found to cleave DNA in the presence of light. These porphyrin

derivatives were also tested on rhabdomyosarcoma cells for phototoxicity and toxicity in the dark. Cell viability was determined using an MTT assay. When exposed to light during the assay the porphyrin toxicity increased compared to when they were left in the dark. Several derivatives were more effective at higher concentrations. Two, H_2TPP-APDEA and H_2TPP-PIPOH, were highly effective at lower concentrations while showing low toxicity in the dark. These two are candidates for testing in animals. These effective novel porphyrin derviatives will be used as the basis for designing new porphyrins with improved properties.

MEDI 312

Investigating the structural criteria for Icmt inhibition through design and synthesis of FTA-triazole based inhibitors

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Mutant K-Ras is a key oncogene in several cancers. For Ras to be constitutively active, methylation by isoprenylcysteine carboxyl methyltransferase (Icmt) is crucial. Icmt inhibition leads to Ras mislocalization, inhibition of oncogenic K-Ras transformation, and signaling impairment of the Ras/Raf/Mek/Erk pathway. A substrate-based drug design approach has resulted in the discovery of a potent inhibitor, STAB (IC_{50} 0.2 ±0.04 μM). We hypothesize that the second aromatic moiety of STAB might be a significant pharmacophore required for enzyme inhibition. The main objective of this project is to synthesize a library of compounds where the internal phenyl ring of STAB is replaced with substituted phenyl groups or various heterocycles. Through the evaluation of this library, we have generated various nanomolar inhibitors of Icmt. In addition, we have also obtained valuable structural information on how sterics, electronics and the orientation of the internal phenyl group affect enzyme interaction and inhibition.

MEDI 313

Design, synthesis, and biological evaluation of novel frame-modified geranylgeranyl pyrophosphate analogs

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Protein prenylation is essential for proper membrane localization and function. Some Ras-*independent* tumors have responded to FTIs. It is reasoned that prenylation

inhibition of another protein(s) could be responsible for these antitumor affects. To identify the true FTI target(s), a combination approach is utilized where pyrophosphate analogs are screened against synthetic Dansyl-GCaaX peptide libraries. This approach revealed that for each analog, both FTase and GGTase exhibit unique patterns of reactivity among various CaaX sequences. Our lab has synthesized and evaluated frame-modified FPP analogs which show promise as FTase substrates. We hypothesize that pyrophosphate chain flexibility is more significant in GGTase-I binding. Our goal is to expand this theme to synthesize unique GGPP analogs that will aid in developing novel chemical tools capable of modulating prenylation of specific proteins. This will allow researchers to more precisely investigate proteins' individual roles in cells as well as the function of their lipid moieties.

MEDI 314

Keeping out of the kinase domain: Structure–activity relationship (SAR) studies of (Z)-3-(2-aminoethyl)-5-(4-ethoxybenzylidene)thiazolidine-2,4-dione, a potent extracellular signal-related kinase-2 (ERK2) docking domain inhibitor

***Kwan-Young Jung**, kjeong@rx.umaryland.edu, Kerrick Nevels, Shilpa Worlikar, Jamal Chauhan, Sarice Smith, Jeremy L Yap, Sagar Shukla, Joseph Slattery, Mary Ensey, Alexander D MacKerell, Paul Shapiro, Steven Fletcher. Department of Pharmaceutical Science, University of Maryland, Baltimore, Maryland 21201, United States*

Extracellular signal-related kinase-1 and 2 (ERK1/2) are hyperactivated in several human cancers, due to gain-of-function mutations in the upstream Ras and Raf proteins. However, the complete inhibition of ERK1/2 through targeting their active sites (kinase domains) is expected to be detrimental, since ERK1/2 are crucial in various “house-keeping” roles in normal cells. Therefore, our aim is to the block specific substrate docking domains on the surfaces of ERK1/2 and, hence, inhibit functions involved in cancer cell proliferation, such as the phosphorylation (activation) of the transcription factor Elk-1 and the ribosomal S6 kinase-1 (RSK-1). We have previously used computer-aided drug design (CADD) to identify ERK2 docking domain inhibitors, which led to the discovery of (*Z*)-3-(2-aminoethyl)-5-(4-ethoxybenzylidene)thiazolidine-2,4-dione. Through conducting structure–activity relationship (SAR) analyses of the phenyl ring, the thiazolidine-2,4-dione core and the ethylamine moiety, we have identified more potent ERK2 docking domain inhibitors.

MEDI 315

Design, synthesis, and studies of novel survivin inhibitors

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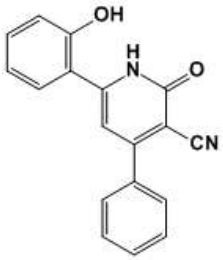
Survivin, a member of inhibitors of apoptosis (IAP) protein family is involved in cell division and antiapoptotic activity. Over-expression of survivin in cancer patients has been associated with decreased survival rates, increased recurrence rates, invasion of lymph nodes, metastasis and angiogenesis. Thus, survivin is one of the viable molecular targets for the treatment of cancer.

Recently, through HTS-NMR and AS/MS affinity based screenings, compound 1 was identified to bind to the dimerization interface of survivin. Structure based design approach was used with compound 1 as the lead structure to design several small molecule inhibitors. Two of the most potent inhibitors are LLP3 and LLP9. In both HUVEC and PC3 cells, LLP3 and LLP9 caused delay in mitosis and imparted major defects in CPC organization and mitotic progression at 50 nM and 100 nM, respectively. Structure-activity relationship studies will be presented in detail.



Compound 1

MEDI 316

Discovery of orally active selective inhibitors of Plk1

Joanne L Pinder*, joanne_pinder@vrtx.com, Steven Durrant, Simon Everitt, Michael Mortimore, Shazia Keily, Ronald Knegtel, Michael O'Donnell, Guy Brenchley, Jean-Damien Charrier, Julian Golec, David Kay, Chau Mak, Sharn Ramaya, Alistair Rutherford, John Studley, Anisa Virani, Peter Weber, Stephen C Young. Department of Chemistry, Vertex Pharmaceuticals (Europe) Ltd, Abingdon, Oxfordshire OX14 4RY, United Kingdom*

Members of the Plk family of Ser/Thr protein kinases play important roles in the entry to, progression through, and exit from cell mitosis. Plk1 is overexpressed in a variety of cancers and these high expression levels often correlate with poor prognosis. Plk1 is therefore considered to be a good target for the development of novel antimitotic cancer therapies. As part of our efforts to discover new cancer therapeutics, we developed a high throughput screen (HTS) against Plk1. This led to the identification of a series of pan-Plk inhibitors based on the pyrrolopyridine scaffold. A structure based drug design

approach enabled us to optimize the HTS hits to obtain a series of inhibitors that were selective for Plk1 against other members of the Plk family. These compounds demonstrated potent inhibition of cellular proliferation *in vitro* and tumour growth in animals following oral administration.

MEDI 317

New structural templates for kinase inhibition

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Dysfunctional cell signalling caused by deregulation of kinases is a major cause of cancer. A new kinase-inhibitory scaffold containing a motif capable of forming the necessary hydrogen bonds to the hinge region, **1** , has been designed.

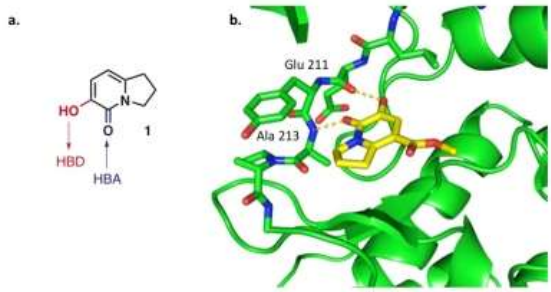
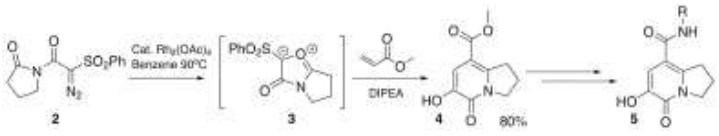


Figure 1. a: 6-Hydroxy-1,2,3-trihydroindolizin-5-one scaffold (1)
b: *In silico* docking of an analogue of 1 in Aurora A

This scaffold has been synthesised using a modified rhodium-catalysed cyclisation-cycloaddition-ring opening cascade reaction via an isomünchnone intermediate (**3**).



Scaffold **4** has been tested against a large number of kinases using a variety of biochemical and biophysical assays, and was found to inhibit several kinases, some of which are well studied in cancer and others are emerging therapeutic targets. Scaffold derivitization has also yielded more potent hits against these kinases. X-Ray

crystallography and *in silico* docking is being used to determine the binding mode of these compounds and to drive the design of more potent and selective compounds.

MEDI 318

Small molecule inhibitors of the c-Myc–Max protein–protein interaction: Targeting the intrinsically disordered (ID) form of c-Myc

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c-Myc–Max is a heterodimeric protein complex of the basic helix-loop-helix-leucine zipper (bHLH-LZ) family that is involved in the transcriptional regulation of the target genes of cell proliferation, cell cycle progression, and apoptosis. Over-expression of c-Myc has been implicated in multiple cancer types, underscoring the importance of research into c-Myc–Max inhibitors. However, the identification of nanomolar c-Myc inhibitors remains elusive. In their monomeric forms, c-Myc and Max are intrinsically disordered (ID) with a lack of recognizable secondary structure and thus do not appear to have any targetable sites. Only upon dimerization via their leucine zipper domains do c-Myc and Max form ordered α-helical structures, thus allowing for recognition of DNA for transcriptional regulation. Taking advantage of recently published data that suggests the existence of small-molecule-induced binding sites in the ID form of c-Myc, we have identified several novel and potent small-molecule inhibitors of c-Myc.

MEDI 319

Structure-activity relationship studies of new and highly potent small molecule Bcl-2/Bcl-xL inibitors

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The Bcl-2 proteins are key regulators of apoptosis. Overexpression of the pro-survival members, including Bcl-2 and Bcl-xL, is a common feature in many tumors and small-molecule inhibitors against these pro-survival Bcl-2 proteins may hold great promise as new anticancer agents. Starting from the crystal structure of a very weak lead compound with a new scaffold, we have designed highly potent and new small-molecule inhibitors of Bcl-2/Bcl-xL. The most promising compound binds to Bcl-2 and Bcl-xL with Ki values < 1 nM, potently inhibits cell growth and induces apoptosis against lung and leukemia cancer cells and is capable of inducing tumor regression in the H-146 lung

cancer xenograft model. Herein we describe the detailed SAR studies of these new and potent Bcl-2/Bcl-xL inhibitors.

MEDI 320

Bromoalkyloxy derivatives of combretastatin A4: Synthesis and biological evaluation

.

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Microtubules play an important role in the search for anticancer drugs. Microtubules are polymeric filaments composed of α-tubulin and β-tubulin heterodimers and play an important role in cell division. Tubulin subunits are continuously attached and detached from the ends of microtubules. This dynamics vary during the cell cycle. Tubulin binding agents that interfere with microtubule dynamics are useful anticancer agents. The tubulin binding agent combretastatin A-4, isolated from African willow *combretum caffrum* has shown potent antitumour effect in several MDR positive human cancers cell lines. The aim was to develop combretastatin analogues with a chimeric sidecahin able to interact with a receptor site to improve potency and selectivity. A series of novel analogues were synthesised by bromoalkylation of the phenolic combretastatin. The three carbon bromo side chain analogue was found to be most active with 15% cells viable at 50 nM. Further cytotoxicity and flow cytometric studies will be presented.

MEDI 321

New synthesis approach for the preparation of a diverse library of acridine based telomerase inhibitors

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Telomerase is a reverse transcriptase enzyme that adds a specific DNA sequence of repeats (“ TTAGGG ”) to the 3' end of DNA strands in the telomere regions. Over activity of telomerase in tumor cells draw the researchers attention towards targeting the telomerase as a therapeutic target for cancer.

Acridine derivatives are well known for their interaction with human DNA and the enzyme telomerase. We will present our results in developing a key synthetic procedure for the preparation of a diverse library of acridine derivatives. The procedure is advancement in the preparation of large nitrogen heterocycles. It starts with a simple

non-air sensitive copper (II) sulfate catalyzed aryl amination of haloarenes, followed by ring closing and additional addition and substitution reactions.

MEDI 322

Design, synthesis and biological evaluation of substituted sulfonamido-1-hydroxynaphthalene compounds as novel small-molecule Mcl-1 inhibitors

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The anti-apoptotic myeloid cell leukemia protein Mcl-1, a member of the Bcl-2 family proteins, has emerged as a promising therapeutic target. Using structure-based design, a new series of sulfonamido-1-hydroxynaphthalene Mcl-1 inhibitors were synthesized based on the lead compound identified from high throughput screening. The initial structure-activity relationship was established using a competitive fluorescent polarization and surface plasmon resonance based assays. The docking model predicted that this class of compounds binds to the BH3 binding site in Mcl-1 protein mimicking two conserved hydrophobic residues from BH3 binding motif. This model was confirmed by using HSQC-NMR spectroscopy demonstrating that this class of compounds binds to the same BH3 domain of Mcl-1 as the Bim BH3 peptide. The most potent analogues inhibit cell growth and induce apoptosis in different cancer cells, including lymphoma, melanoma and pancreatic cancer cells. These findings provide promise for further chemical modifications and development of potent small-molecule Mcl-1 inhibitors.

MEDI 323

Structure-based design of a new class of potent Bcl-2/Bcl-xL inhibitors

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Abstract: Anti-apoptotic Bcl-2 and Bcl-xL proteins are key regulators of apoptosis and attractive new targets for cancer chemotherapy. The design and development of highly potent and specific small-molecule inhibitors of these proteins is a very challenging task

in medicinal chemistry since it is involved in targeting protein-protein interaction. Employing a structure-based scaffold design strategy, we have designed a new class of potent, specific small-molecule inhibitors of Bcl-2/Bcl-xL that can bind with subnanomolar K_i values and function as potent antagonists of Bcl-2/Bcl-xL in functional assays. A 1.4 Å resolution crystal structure of a lead compound complexed with Bcl-xL has provided a basis for further optimization. Our most effective inhibitors induce robust apoptosis in cancer cells lines that depend upon Bcl-2/Bcl-xL for survival and achievecomplete tumor regression in the H146xenograft model. The design, synthesis and evaluation for this new class of compounds will be described.

MEDI 324

Synthesis of pheophorbide-a conjugates with anticancer drugs as potential cancer diagnostic and therapeutic agents

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Pheophorbide-*a*, a chlorine based photosensitizer known to be selectively accumulated in cancer cells, was conjugated with anticancer drugs, doxorubicin and paclitaxel in the purpose of selective cancer diagnosis and therapy. Pheophorbide-*a* was conjugated with anticancer drugs via directly and by the use of selective cleavage linkers in cancer cell. The fluorescence of pheophorbide-*a* and doxorubicin conjugate by excitation at 420 or 440 nm was greatly diminished possibly by the energy transfer mechanism between two fluorescent groups. However, upon treatment in cancer cells, the conjugate showed to be cleaved to restore each fluorescence of pheophorbide-*a* and doxorubicin after 48 h of incubation. Also, pheophorbide-*a* conjugates either with doxorubicin and paclitaxel inhibited the growth of various cancer cells more potently than pheophorbide-*a*, which displayed very weak inhibitory activity. The results indicated that the pheophorbide-*a* conjugates with anticancer drugs could be utilized for selective cancer therapy as well as for the fluorescence detection of cancer.

MEDI 325

Synthesis of potent and selective Autotaxin inhibitors

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Here we describe the discovery and optimization of Piperidinopiperazines and derivatives thereof as potent and selective inhibitors of Autotaxin (ATX) based on a

high-throughput screening (HTS) campaign sampling our in-house compound collection. The compounds optimized subsequently to the Benzotriazole derivatives and characterized herein are potently inhibiting the PDE activity of ATX and also lowering the LPA levels in plasma significantly. X-ray protein crystallographic data demonstrated that these inhibitors bind to the LPC/LPA binding side with an important interaction to one of the Zn atoms. The SAR, optimization of physchem and pharmacokinetic properties as well as *in vivo* activity are also described.

MEDI 326

WITHDRAWN

MEDI 327

Design and synthesis of 8-substituted purines as inhibitors of Nek2 kinase

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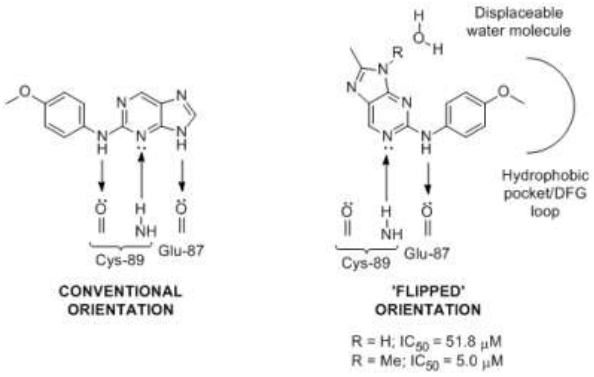
The protein kinase Nek2 plays a key role in centrosome replication and disjunction, a vital event in mitotic spindle formation. Importantly, Nek2 is over-expressed in a variety of cancers.

Structure-activity relationship studies for 8-substituted purine inhibitors were undertaken, with X-ray crystallography revealing a non-conventional binding mode within the ATP-binding domain. This presented new interactions to be accessed through structural modification of the scaffold.



The synthesis, structure-activity relationships, and structural biology of 8-alkylpurine Nek2 inhibitors will be discussed.

MEDI 328

Exploratory data analysis of alkylphosphocholines as antitumor agents

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Alkylphosphocholines (APCs) comprise promising antitumor agents; however, hemolysis limits their use. Hierarchical Cluster Analysis (HCA) and Principal Component Analysis (PCA) were applied to 34 APCs to explore relationships between calculated molecular/structural properties with their hemolytic rates. Molecular dynamics simulations generated a conformational ensemble profile of each ligand, and molecular/structural properties were calculated for the lowest energy conformer. HCA used the complete linkage method and samples were divided into six clusters; PCA was run up to seven factors (PCs). Low hemolytic compounds were influenced by thermodynamic parameters, and presented bulky substituents in the hydrophobic portion. High hemolytic compounds were influenced by electronic, steric and thermodynamic characteristics, and had constrained head groups in *trans* configuration. PC1 retained mainly steric descriptors and, together with PC2, explained 60% of the total data variance. These findings provide useful information about which molecular descriptors are important to hemolysis and the surfactant interactions with biological membranes.

MEDI 329

Effects of histone deacetylase inhibitors on the non-small cell lung carcinoma cell line A549

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Histone deacetylase inhibitors (HDACi), a diverse class of compounds that inhibit the activity of lysine deacetylases (KDAC), have shown promise as cancer therapeutics. Although several HDACi have been introduced into clinical trials and some others approved for use in treatment of cancers, how these inhibitors mediate their effect is not well understood. HDACi were initially considered for cancer therapy due to the observation that cancer cells exhibit global hypoacetylation of histones, leading to decreased transcription of tumor suppressor genes and decreased cell cycle control.

While lysine acetylation is frequently associated with histones, this modification is beginning to be appreciated as a regulator of other proteins including proteins known to be involved in cancer. We investigated how three different HDACi alter proliferation in the non-small cell lung cancrinoma (NSCLC) cell line A549. The inhibitors used were: Trichostatin A (TSA), which inhibits zinc-dependent Class I and II histone deacetylases, Nicotinamide (NAM), which inhibits NAD+-dependent Class III histone deacetylases, and CUDC-101, a dual inhibitor of Class I/II histone deacetylases and epidermal growth factor receptor (EGFR). We found that TSA rapidly decreased proliferation. Additionally, CUDC-101 decreased proliferation, although to a lesser extent than TSA. In contrast, NAM did not decrease A549 proliferation. To investigate how HDACi were mediating these effects on proliferation, we took an unbiased mass spectrometry approach to assess the acetylation status of different proteins following treatment. Understanding how HDACi affect the activities of individual proteins is essential to determining the mechanisms through which HDACi elicit their effects on cancer cells, and gaining insight into causes of resistance to treatment in NSCLC.

MEDI 330

Evolution and structure activity relationship of a series of potent RSK2 inhibitors

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RSK2 is serine/threonine kinase which plays an essential role in cell survival, proliferation and motility making it an attractive target for cancer therapy. A 2,7-disubstituted benzoxazole scaffold was employed as a starting point to develop inhibitors of RSK2. Structure-based drug design and molecular modeling were used to optimize the in vitro potency of the series to yield highly potent, selective RSK2 inhibitors.

MEDI 331

Synthesis of FlavinMonoNucleotide analogs targeting noncovalent interactions with PEBP/RKIP protein

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PEBP (PhosphatydilEthanolamine Binding Protein), more recently renamed RKIP (Raf Kinase Inhibitor Protein), is the product of a metastasis suppressor gene. It is known

that one covalent ligand, locostatin, increases PEBP/RKIP's ability to inhibit cell migration. PEBP/RKIP also possesses a nucleotide binding site, in particular it can non-covalently bind FMN, GTP, UMP and CTP. Aiming to characterize the non-covalent RKIP/PEBP-nucleotide interaction, we have designed and synthetize new FMN analogues and analyze the complex PEBP/RKIP in native conditions by ESI-IT mass spectrometry. Four groups of nucleotide analog ligands were distinguished according to their ability to bind human PEBP/RKIP.

MEDI 332

Design of novel imidazopyridine Type II B-RAFV600E inhibitors

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The Ras-mitogen activated protein kinase (MAPK) signaling pathway transmits signals from receptors on the cell membrane to cytoplasmic and nuclear factors that are responsible for cell proliferation and survival. This pathway is frequently disregulated cancer, leading to uncontrolled proliferation and tumor growth. Thus a potent Raf inhibitor could have a significant impact in treating cancers that are dependent on activated Ras or Raf for survival and proliferation signaling. A series of imidazopyridine analogs which were designed as inhibitors of B-Raf^{V600E} will be described along with the relevant medicinal chemistry employed to explore the SAR for this series and improve selectivity versus p38 and KDR.

MEDI 333

Development of a novel synthetic route to highly potent and efficacious 5,6-dihydroimidazo[1,5-f]pteridine-7-carbonitrile inhibitors of polo-like kinase-1

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In recent years, polo-like kinase-1 (PLK1) has attracted much attention as a primary drug development target in proliferative diseases. During our efforts to find novel and potent PLK1 inhibitors, 5,6-dihydroimidazo-[1,5-*f*]pteridine-7-carbonitrile core was discovered, with promising *in vitro/in vivo* activity. However, the synthetic route was lengthy, suffered from poor yields and lacked a late stage diversification point for efficient analog production. In this poster, we present the development of shorter and

higher yielding synthetic route, enabling multigram preparation of advanced intermediates. In addition, the details of a key cyclization step to form the imidazole moiety will be presented.

MEDI 334

Selective histone deacetylase inhibition by 3-hydroxy-pyridin-2-thione based zinc binding group

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Histone deacetylase inhibitors (HDACi) represent a novel therapeutic option for cancer treatment. Most HDACi fit into a pharmacophoric model which consists of a surface recognition group that interacts with the outer rim of the HDAC channel, a linker that traverses the hydrophobic channel and most importantly a zinc binding group (ZBG) that chelates a zinc ion located at the active site. In 2006, SAHA (Vorinostat) was approved by the Food and Drug Administration (FDA) for the treatment of cutaneous T-cell lymphoma (CTCL). This prototypical HDACi possesses a hydroxamate as a ZBG which has led to potent HDAC inhibition. However, it inhibits all zinc dependent HDAC isoforms leading to severe side effects. Therefore, isoform selective HDACi will have fewer side effects as these agents will be selective towards particular malignancies which have been shown to overexpress specific HDAC isoforms. Using molecular modeling, we modified the pharmacophoric model resulting in 3-hydroxy-pyridine-2-thione as a novel ZBG for HDAC inhibition. A structure activity relationship (SAR) performed on the linker region and the surface recognition group yielded HDAC 6 or HDAC 8 selective inhibitors. HDAC 8 selective compounds may be affective against T-cell derived malignancies which overexpress HDAC 8 while the HDAC 6 selective compounds may be useful for treatment of neurodegenerative diseases such as Alzheimer's and Huntington's diseases which are linked to HDAC 6 activity. The synthesis of these selective HDACi, and their activities against different human cancer cell lines will be discussed.

MEDI 335

Discovery of a novel series of potent sphingosine kinase 1 and 2 dual inhibitors

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Sphingosine kinase (SPHK) is a lipid kinase that catalyses the ATP dependent phosphorylation of sphingosine to sphingosine 1 phosphate (S1P). There are two highly homologous isoforms of SPHK, sphingosine kinase 1 and sphingosine kinase 2. Several reports have suggested that sphingosine kinase is upregulated in response to cellular stress and in a number of human cancers. Additionally, SPHK 1 and 2 double knock-out mice have severe deficits in blood vessel formation suggesting SPHKs play a role in angiogenesis. Interestingly, mice lacking either SPHK 1 or SPHK 2 have lowered serum S1P levels but develop normally, suggesting that inhibition of both isoforms is required to inhibit angiogenesis. Our medicinal chemistry effort led to the discovery of the first spingosine kinase 1 and 2 dual inhibitors. These inhibitors are selective for SPHK and show inhibition of SPHK driven S1P production both in whole cells and in mice.

MEDI 336

Structure based design and SAR development of 5,6-dihydroimidazolo[1,5-f]pteridine derivatives as novel polo-like kinase-1 inhibitors

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In recent years, polo-like kinase-1 (PLK1) has attracted much attention as a primary drug development target in proliferative diseases. It plays a critical role in the cell cycle, controlling the entry into and progression through mitosis. PLK1 over expression in a broad spectrum of human tumor types has been correlated with poor prognosis and survival rates. Inhibition of PLK1 function in animal models as well as in humans has been shown to result in tumor growth suppression.

Herein, we report the synthesis and SAR for novel series of 5,6-dihydropyrrolo[1,2-f]pteridine PLK1 inhibitors. Representative compounds from this series exhibits high enzymatic and cellular activity against PLK1, and are orally bioavailable and active in *in vivo* animal models.

MEDI 337

Studies toward the synthesis of spiroisoxazolines

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A series of natural products isolated from the sponge of *Verongida* have been intensively studied due to the presence of alkaloids with one, or more bromotyrosine residues. Many of these alkaloid metabolites show interesting bioactivity and cytotoxic properties in tumor cell lines. 11-Deoxyfistularin-3 is cytotoxic against human breast carcinoma cell line MCF-7. Many of these bromotyrosine natural products possess the spiroisoxazoline moiety. Purpose of this project was to find a synthetic methodology towards the synthesis of the spiroisoxazoline ring core. Synthesis of the 4,5-dihydroisoxazole precursor to an analogue of 11-deoxyfistularin-3 was accomplished by using 1,3-dipolar cycloaddition with a functionalized alkene. In order to improve and accelerate our process of forming the spiroisoxazoline, 4-acetyl-5-oxo-hexanoic acid ethyl ester, 30% aqueous formaldehyde and aqueous potassium carbonate were used to form 5-acetyl-3-phenyl-4,5-dihydro-isoxazol-5-yl-propionic acid ethyl ester. The 1,3-dipolar cycloadditon of 5-acetyl-3-phenyl-4,5-dihydro-isoxazol-5-yl-propionic acid ethyl ester with analogous nitrile oxide formed 5-acetyl-3-phenyl-4,5-dihydro-isoxazol-5-yl-propionic acid ethyl ester. Finally, 8-methoxy-3-phenyl-1-5-acetyl-3-phenyl-4,5-dihydro-isoxazol-5-yl-propionic acid ethyl ester oxa-2-aza-spiro[4.5]deca-2,7-dien-6-one was synthesized by intramolecular cyclization, and methylation of 5-acetyl-3-phenyl-4,5-dihydro-isoxazol-5-yl-propionic acid ethyl ester. Our synthesis route reduced from 4 to 3 steps, and the spirocyclization/methylation yields increased for the spiroisoxazolines.

MEDI 338

Design, synthesis, and testing of novel histone demethylase inhibitors as epigenetic modulators

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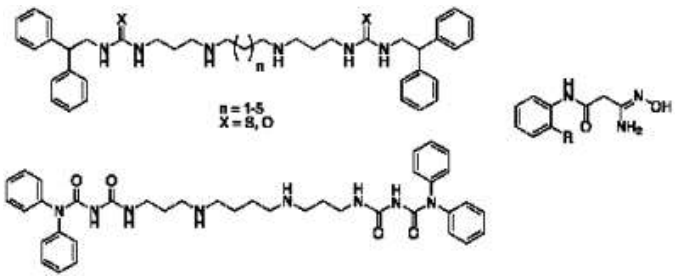

The post-translation modifications of histones play a crucial role in the regulation of gene architecture and expression. Of particular importance is aberrant methylation at specific histone lysine residues, which is associated with the silencing of tumor suppressor genes. The recently discovered enzyme lysine-specific demethylase 1 (LSD1) catalyzes the oxidative demethylation of histone 3 methyllysine 4 (H3K4me1) and histone 3 dimethyllysine 4 (H3K4me2), and is a validated target for antitumor drug discovery. As part of a program aimed at the design, synthesis and evaluation of specific histone demethylase inhibitors, we recently disclosed potent (bis)urea and (bis)thiourea LSD1 inhibitors (Sharma et al., J. Med. Chem. 2010, 53, 5197–5212) that increase levels of H3K4me and H3K4me2 and promote re-expression of aberrantly silenced genes in vitro, and suppress tumor growth in vivo (Figure 1). Herein we report additional novel LSD1 inhibitors, as well as their in vitro and in vivo antitumor effects

MEDI 339

Synthesis and biophysical evaluation of thiazole orange derivatives as DNA G-quadruplex binding ligands

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Guanine-rich telomeric DNA at the end of chromosomes can form a unique DNA secondary structure - G-quadruplex, which is known to inhibit the binding of telomerase to telomeric regions in cancer cells and thus regulate unrestricted cancer cell growth. Hence, G-quadruplex DNA has recently become a promising target in oncology. The formation of G-quadruplex structures is greatly facilitated by G-quadruplex binding ligands such as Thiazole orange (TO). Upon binding to DNA, the fluorescence of TO can increase up to 1000-fold, making it an attractive probe for studying ligand-DNA interactions. However, the selectivity of TO binding to duplex and G-quadruplex DNA is minimal. In the present work, we investigated the feasibility of increasing the TO binding selectivity toward G-quadruplex DNA by introducing side chains that could enhance the binding specificity. TO derivatives containing various side chains were synthesized and their binding to G-quadruplex DNA was evaluated using fluorescence thermal denaturation and circular dichroism. The synthesis of TO derivatives and biophysical measurements will be presented.

MEDI 340

MPC-3100 and MPC-0767, an orally bioavailable Hsp90 inhibitor and its alaninate prodrug: From discovery to the clinic

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The molecular chaperone Hsp90 (heat shock protein 90) is a promising anti-cancer target, since it is known that many oncogenic proteins rely on Hsp90 for both expression and function. Herein, we describe the medicinal chemistry approaches that led to the discovery of MPC-3100, a potent, orally bioavailable purine-based Hsp90 inhibitor with attractive pharmacokinetic properties. The preclinical efficacy of MPC-3100 has been demonstrated in multiple human xenografts in mice. In a Phase I human clinical trial, MPC-3100 was well tolerated at drug exposures shown to have anti-tumor activity in xenograft models. Hsp90 inhibition by MPC-3100 was observed in patients as evidenced by induction of Hsp70 expression in peripheral blood. Finally, data will be presented on a water soluble alanine ester prodrug of MPC-3100, MPC-0767, which is being developed in efforts to improve both the oral dosage forms and bioavailability of MPC-3100.

MEDI 341

Tetrasubstituted phenanthrolines as potent G-quadruplex stabilizers

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Small molecules capable of stabilizing the G-quadruplex structure have been shown to halt the proliferation of cancer cells, making quadruplexes interesting potential targets for development of improved anticancer drugs. We wished to investigate hybrid structures of known phenanthroline-based ligands. We have developed a convenient and high-yielding synthesis of a series of 4,7-diamino substituted 1,10-phenanthroline-2,9-dicarboxamides and evaluated their interactions with various G-quadruplex structures using FRET melting and CD spectroscopy. We will present the outcome of these studies, which resulted in the identification of potent ligands with high selectivity over duplex DNA and high aqueous solubility.

MEDI 342

Orally bioavailable Smac mimetics as antagonists of IAP proteins

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Inhibitors of apoptosis proteins (IAPs) are considered as promising new cancer therapeutic targets and Smac protein is the natural antagonist of IAP proteins. Small-molecule Smac mimetics have been designed and developed as antagonists of IAP proteins. SM-406 is a potent and orally bioavailable small-molecule Smac mimetic designed in our laboratory and is in Phase I clinical development for cancer treatment. Based upon SM-406, a series of new and non-peptidic Smac mimetics were designed, synthesized and evaluated. A number of these new Smac mimetics potently bind to XIAP, cIAP-1 and cIAP-2, efficiently inhibit cell growth and induce robust apoptosis in a

subset of cancer cell lines at low nanomolar concentration. The most promising compounds also show improved pharmacokinetic properties over SM-406/AT-406 and effectively inhibit tumor growth in the MDA-MB-231 xenograft model.

MEDI 343

Structure-based development of biovailable polo-like kinase 1 (Plk1) polo-box domain-binding peptides

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Members of the polo subfamily of protein kinases (Plks) play crucial roles in cell cycle regulation and cell proliferation. Among them, Plk1 has been studied most extensively because of its ability to promote oncogenic transformation represents a potential target for new anticancer therapeutics development. While classical Plk inhibitors are typically directed against the ATP-binding cleft, Plks also contain C-terminal polo-box domains (PBDs) that recognize phospho-Ser (pSer)/phospho-Thr (pThr)-containing motifs, and which provide alternative and potentially specific means of inhibiting Plk function. By examining a series PBD-binding phosphopeptides, we previously identified the 5-mer phosphopeptide “PLHSpT” as minimal sequence that specifically interacts with the Plk1 PBD with high affinity but not with the two closely-related Plk2 and Plk3 PBDs [*Nat. Struct. Mol. Biol.,* **2009** , *16*, 876]. Recently, we discovered a new class of non-canonical PBD-ligand interactions that take advantage of a previously occluded hydrophobic binding channel [*Nat. Chem. Biol.*, **2011** , *7*, 595]. We also devised synthetic methodologies that permit the facile synthesis of these high affinity constructs [*J. Org. Chem.*, **2011** , in press, DOI: 10.1021/jo201599c]. Herein, we utilize these synthetic methodologies to conduct structure activity relationship (SAR) studies with a focus on developing pThr mimetics as a means to improve their drug-like properties, in particular, cell membrance permeability and proteolytic stability.

MEDI 344

Synthesis of carbon-11-labeled chromen-4-one derivatives as new potential PET agents for imaging of DNA-dependent protein kinase in cancer

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The serine/threonine protein kinase DNA-dependent protein kinase (DNA-PK) is an attractive target for cancer treatment and molecular imaging of cancer, since the ability of cancer cells to survive radiotherapy and chemotherapy is often due to their efficiency in repairing the DNA damage that these treatment elicit, and DNA-PK is a key enzyme involved in the repair of DNA double strand breaks (DSBs). Recently a new series of chromen-4-one derivatives has been developed by Griffin et al. as potent and selective inhibitors of DNA-PK to enhance the cytotoxicity of DNA-damaging therapies used in the treatment of cancer. New carbon-11-labeled chromen-4-one derivatives were first designed and synthesized as agents for biomedical imaging technique positron emission tomography (PET) to image DNA-PK in cancer. Unlabeled chromen-4-one derivatives, precursors X-hydroxy-2-morpholino-4*H*-chromen-4-ones (X=8,7,6,5) and standards X-methoxy-2-morpholino-4*H*-chromen-4-ones (X=8,7,6,5), were synthesized from 2-hydroxy-X-methoxybenzoic acids (X=3,4,5,6) in 4 and 3 steps with 20-40% and 36-50% overall chemical yield, respectively. The target tracers, X-[^{11}C]methoxy-2-morpholino-4*H*-chromen-4-ones (X=8,7,6,5), were prepared from their corresponding precursors, X-hydroxy-2-morpholino-4*H*-chromen-4-ones (X=8,7,6,5), with [^{11}C]CH_3OTf through *O*-[^{11}C]methylation and isolated by a simplified solid-phase extraction (SPE) method using a C-18 Sep-Pak Plus cartridge in 40-60% radiochemical yields, decay corrected to end of bombardment (EOB), based on [^{11}C]CO_2, with 185-370 GBq/µmol specific activity at end of synthesis (EOS).

MEDI 345

Design and synthesis of small-molecule radiotracer prototypes for imaging EGFR and HER2 using PET and SPECT

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Small-molecule tyrosine kinase inhibitors specific for EGFR and HER2 show great therapeutic efficacy in subpopulations of cancer patients. The widespread use of these inhibitors is hampered by an inability to predict accurately which patients will be sensitive to anti-EGFR/HER2 therapies. A radiotracer specific for EGFR and HER2 would enable personalization of therapeutic regimens. Previous radiotracers suffered from metabolic instability and rapid dissociation from the receptors. We designed a series of molecules based on the 4-anilinoquinazoline class of tyrosine kinase inhibitors known to dissociate slowly from EGFR and HER2. A convergent synthetic strategy was employed to join these inhibitors to polyethylene glycol linkers bearing various imaging moieties using “click” chemistry. To date we have constructed radiotracer prototypes that are easily optimized and allow for facile introduction of diverse radioisotopes including ^{18}F, ^{123}I, and ^{99m}Tc for use with PET and SPECT imaging, respectively.

MEDI 346

Synthesis and biological evaluation of EGFR /HER-2 inhibitors: Analogs of 5-substituted-4-anilinoquinazoline and 6,7-disubstituted-4-anilinoquinoline-3-carbonitrile – screening for development of novel PET tracers

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The syntheses and biological evaluations of 5-substitued-anilinoquinazolines and 6,7-disubstituted-4-anilinoquinoline-3-carbonitrile analogues are described. The EGFR and HER-2 kinase inhibitory activities, autophosphorylation inhibition, and cell growth inhibition have been analyzed for the two series of compounds and compared with clinical leads (Gefitinib, Erlotinib and EKB-569) on a variety of tumor cell lines harboring different EGFR or HER-2 expression levels or mutational status. The in vitro results demonstrated that the compounds 9, EKB-569 (42) and 43 are suitable candidates as ^{18}F-labeled radiopharmaceuticals for positron emission tomography imaging of cancers.

MEDI 347

Discovery of potent non-ATP competitive MK_2 inhibitors

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A series of non-ATP competitive MK2 inhibitor was discovered using ALIS technology. The screening lead was subjected to chemical principle guided optimization to afford two series of novel, potent and selective MK2 inhibitors, which exhibited cell based anti-TNFα activity at sub-micromolar range.

MEDI 348

Docosahexaenoic acid analogs as imaging probes for lipid mediator pathways

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Docosahexaenoic acid (DHA) is an omega-3 fatty acid that is vital to brain and eye function. Recent investigations established a major role for DHA-derived lipid mediator

pathways for the resolution of inflammation and other bioactions. The development of probes for investigating these pathways as well as for imaging DHA and its metabolites in cells would be valuable for further advances in this area. Therefore, we have designed and synthesized selected DHA analogs to be used as probes, via a terminal “tag” and click-chemistry. Herein we will report the synthesis of one new analog of this type and describe preliminary studies using 15-lipoxygenase (15-LOX), an enzyme linked to inflammation, showing that this DHA analog is capable of being metabolized in the same way as DHA, and thus may be suitable for cell-based studies.

MEDI 349

Development of potent and selective HDAC11 inhibitors: Modulation of the immune response

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The interplay between activity of the histone acetyltransferases and deacetylases (HATs and HDACs, respectively) is responsible for the epigenetic regulation of gene expression and expectedly has significant contributions to a variety of disease states. There are four classes of HDACs and there is emerging data to implicate specific classes with specific activities. Recently, the poorly understood and sole member of the Class IV family, HDAC11, was implicated in the regulation of IL-10 expression and immune tolerance (*Nature Immunol.,* **10** , 92) demonstrating the biological significance of this isozyme for the first time. In this poster we describe the efforts towards the development of isozyme selective inhibitors for HDAC11. This effort utilizes the canonical HDAC inhibitor design composed of the three critical motifs: zinc-binding group, linker, and variable cap groups.

MEDI 350

Heteroaryl imidazolone derivatives as JAK inhibitors

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Cytokines have critical functions in regulating many aspects of immunity and inflammation, ranging from the development and differentiation of immune cells to the suppression of immune responses. Type I and type II cytokine receptors lack intrinsic enzymatic activity capable of mediating signal transduction, and thus require association with tyrosine kinases for this purpose. The JAK family of kinases comprises

of four different members, namely JAK1, JAK2, JAK3 and TYK2, which bind to type I and type II cytokine receptors for controlling signal transduction.

Following cytokine stimulation, JAKs phosphorylate STATs, which dimerize, translocate to the nucleus and activate gene transcription. Recently, selective inhibitors of the JAK family of kinases were suggested as having potential as novel anti-inflammatory agents for Rheumatoid Arthritis and Psoriasis. Two pan-JAK inhibitors (CP-690,550 and INCB-18424) have proven to be efficacious in RA in phase II clinical trials.

In this poster, the design, synthesis and biological activity of a series of heteroaryl JAK inhibitors will be described. The X-ray crystal structure of an initial lead bound in JAK3 was used to understand the binding mode and drive structure-activity relationship studies. Selected compounds showing an appropriate balance between potency and pharmacokinetics were selected for efficacy studies in an in vivo arthritis model.

MEDI 351

Synthesis and biological evaluation of α,β-unsaturated lactones as potent immunosuppressive agents

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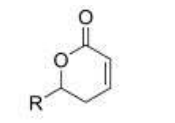
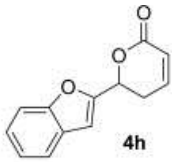
Compounds having α,β-unsaturated lactones display a variety of biological activities. Many research groups have tested both natural and unnatural α,β-unsaturated lactones for as-yet undiscovered biological properties. We synthesized α,β-unsaturated lactones with various substituents at the δ-position and studied their immunosuppressive effects, that is, the inhibition of Interleukin-2 (IL-2) production. Among the compounds synthesized, the benzofuran-substituted α,β-unsaturated lactone 4h showed the best inhibitory activity toward IL-2 production in Jurkat e6-1 T lymphocytes (IC_{50} = 66.9 nM) without cytotoxicity at 10 μM. The results indicated that 4h may be useful as a potent immunosuppressive agent, as well as in IL-2-related studies.



R= aromatic, heteroaromatic adamantane



4h

IC_{50} = 66.9 nM

MEDI 352

Structure-activity relationships and optimization of 3,5-dichloropyridine derivatives as novel $P2X_7$ receptor antagonists

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Screening of a library of chemical compounds showed that the dichloropyridine based analog **8** was a novel $P2X_7$ receptor antagonist. To optimize its activity, we assessed the structure-activity relationships (SAR) of **8** , focusing on the hydrazide linker, the dichloropyridine skeleton and the hydrophobic acyl (R_2) group. We found that the hydrazide linker and the 3,5-disubstituted chlorides in the pyridine skeleton were critical for $P2X_7$ antagonistic activity and that the presence of hydrophobic polycycloalkyl groups at the R_2 position optimized antagonistic activity. On the EtBr uptake assay in *$hP2X_7$*-expressing HEK293 cells, the optimized antagonists, **51** and **52** , had IC_{50} values of 4.9 and 12.9 nM, respectively. The antagonistic effects of **51** and **52** were paralleled by their ability to inhibit the release of the pro-inflammatory cytokine, IL-1b, by LPS/IFN-g/BzATP stimulation of THP-1 cells (IC_{50} = 1.3 and 9.2 nM, respectively). In addition, **52** strongly inhibited iNOS/COX-2 expression and NO production in THP-1 cells, further indicating that this compound blocks inflammatory signaling and suggesting that the dichloropyridine analogs may be useful in developing $P2X_7$ receptor targeted anti-inflammatory agents.

MEDI 353

Immunosuppressive effects of subglutinol derivatives

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Subglutinols A and B are members of the diterpenoid pyrone class of natural immunosuppressive agents isolated from Fusarium subglutinans. To assess their functional mechanisms of immune modulation, the activities of synthetic intermediates of subglutinols A and B were assayed. Subglutnol A and its methyl-g-pyrone derivative, **10,** significantly suppressed IL-2 production by stimulated Jurkat T cells and human and murine $CD4^+$ primary T cells. These compounds also efficiently inhibited the expression of the T-cell activation markers, CD25 and CD69. Moreover, only compound **10** showed a moderate inhibition of Kv1.3 channel activity. These results indicated that subglutinol structure could be utilized to design new immunosuppressive agents.

MEDI 354

Brain penetrant Jun kinase inhibitors for the treatment of multiple sclerosis

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c-Jun N-terminal kinases (JNKs) are involved in the proliferation and maturation of immune cells, e.g.T-cells, in the periphery while also being key players in the pathways associated with neuronal cell death. Thus, CNS-penetrant JNK inhibitors that combine immunomodulatory and neuroprotective efficacy could offer promising therapeutic options for MS and other neurodegenerative disorders.

The prototype JNK inhibitor, ER-358063, significantly improved clinical symptoms and immunohistochemical endpoints when administered systemically at the first onset of disease symptoms. However, some weight loss was observed after chronic administration, which might have been due to the limited selectivity of ER-358063 against other kinases within the kinome.

Compounds ER-409903 and ER-417258, belonging to a new 7-azaindole-based series of selective JNK inhibitors, significantly improved disability score in animal models of MS when administered chronically at 20 mg/kg p.o. q.d. with weight loss no longer being observed over a period of up to 56 days post immunisation.

MEDI 355

Identification of a TYK2 selective lead series

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TYK2, is a member of the Janus family kinases (JAKs) that mediates signal transduction of the IL-12 and IL-23 interleukin receptors via activation of transcription factors. Pyridine **1** , was identified as a hit from a high throughput screen of the Genentech Library. In addition to its attractive ligand efficiency, moderate selectivity against other members of the JAK family (JAK1, JAK2, and JAK3) was observed. Systematic hit to lead (H2L) SAR exploration led to discovery of cyclopropyl amide **2** . This early lead molecule displayed excellent potency, ligand efficiency, selectivity, and ADME properties.

MEDI 356

Benzthiazoles as leukotriene A_4 hydrolase inhibitors

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Inflammatory diseases such as rheumatoid arthritis, chronic obstructive pulmonary disease, atherosclerosis, inflammatory bowel disease, ulcerative colitis and asthma, can be linked to leukotriene B_4 (LTB_4) production. Leukotriene A_4 hydrolase (LTA_4H) catalyzes the conversion of LTA_4 to LTB_4. An LTA_4H inhibitor, therefore, should hold potential therapeutic value against these diseases. The synthesis of benzthiazole inhibitors and the biological trends observed will be discussed.

MEDI 357

Novel scaffold replacement methodology applied to the discovery of P38 MAP kinase inhibitors

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A new application for performing scaffold replacements, fragment linking, and R-group optimization is presented. The application is applied to the discovery of novel P38 MAP kinase inhibitors where the diaryl urea core of doramapimod, a known P38 inhibitor, is replaced to produce promising novel candidate inhibitors.

MEDI 358

Novel phosphate prodrugs of N-acetyl-(D)-glucosamine for the treatment of osteoarthritis

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(*D*)-Glucosamine and other nutritional supplements have emerged as a safe and alternative therapy for osteoarthritis (OA), a chronic and degenerative articular joint disease. To improve the oral bioavailability of (*D*)-glucosamine we used the phosphoramidate ProTide approach, developed by us for antiviral nucleosides. In particular, *N*-acetylglucosamine was converted to a series of arylaminoacyl phosphoramidates with ester and amino acid variation. Compounds were prepared by two routes, with or without sugar protection, and were isolated as phosphate

diastereoisomers. The compounds were assayed for cellular toxicity and for inhibition of IL-1 induced glycosaminoglycan release (i.e., proteoglycan degradation) from bovine and human articular cartilage *in vitro* explant cultures.

MEDI 359

Synthesis of new positron emission tomography (PET) radioligands for PDE10 imaging: In vivo evaluation of [^{18}F]MNI-654 and [^{18}F]MNI-659 in nonhuman primate

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Phosphodiesterase 10 (PDE 10) has been implicated in various neurological disorders, including schizophrenia, Alzheimer's, Parkinson's and Huntington's diseases. We present the synthesis, and in vitro and in vivo evaluation of two fluorinated oxoquinazoline derivatives MNI-654 and MNI-659. These compounds were prepared in eight steps using a convergent synthesis with overall yields of 4 and 18%. They showed subnanomolar binding affinity for rat striatal PDE10, were radiolabeled with fluorine-18. [^{18}F]MNI-654 and [^{18}F]MNI-659 were obtained in a 10±3% radiochemical yield and with radiochemical purity of ≥ 98%. Brain distribution of [^{18}F]MNI-654 and [^{18}F]MNI-659 by PET imaging in non human primates was in accordance with reported data of PDE 10 in monkey. Kinetic modeling and selectivity of the signal for the target demonstrated by performing blockade studies using the structurally unrelated PDE10 antagonist MP-10 suggest that [^{18}F]MNI-654 and [^{18}F]MNI-659 should be evaluated in human.

MEDI 360

Synthesis and biological evaluation of tetrabenazine derivatives for brain vesicular monoamine transporter VMAT2 imaging

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Imaging ligands of VMAT2 could play a crucial role in studying pathology affecting dopamine neurotransmission such as schizophrenia, Parkinson's and Huntington's diseases. In search of new radiotracers for *in vivo* imaging, we explored the structure-activity relationship of tetrabenazine derivatives as VMAT2 ligands. We report herein the synthesis and *in vitro* binding of 27 new tetrabenazine analogues with prosthetic chains bearing either fluorine or iodine in position 9 and 10 of the benzoquinoline as well as replacement of the isobutyl group in position 3 by various alkyl chains. The essential role of the 3-position was confirmed, whereas 9- and 10-derivatives designed for PET or SPECT imaging showed affinities from 1.54 to 86 nM. Four candidates stand out, exhibiting high affinity for VMAT2 (K_i=1.54-2.59 nM vs. K_i=1.57 nM for the known

radiotracer [^{18}F](±)-DTBZ). Radiolabeled versions of the resolved active enantiomer should afford a new generation of VMAT2 radiotracers for *in vivo* imaging.

MEDI 361

Pharmacophore based 3D-QSAR, homology modeling, docking studies and microwave-assisted synthesis of some novel triazolothienopyrimidines as possible adenosine receptors antagonists

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Asthma and chronic obstructive pulmonary disease (COPD) are prevalent inflammatory disorders of the lung and are poorly managed. In the present work, pharmacophore based 3D-QSAR (PHASE, Schrodinger Inc.) and docking studies (Glide v5 XP, Schrodinger Inc.) studies were carried out to explore the physicochemical requirements for selective binding towards A_3 AR in order to design and develop new and safe NCEs with fused thienopyrimidine scaffold as possible A_3 antagonists as it is postulated to be a potential target for the treatment of Asthma. Docking studies were carried out by using the homology model of A_3 AR developed (Prime, Schrodinger) using the X-Ray crystal structure of A_{2A} AR (PDB:3EML). All the designed compounds (thieno[3,2-*e*]-[1,2,4]triazolo[1,5-*c*]pyrimidins) were synthesised using the eco-friendly microwave assissted organic synthesis (MAOS) methods. *In vitro* AR binding studies as well as *in vivo* anti-inflammatory studies indicates that some of the compounds are very potent and the results are in consonance with the *in-silico* studies.

MEDI 362

Highly potent and selective fluorescent antagonist of the adenosine A3 receptor: Use as an imaging tool

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The A_3AR is a G protein-coupled receptor that shows promise as a therapeutic target for cancer, glaucoma, and various autoimmune inflammatory disorders. We synthesised a series of fluorescent congeners containing different linkers and fluorophores based around a non-xanthine antagonist. One of these congeners displayed high affinity at the A_3AR (K_b = 0.5±0.1 nM) and is ≥ 400-fold selective over other AR subtypes. Confocal microscopy revealed clear, displaceable membrane labelling of CHO-A_3 cells, with no visible labelling of CHO-A_1 cells under identical conditions. Treatment of HEK293T cells,

containing a mixed AR population, with 5nM of this fluorescent congener led to specific A_3AR labelling. The subtype specificity, along with the excellent imaging properties, make this fluorescent congener an ideal tool for studying A_3AR expression levels, organisation, and role in cell signalling. This congener could also be used in a competitive binding assay to replace traditional radioligand-based screening.

MEDI 363

Discovery and characterization of novel small molecule inhibitors of Abeta1-42 for the treatment of Alzheimer's disease

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Alzheimer's Disease (AD) is a form of senile dementia, characterized by a progressive loss of memory and cognitive function. It has been hypothesized that formation of beta-amyloid (Abeta) plaques is key to the development and progression of the disease. Therefore, inhibition of Abeta plaque formation has emerged as an attractive way of therapeutic intervention. To investigate whether small molecules can inhibit the aggregation of Abeta, we have employed indole and aza-indole moieties as key fragments in our compound design. In this poster, we will present the Structure Activity Relationship (SAR) of our compound optimization guided by a standard Thioflavin-T (ThT) screening assay. Further characterization and optimization of our compounds, *e.g.* metabolic stability (human & mouse), permeability, etc., allowed the identification of small molecules with promising brain penetration.

MEDI 364

Development of chalcone-based apoE modulators through structure-activity relationship (SAR) study

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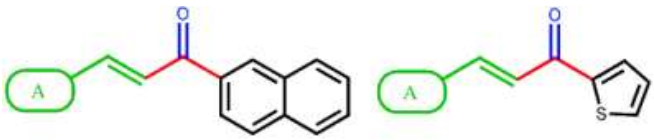
Apolipoprotein E (apoE) is a transport lipoprotein that helps distribute cholesterol and triglycerides in the body and the brain. ApoE polymorphism and high levels of lipoproteins are risk factors for the development of Alzheimer's Disease (AD). Our research group has previously designed and synthesized small molecules to modulate apoE gene expression. Two distinct classes of chalcones exhibited contradictory effects

on apoE gene expression. Further elaborative SAR study with these two specific classes of chalcones (Chart 1) will be presented here.



Ring A = aryl, substituted aryl, heterocycles

Chart 1. Chalcones for apoE modulation study

MEDI 365

Development of apoE inhibitors by structure-activity relationship (SAR) study on triarylamine compounds

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Apolipoprotien (apoE) is a cholesterol and lipid-carrier lipoprotein implicated in aging, atherosclerosis, Alzheimer's Disease (AD), and other neurological and lipid-related disorders. ApoE is a major genetic risk factor for the development of AD. Studies have established that the e4 isoform of the apoE gene increases an individual's risk for developing late-onset AD. We had screened four scaffolds in apoE ELISA assays and demonstrated that specific triarylamines significantly inhibited apoE gene expression. Further structure-activity relationship study performed on the triarylamine scaffold will be presented here. We approached the SAR study by locking two optimized areas of the pharmacophore and varying the rest (Chart 1). Enhancement of efficacy, reduction of lipophilicity, and improved of chemical stability were the primary goals for this study.

R_1R_2NH = morpholine, isobutylamine, *sec*-butylamine
R_3, R_4 = alkyl, aryl, heterocycles, cyclic rings

Chart 1. The triarylamine scaffold with one fixed naphthalne ring, three fixed amines and varying R_3 and R_4 groups.

MEDI 366

Structural modification of (-)-N^6-(2-(4-(biphenyl-4-yl)piperazin-1-yl)-ethyl)-N6-propyl-4,5,6,7-tetrahydrobenzo[d]thiazole-2,6-diamine (D-264): An effort to improve the blood brain barrier crossing ability and multifunctional property in lead compounds for the treatment of Parkinson's disease

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Parkinson's disease (PD) is an age-related, progressive neurodegeneration disorder, characterized by gradual loss of dopaminergic neurons in the substantia nigra region of the brain. The currently available therapies provide only symptomatic relief without addressing the underlying pathophysiology. Our hypothesis is to develop multifunctional ligands, with D2/D3 agonist, antioxidant and neuroprotection property. The titled compound is one of our lead molecule which has shown neuroprotection property in both *in vitro* and *in vivo* animal model of PD. The goal behind this study is to enhance the entry of the titled compound into the brain without compromising it's agonist potency. The structural modification is mainly centered around the introduction of hydroxyl group at various positions on the accessory binding, biphenyl ring of this hybrid molecule. This modification will reduce the lipophilicity and the introduction of more than one hydroxyl group at a suitable position can further potentiate it's antioxidant and neuroprotection property. Various analogs of the titled compound have been designed and synthesized. Compound D-433 with hydroxyl substitution exhibited the highest selectivity in binding (D2/D3=341) and functional GTPγS assay (D2/D3 =123). Interestingly, in both reserpine-induced hypolocomotion and 6-OHDA lesioned animal model of PD, D-433 exhibited longer duration of action compared to D-264. This is a clear indication of more facile entry of D-433 into the brain. Antioxidant, neuroprotection and alpha synuclein aggregation inhibition assays are currently under study.

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MEDI 367

Structure activity relationships (SAR) of 3-chloro-3'-((2-cyclopentyl-3-oxo-2,3-dihydrobenzo[d]isothiazol-6-yloxy)methyl)biphenyl-4-carboxylic acid analogs that are metabotropic glutamate receptor subtype-2 (mGluR2) positive allosteric modulators

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Modulation of metabotropic glutamate receptor subtype 2 (mGluR2) by small molecules represents a promising approach for the treatment of diseases caused by aberrant glutamatergic transmission such as schizophrenia, anxiety or drug dependence. Our ongoing program is focused on the design and synthesis of new brain penetrant, systemically active small molecule mGluR2 positive allosteric modulators (PAMs). Recently, we reported the design, synthesis and characterization of 3-chloro-3'-((2-cyclopentyl-3-oxo-2,3-dihydrobenzo[d]isothiazol-6-yloxy)methyl)biphenyl-4-carboxylic acid, a potent, selective and orally active mGluR2 PAM.[1] This brain penetrant benzisothiazol-3-one derivative decreased cocaine self-administration in rats, providing *in vivo* proof-of-concept for the use of mGluR2 PAMs for the treatment of cocaine dependence. Further investigation of the SAR around this compound provided a series of benzisothiazolone-based mGluR2 PAMs that were characterized *in vitro*. Details of the structure activity relationships (SAR) of new potent and selective mGluR2 PAMs in this series will be presented.

1. Dhanya, R-P.; Sidique, S.; Sheffler, D. J.; Highfield Nickols, H.; Herath, A.; Yang, L.; Dahl, R.; Ardecky, R.; Semenova, S.; Markou, A.; Conn, P. J.; Cosford, N. D. P. Design and Synthesis of an Orally Active Metabotropic Glutamate Receptor Subtype-2 (mGluR2) Positive Allosteric Modulator (PAM) that Decreases Cocaine Self-administration in Rats. *J. Med. Chem*. **2011** , *54(1),* 342–353.

MEDI 368

Design, synthesis, and evaluation of novel metabotropic glutamate receptor subtype-2 (mGluR2) positive allosteric modulators (PAMs): Refinement of SAR

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Metabotropic glutamate receptors (mGluRs) are G protein-coupled receptors that regulate synaptic strength in the central nervous system (CNS). Group II mGluRs (mGluR2 and mGluR3) are primarily localized presynaptically and modulate glutamate release. Small molecule modulators of Group II mGluRs have significant potential as therapeutic agents for several neurological and psychiatric disorders such as anxiety, depression, schizophrenia and drug addiction. We recently reported our preliminary results on a novel series of mGlu2 receptor positive allosteric modulators (PAMs).[1] Our lead optimization process involved not only *in vitro* assays measuring potency against mGluR2, but also selectivity against other mGluR subtypes and evaluation in *in vitro*

ADME/T assays that are helpful for predicting the drug-like properties of compounds. Expansion of the SAR in this series led to new analogues with promising *in vitro* potency, selectivity and ADME/T profiles. Based on the *in vitro* data, the most promising analogues were selected for comprehensive *in vivo* evaluation, including rat pharmacokinetic (PK) experiments and behavioral studies. This presentation will discuss the design, synthesis and structure activity relationships (SAR) of new potent and selective mGluR2 PAMs.

1. Dhanya, R-P.; Sidique, S.; Sheffler, D. J.; Highfield Nickols, H.; Herath, A.; Yang, L.; Dahl, R.; Ardecky, R.; Semenova, S.; Markou, A.; Conn, P. J.; Cosford, N. D. P. Design and Synthesis of an Orally Active Metabotropic Glutamate Receptor Subtype-2 (mGluR2) Positive Allosteric Modulator (PAM) that Decreases Cocaine Self-administration in Rats. *J. Med. Chem*. **2011** , *54(1),* 342–353.

MEDI 369

Computational studies of conotoxins as nicotinic acetylcholine receptor (nAChRs) antagonists

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Several diseases such as schizophrenia, Tourette's syndrome, Parkinson's, and Alzheimer's are caused by improper regulation of the neurotransmitter dopamine. Native α-conotoxin MII (α-CTxMII), a neurotoxic peptide from the venom of the marine cone snail, is a potent competitive neuronal nicotinic acetylcholine receptor (nAChRs) antagonist. Neuronal nAChRs are known to regulate dopamine release at nerve cells in response to nicotine and/or acetylcholine binding. In particular the $\alpha_6\beta_2$ subunit is believed to reside at the presynapse in the nigrostriatal pathway and is suspected to be involved in motor behavior. The antagonistic property of α-CTxMII makes it an attractive starting point for developing medications for neurological disorders. Unfortunately, α-CTxMII is unable to differentiate between the $\alpha_3\beta_2$ or $\alpha_6\beta_2$ subunits of nAChRs resulting in system wide inhibition of dopamine release. It has been shown that the His12 residue is critical for the binding of α-CTxMII to the $\alpha_6\beta_2$ subunit. The α-CTxMII-E11A shows specificity towards the $\alpha_6\beta_2$ subunit of nAChRs and therefore represents a first generation of specific nAChRs antagonists. Computational evaluation of the amino acid environment in α-CTxMII and several variants (E11A, and N5R-E11A-H12K) are being conducted in order to reveal the electrostatic environment, resulting pKa and the impact of the protonation states on toxicity.

MEDI 370

Thiazolo[4,5-d]pyrimidines and 5-(alkylthio)-4-(arylamino)pyrimidine derivatives as corticotropin releasing factor receptor 1 (CRFR1) antagonists

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Adaptive responding for threatening stressors is of fundamental importance for survival. Hyperactivation of corticotropin releasing factor (CRF) in stress response system pathways is linked to stress-related psychopathology. The CRF receptor antagonists, particularly CRF receptor 1, have been proposed as novel therapeutic agents for depression, anxiety and addiction disorders. CRF is 41 amino acid containing peptide released from Para ventricular nucleus (PVN) of hypothalamus and is a critical integrator of the hypothalamic-pituitary-adrenal (HPA) axis in response to stress. CRF mediates is actions through two G protein-coupled receptors such as CRF receptor 1 (CRFR1) and CRF receptor 2 (CRFR2). While CRFR1-mutant mice display a depleted stress response and display anxiolytic-like behavior, whereas CRFR2-mutant mice are hypersensitive to stress and display anxiogenic-like behavior. Thus CRFR1 antagonists may provide novel therapeutic agents for treating anxiety, depression and addictive disorders.

Numerous peptide and non-peptide molecules have been shown to inhibit CRF mediated stress disorders through CRFR1. In our studies we have prepared Thiazolo[4,5-d]pyrimidines and 5-(alkylthio)-4-(arylamino)pyrimidine derivatives to serve as CRFR1 antagonists. These derivatives were analyzed for mRNA expression of several markers of psychopathology including; CRF1, serotonin transporter (SERT), the cAMP response element-binding (CREB), monoamine oxidase-A (MAO-A), dopamine transporter (DAT), dopamine β-hydroxylase (DBH) and cAMP levels in αT3-1 pituitary mouse cell line and compared with Antalarmin. Some of the derivatives showed comparable results with Antalarmin. Those molecules that will show comparable parameters of interaction with CRFR1 as Antalarmin will be further evaluated in animal studies.

MEDI 371

Development of drug-like small molecule group II metabotropic glutamate receptor (mGluR) positive allosteric modulators (PAMs) having differential selectivity: Discovery of mGluR PAMs possessing either selective or balanced mGluR2/mGluR3 activity

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Dysfunctional glutamatergic transmission contributes to the pathology of many diseases including schizophrenia, anxiety, and drug addiction. One approach to address this condition is modulation of Group II mGluRs by small molecules. Group II metabotropic glutamate receptors (mGluR2 and mGluR3) are found pre- and postsynaptically and couple to G_i and G_o-proteins to negatively regulate the activity of adenylyl cyclase and also function as glutamate autoreceptors to modulate presynaptic glutamate release. We have an ongoing program focused on designing and optimizing small molecule modulators of Group II mGluRs as starting points for further therapeutic development and *in vivo* evaluation. In the present study, we sought to develop modulators possessing varying degrees of selectivity between mGluR2 and mGluR3. In the course of our efforts, we discovered both mGluR2 selective and balanced mGluR2/mGluR3 positive allosteric modulators (PAMs) having comparable PAM activity at both receptors. Our strategy involved the identification of several key fragments from a series of mGluR2 PAM scaffolds and combination of these fragments in a matrix approach to generate a focused library of new structures. In addition to the unprecedented selectivity, these PAMs have favorable ADME/T and pharmacokinetic properties and represent systemically active mGluR PAMs to be further characterized in relevant tests, including models of cocaine dependence.

MEDI 372

Heterocycle-fused 4-phenyl tetrahydroisoquinolines as dual NET/DAT inhibitors

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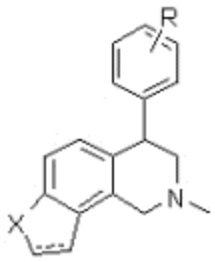
Monoamine reuptake inhibitors have been used to treat a number of CNS disorders, especially depression. As part of our pursuit of novel monoamine reuptake inhibitors, we designed several series of heterocycle-fused tetrahydroisoquinolines as potent dual NET/DAT inhibitors. Here we report the synthesis and in vitro evaluation of these compounds in NET (norepinephrine transporter), DAT (dopamine transporter) and SERT (serotonin transporter) binding assays.



*Eli Lilly and Company, 893 S. Delaware St. Indianapolis, Indiana 46285; **AstraZeneca Pharmaceuticals LP, 1800 Concord Pike, P.O. Box 15437, Wilmington, DE 19850-5437

MEDI 373

Synthesis and identification of fluorinated (2S,4R,5R)-2-(bis(4-fluorophenyl)methyl)-5-((4-hydroxybenzyl)amino)tetrahydro-2H-pyran-4-ol, 4-((((3S,6S)-6-(bis(4-fluorophenyl)methyl)tetrahydro-2H-pyran-3-yl)amino)methyl)phenol and analogs thereof as new generation triple uptake inhibitors for antidepression therapy

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Anti-depressants are crucial in the fight against major depression disorder (MDD) which affects nearly 20% population worldwide. The MDD represents a potentially fatal health problem because majority of patients tend to have thoughts of suicide or life-threatening behaviors. Over the past two decades, the monoamine therapy was the primary choice for treatment. The monoamine therapy relies on selective reuptake inhibition of serotonin (5-HT) and norepinephrine (NE) neurotransmitters. Recently, several pre-clinical as well as clinical studies have strongly indicated that dopaminergic inhibition is also associated with depression. More recently, triple uptake inhibitors (TUIs) have emerged as a new generation potent anti-depressants. Reports from pre-clinical studies denote that the TUIs could perhaps result in a rapid onset of action as well as improved efficacy by encompassing their ability to inhibit all three neurotransmitters. In addition, pharmacological studies strongly indicated that the TUIs may provide pain relief and address symptoms of anhedonia. As a part of our ongoing research on the discovery and development of novel TUIs, we have designed and synthesized a series of fluorinated di- and trisubstituted pyran derivatives. From the uptake studies with all three monoamine transporters, we have indentified compounds like **D-471** (K_i of 38.4 nM, 4.81 nM and 59.0 nM for DAT, NET, and SERT respectively) as potent TUIs. Detail SAR studies and pharmacological characterization will be presented. This work is

supported by National Institute of Mental Health/ National Institute of Health MH084888 (AD).

MEDI 374

Structure-activity relationship study of the neuroprotective effects of Vitamin K derivatives

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Historically known for its role in blood coagulation, Vitamin K has begun to emerge as a potentially important nutrient for brain function. While the full extent of its involvement in the brain has not yet been fully explored, some studies have related suboptimal Vitamin K status with age-related cognitive decline. Furthermore, it was recently reported that Vitamin K was able to protect neurons and oligondentrocytes from oxidative injury *ex vivo*. In this study, we take a chemical approach to define the optimal and minimum pharmacophore responsible for the neuroprotective effects of Vitamin K. In doing so, we have developed a series of compounds with favorable drug characteristics that provide nearly 100% protection at nanomolar concentrations in a well-defined model of neuronal oxidative stress.

MEDI 375

Synthesis and evaluation of clickable active site-directed γ-secretase photoaffinity probes

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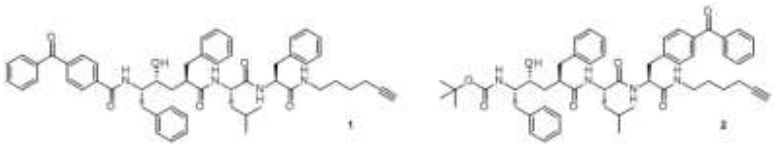
γ-Secretase is responsible for generating the amyloidogenic Aβ42 peptide which is believed to be associated with Alzhiemer's disease. Currently, there are many organizations that are investing efforts in developing both inhibitors and modulators of γ-secretase. Therefore, an improved understanding of the γ-secretase complex is integral in helping develop potential therapeutics. Herein we describe the synthesis of two transition state inhibitors (**1** and **2**) of γ-secretase which incorporate a photoactivatable benzophenone as well as a 'clickable' alkyne moiety, thus allowing for conjugation of azide-linked reporter tags (e.g. fluorescent, biotin) via a copper catalyzed 3+2 cycloaddition reaction. Furthermore, we show the utility of this approach through photoaffinity labeling of **1** and **2** in HeLa membranes followed by conjugation with TAMRA-azide and analysis of the labeled proteins by in gel fluorescence. These

compounds complement the chemical biology tool box that is available to help further elucidate the functions of the γ-secretase complex.



MEDI 376

Structure activity relationship study of N^6-(2-(4-(1H-indol-5-yl)piperazin-1-yl)ethyl)-N^6-propyl-4,5,6,7-tetrahydrobenzo[d]thiazole-2,6-diamine analogs: Development of highly selective D3 dopamine receptor agonists and their pharmacological characterization

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Parkinson's disease (PD) is a progressive, neurodegenerative disorder that results from the death of dopamine-producing cells in the substantia nigra region of the midbrain. Here we report a structure-activity relationship study based on our previously reported hybrid, pharmacophore structure. Our current series of molecules aim to investigate the chemical and molecular flexibility, along with the basicity of the aryl-piperazine region of our hybrid structure in dopamine D2/D3 receptor binding. Our efforts have produced two separate classes of compounds based on their affinity for D2/D3 receptor. Binding assays were carried out with HEK-293 cells expressing either D2 or D3 receptor. Competitive binding with tritiated spiroperidol was used to evaluate inhibition constants (Ki) of test compounds. Functional activity of selected compounds in stimulating [35S]GTPγS binding was assessed in CHO cells expressing human D2 receptor and AtT-20 cells expressing human D3 receptor. SAR results indicate that lead compound D-440 (K_i D2 = 1,073 nM, K_i D3 = 1.84 nM, D2/D3 = 583.2) displays high selectivity for the D3 receptor, with affinity for the D2 receptor in the micro-molar range, while maintaining D3 affinity in the low nano-molar range. Functional data (EC_{50} D2 = 114 nM, EC_{50} D3 = 0.26 nM, D2/D3 = 438) also indicate selective, agonist activity of D-440 at the D3 receptor. Compounds with high D3 receptor affinity and less selectivity are being developed. A comparison of these two distinct classes of D2/D3 ligands in PD animal models is also under way. Future studies will explore the potential use of these compounds as neuroprotective therapy for PD.

Supported by NS047198 (AKD).

MEDI 377

Further structure activity relationship studies of 4-((((3S,6S)-6-benzhydryltetrahydro-2H-pyran-3-yl)amino)methyl)phenol and its analogs: Identification of novel triple uptake inhibitors as new generation antidepressants

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Major depression disorder is significant health problem with 10-20% of all adults suffering from this disease. Monoamine therapies have so far been the most successful approach for treating depression. Although dopaminergic inhibition has been strongly associated with depression evidenced by preclinical and clinical studies, currently available treatment involves inhibition of serotonergic and noradrenergic system but not dopaminergic neurotransmission. Recently, triple reuptake inhibitors (TUI), which inhibits uptake of all three neurotransmitters, have recently been implicated in new generation of potent antidepressants. Preclinical studies indicate that a drug inhibiting the uptake of all three of these neurotransmitters could produce a more rapid onset of action and should possess greater efficacy compared to traditional antidepressants and also address anhedonia due to additional dopaminergic activity. In our on-going SAR studies to discover new molecules for development of novel TUIs, we have designed and synthesized several asymmetric di- and tri-substituted pyran derivatives. Uptake inhibition studies with all three monoamine transporters indicated variety of activities depending upon the nature of substitutions either on the pyran ring or on the N-benzyl moiety. SAR studies indicate the compound **D-485** showed triple reuptake inhibitory (TUI) activity profile, as these molecules exhibited potent uptake inhibition for all the monoamine transporters ((K_i of 234.0 nM, 2.68 nM, and 33.6 nM for DAT, SERT, and NET respectively). Synthesis and SAR studies will be presented. This work is supported by National Institute of Mental Health/ National Institute of Health MH084888 (AKD).

MEDI 378

Neuroprotective activities of a common structural motif in neuroprotective natural products

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Stroke has reached epidemic levels globally; over 15 million people suffer from stroke worldwide annually. Currently, the available options for the treatment of stroke-related brain damage are limited. In our efforts to discover compounds with neuroprotective properties as therapies for ischemic stroke, we recognized that structurally diverse natural neuroprotective molecules (e.g. limonoids, cardiac glycosides & estrogen-like compounds) shared a common structural motif. In order to determine the structural elements required for potent neuroprotective activity, we synthesized the core structure

and its analogues and evaluated their neuroprotective activity. Some of the analogues showed dose-dependent neuroprotective activity at micromolar concentration in terms of neuronal survival against hydrogen peroxide induced cell death *in vitro*. The results will be useful in establishing the structure-activity relationship requirements for developing more potent neuroprotective agents.

MEDI 379

Identification of highly potent and selective dopamine D_3 ligands

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Dopaminergic neurotransmission is mediated by five dopamine receptors (D_1-D_5), which can be grouped into the D_1-like (D_1 and D_5) and D_2-like (D_2, D_3, and D_4) receptor subtypes. The dopamine 3 (D_3) subtype receptor has been implicated as an important target for agents currently used clinically for the treatment of schizophrenia, Parkinson's disease, depression, and other neurological diseases. Although potent and selective dopamine D_3 receptor ligands based upon *in vitro* binding data have been reported, ligands that are highly active and selective *in vivo* at the D_3 receptor are still lacking. We report herein the identification of two novel D_3 ligands that are highly potent and selective both *in vitro* and *in vivo* at the D_3 receptor.

MEDI 380

Novel 6-aminonicotinic acids as γ-aminobutyric acid receptor ligands: Synthesis, pharmacology, and modeling

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As the major inhibitory neurotransmitter in the central nervous system, γ-aminobutyric acid (GABA) is crucial for the overall function of neurotransmission. To target GABA-related diseases such as anxiety, epilepsy, schizophrenia, and depression a better understanding of the GABA system is necessary and can be obtained via subtype-selective ligands. A series of restricted GABA isosteres were pharmacologically characterized at native $GABA_A$ receptors leading to the identification and development of 6-aminonicotinic acid as a new GABA-bioisosteric scaffold with potential for subtype-selectivity by introduction of different substituents. A series of 2-,4- and 5-substituted 6-aminonicotinic acid analogs were synthesized and pharmacologically characterized at

native $GABA_A$ receptors to probe the binding site. The results revealed strict demands for the substitutions pattern in order to retain binding affinity; only the 2- and 4-positions allowed substitutions. Rational development of the 6-aminonicotinic acid analogs is ongoing by use of a recently developed homology model of the $GABA_A$ receptor.

MEDI 381

Design and characterization of new peptide-based vectors for blood-brain barrier targeting and CNS drug delivery

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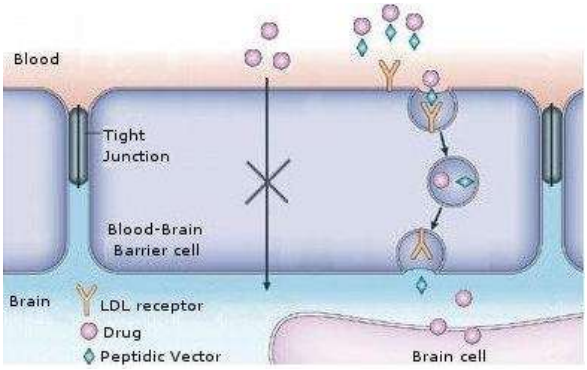
Drug delivery to the brain is hindered by the presence of the blood–brain barrier (BBB). To accomplish the task of nutrient transport, the brain endothelium is endowed with various transport systems, including receptor-mediated transcytosis (RMT). This system can be used to shuttle therapeutics into the brain as a non-invasive manner. In this field, members of the low density lipoprotein receptor (LDLR) family are relevant as drug delivery systems. The main goal of this project is dedicated to the development of new peptide-based ligands of LDLR as potential BBB-vectors.



The screening of a phage-display library directed to LDLR led to the identification of a cyclic 15-mer peptide with high *in vitro* affinity. A chemical optimisation led to the discovery of a cyclic 8-mer lead peptide containing an unnatural amino acid. In order to assess its ability to act as a BBB-vector, it was coupled to an opioid peptide known to be unable to cross the BBB on its own. Brain uptake as well as the nociceptive pharmacological effects of such a conjugate was then measured *in vivo*. These first results were then assessed by biphotonic microscopy imagery.

MEDI 382

Development of high affinity, highly selective agonist ligands for positron emission tomography imaging of the dopamine D_2 receptor

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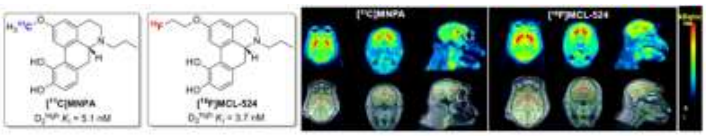
Noninvasive imaging of molecular processes in living subjects using positron emission tomography (PET) and single photon emission computed tomography (SPECT) is a valuable tool for the investigation of human neurochemistry and neuropharmacology *in vivo*. It is hypothesized that, in Parkinson's, schizophrenia, and other DA-dependent neurological disorders, the majority of D_2 receptors prefer to be in the D_2^{high} state. Therefore, an *agonist* is expected to be more sensitive to endogenous DA concentration changes than an antagonist tracer, and could be a superior probe for quantifying DA concentration. We recently reported the development of high-affinity, highly selective fluorinated aporphines as potential D_2 receptor imaging agents. Preliminary PET studies indicate that at least one ligand, **MCL-524** , has potential as a viable PET radiotracer, as compared to [^{11}C]MNPA (fig. 1). The synthesis of cold analogs, radiolabeled ligands, *in vivo* PET imaging, and biodistribution will be presented.



MEDI 383

Fully automated synthesis of PET TSPO radioligands [^{11}C]DAA1106 and [^{18}F]FEDAA1106

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The translocator protein 18 kDa (TSPO), formerly known as peripheral-type benzodiazepine receptor (PBR), is an attractive target for molecular imaging of neuroinflammation and tumor progression. [^{11}C]DAA1106 (*N*-(2-[^{11}C]methoxy-5-methoxy-benzyl)-*N*-(5-fluoro-2-phenoxyphenyl)-acetamide) and [^{18}F]FEDAA1106 (*N*-(5-Fluoro-2-phenoxyphenyl)-*N*-(2-(2-[^{18}F]fluoroethoxy)-5-methoxybenzyl)acetamide) are two promising brain TSPO/PBR radioligands progressing to human PET (positron emission tomography) studies, originally developed by Zhang et al. Wishing to study these two compounds in our laboratory, we decided to make our own materials by following the literature methods. In order to facilitate clinical PET studies, we report here a fully automated radiosynthesis of [^{11}C]DAA1106 and [^{18}F]FEDAA1106. The precursor

DAA1123 was synthesized from 1,4-difluoro-2-nitrobenzene and phenol in 4 steps with 63% overall chemical yield. The direct methylation of DAA1123 with methyl iodide provided authentic standard DAA1106 in 70% yield. The target tracer [^{11}C]DAA1106 was prepared by *O*-[^{11}C]methylation of DAA1123 with [^{11}C]CH_3OTf in CH_3CN under basic condition (NaH) at 80 ^{o}C for 3 min and isolated by HPLC combined with solid-phase extraction (SPE) purification in 60-70% decay corrected radiochemical yields from [^{11}C]CO_2 at end of bombardment (EOB). The precursor tosyl-FEDAA1106 was synthesized from DAA1123 and ethane-1,2-diyl bis(4-methylbenzenesulfonate) in one step with 71% yield. The authentic standard FEDAA1106 was synthesized from DAA1123 and 2-fluoroethanol in 2 steps with 61% overall chemical yield. The target tracer [^{18}F]FEDAA1106 was synthesized by the nucleophilic substitution of tosyl-FEDAA1106 in DMSO with K[^{18}F]F/Kryptofix 2.2.2 at 150 ^{o}C for 15 min and isolated by HPLC combined with SPE purification in 30-60% decay corrected radiochemical yield from [^{18}F]fluoride at EOB. The radiosynthesis was performed in a home-built automated multipurpose ^{11}C- and^{18}F-radiosynthesis module, allowing measurement of specific activity during synthesis. The specific activity for [^{11}C]DAA1106 and [^{18}F]FEDAA1106 was 370-740 GBq/µmol and 37-222 GBq/µmol at EOB, respectively.

MEDI 384

Synthesis, structural characterization and in vitro antimicrobial activity of Pd(II) complexes incorporating ligand, 2-(2-thienyl)2,3-dihydro-1H-perimidine

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Pyrimidine and its derivatives have received great deal of attention in various medicinal and industrial fields [1]. As a ligand, pyrimidine provides potential binding sites for metal ions, and information on their coordinating properties which is important to understand the role of metal ions in biological systems [2]. Therefore, A novel series of Pd(II) complexes derived from 2-(2-thienyl)2,3-dihydro-1H-perimidinene has been prepared and characterized on the basis of various physico-chemical and spectroscopic techniques viz., elemental analyses, IR, ^{1}H and ^{13}C{^{1}H}NMR. A square planar geometry has been assigned around Pd(II) ion on the basis of UV-vis data. The structure of ligand, 2-(2-thienyl)2,3-dihydro-1H-perimidine has also been ascertained on the basis of single crystal X-ray diffraction. All the Pd(II) complexes together with the corresponding ligand were evaluated for their ability to *in vitro* suppress the growth of *E.coli, S. aureus, P. aeruginosa, Citrobacter sp., B. subtilis* and *S. acidaminiphila.* Results suggests that Pd(II) complexes are more active than their corresponding ligand.

MEDI 385

Novel nitrotriazole-based amides and sulfonamides as potential antitrypanosomal drugs.

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The protozoan parasites *Trypanosoma cruzi, Trypanosoma brucei* and various *Leismania* species are the causative agents of Chagas disease, human African trypanosomiasis (HAT) and different forms of Leishmaniasis, respectively. Over 10 million people are infected by *T. cruzi* and up to 80,000 by *T.b.gambiense* or *T.b.rhodesiense*, resulting in more than 40,000 deaths per year. Drugs currently used in the treatment of Chagas are old, active mainly in the acute rather than chronic stage of the disease and require a long treatment period with significant dose-dependent toxicity. We have demonstrated in previous work that 3-nitro-1,2,4-triazole-based amides and sulfonamides demonstrate significant antichagasic activity, and in some cases anti-HAT activity. Exploring further this class of compounds we have synthesized 15 more analogs (including a urea) to further evaluate their *in vitro* antiprotozoan activity and establish additional SARs. Nine out of 15 compounds were active against *T. cruzi* (IC50 < 4 µM) with selectivity indexes (SI=toxicity to L6 cells/toxicity against *T. cruzi* amastigotes) between 66-747 while the rest of the compounds were moderately active (IC50 from 6.0 -60 µM) but with SI < 50. Three of the active compounds against *T. cruzi* were also active (IC50 <0.5 µM) or moderately active (IC50 from 0.5-6.0 µM) against *T.b. rhodesiense,* with SI between 121-235. The moderately active compounds against *T.b. rhodesiense* were also moderately active against *T.b. brucei.* However, the anti-HAT activity of these compounds was increased 19 to 23 fold in bloodstream-form *T.b. brucei,* overexpressing the type I nitroreductase, suggesting the involvement of this enzyme in their activation. Finally, 3 compounds with or without antichagasic activity were moderately active against *L. donovani* (IC50 from 1.0-6.0 µM). Seven antichagasic compounds were more potent than the reference compound benznidazole. Detailed SARs will be presented.

MEDI 386

Conformation of the diacetate of virginiamycin m_1 (pristinamycin IIa, streptrogramin a)

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Several *Streptomyces* species produce streptogramin antibiotics consisting of the macrolactone virginiamycin M_1 (A) and a series of closely related hexacyclicdepepsipeptides (B). Common names for the macrolactone include Virginiamycin M1 (VM1), pristinamycin IIA and streptogramin A. A and B bind

synergistically to the 50S ribosome thus preventing protein synthesis by susceptible bacterial species. VM1 and its two acetate ester derivatives are potent gastrin and brain cholecystokinin (CCK) antagonists (Lam et al., *J. Antibiotics* 1991, 44:613; *J. Antibiotics* 1993, 46:623), binding specifically to CCK-B but not CCK-A receptors. Their role as CCK antagonists makes knowledge of their 3D structure in solution of great interest. The conformations of VM1 bound to the 50S ribosome (Hansen et al., *J. Mol. Biol.* 2003, 330:1061) and VM1 and VM1 monoacetate in solution (Ng et al., *Biochim. Biophys. Acta* 2007, 1774:610) have been reported. We report spectroscopic studies of VM1 diacetate and the conformation by X-ray crystallography.

MEDI 387

Synthesis and evaluation of novel trisubstituted benzimidazoles targeting FtsZ as antimicrobial agents

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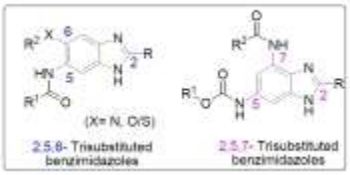
Filamenting temperature-sensitive protein Z (FtsZ), a tubulin homologue, is the most crucial and abundant protein in bacterial cell division. FtsZ polymerizes in the presence of GTP to form a highly dynamic structure, Z-ring. With other several cell division proteins recruitment, Z-ring construction results to septum formation and eventually cell division. Since FtsZ is highly conserved in GTP binding site, inactivation FtsZ preventing Z-ring formation and caused cell elongation which ultimately leads to the cell death. Therefore, FtsZ is an excellent target for the drug discovery of broad-spectrum antibacterial agents against various bacterial pathogens. We will present here novel trisubstituted benzimidazole targeting FtsZ, and their biological activities against *F. tularensis, Y. pestis, B. thailandensis*, and *M. smegmatis*.



MEDI 388

Synthesis and biological evaluation of novel antitubercular trisubstituted benzimidazoles and C-seco taxoids targeting FtsZ

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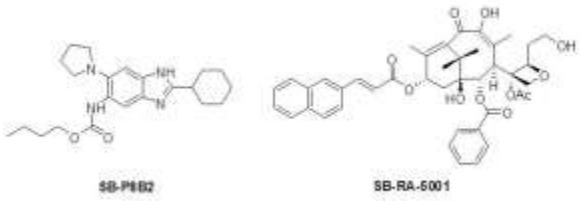
FtsZ protein, which bears limited sequence homology to tubulin in eukaryotic cells, is involved in bacterial cell division. Interference of the assembly-disassembly of this essential protein has been shown to affect the cell division processes, leading to cell elongation due to inhibition of septation. Based on rational drug design we have synthesized libraries of novel trisubstituted benzimidazoles and C-seco taxoids. These compounds have been shown to target *Mtb* FtsZ protein and exhibit excellent activity against drug-sensitive and resistant *Mtb* strains. Selected compounds showed substantial *in vivo* activities in the rapid model. Herein we will present the synthesis, *in vitro* and *in vivo* evaluation of lead compounds against *Mtb* strains.



MEDI 389

Synthesis, biological evaluation, and molecular modelling studies of some novel 1,3,5-triazine analogs

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Triazine derivatives having active Pharmacophore on its 2, 4, and 6 positions have been shown in the literature to exhibit impressive pharmacological properties such as anticancer, antimalarial, antiviral, antifungal and herbicidal etc. Literature is replete with wide variety of examples showing that incorporation of bioactive pharmacophores in the existing drug molecules sometimes exerts a profound influence on the biological profiles of these molecules. In view of this trend, it was reasoned that fusion of carbazole and azacarbazole nucleus, which are present in many drugs, with known bioactive pharmacophores such as pyrazole, isoxazole,pyrimidine, 1,5-benzodiazepine, 1,5-benzothiazepine etc. on to the s-triazine moiety can further enhance the biological proficiency of resultant molecules. Apart from japp-klingemann, Fischer-indolization,

cyclization reactions, Nucleophilic substitution reaction was extensively used to incorporate these bioactive pharmacohores on to s-triazine nucleus. Oxoketenedithioacetals have been exploited extensively for the construction of five, six and seven membered heterocycles. These were prepared by the reaction of CS_2 and CH_3I on compounds having active methylene group such as carbazole and azacarbazoles. Their reaction with different nucleophiles like hydrazine, hydroxylamine, urea, thiourea, o-phenylenediamine, have been shown to generate corresponding five, six and seven membered nitrogen containing heterocycles .

The synthesized compounds were characterized and showed promising activity in their antibacterial and antifungal in-vitro assay (92.85% and 90.38% with reference to ciprofloxacine and fluconazole against E. Coli and A. Niger). Furthur CoMFA studies were performed on SYBYL and MOE .The Pharmacophore based model showed the superiority over the common structure based model with conventional q^2 =0.58. Based upon synthesis, biological activities and molecular modeling studies we will like to further explore newer analogs.

MEDI 390

Mechanism of action and inhibition of head-to-head and head-to-tail prenyl synthases

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We report the results of an *in vitro* assay targeting malaria parasite *Plasmodium falciparum*. Based on growth “rescue” and enzyme inhibition, geranylgeranyl diphosphate synthase (GGPPS) is a major target for the most potent leads, BPH-703 and BPH-811, lipophilic analogs of zoledronate. Crystal structures of these inhibitors bound to a *Plasmodium* GGPPS reveals that their headgroups bind to $3Mg^{2+}$, while their side-chains occupy a long tunnel. Testing results show major decreases in parasitemia, and 100% survival. We also report crystal structures of three inhibitors bound to *Staphylococcus* dehydrosqualene synthase. WC-9 binds to the homoallylic (S2) site. With BPH-651, the quinuclidine binds in the allylic (S1) site, and the side-chain binds in the S2 with diphosphate and Mg^{2+}. With SQ-109, one structure demonstrates the side-chain binds to S1 or S2 and the adamantane binds in S1. In the second, the side-chain binds to S2, while the headgroup binds to a hydrophobic pocket.

MEDI 391

Synthesis of erythrosine and rosebengal based photosensitizers for photodynamic antimicrobial chemotherapy

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Drug resistance is a serious problem in antimicrobial therapy. Many bacterial and fungal pathogens have become resistant to one or more antimicrobial agents. Photodynamic antimicrobial chemotherapy (PACT) is an emerging alternative method for the effective treatment of resistant microbial infections. In this method, a combination of light and photosensitizing compounds is used to eradicate bacteria or fungi at infected area, typically via oxidative damage by singlet oxygen. Many porphyrin based photosensitizers have been synthesized and studied for anticancer photodynamic therapy and PACT, there have not been much studies on fluorescein based dyes as photosensitizers for PACT yet. In this research, we have synthesized several novel erythrosine B and rosebengalanalogues and analyzed their effectiveness as photosensitizers for several fungi. The synthesis and antifungal activity of these analogs will be discussed.

MEDI 392

Dual functionalized 2'β-substituted-6β-(hydroxymethyl)penicillin sulfones as inhibitors of β-lactamase

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6β-(Hydroxymethyl)penicillin sulfones are potent and broad spectrum inhibitors of serine β-lactamases. We have now prepared and evaluated a focused library of 2'β-substitute-6β-(hydroxymethyl)penicillin sulfones. The 2'β-substituent can have substantial influence on the inhibitory activity and on the ability to penetrate Gram negative microorganisms.

MEDI 393

Aminopyrimidine kills *Mycobacterium tuberculosis* by inhibition of decaprenylphosphoryl-β-d-ribose 2′-epimerase

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New antibiotics are in urgent need to combat tuberculosis pandemic. Here, we describe the synthesis and characterization of aminopyrimidine (AMP), a new class of antimycobacterial agents that kill *Mycobacterium tuberculosis* in vitro and in mouse models of TB. We identified the enzyme decaprenylphosphoryl-β-d-ribose 2′-epimerase as a major AMP target using genetics. Inhibition of the enzyme disrupt the protective and structural function of the cell wall, thus leading to bacterial cell death.

MEDI 394

Design, synthesis and biochemistry evaluation of novel (*E*)-Cinnamic *N*-acylhydrazone antichagasic candidates

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Human parasitic diseases are the foremost threat to human health and welfare around the world. American trypanosomiasis, or Chagas´ disease, is a neglected disease against which the efficacy of currently available drugs ranges from limited to none. Thus, there is an urgent need for new chemotherapeutic agents. Cruzain is the major cysteine protease of Trypanosoma cruzi and an attractive target for the antitrypanosomal chemotherapy. In this context we design, using molecular modeling, synthesized a series of the N-acylhydazones and evaluation biochemistry inhibitory tests against cruzain. Molecular modeling (docking) studies suggest a good complementarity between compounds and activity site of cruzain, through the interaction of the hydrazine carbonyl group and Cys25. All (E)-Cinnamic N-acylhydrazone derivatives tested against cruzain were active with 50% nhibitory concentration (IC50) between 40 and 84 mmol. The structural scaffold of the molecules studied herein suggests a good starting point for the design of new potent antichagasic candidates.

MEDI 395

Virtual screening strategies for the discovery of new inhibitors of Trypanosoma brucei aldolase

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The parasite *Trypanosoma brucei* is the causative agent of sleeping sickness (Human African Trypanosomiasis), a neglected tropical disease that affects approximately 70,000 people. Due to its relevance for the parasite survival, the glycolytic pathway has been studied in detail in trypanosomatids. The enzyme aldolase from *T. brucei* has been identified as an attractive target for the development of new chemotherapy agents. In the present work, we have employed a virtual screening strategy based on the structure of the enzyme and a ZINC fragment-like library (450,000 compounds). The docking of the compounds into the active site of enzyme was performed employing the DOCK and GOLD programs. An in-depth analysis of the binding mode of the top ranking molecules will be discussed in detail, revealing essential structural and chemical requirements for competitive enzyme inhibition. These compounds were biologically evaluated and the preliminary results will also be described.

MEDI 396

Synthesis and modification of natural sterols possessing antileishmanial activity

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In Mexico, *Pentalinon andrieuxii* roots have been used traditionally for the treatment of leishmaniasis (a parasitic disease affecting 12 million people worldwide). Research aimed at the identification of the natural products responsible for this activity and ultimately the discovery of new leads for the treatment of leishmaniasis led to the isolation and structural elucidation of 20 compounds, of which 18 were known. Five sterols (e.g., pentalinonsterol) showed potent in vitro and in vivo leishmanicidal activity. The most potent compounds, however, were obtained in only very limited quantities. These sterols, therefore, were prepared on larger scale via semi-synthesis from readily available starting materials. The synthetic routes were then modified to enable the systematic modification of the sterol functionality for structure-activity relationship studies, evaluation of their pharmacological profiles, and elucidation of their mechanism of action. An overview of these efficient and cost-effective semisynthetic strategies will be presented.

MEDI 397

Antifungal activity of semisynthetic β-1,3-glucan synthase (GS) inhibitors

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New β-1,3-glucan synthase inhibitors derived from enfumafungin that showed oral activity in pre-clinical models of disseminated fungal disease were described recently. Modifications of the A ring substituents were conducted to evaluate the role of this region in the anti-fungal activity. Ether linkage replacements were examined initially to alter the base character of the C-3 sidechain. Further explorations of the A-ring were carried out by exploiting a transition metal-catalyzed C-H insertion to allow selective cyclization between the 3- and 24-positions. The resulting cyclic sulfamates were further modified at the nitrogen atom. Also, presumed intramolecular participation of neighboring functional groups enabled directed substitution of the C-25 hydroxyl group with acyl hydrazides. These efforts identified analogs with *in vitro* potency as β-1,3-glucan synthase inhibitors and activity in fungal susceptibility assays vs. *C. albicans* MY1055. First in-class compounds were advanced into models of disseminated candidiasis.

MEDI 398

Semisynthetic β-1,3-glucan synthase (GS) inhibitors with potent antifungal activity

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Semi-synthetic derivatives of the triterpene enfumafungin were recently described as new inhibitors of fungal β-1,3-glucan synthase that showed good oral anti-fungal activity in animal models. Modifications of the CD rings and the pendant side shain of the molecule were conducted to evaluate the role of these regions in the anti-fungal activity. Conversion of the carboxylic acid to esters, amides and heterocycles led to compounds with good *in vitro* potency. Introduction of hydroxyl and keto groups onto the C-ring were achieved via metal-catalyzed oxidations. Notably, the introduction of a carbonyl at C-12 yielded compounds that showed good GS activity, anti-fungal activity (vs. *C. albicans* MY1055), selectivity (vs. *S. aureus*) and were less sensitive to serum effects; these analogs demonstrated *in vivo* efficacy in models of disseminated candidiasis. Radical-mediated decarboxylation resulted in remote functionalization of the pendant side chain allowing investigation of this region. The effects of these modifications will be described.

MEDI 399

Discovery of antimicrobial agents for α-subunit of tryphtophan synthase: Protein conformational sampling, docking and experimental assays

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In this research, we performed both computational methods and experimental assays to discover potential antibiotic candidates that target α-subunit of tryptophan synthase (TRPS). TRPS catalyzes the final two steps of tryptophan biosynthesis. The enzyme complex is only found in microorganisms and plants, not in humans and animals, which makes it an ideal drug target. In this study, we first virtually screened compounds from NCI diversity set I using TRPS crystal structures and ensembles from molecular dynamics (MD) simulations. A newly development analysis tool, T-Analyst, is used to cluster and select representative structures from MD for docking studies. The top ranked compounds are then tested by the minimum inhibitory concentration (MIC) and fluorescence assays. Results of using a combination of these methods will be presented.

MEDI 400

Synthesis and evaluation of novel saponin barbiturates as antifungal compounds

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Current trend of increase in frequency and spectrum of invasive fungal infection requires development of novel antifungal agents. Life threating fungal infections is a threat particularly to immune-compromised patients. Invasive candidiasis is now third to fourth most common bloodstream infection according to surveys in the United States.

Saponins have been identified as potential antifungal agents. The need for extensive SAR studies and to better understand these compounds we are directing our efforts to synthesize novel saponin barbiturates. The synthesis starts with barbiturate addition to desirable unprotected saccharide under basic conditions followed by addition of chloromethyl ether activated steroids. Antifungal properties of these compounds will be discussed.

MEDI 401

Understanding cephalosporin-derived inhibitors of β-lactamase

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Our group has developed several mechanism-based inhibitors of β-lactamase, including several different inhibitors possessing the cephalosporin scaffold. The cephalosporin-derived inhibitors have the most potential for future drug development, due to their ability to be modified at either C3 or C7. We will illustrate the various types of cephalosporin-derived inhibitors, as classified by inhibitory mechanism and show how structural modification can alter their inhibitory profile.

MEDI 402

Novel benzoxaboroles as a new class of ß-lactamase inhibitors

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ß-lactamases are the primary cause of resistance to ß-lactam antibiotics. This resistance can be overcome by co-administering the antibiotic with a ß-lactamase inhibitor. However, continuous evolution of this resistance mechanism reinforces an urgent and serious need to improve ß-lactamase inhibitors and maintain the clinical utility of ß-lactam antibiotics. Boronic acids inhibitors of ß-lactamases have been reported where the boron acts as a serine trap, inactivating the ß-lactamase hydrolytic activity. Since boronic acids are often associated with poor drug-like properties, we report here a new class of boron-based ß-lactamase inhibitor, benzoxaboroles, where the boron atom is incorporated into a fused aromatic ring system, which typically improves drug-like properties.

Screening our chemical library of boron-containing compounds, we identified benzoxaboroles with promising and selective inhibitory activity against a panel of ß-lactamase enzymes. In this disclosure, we describe our research effort leading to benzoxaboroles that inhibit both class A and C ß-lactamases with Ki values in low nanomolar range. We also present *in vivo* data on selected compounds that restore antibacterial activity of cefepime against *Enterobacteriaceae* expressing β-lactamase enzymes.

MEDI 403

Benzoic acids target both *cis*- and *trans*-prenyl transferases: A crystallographic investigation

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We have developed a series of benzoic acid inhibitors of undecaprenyl diphosphate synthase (UPPS) as well as geranylgeranyl diphosphate synthase (GGPPS) and determined their structures using x-ray crystallography. The UPPS structures show that benzoic acid inhibitors can bind to five sites and the best IC_{50} was 160 nM. The inhibitor structures are remarkably similar to previously reported anti-bacterials that block cell wall biosynthesis, thought to target translation/termination and/or a gene of unknown function. One of the most potent earlier leads has a very similar pharmacophore to the new compounds as well as an IC_{50} of ~1 μM versus SaUPPS, leading to the conclusion that UPPS is a major target. We also find that these benzoic acids inhibit PvGGPPS and that in each of six structures, the polar benzoate groups bind to Arg/Lys in the isopentenyl diphosphate substrate-binding site, while the hydrophobic tails bind to the farnesyl-side chain binding site.

MEDI 404

Synthesis of unsymmetrical cyclotriazadisulfonamide (CADA) analogs as specific T-lymphocyte CD4 receptor down-modulating agents

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Cyclotriazadisulfonamide (CADA) compounds have significant anti-HIV activity in human CD4 T-lymphocytes by specifically down-modulating CD4 receptor expression. The CD4 protein is the main human receptor protein that enables infection by HIV. Having this unique mechanism of action, CADA compounds have the potential of

preventing drug resistance as they act against a cellular and not a viral target. Recently, an unsymmetrical CADA analog having a cyclohexylmethyl tail group and one 4-methoxybenzesulfonamide side arm (VGD020) was found to have high potency towards CD4 down-modulation (IC_{50}: 46 nM) and improved anti-HIV activity. A new series of unsymmetrical CADA compounds having the benzyl tail group has now been synthesized to determine if side-arms other than 4-methoxybenzenesulfonamide lead to higher potency for CD4 down-modulation. Varying one sulfonamide side arm and keeping the other side arm fixed as p-toluenesulfonamide showed that high electron density of the second sulfonamide side arm is crucial for CD4 down-modulation.

MEDI 405

Synthetic CCR5-derived peptides that inhibit HIV entry

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HIV/AIDS continues to be a global health problem responsible for millions of deaths each year. Despite approval and clinical use of a variety of anti-HIV therapeutics, the emergence of HIV strains resistant to existing therapies and side effects of drug regimens make new target identification and lead discovery a continuing priority. Entry inhibitors are an emerging class of therapeutics that interfere with attachment, fusion, or entry of HIV-1 into cells. HIV entry occurs through recognition of HIV's viral envelope glycoprotein gp120 with target cell receptors CD4 followed by interactions with GPCR coreceptors CCR5 or CXCR4. We describe studies that allowed us to identify synthetic peptides derived from the second extra cellular loop of CCR5 that have the ability to inhibit viral entry by CCR5- as well as CXCR4-using HIV strains. Using NMR we prove that these peptides bind gp120 directly and thus can be used as templates to design a new group of HIV entry inhibitors.

MEDI 406

Synthesis of novel cada analog prodrugs designed to act as anti-hiv agents via down-modulation of the cd4 receptor

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Cyclotriazadisulfonamide (CADA) inhibits HIV replication by specifically down-modulating expression of the of the CD4 receptor protein on host cells. Many analogs of CADA have been synthesized in order to enhance potency, reduce toxicity, and improve physical properties, especially solubility and cell permeability. Current studies are aimed at developing a pro-drug approach involving novel bis(aminomethylbenzenesulfonyl)

CADA analog ES04. This compound is expected to have a CD4 down-modulation potency that is similar to that of CADA, according to a 3D-QSAR model. ES04 is the parent compound for prodrugs bearing dipeptide chains that are covalently bonded to the two amino groups of the aminomethylbenzenesulfonyl side arms. Cleavage of these chains by dipeptidyl-peptidase IV is expected to convert the prodrugs into ES04. The synthesis of ES04 uses a new palladium-catalyzed macrocyclization method involving the bis(cyanobenzenesulfonyl) analog of CADA. The anti-HIV and CD4 down modulation activities of the novel CADA compounds are presented.

MEDI 407

Development of anticoxackievirus agents targeting 3C protease

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Anti-viral agents against Coxsackievirus B3 (CVB3) were developed with a strategy to inhibit 3C protease (CVB3 $3C^{pro}$), a well known target for the development of therapeutic agents for CVB3 mediated myocarditis or pericarditis. Hetero-aromatic group substituted peptidomimetic analogs with a Michael acceptor were synthesized and evaluated for the inhibitory activity against CVB3 $3C^{pro}$ and antiviral effects. The substitutions of heteraromatic groups generally increase the inhibitory activity of CVB3 $3C^{pro}$. The potent protease inhibitors (**9c and e**) with quinoline groups with IC_{50} values 130~ 280 nM also significantly inhibited the CVB3 mediated cell cytotoxicity. The binding mode of one of the potent inhibitor (**9e**) was explored by a molecular docking study.

MEDI 408

Convergent synthesis of phosphonate analogs bearing a biolabile moiety

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Phosphonates are represented as pharmacophores in various classes of biological agents. Herein we report a straightforward method to synthesis the biological activity of a large class of drug through one step reaction with phosphonate synthons[1] under various conditions such as Mitsunobu, acyclic cross-metathesis and nucleophilic substitution. This concept has been validated by the discovery of new antiviral agents.

MEDI 409

Design and synthesis of imidazopyridine compounds as potent HCV antiviral agents

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A series of imidazopyridines substituted with a critical oxazolidinone moiety were identified as inhibitors of the HCV replicon system and exhibited nM Kd's for binding to purified NS4B protein. Despite excellent potencies, these oxazolidinones suffered from poor dose escalation and a high CYP liability. Optimization of this series provided the discovery of a piperazinone subseries which afforded improvements in both potency and PK and provided a potential development candidate.

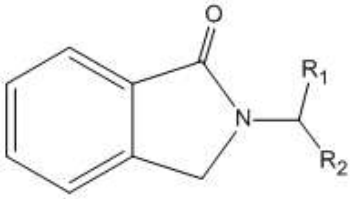
MEDI 410

Inhibitors of West Nile Virus protease based on the isoindolin-1-one scaffold

***Sridhar Aravapalli**[1], sxaravapalli@wichita.edu, Dengfeng Dou[1], Tzutshin Wong[1], Christopher S Groutas[1], Tadahisa Teramoto[2], Padmanabhan R[2], William C Groutas[1]. (1) Chemistry, Wichita State University, Wichita, KS 67206, United States (2) Microbiology and Immunology, Georgetown University Medical Center, Washington, DC 20057, United States*

West Nile Virus (WNV), a member of the Flavivirus genus of the Flaviviridae family, has emerged as an important mosquito-borne viral pathogen. No effective vaccines or antiviral agents are currently available for the prevention or treatment of WNV. WNV NS2B/NS3 protease is essential for viral replication, consequently, NS2B/NS3 pro emerged as an important validated target for the design and development of novel therapeutics against WNV.

The isoindolin-1-one scaffold was utilized in the design and solution phase synthesis of focused libraries of compounds for screening against West Nile Virus (WNV) protease.Exploratory studies have lead to the identification of WNV protease inhibitors (structure I below) which could potentially serve as a launching pad for a hit-to-lead optimization campaign.



Structure (I)

The synthesis and screening results of derivatives (I) will be presented.

MEDI 411

Synthesis of novel sultams, a family of non-nucleoside reverse transcriptase inhibitors

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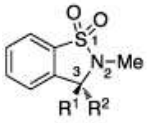
A number of non-nucleoside inhibitors of HIV reverse transcriptase (NNRTIs) have been synthesized. Congeners of 3-phenyl-2,3-dihydro-1,2-benzisothiazole 1,1 dioxide (NSC-108406) have been synthesized that show EC_{50}'s in the sub-μM range. Among these analogues, the varying substituent at the R^1-3 position of the sultam has been changed with the aid of molecular modeling, with most substituents differing only in a meta position of a phenyl ring or in an ethynylalkyl or -cycloalkyl substituent. One of the most active to be tested was an (*S*)-3-(*m*-methylphenyl)-2-methyl-2,3-dihydro-1,2-benzisothiazole 1,1 dioxide with an EC_{50} of 0.037 μM. The project involves the synthesis of ethynylalkyl and *meta*-substituted phenyl analogues via alkylation of *pseudo*-Cl-saccharin, reduction by rhodium catalyst or Luche reduction, and methylation on the nitrogen atom in the sultam ring. Structure–activity relationships will be discussed.



For (*S*)-R^1, where R^2 = H:
3-Me-Ph-; 3-Cl-Ph-;
3-Br-Ph-; 3-I-Ph-;
3-cyclopropyl-Ph-;
cyclopropylethynyl-;
cyclobutylethynyl-;
t-Bu-ethynyl-

For R^1 = R^2:
cyclopropylethynyl-;
cyclobutylethynyl-;
t-Bu-ethynyl-

MEDI 412

Discovery and development of sulfonylpyrrolidine compounds that inhibit human respiratory synctial virus activity

***Daljit S Matharu**[1], dsm18@ku.edu, James W Noah[2], William Severson[3], Donghoon H Chung[3], Blake Moore[2], Fuli Jia[2], Xiaolin Xu[2], Clinton Maddox[2], Lynn Rasmussen[2], Melinda I Sosa[2], Nichole A Tower[2], Sampath Ananthan[2], Lucile White[2], Colleen Jonsson[3], Jennifer E Golden[1], Jeff Aubé[1]. (1) Specialized Chemistry Center, University of Kansas, Lawrence, KS 66049, United States (2) Southern Research Specialized Biocontainment Screening Center, Southern Research Institute, Birmingham, AL 35205, United States (3) Center for Predicitve Medicine, University of Louisville, Louisville, KY 40292, United States*

Due to the limit in therapeutic options for human respiratory syncytial virus (RSV), a high throughput screen of the NIH Molecular Libraries Small Molecule Repository (MLSMR) was carried out with a focus on identifying novel, small molecule inhibitors that could be optimized through a medicinal chemistry effort utilizing structure-activity relationships. Hit compounds were validated and optimized for potency and HEp-2 cellular cytotoxicity. Pursuit of a sulfonylpyrrolidine hit scaffold resulted in a compound that inhibited a virus-induced cytopathic effect in the entry stage of infection (EC_{50} = 2.25 ± 0.82 µM). The inhibitor demonstrated marginal cytotoxicity (CC_{50} = 30.91 ± 1.09 µM) and reduced viral titer by 200-fold as determined by a plaque reduction assay. Compared to Ribavirin, the only FDA-approved RSV small molecule available, the sulfonylpyrrolidine inhibitor obtained from this effort demonstrated an improved in vitro potency and therapeutic window.

MEDI 413

Synthesis and evaluation of gallic acid derivatives as potential therapeutic targets

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Gallic acid (GA) and its related compounds are widely distributed in plants. It has been reported to possess anticarcinogenic, antioxidative, antimutagenic, anti-allergic and anti-inflammatory activities. Gallic acid has been a building block of choice for different pharmaceutical leads due to the presence of this moiety in several bioactive natural products. Hence, numerous derivatisations have been done and are reported for various therapeutic applications, possibly linked to its antioxidant potential.

The aim of the present work was to conjugate GA with naturally occurring phenolic compounds having well documented antioxidant properties. GA-antioxidant compounds were synthesized and their structural formulae were confirmed by spectral studies including IR, ^{1}H-NMR, ^{13}C-NMR and ESI-MS. *In vivo* studies were carried out to evaluate the therapeutic potential of synthesized compounds.

MEDI 414

Luciferase gene transfection mediated by cationic liposomes comprising novel *trans*-2-aminocyclohexanol-based amphiphiles

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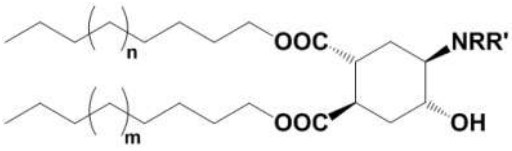
Incorporation of *trans*-2-aminocyclohexanol-based amphiphiles as helper lipids in DOTAP-cationic liposomes enhances substantially the transfection of the *Gaussia* luciferase plasmid into HeLa and B16F1 cells. The efficiency of transfection strongly depends on the structure of lipophilic chains and NRR' groups.



MEDI 415

Efficient cellular delivery of methotrexate by liposomes containing novel amphiphiles with pH-triggerable conformations

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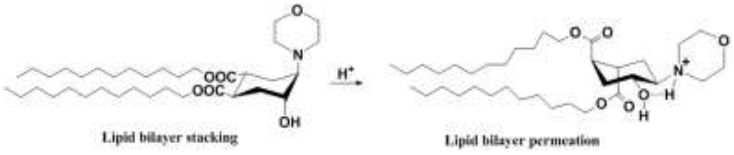
We suggested recently a novel type of pH-sensitive delivery system, 'fliposomes', which contain *trans*-2-aminocyclohexanol-based amphiphiles that perform a conformational flip and trigger an instant cargo release in acidic media. Here we report our latest studies on the cellular uptake in HeLa and B16F1 cells of the methotrexate-loaded fliposomes, which indicate that the latter can serve as viable drug delivery systems.



MEDI 416

Synthesis-based design: A holistic approach to lead development

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The work presented details the synergistic use of computational and biophysical techniques with synthetic knowledge for the facile synthesis of bioactive molecules, termed **synthesis-based design** . This approach starts with the use of an array of high-throughput techniques, from virtual and assay-based fragment screening and the native ligand, protein, or peptide, to identify binding moieties. Structural techniques including X-ray crystallography and NMR are then employed to validate the initial models and further understand the nature of these binding interactions. A subsequent round of virtual-screening and bioistosteric replacement, followed by structural elucidation are used to identify and refine a series of key binding interactions. Finally, these are spatially linked via easily tractable synthetic steps. Several examples of this approach will be presented.

MEDI 417

Rational design, synthesis, and biological analysis of GPR55 antagonists

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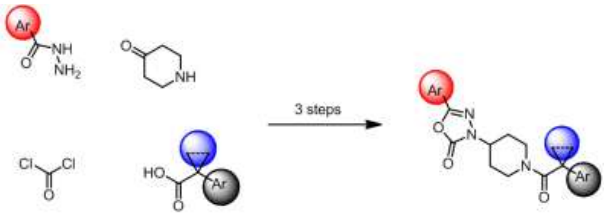
The research presented involves the design, synthesis, and biological analysis of GPR55 antagonists. The molecular scaffold is based upon a structure that has been found to selectively antagonize GPR55. Utilizing an elegantly simple and novel synthetic route to diversify the original molecule at multiple positions has allowed for preparation of various analogs and the successful synthesis of gram quantities of one of the compounds.



MEDI 418

Discovery of triazolopyridines as potent and selective acyl-CoA: Diacylglycerol acyltranferase 1 (DGAT1) inhibitors

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Michael Poss[2], Dong Cheng[3], R. Michael Lawrence[2]. (1) Metabolic Diseases Chemistry, Bristol-Myers Squibb, United States (2) Early Discovery Chemistry, Bristol-Myers Squibb, United States (3) Metabolic Diseases Biology, Bristol-Myers Squibb, United States (4) Preclinical Candidate Optimization, Bristol-Meyers Squibb, United States

Acyl-CoA:diacylglycerol acyltranferase 1 (DGAT1) is the rate limiting enzyme that catalyzes the final step in triacylglyceride synthesis. It has been reported that genetic deletion of DGAT1 or pharmacological inhibition with a small molecule DGAT1 inhibitor rendered animals resistant to diet-induced obesity. Consequently, DGAT1 inhibition has the potential for the treatment of obesity and type II diabetes. DGAT1 belongs to the acyl-CoA:cholesterol acyltransferase (ACAT) gene family. Several ACAT inhibitors were reported to induce adrenal toxicity in preclinical studies and these side effects might be related to ACAT1 inhibition. For these reasons, our goal was to identify potent DGAT1 inhibitors with high selectivity against ACAT1.

Through our research, we have identified a novel class of 1,2,4-triazolopyridine DGAT1 inhibitors. Optimization studies led to the discovery of potent DGAT1 inhibitors with high selectivity against ACAT1. The synthesis, SAR and pharmacology of these triazolopyridine and tiazolopyrazine based DGAT1 inhibitors will be presented.

MEDI 419

Discovery and initial SAR of potent antagonists of NPBWR1 (GPR7)

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The prevalence of obesity is increasing globally at alarming rates which is driven by social and economic shifts. Furthermore, obesity is associated with the pathogeneses of major metabolic diseases, especially diabetes and cardiovascular diseases. However, at the present time, no satisfactorily safe and effective obesity drugs are commercially available. The drugs that have been approved in the United States for the long-term treatment of obesity are minimally effective and have significant side effects. G protein-coupled receptor 7 (GPR7) was deorphanized with the identification of endogenous ligands neuropeptide B (NPB) and neuropeptide W (NPW) in 2002. Shortly thereafter it was reclassified as Neuropeptide B/W receptor-1 (NPBWR1). Since then there have been several studies that have suggested NPBWR1 to be involved in feeding behavior, energy homeostasis, neuroendocrine function, and modulating inflammatory pain. As

such, NPBWR1 has emerged as an interesting new therapeutic target. In an effort to probe NPBWR1 as a novel anti-obesity target, we wished to develop a small molecule antagonist. This presentation will disclose a new class of NPBWR1 antagonists discovered from a High Throughput Screening (HTS) campaign from the Merck collection. Basic SAR exploration of this piperazine core lead class facilitated with parallel synthesis will be discussed.

MEDI 420

Discovery of potent dihydrocinnamic acids as free fatty receptor 1 (FFA1/GPR40) agonists

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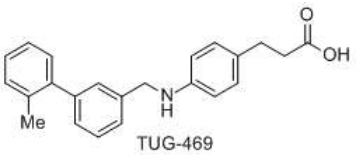
The free fatty acid receptor 1 (FFA1/GPR40) enhances glucose-stimulated insulin secretion from pancreatic beta-cells and is recognized as an interesting new antidiabetic target. We recently described the identification of the potent and selective FFA1 agonists TUG-469, which increase insulin secretion from INS-1E cells at high but not at low glucose concentration. Around the same time, Takeda disclosed their clinical candidate TAK-875, also an FFA1 agonist. Inspired by the similarities between the two compounds, we have continued the structure-activity investigation.



TUG-469
EC_{50} = 19 nM

MEDI 421

Synthesis of alkoxyalkyl esters of 5-fluorouridine-3',5'-cyclic monophosphate: Intravitreal prodrugs for sustained drug release to the posterior segments of the eye

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Many blinding diseases that affect the retina are due to abnormal growth of vascular cells and scar tissue. For example, cellular proliferation occurs in proliferative vitreoretinopathy (PVR), a complication after ocular trauma, and the most common cause of failure after retinal reattachment surgery. There is evidence that post-surgical application of antiproliferative drugs to the retina surface inhibits retinal detachment due to PVR, but the efficacy of such treatments is limited by the short half-life of soluble compounds after intravitreal injection. To avoid quick clearance of 5-fluorouridine, we synthesized alkoxyalkyl esters of 5-fluorouridine-3',5'-cyclic-monophosphate that are injectable as suspensions and dissolve slowly in the vitreous over a period of 3-6 months. To prepare these compounds, we developed a process based on H-phosphonate coupling which gave 3'-alkoxyalkyl phosphate intermediates that readily cyclized (MSNT/pyridine). The prodrugs were evaluated for antiproliferative activity in retinal pigment epithelia and glial cells, major components of PVR epiretinal membranes.

MEDI 422

Frontal analysis for characterization of binding sites in molecularly imprinted polymer of adenosine 5'-monophosphate: A biomimetic sensor of nucleoside phosphorylation mediated by adenylate kinase

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Nucleoside analogues play an important role in antiviral and anticancer therapies. They are transformed into their active 5'-triphosphate analogues by nucleoside kinase to exert their pharmacological activity. In particular, adenosine 5'-monophosphate (AMP) is a substrate of adenylate kinase (AMPK). The AMP is closely linked to the active site through polar bonds involving two arginine, glutamine, and two threonine. In order to screen and select new substrates for AMPK, we have designed polymer sensors that mimic its active site. We applied an ionic-noncovalent dual approach to prepare the desired imprinted polymer. We used frontal analysis to study binding characteristics of our polymer and to compare it with enzyme. We demonstrated that the interactions MIP/substrate are in the same order than interactions enzyme/substrate. This shows that MIP can be used as a screening tool for enzymatic activity

MEDI 423

Pyridopyrimidinone analogs as orally efficacious GPR119 agonists

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Type 2 diabetes comprises 90% of people with diabetes around the world. Novel oral diabetic medications without the side effects associated with earlier approaches (i.e. hypoglycemia, weight gain), are currently active areas of research in pharmaceutical industry. In these emerging approaches G protein coupled receptor 119 (GPR119) agonists have shown great promise with a glucose dependent insulin secreting mechanism. Here we describe the SAR studies leading to the discovery of a potent and orally efficacious pyridopyrimidinone based GPR119 agonist.

MEDI 424

Carboxylic acid bioisosteres in free fatty acid receptor 1 (FFA1/GPR40) agonists

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The free fatty acid 1 receptor (FFA1/GPR40) is highly expressed on pancreatic β-cells and amplifies glucose-stimulated insulin secretion, making it an attractive target for the treatment of type 2 diabetes. Series of potent FFA1 agonists have been identified starting with free fatty acids as lead structures. These typically comprise a carboxylic acid groups that is crucial for the receptor interaction. Bioisosteres are replacement groups that often elicit effects similar to the group they replace in biological systems, and represent a rational approach in lead optimization. The described structure-activity relationships study investigates the effect of bioisosteric replacement of a carboxylic acid group in FFA1 agonists.

MEDI 425

Discovery of potent and selective GPR120 agonists

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G protein coupled receptor 120 (GPR120) is a 7-transmembrane receptor which responds to unsaturated long-chain free fatty acids and is expressed in adipose tissue and the intestinal tract. The receptor is reported to regulate secretion of glucagon like peptide 1 (GLP-1) and cholecystokinin (CCK) from entroendocrine STC-1 cells, and was recently found to mediate antiinflammatory and insulin sensitizing effects of omega-3 fatty acids. GPR120 is therefore currently receiving attention as a new potential target for treatment of type 2 diabetes. We here describe the discovery of potent and selective GPR120 agonists which will enable studies to explore the receptor as an antidiabetic target and may serve as leads for development of new antidiabetic therapeutics.

MEDI 426

Rational design, synthesis, and structural characterization of D-Phe-Pro-D-Arg-derived thrombin inhibitors

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Novel hexapeptides, pentapeptides and tetrapeptides were designed using *in silico* structure-based design approaches and further tested for their ability to inhibit *α*-thrombin *in vitro*. Initial molecular docking experiments generated a candidate group of compounds with both L- and D- amino acids, containing the D-Phe(P3)-Pro(P2)-D-Arg(P1)-P1'-P2'-P3'-$CONH_2$ sequence. The use of D-Arg in the P1 position made the designed peptides inhibitors stable to proteolysis. The structure-activity relationship revealed the lead compounds as being tetrapeptides from the series D-Phe-Pro-D-Arg-P1'-$CONH_2$. The P1' position was scanned with L and D-isomers covering the major chemical classes of natural or unnatural amino acids, such as L-2-thienylalanine (L-Thi). The lead tetrapeptide, D-Phe-Pro-D-Arg-D-Thr-$CONH_2$, has a K_i of 0.85 uM. The three-dimensional structures of three complexes of human α-thrombin with three lead peptidic inhibitors (with L-isoleucine (p3), L-cysteine (p4) or D-threonine (p6) at the P1' position of the lead D-Phe-Pro-D-Arg-P1'-$CONH_2$ sequence) were determined by X-ray crystallography. All the inhibitors bind in a substrate-like orientation to the active site of thrombin. The X-ray analyses of all three complexes show the upstream residues sitting deeper in the S2 and S3 pockets while the cleavable bond adopts an unfavorable geometry for nucleophilic attack by the serine side chain (3.69Å, 2.85Å and 2.96Å distance between the Ser195 Oγ and the arginine carbonyl carbon for p3, p4 and p6, respectively). Thus, our crystal structures of human *α*-thrombin complexes with peptidic inhibitors with D-Arg in the P1 position provide insights into the main structural features that enabled them to be totally stable to proteolysis.

MEDI 427

Synthesis and pharmacology of a potent and orally active CETP Inhibitor, (-)-K-18597

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Inhibition of cholesterol ester transfer protein (CETP) is known to enhance HDL-C and lower LDL-C levels for treatment of Coronary Heart Disease. We have identified a potent CETP inhibitor, K-18597 (IC_{50}: 0.09 μM *vs* anacetrapib 0.1 μM), that does not affect blood pressure in rats, nor does it raise aldosterone levels in H295R cells, unlike torcetrapib. Following 2-weeks multiple dosing in hamsters, K-18597 (3 mg/kg/day) and anacetrapib (10 mg/kg/day) significantly increased HDL-C by 78% and 71%, respectively, and decreased LDL-C by 20% and 22%, respectively. In hamsters, K-18597 but not anacetrapib showed a longer duration of CETP inhibition after a single dose, and significantly reduced plasma TG and liver TC levels after 2 weeks dosing. The structure-activity-relationship, synthesis and pharmacology of K-18597 and its related compounds are presented.

MEDI 428

Calixarene phosphonic acids: Synthesis and biological activity

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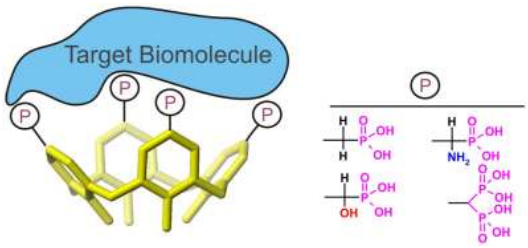
Calix[4]arenes[1] being capable to form host-guest supramolecular complexes with biologically important molecules can influence biochemical processes and serve as molecular platforms for drug design[2].

The aim of this study was to synthesize the calix[4]arene derivatives functionalized at the macrocyclic upper rim with bio-relevant phosphonic, aminoposphonic, α-hydroxyphosphonic, methylenbisphosphonic acids and investigation of their biological activity.



It was shown that the calix[4]arenes functionalized with fragments of hydroxyphosphonic, aminophosphonic and methylenebisphosphonic acid selectively inhibit different ATPases at micromolar and sub-micromolar concentrations.

The calix[4]arene tetrakis-bisphosphonic acid inhibits specifically the fibrin polymerization[4] in fibrinogen+thrombin reaction as well as monomeric fibrin desAABB polymerization in concentration up to 0.5×10^{-6} M.

The chiral calix[4]arene α-aminophosphonic acids show inhibitory activity toward porcine kidney alkaline phosphatase that depends on the absolute configuration of the α-carbon atoms. Calix[4]arenes bearing methylenebisphosphonic acid fragments display strong inhibition of calf intestine alkaline phosphatase. The kinetic studies revealed that some compounds of this class are potent inhibitors of protein tyrosine phosphatases such as *Yersinia* PTP and PTP1B with inhibition constants in the micromolar range.

[1] S. Cherenok et al. Topics Heterocyclic Chemistry. **2009** . 20. 229-273.

[2] R. Rodik et al. Current Medicinal Chemistry. **2009** . 16(13). 1630-1655.

MEDI 429

Design, synthesis, and evaluation of some novel hetero-fused pyrimidines as possible adenosine receptor antagonists

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Adenosine receptors (ARs) classified as A_1, A_{2A}, A_{2B} and A_3 subtypes, have emerged as potential drug targets and play significant role with varied biological functions. A combination of docking studies [**Glide (** Schrodinger**), GOLD** and **LigandFit** (Accerlys-Discovery Studio 2.1 version)], pharmacophore mapping [PHASE (Schrodinger Inc.)] and 3D QSAR studies [MSA and MFA, Cerius2 version 4.10] were carried out to explore

the physicochemical requirements for selective binding towards A_{2A} and A_3 AR in order to design a new series of hetero-fused pyrimidines as potent and selective human A_{2A} and A_3 receptor antagonists [***BMCL, 20 (2010) 1634***]. As the crystal structure of A_3 AR is not available, an improved homology model of A_3 AR has been developed using the X-ray crystal structure of A_{2A} AR (pdb: 3EML) employing Prime (Schrodinger Inc.) program. All the designed compounds [2-substituted thieno(2,3-*d*)pyrimidines and 8-alkyl/aryl-1-phenyl-1,2,4-triazolo(4,3-*c*)pyrazolo(4,3-*e*)pyrimidin-6(5*H*)-thiones] were synthesized in good yields following eco-friendly microwave-assisted organic synthesis and screened *in vitro* for their affinity as well as selectivity as possible AR antagonists. All the designed compounds with carbamoyl substitution at NH_2 group at C5 position of pyrimidine ring was found to have very high affinity towards A_3 ARs, whereas absence of substitution at NH_2 group cause increase in the selectivity as well as affinity towards A_{2A} AR.

MEDI 430

Rational development of reversible inhibitors of the Vitamin D receptor-coregulator interactions

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The vitamin D receptor is a nuclear hormone receptor that regulates cell proliferation, cell differentiation, and calcium homeostasis. The receptor is activated by 1,25-dihydroxyvitamin D_3, which induces the disruption of VDR-corepressor binding and promotes the VDR-co-activator interactions. VDR-coregulator (coactivator and repressors) interactions are essential for the VDR-mediated gene expression and present a novel anti-cancer target through the regulation of genes responsible for cell growth and cell differentiation. Small molecules have been designed based on reported crystal structures of VDR-coactivator complexes. The synthesis of these molecules as well as their mode of binding is presented.

MEDI 431

Rapid purification of a diverse range of peptides using flash chromatography with ELSD and UV detection

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Newly discovered peptide sequences are providing novel drug development candidates for use in modern medicines. Purification of natural products and synthetic peptides is an essential step in the drug discovery process, and is typically accomplished using preparative chromatography, which can be expensive and time consuming. Flash chromatography is a fast and cost-efficient approach to purify synthetic peptides and other small molecules.

This work demonstrates purification and recovery of a diverse range of peptides using a Reveleris® Flash Chromatography System with ELSD and UV detection. Flash chromatography with automated optimization reduces purification time and solvent use compared to FPLC and preparative HPLC. A new C18 media phase expands the loading capacity and size limitations for high resolution peptide purification.

MEDI 432

WITHDRAWN

MEDI 433

Advanced detection techniques for flash chromatography

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UV detection is the traditional method used in flash chromatography to monitor and fractionate peaks during purification. There are few options available to chromatographers to intelligently purify compounds invisible to UV detection. These invisible compounds may not be detected with UV due to the absence of chromophores, or their absorbance may be “lost” in that of the solvents used in flash chromatography. In other cases, the compounds absorption spectrum may be unknown and the user selected an incorrect wavelength to monitor.

In order to overcome the limitations that “invisible” compounds pose, advanced detection techniques, including All-Wavelength Collection, Evaporative Light Scattering Detection, and others are becoming more commonly used. These advanced techniques allow users to easily fractionate compounds without the need for follow-up TLC to determine where the purified compound eluted. Applicability of these advanced techniques for Flash Chromatography are demonstrated on several examples for both Natural Products and Synthetic Chemistry.

MEDI 434

WITHDRAWN

MEDI 435

Improvement in solubility of bicyclic molecules focusing on dihedral angle and symmetry

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Aqueous solubility is essential for drug candidates, and improvement of the aqueous solubility of bioactive compounds is a major issue for medicinal chemists. The strategy of introducing hydrophilic group(s) into molecules is generally used for this purpose, but is not universally effective. We proposed an alternative strategy for improving aqueous solubility, that is, modification of bicyclic molecules in ways that would disrupt molecular planarity by increasing the dihedral angle or that would disrupt the molecular symmetry. Such planarity- or symmetry-disruption has the effect of decreasing the efficiency of crystal packing, which in turn results in an increase of aqueous solubility. Improvement of aqueous solubility by 350-fold was achieved in one example. Furthermore, to clarify the mechanisms of improvement of aqueous solubility, we examined the changes in physicochemical properties of the compounds. Possible advantages of this approach are discussed.

[1] *J. Med. Chem.* **2011** , *54*, 1539-1554.

MEDI 436

Site-directed mutagenesis of intrinsic factor and its potential use as a drug delivery agent

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Oral delivery of peptides such as insulin and PYY has been successfully achieved by conjugation of these peptides to vitamin B_{12} (B_{12}), thereby utilizing the dietary uptake pathway for the vitamin. Intrinsic factor (IF) is a glycoprotein that carries and protects B_{12} during gastrointestinal passage. Although this protein serves a critical function in the B_{12} uptake pathway, up until now, its use as a delivery agent has not directly been explored. Herein, we describe the site-directed mutagenesis, overexpression, and utilization of IF as a drug delivery agent.

MEDI 437

Method development for equilibrium and kinetic binding in vitro bioequivalence of colesevelam hydrochloride in simulated intestinal fluid (SIF)

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Colesevelam hydrochloride is a high-capacity bile acid-binding molecule, which is a non-absorbed, polymeric, lipid-lowering and glucose-lowering agent, initially marketed

as Welchol. As generic versions of marketed colesevelam tablet products are being developed for release in the market, equivalence between the generic and innovator products must be established to satisfy the FDA guidance for this class of product. To compare the bile acid-binding activity of these products, the equilibrium and kinetic binding profiles of colesevelam hydrochloride must be compared for both the generic and innovator products. An HPLC method with UV detection has been developed and validated to detect free bile acids (glycocholic acid, glycochenodeoxycholic acid, and taurodeoxycholic acid) in simulated intestinal fluid (SIF). This method also accommodates conducting binding studies both with and without acid pre-treatment of the products, with no matrix interference observed. The key parameters of the study, as well as the method will be discussed.

MEDI 438

Precise delivery of active molecules(drugs) using diode laser

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Current strategies to enhance temporal or spatial control of drug release focus on incorporating components into the liposome membranes to achieve thermal, pH, photochemical, or enzymatically triggered release.. Light is a very appealing tool for controlling release of active molecules in a spatiotemporally controlled manner due to its direct control and site specificity. Low energy light is preferred in vivo applications due to the low toxicity and deeper tissue penetration To utilize the low energy light for initiating the release, new chemical bonds cleaved by such low energy light need to be developed.

We designed and prepared a series of substituted olefins as singlet oxygen-mediated cleavable linkers. The substituted olefins were then tested for their reactivity with singlet oxygen using a diode laser.

These new olefinic linkers have promising characters such as facile and high yield synthesis, fast cleavage, and re-generation of parent drug a after the cleavage.

MEDI 439

Interaction of nucleic acids with the glycocalyx

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Mammalian cells resist the uptake of nucleic acids. Herein, we report on a physical basis for that resistance. To create a sensitive probe for nucleic acid–cell interactions, we conjugated lipids to fluorescently labeled DNA oligonucleotides. We found that these conjugates are incorporated readily into the plasma membrane, but are not stable there. The stability of lipid oligonucleotide conjugates in the plasma membrane decreases with oligonucleotide length. Conversely, the stability of embedded conjugates increases markedly in cells that lack the major anionic components of the glycocalyx—sialic acid and glycosaminoglycans, and in cells that had incorporated cationic lipids into their plasma membrane. We conclude that the anionic components of the glycocalyx provide a formidable barrier to the uptake of nucleic acids by mammalian cells. This conclusion has implications for genomic stability, as well as the delivery of genes and siRNAs into mammalian cells.

MEDI 440

Synthesis, in vitro, and in vivo biology of dual-targeting DNA supercoiling inhibitors for the treatment of bacterial infections

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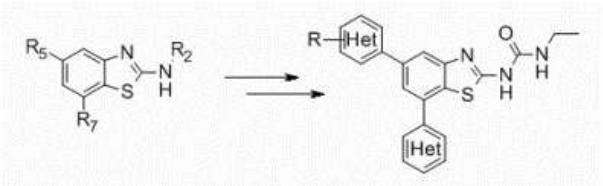
The emergence of new resistant strains of pathogenic bacteria presents an increasingly serious challenge to global health. We have identified a series of potent bacterial DNA gyrase/topoisomerase type IV inhibitors with a novel mechanism of action distinct from fluoroquinolone-based drugs. This series possesses high potency against a broad range of bacterial species, including those responsible for community acquired bacterial pneumonias (CABP). By optimizing the substitution patterns off the benzothiazole core, we have improved antibacterial activity and drug-like properties as measured *in vitro* and *in vivo*. Heterocyclic substituents at R_5 and R_7, coupled with the ethyl urea moiety at R_2, improve potency to sub-0.063 µg/mL levels. Pharmacokinetic and efficacy studies show that lead members of this series can be delivered both intravenously and orally, are well-tolerated, and demonstrate class-leading efficacy in a neutropenic mouse model of *S. aureus* infection.



MEDI 441

Multiple approaches to inhibiting caspase-6 for neurodegenerative diseases

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Caspase-6 is a cysteine protease implicated in development of neurodegenerative diseases such as Alzheimer's and Huntington's. Selective probe molecules and drug leads have been difficult to develop for caspases, though, hampering target validation. In a three-way collaboration with CHDI, the Small Molecule Discovery Center at UCSF, and Genentech, we have taken three, orthogonal approaches to targeting caspase-6 with small molecules. In the process, we have found potent binders and surprising mechanisms-of-action. For instance, high-throughput screening led to the development of novel uncompetitive and substrate-specific inhibitors of Caspase-6. Two fragment-based screens were also performed; SPR-screening led to the discovery of a small-molecule binding site on the zymogen form of Caspase-6, and Tethering-based screen identified inhibitory fragments that do not bind the active-site cysteine. Through the combination of lead-discovery approaches, we have made significant progress on this challenging target.

MEDI 442

Collaboration between pharma and academia: The combination of organocascade catalysis and affinity selection mass spectrometry for lead identification

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Organocascade catalysis is a concept of using simple organic molecules as catalyst, such as imidazolidinones, to enable the merger of multiple stereoselective catalytic chemical transformations and sequencing them into a cascade event. All chemical events in organocascade catalysis are governed independently by the organic catalyst and thus sequence of organocascade can be designed to accommodate various combinations of stereoselective catalytic transformations without loss of efficiency and selectivity. This character of organocascade catalysis, in combination with multiple building blocks allows for generation of diverse mixtures of complex small molecules with lead/ drug like properties within the same reaction vessel. In addition, since catalysts themselves are organic molecules, the generated mixtures do not require purification prior to screening against a biochemical target of interest.

Mixture-based screening for biologically active compounds has traditionally been hindered by the enormous deconvolution efforts required in identifying the active component. Affinity-based selection strategies have recently emerged as a complement to traditional high throughput screening for the rapid discovery of lead compounds for the large number of protein targets emerging from -omics technologies. In particular, affinity selection mass spectrometry (ASMS) offers a rapid way to screen large mixtures generated from organocascade catalysis and, through mass-based deconvolution, identify the ligand(s) bound to the protein target.

Herein, we describe the results of a collaboration between Princeton University and Merck & Co., Inc. to demonstrate the utility of this strategy by generating diverse mixtures of complex small molecule libraries by organocascade catalysis and screening by ASMS to identify both known and a new structural series of inhibitors for dipeptidyl peptidase 4, a serine protease that rapidly degrades two incretin hormones that enhance glucose stimulated insulin sectretion, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) and is a target for the treatment of type II diabetes.

MEDI 443

Development of novel agents for the treatment of Schizophrenia

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This presentation will discuss the development of $mGlu_5$ positive allosteric modulators (PAMs) for the treatment of schizophrenia and related psychiatric disorders, and the caveats encountered during the discovery process. Importantly, we will discuss the

industrial/academic collaboration between JNJ (Janssen) and Vanderbilt, division of labor, intellectual property strategy and challenges in a collaboration of this type and magnitude. In addition to the logistical aspects, we will also review key scientific findings with novel tool compounds (both pure $mGlu_5$ PAMs and ago-PAMs), from the academic component of the collaboration, which informed the discovery effort and enabled the team to avoid potential pitfalls. We will also comment on the timeline to the first joint $mGlu_5$ PAM NME, and how an industrial/academic collaboration influenced the timeline.

MEDI 444

Cystic fibrosis drug discovery and development collaboration

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Vertex Pharmaceuticals and the Cystic Fibrosis Foundation (CFF) have been collaborating in a drug discovery and development program for the past 13 years. Results of the collaboration include three investigational oral drugs in clinical development that address the basic defect responsible for cystic fibrosis (defective or missing CFTR protein). Ivacaftor (also known as VX-770) was submitted to the U.S. FDA and EU EMA in October 2011 based on Phase III studies in a subgroup of CF individuals with a specific *CFTR* mutation called G551D. Guiding principles, operational aspects of the collaboration, important milestones, and how the relationship has evolved will be described.

MEDI 445

Vyndaqel: A transthyretin kinetic stabilizer that halts peripheral neuropathy is a first-in-class drug for a human amyloid disease

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High affinity small molecule binding to the normally folded structural ensemble of an aggregation-prone protein stabilizes its native state, lowering the population of misfolded, misassembly competent states that lead to aggregates. Crafting small molecules that bind the normally folded conformational of an aggregation-prone protein is a promising strategy to treat amyloid diseases. Here, we focus on transthyretin (TTR) amyloidosis: demonstrating that preferential ligand stabilization of the native tetrameric state of TTR over the dissociative transition state dramatically raises thekinetic barrier of dissociation in turn slowing and sometimes halting the process of TTR amyloid fibril formation. Clinical analysis has shown that Tafamidis, a small molecule kinetic stabilizer of TTR, halts the progression of Familial Amyloid Polyneuropathy. Tafamidis may also

ameliorate the cardiomyopathies associated with amyloidogenesis of wild-type TTR or selected mutants. This seminar will also focus on the intimate cooperation between academia and industry that led to this first-in-class drug.

MEDI 446

Computer lead optimization boosters for medicinal chemists

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In times of restructurings, more computation has to be accomplished by MedChems themselves. For software development, this prompts to acknowledge strong boundary conditions:

- MedChem core expertise is synthesis, so the learning barrier for new software must be absent, and results must be delivered in seconds.

- MedChems are "pattern recognizers" (C. Lipinski), so good visualization is key - especially in 2D.

- We all need to communicate to colleagues, management, and customers. Therefore software must generate graphics, tables/reports with high aesthetics which seamlessly integrate into Office tools etc.

Several years of research have now addressed these issues, and we are now ready to present a collection of tools we think are of high interest to MedChem staff.

The software is a monolithic suite that supports for example drag&drop of almost anything, even 2D and 3D graphics into PowerPoint, Word etc. with a single click.

Novel computational tasks included are:

1. The popular affinity assessment “Hyde” – including its visualization of WHERE a molecule has room for improvement

1. The industry standard scaffold replacer “ReCore” that – within seconds – gives proposals for iterative optimization respecting pharmacophores and/or synthesis vectors.

1. 2D protein-ligand display (“PoseView“, recently also linked into the PDB website).

1. The world's fastest full protein preparation which takes into account crystallographic ambiguities such as H-positions, and even tautomers on both protein and ligand side.

Experience in several big pharmas revealed that the time won can be re-invested in core MedChem tasks. We will showcase example workflows highlighting successes plus take a glance at the science behind.

MEDI 447

Design, synthesis and biological evaluation of comformation restricted analogs of FTY720

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Sphingosine-1-phosphate (S1P) is a signaling lipid molecule, which has been implicated in a wide variety of biological processes including cell growth regulation, apoptotic suppression, invasion, angiogenesis and vascular maturation, immune cell migration and so forth. FTY720 (Fingolimod), a synthetic analog of S1P, is not only a FDA approved drug for relapsing remitting multiple sclerosis (RRMS) but also an important tool molecule to investigate the biology of S1P receptors and related enzymes, sphingosine kinase (SphKs) for example. It turned out that phosphorylated FTY720 by SphK2 *in vivo* is a low-nanomolar agonist of all the S1P receptors except $S1P_2$ and induces lymphopenia by sequestering lymphocytes into the secondary lymphoid tissues, which is a novel mechanism different from that of those classic immunosuppressive agents.

In this presentation, we will show the synthesis and biological evaluation of a library of conformationally constrained analogs of FTY720. Some of those compounds are great substrates for SphK1 or SphK2 (much better than FTY720), and induce lymphopenia at low doses. VPC122096, for example, is a cyclopentyl-incorporated analog of FTY720 and show a promising potential to be an effective S1P receptor pro-drug since it is effectively and effiently phosphorylated *in vivo* and induces lymphopenia.

To elucidate the stereochemistry-activity relationship, we developed the chemical synthesis to access all of the four stereoisomers with high optical purity. Each stereoisomer was tested individually for the SphKs activity and lymphopenia induction. It turns out that the configuration of one chiral carbon is critical for the enzyme recognition while the other is not. And the two isomers that are good substrates of SphKs induce lymphopenia even at dose as low as 0.1 mg/kg, which is the same, if not more, potent as FTY720

MEDI 448

Small molecules targeting IL-6/GP130 homodimerization in the IL-6/JAK/STAT pathway

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The IL-6/JAK/STAT pathway is a key signal transduction pathway activated in many cancers which results in the translocation of phosphorylated STAT dimers to the nucleus where they regulate gene transcription. The process is activated by interleukin-6 (IL-6) through an IL-6/GP130 homodimerization event. Inhibition of this homodimerization and subsequent disruption of downstream phosphorylation would provide a new target for cancer therapy. Therefore, two series of compounds (indoline- and indole-containing scaffolds) were initially designed and synthesized based on the structure of madindoline A, a weak inhibitor of IL-6. Molecular modeling suggests their binding to the D1 domain of GP130, thereby preventing interaction with IL-6. These results are supported through binding studies with the GP130 protein and observed inhibition of pSTAT3. Subsequent modification has led to additional compounds which effectively inhibit the pathway. The design, synthesis, and biological evaluation of these analogues in various cell lines will be reported and discussed.

MEDI 449

Overexpression, isolation, and oral delivery of the appetite suppressant PYY(3–36)

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Injections of PYY(3–36) have shown positive effects on appetite regulation. With nearly 400 million adults worldwide considered obese, these positive effects have sparked an increased interest in PYY research, including release profiles, receptor targets, and medicinal applications. A major area of interest is oral delivery of PYY(3–36) that can display clinically relevant outcomes related to weight loss in what would be a highly patient compliant route. The vitamin B_{12} pathway has already been successfully used for oral delivery of other peptides including erythropoietin and insulin. We present the overexpression and isolation of a recombinant PYY(3–36) as well as the synthesis, purification, and characterization of a B_{12}–PYY(3–36) conjugate for oral delivery in *in vivo* studies.

MEDI 450

Structure-activity relationship study of azaindenoisoquinoline topoisomerase I inhibitors

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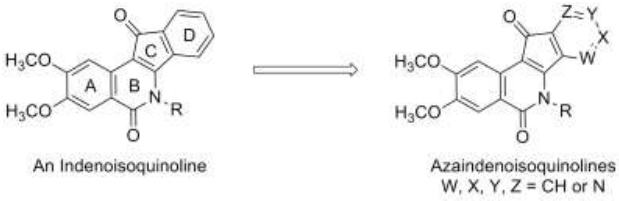
The synthesis and structure-activity relationship study of 7-, 8-, 9-, and 10-azaindenoisoquinolines as topoisomerase I (Top1) inhibitors will be presented. A series of QM calculations were performed on the model drug-Top1-DNA ternary complexes in an attempt to explain the effect of the introduction of a nitrogen atom into the indenoisoquinoline system on the Top1 inhibitory activity. The results of these calculations demonstrate how changes in dispersion and charge-transfer interactions affect the binding of the drug to the Top1-DNA cleavage complex, thus modulating the drug's Top1 inhibitory activity. The present study shows that 7-azaindenoisoquinolines possesses the greatest Top1 inhibitory activity and cytotoxicity. Additionally, the introduction of the methoxy group into the D-ring of 7-azaindenoisoquinoline improved its biological activity, leading to new lead molecules for further development.



MEDI 451

Reducing neuronal tau using new chemical inhibitors of Hsp70

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Intracellular accumulation of the microtubule-associated protein tau is linked to Alzheimer's disease (AD). One emerging way to treat this disease may be to accelerate tau degradation. The level of tau is normally regulated by molecular chaperones, such as heat shock protein Hsp70, which actively facilitate tau degradation. MKT-077 (1-ethyl-2-[[3-ethyl-5-(3-methylbenzothiazolin-2-yliden)]-4-oxothiazolidin-2-ylidenemethyl] pyridinium chloride) reduces tau levels in cellular and brain slice models. However, the positive charge moiety in MKT-077 prevents its entry into the brain, so it is not directly usable in pre-clinical studies. We recently developed uncharged MKT-077 derivatives, and their Hsp70 binding properties are evaluated using a fluorescence polarization

assay. Furthermore, their anti-tau potential is assessed in a cell-based model. From this work, we have produced brain-penetrating Hsp70 inhibitors that can be used to understand the mechanism of Hsp70-mediated tau degradation. Further, these compounds may serve as promising leads for the development of AD therapies that utilize an under-explored mechanism.

MEDI 452

Identification and validation of new topoisomerase type II inhibitors for the treatment of multi-drug resistance *Staphylococcus aureus* through computer-aided drug design

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Methicillin resistant *S. aureus* (MRSA), is among the major drug resistant bacteria and is growing at an alarming rate due to mutations that render them resistant to commonly used antimicrobials. DNA gyrase regulates supercoiling of DNA driven by ATP hydrolysis. It is an essential enzyme involved in bacteria replication. Shape Signatures is a novel molecular screening tool developed in our laboratory, which was used for rapid screening of a large database for agents with similar shape as the known gyrase B inhibitor, Novobiocin. The binding energetics and physico-chemical properties of the top hits from this initial scan were further validated by molecular docking using the GOLD and GLIDE docking tools and their binding stability confirmed through molecular dynamics simulations. Three rhodanine-substituted derivatives had significant antimicrobial activity against *S.aureus* Carolina and ISP 794 strains, as determined by minimal inhibitory concentration assays, with Novobiocin as the positive control. Biochemical evidence supports the fact that the lead compound decreases the ATPase activity of gyrase. The inhibition of the DNA supercoiling activity of gyrase by these compounds is being evaluated through relaxation assays. Another potential lead identified through docking experiments, which is also a known folate inhibitor, had a promising GLIDE score of -12.64 at the ATP binding pocket of gyrase B. It made significant backbone hydrogen bonding interactions at the receptor site and thereby may delay bacterial resistance. This compound is currently being synthesized for further in vitro validation of its biochemical and biological activity.

MEDI 453

Synthesis of non-hydrolyzable, lipid-linked inositol glycans with selective anti-cancer activity

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Inositol glycans (IGs) are naturally occurring oligosaccharides that can stimulate insulin-sensitive cells. Several synthetic IG analogues have been shown to activate the insulin signaling pathway, resulting in metabolic changes including the stimulation of pyruvate dehydrogenase (PDH) phosphatase that can further stimulate aerobic metabolism in cells. Cancer cells shift to anaerobic metabolism (Warburg Effect) in part to escape mitochondria-based intrinsic apoptosis. So, a strategy to control cancerous growth might be to stimulate aerobic metabolism in cancer cells and reverse the Warburg effect. The IG's ability to stimulate aerobic metabolism could force cancer cells to restore normal citric acid cycle and oxidative phosphorylation in mitochondria, possibly leading to the induction of intrinsic apoptosis.

A lipid-linked IG analogue, GlcN-(α1-6)-*myo*-Inos-2-palmitate, **IG-1** , has been previously shown to be selectively cytotoxic towards a variety of cultured human cancer cell lines as well as *in vivo* in a murine cancer model. Its medicinal utility, however, is limited by its instability under physiological conditions due to the presence of a hydrolyzable ester linkage in the molecule. To overcome this limitation, a non-hydrolyzable ether-linked analogue, **IG-1E** , has been synthesized and evaluated for cytotoxicity towards cancer cells. Preliminary data show promising selective cytotoxicity of **IG-1E** towards cultured human cancer cell lines. A series of non-hydrolyzable, lipid-linked IG analogues with varying lipid chain length have also been synthesized and evaluated for cytotoxicity toward cancer cells. Synthesis and comparative biological activity of these novel anti-cancer small molecules will be summarized in this presentation.

MEDI 454

Synthesis and evaluation of mitochondria-targeted nitroxide analogs of XJB-5-131 and JP4-039

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The simplified gramicidin S analogs XJB-5-131 and JP4-039 possess an (*E*)-alkene peptide isostere allowing the molecules to adopt a type II′ β-turn as well as a nitroxide

subunit for scavenging of reactive oxygen species. These compounds have been shown to be successful mitochondrial targeting agents and are enriched in the mitochondria by a factor of 600 and 30, respectively. They are active in several disease models that result from oxidative damage, including lethal hemorrhagic shock and traumatic brain injury models. They also display radioprotective and radiomitigative properties.

Several new analogs of JP4-039 were synthesized and studied. Analogs with varying nitroxides were analyzed for radical and electron scavenging potential. BODIPY®-labeled analogs retained biological activity and were used to image the compound in mitochondria.

MEDI 455

Synthesis and biological evaluation of small molecule activators of the N370S mutant form of glucocerebrosidase as a potential therapy for Gaucher disease

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Gaucher's disease is a lysosomal storage disorder in which macrophages, the housekeeping cells of the body, produce insufficient amounts of or non-fully functioning versions of the enzyme β-glucocerebrosidase (β-GLU). After bodily cells die, macrophages use β-GLU to break down glucocerebroside, a major constituent of cell walls. With deficient functional β-GLU, glucocerebroside accumulates within lysosomes of macrophages, giving rise to characteristic appearing Gaucher cells. Clinical symptoms encountered in Gaucher's disease include enlargement of liver and, spleen, anemia, low platelets and at times, involvement of bone, lung or brain. Previous efforts have focused on costly enzyme replacement therapy and substrate (glucocerebroside) reduction therapy. As an alternate and potentially less costly and more selective therapy, we screened for small molecules with the potential to enhance enzymatic activity by activating the malfunctioning N370S mutant β-GLU. This project included a parallel synthetic endeavor to optimize high throughput screening hit activity in developing N370S β-GLU activators. Furthermore, lead compounds were found to also act as chemical chaperones that can bind to and stabilize the misfolded N370S β-GLU and then facilitate translocation from the endoplasmic reticulum to the lysosome. This may be an important therapeutic strategy that could potentially restore proper glucocerebroside recycling mechanisms, therefore successfully treating this disease.

MEDI 456

Chemically self-assembled antibody nanostructures (CSANs) for targeted drug delivery

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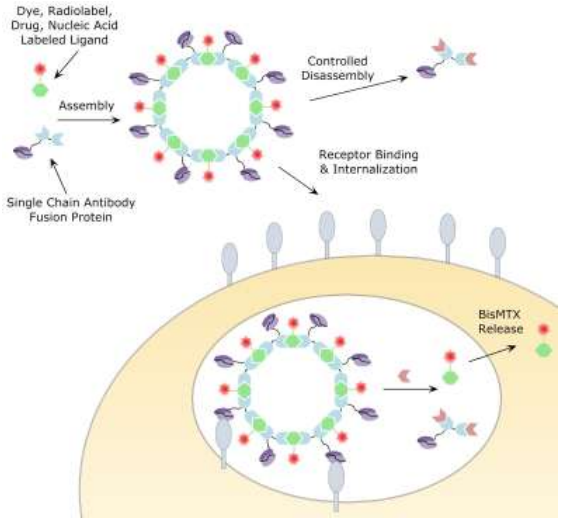
Exploiting the specific nature of methotrexte/dihydrofolate reductase binding has allowed us to form protein nanorings. Further, through using these stuctures to display T-cell specific single chain variable fragments (scFvs) we have prepared Chemically Self-assembled Antibody Nanostructures (CSANs). CSANs can be used for the delivery of dyes and drugs to T-leukemia cells. The disassembly of the nanostructures within the cells results in cytotoxicity. We are currently exploring the biodistribution of CSANs in vivo.



MEDI 457

Examining endocannabinoid oxygenation by COX-2: Synthesis of achiral substrate-selective COX-2 inhibitors

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Cyclooxygenase-2 (COX-2) is an inducible enzyme that oxygenates arachidonic acid (AA), 2-arachidonylglycerol (2-AG), and arachidonylethanolamide (AEA). 2-AG and AEA are endocannabinoids that exert analgesic and anti-inflammatory effects *in vivo*;

oxygenation of these endocannabinoids by COX-2 is believed to reduce their therapeutic effects at sites of inflammation and tumorigenesis. Our laboratory has reported that several (*R*)-profens, which are weak inhibitors of AA oxygenation by COX-2, are potent inhibitors of 2-AG oxygenation *in vitro* and in intact cells. The (*R*)-profens are tools with which to probe the importance of COX-2 oxygenation of endocannabinoids in different biological settings. A complication of the use of (*R*)-profens as *in vivo* probes of endocannabinoid oxygenation is their conversion to the (*S*)-enantiomers, which are potent inhibitors of AA oxygenation. Herein we describe the synthesis and COX-2 inhibitory activity of achiral profen molecules that cannot interconvert *in vivo.*