Division of Medicinal Chemistry

Scientific Abstracts

for the

245th National Meeting and Exposition

April 7-11, 2013

New Orleans, LA

American Chemical Society
Division of Medicinal Chemistry
245th ACS National Meeting, New Orleans, LA, April 7-11, 2013

J. Barrish, Program Chair

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Harnessing Atypical Molecular Interactions in Drug Design
B. Beno, Organizer; K. Yeung, Organizer; B. Beno, Presiding; K. Yeung, Presiding
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Drugging Individual Isoforms of PI3K: New Insights into Function
D. Sutherlin, Organizer; D. Sutherlin, Presiding Papers 7-12

General Oral Session
J. Barrish, Organizer; T. Bannister, Presiding Papers 13-24

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Global Health Challenges: The Need for New Anti-Infectives and Antivirals
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MEDI 1

Underexplored molecular interactions in ligand binding sites

***Bernd Kuhn**, bernd.kuhn@roche.com. Discovery Chemistry, F. Hoffmann-La Roche Ltd, Basel, Switzerland*

Molecular recognition in biological systems relies on the existence of specific attractive interactions between two partner molecules. In the last decade, several types of interactions have been newly identified or characterized in more detail using systematic mining of structural data, theoretical calculations, and case studies.[1] Examples of this are halogen bonds,[2] orthogonal multipolar interactions,[3] and weak hydrogen bonds.[4] We review structural preferences and energetic aspects of selected non-classical interactions and highlight their use with practical examples from medicinal chemistry projects.

[1] http://dx.doi.org/10.1021/jm100112j

[2] http://dx.doi.org/10.1002/anie.201006781

[3] http://dx.doi.org/10.1002/anie.200462213

[4] http://dx.doi.org/10.1021/ja066341f

MEDI 2

HEFLibs: Chemical probes for detecting halogen bonding in fragment-based lead discovery

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Halogens, especially the lighter fluorine and chlorine, are widely used substituents in medicinal chemistry. Traditionally they were viewed as hydrophobic moieties and Lewis bases in accordance with their electronegativities. However, compounds containing chlorine, bromine or iodine bound to an aromatic scaffold R can also form halogen bonds, directed close contacts of the type R-X…Y-R', where the halogen X acts as a Lewis acid and Y can be any electron donor moiety. In protein-ligand environments, these non-covalent interactions can be formed between a halogenated ligand and any accessible Lewis base in the binding pocket, which makes them useful interactions for drug discovery. Several recent studies have highlighted the use of halogen bonding for scaffold decoration to optimize compound affinities and selectivities.

In order to enable the identification of halogen bonds as core interactions at the early lead discovery stage, we have developed halogen-enriched fragment libraries

(HEFLibs). These libraries share the advantages of regular fragments as chemical probes of small size and high solubility. Additionally, they are designed to enable the identification of unique binding modes based on halogen bonding that are complementary to those obtained from classical fragment-based screening. We recently applied the HEFLib approach to develop biologically active small molecules that stabilize the p53 mutant Y220C, a challenging test case where several other screening and design approaches had previously been less successful.

MEDI 3

WITHDRAWN

MEDI 4

Unique interactions in the design and identification of selective kinase inhibitors

***Stephen T. Wrobleski**, stephen.wrobleski@bms.com, Shuqun Lin, T. G. Murali Dhar, Alaric J. Dyckman, John Hynes, Jr., Hong Wu, David Nirschl, Sidney Pitt, Rosemary Zhang, Yi Fan, Arthur M. Doweyko, John S. Tokarski, Kevin F. Kish, John S. Sack, Mary F. Malley, Susan E. Kiefer, John A. Newitt, Mark R. Witmer, Punit H. Marathe, Hongjian Zhang, Murray McKinnon, James Trzaskos, Joel C. Barrish, John H. Dodd, Gary L. Schieven, Katerina Leftheris. Research and Development, Bristol-Myers Squibb, Princeton, NJ 08543, United States*

The identification of small molecule kinase inhibitors which are ultimately established as safe and effective treatments for human diseases remains a significant challenge within the pharmaceutical industry. Optimization of molecular interactions between small molecule inhibitors and their intended protein target to attain the desired potency and selectivity profile is critical to overcoming this challenge. While the optimization of classical hydrogen bonding and van der Waals lipophilic interactions in ligand design is commonly considered, several unique or atypical molecular interactions are being explored with increased frequency. This presentation will serve to highlight two such interactions, non-bonding heteroatom-sulfur interactions and aryl C-H carbonyl interactions, in the context of designing and identification of novel p38α kinase inhibitors. X-ray crystallographic data will be presented as supporting evidence for the proposed atypical interactions.

MEDI 5

Complex interplay of electrostatics and hydration effects in protein-ligand binding: Studying fluorine dipolar interactions and cation-pi interactions using model systems and new families of ligands for epigenetic protein motifs

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The many weak interactions that might be involved in protein-protein and protein-ligand binding are well understood on a functional group-by-functional group basis. But the cooperation of many such “simple” interactions to drive binding always involves complex, non-additive effects that are difficult to predict and understand. This makes the dissection of the energetic contributions of individual functional groups to an overall complexation event a process that is fraught with difficulty. We will report here data arising from model recognition systems, protein structural surveys, and a series of structure/function relationships within a new family of antagonists of epigenetic reader protein interactions. Areas of discussion will include efforts to quantify the magnitude of the dipolar interactions of fluorine, the role of cation-pi interactions in protein-ligand recognition, and attempts to understand the roles of protein hydration and hydrophobicity in the recognition processes of epigenetic reader proteins.

MEDI 6

$n \rightarrow \pi^*$ Interactions in proteins and small molecules

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In 1951, Linus Pauling first reported on the hydrogen bonds between backbone amides that are common in the α-helices and β-sheets of proteins. We have discovered an analogous interaction. This interaction arises from the delocalization of a lone pair of electrons (n) from an oxygen atom to the anti-bonding orbital (π^*) of the subsequent carbonyl group in a polypeptide chain. The signature of this $n \rightarrow \pi^*$ interaction is most evident in the pyramidalization of the acceptor carbonyl group. Our *ab initio* calculations predict significant $n \rightarrow \pi^*$ interactions in certain regions of the Ramachandran plot. We have validated these predictions by a statistical analysis of a large, non-redundant subset of protein structures determined to high resolution. We find $n \rightarrow \pi^*$ interactions to be especially abundant in common secondary structures such as α-, 3_{10}-, and polyproline II helices, and twisted β-sheets. n)(π Pauli repulsion attenuates the $n \rightarrow \pi^*$ interaction with olefins and compromises their utility as peptidomimetics. In addition to their evident effects on peptide and protein conformation, $n \rightarrow \pi^*$ interactions could play important roles in protein folding and function, and merit inclusion in computational force fields. Finally, we have identified important $n \rightarrow \pi^*$ interactions within small molecules (such as aspirin) and with the chromophore of GFP and other fluorescent proteins, and noted that an $n \rightarrow \pi^*$ interaction could have directed the prebiotic genesis of ribonucleotides.

MEDI 7

NVP-BYL719: Exploring selective inhibition of PI3Kα as a therapeutic strategy in oncology

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The phosphoinositide 3-kinases are involved in a variety of cellular functions, including cell growth, proliferation, survival, and metabolism. They participate in the phosphorylation of the inositol head group of phosphatidylinositide lipids, a critical step in the activation of the PI3K pathway which plays an important role in cancer. A number of genetic abnormalities in PI3K signalling have been implicated in oncogenesis and are common to a variety of human cancers. Among these genetic lesions, gain of function mutations in the PIK3CA gene encoding the p110α catalytic subunit have been found in 30% of solid tumors. These observations have prompted interest in the development of a second generation of PI3K inhibitors which would exhibit selectivity for the alpha isoform. Such inhibitors might find therapeutic application for the treatment of PI3Kα mutant tumors while possibly avoiding undesired effects arising from the inhibition of the other isoforms. In this lecture, we describe the process that led to the identification of NVP-BYL719, a potent and selective PI3Kα inhibitor. A preliminary, preclinical evaluation of NVP-BYL719 in comparison with the pan-PI3K inhibitor, NVP-BKM120, will be presented. The biological profiles will be discussed in relation to the distinct structures of these inhibitors and their binding interactions with PI3K.

MEDI 8

Discovery and optimization of pyrimidone PI3K□inhibitors

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Phosphoinositide 3-kinase (PI3K) pathway activation plays a major role in cancer as a result of abnormalities in major components of this signalling cascade, including activating point mutations and/or amplification of the *PIK3CA* gene, as well as loss of negative regulatory proteins such as Phosphatase and TENsin homologue (PTEN). It has been reported that conditional knock-out of *PIK3CB*, and not *PIK3CA*, leads to tumor growth inhibition in PTEN-deficient genetic context, as well as to prevent prostate tumor formation induced by *PTEN* loss with concomitant diminution of AKT phosphorylation. We report herein the discovery and optimization of a novel series of PI3Kb isoform-selective small molecular mass inhibitors and their potential application as anti-cancer agents in PTEN-deficient tumors.

MEDI 9

GS-1101, a potent PI3Kδ inhibitor for the treatment of hematological malignancies

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Deregulation of the PI3K/Akt pathway is a commonly observed defect in human malignancies. Of the class IA PI3Ks (p110α, p110β, p110δ), PI3Kδ's expression is largely restricted to cells of hematopoietic origin. Mice deficient in PI3Kδ present no gross abnormalities and live a normal lifespan. However, effects on intracellular signaling, proliferation, migration, and differentiation have been observed in both myeloid and lymphoid cells with the most pronounced effects on B cell development and survival. Therefore, selective targeting of PI3Kδ signaling in hematological tumor cells could provide an attractive approach for therapeutic intervention. GS-1101 is a potent PI3Kδ inhibitor with an IC_{50} of 2.5nM against the purified p110δ subunit and 65nM wholeblood cellular potency against PI3Kδ. GS-1101 demonstrates 45-400 fold selectivity over the other class I PI3Ks and no activity against class II, III PI3K family members, or mTOR and DNA-PK. Furthermore, a genome wide screen of >420protein kinases did not detect inhibitory activity. In B cell malignances, a potential mechanism for PI3K pathway activation is tonic antigen-independent BCR signaling that requires PI3Kδ for the transduction of proliferation and survival signals. In this regard, GS-1101 blocks constitutive oncogenic signaling, resulting in apoptosis, Interestingly, the protective effects of the tumor microenvironment or the addition of survival factors does not overcome the ability of GS-1101 to induce primary tumor cell killing. In addition to a direct induction of apoptosis, GS-1101 can inhibit induced survival mechanisms by blocking the protective effect of a number of different microenvironmental stimuli by preventing activation of downstream signaling. Similarly, GS-1101 has been shown to overcome both bone marrow stromal cell (BMSC)- and endothelial cells (EC)-mediated cell protection, indicating that GS-1101 inhibits BMSC- and EC-derived prosurvival signals. Together these data indicate that GS-1101 directly induces apoptosis and inhibits microenvironmental interactions, leading to decreased cellular survival, proliferation, and migration.

MEDI 10

Discovery of potent and selective PI3K delta inhibitors for the treatment of respiratory indications

***Nicole Hamblin**, nicole.j.hamblin@gsk.com. Respiratory Therapy Area, GlaxoSmithKline, Stevenage, Hertfordshire SG1 2NY, United Kingdom*

PI3K delta is a lipid kinase which is expressed primarily in leukocytes. It plays a key role in immune cell signalling across a broad range of cell types and is activated in response to multiple triggers of relevance to respiratory disease. These include allergens, inflammatory cytokines, smoke and viruses. We believe that inhibitors of PI3K delta delivered directly to the lung, by the inhaled route, will therefore have therapeutic potential in the control of inflammatory processes leading to exacerbations associated with both asthma and COPD.

This presentation will begin by describing the medicinal chemistry program around a series of indazole containing PI3K delta inhibitors, leading to highly potent and selective compounds with properties suitable for inhaled delivery. Medicinal chemistry considerations specific to the development of an inhaled candidate compound will be discussed, along with hypotheses for the exquisite PI3K isoform selectivity observed in this series. The importance of crystallography and modelling in interpreting SAR and driving compound design will also be highlighted.

The biological profile of the resulting clinical candidate, Compound A, will be presented, including reduction of cytokine release from stimulated human lung tissue *in vitro* and prevention of inflammatory responses associated with allergic airway inflammation in rats. Recent data showing the potential for a PI3K delta inhibitor to complement inhaled steroids in the treatment of asthma and COPD patients will also be discussed.

MEDI 11

Development of the potent PI3K-δ,γ inhibitor IPI-145 in hematologic malignancies and inflammatory disease indications

James R Porter[1]*, james.porter@infi.com, Julian Adams*[1]*, Alfredo Castro*[1]*, Jonathan P DiNitto*[1]*, Joi Dunbar*[1]*, Kerrie Faia*[1]*, Patrick Kelly*[1]*, Lian-Sheng Li*[2]*, Charlotte McKee*[1]*, Jylle Nevejans*[1]*, Wei Niu*[1]*, Vito J Palombella*[1]*, Melissa Pink*[1]*, Pingda Ren*[2]*, Christian Rommel*[2]*, John Soglia*[1]*, Kerry White*[1]*, David G Winkler*[1]*. (1) Infinity Pharmaceuticals, Inc., Cambridge, MA 01969, United States (2) Intellikine, Inc, La Jolla, CA 92037, United States*

The class I phosphatidylinositol 3-kinases (PI3K) play pivotal roles in cell signaling and regulate a variety of cellular functions. PI3K-δ and PI3K-γ isoforms are necessary for adaptive and innate immunity and are important mediators in inflammatory disorders and hematologic malignancies. Expression of these isoforms is largely restricted to, and required for, cells of the immune system. Selective targeting of PI3K signaling in immune cells could provide an effective treatment strategy while limiting potential undesirable effects of inhibitors that broadly block signaling of all PI3K isoforms in a wide variety of cells. IPI-145 is a potent PI3K-δ,γ inhibitor with remarkable selectivity over other protein kinases and has demonstrated activity in preclinical models of inflammatory disease. Therefore, IPI-145 is being developed as an orally administered potential therapeutic in hematologic malignancies and inflammatory disease indications.

MEDI 12

Discovery of benzoxazepin PI3K inhibitors and optimization of p110-alpha selectivity

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PI3K is a clinically validated target for the treatment of cancer. During our search for novel chemical matter that selectively inhibit PI3K, we discovered a structural series based on the benzoxepin scaffold. Compounds in this class are potent and selective for the Class I PI3K isoforms. The inhibitors have shown good in vitro stability which has resulted in good preclinical pharmacokinetics. We will describe our ligand optimization efforts including the use of structure-guided hypotheses together with physicochemical property information to generate compounds that exclusively target the oncogenic PI3K-alpha isoform and had good in vivo anti-tumor activity.

MEDI 13

Small molecule inhibitors of KLF5 expression: Tools for targeting colorectal cancer

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We have used an ultra high throughput screen of the NIH Molecular Libraries Small Molecule Repository (MLSMR) using a luciferase reporter cell-based assay, follow-up mechanistic studies, and medicinal chemistry optimization efforts to discover a potent and selective inhibitor of expression of the transcription factor Krüppel-like factor 5 (KLF5). Malignant epithelial cells in intestinal crypts have elevated levels of KLF5, also called intestinal-enriched Krüppel-like factor (IKLF). While many antitumor agents target proteins regulated by transcription factors, small molecule therapeutics rarely lessen the production of a transcription factor itself by design, an appealing strategy since one transcription factor can stimulate multiple pathways aiding tumor progression, with devastating consequences.

We herein disclose a potent and selective small molecule inhibitor of KLF5 expression that reduces proliferation of most types of colon cancer cells. SAR studies and optimization of lead-like and drug-like properties are discussed. Preliminary in vivo efficacy studies will also be presented. We anticipate that this tool compound will aid efforts to elucidate KLF5's role in regulating cellular proliferation and tumor formation in the intestinal epithelium. Further, we hope that this compound may help demonstrate that specifically lowering expression levels of a transcription factor can be effective means of cancer chemotherapy.

MEDI 14

Synthesis, pharmacological evaluation, and behavioral studies in mice of difluoromethyl ketones as novel and selective agonists of the GABA-B receptor

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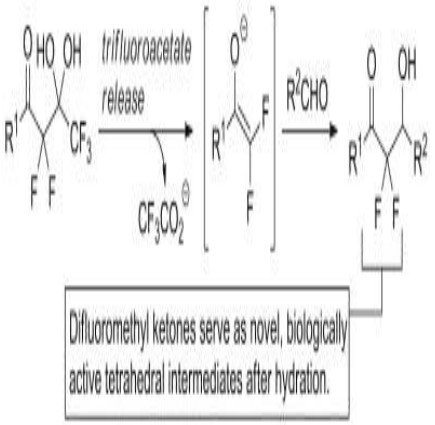

The development of new synthetic methodologies for the preparation of fluorine-containing molecules is an area of intense investigation in the pharmaceutical industry. Difluoromethyl ketones are prominent examples of such fluorinated compounds, because the ketone reverts to a hydrate in the presence of water which may impart promising new biological activity. Recently, we have discovered that trifluoroacetate release is a powerful synthetic process for executing aldol reactions with difluoroenolates and for assembling difluoromethyl ketones. Pharmacological evaluation of these scaffolds has lead to the identification of selective agonists of the GABA-B receptor. These unique molecules are not based on the structure of GABA and this feature distinguishes them from nearly all of the other known selective GABA-B agonists. This presentation will describe the synthesis, discovery, and pharmacological evaluation of novel difluoromethyl ketones as agonist of the GABA-B receptor. Preliminary behavioral studies in mice for the lead compound will be disclosed.

MEDI 15

Carboranes increase the potency of small molecule inhibitors of nicotinamide phosphoribosyltranferase

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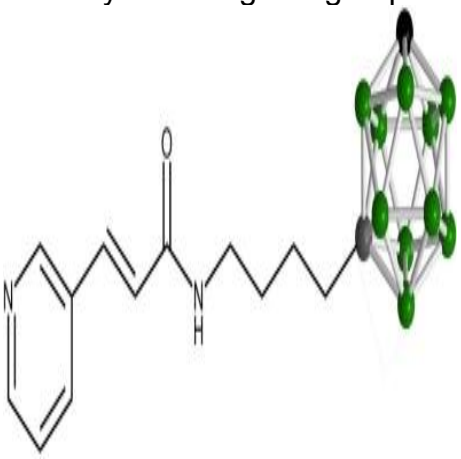
Nicotinamide Phosphoribosyltranferase (Nampt) is the first and rate limiting enzyme in the mammalian NAD^+salvage pathway, converting nicotinamide to nicotinamide

mononucleotide. Nampt activity plays a central role in metabolism, cellular proliferation, cell survival and the inflammatory response, making this enzyme a new and intriguing target for the treatment of many diseases, including cancer, Alzheimer's, Diabetes and Arthritis.

Over the past 10 years, carboranes have been investigated as a pharmacophoric unit in drug design, typically through the substitution of a benzene ring in the structure of a known compound. Here, we systematically compare the three isomers of carborane (*ortho, meta, para*) with similarly sized organic groups in the structure of small molecule inhibitors of Nampt. The inclusion of a carborane produces agents with exceptionally high antiproliferative activity against three human tumor cell lines in vitro. Inhibitors incorporating a carborane exhibited between 10 and 10,000-fold higher potencies than similarly sized organic groups.



Given the tremendous unmet need for more efficacious and affordable chemotherapeutic agents, our findings provide additional evidence that these clusters may provide a manner in which to improve the efficacy and specificity of new drugs, one not provided through the use of organic chemistry alone.

MEDI 16

SAR, identification of the molecular targets and therapeutic potential of original anticancer natural products: Flavaglines

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Flavaglines are a family of anticancer natural products that relieve the resistance to cancer chemotherapies and display a strong cytotoxicity that is specific to cancer cells. We identified the first synthetic flavaglines that inhibit cell proliferation and viability (IC_{50}~1 nM) at lower doses than did the parent natural compounds. These synthetic flavaglines retain their potency against multiresistant cell lines, induce apoptosis

independently of “classical” apoptosis pathways and potentiates the effects of chemotherapeutic agents.

Not only flavaglines are not toxic to non-cancer cells, but they protect normal cells from various stresses. Thus, we demonstrated for the first time that these compounds protect the heart and neurons from the adverse effects of cancer chemotherapies involving anthracyclines and cisplatin.

An extensive SAR study, which led to the discovery of original derivatives with enhanced pharmacological properties, will be also presented.

A ligand for affinity chromatography was designed and synthesized based on this SAR information, and used for the identification of prohibitins-1 and -2 as the molecular targets.Prohibitin-1 (PHB1) and its homologue prohibitin-2 (PHB2) are pleiotropic proteins that act as a hub for many signaling pathways to regulate metabolism, cell migration, division and survival. We demonstrated that the binding of flavaglines to PHBs prevents interaction between PHBs and CRaf and, thereby, inhibits CRaf activation and subsequently CRaf-MEK-ERK signaling, which is critical to survival and proliferation of cancer cells.

We will present the SAR, *in vivo* activity, and the identification and validation of PHBs as the molecular target for flavaglines.

MEDI 17

Chemical improvement of pharmacological properties of irreversible VDR-coactivator inhibitors and their evaluation in vivo using an ovarian cancer animal model

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The vitamin D receptor (VDR) interacts with coregulators, including coactivator and corepressors, to regulate genes responsible for cell differentiation, proliferation and calcium homeostasis. Selective regulation of VDR target genes, using a VDR ligand-based approach, has been unsuccessful so far inducing both differentiation and hypercalcemia at effective compound concentrations. Earlier, our group successfully discovered indole-based small molecules by using HTS, which modulate transcription through the inhibition of the protein-protein interactions of VDR and coactivator proteins (Nandikhonda et al *J. Med. Chem.* 2012, *55*, 4640-4651). To further our efforts, we herein report the extensive SAR studies and detailed biochemical evaluations of 2nd generation indole-based inhibitors, which have been designed by taking cue from 1st generation molecules and applying a microwave-assisted multi-component Aza-Friedel-Crafts reaction. These newly synthesized compounds exhibited improved solubility, permeability, potency and selectivity in comparison with the parent molecules.

Furthermore, VDR target genes were selectively regulated in the presence of these compounds. The data from an ovarian cancer xenograph model confirmed the antiproliferative effect of these inhibitors, first observed with cultured cancer cells, showing significant reduction in cancer growth without inducing hypercalcemia. Current investigations are focused on the quantification of gene transcription levels in the cancer tissue to identify the changes of gene regulation leading to VDR-mediated antiproliferation.

MEDI 18

ANCHOR.QUERY: A pharmacophore-based interactive screening technology for the discovery of potent and selective MDM2/p53 antagonist

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We introduce the web-based designer pharmacophore freeware ANCHOR.QUERY (http://anchorquery.ccbb.pitt.edu/) for the rapid and efficient discovery of protein interacting (ant)agonists by screening the chemical space of multicomponent reactions (MCRs). ANCHOR.QUERY builds on the role anchor residues have in PPIs, and redesigns these entry points with anchor-biased virtual multicomponent reactions, delivering tens of millions of readily synthesizable novel compounds. We present the discovery of several potent p53–Mdm2 antagonists. All compounds were efficiently synthesized by MCR chemistry. Several cocrystal structures will be discussed as well as their potent activity in acute myeloid leukemia (AML) patient derived cells.

Czarna, A., et al (2011) p53/Hdm2 Antagonists. Angew. Chem., 122: 5480–5484. doi: 10.1002/ange.201001343

Koes D, et al. (2012) Enabling Large-Scale Design, Synthesis and Validation of Small Molecule Protein-Protein Antagonists. PLoS ONE 7(3): e32839. doi:10.1371/journal.pone.0032839

Huang, Y., et al. (2012), Exhaustive Fluorine Scanning toward Potent p53–Mdm2 Antagonists. ChemMedChem, 7: 49–52. doi: 10.1002/cmdc.201100428

MEDI 19

Substrate specificity of lysine deacylase enzymes in vitro

***Christian A. Olsen**, cao@kemi.dtu.dk, Andreas S. Madsen. Department of Chemistry, Technical University of Denmark, Kgs. Lyngby, Denmark*

Histone deacetylase enzymes (HDACs and sirtuins) have received considerable attention due to their potential as targets for therapeutic intervention in a variety of disease states, including several types of cancer. Methods for accurate biochemical profiling of putative drug candidates are therefore desirable.

Here, the evaluation of a panel of diverse fluorogenic substrates against the panel of human zinc-dependent HDACs 1–11 as well as the NAD-dependent sirtuins (SIRT1–7), will be discussed. Kinetic parameters describing a selection of the enzyme–substrate interactions in further detail were performed, and a selection of inhibitors were evaluated. Our investigations show noteworthy trends in substrate K_m vs. k_{cat} values for class-IIa HDACs, which raise important questions regarding the inherent function of this isozyme sub-class. Efficient fluorogenic substrates for SIRT5 screening will be presented, and finally, we have shown that HDAC3 harbors lysine decrotonylase activity, albeit at a considerably lower rate than its deacetylase acitivity.

MEDI 20

Identification of hybrid scaffolds as pontent multitarget FAAH/COX inhibitors

*Marco Migliore[1], Marino Convertino[1], Damien Habrant[1], Angelo Favia[1], Clara Albani[1], Glauco Tarozzo[1], Andrea Cavalli[1,3], Daniele Piomelli[1,2], Rita Scarpelli[1], **Marco De Vivo**[1], marco.devivo@iit.it. (1) Department of Drug Discovery and Development, Italian Institute of Technology, Genoa, Italy (2) Department of Anatomy and Neurobiology, University of California, Irvine, United States (3) Department of Pharmaceutical Sciences, University of Bologna, Italy*

Pain and inflammation remain areas of substantial unmet patient need. Current drugs used to treat these conditions have, however, moderate efficacy and can produce a variety of untoward side effects. In this study, we identified a novel hybrid scaffold as a multitarget inhibitor that simultaneously block cyclooxygenase-1 (COX-1), COX-2 and fatty acid amide hydrolase (FAAH). This multitarget strategy may result in improved analgesic efficacy and reduced side effects related to anti-pain drugs, as demonstrated by recent published works (Naidu, et al (**2009**) *J Pharmacol Exp Ther* 329, 48-56; Fowler, C.J. et al. (**2012**) *J Enzym Inhib Med Chem* Jan 6*;* Sasso, et al (**2012**) *Pharmacol Res* 65, 553). These hybrid compounds are active in the nanomolar range on the three targets, being the most potent multitarget FAAH/COXs inhibitors reported to date. Thus, those compounds may represent promising starting points for the discovery of new analgesic and anti-inflammatory drugs.

MEDI 21

Repurposing CNI-1493 for the treatment of neurodegenerative diseases

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Semapimod (formally known as CNI-1493) has undergone phase II clinical trials in Crohn's disease and although it lacked statistically meaningful efficacy in these trials, it was demonstrated to be a well-tolerated drug (non-toxic) with largely minimal, self-limiting side effects. We recently have identified CNI-1493 as a potential drug candidate for the treatment of neurodegenerative diseases such as Alzheimer's and Parkinson's diseases. In our AD animal studies we could demonstrate that CNI-1493 is able to improve cognitive function, decrease Aβ levels and inhibit microglial activation. The molecular mechanisms underlying CNI-1493's effects in Alzheimer's diseases will be presented.

MEDI 22

Centanamycin analogs: From small molecule design to malaria vaccine development

Moses Lee[1]*, lee@hope.edu, Pravin Patil*[1]*, Sameer Chavda*[1]*, Stephanie K. Yanow*[2]*, Michael F. Good*[3]*. (1) Department of Chemistry, Hope College, Holland, MI 49422, United States (2) School of Public Health, University of Alberta, Edmonton, Alberta T6G 1C9, Canada (3) Institute for Glycomics, Griffith University, Gold Coast, Queensland 4222, Australia*

According to the U.S. Centers for Disease Control and Prevention, in 2010, an estimated 216 million cases of malaria occurred worldwide and 655,000 people died, most (91%) in Africa. The deaths are mostly pregnant women and young children. Due to the prevalence of drug resistant *Plasmodium*, a parasite that causes malaria, there is an immediate need for new modalities for treating or controlling the disease. Based on the high AT-content of the malaria genome, we have designed and tested centanamycin (CM), an AT-sequence and minor groove selective DNA alkylating molecule. CM is highly cytotoxic against *Plasmodium falciparum* grown in culture and it is highly active against multiple strains of rodent malaria in vivo, following a single i.p. or oral administration. It also blocks transmission of parasites in mosquitoes, and as a potential vaccine, CM attenuated parasites protect mice from further malaria infection. In this study, a series of CM analogs were synthesized and tested for cytotoxicity against *Plasmodium falciparum* grown in culture. CM and one of the analogs were examined for their ability to attenuate parasites and protect animals against infection. Results from these experiments will be presented.

MEDI 23

Rational design and synthesis of metabolically stable phosphate analogs for ss-siRNA activation of RNAi in animals

***Thazha P Prakash**, tprakash@isisph.com, Walt F. Lima, Heather M. Murray, Garth A. Kinberger, Wenyu Li, Punit P. Seth, Eric E. Swayze, Stanley T. Crooke.Isis Pharmaceuticals, Carlsbad, California 92011, United States*

RNA interference (RNAi) mediated inhibition of gene expression in general uses double stranded RNA (siRNA) and requires cationic lipid formulation or complex conjugates to achieve potent target reduction in animals. In contrast, RNase H based single stranded antisense oligonucleotides have shown activity in multiple species (including humans) without formulation. In addition, a single stranded RNA (ss-siRNA) delivered to cells using cationic lipids has been shown to activate the RNAi pathway but with less efficiency relative to double stranded siRNA. This demonstrates that a double stranded structure is not necessary to elicit RNAi. This observation suggests that the dsRNA structure could be simplified to a single stranded oligonucleotide that would activate RNAi in cells and in animals.

The metabolic instability of ss-siRNAs compared to double-stranded siRNAs likely contributed to the poor activities observed for the ss-siRNAs. We recently reported results from our effort to identify chemical modifications to improve the metabolic stability of ss-siRNA.[1] We performed an extensive chemical SAR and identified ss-siRNAs containing the 2'-F, 2'-*O*-Me, 2'-*O*-MOE and phosphorothioate modifications with *in vitro* potency similar to the corresponding siRNA. In addition, we also reported that 5'-phosphateis a critical determinant for ss-siRNA activity *in vivo*. In this presentation, a detailed report of our efforts to identify a stable phosphate mimic for achieving ss-siRNA to achieve robust *in vivo* activity will be discussed. We utilized known crystal structure of the Ago2- bound guide strand for designing chemical modifications to improve the metabolic stability of 5'-phosphate. This rational approach allowed us to identify 5'-(*E*)-vinyl phosphonate as a metabolically stable phosphate mimic for eliciting RNAi in mice.

1. Lima, W. F.; Prakash, T. P.; Murray, H. M.; Kinberger, G. A.; Li, W.; Chappell, A. E.; Li, C. S.; Murray, S. F.; Gaus, H.; Seth, Punit P.; Swayze, E. E; Crooke, S. T *Cell* **2012** , *150*, 883-894

MEDI 24

PubChem BioAssay: A public information resource for medicinal chemistry research

***Yanli Wang**, ywang@ncbi.nlm.nih.gov. National Library of Medicine (NLM), National Center for Biotechnology Information (NCBI), National Institutes of Health (NIH), Bethesda, Maryland 20894, United States*

The PubChem BioAssay database (http://pubchem.ncbi.nlm.nih.gov) is a public repository for archiving biological test results for small molecules including drugs. It has become an increasingly important resource for drug development and medical chemistry research. PubChem's data content is derived from the voluntary contributions

of industrial, academic and government organizations and laboratories. PubChem BioAssay currently contains 600,000 bioassay depositions, 2.7 million tested substances, eight thousands of protein targets, and 190 million bioactivity outcomes, which are generated from HTS screenings, medicinal chemistry studies, chemical biology experiments as well as from literature extraction projects. The goal of PubChem is to optimize the utility of such rich information, and to provide services to make the biological activity data easily accessible to the public. PubChem can be accessed and searched through the NCBI Entrez information retrieval system (http://www.ncbi.nlm.nih.gov/pcassay/). PubChem also provides an integrated cheminformatics system to facilitate the utilization of the information. A suite of bioactivity analysis tools are developed to integrate the chemical and biological activity information, and to support data retrieval, download, navigation and in-depth analysis that facilitates identifying medically interesting compounds and biological targets (http://pubchem.ncbi.nlm.nih.gov/assay/). The BioAssay data is fully downloadable at ftp://ftp.ncbi.nlm.nih.gov/pubchem/Bioassay/. PubChem provides a deposition system at http://pubchem.ncbi.nlm.nih.gov/deposit and welcomes contributions from the medical chemistry research community. Detailed descriptions for the PubChem BioAssay resource is available at http://www.ncbi.nlm.nih.gov/pubmed/22140110.

MEDI 25

Boron in drug discovery

***Stephen J Baker**, sbaker@anacor.com. Anacor Pharmaceuticals, Inc., Palo Alto, California 94303, United States*

Boron provides some unique chemical properties to small molecules that can be exploited for drug discovery, and over the last decade, pioneering research has demonstrated boron's potential in therapeutic areas including cancer, infectious diseases and inflammation.

The electrophilic, empty p orbital, the Lewis acidity, and boron bond lengths provide chemists with the ability to inhibit different targets using a host of different binding modes. Current research is now uncovering how chemists can optimize some of these properties.

Boron therapeutics have demonstrated predictable pharmacokinetics and metabolism, and have proven to be similar to other small molecule programs in their safety profiles. As more boron therapeutics advance through clinical trials, and as we learn more about the abilities of these molecule, they are likely to become commonplace in future medicinal chemistry programs.

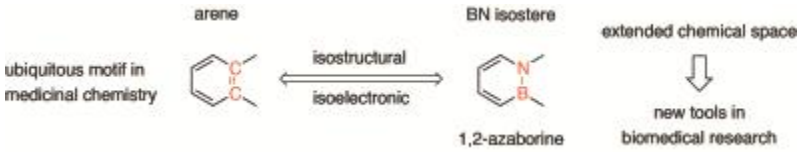
This presentation will review Anacor's experience researching and developing boron-containing small molecules including chemistry, pharmacokinetics, metabolism, safety and clinical studies.

MEDI 26

BN/CC Isosterism: A new approach to expand the chemical space in biomedical research

***Shih-Yuan Liu**, lsy@uoregon.edu. Department of Chemistry, University of Oregon, Eugene, Oregon 97403-1253, United States*

BN/CC isosterism has recently emerged as a viable strategy to increase structural diversity. In particular, the chemistry of 1,2-azaborines, which are BN isosteres of the ubiquitous family of arenes, has attracted attention as novel aromatic compounds relevant to biomedical research. I will describe our recent contributions in the synthesis, characterization, and reactivity studies of 1,2-azaborine heterocycles. Furthermore, emerging investigations of 1,2-azaborines in the context of biological systems will also be discussed.



MEDI 27

Synthesis of chiral inhibitors of the HCV-RNA dependent RNA polymerase: Discovery of a clinical candidate

***J. Brad Shotwell**, brad.j.shotwell@gsk.com. Antiviral Medicinal Chemistry, GlaxoSmithKline, Research Triangle Park, NC 27709-3398, United States*

Hepatitis C virus (HCV) afflicts an estimated 170 million people worldwide, including 4 million people in the US. People infected are at risk of developing chronic liver disease, cirrhosis, and cancer. The current standard of care includes injectable interferon combined with oral agents, and is limited by negative side effects, modest efficacy, and numerous contraindications. HCV polymerase is an enzyme essential for viral RNA replication and proliferation and is an attractive target. A series of chiral compounds were prepared by a highly diasteroselective Evan's Aldol reaction. This series has been shown to be potent inhibitors of HCV-RNA dependent RNA Polymerase.

MEDI 28

Drug design based on the carbon/silicon switch strategy

***Reinhold Tacke**, r.tacke@uni-wuerzburg.de. Institute of Inorganic Chemistry, University of Würzburg, Würzburg, Germany*

Silicon chemistry has been demonstrated to be a novel source of chemical diversity in drug design, and this field is currently being developed into a practical and commercial enterprise [1]. The carbon/silicon switch strategy (sila-substitution of known drugs) is one of the methods that are currently used for the development of silicon-based drugs (for recent publicatons, see refs 2-4). Selected examples of this approach will be presented.

[1] W. Bains, R. Tacke, *Curr. Opin. Drug Discovery Dev.* **2003** , *6*, 526-543.

[2] R. Tacke et al., *ChemBioChem* **2007** , *8*, 1688-1699.

[3] R. Tacke et al., *ChemMedChem* **2008** , *3*, 152-164.

[4] R. Tacke et al., *ChemMedChem* **2011** , *6*, 2070-2080.

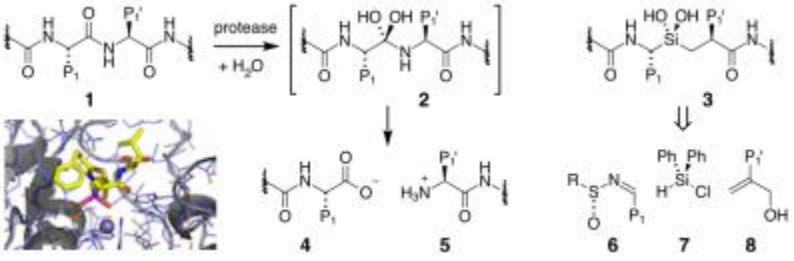
[5] R. Tacke et al., *ChemMedChem* **2012** , *7*, 523-532.

MEDI 29

Silanediol peptidomimetics as carbonyl hydrate analogs and protease inhibitors

Scott McN. Sieburth*, scott.sieburth@temple.edu, Swapnil Singh, Buddha B. B. Khatri, Hoan Quoc Duong, Yingjian Bo. Department of Chemistry, Temple University, Philadelphia, PA 19122, United States*

Inhibition of proteolytic enzymes is an important drug design strategy. Nonhydrolyzable mimics of the hydrated amide **2** can be platforms from which to design substrate analog inhibitors. We have studied the simulation of **2** by the silanediol functional group in peptide-like structures **3** and found them to be excellent inhibitors of metallo-, aspartic and serine protease enzymes. Recent advances in inhibitor design and synthetic methods for assembling structures will be described.



MEDI 30

Selenium-containing antibacterial agents

Jason A Wiles*, jwiles@achillion.com. Achillion Pharmaceuticals, New Haven, CT 06511, United States*

This presentation will focus on our exploration of selenophene-based inhibitors of bacterial topoisomerases that do not share cross resistance with fluoroquinolones. The synthesis, antibacterial activity, and efforts to reduce potential cardiotoxicity of this class of agents will be discussed.

MEDI 31

From basic science to advanced medicine

***Ada Yonath**, ada.yonath@weizmann.ac.il. Department of Structural Biology, Weizmann Institute, Rehovot, Israel*

Ribosomes, the universal cellular machines that translate the genetic code into proteins, are targeted by many antibiotics that paralyze them by binding to their functional sites. Antibiotics binding modes, inhibitory action and synergism pathways have been determined for almost all ribosomal antibiotics. These show the principles of differentiate between patients and pathogens, suggest mechanisms leading to bacterial resistance and paved ways to design advanced therapeutics capable of minimizing antibiotics resistance.

MEDI 32

Understanding how antiretroviral therapy for HIV infection really works

***Robert F. Siliciano**, rsiliciano@jhmi.edu. Johns Hopkins University School of Medicine, Baltimore, United States*

Highly active antiretroviral therapy (HAART) can reduce viremia to below the limit of detection of current clinical assays (50 copies of HIV RNA/ml plasma), but viral reservoirs and low level residual viremia persist. Recent studies of HAART intensification show that the residual viremia is not due to ongoing replication, but rather release from stable reservoirs. Pharmacodynamic studies of antiretroviral drugs have shown that some classes of drugs have steep, highly cooperative dose response curves, reflecting a unique form of intermolecular cooperativity that allows for up to 10 logs of inhibition of a single round of replication by some of the best drugs. These results explain the ability of HAART to halt virus evolution in adherent patients. A biophysical model to explain the cooperative inhibition of infectivity will be described. This model also explains the effects of resistance mutations that alter not only the IC50 but also the shape of dose response curves. Correct analysis of the residual activity of drugs against resistant viruses requires an understanding of the effects of mutations on the shape of the dose response curves. This work has allowed the development of methods for calculating the combined inhibitory potential of drug combinations, permitting the first a direct comparison of the antiviral activity of different drug regimens and the definition of a minimum threshold for effective HAART. This quantitative approach to understanding HAART may be useful in the choice of simpler HAART

regimens for patients with wild type virus and more rational selection of salvage regimens for patients with resistant virus.

MEDI 33

HCV antiviral resistance: A significant challenge with paths to solutions

***Guofeng Cheng**, guofeng.cheng@gilead.com. Gilead Sciences, United States*

Selection of antiviral resistance in the clinic poses a significant challenge to the development of HCV antiviral drugs. Monotherapy with direct-acting antivirals is insufficient to treat chronic HCV infection due to the pre-existence of drug-resistant viral variants. Multiple approaches to limit or overcome HCV resistance are emerging. These include, (1) targeting the highly conserved NS5B polymerase active-site which imposes a large fitness cost on mutants, (2) optimization for new generation inhibitors against lower resistance barrier targets (e.g. NS3 protease and NS5A) using crystallographic studies and extensive structure-activity-relationship analyses, (3) optimization of inhibitor pharmacokinetic properties to enable pharmocologic barriers to resistance profiles to pose high genetic barriers to resistance and (4) the use of combinations of agents with orthogonal resistance profiles to pose high genetic barriers to resistance. Overall, these approaches are enabling high sustained viral response (SVR) rates and options for abbreviated curative treatment courses. Future single tablet regimens (STRs) may further minimize resistance by improving patient adherence.

MEDI 34

Toward a universal β-lactamase inhibitor: A collaborative, interdisciplinary, Canada-UK team effort

***Gary I. Dmitrienko**[1], dmitrien@uwaterloo.ca, Valerie J. Goodfellow[1], Laura Marrone[1], Ahmad Ghavami[1], Anthony P. Krismanich[1], Nan Chen[1], Carol A. Tanner[1], Jarrod W. Johnson[1], Dylan R. Pillai[2], Dustin King[3], Michael Gretes[3], Natalie C.J. Strynadka[3], James Spencer[4]. (1) University of Waterloo, Canada (2) Department of Pathology and Laboratory Medicine, University of Calgary, Canada (3) Department of Biochemistry, University of British Columbia, Canada (4) School of Cellular and Molecular Medicine, University of Bristol, United Kingdom*

The carbapenems represent a last line of defence class of β- lactam antibiotics that, until recently, were unaffected by clinically significant β-lactamases that inactivate all other classes of β- lactams. Classes A, C and D β-lactamases rely on a nucleophilic serine hydroxyl group whereas Class B enzymes employ zinc ions for catalysis. Class A, B and D carbapenemases are now encountered commonly in hospitals. Mechanism-based inhibitors for the Class A β-lactamases, discovered in the 1980s, are much less effective against Class A and Class D carbapenemases and are totally ineffective against Class B enzymes.

An interdisciplinary team funded by the Canadian Institutes for Health Research and the Medical Research Council in the UK is seeking solutions to carbapenem resistance. Progress in identifying compounds capable of inhibiting both the serine and the metallo-carbapenemases based on rational design as well as on natural product leads will be outlined.

MEDI 35

Siderophore conjugated lactivicin compounds with activity against gram-negative pathogens

***Jeremy T. Starr**, Jeremy.Starr@pfizer.com, Matthew F. Brown, Seungil Han, Veerabahu Shanmugasundaram, Eric McElroy, Brian S. Gerstenberger, Michael D. Huband, Megan M. Lemmon, Chao Li, Sandra P. McCurdy, Mark C. Noe, Mark R. Rauckhorst, Andrew P. Tomaras, Jennifer A. Young, Richard P. Zaniewski.Pfizer Global Research and Development, United States*

Novel siderophore conjugated analogs of the natural product, lactivicin, were designed, guided by X-ray crystallography of a covalent complex of a lactivicin derivative with *Pseudomonas aeruginosa* (Pae) Penicillin Binding Protein 3 (PBP3). Analogs bearing a variety of sideophore mimicking groups extending into open regions of the active site were synthesized and evaluated. The targeted analogs exhibited Minimum Inhibitory Concentrations (MIC) against pathogenic Gram-negative organisms: Pae (0.5 - 32 µg/mL), *Klebsiella pneumoniae* (0.5 – 32 µg/ mL), *Acinetobacter baumaunii* (0.06 – 32 µg/mL), and *Escherichia coli* (0.25 – 2 µg/mL) and potent inhibition of Pae PBP1a, 1b and PBP3 (IC50 0.03 – 2.5 µM). A lead compound employing a novel siderophore mimic, 3,4-dihydroxyphthalimide, displayed enhanced Gram-negative inhibition and useful pharmacokinetics in rat. An X-ray cocrystal structure of the lead compound covalently bound in Pae PBP1a revealed a dual function of the siderophore as both a recognition element for active transport into the Gram-negative cell and enhanced potency through a productive aromatic-stacking interaction with Tyr733. The binding modes of lactivicin analogs and BAL30072 in X-ray cocrystal structures were compared. Differences observed in the susceptibility to β-lactamases of BAL30072 compared to lactivicin analogs support the hypothesis that placement of the siderophore sidechain opposite to the aminothiazole sidechain confers broader resistance to β-lactamase hydrolysis than placement of the siderophore proximal to the aminothiazole.

MEDI 36

Discovery of cathepsin D-selective BACE1 inhibitors

***Kevin W. Hunt**[1], kevin.hunt@arraybiopharma.com, Guy Vigers[1], Darin Smith[1], Mary Geck-Do[1], Darrin Dutcher[1], Adam W Cook[1], Allen A. Thomas[1], Tony P Tang[1], Ryan J Watts[2], Christopher T Clark[1], Dolo Diaz[2], Andrew T Metcalf[1], Indrani W Gunawardana[1], Nicholas C Kallan[1], Robert K DeLisle[1], Hans Purkey[2], Michael Siu[2], Michael Burkard[1], Joseph P Lyssikatos[2], Groneberg Robert[1], Regal Kelly[1]. (1) Array BioPharma, Boulder,*

Colorado 80301, United States (2) Genentech, Inc., South San Francisco, California 94080, United States

The BACE1 enzyme is an aspartyl protease that initiates the production of the amyloid beta protein (Aß), a small peptide that is likely a primary driver of neurodegeneration. Inhibition of BACE1 *in vivo* effectively decreases central nervous system (CNS) Aß levels in multiple species, including human. While the *in vivo* data provide important proof of mechanism for BACE1 inhibition and Aß lowering, concern remains for the selectivity vs. related aspartyl proteases. Among these, Cathepsin D (CatD) is an essential lysosomal protease abundantly expressed in CNS neurons. Animals deficient in CatD develop intestinal necrosis, lymphopenia, retinal atrophy, and neuronal ceroid lipofuscinosis. Through the utilization of structure-based design and tradition SAR studies, we have optimized non-selective inhibtors to achieve >1000 fold selectivity for BACE1 vs. CatD. The key SAR studies will be presented as well as preclinical safety data that further validate the necessity for high BACE1 vs. CatD selectivity.

MEDI 37

Discovery and optimization of potent GPR40 full agonists containing tricyclic spirocycles

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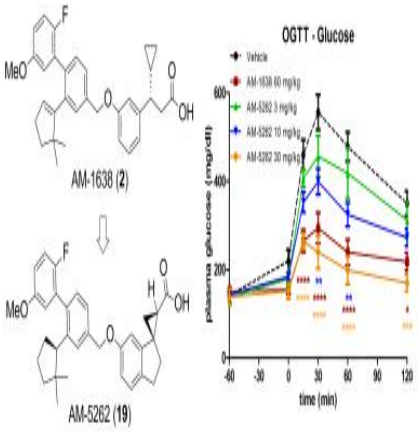
GPR40 (FFAR1 or FFA1) is a target of high interest being pursued to treat type II diabetes due to its unique mechanism pointing to little risk of hypoglycemia. We recently reported the discovery of AM-1638 (**2**), a potent full agonist of GPR40. Here in, we present the discovery of full agonists containing conformationally constrained tricyclic spirocycles and their structure–activity relationships leading to more potent GPR40 full agonists such as AM-5262 (**19**) with improved PK and selectivity profiles.

Our efforts defining conformational constraints started by constraining the flexible phenylpropanoic acid region with a 5-membered ring, followed by exploring different connections of a cyclopropane to the 5-membered ring. We then further looked at different ring sizes of the tricyclic spirocycles and many of these modifications resulted in potent GPR40 full agonists.

AM-5262 binds to the same ligand site on GPR40 as AM-1638, enhanced glucose stimulated insulin secretion (mouse and human islets), and improved glucose homeostasis *in vivo* (OGTT in HF/STZ mice) when compared to AM-1638.



MEDI 38

Design and synthesis of potent, selective, and orally bioavailable macrocyclic TF-FVIIa inhibitors

Xiaojun Zhang[1], *xiaojun.zhang@bms.com, Wen Jiang*[1], *Swanee Jacutin-Porte*[1], *Peter W Glunz*[1], *Vladimir Ladziata*[1], *Yan Zou*[1], *Xuhong Cheng*[1], *Alexandra H Nirschl*[1], *James A Johnson*[1], *Monique Philips*[1], *Nicholas R Wurtz*[1], *Brandon L Parkhurst*[1], *Indawati Delucca*[1], *Joseph M Luettgen*[2], *Robert Knabb*[3], *Alan R Rendina*[2], *Timothy M Harper*[4], *Anzhi Wei*[6], *Luciano Mueller*[5], *Daniel L Cheney*[7], *Dietmar Seiffert*[2], *Pancras C Wong*[2], *Ruth R Wexler*[1], *Scott Priestley*[1]. *(1) Department of Discovery Chemistry, Bristol-Myers Squibb Research, Pennington, New Jersey 08534, United States (2) Discovery Biology, Bristol-Myers Squibb Research, Pennington, New Jersey 08534, United States (3) Department of GCR Cardiovacsular, Bristol-Myers Squibb Research & Development, Princeton, New Jersey 08543, United States (4) Department of PCO, Bristol-Myers Squibb Research, Pennington, New Jersey 08534, United States (5) Department of Mechanistic Biology, Bristol-Myers Squibb Research, Princeton, New Jersey 08543, United States (6) Department of Protein Science & Structure, Bristol-Myers Squibb Research, Princeton, New Jersey 08543, United States (7) Department of CADD, Bristol-Myers Squibb Research, Pennington, New Jersey 08534, United States*

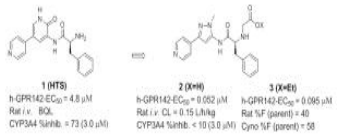
Inhibitors of the Tissue Factor/Factor VIIa (TF-FVIIa) complex are promising novel anticoagulants which show excellent efficacy and minimal bleeding in preclinical models. Based on the X-ray crystal structure of a phenylpyrrolidine phenylglycineamide lead bound in the active site of TF-FVIIa and molecular dynamics conformational calculations, a series of novel macrocyclic TF-FVIIa inhibitors was designed and synthesized. Optimization of the macrocycle linker, P', and P2 groups lead to potent and selective TF-FVIIa inhibitors. Fluorination of the P1 group reduced basicity and

significantly improved oral bioavailability. The resulting lead compound has good oral pharmacokinetics in dog and anti-thrombotic activity in a rabbit model of arterial thrombosis.

MEDI 39

Amino-pyrazole phenylalanine based GPR142 agonists for the treatment of type II diabetes

Ming Yu[1], *yum@amgen.com, Mike Lizarzaburu*[1], *Alykhan Motani*[1], *Zice Fu*[1], *Xiaohui Du*[1], *Leping Li*[1], *Jiwen (Jim) Liu*[1], *Xianyun Jiao*[1], *SuJen Lia*[1], *Peter Fan*[1], *Angela Fu*[1], *Qingxiang Liu*[1], *Michiko Murakoshi*[2], *Futoshi Nara*[2], *Kozo Oda*[2], *Jeff D. Reagan*[1], *Nobuaki Watanabe*[2], *Yumei Xiong*[1], *Mami Yamazaki*[2], *Ying Zhang*[1], *Run Zhuang*[1], *Daniel C.-H. Lin*[1], *Jonathan B. Houze*[1], *Julio C. Medina*[1]. *(1) Department of (1)Medicinal Chemistry; (2)Metabolic Disorders; and (3)Pharmacokinetics and Drug Metabolism, Amgen, Inc., South San Francisco, CA 94080, United States (2) Department of (1)Cardiovascular-Metabolics Research Laboratories; (2)Biological Research; (3)Drug Metabolism & Pharmacokinetics Research Laboratories; and (4)R&D Administration & Support, Daiichi-Sankyo Co., LTD., Shinagawa-Ku; Edogawa-Ku, Tokyo 140-8710; 134-8630, Japan*



GPR142 is expressed predominantly in islet beta-cells and plays an important role in regulating insulin secretion and glucose homeostasis. Studies in rodents suggested that a suitable small molecule GPR142 agonist could be of benefit in the treatment of type II diabetes. This presentation highlights the optimization of the amrinone-phenylalanine lead from HTS hit **1** (EC_{50}=4.8 μM on an IP assay using h-GPR142 transfected CHO-cells). The first lead optimization milestone was the discovery of an *N*-thiazol-5-yl-methyl substitution on the phenylalanine nitrogen which offered 50-fold improvement of potency. Replacement of the pyridone B ring with a 1-methyl-pyrazole further improved potency and lowered serumEC_{50} shift. An acetic acid appendage on the phenylalanine nitrogen completed the SAR campaign with the identification of tool compound **2** , which featured good potency (0.052 μM) and low *in vivo* clearance (rat CL=0.15 L/h/kg).

Compound **2** stimulated insulin secretion from islets isolated from wild type mice but not the GPR142 deficient ones. Compound **2** (dosed s.c.) and its orally bioavailable prodrug **3** demonstrated statistically significant, dose-dependent glucose lowering effects in oral glucose tolerance tests conducted in regular mice as well as in a mouse model bearing transplanted human islets (KcHIT mice).

MEDI 40

Thermodynamic signature of various lead series for hematopoietic prostaglandin D synthase

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Hematopoietic prostaglandin D synthase (HPGDS) is primarily expressed in mast cells, antigen-presenting cells, and Th-2 cells. HPGDS converts prostaglandin D2 (PGD2) from prostaglandin H2, the common substrate of numerous prostanoid enzymes. PGD2 is a mediator thought to play a pivotal role in airway allergy and inflammatory processes. The lead generation phase of this program identified several lead series that inhibited H-PGDS activity. These lead series had very broad structural diversity. In this talk we will describe the biophysical characterization utilizing ITC, SAR and cocrystal structures that allowed identification of critical interaction to a conserved water molecule. This water mediated hydrogen bond changed the thermodynamic signature of a lead series from being entropic to enthalpic. The thermodynamic signature of an enthalpic lead series translated into series that illustrated specific SAR in our enzyme functional assay. This critical understanding of binding requirement allowed the optimization of a pyridine lead series resulting in an orally potent and selective inhibitor of HPGDS that reduces the antigen-induced response in allergic sheep.

MEDI 41

Aromatic amines as potent inhibitors selective for estrogen receptor α over β

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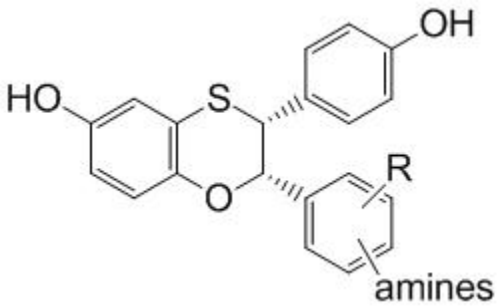
Dihydrobenzoxathiin-derived compounds with variable amino side chains were prepared and evaluated for anti-estrogen activity. Structure-activity relationship with regard to substitutions and amino moieties will be discussed. Compounds displayed good selectivity for affinity of ERα over ERβ, and were highly potent in the inhibition of human carcinoma MCF-7 cell growth.



MEDI 42

Rationalizing non-standard interactions in ligand design: The duality of halogens

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Non-standard intermolecular interactions such as CH donors, halogen bonds, close sulfur contacts and cation-π interactions have recently been recognized as significant factors in protein-ligand binding. However, exploiting these interactions in structure-based drug design projects (SBDD) has been difficult, because they are inadequately modeled using MM force-field based methods. Atom-centered charges typically used in force-fields cannot capture the anisotropic charge distributions responsible for some non-standard interactions. To address these challenges, a model of intermolecular interactions based on Extended Hückel Theory (EHT) is proposed, which accounts for the effect of electron delocalization and geometry on interaction strength. The qualitative and semi-quantitative accuracy of the model is demonstrated using case studies that highlight the importance of non-standard interactions in a number of systems, including native ligands of the thyroid hormone receptor.

MEDI 43

Structure guided optimization of novel, selective, and orally bioavailable inhibitors of Pim kinases

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Proviral Insertion of Moloney virus (PIM) 1, 2 and 3 kinases are serine/threonine kinases that normally function in survival and proliferation of hematopoietic cells. Over expression of PIM1, 2 and 3 is frequently observed in many human malignancies, including multiple myeloma, non-Hodgkins lymphoma, and myeloid leukemias. PIM1 was discovered as an oncogene in mice, where PIM1 over expression driven by proximal insertion of the Moloney provirus results in lymphoma. As such, there is interest in determining whether selective Pim inhibition can improve outcomes of human cancers with over expressed PIMs. Herein, we describe our initial efforts towards this goal. The structure guided optimization of a singleton HTS hit in which the potency against all three Pim isoforms was increased >10,000 fold to yield compounds with pan Pim Ki's <10 picoM is described. Within this series a compound was identified with suitable PK properties and kinase selectivity to establish a PK/PD-efficacy relationship in both acute myeloid leukemia (KG-1 cell line, Pim1 over expression) and multiple myeloma (KMS11-luc cell line, Pim2 over expression) as determined by *in vivo* inhibition of pS6RP phosphorylation and tumor growth inhibition in mouse xenograft models.

MEDI 44

Highly potent anti-angiogenic and vascular disrupting agents with an isoquinoline scaffold as potential novel payloads for antibody-drug conjugates in cancer

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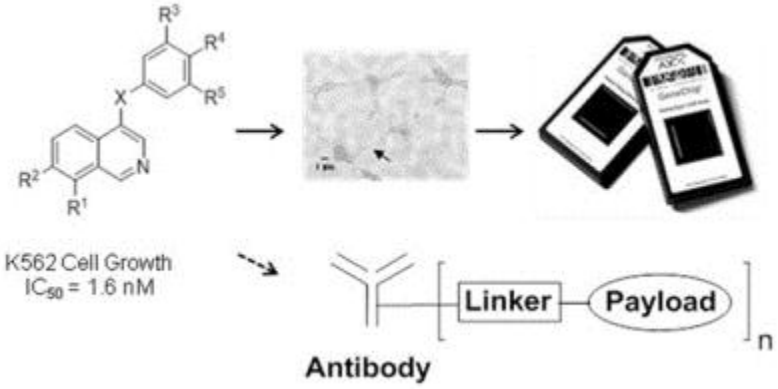
A recent search in the Integrity^{sm} database highlights that all of the 18 tubulin targeting antibody-drug conjugates (ADC) in clinic trials use analogues of maytansin or auristatin as their toxin payload. Alternatively, the use of novel tubulin-binders that exhibit anti-proliferative, anti-angiogenic and vascular disrupting activity is an intense area of research. Compounds that are under development include CA4P, ASA404, ZD6126, ABT-751, AVE8062A, OXi4503 and BNC105P[1]. However, the efficacy of tubulin binding agents is often limited by the development of multidrug resistance. Therefore, there is an interest to identify chemotypes as payloads that can escape resistance mechanism, provide broader clinical benefits and offer an alternative to natural cytotoxins that are challenging and expensive to scale up. An internal screening effort led to the identification of 4-benzyl-7,8-substituted isoquinolines that act as tubulin polymerization inhibitors. Subsequent lead optimization led to the synthesis of compounds with anti-proliferative activity in the single digit nM range after 72h in K562 cells[2]. This activity was also maintained in drug-resistant human cancer line HCT15, UO-31, NCI-H69/Lx4, NCI-H69/AR and HL60-MX2. The synthesis and SAR of this chemical series suitable for ADC generation will be presented together with a genome wide transcriptional analysis on endothelial cells that provides attractive entry points for the development of biomarkers in a clinical setting.



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2-Belzacq-Casagrande A.S *et al. Invest. New Drugs*, **2012** , Aug 10

MEDI 45

Imidazopyridine compounds as selective inhibitors of Fibroblast Growth Factor Receptors (FGFR)

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Recent data in a number of tumor types have identified Fibroblast Growth Factors (FGF) and Fibroblast Growth Factor Receptors (FGFR) signaling as being key to the molecular pathology of cancer[1]. A fragment screening approach against FGFR1 was conducted at Astex Pharmaceuticals to detect low molecular weight compounds that bind to the hinge region of the kinase. The screen produced several fragment molecules

and Astex identified an imidazopyridine hit as an interesting starting point due to its encouraging ligand efficiency value. This compound was further modified in order to provide potent *in vitro* and *in vivo* FGFR inhibitors displaying selectivity towards VEGFR2[2, 3] but also, towards Flt3[4].

The design and the chemical access of the compounds as well as the influence of the different modifications on the kinase selectivity, the biological activities and the physicochemical properties will be presented and discussed.

[1] Beenken, A and Mohammadi, M. *Nature Reviews-Drug discovery* **2009** , *8*, 235-253

[2] Squires, M. et al. *Mol. Cancer Ther.*, **2011** , *10 (9)*, 1542-1552

[3] Berdini, V. et al. WO2009/150240 A1

[4] Saxty, G. et al. WO2010119285 A1

MEDI 46

Discovery of a highly potent and in vivo efficacious Bcl-x_L selective inhibitor

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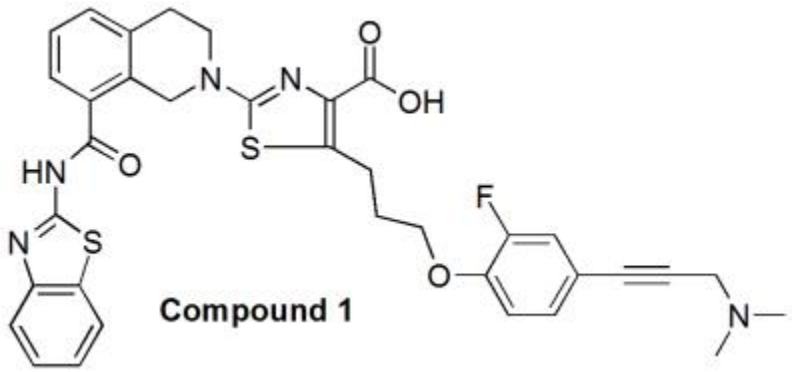
Bcl-2 family proteins are key regulators of apoptosis and thus attractive targets for cancer therapy. The overexpression of Bcl-x_L is well correlated with drug resistance and disease progression of multiple solid tumors and hematologic malignancies. The dual Bcl-x_L/Bcl-2 inhibitor navitoclax is currently in clinical development; however a small molecule that is potent against and selective for Bcl-x_L has not yet been reported. In order to explore the effects of selective Bcl-x_L inhibition, based on a HTS hit, we used structure-based-design and NMR-based fragment screening to generate small molecule **1** . This compound binds to Bcl-x_L with low picomolar affinity and shows vast selectivity over related Bcl-2 protein family members. Compound **1** causes mechanism dependent apoptosis in tumor cell lines that depend upon Bcl-x_L for survival, as well as strong synergy with chemotherapies *in vitro*. Additionally, dosing in immunocompromised mice

xenografted with cells derived from a small cell lung cancer line afforded tumor growth inhibition as a single agent. A rapid decrease in platelets driven by Bcl-x_L inhibition was observed, with recovery at 72 hours as consistent with the platelet recovery kinetics of navitoclax. This is the first *in vivo* characterization of a truly selective Bcl-x_L inhibitor. Compound **1** thus represents an excellent tool for studying Bcl-2 family biology as well as basis for further development of Bcl-x_L selective inhibitors for the treatment of cancer.



Compound 1

MEDI 47

Discovery of AS2521780, a novel, potent, selective PKCθ inhibitor as an immunosuppressive agent

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Protein kinase C theta (PKCθ) is a serine/threonine kinase predominantly expressed on T lymphocytes and the skeletal muscle. Pharmacological studies revealed that PKCθ plays an important role in T cell signaling leading to the production of IL-2 and T cell activation, and it is also well validated by the extensive studies with knockout mice. Therefore, PKCθ inhibitors offer significant potential as new treatments for transplant rejection and autoimmune diseases.

As part of our research program directed at the development of new PKCθ inhibitors, we have investigated a novel series of 2,4-diaminopyrimidine derivatives bearing a cross-linked cyclic moiety in the side chain. From this series, AS2521780 was identified as a potent and selective PKCθ inhibitor which was efficacious both in rat heterotopic cardiac transplant and monkey renal transplant models. The synthesis and SAR of this novel series of PKCθ inhibitors will be discussed. In addition, pharmacological profile of AS2521780 will be presented.

MEDI 48

Chemical modifications of asiaticoside for structure-activity relationship studies and synthesis of asiaticoside biologically active probe for cellular mechanistic investigation toward human periodontal ligament regeneration

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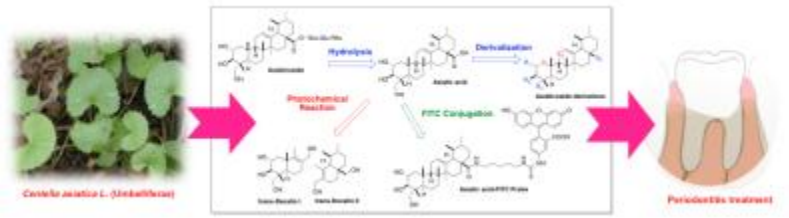
Asiaticoside is a triterpenoid saponin isolated from *Centella asiatica L.* which known as Bua Bok in Thailand. The extract of *C. asiatica* has been used for diverse cosmetic and medical purposes, especially wound healing and scar reduction treatment since the ancient period. Recently, Pavasant and co-workers reported the effect of asiaticoside toward human periodontal ligament cells (HPDLs) that it had no cytotoxicity toward HPDLs and promoted type I collagen synthesis and osteogenic differentiation (Nowwarote et al., *Phytother. Res.* 2012). These results suggested that asiaticoside has potential as an alternative periodontal tissue healing therapeutic agent by stimulating both soft and hard tissue formation. However, high concentration of asiaticoside up to 100 µg/mL was needed for significant tissue regeneration. Moreover, mode of action of asiaticoside toward periodontal tissue regeneration was remained unexplained.

To examine an essential pharmacophore, develop new therapeutic agents that possess high potency and understand an intracellular mechanism of asiaticoside toward HPDLs, the first study on photochemical degradation of pentacyclic moiety of asiaticoside is performed. Importantly, the novel asiaticoside-fluorescent biologically active probe is prepared for initial molecular mechanistic study toward pro-healing effect on HPDLs. The activities on proliferation, protein synthesis and osteogenic differentiation in HPDLs of newly synthesized asiaticoside analogs and asiaticoside-fluorescent probe will be discussed and compared with asiaticoside.



MEDI 49

CoMSIA studies on a novel series having tartarate diamides as TACE inhibitors

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A dataset of 78 compounds containing pyrolidine based tartrate diamide having selective tumor necrosis factor-α converting enzyme (TACE) inhibitory activity were selected for comparative molecular similarity indices (CoMSIA). CoMFA model was obtained with acceptable statastical values by using database alignment. Same alignment rule was utilized to develop CoMSIA models. Various model were developed by using combination of different parameters as steric, electrostatic, hydrophobic, H-bond acceptor, H-bond donor. In this presentation the best output of the CoMSIA model would be discussed along with the contour maps. The optimal CoMSIA model (HAD) was obtained with cross-validated r^2=0.531 with 5 components, non-cross-validated r^2=0.930, standard error of estimates=0.235 and F-value=138.826 with predictive r^2 =0.619. The statistical parameters from this model indicate that the data is being well fitted and also have high predictive ability. Moreover, the resulting 3D-CoMSIA contour maps provide useful guidance for designing of highly active TACE inhibitors.

MEDI 50

New cathepsin B and K inhibitors utilizing thiosemicarbazones

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The design and synthesis of 20 thiosemicarbazones containing P_1 arginine, lysine, ornithine, citrullene, and leucine sidechains as inhibitors as cathepsin B and cathepsin K based on SAR data has been accomplished. A library of 20 of these C-terminal aldehyde thiosemicarbazones with variations in the P_2 and P_3 positions are described. Several of these compounds have proven to be very potent inhibitors of human cathepsin B and K activity as measured using either spectrophotometric (BANA) or fluorometric assay (Cbz-Phe-Arg-AMC) techniques. The thiosemicarbazones showed mixed and non-competitive inhibition. Compounds showing the weakest inhibition of cathepsin B activity and the strongest inhibition of cathepsin K activity (IC_{50} values range from 1.2 to 2.4 nM) were those that contain a C-terminal leucine aldehyde or thiosemicarbazone with either a citrullene or glutamine in the P_3 position.

MEDI 51

Discovery of ASP9133, a novel muscarinic receptor antagonist with selective inhibition of bronchoconstriction against salivation

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Chronic obstructive pulmonary disease (COPD) is characterized by progressive airflow obstruction that is only partly reversible and inflammation in the airways. The major reversible component of the airflow obstruction is believed to be cholinergic. Currently, two inhaled muscarinic antagonists are used for management of COPD. Ipratropium is a short-acting agent for requiring up to four doses per day. Tiotropium is an once-daily agent and first-line drug. However, there are some evidences that the bronchodilatory effect of tiotropium at its clinical dose is not likely to be maximum, based on dose-limitation by an adverse effect (dry mouth), implying that there is still some room for improvement of efficacy of this type of drug. Therefore, we hypothesized that a novel muscarinic antagonist, which shows potent and more selective inhibition of bronchoconstriction against salivation compared to tiotropium, could give more improvement of lung function without any significant increase of incidence of dry mouth.

Through our muscarinc receptor binding assay and *in vivo* screening implemented to achieve this goal, we identified ASP9133 as a clinical candidate. ASP9133 shows more selective inhibition of bronchoconstriction against salivation than either tiotropium or other clinically developing muscarinic antagonists (i.e., aclidinium and glycopyrronium). In this presentation, we will show the synthesis, a docking study and pharmacological profiles of ASP9133.

MEDI 52

Isoquinoline derivatives as potent CRTH2 receptor antagonists: Lead generation, optimization, and pharmacological effects of the potent CRTH2 receptor antagonists

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Chemoattractant receptor–homologous molecule expressed on Th2 lymphocytes (CRTH2), which was identified as a G protein-coupled receptor, is expressed predominantly on Th2 cells, and plays a key role in allergic diseases, driving the IgE response, eosinophilia, and release of proinflammatory cytokines.CRTH2 is involved in complex inflammatory processes, and a CRTH2 antagonist might have beneficial effects in a variety of inflammatory diseases since activation of CRTH2 receptor

promotes the release of histamine from basophils and degranulation of eosinophiles. We designed a novel 1,4-disubstituted Isoquinoline scaffold and performed its optimization to identify compounds showing excellent antagonistic activity against the CRTH2 receptor. We will present the synthesis and SAR study of 1,4-disubstituted Isoquinoline derivatives, and in addition, the in vivo effects of the representative compound.

MEDI 53

SAR and rational design of novel, selective PI3Kδ inhibitors

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Phosphoinositide 3-kinases (PI3Ks) are lipid kinases that play a key role in the control of a wide number of cellular functions including metabolism, cell growth and motility. In terms of tissue distribution, PI3Kα and β are ubiquitously expressed whereas PI3Kδ and γ are mainly expressed in leukocytes. In conjunction with mouse genetic studies, these enzymes are viewed as promising targets for the treatment of a number of inflammatory and oncologic diseases. Due to the high levels of expression of PI3Kα and β in various tissues along with a different signaling route for PI3Kγ through GPCRs, a highly selective PI3Kδ compound was desired. Through SAR and Structure-based design, analog **20** was identified to increase biochemical selectivity, potency and solubility of this series that resulted in superior cellular selectivity with acceptable *in vivo* PK properties. Compound **20** was also found to be efficacious *in vivo*, which included evaluation in a keyhole limpet hemocyanin (KLH) study and a pAKT inflammation study. Therefore, this class of compounds should show great promise as a therapeutic for numerous inflammation disease states.

MEDI 54

Role for hydration in rationalizing the potency and selectivity of novel Itk inhibitors

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Interleukin-2 inducible T-cell kinase (Itk) is an important member of the Tec family of non-receptor tyrosine kinase that plays a central role T-cell receptor (TCR) induced T-cell proliferation and secretion of the critical pro-inflamatory cytokines. Its inhibition is seen as an attractive target for the treatment of autoimmune and allergic diseases.

This poster will describe the design of novel, potent and selective inhibitors of Itk, starting from a fragment generated *de novo*, the 3-aminopyrid-2-one motif.

Structural information was used to build in potency and to rationalize the subtleties of the Itk SAR: functionalisation of the 3-amino group enabled rapid enhancement of the inhibitory activity against Itk, while introduction of a substituted heteroaromatic ring in position 5 of the pyridone fragment was key to achieving optimal selectivity over related kinases. Careful analysis of the hydration patterns of the Itk active site was required in order to understand the observed selectivity which could be rationalized by consideration of the replacement of a thermodynamically unfavorable water molecule by the inhibitor and the improved hydration of the bound ligand.

MEDI 55

WITHDRAWN

MEDI 56

Discovery and SAR of a novel series of ethanolamine-based direct-acting agonists of sphingosine-1-phosphate 1 (S1P1)

***John L Gilmore**, john.gilmore@bms.com, James Sheppeck, Ding Ren Shen, Melissa Yarde, Mary Ellen Cvijic, Virna Borowski, Kathleen Gillooly, Tracy Taylor, Kim W McIntyre, Paul Levesque, Georgia Cornelius, Celia Darienzo, Anthony Marino, Praveen Balimane, Luisa Salter-Cid, Joel C Barrish, Percy H Carter, Jenny Xie, Alaric J Dyckman. Department of Research and Development, Bristol Myers Squibb, Princeton, New Jersey 08543, United States*

Sphingosine-1-phosphate (S1P) is the endogenous ligand for the sphingosine-1-phosphate G-protein coupled receptors (S1P1-5). The interaction of S1P with the S1P receptors plays a fundamental physiological role in many processes including vascular stabilization, heart development, lymphocyte homing, and cancer angiogenesis. Agonism of S1P1, in particular, has been shown to block lymphocyte trafficking from the thymus and secondary lymph nodes resulting in immunosuppression. As a result,

agonists of this type hold promise as therapeutics for autoimmune disorders. This presentation will outline the identification and synthesis of a potent and selective series of direct-acting agonists of S1P1 based on an ethanolamine template. Compounds in this series demonstrated efficacy when administered orally in a rat model of arthritis as well as in the mouse experimental autoimmune encephalomyelitis (EAE) model of multiple sclerosis.

MEDI 57

Design and synthesis of carbazole carboxamides as novel inhibitors of Bruton's tyrosine kinase (BTK)

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Di-substituted carbazole-1-carboxamides were designed and synthesized as novel, orally bioavailable inhibitors of Bruton's tyrosine kinase. Preliminary SAR will be discussed, with the goal of improving BTK potency and kinase selectivity.

MEDI 58

Assay for p38α recruitment site binders: Identification of rooperol as a novel p38α kinase inhibitor

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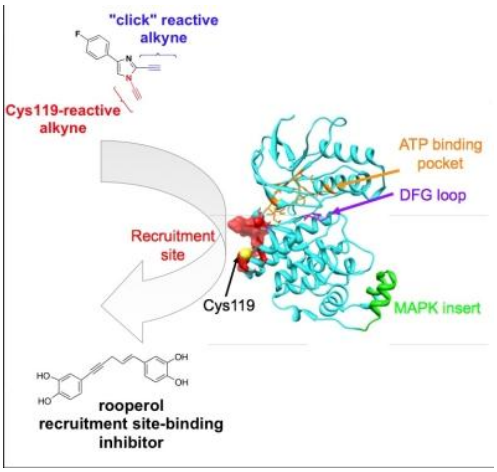
The mitogen-activated protein kinases (MAPK) p38α is a serine/theronine kinase that serves an important role in the production of inflammatory cytokines including necrosis factor alpha (THFα) and interleukin-1 beta (1L-1β). MAPK-substrate specificity has been shown to be mediated through docking interactions involving substrate docking motifs that interact with kinase recruitment domains. Blocking docking interactions between kinase network partners is a promising alternative approach to targeting the ATP-binding site for selectively inhibiting kinase signaling. Here we report the identification of a small molecule, cell permeable covalent p38α recruitment site (DRS) probe. Using “click” chemistry, this probe can be used to fluorescently to label p38α. An assay employing this probe was used to identify the natural product rooperol as a p38α DRS inhibitor (IC_{50}= 18.6 μM).



MEDI 59

Cox-1 and Cox-2 pro-drugs for dermatological vesicant suppression

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Both nitrogen and sulfur mustards induce painful inflammation and vesication of human skin. Hairless mice are well established as surrogate model to screen potential therapeutics and prophylactics targeting such dermatological toxicants. We have found that a pro-drug class in which either a COX-1 or COX-2 inhibitor is linked to an inhibitor of acetylcholinesterase (AChEI) by a hydrolysable or metabolizable bond provides protection against mustard-induced injury and/or an accelerated wound healing. The general platform is (COX inhibitor) – (labile bond) – (AChEI). Successful COX inhibitors of these pro-drugs include non-steroidal anti-inflammatories (NSAIDs) such as Lumiracoxib, Celecoxib, Diclofenac, Indomethacin, and Naproxen. Successful AChEIs include Galantamine and pharmacophore cores of Pyridostigmine, Neostigmine, and acetyl choline. Labile bonds included ester, carbonate, and carbamate. Release times for the pro-drug constituents using mouse skin homogenate and relative inflammation suppressions will be presented along with an SAR correlation.

MEDI 60

WITHDRAWN

MEDI 61

Design, synthesis, and biological evaluation of bi-dentate c-Jun N-terminal kinase inhibitors

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It is reported that up-regulation of JNK activity is associated with a number of disease states such as type- 2 diabetes, obesity, cancer, inflammation, and stroke. Therefore, JNK inhibitors are expected to be effective therapeutic agents against a variety of diseases. In this paper, we describe the synthesis and SAR of a novel series for bi-dentate JNK inhibitors. Compounds are synthesized using a weak ATP mimetic coupled with a variety of JIP1 peptides. Compounds are very potent, selective sub nanomolar JNK inhibitors. These bi-dentate JNK inhibitors also showed *in vivo* activities in diabetes mice model.

MEDI 62

CYP17 lyase inhibitors as therapeutic agents for the treatment of prostate cancer

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Prostate cancer is one of the leading causes of death in men in the U. S. and Europe. Current treatments involving the use of androgen ablation therapy via orchidectomy or chemical castration have had limited success due to their focus only on inhibiting androgens produced by the testes, which comprises 90% of circulating androgens. Low levels of androgens produced by the adrenals are sufficient to fuel prostate cancer growth, ultimately leading to castration-resistant prostate cancer. Our approach to addressing this unmet medical need has been to identify and develop a reversible inhibitor of CYP17 lyase, a dual function P450 enzyme expressed in the testes and adrenals, for complete suppression of androgen biosynthesis and with an additional focus on minimal glucocorticoid and mineralcorticoid perturbation. Herein, we describe the identification of a small molecule inhibitor of CYP17 lyase with specificity over hydroxylase and selectivity against CYP11B1 and CYP21.

MEDI 63

Design, synthesis, biophysical and structure-activity properties of a novel dual MDM2 and MDMX targeting stapled □elical peptide, ATSP-7041, that exhibits potent in vitro and in vivo efficacy in xenograft models of human cancer

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We describe the stapled á-helical peptide ATSP-7041, a novel dual inhibitor of MDM2 and MDMX that reactivates p53-dependent pathway in multiple cancer cell lines *in vitro* and *in vivo*. ATSP-7041 binds both MDM2 and MDMX with nanomolar affinities, exhibits sub-micromolar cellular activity in cancer cell lines in the presence of serum, and demonstrates evidence of specific on-target mechanism *in vitro* by gene expression profiling. A high resolution X-ray crystal structure of ATSP-7041 bound to MDMX revealed its molecular interactions to the target protein, including multiple contacts between both key pharmacophoric amino acid side chains and the hydrocarbon staple moiety. ATSP-7041 is the first example of a negatively charged, amphipathic stapled á-helical peptide having potent efficacy *in vitro*. A series of ATSP-7041 analogs provide insight to the biophysical properties and structure-activity relationships that underscore its lead optimization.

MEDI 64

Synthesis and biological evaluation of 5, 5' substituted apogossypol and apogossypolone derivatives as anticancer agents

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Apogossypol (ApoG) and Apogossypolone (ApoG2) have been identified as important apoptosis-based anti-cancer drug candidates. However, Structure-activity relationships (SAR) of ApoG and ApoG2 had never been explored. We have developed novel synthetic schemes and synthesized 5, 5' substituted ApoG and ApoG2 derivs. We found that installation of suitable amide, ketone or alkyl groups at 5, 5' position of ApoG and ApoG2 significantly improve their in intro and in vivo anti-cancer activities. BI97C1, an apogossypol derivative, displays in vivo efficacy in transgenic mice models and also demonstrated superior single agent antitumor efficacy in a prostate cancermouse xenograft model. Further, BI97C1 synergistically sensitized PC-3 cells to the cytotoxic effects of docetaxel. Therefore, BI97C1 represents a potential drug lead for the development of novel apoptosis-based therapies against cancer.

MEDI 65

Design, synthesis, biological evaluation, and co-crystal study of novel small molecule inhibitors of protein kinase CK2, 2-benzylidene-4H-benzo[1,4]thiazin-3-one compounds

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Casein Kinase 2 (CK2) is a highly conserved and ubiquitously expressed serine/threonine kinase, which exists as a tetrameric complex containing two catalytic (α or α′) and two regulatory (β) subunits. CK2 is constitutively active in many cancers and has been implicated in tumorigenesis and cellular transformation. Elevated level of CK2 activity has been associated with the malignant transformation of several tissues and is associated with aggressive tumor growth. CK2 regulates several key oncogenic signaling pathways, including PI3K, AKT, NFκB, and Wnt signaling pathway. A few ATP competitive small molecule kinase inhibitors of CK2 have been identified by different investigators, which show moderate in vitro kinase inhibitory activity. Recently, Cylene has disclosed CX-4945, a selective, orally available small molecule inhibitor, which is in phase 1 clinical trial shows high in vitro kinase inhibition of CK2 but has very poor cytotoxicity on the cancer cells.

There remains a need for additional novel agents targeting CK2 with the necessary balance of kinase inhibition and cytotoxicity on cancer cells and which can interfere with the critical function of CK2 in cancer-linked pathways. Herein we disclose the discovery and biological activity of a series of potent and selective inhibitors of CK2 derived from the 2-benzylidene-4*H*-benzo[1,4]thiazin-3-one scaffold. Co-crystallographic studies with one of the active molecules of this series, ON 108600 bound to CK2 kinase domain shows that this molecule prevents both ATP and GTP interaction with the catalytic domain.

MEDI 66

ON 108110, a novel kinase inhibitor: Description of the synthesis, kinase profiling, and co-crystal structure

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While screening a library of compounds synthesized in our laboratory against a panel of tumor cell lines, we came across a series of 2-benzylidene-4*H*-benzo[b][1,4]thiazin-3-one compounds that preferentially kill the cancer cells and spare the normal cells in cytotoxicity assay. To understand the mechanism of cytotoxicity of these compounds, we selected one of the active molecules 108110 from this library and screened against a panel of 355 functional recombinant kinases in *in vitro* and it found to be a very potent inhibitor of CK2 and PIM3 kinases. Casein kinase 2 (CK2) and Pim kinases (Pim-1, 2 and 3) are a class of serine/threonine kinases that are highly homologous in their kinase domains and have been implicated in several normal biological process including cell survival, proliferation, differentiation and apoptosis. It is well known that constitutive activation or over expression of these kinases also results in cellular transformation and tumorigenesis. Consequently, 108110 as an inhibitor of these kinases may be a promising candidate for drug development against the cancers where these kinases are involved. Here in we describe the synthesis, characterization, structure activity relationship (SAR), cytotoxicity, kinase profile and CK2 protein bound crystal structure of ON 108110.

MEDI 67

Design, synthesis, and biological evaluation of a novel anticancer agent ON 015640 with tubulin depolymerizing activity

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Microtubules are cytoskeletal structures that are formed by self-assembly of α and β tubulin heterodimers and are involved in many cellular functions. Their most important role is in the formation of the mitotic spindle, and they are essential to the mitotic division of cells. Tubulin is an α,β- heterodimeric protein that is the main constituent of microtubules. Tubulin is the target of numerous small molecule anti-proliferative ligands that act by interfering with microtubule polymerization/depolymerization dynamics. Many tubulin binding compounds, such as paclitaxel and vinblastine, are in clinical use for various types of cancers, they suffer from undesired side effects. More recently, alternative components of the mitotic machinery have been targeted in an attempt to develop novel anti-cancer agents.

Despite the unprecedented success of microtubule disrupting agents in cancer chemotherapy, multidrug resistance (MDR) is a major limitation of cancer

chemotherapy, and MDR tumors are usually resistant to tubulin-binding drugs. It is therefore desirable to discover novel anti-tubulin agents with fewer side effects, improved pharmacokinetic properties and better efficacy against MDR cancer cells.

Here, we describe a new class of styryl benzyl sulfone, a small molecule anti-tubulin agent, which appear to satisfy many of the criteria for successful development of new anti-cancer agents. Preliminary drug development studies led to the identification of **ON 015640** , which exhibit potent cytotoxicity against wide spectrum of cancer cell lines and could readily inhibit the polymerization of tubulins. The stereo-specific synthesis, structure-activity relationship and biological activity of this compound will be discussed.

MEDI 68

Synthesis of 2,6-difluoro-*N*-(3-[^{11}C]methoxy-1*H*-pyrazolo[3,4-*b*]pyridine-5-yl)-3-(propylsulfonamidio)benzamide as a new potential PET agent for imaging of B-Raf^{V600E} in cancers

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The Raf family consists of serine/threonine kinases A-Raf, B-Raf and C-Raf (Raf-1). The V600E mutation of B-Raf kinase results in constitutive activation of the Ras/Raf/MEK/ERK (MARK) signaling pathway and is present in approximately 7% of all cancers. B-Raf^{V600E} has become an attractive target for cancer therapy, and a novel series of pyrazolopyridine inhibitors of B-Raf^{V600E} has been recently developed by Wenglowsky et al. B-Raf^{V600E} is an attractive target for molecular imaging of cancer as well. Here we report the first design and synthesis of 2,6-difluoro-*N*-(3-[^{11}C]methoxy-1*H*-pyrazolo[3,4-*b*]pyridine-5-yl)-3-(propylsulfonamidio)benzamide as a new potential imaging agent for biomedical imaging technique positron emission tomography (PET) to image B-Raf^{V600E} in cancers. The authentic standard 2,6-difluoro-*N*-(3-methoxy-1*H*-pyrazolo[3,4-*b*]pyridine-5-yl)-3-(propylsulfonamidio)benzamide (IC_{50} 4.8 nM for B-Raf^{V600E}) was synthesized from 2,6-difluorobenzoic acid and 3-amino-5-hydroxypyrazole by the published procedures in 9 steps with 1% overall chemical yield. Direct desmethylation of the reference standard with chlorotrimethylsilane (TMSCl)/NaI gave the precursor 2,6-difluoro-*N*-(3-hydroxy-1*H*-pyrazolo[3,4-*b*]pyridine-5-yl)-3-(propylsulfonamidio)benzamide for radiolabeling in 70% yield. The target tracer was prepared from the precursor with [^{11}C]CH_3OTf through *O*-[^{11}C]methylation and isolated by HPLC in 40-50% decay corrected radiochemical yields from [^{11}C]CO_2 at EOB with 370-740 GBq/μmol specific activity at EOB.

MEDI 69

Synthesis of radiolabeled protein disulfide isomerase (PDI) inhibitors as new potential PET agents for imaging of the enzyme PDI in neurological disorders and cancer

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Protein disulfide isomerase (PDI) is an enzyme primarily involved in protein folding diseases including neurological disorders and cancers. PDI is considered a potential drug target, and recently a novel series of small-molecule PDI inhibitors, substituted β-tetrahydrocarbolines, has been developed. PDI has become an attractive target for biomarkers for diagnostic *in vivo* imaging agents. Here we report the first design and synthesis of radiolabeled PDI inhibitors as new potential imaging agents for biomedical imaging technique positron emission tomography (PET) to image PDI. Unlabeled substituted β-tetrahydrocarboline precursors and reference standards were synthesized from tryptamine and α-ketoester in 2 steps with moderate to excellent yields. Carbon-11-labeled substituted β-tetrahydrocarbolines were prepared from their corresponding phenolic hydroxyl precursors with $[^{11}C]CH_3OTf$ through *O*-$[^{11}C]$methylation and isolated by simplified SPE in 50-60% decay corrected radiochemical yields from $[^{11}C]CO_2$ at EOB with 185-370 GBq/μmol specific activity at EOS. A fluorine-18-labeled substituted β-tetrahydrocarboline was prepared from its corresponding halo-precursors (X = Cl, Br, I) by the nucleophilic substitution with K$[^{18}F]$F/Kryptofix 2.2.2 and isolated by HPLC combined with SPE purification in 25-40% decay corrected radiochemical yield from $[^{18}F]$fluoride with 37-222 GBq/μmol specific activity at EOB.

MEDI 70

Structure-base targeting of SMYD3: An histone methyltransferase involved in colorectal tumorigenesis

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Protein lysine methyltransferases (PKMT) came to light the as new important targets for cancer therapy. In colorectal cancer (CRC) three components of the PKMT family have been found to be upregulated in cells and tissues: SMYD3, EZH2 and SUV39H1. Their upregulation correlates with changes in the methylation pattern of lysine residues on target histones. In cellular models of normal and cancerous colonocytes, SMYD3 is highly modulated in response to deregulated CRC pathways and this fact prompted us to search for novel small-molecule inhibitors.

Here we present a structure-based drug design (SBDD) approach aimed to identify new ligands with drug/lead-like properties as new inhibitors of SMYD3. We provide *in vitro* evidence that two compounds are able to inhibit the catalytic activity of SMYD3 pointing out their role as potential valuable scaffolds for novel anticancer therapies.

MEDI 71

NH- and N-Methyl-diarylidenylpiperidones: Synthesis and cytotoxicity against the growth of murine cancer cells in culture

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Curcumin is a naturally occurring and biologically active compound isolated from the root of turmeric. It has a wide range of biological activity and its biological mechanism is complex. Curcumin also effectively inhibits tumor cell proliferation, induces apoptosis, as well as migration and invasion through interference with the STAT3 signaling pathway. Despite its significant biological properties, curcumin's clinical effectiveness is limited by low bioavailability due to glucuronidation and sulfation of the hydroxyl groups. Hence there is an effort underway to design curcuminoids that have improved bioavailability. In this study twenty diarylidenylpiperidones analogs of curcumin, and related to an anticancer STAT3 inhibitor 2,6-bis-(4,4'-difluorobenzylidene)-4-piperidone were synthesized and tested for cytotoxicity against B16 (murine melanoma) and L1210 (murine lymphoma) in culture. Two dimethoxy analogs (2,5- and 3,5-) investigated in this study were found to be even more potent that the previously reported 2,6-bis-(4,4'-difluorobenzylidene)-4-piperidone and other halogen-containing analogs.

MEDI 72

Identification of small molecule substrate-competitive kinase inhibitors

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The dysregulation of protein tyrosine kinases (PTKs) has been implicated in diseases including cancer. Current approved therapeutics targeting PTKs are ATP-competitive inhibitors. Although potent, the ATP pockets of protein kinases share a high sequence homology and therefore, selectivity is difficult to achieve. We believe that substrate-competitive inhibition of PTKs can offer advantages such as improved selectivity as well as the ability to address the clinically relevant mutations. Thus, we aim to develop small molecule substrate-competitive PTK inhibitors. A library of approximately 300 biphenylethylacetimides was screened against wild type c-Src as well as the c-Src T338M gatekeeper mutant. One compound of interest notably inhibited the c-Src T338M gatekeeper mutant with an IC_{50} of 26 μM. Additionally, Lineweaver-Burke plot analysis further suggests binding in the desired ATP-noncompetitive, substrate-competitive mode. Current work includes the synthesis and evaluation of derivatives replacing the acetyl group of the lead compound as well as cell proliferation studies.

MEDI 73

Small molecule inhibitors of *CYP24A1* for treatment of various cancers

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Recently, vitamin D, has been recognised as having anticancer activity. Analogues of calcitriol have enhanced anti-tumour activity, reducing the calcaemic effect. Selective inhibitors of CYP24A1, which metabolises and inactivates vitamin D, increase the lifetime and thereby the anti-cancer functions of calcitriol. The aim of this project is to develop new, potent and selective inhibitors of CYP24 in order to enhance the endogenous vitamin D levels and favour its anti-tumour activity.

Through molecular modelling studies, the CYP24A1 active site has been characterised. Different series of potential inhibitors were designed in order to mimic completely the calcitriol disposition in the binding pocket and to interact with the haem iron of the enzyme catalytic site. For each of them a synthetic pathway was developed.

The CYP24A1 inhibitory activity (IC_{50}) and the value of the Ki (dissociation constant), compared with ketoconazole as the standard, were evaluated. New potent inhibitors were found.

MEDI 74

Synthesis and evaluation of novel isothiocyanates

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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 75

Synthesis and evaluation of alkyl and aryl isothiocyanates as anticancer agents

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Studies have shown that vegetables of the *Brassica* family reduce the risk of developing cancer; especially in the GI tract. The main components that lessen the risk of cancer are isothiocyanates (ITCs) which come from the metabolic degradation of glucosinolates. Previous research has indicated that synthetic ITCs are just as effective (or more) than the naturally occurring ITC, L-sulforaphane, at chemoprevention and chemotherapy. In order to analyze the correlation between structure and activity, a panel of non-natural ITCs has been synthesized and their chemotherapeutic properties tested against MCF-7 cells using an antiproliferation assay.

MEDI 76

Role of epigallochatechin-3-gallate as an anti-cancer agent in various cell lines

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Epigallocatechin-3-gallate (EGCG), the major component of polyphenols in green tea, is a potent antioxidant that has many therapeutic applications including the treatment of cancers and inflammations. In this study, we examine the effect of EGCG and its hydrophobic derivative on cell biology of human epidermoid carcinoma A431, wildtype MCF-10A and mammary adenocarcinoma MCF-7 cells with the use of the quartz crystal microbalance with dissipation monitoring (QCM-D). The QCM-D detection is based on changes in mass and viscoelastic property of cells. We are particularly interested in the effect of these molecules on epidermal growth factor receptor-mediated cell signaling, the pathway that is essential to cell growth, survival, differentiation, and migration. Our study will shed light on why EGCG is an effective cancer-preventative agent.

MEDI 77

Allylic oxidation of dehydroisoandrosterone (DHEA) derivatives using the Petrow reaction

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Allylic oxidation of Δ^5-steroids usually occur at position 7. However, in the presence of a few reagents, e.g., selenium dioxide, C-4 functionalization is observed. The Petrow allylic acetoxylation reaction utilizes bromine, followed by silver acetate in pyridine and has provided a useful means of introducing substituents at C-4. [1-3] Functionalization at position 4 of these substrates can open a route to the preparation of the withanolides, potent anti-tumor agents.[4] The Petrow reaction proceeds by the addition of the halogen, then elimination of HBr, followed by substitution with rearrangement of the 6β-bromine atom. When the 3β-substituent is an ester moiety, acyl migration to C-4 is observed. The intermediacy of a dioxolenium cation in such cases has been proposed.[5] This hypothesis is being tested by using a variety of new 3-substituted Δ^5-steroids.

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MEDI 78

WITHDRAWN

MEDI 79

N-fused imidazoles as novel anticancer agents that inhibit catalytic activity of topoisomerase IIα

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In anticancer drug discovery, DNA topoisomerase has been recognized as an important target. Several clinically important antitumor drugs such as doxorubicin, etoposide, amsacrine, and ellipticine target topoisomerase II. Based on knowledge and structure based approaches, we have considered N-fused imidazoles as potential topoisomerase II inhibitors. They were synthesized by multicomponent reactions which are diversity feasible, and evaluated against hTopoIIα in several *in-vitro*assays. In comparison to etoposide, these compounds exhibited potent catalytic inhibition of hTopoIIα while not showing DNA intercalation. Molecular docking studies, molecular dynamics simulation analysis and ATPase-kinetics assay revealed that these compounds inhibit hTopoIIα by blocking ATP-binding site of enzyme. Further, compared to etoposide and 5-fluorouracil, these compounds showed higher anticancer activity in cancer cell lines, and less toxic to normal cells. They also showed potent inhibition in cell migration, and exerted apoptotic effect in G1/S phase. Taking these molecules as lead, functionalisation/derivatisation has shown higher hTopoIIα inhibitory activity.

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MEDI 80

Novel isosteviol derivatives as potential anticancer agents

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Diterpenes have generated considerable interest in medicinal chemistry because of their variety of pharmacological activities. We will present our work on the design, synthesis and anticancer evaluation of the range of diterpene analogs. The tetracyclic-diterpenoid isosteviol (ent-16-ketobeyeran-19-oic acid) can be readily obtained in large quantity from the acid hydrolysis of steviol glycosides. We will present our efforts to synthetically modify isosteviol and provide a range of functionalities and substitutions. Using a strategy of preparing key scaffolds from isosteviol followed by scaffold decoration several libraries of diterpene analogs have been prepared. The synthesis and anticancer activity of these derivatives against a variety of cancer cell lines will be reported.

MEDI 81

***Mycobacterium tuberculosis* proteasome inhibitors**

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The World Health Organization estimates that in 2012 over 2 million people will die from TB, caused by the bacteria *Mycobacterium tuberculosis* (*Mtb*). *Mtb* is difficult to eradicate because the bacteria are often in a latent state and unresponsive to current drugs. Inhibition of cellular components that are required for the bacteria's survival in the latent phase might help to eliminate this disease. One such target is the proteasome, the largest protein complex involved in protein degradation. The proteasome has been shown to be essential for TB in its latent phase. Genomic and crystallographic studies show that the *Mtb* proteasome is similar to, but not exactly like, the human proteasome. Ligands specifically designed to have greater affinity for the *Mtb* proteasome over the human proteasome were modeled *in silico*, synthesized and assayed for their potency on Mtbcells. The modeling, synthetic methods and biological assay results will be discussed.

MEDI 82

Dual EGFR/ IGFR inhibitor: A novel approach to overcome resistance

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Inhibition of EGFR has been used successfully to treat cancer patients. However, drug resistance develops after a few weeks of treatment and this is one of the major problems associated with this target. There are two possible mechanisms of resistance: the development of secondary mutations and over-activation of parallel pathways. We have previously reported that co-targeting IGFR and EGFR kinases by dual inhibitors may offer a promising approach to anti-cancer therapy. A dual EGFR/IGF-1R inhibitor is expected not only to be beneficial in addressing the problems of resistance but may also provide unique opportunities for pharmacological intervention. The SAR is described which led to the identification of a novel, small molecule dual EGFR/IGF-1R inhibitor with potent *in vitro* activity in cell-free and cell-based assays and potent *in vivo* efficacy.

MEDI 83

Can elevated VPAC1 signaling blunt the hyperproliferative capacity of Hut-78 lymphoblastic T cells?

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Annually, thousands of Americans are diagnosed with T-cell leukemia. Vasoactive intestinal peptide receptor 1 (VPAC1) expression in patients with T-cells leukemia or in over 20 T-cell lines from human and rodents is low or silenced compared to healthy, mature T-cells. This discrepancy in VPAC1 expression may not be authentic aberrant expression due to leukemic transformation. It would follow that VPAC1 deficiency would provide a growth advantage. Vasoactive intestinal peptide (VIP) signaling mediated by the VPAC1 receptor blocks cell cycle progression during human T-cell activation. We hypothesize that the exogenous addition of VIP ligand to Leukemic T-cell transfectants overexpressing of VPAC1 will suppress proliferation. To this end, Hut-78 T cells were transfected with mouse VPAC1 cDNA and monitored by flow cytometry. Results from this experimental procedure showed successful overexpression VPAC1 protein, albeit at a low efficiency. Once T-cell populations have been established, proliferation assessment studies will be initiated +/- exogenous VIP.

MEDI 84

Targeting Hsp90: Development of small molecule C-terminal inhibitors

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Hsp90 represents one of the most promising biological targets identified for the treatment of various diseases including cancer and neurodegenerative disorders, because it exhibits a wide range of functions stemming from its ability to assist in the proper folding, stability, and function of various proteins. Any interference of Hsp90 chaperone activity leads to disruption of client proteins' maturation, which can induce cell death. Since many of the proteins chaperoned by Hsp90 are associated with cancer growth as well as resistance to therapy, inhibiting the Hsp90 protein folding machinery is an attractive approach for effectively disrupting multiple pathways simultaneously.

Although significant research has focused on inhibiting the N-terminal nucleotide-binding pocket, clinical trials with Hsp90 N-terminal inhibitors have resulted in limitations, including induction of the pro-survival heat shock response, and toxicity. In contrast, we have pursued the development of Hsp90 inhibitors that bind to the C-terminal binding site, and exhibit alternative behaviours.

MEDI 85

Identification and optimization of small molecule NAMPT inhibitors as potential treatments for cancer

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Nicotinamide phosphoribosyltransferase (NAMPT) serves as a key mediator of tumor metabolism by participating in nicotinamide adenine dinucleotide (NAD^+) biosynthesis. Specifically, NAMPT catalyzes the conversion of nicotinamide (NAM) and phosphoribosyl pyrophosphate (PRPP) to nicotinamide mononucleotide (NMN), a precursor to NAD^+. Due to its critical role as a co-factor of enzymes involved in cell metabolism and DNA repair, NAD^+ is particularly important to rapidly proliferating cells. Therefore, inhibition of NAMPT and downstream depletion of NAD^+ represents a novel approach to cancer chemotherapy. Herein we describe the identification and optimization of small molecule NAMPT inhibitors. Structure- and properties-based drug design techniques were employed to identify a lead compound with potent biochemical and cell-based NAMPT inhibition activity, good oral bioavailability in multiple preclinical species, and excellent efficacy in mouse xenograft studies. The SAR surrounding the lead series as well as the biological characterization of the lead compound will be

described. Crystal structures of small molecule inhibitors in complex with the NAMPT protein will also be discussed.

MEDI 86

Modified adenosines affect the conformation and stability of G-quadruplex DNA

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G-quadruplex DNA, a DNA secondary structure found in guanine-rich sequences, is biologically relevant, for instance, the formation of G-quadruplex structures inhibits the binding of telomerase that is mainly expressed in cancer cells and subsequently regulates its functions. G-quadruplex DNA can exist in various conformations under physiological conditions. In recent years, the conformations of G-quadruplex DNA have been extensively studied because structure-function relationships may exist. Our previous study showed that oxidized adenosine (a native DNA lesion, OxodA) in the loop of telomeric DNA G-quadruplexes unexpectedly enhances their stability and affects their conformations. In the present work, we replace OxodA with two bulkier modified adenosines 8-NH_2-dA and 8-Br-dA and investigated their effect on the conformations and stability of the corresponding telomeric G-quadruplexes. 8-NH_2-dA increases the stability of G-quadruplex DNA in both Na^+ and K^+ while 8-Br-dA only affects the stability in K^+ but has no significant effect in Na^+. The effect of these two modified adenosines on the conformations of G-quadruplex DNA has also been determined using native PAGE and circular dichroism.

MEDI 87

3D-QSAR assisted drug design: Identification of a potent quinazoline based Aurora kinase inhibitor

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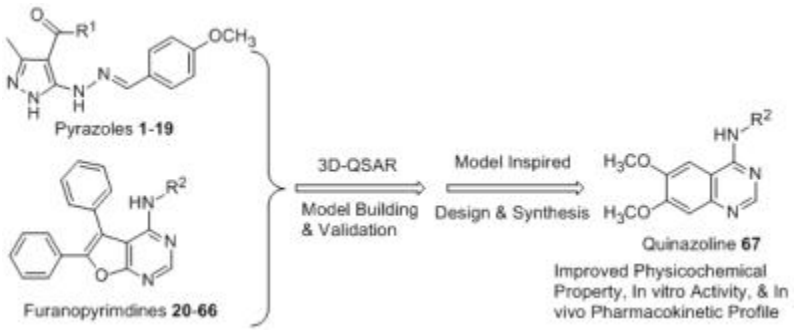
We describe 3D-QSAR assisted design of an Aurora A inhibitor **67** with improved physico-chemical properties, in vitro activity, and in vivo PK profiles than the initial lead **24** . Three different 3D-QSAR models were built and validated using a set of 66 pyrazole (Model I) and furanopyrimidine (Model II) compounds with Aurora kinase A IC_{50} ranging from 33 nM to 10.5 mM. The best Model III, constructed using 24 training set ompounds from both series, showed robustness (r^2_{CV} = 0.54 and 0.52, for CoMFA and CoMSIA) as well as superior redictive abilities for forty two test set compounds

(R^2_{pred}= 0.52 and 0.67, for CoMFA and CoMSIA). Superimposition of CoMFA and CoMSIA Model III over the crystal structure of Aurora A, suggests the possibility to improve the activity of the ligands by decreasing the steric clash with Val147 and Leu139 and by increasing the hydrophobic contact with Leu139 and Gly216 residues in the solvent exposed region of the enzyme. Based on these suggestions, rational redesign of furanopyrimidine **24** (cLogP = 7.41; Aurora A, IC_{50} = 43 nM; HCT-116, IC_{50} = 400 nM) led to the identification of quinazoline **67** (cLogP = 5.28; Aurora A, IC_{50} = 25 nM; HCT-116, IC_{50} = 23 nM). Rat in vivo pharmacokinetic study showed that **67** has better systemic exposure after iv administration than **24** , and has potential for further development.



MEDI 88

Easy and effective affinity column for microtubule-binding compounds

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Paclitaxel and other microtubule-binding compounds are present in their natural sources at concentrations on the order of 0.01 % to 1%. They are usually purified by crystallization, and this process results in loss of compound. We have developed a reusable affinity column by binding tubulin to sepharose beads. This column selectively binds paclitaxel and some other compounds from mostly aqueous solutions, and they can easily be released. Based on fluorescent labeling experiments, we can recover more than 95% of the paclitaxel, and the tubulin is not easily depolymerized at room temperature. This column could be used for purification of microtubule-binding compounds, prospecting for new compounds with these properties, or for assessing the effectiveness of known microtubule-binding compounds that have been derivatized.

MEDI 89

Modified porphyrins for photodynamic therapy

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Photodynamic therapy (PDT) is a cancer treatment that kills cells with light. Improved PDT drugs are needed, especially with low dark toxicity. An ideal PDT drug exhibits high cytotoxicity in the light with low toxicity in the dark. The drug must be soluble in water to be delivered through the blood, but lipid soluble to cross the cell membrane. A series of new porphyrin derivatives were analyzed as photosensitizers on a set of tumor-derived cell lines in the light and in the dark. Several porphyrins showed high toxicity at low concentrations in the light with low dark toxicity, making them good candidates for PDT agents. The distribution coefficient (logD) and cell uptake were measured for each derivative to compare physical properties with biological activity but these properties did not correlate well with activity. These compounds will be used to develop a next generation of derivatives with superior properties.

MEDI 90

Development of novel androgen receptor down-regulating agents for the treatment of all stages of prostate cancer

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Androgens and androgen receptor (AR) play crucial role in development and progression of prostate cancer (PC). Current treatments are centered on blocking androgen-signaling axis, but the emergence of castration resistant PC (CRCP) prevails. This resistant PC tumor continues to grow in the presence of low circulating endogenous ligands by virtue of the presence of active and functional AR. Thus, our current strategy to effective CRCP therapy is the development of novel AR down-regulating agents (ARDAs). We have previously formulated SAR for some steroidal analogs of our clinical candidate VN/124-1 as ARDAs. Based on insights of our previous study, we have now successfully designed and synthesized novel series of steroidal and non-steroidal agents that exhibit potent anti-prostate cancer activities. This poster will present design strategy, syntheses, biological data and SAR of these promising novel compounds.

MEDI 91

***Agave Americana* homemade therapeutic treatment: Characterization of chemical compounds**

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Puertorricans have attributed therapeutic effects to a homemade aqueous preparation of *Agave americana's* (Maguey) roots. Positive results in the treatment of diabetes type II have been claimed, from this beverage, even though there is no evidence of “in vivo” experiment validating this fact and there is no insight of the chemical components responsible for such effects. There are many studies of the chemical compounds present in Maguey's leaves, but none related with the chemical composition of their root. The goal of this project is the characterization of chemical compounds potentially responsible of therapeutic effects in Maguey's root. PARABEN, an antifungal compound, and Iron (~11ppm) had been characterized in recent experiments from Maguey's root aqueous extract using techniques as Soxhlet extraction, high pressure liquid chromatography (HPLC) and nuclear magnetic resonance (NMR).Bioassays for the inhibition of plasminogen activators were also performed in order to study if the Maguey's root extract has antimetastatic properties. The final characterization of PARABEN, the analytical quantization of iron by atomic absorption and the chromatographic and spectroscopic analysis for those extracts with positive bioassays results will be presented.

MEDI 92

Series of potent histone deacetylase inhibitors with unprecedented selectivity for the HDAC6 isoform

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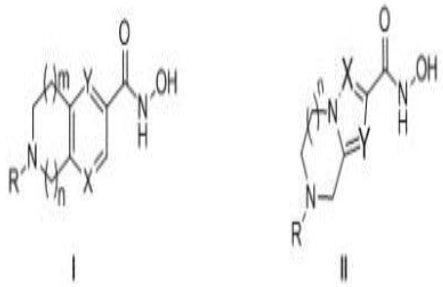
Histone deacetylase 6 (HDAC6) is a member of a class of zinc-dependent amidohydrolases commonly referred as histone or lysine deacetylases (HDACs or KDACs). Known substrates of HDAC6 include cytoskeletal proteins α-tubulin and cortactin, β-catenin, and the chaperone Hsp90. HDAC6 regulates many important biological functions such as cell migration, immune synapse formation, viral infection and possibly degradation of misfolded proteins through autophagy and thus represents a potential target of interest for the development of therapeutics.

In the search for isoform-selective histone deacetylase (HDAC) inhibitors, we prepared a series of hydroxamic acids. Screening these compounds against a panel of HDAC enzymes led to the identification of bicyclic heterocycles (**I** and **II**) as potent inhibitors of HDAC6 with excellent selectivity over the other sub-types in enzymatic and cellular assays. The design, synthesis and SAR profile of these compounds will be presented.



MEDI 93

Targeting the miRNA pathway with small-molecule modulators of Argonaute protein

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The deregulation of miRNAs expression and activity is associated with a variety of human pathologies, especially hematological malignancies. Because targeting miRNA expression can modify the disease phenotype, the understanding of the role of miRNAs in pathological processes is currently spurring the development of specific oligonucleotides or plasmid- and virus-based constructs able to modulate miRNA levels. In this context, the usage small-molecules may constitute an improved strategy to circumvent problems of delivery and immunogenic response as well as a very attractive way to devise new therapeutic tools. Here we present a new lead-like modulator of Argonaute 2 (Ago2) protein, which is a component of the RNA-induced silencing complex (RISC) with a central role in RNA silencing. We show that this small-molecule is able to interfere with the miRNAs-loading into the Ago2 complex and that the disruption of this binding results in an improvement of differentiation capability of leukemia cells.

MEDI 94

Imaging EGFR and HER2 with small-molecule imaging agents for PET and SPECT

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Due to the dependence of many cancers on the overexpression and mutation of HER2 and EGFR, the inhibition of HER2 and EGFR has been a therapeutic target of great interest. Unfortunately, only subpopulations of patients are sensitive to anti-HER2/anti-EGFR treatments. Consequently, efforts have been made toward using PET and SPECT to identify patients who will respond positively to anti-HER2/EGFR therapies. Here we outline a convergent synthesis which enables incorporation of various radioisotopes into a series of tyrosine kinase inhibitors based on the common 4-anilinoquinazoline scaffold. This approach allows for rapid diversification and optimization of potential imaging agents. Additionally, our strategy uses extended aniline headgroups known to inhibit HER2 and the inactive conformation of EGFR. To our knowledge, this has not been done previously in the synthesis of radiolabeled imaging probes for EGFR and HER2. The authors would like to acknowledge the U.S. Department of Energy for funding this research. (DE-SC0001781).

MEDI 95

New organoseleniums for anticancer agents: Synthesis of alkylselenopyridazine derivatives via allyic alkylation of diselenides

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We designed organoselenium analogs of pyridazine in which an allylselenium moiety was introduced at the 3-position of the pyridazine nucleus and the 6-position was substituted with an oxygen and sulfur atom. Novel 3-allylseleno-6-alkoxy(or alkylthio)pyridazines were prepared through the alkoxylation (or alkylthiolation) of 3-allylseleno-6-chloropyridazine and the related alcohol (or thiol) in order to discover potential antitumor candidates. Elemental selenium suspended in dimethylformamide reacts with hydrazine hydrate at rt to give dark green solution containing diselenide anion. The diselenide anion thus formed reacts in situ with the 3,6-dichlorpyridazine. The dichloropyridazinyl diselenide can be reduced to 3-chloropyridazinyl selenolate anion using hydrazine hydrate at rt. The anion thus formed reacts with allyl bromide to give the 3-allylseleno-6-chloropyridazine. The final 3-allylselenopyridazines were prepared from 3-allylseleno-6-chloropyridazine with a various nuclephillic agent. We searched another synthetic method to improve low yields. Another synthetic route for the targets was proceeded via alkylthiolation, deselenylation, hydrolysis and allylation from dichloropyridazine.

MEDI 96

Probing Aziridinomitosene cytotoxic effects in human carcinomas

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Aziridinomitosenes (AZM) are compounds with a structural backbone related to the anticancer/antibiotic mitomycin C (MC). In order to display its cytotoxicity, MC must be reduced and maintained under hypoxic conditions, which limits its use to solid tumors. AZMs do not have these requirements, thus offering a potential treatment for various carcinomas. Synthetic AZM analogs with alkyl substitutions at C6 and C7 have led to increased potency. The C6-methyl analog exhibits the highest potency, with IC_{50} values that are 300 times more potent than MC in experiments with HeLa and HL-60 cells. Caspase-3 studies indicate that MC induces protease activity greater than the AZMs. Nuclear morphology experiments indicate that MC produces nuclear swelling, while C6-methyl AZM causes nuclear condensation, suggesting a different cytotoxic mechanism. Additional studies are coordinated to isolation of nuclear and mitochondrial DNA for detection of interstrand crosslinks, and investigating reactive oxygen species levels post AZM treatment.

MEDI 97

In vitro antitumor activity study of new ferrocenecarboxylate derivatives on human colon and breast carcinoma cells (HT-29 and MCF-7)

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Ferrocene is a widely used compound due to its unique chemistry. One of its variants, ferrocene carboxylic acid, was used to synthesize halogen-substituted phenolic ester derivatives, which were cytotoxically examined *in vitro* with colon cancer and breast cancer cell lines (HT-29 and MCF-7) by means of the MTT biological assay. The IC_{50} of each compound was obtained. Results showed that ferrocene by itself has no significant cytotoxicity, but as moiety in organic molecules, it can be transported into the cell having anti proliferative effects. 4-chlorophenol ferrocenecarboxylate showed to be active against both types of cells; however, the 4-fluorophenol derivative is completely inactive. This shows promising data for the further development of effective therapeutic treatments. Further studies of cyclic voltammetry will be performed in order to determine the redox properties of the compounds.

MEDI 98

Sphingosine kinase inhibitors containing 5-membered heterocyclic subunits

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Cancer arises from many diverse genetic mutations, which makes developing targeted therapies particularly difficult. However, these mutations give rise to a tumorigenic state united by several hallmarks, namely increased proliferation and resistance to apoptosis. To maintain this state, cancer cells display addictions to certain cellular processes that can be exploited to target cancer selectively. One such nononcogene addiction is the overreliance of cancer cells on the action of sphingosine 1-phosphate (S1P), a lipid signaling molecule shown to promote cell survival, migration, and proliferation. Because the sphingosine kinases (SKs) are the sole producers of S1P, they represent attractive drug targets. Our laboratory has synthesized potent sphingosine substrate-based SK inhibitors, and current work involves improving the molecules' pharmacokinetic properties. Inhibitors containing oxadiazole functionalities display some of the desired biological properties, therefore a thiadiazole analogue will be synthesized as a point of comparison. Synthesis and biological data of these inhibitors are described.

MEDI 99

Investigation of acyl peptide enzyme hydrolase activity in cancer cells

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Acyl Peptide Enzyme Hydrolase (APEH), a member of the prolyl-oligopeptidase family, is involved in cleaving N-acyl peptides to an acyl amino acid and a free N-terminal peptide. While the enzymatic function of APEH was described almost 40 years ago, the biological function of APEH is largely unknown. Mining of micro-array databases demonstrates that APEH is up-regulated in many human cancers. For example, APEH is over-expressed 5.7-fold in bladder cancers (Oncomine). Significant up-regulation of APEH is also seen in melanomas, mesotheliomas, and colorectal adenocarcinomas (Oncomine, BioGPS). What biological role APEH is performing in cancers is unclear. We are investigating the activity of APEH in cancer cell lines to see if APEH activity correlates with expression. Using this information, we will investigate the biochemical role of APEH in cancers and may elucidate APEH as a potential biomarker or therapeutic target in certain human cancers.

MEDI 100

Identification of a new class of microtubule polymerization inhibitors for the treatment of cancer

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Despite all the efforts, cancer remains a leading cause of death worldwide. Among the various structural proteins found in eukaryotes, microtubules play an essential role in the development and maintenance of cell structure, transport and in the signaling pathways during the process of mitosis. Due to the success of anticancer agents that interact with this molecular target, it is considered that microtubules represent an attractive target for cancer therapy, which can lead to development of more potent and selective drugs. This presentation will describe the use of a computational approach for virtual screening of a focused small library of synthetic compounds to identify modulators of tubulin polymerization with potential anticancer activity. The biological evaluation (*e.g.*, biochemical activity, cellular activity and analysis of the binding mechanism) of these compounds and their structure-activity relationships will also be discussed.

MEDI 101

Synthesis and the biological evaluation of triazole-based novel antiandrogens

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Prostate cancer is the second leading cause of death in American male population. Androgen molecules, through the androgen receptor, affect the normal development and maintenance of the prostate. Androgen ablation is a common therapy for prostate cancer, often through the subminitration of androgen receptor antagonists. Unfortunately prolonged exposure to anti-androgens initiates mechanisms of resistance which render treatment ineffective. To respond to the urgent need for novel anti-androgen therapies, we have developed a new class of small molecules containing the triazole moiety, which inhibit prostate spefic androgen production in prostate cancer cell lines LNCaP. Herein we will discuss our findings on the synthesis and SAR of a novel scaffold inspired by the structure of bicalutamide.

MEDI 102

Indole-based chalcones as inducers of Methuosis

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Most anticancer chemotherapeutic drugs function by eventually inducing apoptosis to kill tumor cells. Due to increasing drug resistance exhibited toward apoptosis, an alternative mechanism to kill malignant cells is necessary. Methuosis, a recently identified novel mechanism for non-apoptotic cell death, occurs by displacement of much of the cytosolic space with vacuoles derived from macropinosomes. As the vacuoles begin to fuse and increase in size, the cell decreases its metabolism and eventually the cell membrane ruptures, killing the cell. Recently, indole-based chalcones have been identified as inducers of methuosis. Herein, we describe chemical synthetic methods to obtain analogs of indole-based chalcones aimed at improving their potency against human glioblastoma cells. Additionally, we address the need for functionalized indole-based chalcones to probe the unidentified receptor and potential advantages of a "prodrug" approach to selectively target cancer cells.

MEDI 103

Cyclic thiosulfinates as inhibitors of thioredoxin reductase and breast cancer cell growth

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The biologically activity of freshly crushed garlic is generally attributed to allicin (diallylthiosulfinate), and its activity is mainly thought to be derived from interaction with protein thiol groups. However, allicin is chemically unstable, which reduces its potential therapeutic use. We now have prepared novel cyclic thiosulfinates via mono-oxidation of cyclic dihydro-1,2-dithiins, which can be purified by silica gel chromatography, and are stable on prolonged storage. Several of the cyclic thiosulfinates inhibit i*n vitro* growth of multiple breast cancer cell lines at submicromolar concentrations. These effects appear to be correlated to inhibition of thioredoxin reductase, a redox enzyme with a cysteine-selenocysteine redox couple that has received major interest as a potential anti-cancer target. We present the novel cyclic thiosulfinates, and their *in vitro* biological activities as potential novel anti-cancer leads.

MEDI 104

Discovery and characterization of a novel Rac-GTPase inhibitor

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The RhoGTPase Rac1 is overexpressed in aggressive cancers, and its activation is required for cell migration and invasion during cancer metastasis. NSC23766 has been demonstrated to inhibit the interaction of the activating Guanine Exchange Factor (GEF) Tiam1 and Rac1, and is frequently used as a molecular probe. We now present a novel small molecule that inhibits Rac1 activation in metastatic cancer cells (MDA-MB-435) with an IC_{50} of 1.1 μM. Not only is the new compound active at a ~100 times lower concentration than NSC23766, it also is able to inhibit the interaction of Rac1 with other GEFs, notable Vav2, which has frequently been observed to be involved in cancer cell metastasis. Molecular docking has been used to elucidate the possible binding interactions of the new inhibitor with Rac1. Furthermore, inhibition of downstream effects and migration of metastatic cancer cells has been observed at concentrations of 2-4 μM. Further study could lead to the development of a novel therapeutic agent in metastatic cancers with high Rac1 activity.

MEDI 105

Repair mechanism of DNA interstrand crosslinks by O^6-alkylguanine transferase involved in the drug resistance to chloroethylnitrosoureas: A theoretical investigation

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Chloroethylnitrosoureas (CENUs) are effective alkylating agents for the treatment of a variety of tumors including cerebroma, melanoma and lymphoma. However, further development and clinical application of CENUs were obstructed due to the drug resistance induced by O^6-alkylguanine-DNA alkyltransferase (AGT). The AGT-mediated repair of DNA interstrand crosslinks (ICLs) was considered as the crucial process of the drug resistance to CENUs. In this work, the mechanism of DNA ICLs repair was investigated using molecular dynamics (AMBER), density functional theory (DFT-B3LYP) and QM/MM methods. The results indicated that the formation of AGT-DNA crosslink need to overcome a much lower energy barrier than that of ClEt-AGT, which suggested that the O^6,N1-EtG intermediate should be the favorable substrate to be repaired by AGT. Moreover, the formation of AGT-DNA crosslink was competitive with the formation of DNA ICLs, which was the most important DNA damage for the cytotoxicity of CENUs.

MEDI 106

Design, synthesis, and in-vitro biological activity of novel 2-alkyl/aryl-N-substituted-1H-benzimidazole-5-carboxamide derivatives as anticancer agents

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The primary functions of cancer chemotherapeutic agents are not only to inhibit the growth or kill the cancer cells, but conventional cancer chemotherapy is highly inadequate as a result of the lack of selectivity between cancer and normal cells. This calls for novel cancer therapies for selectively targeting cancer cells without toxicity to normal cells. Extensive literature review revealed that compounds with substituted benzimidazole moiety showed potent anticancer activity. Amide linkage in the compound also gives additional important characteristic to compound for anticancer activity. Hence, 2-alkyl/aryl-*N*-substituted-1*H*-benzimidazole-5-carboxamide derivatives were designed based upon literature review and knowledge based structure activity relationship studies. All designed molecules were docked on human Topoisomerase-IIα ATPase-AMP-PNP complex [PDB: 1ZXM], a co-crystal structure taken from protein data bank (PDB) using Surflex. In all, 18 novel 2-alkyl/aryl-*N*-substituted-1*H*-benzimidazole-5-carboxamide derivatives, showing good docking score and important H-bonds with amino acids of protein, were synthesized. 2,4-diamino benzoic acid was reacted with various aliphatic and aromatic acids to yield 2-alkyl/aryl-1*H*-benzimidazole-5-carboxylic acid. This will further reacted with various aliphatic and aromatic amines in presence of DCC as acid-amine coupling agent to synthesize target compounds. All synthesized compounds were characterized by FT-IR, ^{1}H NMR and Mass spectral analysis. Anti cancer activity of compounds was evaluated *in-vitro* on various cell lines viz. A-375 [Human Malignant Melanoma; Skin], DU-145 [Human Carcinoma; Prostate] and HCT-15 [Human Colorectal Adenocarcinoma; Colon] by XTT assay method using Doxorubicin as reference standard. Few of the synthesized compounds showed good anti proliferative activity against all cancer cell lines. Structure activity relationship (SAR) study compares effectiveness of synthesized compounds. The designed series of compounds can further exploit in search of novel anticancer agents.

MEDI 107

Design, synthesis, and pharmacological evaluation of bis-compounds containing benzothiazole and Schiff base as analgesic, anti-inflammatory, and anticancer agents

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Chronic inflammation is one of the major concerns for majority of human malignancies based on pathogenesis and alteration in biochemical processes. Approximately, 25% of all cancers are getting engaged with chronic inflammation and pain. Extensive literature review revealed that compounds containing benzothiazole**/** schiff base**/** bis type of structural features have wide varieties of pharmacological activities. Thus, bis-benzothiazole schiff bases were designed and synthesized which contain all three

features. Benzothiazole moiety was synthesized using various substituted aromatic amines, potassium thiocyanate, bromine and acetic acid as solvent. Further, it was combined with aromatic linker, o-phthaldehyde via schiff base using Dean-stark assembly. All synthesized compounds were identified and characterized by FT-IR, ^{1}H NMR, and Mass spectroscopy. Analgesic and anti-inflammatory activity of compounds were checked by acetic acid induced writhing method and carrageenan induced rat paw edema method, respectively. Compounds containing fluoro, nitro and bromo substitution at six position showed good activity compared to standard diclofenac sodium. Based on the prominent anti-inflammatory activity and low ulcerogenic potential, compounds **4c** (6-fluoro) and **4h** (6-nitro) were screened for anticancer activity on A-375 cell line (Human Malignant Melanoma; Skin), DU-145 cell line (Human Prostate; Carcinoma), HCT-15 cell line (Human Colon; Adenocarcinoma) by XTT assay method using doxorubicin as a reference standard. Both compounds showed good anticancer activity against all three cell lines. Overall, designed bis-benzothiazole schiff base compounds showed good pharmacological profile and can be proved as valuable candidate for future investigations as anticancer agents.

MEDI 108

Design, synthesis, and antiproliferative activity of N-(6-(4-amino-1-((2-4-methyl piperazin-1-yl)quinolin-3-yl)methyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)benzo[*d*]thizol-2-yl)acetamide

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Literature review revealed that quinoline, benzothiazole, pyrazolo-pyrimidine, etc. possess potent anti proliferative activity. Thus, we design and synthesize *N*-(6-(4-amino-1-((2-4-methylpiperazin-1-yl)quinolin-3-yl)methyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)benzo[*d*]thizol-2-yl)acetamide(**10**) using various name reactions like Vilsmeier-Haack, Appel & Suzuki reactions. 2-chloroquinoline-3-carbaldehyde(**2**) was synthesized by heating acetanilide(**1**)/$POCl_3$/DMF at 80°C for 12 h. It further stirred with methanol/$NaBH_4$ at 0°C for 4 h to yield (2-chloroquinolin-3-yl)methanol(**3**). Suspension of **3** in DCM, triphenylphosphine and CBr_4 stirred at 0°C for 12 h to yield 3-(bromomethyl)-2-chloroquiniline(**4**). 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine(**5**) in DMF was stirred with KOtBu for 10 min and compound **4** dissolved in DMF was added with stirring to yield 1-((2-chloroquinolin-3yl)methyl)-3-iodo-1*H*-pyrazolo[3,4-*d*]pyridine-4-amine(**6**). A mixture of **6** & 1-methyl piperazine(**7**) were mixed in 1,4-dioxan and refluxed for 18 h at 110°C to yield 3-iodo-1(2-(4-methylpiperazin-1-yl)quinolin-3-yl)methyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine(**8**). A mixture of **8** & *N*-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*]thiazol-2-yl)acetamide(**9**) were mixed in 1,4-dioxan and refluxed with K_2CO_3, $Pd(PPh_3)_4$ and deionized water for 6 h at 100-115°C to yield desired product **10** . Structure elucidation was done by FTIR, Mass, and ^{1}H-NMR. It was evaluated for cytotoxicity on U937, ARH7 and RPMI 8226 by MTT assay with doxorubicin as standard showing EC_{50} value of 6.8µm, 795nm and 3.98µm,

respectively. Designed compound can further exploit to develop novel anticancer agents.

MEDI 109

Synthesis, anticancer activity, and COMPARE analysis of N-trifluoromethylalkyl-N'-aryl/hetaryl ureas

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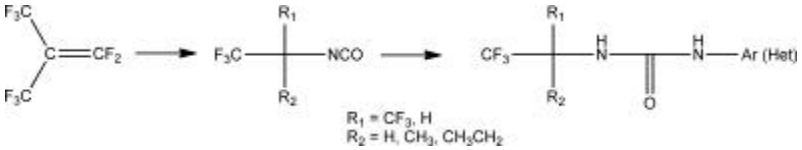
A large number of N-trifluoromethylalkyl-N'-aryl (or hetaryl) ureas were synthesized starting from perfluoroisobutene.



Their *in vitro* antiproliferative activities against the human cancer cell lines were evaluated at the National Cancer Institute (NCI, USA). The most sensitive cell lines relative to the tested compounds are PC-3, SNB-75, UO-31, SR, HS 578T, HCC-2998, NCI-H322M. Possible mechanisms of actions suggested by the COMPARE analysis include alkylating agent, DNA antimetabolites, inhibition of topoisomerase II.

MEDI 110

Synthesis and NMR study of fluorinated aryl(sulfone)phthaleins

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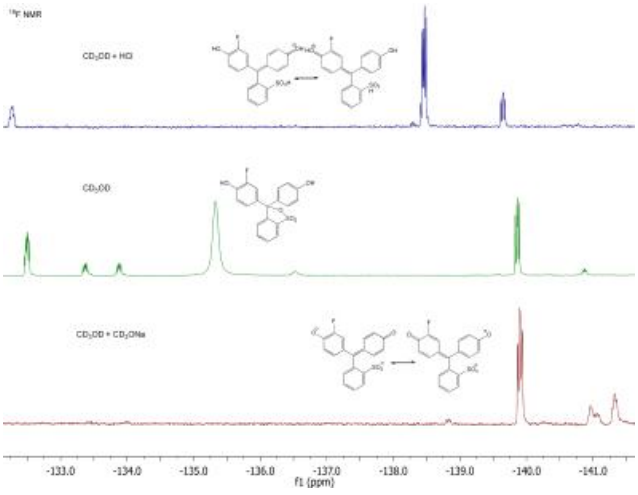
Fluorinated arylphthaleins and arylsulfonephthaleins are pH indicators for potential biomedical applications including molecular imaging. A number of the above compounds have been synthesized by direct fluorination of the aryl(sulfone)phthaleins by fluorine gas under acidic conditions. The fluorinated arylsulfonephthaleins have also been obtained by the Friedel-Crafts reaction. The products have been isolated and analyzed by MS and NMR. The conformers of the neutral, acid and base forms are well distinguished in ^{19}F NMR spectra.



MEDI 111

Synthesis, photophysical and in vitro evaluation of NIR meso-functionalized BODIPY dye

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NIR molecular probes enhance disease diagnosis and therapy due to its deeper tissue penetration potential. We have designed and synthesized meso-functionalized NIR BODIPY with excitability of >680 nm and other excellent optical properties such as molar extinction coefficient, fluorescence quantum yield etc. The BODIPY class of dyes has an added advantage of a carrying carboxylic acid functionality for conjugation to targeting vectors. The dyes show promise as useful photostable, NIR molecular probes for diagnosis and photoinduced therapies.

MEDI 112

Preparation of biopolymeric particles from natural inulin

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Inulin, inulin-silica and modified inulin particle were prepared and used as drug delivery devices. Inulin-silica composite micro particles were synthesized in the presence of

tetraethyl orthosilicate (TEOS) via a water-in-oil microemulsion polymerization technique. To generate pores, silica was removed from composite inulin particles. Furthermore, bare-inulin and porous-inulin particles were quaternized successfully by the treatment of 3-chloro-2-hydroxypropyl trimethyl ammonium chloride aqueous solution to generate the positive charge on the biopolymeric particles. SEM, optical microscopy, DLS, zeta potential measurement were used for the size, charge and morphology of the particles. Thermogravimetric analyzer (TGA) and FT-IR spectroscopy were utilized for thermal and functional structural characterization of p(inulin) particles. The antimicrobial activity of synthesized inulin particles was also investigated. Fluorescence sodium salt (FSS) and Rhodamine 6G (R6G) were used as model drugs for the release studies in phosphate buffer solution (PBS) at pH 7.4.

MEDI 113

Biocompatible collagen-synthetic interpenetrating polymeric hydrogels

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Collagen as an important part of the fibrous proteins in the living organism found in many tissues, especially tendons main structure contains collagen. Here, natural collagens modified with different synthetic polymers were prepared as composites to enhance collagen natural characteristics. Hema and acrylamide monomers were used to synthesize collagen based interpenetrating polymeric networks (IPN). The swelling behaviors of the prepared hydrogels in distilled water were investigated. MTT and Commet Assay were used for the determination of the biocompatibility. Furthermore, two kinds of model drugs, Trimetoprim (TMP) and Sulfamethoxazol (SM) were used as antibacterial active agents for the release studies from the synthesized IPN hydrogel-collagen matrices. It was shown that collagen-synthetic polymer matrices can be readily prepared and used as drug delivery application for release of active agents. Therefore, these system have great potential in would dressing applications.

MEDI 114

Ethynyl flavones as inhibitors of human cytochrome P450 enzymes

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Cytochrome (CYP) P450 enzymes are a superfamily of heme-containing proteins found in all living organisms. The main function of these enzymes during detoxification is to catalyze the oxidation of organic substances through monooxygenation reactions.

CYP450 enzymes are also involved in the bioactivation of environmental procarcinogens, leading to the production of carcinogenic species.

Previous studies have shown that a number of aromatic acetylenes and flavonoids act as inhibitors of P450 enzymes. We have previously shown that ethynylcoumarin derivatives, which have structural similarities to proparglyflavone analogs, can cause inactivation of certain P450 enzymes such as P450s 1A1, 1A2, 2B6, and 2B1.

For this project, we have focused our efforts on the design and synthesis of a group of flavonoids with an ethynyl moiety at different locations on the ring system. These target compounds will be used in a structure-activity relationship study.

MEDI 115

Predicting metabolic-site-specific kinetic parameters for CYP2D6-mediated drug metabolism

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Michaelis-Menten constant (K_M), maximum metabolic rate (V_{max}), and intrinsic clearance (CL_{int}) are important kinetic parameters characterizing the activities of cytochrome P450 isoenzymes. CYP2D6 constitutes ~2% of the total enzyme content of human liver tissue, but contributes to the metabolism of approximately 25% of marketed drugs. We have developed metabolic-site-specific kinetic parameter models for substrates of CYP2D6 utilizing our state-of-the-art Artificial Neural Network Ensemble (ANNE) modeling methodology incorporating both rapidly calculated molecular descriptors and atomic descriptors representing charge, reactivity, steric effects, and local environment of the atomic metabolic site. Experimental kinetic parameter data for *in vitro* metabolic studies of over 100 CYP2D6-mediated reactions were carefully curated from original literature. Models were validated with external test sets constituting 15-20% of the total data for each respective model. The root-mean-squared errors (RMSEs) of the test sets for $\log K_M$, $\log V_{max}$, and $\log CL_{int}$ models were approximately 0.6, 0.6, and 0.7 log units, respectively.

MEDI 116

Quest for new mechanism-based inhibitors of cytochrome P450 enzyme 1A1 and 1A2

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Cytochrome P450 enzymes are involved in the metabolism of many procarcinogens, carcinogens, and pharmaceuticals such as polycyclic aromatic hydrocarbons (PAHs), arylamines, heterocyclic amines, sterols, fatty acids, vitamins, and steroids. P450s are expressed in many tissues including liver, kidney, and lung. The role of P450 enzymes in bioactivation, tumor formation and development makes them an attractive target for cancer prevention and treatment. Our earlier studies on anthraquinone/quinone inhibitors of P450 enzymes indicated that the presence of a methyl group adjacent to an amino group could be responsible for its mechanism-based inhibition of P450 enzymes 1A1 and 1A2. With the goal of finding new mechanism-based inhibitors for P450 enzymes 1A1 and 1A2, a 2D-pharmacophore-based database search was conducted for compounds containing 1-amino-2-methyl substituents on polyaromatic/heterocyclic core structure. A series of 12 compounds were selected from the database hits through docking studies and subjected to bioassay for P450 inhibition. Four of these compounds proved to be mechanism-based inhibitors of P450 enzyme 1A1. Further molecular modeling studies were conducted to understand the specificity and potency of these compounds.

MEDI 117

Structural characterization of L-β-methyl-amino-alanine bicarbonate interaction reveals co-existence and conformational equilibria of multiple complexes at physiological condition: A comprehensive NMR study

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β-N-methylamino-L-alanine may be a risk factor for amyotrophic lateral sclerosis, Parkinson's and Alzheimer's disease. Neuronal assays suggest that the BMAA/bicarbonate allows for the formation of a carbamate adduct that might produce structures capable of activating glutamate receptors. Present are the highlights of a NMR based structural characterization of BMAA/Bicarbonate interaction and the adduct formations.

A systematic study of the structure of BMAA as a function of temperature, pH, and at close to physiological conditions the BMAA/bicarbonate adducts formation at varying BMAA/bicarbonate ratios was studied. Two adducts coexists simultaneously with BMAA in solution and these adducts undergo an exchange between complex and free form BMAA on the NMR time scale. Though these results add to an additional dimension to the complexity of BMAA's neurotoxicity, it provides an opportunity to address the molecular level mechanism of BMAA: Bicarbonate adducts responsible for the function.

MEDI 118

Peptide amphiphiles as new transporters for the delivery of phosphopeptides

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Peptide Amphiphiles (PAs) have been known as promising tools in drug and gene delivery systems due to their biocompatibility and bioactivity. A series of four PAs containing arginine and lysine residues linked to one or two hydrophobic tails with different chain lengths (i.e., (NH(Ac)-Lys(Palm)-Arg-Lys(Palm)-COOH), (NH(Ac)-Lys(My)-Arg-Lys(My)-COOH), (NH(Ac)-Arg-Lys(Palm)-Arg-COOH), and (NH(Ac)-Arg-Lys(My)-Arg-COOH), where My and Palm are myristoyl and palmitoyl, respectively) were synthesized using solid-phase Fmoc chemistry. All synthesized PAs did not show significant toxicity in human ovarian cancer (SK-OV-3), human leukemia cancer (CCRF-CEM), and human colorectal (HCT-116) cells. The cellular uptake of fluorescent-labeled phosphopeptide F-GpYEEI was evaluated in the presence or absence of all synthesized PAs in human ovarian cancer cells (SK-OV-3) after 1 h incubation using flow cytometry (FACS). (NH(Ac)-Lys(Palm)-Arg-Lys(Palm)-COOH) was found to be more efficient transporter compared to the other synthesized PAs. The cellular uptake of F-GpYEEI was improved (3 folds) in the presence of this PA.

MEDI 119

Minimizing in circulation drug leackage by single walled carbon nanohorn supported PEGylated immunoliposome

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Nanoparticle mediated drug delivery plays an increasingly important role in the treatment of cancers and inflammatory diseases. However, how to minimize basal drug release and thus the accompanying side effect is still a challenging problem. In this study, we have synthesized carbon nanohorn (CNH) supported liposome particles. A model drug, paclitaxel, was loaded into CNH, which displays a much higher loading capacity than that of liposomes. Lipids with different pH sensitivity were assembled into the lipid bilayer. Our results showed a highly pH dependent release of drug in presence of serum at body temperature indicating a possibility of eliminating the basal drug release under physiological conditions. Structure, loading capacity, toxicity were studied. Breast cancer cell binding affinities of particles grafted with mouse anti Her2 monoclonal antibody or herceptin were determined and compared.

MEDI 120

Protein nanocapsules as biocompatible carriers for the targeted delivery of coagulation proteins to sites of internal injury

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Internal hemorrhage is the foremost cause of death on the battlefield and the second leading cause of death in civilian trauma. While there are multiple products available to treat external hemorrhage, no product has been developed that can target and control internal hemorrhage. The development of a biocompatible nanoparticle carrier that can deliver thrombin, a coagulation protein, to the site of internal injury is currently being researched. Porous polymer nanoparticles are fabricated through the radical polymerization of monomers in a solution containing thrombin. Targeting peptide sequences, also known as protease degradable cross-linkers, such as the IEGR sequence, can be incorporated into the nanoparticle shell in varying concentrations. This can influence the targeting ability and the rate at which the particle will degrade. Non-protease degradable cross-linkers are also incorporated in order to create control particles. Progress towards nanoparticle formation and drug delivery will be discussed in detail.

MEDI 121

Metalloporphyrins as synthetic livers

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Several problems are associated with use of biological systems in studying drug metabolism.

• In vitro studies produce small quantities of primary metabolites that are hydrophilic and difficult to isolate.

• Animal studies necessitate sacrifice of animals and are expensive. Liver slice preparations of variable potency make it difficult to quantitate oxidant stoichiometry.

• Many metabolites are not amenable to synthesis by conventional routes.

We present examples of porphyrin-mediated oxidations of sophisticated pharmaceutical entities. The reactions are generally applicable and have been used on numerous substrates. This is an efficient method for the systematic identification of the entire spectrum of metabolites.

Our proprietary *in vitro* chemical technology (“synthetic livers”) allows us to mimic the *in vivo* metabolism of chemical entities used in pharmaceuticals, cosmetics, polymers, agricultural and synthetic dyes. Biomimiks™ enables prediction of metabolism patterns,

pathways and profiles and introduces a new paradigm for drug discovery and mimicking drug-drug interactions for clinical diagnostics.

MEDI 122

Interaction between recoverable oxygen carrier and porcine whole blood: Changes in relative viscosity of the mixture

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The oxygen carrier study was a perfluorocarbon bromide (PFOB) based emulsion, stabilized with 1,2-dioleoyl-sn-glycero-3-phosphate (DOPA) lipid, and coated with a calcium phosphate ($CaHPO_4$). Encapsulating the emulsion in a protecting layer improves its longevity and allows for great amounts of oxygen to be delivered. Due to a small particle size and a high density, this emulsion system is removed from the circulatory system via centrifugation and is referred to as recoverable oxygen carrier (rOC). Study of the emulsion's ternary diagram isolated one composition, desired properties of size, phase, and stability. Once encapsulated with $CaHPO_4$, compatibility tests were done in whole porcine blood to understand the relationship between the blood's immune response factors and the rOC. There was an overall concentration rOC (0.3 vol.%) discovered by a change in the medium's relative viscosity. Below this limit, the rOC could transport freely within the blood and be of no hindrance to normal function.

MEDI 123

Electronic properties of CNNs: A journey toward nanomedicine

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Different computational techniques have been applied to study theoretical physicochemical properties of carbon packed nanoneedles that can be directly related to reactivity.

The versatility of CNNs as well as the possibility to control their length in terms of number of layers makes them potentially useful as specifically targeted drug delivery systems.

In addition, infinite-length CNNs are likely to have semi-conducting properties, allowing their use as semiconductors in nanostructure devices.

More research is needed to tailor the use of CNNs for specific drugs, to improve the release of the drugs, and to complement the theoretical studies with toxicity studies

MEDI 124

Polarity of diacetylated phosphatidylcholine solutions

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1,2-Diacetyl-*sn*-glycero-3-phosphatidylcholine (DAcPC) dissolves in water in similar concentrations as in the fluid bilayer. Hydrated DAcPC can be used to study drug solvation in the medium imitating the headgroup region of the bilayer. We measured polarity of hydrated DAcPC using fluorescent dyes. Two widely used measures of polarity, the dielectric constant and Reichardt's $E_T(30)$ value, obtained for aqueous solutions of DAcPC will be presented and compared to the literature values obtained in liposomal bilayers.

MEDI 125

Surface tension of aqueous solutions of phosphatidylcholine headgroups

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Aqueous solutions of 1,2-diacetyl-*sn*-glycero-3-phosphatidylcholine (DAcPC) with similar water concentrations as in the fluid bilayer can be used as a surrogate of bilayer headgroup region to study: (1) solvation of drugs, which determines their bilayer location and the rates of passive trans-bilayer transport and (2) molecular interaction mechanisms of xenobiotics and membrane proteins with the bilayer headgroup region. Surface tension, as the amount of energy per unit surface area a molecule needs to make a cavity in a solvent to remain dissolved,is an important parameter affecting passive diffusion of drug molecules across bilayers. We measued the surface tension of DAcPC using an in-house built DuNoüy tensiometer. The surface tension values of DAcPC solutions will be presented and compared with literature value obtained for phosphatidylcholine monolayers.

MEDI 126

Biological compatibility of NIH 3T3 fibroblasts conducted on electrospun nanofibers containing multi-wall carbon nanotubes for potential regeneration of ligament tissue

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Over two million people in this country visit a musculoskeletal specialist yearly and nearly half of these visits are due to soft tissue damage to ligaments and tendons. Many anterior cruciate ligament reconstructions are conducted nationwide; however, recuperation and rehabilitation treatments for injuries to these are physically demanding. Injuries to the soft collagenous tissues often result in a significant decrease in the quality of a patient's life. Due to inefficient and invasive surgeries, tissue-engineering strategies are gaining momentum as an alternative to the current injury treatments that fail due to their inability to fully restore proper joint biomechanics. An alternative material for the anterior cruciate ligament replacement is researched for biocompatibility. Engineered ligament tissue is ultimately formed by culturing cells within a fibrous network under appropriate combinations of biochemical and mechanical conditions to induce synthesis of alignment-like extracellular matrix with oriented fibrils. Fiber orientation is induced by electrospinning onto a rotary disc, a drum, between two ground rods, or by resulting mechanical stretching. These electrospun nanofibers provide a high surface area for cell attachment and matrix depositions to induce cell orientation and proper nutrient transport. The recent incorporation of carbon nanotubes to electrospun nanofibers enhances the mechanical properties of these fibers. MTT cell proliferation assays conducted on seeded electrospun nanofibers demonstrate their biocompatibility *in vitro*. Results show that fibroblast cell proliferation and growth behavior vary by electrospun nanofibers type and carbon nanotube percent composition. Various nanofiber analyses suggest a positive response to NIH 3T3 presence over different incubation time periods. Biocompatibility between nanofibers and fibroblasts reveal a promising biomaterial for tissue-engineering ligaments. A functional engineered ligament must integrate reparative cells, NIH 3T3 fibroblasts, with the capability to proliferate and direct cell contact/ distribution. This work suggests that electrospun nanofibers with incorporated carbon nanotubes are a significant alternate to reconstructive surgery.

MEDI 127

Reactions during storage of the molecular libraries small molecule repository

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Molecular Libraries Small Molecules Repository (MLSMR) is the NIH compound collection designed for biochemical probe and drug discovery screening (http://mli.nih.gov/mli/compound-repository/). The collection of about 400,000 individual compounds was initiated in 2004. Each compound passed acceptance criteria: purity and identity by LCMS analysis. The storage conditions are mild: nitrogen atmosphere, -20°C. Working solutions, 10mM in DMSO, undergo periodic thawing for distribution to screening centers and QC analysis is performed to verify integrity. We have begun to

look in detail at the samples that failed QC after storage. The effort is to find trends in stability that can be used in selection criteria for library enhancement. We have found examples of hydrolysis, oxidation and condensation reactions including rapid hydrolysis of specific esters and amides, aromatization and the condensation of a secondary amine with carbon dioxide to produce a symmetrical urea.

MEDI 128

Multi-fragment screening of protein-protein interaction modulators via sulfo-click kinetic target-guided synthesis

Iredia D Iyamu[1]*, idi@mail.usf.edu, Katja Nacheva*[1]*, Sameer S Kulkarni*[1]*, David Flanigan*[1]*, Megan Barber*[1]*, Niranjan K Namelikonda*[1]*, Kenichiro Doi*[2]*, Jeremiah D Tipton*[1]*, Hong-Gang Wang*[2]*, Roman Manetsch*[1]*. (1) Department of Chemistry, University of South Florida, Tampa, Florida 33612, United States (2) Department of Pharmacology and Penn State Hershey Cancer Institute, Penn State College of Medicine, Hershey, Pennsylvania 17033, United States*

Although protein-protein interactions possess significant biological importance, identification of small protein-protein interaction modulators (PPIMs) remains challenging due to the flexible nature of proteins. Several fragment-based approaches have been used to identify ligands with good ligand efficiencies, but failure to provide insight into efficient fragment evolution has made the drug discovery process complicated. Herein, we report the development of a drug discovery approach that generates only biologically active compounds, known as kinetic target-guided synthesis (TGS). A sulfo-click reaction between thio acids and sulfonyl azides was successfully employed for Bcl-X_L-and Mcl-1-templated screenings. After obtaining encouraging results, efforts were made to increase the throughput of kinetic TGS by approximately 100-fold. The development, high throughput and use of the new kinetic TGS will be discussed.

MEDI 129

Probe development at The Scripps Research Institute's Molecular Screening Center

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Scripps Florida is a full service NIH screening and chemistry center for discovering proof-of-concept molecules, or molecular probes, typically against novel targets with no known small molecule modulators. It is expected that these compounds will be useful in understanding important biological disease mechanisms and ultimately in developing

new treatments for human diseases. We develop ultra high throughput screens of the NIH Molecular Libraries Small Molecule Repository (MLSMR), encountering a wide range of targets (enzymes, GPCRs, ion channels, PPIs), and a wide range of therapeutic areas, screening protocols, chemistry, and biology. Follow-up chemistry optimization, including addressing potency, selectivity, and DMPK issues, are central to the effort. Data (and compounds) are freely shared upon completion of the project, as the aim is to seed future discovery in new fields where proof-of-concept molecules no not yet exist. This talk will give a quick description of the efforts, how they are integrated, and a case study of a probe development project. The case study will cover efforts from uHTS development, to hit ID, to SAR studies, and to the selection of a designated probe compound.

MEDI 130

Rapid technique for new scaffold generation

***Tim Cheeseright**, tim@cresset-group.com, Martin Slater, Mark Mackey. Cresset BioMolecular Discovery Ltd, Welwyn Garden City, Herts AL7 3AX, United Kingdom*

Scaffold hopping remains a central task in medicinal chemistry for generating and protecting intellectual property. We present a technique for rapidly generating reasonable yet novel scaffold replacements using molecular fields.

The method is embodied in the scaffold hopping software **spark** V10 and will be presented together with a number of case studies.

Direct comparison with the recently published method that utilizes quantum mechanical calculations (NEAT) will show that similar or better results can be obtained in a few minutes on a desktop PC. Limitations and future optimizations will be discussed.

The use of our method for growing or linking fragments in fragment based drug discovery will be presented with respect to the preparation of selective ligands targeting a selective, slow off-rate kinase inhibitor for COPD. Advantages and disadvantages of our ligand based method over structure based methods will also be presented.

MEDI 131

Introducing disulphide bridge mimicking building blocks into cyclic peptides

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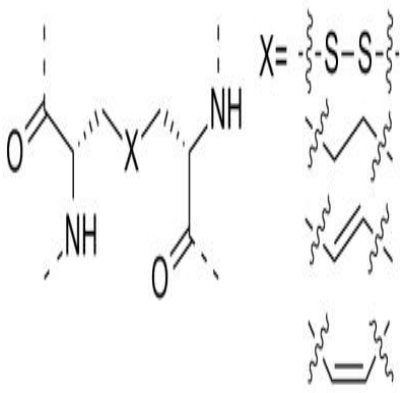
We have previously published a protocol for synthesizing orthogonally protected building blocks to be used as disulphide-bridge mimetics as well as schemes for the selective removal of any one of the four protecting groups on the building block. We have also shown that it is possible to introduce a carbon isostere of a disulphide bridge by utilizing ring-closing metathesis on allylglycine-residues included in the sequence of the peptide in place of cysteine residues, even though this significantly harder to achieve than anticipated. The RCM approach has the limitation of the product being a mixture of the *E* and *Z*isomers of the double bond, as proven by NMR analysis.



In this work we present a method for using the building-block approach for including The disulphide bridge mimetics in a peptide. We also show that the replacement of the disulphide bridge with a non-natural building block does not significantly lower the biological activity compared to the parent peptide.

MEDI 132

Taming the G protein-coupled receptor GPRC6A

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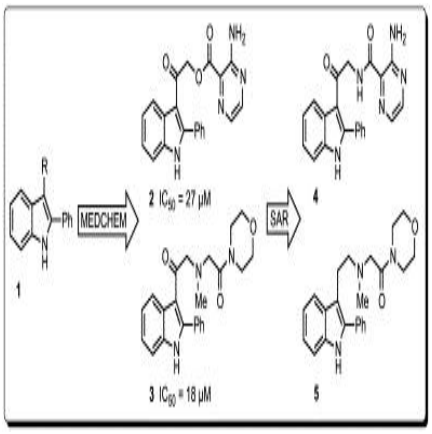

GPRC6A is an L-amino acid sensing receptor with wide tissue expression and unknown physiological function. Using a chemogenomic approach we identified 3-substituted 2-phenyl-indoles **1** as allosteric modulators of GPRC6A. Potent allosteric modulators would be of value as pharmacological tools *in vitro* and *in vivo*. Synthesis routes to provide **2-5** and a wide range of analogues were developed, and a thorough structure-activity relationship study is currently underway, aiming at generating more potent and selective modulators of GPRC6A in the near future.

MEDI 133

Strategies for on-line monitoring of wound infection

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Wound infection is a severe complication during wound healing causing diagnostic and therapeutic problems. Infection is characterized by an excessive stimulation of neutrophil granulocytes, resulting in the release of proteolytic enzymes like human neutrophil elastase (HNE) or myeloperoxidase (MPO) into the plasma. Infected wound fluids showed significant higher substrate hydrolysis or oxidation compared to non infected wounds. To allow integration of sensors in typical bandage materials, we successfully immobilized the elastase substrate on collagen, modified collagen, polyamide, polyester and silica gel. This immobilised chromogenic peptide based elastase substrate was indeed only converted by infected wound fluids. Similarly, immobilisation of fast blue RR as MPO substrate was performed. Again, elevated MPO

activities in infected wounds led to formation of dark red colour. These novel enzyme responsive materials show high potential for on-line monitoring of wound infection.

MEDI 134

Applications of aminoacyl nucleolipid bioconjugates in medicinal chemistry

***Pradeepkumar Patel**, pradeepkumar.patel@student.shu.edu, David Sabatino. Department of Chemistry and Biochemistry, Seton Hall University, South Orange, NJ 07079, United States*

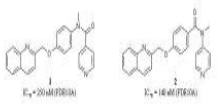
Aminoacyl nucleolipids encompass a relatively new class of bio-conjugates owning the ability to form higher-order structures with interesting bio-physical and therapeutic properties. Considering these bio-conjugates may potentially behave as cationic lipids at physiological conditions, we've begun exploring their potential in gene therapy applications. In this presentation, the synthesis, characterization and medicinal chemistry applications of aminoacyl nucleolipids is described. Briefly, aminoacyl nucleolipids were designed to contain key structural motifs that may participate in highly specific and efficient oligonucleotide binding interactions. Their synthesis is highlighted by a chemically robust and versatile EEDQ coupling procedure for the preparation of bio-conjugates in 53-78% yields. Following characterization, the bio-conjugate-oligonucleotide interactions were assessed by by native gel shift mobility assays, thermal denaturation experiments and CD spectroscopy paving the way for gene therapy applications in cell-based studies.

MEDI 135

N-Methylanilide and N-methylbenzamide derivatives as novel selective phosphodiesterase 10A (PDE10A) inhibitors

***Paul Kilburn**[1], jpk@lundbeck.com, Jan Kehler[1], Morten Langgaard[1], Mogens Larsen[1], Claus Christoffersen[2], Jacob Nielsen[3], Mette Erichsen[1], Sebastion Petersen[1]. (1) Department of Medicinal Chemistry, Lundbeck A/S, Valby, Copenhagen DK2500, Denmark (2) Department of Molecular Pharmacology, Lundbeck A/S, Denmark (3) Department of Neurobiology, Lundbeck A/S, Denmark*

PDE10A is a rather recently identified phosphodiesterase with a quite remarkable localization since the protein is abundant only in brain tissue. Based on this unique localization, research has focused extensively on using PDE10A modulators as a novel therapeutic approach for dysfunction in the basal ganglia circuit including Parkinson's disease, Huntington's disease, schizophrenia, addiction and obsessive compulsive disorder. Medicinal chemistry efforts identified the N-methyl-N-[4-(quinolin-2-ylmethoxy)-phenyl]-isonicotinamide (**1**) as a nanomolar PDE10A inhibitor. Herein we will present the syntheses and SAR of analogous N-methylanilides and their corresponding N-methylbenzamides (**2)** .



MEDI 136

Discovery of novel tricyclic pyrrolidine derivatives as potent a4b2 nicotinic acetylcholine receptor ligands and their efficacy in animal models of depression

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The neuronal nicotinic acetylcholine receptors (nAChRs) play an important role in several brain functions. The nAChRs are also involved in several brain pathologies such as depression, anxiety, mood disorders, cognitive disorders, like Alzheimer's diseases and schizophrenia, Parkinson's disease,some forms of epilepsy and tobacco smoking addiction. nAChRs are a heterogeneous family of pentameric subtypes. The discovery of potent and selective a4b2ligands has attracted the scientific community over the last decade leading to the formulation of reliable a4b2pharmacophores and QSAR models. In our quest to find novel a4b2 modulators, we have designed and synthesized novel series of tricyclic conformationally constrained pyrrolidine derivatives with favorable ADME properties. The design, synthesis, SAR and pharmacological profile of these novel compounds in animal models of depression will be presented

MEDI 137

Novel series P2X3 receptor antagonists: Discovery of potent and orally efficacious pyrrolinone derivatives

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Kanda[2], Maki Tomari[2], Yoshikazu Tanaka[2], Fumiyo Takahashi[2], Shigenori Yagi[3], Emiko Shigetoshi[1], Yukio Takahara[1], Chie Takeyama[1], Hiroki Tsuji[1], Shoichi Yamamoto[1], Shunji Shinohara[1], Hiroyuki Kai[1]. (1) Department of Medicinal Research Laboratories, Shionogi & Co., Ltd., Toyonaka-shi, Osaka 561-0825, Japan (2) Department of Innovative Drug Discovery Research Laboratories, Shionogi & Co., Ltd., Toyonaka-shi, Osaka 561-0825, Japan (3) Department of Drug Developmental Research Laboratories, Shionogi & Co., Ltd., Toyonaka-shi, Osaka 561-0825, Japan

P2X3 receptor is an ion channel coupled receptor, activated by ATP, and mainly located in peripheral sensory neuron. P2X3 receptor antagonists reportedly show analgesic effects in neuropathic and inflammatory pain models. To discover P2X3 receptor antagonists of novel chemotype, we performed high throughput screening of chemical library using FLIPR Ca-influx assay system. As a consequence, hit compound, which has pyrrolinone skeleton, was identified. We performed the Hit to Lead SAR from the hit compound, and obtained lead compound with strong inhibitory effect on P2X3 receptor (IC50: 25 nM). Further improvement of the potency and PK profiles of lead compound finally led to the discovery of best compound, which demonstrated outstandingly strong analgesic effect with oral administration against hyperalgesia in the partial sciatic nerve ligation model for neuropathic pain. A docking study with the compounds and an effective homology model of human P2X3 is also presented.

MEDI 138

Synthesis and biological evaluation of 3-aryl-3-arylmethoxy pyrrolidines on monoamine transporters

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A series of 3α-arylmethoxy-3β-aryltropane and piperidine derivatives have been found to be exhibit potent affinity (nM) for dopamine transporters (DAT) and serotonin transporters (SERT) in rat brain tissue, respectively. The aim of the present study is to synthesize and evaluate novel 3-arylmethoxy-3-arylpyrrolidine derivatives that would have affinity towards multiple transporters. We have synthesized a series of 3-arylmethoxy-3-arylpyrrolidine analogs via a four-step process from 1-Boc-3-hydroxypyrrolidine. The binding affinity for DAT, SERT and norepinephrine transporters (NET) has been determined in rat brain tissue. The synthetic details and results of this SAR study will be presented.

MEDI 139

Drug discovery of novel *N*-substituted oxindoles as potent and high selective muscarinic M_1 and M_4 receptor partial agonist

***Kentaro Takai**, kentaro-takai@ds-pharma.co.jp, Takaaki Sumiyoshi, Yoshiharu Uruno, Kengo Tojo, Atsushi Suwa, Yoko Takahashi, Yasuko Konishi, Takeshi Enomoto, Harumi Matsuda, Mutsuko Sakai, Tomokazu Nakako, Akihiko Kiyoshi, Yasuaki Uematsu, Atsushi Kitamura.Drug Research Division, Dainippon Sumitomo Pharma Co., Ltd., Suita, Osaka 564-0053, Japan*

Muscarinic acetylcholine receptors (mAChRs) are promising targets for the treatment of schizophrenia according to the results of muscarinic M_1/M_4 agonist xanomeline in clinical trials. However the development of xanomeline was discontinued by gastrointestinal distress caused by activation of peripheral M_3 agonist activity. Although high selective muscarinic agonist is hopeful, it has been challenging issue because of the high sequence homology and conservation of the orthosteric ACh binding site among the mAChR subtypes. We identified oxindole derivatives as muscarinic agonist and disclosed pyrrolidine linker improved M_1/M_4 selectivity (ethyl 4-{[(3S)-3-(2-oxo-2,3-dihydro-1H-indol-1-yl)pyrrolidin-1-yl]methyl}piperidine-1-carboxylate). In addition, we investigated M_4 partial agonist to minimize the risk of extrapyramidal side effects (EPS) and discovered ethyl (3-exo)-3-{[(3S)-3-(2-oxo-2, 3-dihydro-1H-indole-1-yl)pyrrolidine-1-yl]methyl}-8-azabicyclo[3.2.1]octane-8-carboxylate (**1**). Replacement of piperidine to tropane was effective to partialize M_4 agonist activity. Compound **1** improved positive symptoms in rodents without induction of significant peripheral side effects and EPS.

MEDI 140

Structure activity relationships of 7-azaindolines as selective M_4 muscarinic acetylcholine receptor agonists

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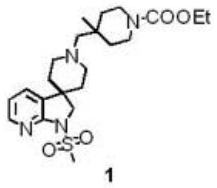
Muscarinic acetylcholine receptors (mAChRs) in central nervous system (CNS) have emerged as potential drug targets for schizophrenia therapy since the remarkable improvement was shown in the clinical trials of Xanomeline, M_1/M_4 agonist. M_4 knockout mice information indicated the anti-psychotic effect of Xanomeline is derived from M_4 mAChR co-expressed with dopamine D_1 receptor. Therefore, selective M_4 mAChR agonist is expected to be a good anti-psychotic drug, but drug discovery of selective M_4 mAChR agonist is not easy due to high homology among mAChR subtypes. In order to find selective M_4 mAChR agonist, we have done the structure and activity relationship

study on 7-azaindolines and identified the candidate compound **1** , which has high selectivity for M_4 over M_1, M_2, M_3, and M_5. Compound **1** had a good PK profile and showed an efficacy against methamphetamine-induced hyperlocomotion in rats (ED50: 1.44 mg/kg, p.o.). Different from Xanomeline, **1** had no activity toward M_1, thus **1** is expected to have safer profile than Xanomeline. We will disclose the details of lead generation to structural optimization of our compounds.



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MEDI 141

Designing of potent and selective $\alpha_4\beta_2$ nicotinic acetylcholine (nAChR) antagonists from mixture based α-conotoxin combinatorial libraries for studying tobacco addiction

***Jayati Banerjee**, jbanerjee@tpims.org, Reena Gyanda, Yi-Pin Chang, Richard Houghten, Christopher Armishaw. Torrey Pines Institute for Molecular Studies, Port St Lucie, Florida 34987, United States*

The discovery of potent and selective nicotinic acetylcholine receptor (nAChR) antagonists is crucial for the design of safe and effective smoking cessation medications. α-Conotoxin GID is a non-selective $\alpha_4\beta_2$ nAChR peptide antagonist. The presence of two disulfide bonds in α-GID forms three intervening hypervariable loops of amino acids that can be systematically optimized to fine-tune nAChR selectivity. We have used a synthetic combinatorial strategy to develop GID analogs as potent and selective α4β2 nAChRs antagonists. Through direct pharmacological screening and deconvolution of mixture-based positional scanning synthetic combinatorial libraries (PS-SCLs) based on the three loops of α-conotoxin GID, we have identified potent amino acid residues that confer selective $\alpha_4\beta_2$ nAChRs. Second generation libraries of individual GID analogs derived from the active residues identified from PS-SCL screening were synthesized and screened accordingly, with several analogs showing increased potency and selectivity for $\alpha_4\beta_2$ nAChRs, with potential for developing therapeutics for treating tobacco addiction

MEDI 142

Selectively targeting nicotinic acetylcholine receptors with α-conotoxin mixture-based combinatorial libraries

***Yi-Pin Chang**, ychang@tpims.org, Jayati Banerjee, Reena Gyanda, Richard A. Houghten, Christopher J. Armishaw. Torrey Pines Institute for Molecular Studies, Port St. Lucie, Florida 34987, United States*

Tobacco addiction is a global public health problem. Nicotine addiction is mediated through the activation of multiple subtypes of nicotinic acetylcholine receptor (nAChR), among which the α4β2 and α3β4 subtypes have been identified as important targets for developing novel smoking cessation drugs. α-Conotoxins are disulfide-rich peptides isolated from venomous cone snails. They exhibit exquisite nAChR selectivity and represent excellent structural templates for developing novel pharmacological probes and drug leads. Here we present the synthesis and functional screening of positional-scanning synthetic combinatorial libraries based on key α-conotoxin structural frameworks against different nAChR subtypes. Libraries were constructed using the tea bag method with Boc-SPPS and the disulfide bonds formed by co-solvent assisted oxidative folding. Our data suggests that potent amino acid residues can be identified through iterative deconvolution, thus paving the way for the design of selective nAChR antagonists as chemical probes, with the potential to develop therapeutics for treating tobacco addition.

MEDI 143

Design, synthesis, and biological evaluation of novel cannainoid antagonist

***Abha Verma**, averma2@uno.edu, Sari Izenwasser, Mark L Trudell. Department of Chemistry, University of New Orleans, New Orleans, LA 70148, United States*

Cannabinoid receptor antagonists have been suggested to have potential utility as medications for cannabinoid abuse and psychostimulant addiction. Recent studies in our laboratories have shown that 1,5-diaryl-1,2,3-triazoles exhibit potent affinity (nM) for CB1 receptors. A series of 1,5-diaryl-4-substituted-1,2,3-triazole,derivatives have been successfully synthesized and evaluated at CB1 receptors. The [1,2,3]triazole ring system was readily assembled using click chem. to provide the unique 1,4,5-trisubstituted [1,2,3]triazoles in good yields. The lead molecule also showed high selectivity for CB1 receptor as compared to CB2 receptor. The synthesis, binding affinity and locomotor stimulant effects of novel diaryl-1,2,3-triazoles will be presented in this presentation.

MEDI 144

Design, synthesis, and biological evaluaton of 3--aryl--3--arylmethoxyazetdine derivatves at monoamine transporter ligands

Amber N Thaxton[1]*, athaxton@uno.edu, Mark L Trudell*[1]*, Sari Izenwasser*[2]*, Dean Wade*[2]*. (1) Chemistry, The University of New Orleans, New Orleans, LA 70148, United States (2) Psychiatry and Behavioral Sciences, The University of Miami Miller School of Medicine, Miami, FL, United States*

A series of 3-aryl-3arylmethoxyazetidine analogs were found to exhibit high affinity (nM) for the serotonin transporter (SERT) in rat brain tissue. A four- or five-step synthesis starting from 1-Boc-3-azetidinone was used for the construction of the novel azetidine derivatives. Binding studies for SERT and DAT were completed by competitive inhibition against [^{3}H]citalopram and [^{3}H]WIN 35,428 , respectively, in rat brain tissue. To date, the 3-phenyl-3-(3,4-dichlorophenyl)methoxyazetidine was found to exhibit the highest affinity and selectivity for SERT (K_i = 4.5 nM; DAT/SERT = 800). The synthetic details and preliminary SAR studies of the 3-aryl-3arylmethoxyazetidine scaffold at monoamine transporters will be presented.

MEDI 145

Design and synthesis of tetratcaine deriviatives as CNG channel blockers

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Cyclic nucleotide-gated (CNG) ion channels are important in the light transduction process of eyesight. A specific form of retinitis pigmentosa causes CNG channels to remain open, leading to a buildup of calcium in the cell that results in blindness. Potential treatments include ion channel blockers that bind inside open channels to regulate the influx of cations. Tetracaine has been shown to block CNG channels with moderate affinity and specificity. This research focuses on the design and synthesis of novel derivatives of tetracaine, in order to develop potent blockers of CNG channels, and to better understand the functional architecture of the pore. We will present results that include a series of molecules with electron-withdrawing groups incorporated on the central aromatic ring, as well as derivatives that vary the connectivity of the tail to the ring. Early results indicate that the acidity of the aniline amine is essential for blocking.

MEDI 146

Competition of β-methylamino-L-alanine (BMAA) with serine and other natural amino acids in Drosophila melanogaster

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Amyotrophic Lateral sclerosis/Parkinsonism-dementia complex (ALS/PDC) is a variant form of ALS. β-methylamino-L-alanine (BMAA), a non-natural amino acid produced by many species of cyanobacteria is associated with the cause of ALS/PDC. BMAA and an equivalent concentration of either serine or arginine, were fed to female age-matched Canton S fruit flies. We used three independent trials of ten Drosophila melanogaster per vial, per treatment. The control group were fed with a special gel-pellet containing: 1. Regular fly food (control); 2. BMAA alone (25 or 50 mM); 3. amino acid alone (25 or 50 mM); 4. the combination of equimolar BMAA and the tested competing amino acid. Viability and locomotor ability were measured over a 5-day acute period.. My results show serine and arginine rescue the acute loss of viability when co-fed with BMAA.

MEDI 147

Synthesis and biological evaluation of Alpha 5 GABAergic subtype selective ligand PWZ-029

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$GABA_A$ complexes are a class of receptors that respond to the neurotransmitter GABA the chief inhibitory neurotransmitter in the vertebrate CNS. A widely accepted pharmacological target for enhancing cognition is the benzodiazepine-binding site on the gamma-aminobutyric acid type A ($GABA_A$) receptor complex. Inverse agonists acting at a5 subunits containing GABAA receptors are thought to act as cognitive enhancers while eliminating unwanted side effects associated with non-selective compounds. From the recent work of Rowlett, Cook et.al. It was demonstrated that novel a5 selective inverse agonist PWZ-029 was evaluated as a cognitive enhancer in rhesus monkeys in the CANTAB paradigm. This ligand (PWZ-029) is about 60-fold more selective for the α5 subunit compared to α1,α2 and α3. It is demonstrated that PWZ-029 significantly attenuated scopolamine-induced impairment of contextual memory. In the ORD task, PWZ- 029 showed only a modest trend for enhancement of performance, but when task difficulty was increased by testing with difficult trials only, PWZ-029 robustly increased performance. In addition, PWZ-029 enhanced performance in the DNMS task using the 10 minute delay with distracters. This ligand also exhibited anxiolytic activity in some primates and was an orally active anticonvulsant in rats. $GABA_A$ receptor complexes that contain subunits are abundantly expressed in the hippocampus and therefore considered to be a therapeutic target for treating cognitive disorders, like Alzheimer and ADHD.

MEDI 148

Gabapentin hybrid peptides and bioconjugates synthesis and study of their interaction with TRPV1

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Gabapentin 1-(aminomethyl)cyclohexane acetic acid (Gbp, also known as Neurontin), a structural analog of g-aminobutyric acid (GABA), is effectively utilized for the treatment of neuropathic pain, however, it undergoes facile intramolecular cyclization to form the toxic five-membered cyclic lactam 2-aza-spiro[4,5]decan-3-one.

To stabilize conformationally constrained gabapentin, we carried out the construction of small peptidomimetics by *N*-acylation of Gbp with carbonyl activated *N*-protected amino acids and small peptides to acheive Cbz-*L*-Val-Gbp-OH, Cbz-*L*-Ala-Gbp-OH, Boc-*L*-Ala-*L*-Phe-Gbp-OH, Cbz-Gly-*L*-Ala-bAla-Gbp-OH.

Treatment of *N*-Boc-protected Gbp with *L*-valine methyl ester, *L*-pnehyl-*L*-tryptophan methyl ester and benzylamine gave Gbp conjugates. Analogous reaction was performed between *N*-Boc-Gbp and L-menthol, cholesterol, thiophenol and cysteinyl *L*-phenylalanine methyl ester.

Gbp conjugates were evaluated for binding the human capsaicin receptor (TrpV1) by homology modeling and molecular docking. These data suggest that novel Gbp conjugates may bind TrpV1 and inhibit its function in the sensation of pain without toxic effects that result from cyclization.

MEDI 149

Novel nitrotriazole-based piperazines 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 20 million people are infected by these parasites, resulting in 100,000 deaths per year. Despite the fact that in the past 20 years the number of incidences for HAT and Chagas has declined due to vector control initiatives, the number of cases in nonendemic regions such as the United States, Australia, Europe and Japan is on the rise. Drugs

currently used in the treatment of Chagas are old and problematic. We have found previously that 3-nitro-1,2,4-triazole-based aromatic and aliphatic amines demonstrate significant trypanocidal activity, in particular against *T. cruzi* amastigotes in infected L6 cells. Here we further evaluated *in vitro* the class of amines, including piperazines, as antitrypanosomal agents to establish additional SARs. All synthesized compounds were active or moderately active against *T. cruzi,* however 2 of them did not fulfill the selectivity criteria. Five derivatives were active or moderately active against *T.b. rhodesiense* while one derivative was moderately active against *L. donovani*. Thirteen out of 16 active compounds against *T. cruzi*, demonstrated selectivity indexes (toxicity to L6 cells/toxicity against *T. cruzi* amastigotes)from 116-1725 and were up to 39-fold more potent than the reference compound benznidazole. Detailed SARs will be presented.

MEDI 150

Synthesis, biological evaluation, and structure optimization of 4-oxo-5-cyano thiouracil derivatives as potent and selective small-molecule SecATPase inhibitors

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The urgent need for antibacterial agents cannot be undermined. With the emergence of multi drug-resistant bacteria or superbugs the need to develop drugs with novel mechanism of action or new targets is imperative than ever before. Some notorious examples of resistant pathogens include Methicillin-resistant *Staphylococcus aureus* (MRSA), β-lactum resistant (*Escherichia coli, Acinetobacter baumanii*) and vancomycin-resistant *Enterococci*. Several pathways are known to operate in bacteria for protein translocation. Of these, Secretion (Sec) pathway is most ubiquitous and is considered to be the most essential for survival. SecATPase is a central component of Sec pathway, and also a novel and attractive target for developing new broad spectrum antibacterial agents. We have achieved the design, syntheses and biological evaluation of entirely novel structural classes of small-molecule SecA inhibitors with nM inhibition.

MEDI 151

Structure-activity relationships of alkanediamide-linked bisbenzamidines as potential antimalarial agents

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We previously reported on the excellent anti-trypanosomal and anti-*pneumocystis carinii* activity of several bisbenzamidines linked with an alkanediamide chain. To further evaluate the potential anti-protozoal properties of these compounds, an expanded series of 15 alkanediamide-linked bisbenzamidines were synthesized and screened against *Trypanosoma cruzi*, *Leishmania donovani* and *Plasmodium falciparum* and their cytotoxicity towards rat skeletal myoblasts was determined. These compounds were the most active toward *P. falciparum* with nine of the compounds demonstrating IC_{50} values in the low nanomolar ranges. The details of the structure-activity relationship data for these compounds will be presented.

MEDI 152

Ion effects on peptidyl-tRNA hydrolase activity

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Peptidyl-tRNA Hydrolase (Pth) is a critical protein that recycles Peptidyl-tRNA formed as a result of premature termination of translation. Accumulation of Peptidyl-tRNA decreases the ability of the cell to produce viable proteins, quickly becoming fatal. The sequence for Pth is highly conserved across many bacteria, making Pth a promising target for antibiotic research. In order to cleave Peptidyl-tRNA, Pth requires the presence of a divalent ion. This divalent ion is believed to be used to activate water for use in the breaking of the C-terminal end of the peptide and the 2′- or 3′-hydroxyl of the ribose at the end of the tRNA. It has been found that Magnesium serves this function. The purpose of this research was to gain a deeper understanding of the mechanism of Pth and how its function would be affected by the presence of various ions and compounds.

MEDI 153

Inhibitors of iron-regulated heme oxygenase (HemO) of Pseudomonas aeruginosa as novel antivirulant agents

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During a bacterial infection, iron, a requirement for bacterial survival and virulence, is typically acquired from the host's heme-containing proteins. *Pseudomonas aeruginosa* has evolved two systems to take in heme from its environment; each pathway leads to the oxidative cleavage of heme by bacterial heme oxygenase (HemO), releasing $Fe^{3+}$and producing carbon monoxide and both δ- and β-biliverdin. Computational screens have identified several promising HemO inhibitor candidates, one of which is further optimized by structure-activity relationships of synthesized analogs. The binding affinities of the inhibitors were determined by *in vitro* and *in vivo* fluorescence assays.

The binding conformation of the inhibitors was studied by STD-NMR, and confirmed by computation docking studies. Further antimicrobial activity against mucoid and non-mucoid clinical isolates demonstrate the potential of these inhibitors with reduced risk of developed resistance in antimicrobial therapy.

MEDI 154

Design, synthesis, and evaluation of novel anti-CHIKV compounds

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Chikungunya virus (CHIKV) is a mosquito-borne pathogen responsible for major outbreaks of febrile arthralgia in humans. No antiviral treatment is currently available.

The viral genome encodes four non-structural proteins (nsPs), which could represent suitable antiviral targets. The nspP2 protein in particular is a protease essential for the formation of the mature nsPs.

A virtual screening study of a library of small molecule compounds, performed on the structure of a homology model of the CHIKV nsP2, allowed the identification of one hit which prevented virus-induced cell death at low μM concentration.

Optimisation studies guided the selection of structural analogues of the original active molecule, which were found to inhibit the virus cytotoxic effect in Vero cells.

Based on these results, different series of new derivatives were designed and synthesised. Inhibition of virus-induced cell death was evaluated for the new compounds and several showed μM activity.

MEDI 155

Antibacterial triazole-based amphiphiles: A click chemistry approach to biscationic amphiphiles

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Bis-alkylated biscationic amphiphiles such as dialkyl 4,4'-bipyridinium have demonstrated potent antimicrobial properties. Our studies have correlated their antimicrobial properties with the alkyl chain length and symmetry, noting that longer chains have greater antimicrobial properties until water solubility is decreased. With this knowledge we investigated bis-alkylated bicephalic amphiphiles rapidly prepared via the copper(I)-catalyzed azide-alkyne cycloaddition (“CuAAC click”) reaction. The aim of

these syntheses was to construct biscationic amphiphiles with head groups resembling a 3,3'-bipyridine core – altering the symmetry of the molecule in hopes of increasing water solubility and in turn antimicrobial properties. The “click” reaction proved useful in the synthesis of monoalkylated molecules from the linkage of in-situ generated alkyl azides with 3-ethynylpyridine, which were subjected to further alkylation.

MEDI 156

In vitro activity of nucleoside analogs on the veterinary protozoan parasite *Tritrichomonas foetus*

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*Tritrichomonas foetus*is the causative agent of bovine trichomoniasis, a disease characterized by infertility, early embryonic death, rare abortions and uterine infections in cows and heifers. Even though trichomoniasis is a reportable disease, there is no treatment. Based on our recent findings that *Ara*-F-Ado [9-(2-deoxy-2-fluoro-β,D-arabinofuranosyl)adenine] is a potent inhibitor of *T. vaginalis* (IC_{50}90 nM), we performed a structure-activity analysis in *T. foetus* on various adenosine and 7-deazaadenosine analogues. A*ra*-F-Ado was found to be an effective inhibitor of *T. foetus* with an estimated IC_{50} of 5-9 μM. From the 7-deazaadenosine compounds tested toyocamycin showed strongest inhibition of *T. foetus* (IC_{50}9.3 μM). *Ara*-F-Ado was also shown to be an inhibitor of the human protozoal parasites *Entamoeba histolytica* and *Giardia* with IC_{50}4.5 μM and 25 μM, respectively.

MEDI 157

Synthetic approach for 6'-deamino and hydroxyl analogs of carbocyclic sinefungin

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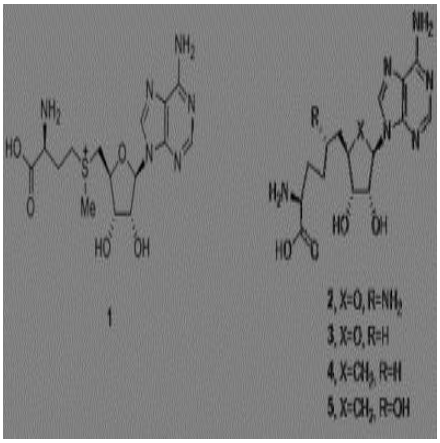
The significant antiviral properties of sinefungin (**2**), a structural analogue of AdoMet (*S*-adenosyl-L-methionine (**1**), have been attributed to its potent inhibition of viral mRNA methyltranferases. 6'-Deaminosinefungin (**3**), a simplified sinefungin analogue, has been found to be another efficient cofactor inhibitor of viral biomethylations. In the rational design of derivatives of **2** and **3** , as a means to improve their antiviral scope and reduce their associated cytotoxicity, two 6'-position modified carbocyclic sinefungins, 6'-deaminocarbocyclic sinefungin(**4**) and its hydroxyl analogue (**5**) were sought in our laboratories at Auburn. Synthetic approaches to these two compounds and their comparison will be presented. The synthesis of compound **4** and **5** were

completed in 7 and 13 steps, with 21% and 5.1% overall yield, respectively. Support from the Molette Fund and Auburn University is appreciated.



MEDI 158

Development of an ICI56,780 probe for mechanism of action studies

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With the exception of 8-aminoquinolines, very few antimalarial compound series have demonstrated activity against the exoerythrocytic (EE) stages in the liver as well as erythrocytic and gametocyte stages. Previously, it has been reported that quinolone ester ICI56,780 produced a radical cure (eradicate dormant EE parasites) in *Plasmodium cynomologi* infected rhesus monkeys, however, rapid induction of resistance hampered its further development. Many of these studies were conducted over 20 years ago without an adequate evaluation in current preclinical efficacy models or without assessing physicochemical properties of the compounds. Herein we describe a limited structure-activity relationship study on ICI56,780 analogues and the development of a photoaffinity probe to study the mechanism of action of ICI56,780. We are grateful to NIH (GM097118) for financial support.

MEDI 159

Design and synthesis of bacterial RNA polymerase inhibitors

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The increasing occurrence of multi drug resistant bacterial infections has underlined the urgent need for the development of new and more potent antibiotics.

Bacterial RNA polymerase (RNAP) is a validated target that allows efficacy and selective toxicity.

Unfortunately the efficacy of clinically used RNAP inhibitors (rifamycins) is threatened by the emergence of bacterial resistance.

The recent identification of the binding region of Myxopyronin B (MyxB), a natural product antibiotic, offered us the possibility to use a structure based design approach for the identification of new drug-like RNA polymerase inhibitors. A structure-based virtual screening on the MyxB binding region was performed and we identified two compounds which showed selective inhibitory activity towards *E. Coli* RNAP in the micromolar range. A SAR expansion programme based upon one of these active molecules has been undertaken in order to identify the factors determining potency and selectivity and the biological results will be presented.

MEDI 160

Synthesis and evaluation of peptidomimetic inhibitors of *Porphyromonas gingivalis* biofilm formation

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Porphyromonas gingivalis is a periodontal pathogen that initially colonizes the oral cavity by adhering to *S. gordonii* via interaction of the minor fimbrial antigen Mfa1 with a specific motif of the streptococcal SspB protein designated BAR. Synthetic peptides representing BAR function are potent inhibitors of *P. gingivalis* adherence/biofilm formation, but are costly to synthesize and are susceptible to proteolytic cleavage. Thus rationally-designed small molecule peptidomimetics of BAR that inhibit *P. gingivalis* adherence to *S. gordonii* may represent potential therapy. A small-molecule click chemistry strategy was used whereby the azide-bearing and acetylenic partners constitute trisubstituted oxazole and diaminotrazine frameworks respectively. Eight azide-bearing compounds were synthesized as mimics of the NITVK motif of BAR. Two compounds partially inhibited planktonic growth of *P. gingivalis* and three of the compounds were found active at varying levels in inhibition of adherence to streptococci. The synthesis of the heterocyclic click partners and the evaluation of their inhibitory efficacy will be presented.

MEDI 161

Identification of novel DprE1 inhibitors for the treatment of tuberculosis

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Mycobacterium tuberculosis (*M. tb*) is the leading cause of mortality due to a bacterial pathogen. The CDC estimates that about one third of the world's population is infected with *M. tb.* It is anticipated that there will be more cases of TB this year than any other point in history. Insufficient progress has been made in the treatment of TB in the last fifty years, which has allowed for the appearance of multidrug resistant strains (MDR-TB) and extensively drug-resistant strains (XDR-TB). One target that recently has shown promise is DprE1, an essential protein for viability. DprE1 is essential for the conversion of decaprenylphosphoryl-β-D-ribose (DPR) to decaprenylphosphoryl-β-Darabinofuranose (DPA),which is an essential component of the cell wall. DprE1 is highly conserved within mycobacteria and the lack of an alternative pathway makes DrpE1 a lucrative drug target.

Our approach to target DprE1 is two fold. The first method utilizes an activated Cys residue in the active site of DprE1. We have used the recently solved structure of DprE1 to construct a new class of electrophilic inhibitors that can covalently bind to DprE1. The feasibility of these compounds has been validated by a Kirby-Bauer disc diffusion assay. The second method uses a traditional class of non-covalent inhibitors. Using AutoDock Vina we have conducted a large virtual screen using a large library of small molecules obtained from the Zinc Database. The top computational hits were subsequently visually screened using PyMOL. The top hits from the visual inspection were then empirically evaluated using a Kirby-Bauer disc diffusion assay. Using this method we have been able to identify several promising new inhibitors.

MEDI 162

SAR studies on a series of reversible competitive inhibitors of cruzain from *Trypanosoma cruzi*

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The enzyme cruzain (EC 3.4.22.51) is the major cysteine protease of *Trypanosoma cruzi*, a parasite that causes a disease in humans called Chagas' disease. Cruzain is essential for the survival of the parasite and is involved in parasitic nutrition, replication,

and evasion of the host immune system. Current treatment options have low efficacy and serious side effects. Thus, there is an urgent need for new drugs to treat Chagas' disease. In this context, the goal of this work is the development of cruzain inhibitors applying a combination of medicinal chemistry approaches (*e.g.,* design, molecular modeling, synthesis, biochemical and biological evaluation). A series of synthetic analogs of a lead benzimidazole derivative (K_i = 2 μM, competitive inhibitor) was designed, synthesized and tested *in vitro* against the target enzyme. The detailed SAR results and *in vitro* anti-*T. cruzi* properties of these compounds will be presented.

MEDI 163

Fungal bis-naphthopyrones as inhibitors of botunlinum neurotoxin serotype A

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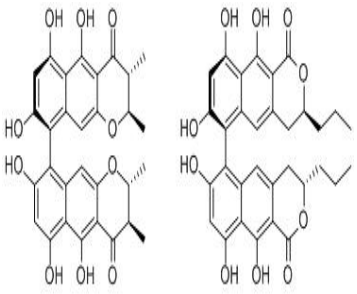
An in silico screen of the NIH Molecular Library Small Molecule Repository (MLSMR) of ~350,000 compounds and confirmatory bioassays led to the identification of chaetochromin A as an inhibitor of botulinum neurotoxin serotype A (BoNT/A). Subsequent acquisition and testing of chaetochromin A analogs uncovered two compounds with improved activity, talaroderxines A and B. These are the first fungal metabolites reported to exhibit BoNT/A inhibitory activity.



MEDI 164

***Trypanosoma cruzi* dihydrofolate reductase inhibitors: A potential Chagas disease treatment**

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Chagas' disease is a parasitic infection caused by *T. cruzi* that is currently endemic in Latin America. Current treatments using drugs, nifurtimox and benznidazole are accompanied with a high levels of toxicity. Although vector control and serological screening have significantly reduced the transmission, there is still an urgent demand for effective treatments. Our drug design strategy against Chagas' disease is focused on the dihydrofolate reductase activity of *T. cruzi* (TcDHFR) as a potential drug target. DHFR catalyzes the reduction of folate to dihydrofolate and to tetrahydrofolate by use of the cofactor NADPH. This biological process is essential for the survival of the parasite. Hence inhibition of TcDHFR is an attractive strategy for the development treatments for Chagas' disease. Our research is focused on developing inhibitors that are selective to TcDHFR compared to hDHFR. Design, synthesis and evaluation of several selective highly potent TcDHFR inhibitors will be presented.

MEDI 165

Synthesis and evaluation of novel combilexin-like molecules anchored by a minor groove binder

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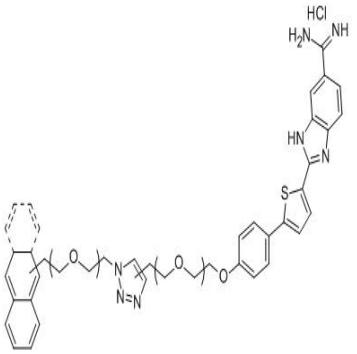
Trypanosomiasis and Leishmaniasis remain modern day scourges for tropical regions, particularly Africa, India, and South America. These kinetoplastida unicellular protozoa have kinetoplast DNA (kDNA) which contains many phased poly-AT sequences – a potential drug target. We report the synthesis of combilexin-like molecules with the potential to groove bind and intercalate kDNA (figure 1). These hybrid molecules contain a DNA minor groove binding fragment, DB818, linked to intercalating units using click chemistry. The combination of the AT binding ability of DB818 with intercalators has the potential to yield a new class of DNA recognition units and novel therapeutics. Preliminary DNA binding and biological data will be presented.



Monoamidine DB818-intercalator combilexin

MEDI 166

Molecular docking and structure-activity studies of functionalized fullerene nanoparticles as potential HIV-1 PR inhibitors

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This study is carried out to investigate the interactions of C_{60} derivatives with HIV-1 PR as possible effective substrates to deactivate the HIV-1PR. A series of 49 fullerene-C_{60} derivatives have been considered to explore the binding affinity. For this purpose a quantum-mechanical analysis has been performed, followed by QSAR model development and molecular docking. Eleven models have been developed (dataset was splitted to training set=43 and test set=6) to justify the results statistically. All models have shown a very good correlation, confirmed by r^2 and leave-one-out q^2 statistical parameters. The best QSAR model yielded a cross-validated r^2 value of 0.882. Docking calculations indicate that some of the fullerene derivatives form strong hydrogen bonds with the amino acid residues in the catalytic site of HIV-1PR, in addition to hydrophobic interactions of the fullerene core. The strengths and challenges of applied approaches will be discussed, and their comparative analysis will be presented.

MEDI 167

Novel hepatitis C virus entry inhibitors, part 1: The discovery and optimization of 2,4,6- substituted triazines as potent HCV entry inhibitors

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Successful treatment of HCV infection will likely require combination therapy with multiple inhibitors of different HCV targets to overcome resistance. As part of an effort to find new classes of anti-HCV drugs, a high throughput screening campaign identified a potent HCV entry-specific triazine-based inhibitor. In this presentation we describe the discovery and subsequent optimization of the hit compound N^2-(4-nitrophenyl)-N^4-pentyl-6-(2,2,2-trifluroethoxy)-1,3,5-triazine-2,4-diamine to provide a number of HCV entry inhibitors with low to sub-nanomolar activity against genotypes 1a and 1b. Details of the preparation of the inhibitors and their antiviral activities will be presented.

MEDI 168

Novel hepatitis C virus entry inhibitors, part 2: Trisubstituted triazines and pyrimidines

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Trisubstituted triazines derived from the screening lead N^2-(4-nitrophenyl)-N^4-pentyl-6-(2,2,2-trifluoroethoxy)-1,3,5-triazine-2,4-diamine were synthesized and characterized to assess their potential as inhibitors of hepatitis C virus (HCV) entry. Extensive investigation was performed on each substituting arm of the triazine ring and clear SARs were established for antiviral activity. Further study examined exchange of the nitrogen atom at position 3of the triazine core and the C-2 carbon atom of the aniline branch in N^2-(4-chlorobenzyl)-N^4-phenyl-6-(2,2,2-trifluoroethoxy)-1,3,5-triazine-2,4-diamine offered pyrimidine derivative N^4-(4-chlorobenzyl)-N^6-(pyridin-2-yl)-2-(2,2,2-trifluoroethoxy)pyrimidine-4,6-diamine which exerted only a minor impact on potency, revealing an unique isosteric relationship between the triazine-NH-benzene substructure and the 5-H-pyrimidine-NH-(2-pyridine) moiety.

MEDI 169

Novel hepatitis C virus entry inhibitors, part 3: Triazine- and pyrimidine-containing aryl amides

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A class of tri-substituted triazine and pyrimidine derivativeshas been characterized as hepatitis C virus (HCV) inhibitors that interfere with the viral entry process. Previous studies established the SARs associated with the substitution pattern of the triazine/pyrimidine core on antiviral activity. In this study, the impact of structural variation of the benzamide moiety was investigated. The results revealed that a variety of functional groups were tolerated and EC_{50} values reached sub-nM for optimized compounds. Additionally, subtle changes were found to lead to significant alteration of potency. For example, moving the two terminal methyl groups from the 1,3-propyl diamine moiety in 4-((4-((4-chlorobenzyl)amino)-6-(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)amino)-N-(3-(diethylamino)propyl)benzamide to the middle of the 1,3-propyl diamine fragment, as in 4-((4-((4-chlorobenzyl)amino)-6-(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)amino)-N-(3-(dimethylamino)-2,2-dimethylpropyl)benzamide, led to an improvement of 4-6 fold in activity against genotype 1a/1b HCV subtypes.

MEDI 170

Novel hepatitis C virus entry inhibitors, part 4: The discovery of acyclic acylsulfonamide-bearing triazines as potent HCV entry inhibitors

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In this presentation, we describe the synthesis and SAR of a series of acyclic triazines which function as entry inhibitors of the hepatitis C virus. An early lead in this series, 4-(4-(1-(4-chlorophenyl)cyclopropylamino)-6-(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-ylamino)benzoic acid, served as the starting point for optimization. These SAR studies led to the identification of an acylsulfonamide series in which the acylsulfonamide moiety serves as a replacement for the carboxylic acid present in the early lead. A number of compounds from this chemotype displayed enhanced inhibitory activity toward genotype 1a and 1b virus infectivity when compared to the parent series. The details of these findings will be described.

MEDI 171

Novel hepatitis C virus entry inhibitors, part 5: From acyclic to macrocyclic structures

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The first macrocyclic structure derived from the hepatitis C virus (HCV) entry inhibitor 3-((4-(pentylamino)-6-(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)amino)benzamide, prepared*via* ring-closure of the pentylamino group and the benzamide moiety using a methylene spacer, demonstrated activity only against genotype 1b infectivity. This observation was hypothesized to be due to the macrocycle restraining the phenyl ring from freely adjusting its conformation to that required for activity against genotype 1a virus. Enlargement of the macrocycle ring combined with the introduction of functional groups at C-4 of the phenyl ring, generated compounds with excellent activities towards both genotype 1a and 1b HCV. An alternate valid strategy switched the 1,3-ring junction to a 1,4-ring junction on the phenyl ring, allowing the phenyl group to freely rotate along its 1,4-axis as an approach to modulating its conformation.

MEDI 172

Novel hepatitis C virus entry inhibitors, part 6: Synthesis and SAR of a series of potent macrocyclic triazine derivatives as pan-genotypic HCV entry inhibitors

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Central to an effort to optimize a series of functionalized acyclic triazine derivatives which are potent inhibitors of hepatitis C virus (HCV) entry, we designed and synthesized a series of macrocyclic triazines. These macrocycles provided a significant improvement in potency against genotype 1a and 1b virus infectivity while also expanding genotype coverage to include genotypes 2-6. These pan-genotypic inhibitors were constructed by the introduction of an alkylamine-based linker between the hydroxyl group and carboxylic acid motif of 2-((4-carboxyphenyl)amino)-4-((4-hydroxybenzyl) amino)-1,3,5-triazine using what proved to be an efficient macrocylization strategy. Details as to the preparation of development of SAR in this macrocycle series will be described.

MEDI 173

Novel hepatitis C virus entry inhibitors, part 7: The role of tether conformation on pan-genotype potency

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Triazine macrocycles represent a class of potent inhibitors of the hepatitis C virus (HCV) entry pathway. A parent compound in this class demonstrates EC_{50} values of < 25 nM for HCV genotypes 1a, 1b, 2a, 2b, 3a, 4a, and 5a. To interrogate the role of tether conformation on pan-genotype potency, analogs of the parent compound were prepared in which placement of a phenyl ether subunit was modulated. Two analogs representing placement of this subunit both more proximal and more remote to the triazine core demonstrated potency similar to the parent compound. Conformationally more constrained analogs demonstrated a loss in potency. Computational modeling was used to identify conformationally conserved regions of the macrocycle and to provide insight into the trends in potency.

MEDI 174

Development of small molecule cyclophilin inhibitors

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Peptidyl-prolyl *cis-trans* isomerases (PPIases) are a class of enzymes that convert the *cis* isoform of a proline residue within a peptide to its more stable *trans* isoform. PPIases are divided into three families: cyclophilins, FK506 binding proteins (FKBP's), and parvulins. There are 17 isoforms of cyclophilins present in humans which mediate a variety of biological functions. Cyclophilin A has been studied as a potential target to prevent human immunodeficiency virus type 1 (HIV-1) and hepatitis C virus (HCV) infection and virion packaging. Acylureas,are literature compounds presented as potent (single digit nanomolar) cyclophilin A inhibitors. The 2,6-dichlorobenzene ring is perpendicular to the acyl urea due to a large rotational barrier resulting from the two chlorine atoms. Design, synthesis, and testing of these rotationally restricted amides will be presented.

MEDI 175

Improving exposure of ACC inhibitors via a prodrug strategy

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Acetyl CoA Carboxylase (ACC) is a key lipid handling enzyme involved in the processes of both fatty acid oxidation (FAO) and de novo lipogenesis (DNL). ACC inhibition therefore offers a potentially novel approach to the treatment of metabolic diseases and type 2 diabetes. In our search for novel inhibitors of ACC, we identified molecules with significant in vitro activity, but were plagued by poor absorption when delivered orally, making assessment of pharmacodynamic outcomes unreliable. The team then applied a prodrug strategy to improve plasma exposure of parent drug. We hereby detail the synthesis and pharmacokinetic evaluation of a number of prodrugs, all of which improved plasma exposure of the corresponding parent alcohol. Species differences between the prodrugs will also be discussed.

MEDI 176

Design of novel and selective SIRT6 inhibitors with a structure-based approach

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SIRT6 is a member of the sirtuin family and has been recently shown to be crucial for a number of processes including telomere maintenance, DNA repair and genome stability, regulation of inflammatory cytokines and epigenetic control of acetylated histones. No selective inhibitors of SIRT6 exist yet.

In this work we report on a structure-based drug design (SBDD) approach aimed at targeting the catalytic pocket. By virtual screenings of large compound collections we identified new drug-like inhibitors of SIRT6 with IC_{50} values in the low-micromolar range concentration and good selectivity profiles against other sirtuins (SIRT1 and SIRT2). New families of compounds able to inhibit SIRT6 hold promise as a means to sensitize cancer cells to chemotherapeutics and/or as anti-inflammatory agents.

MEDI 177

Activation of SIRT1 by 2,8-disubstituted quinolines: SAR and physicochemical properties

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The sirtuins are an ubiquitous, highly conserved family of seven NAD^+-dependent deacylases (SIRT1-7) that may have evolved as cellular energy sensors. Mammalian SIRT1 regulates key metabolic and inflammatory pathways by deacetylating several endogenous substrates including PGC-1a, NF-kB and FOXO transcription factors. Increasing SIRT1 activity by overexpression or chemical activation has shown protection against various disease states including diet-induced insulin resistance, suppression of tumors, and improvement in cardiac and vascular function. Sirtris has developed small-molecule SIRT1-activating compounds (STACs) that modulate metabolic and inflammatory disease markers in rodent models. Evolution of the chemical scaffolds initially identified through high-throughput screening has led to compounds in structurally distinct series that increase SIRT1 deacetylase activity. The quinoline series will be discussed, including SAR and optimization of physicochemical properties. SIRT1 activation by two distinct quinoline frameworks, differing in connectivity of the substituents to the quinoline core, highlights the importance of side chain proximity for SIRT1 activation.

MEDI 178

Synthesis and biological evaluation of diaryl ether cannabinoids

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A class of novel compounds consisting of a diaryl ether scaffold has exhibited affinity for the cannabinoid CB_1 receptor. In order to understand structure-activity relationships (SARs) of these compounds, several synthetic methods have been developed to produce general diaryl ether scaffolds that could be further modified to yield potentially therapeutic cannabinoids. An early result of these experiments was the discovery of AMS167, a novel high-affinity (K_i = 1.2 nM) CB_1 receptor neutral antagonist. Modified versions of this lead compound have been synthesized and we are currently awaiting bioassay results. Additional novel diaryl ethers have been proposed (and synthesized), though pending bioassay results will have the greatest influence on the future course of this project. Future goals of this project involve further manipulation of the diaryl ether

scaffold, including fusing the structures into planar dibenzofuran analogs and incorporating other aromatic heterocycles, such as indole, into the scaffold.

MEDI 179

Evaluation of lipolytic effect of pehnyl propanolamine derivatives in adipocytes

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The prevalence of obesity is increasing at an alarming rate, but, unfortunately, only a few medications are currently on the market. Attempts are been made to synthesize the molecules for anti-obesity effect. Thermogenesis is one of the major strategies worked for synthesis and evaluation of anti-obesity molecules. β-3 receptor agonists are studied in the past for their thermogenic and lipolytic activity. Phenyl ethanolamine derivatives are very well studied for their anti-obesity property via activation of β-3 adrenergic receptor. In the present study, new phenyl propanolamine derivatives were synthesized by the Mannich reaction and successively by reduction. The synthesized molecules were screened for their lipolysis activity at 25μM and 50μM concentrations in the mature adipocytes nor epinephrine was used as positive standard. Cytotoxicity study of the compounds on the mature adipocytes was carried out using MTT assay. Results indicate that all the synthesized molecules were active for lipolysis on adipocytes.

MEDI 180

Discovery of aryl sulfamides as elovl-6 inhitibors

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Elovl6, a member of long chain fatty acid elongase, is a microsomal enzyme, which is responsible for the elongation of saturated and unsaturated long chain fatty acids and has an important role in regulation of lipid metabolism. The improvement of high-fat diet induced insulin resistance in the elovl6 deficient mice suggest that elovl6 inhibitor has possibility to be a new target for the treatment of metabolic disorders such as insuline resistance, diabetes and cardiovascular. In this presentation, we will present the discovery of a novel series of 3-susbstituted phenylsulfamides as elovl6 inhibitors. The details of the structure-activity relationships, DMPK profiles and the effect on the elongation index of fatty acids (C16/C18 ration) in mice liver will be discussed.

MEDI 181

1'-Acetoxychavicol acetate, a TRPA1 agonist, suppresses obesity due to high energy diet in mice

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We are searching for food components preventing obesity by enhancing energy metabolism. We focus on compounds which activate thermosensitive TRP (transient receptor potential) ion channels. TRPA1 is cold sensor candidate. Here we investigated whether 1-acetoxychavicol acetate (ACA), a TRPA1 agonist and pungent principle of galangal, can suppress body fat accumulation in mice due to high energy diet. TRPA1 activity for racemic and *S*-form of ACA showed similar EC_{50} values and maximum responses in TRPA1-expressing cells. Next, C57BL/6J male mice were fed a high-fat, high-sucrose diet. Racemic ACA was added at 0.025 and 0.05% level. After 1 month of feeding, total energy intake were equal. Visceral fat weights decreased significantly. Blood glucose concetration was lower in both ACA groups. Expression of uncoupling protein 1 in interscapular brown adipose tissue increased in both ACA diets. These results indicate that ACA can suppress visceral fat accumulation.

MEDI 182

Thiadiazoles as new inhibitors of diacylglycerol acyltransferase type 1

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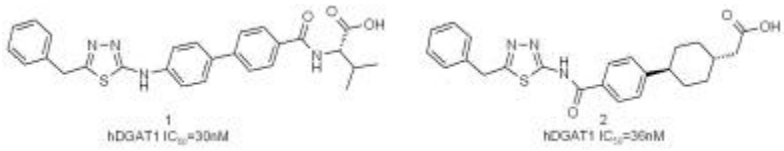
Triacylglycerides (TG) are the principal form of energy storage in eukaryotes. An imbalance in the metabolism of triacylglycerides can participate in the pathogenesis of several metabolic disorders such as obesity, insulin resistance and type 2 diabetes.[1]

We aimed to identify new DGAT-1 inhibitors by combining ligand-based modeling from known DGAT-1 inhibitors, High Throughput Parallel Synthesis (HTPS) and rescaffolding chemistry to generate leads amenable to optimization. Three lead series were thus found with IC_{50}s below 100 nM in a DGAT-1 enzymatic assay.

The most potent inhibitors belonged to a 2-aminothiadiazole series represented by compound **1** which displayed an IC_{50} of 30 nM in the enzymatic assay.

Pharmaco-modulation allowed the discovery of compound **2** , a new very potent heterocyclic DGAT-1 inhibitor.[2]



Synthesis, structure-activity relationship, molecular modelling and biological data will be presented in this poster.

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MEDI 183

Discovery of adipamides as small molecule NPY Y4 receptor agonists

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The NPY Y4 receptor is a class A G-protein coupled receptor, located primarily in the gastrointestinal tract and to a lesser extent in the brain. The endogenous ligand for the receptor is pancreatic polypeptide (PP), a gut hormone which is released in pancreatic islets in response to nutrient ingestion. Several lines of evidence, including studies with mice over expressing PP and PP treatment of patients with Prader-Willi syndrome (a condition characterized by hyperphagia and morbid obesity), demonstrate PP's anorectic effects and suggest that agonists of the Y4 receptor may potentially be useful in treating obesity.

PP, a 36 aminoacid peptide with a short half-life (~ 6 min in plasma), is not an ideal drug candidate. There are no small molecule Y4 agonists reported in the literature. To date, discovery and development of orally bioavailable, small molecule Y4 agonists has remained a challenge. Through HTS of the BMS compound collection, a disulfide molecule was identified to have Y4 agonist activity. Optimization studies of this hit led to

discovery of adipamide derivatives as potent and selective Y4 receptor agonists. The SAR and profiles of this series will be presented.

MEDI 184

Design and synthesis of novel heterocycle-based inhibitors of plasminogen activator inhibitor-1

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Plasminogen activator inhibitor-1 (PAI-1) is an endogenous serine protease inhibitor, pathologic levels of which have been implicated in a variety of conditions, including atherosclerosis, myocardial infarction, type 2 diabetes, and cancer. The development of potent and selective inhibitors of PAI-1 has therefore become a priority. A variety of novel compounds based on a heterocyclic core have been synthesized and found to be potent and selective inhibitors of PAI-1. The design, synthesis and structure-activity relationships of these compounds with PAI-1 will be discussed.

MEDI 185

Synthesis and characterization of Arg-Gly-Asp (RGD) peptidomimetics functionalized onto gold nanoparticles

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One of the challenges for developing therapeutic nanoparticles involves attaching appropriate chemical moieties that will target cells that overexpress specific surface receptors. We have initiated a project to design and prepare functionalized gold nanoparticles (AuNPs) that selectively target cancer cells that overexpress the integrin $\alpha_v\beta_3$receptors. We have devised a convergent strategy that uses novel, multivalent RGD peptidomimetics attached to the AuNP surface as a means for enhancing cellular selectivity, affinity and uptake. In this study, we describe the synthesis of a novel RGD peptidomimetic, its ligation to a Newkome-type dendron and its attachment to AuNPs. The characterization and evaluation of the functionalized AuNPs will be discussed.

MEDI 186

Generating novel aryl thiazole based inhibitors of TMEM16a

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Development of TMEM16A modulators is useful to probe the basic biochemical and biophysical characteristics and physiological functions of this relatively new class of chloride channels. TMEM16a inhibitors decrease CaCC function in vascular smooth muscle cells, relaxing murine and human blood vessels, providing support for TMEM16a as an anti-hypertensive drug target. TMEM16a inhibitors have recently been shown to inhibit proliferation of pancreatic cancer cells, demonstrating new potential for anti-cancer applications. It has also been shown that TMEM16a mRNA and protein are highly expressed in LNCaP and PC-3 cells, implicating the possibility that TMEM16a is involved in prostate cancer.

Prof. Alan Verkman screened roughly 110,000 compounds and discovered that there were four classes of molecules that inhibited TMEM16a with an IC_{50}<10μM. *The central hypothesis of this project is to explore the chemical structure of the aryl thiazole lead inhibitor scaffold, to generate new inhibitors with improved potency of IC_{50}<1μM.*

MEDI 187

Molecular docking, in silico structure-based design, and kinetic evaluation of D-Phe-Pro-D-Arg-derived direct thrombin inhibitors

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New peptidic non-covalent direct thrombin inhibitors (DTIs) were designed by generating peptide lead compounds derived from the substrate sequence Phe(P3)-Pro(P2)-Arg(P1). The free energy of interaction between each ligand and thrombin was calculated with the built-in molecular mechanics force field (MMFF) provided by the docking software *SCULPT* (Accelrys). During the original screening, the hexapeptides [D-Phe(P3)-Pro(P2)-D-Arg(P1)-P1¢-P2¢-P3¢-$CONH_2$] and pentapeptides [D-Phe(P3)-Pro(P2)-D-Arg(P1)-P1¢-P2¢-$CONH_2$] were used as scaffolds for developing the optimized final tetrapeptide lead sequence, D-Phe(P3)-Pro(P2)-D-Arg(P1)-P1¢-$CONH_2$. Once the lead tetrapeptide scaffold was found to have higher affinity for thrombin than the hexa and pentapeptides, based on structure-activity relationship (SAR) studies on thrombin inhibition conducted *in vitro*, new peptide candidate inhibitors were further designed as derivatives of the tetrapeptide motif D-Phe(P3)-Pro(P2)-D-Arg(P1)-P1¢-$CONH_2$. Trials for optimization of P3 position were further performed with nonnatural amino-acids, such as D-3,3-di-Phenylalanine, trans and dihydrocinnamic acids, (L)/(D)-Tic [1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid], (L)/(D)-Thi [Thienylalanine] and D-Naphthylalanine (D-Nal). The thrombin:peptide complex was minimized using the *SCULPT* built-in molecular mechanics force field (MMFF94). After each round of

minimization, the free energy of interaction (scoring function) was assessed using both Van der Waals and electrostatic force fields. Preliminary kinetics for in vitro inhibition of alpha thrombin cleavage of the chromogenic substrate S2238 established a new structure-activity relationship (SAR) for the tetrapeptides with new unnatural aminoacids at (P3) position.

MEDI 188

Cooperative contributions of ligand groups to binding affinity: Two new types of ligand functional group cooperativity demonstrated with thrombin inhibitors

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There is currently an insufficient understanding of some of the intermolecular factors that control the thermodynamics of ligand binding. One such factor is the potential cooperative contribution of ligand groups to binding affinity. In previous studies we revealed a positive ligand group cooperativity between a hydrogen bond and aliphatic side chains for a series of thrombin inhibitors, as well as a water-mediated positive cooperativity between a thermolysin inhibitor carboxyl group and an aliphatic side chain. In the present study, using thrombin as a model system, we present two new types of ligand functional group cooperativity within inhibitors. The first type is a demonstration of positive hydrophobic-hydrophobic side chain cooperativity and the second is positive cooperativity among hydrogen bonding ligand groups. Understanding, and quantifying, various types of cooperativity, as we are doing with model systems, is important to provide a foundation for developing improved scoring functions.

MEDI 189

Design, syntheses, and characterization of novel chlorin photosensitizers for photodynamic therapy

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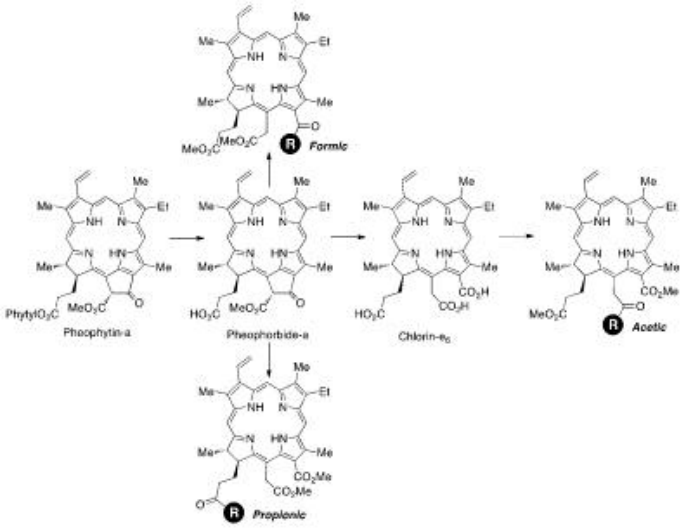
Photodynamic therapy capabilities of chlorophyll derivatives have proven to have advantageous biological effects depending on the presence and position of certain amino acid residues. In the present work, a number of chlorin-e_6 derivatives were synthesized and characterized. Different regioisomeres of mono-L-aspartyl chlorin-e_6 and mono-L-lysine chlorin e_6 were synthesized starting from pheophytin-a, extracted from *Spirulina* alga.



Syntheses of chlorin-e6 regioisomers, photo-cytotoxicity and dark-cytotoxicity evaluations have been completed for compounds in which all three acidic side chains in chlorin-e_6 have been conjugated.

MEDI 190

Structure based approach to silence transcription by targeting the major promoter region G-quadruplex formed in the PDGFR-β gene

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Overexpression of the platelet derived growth factor receptor β (PDGFR-β) has been associated with various types of cancers and fibrotic disorders. In addition, the PDGFR-b signaling pathway has been implicated as an important target for the treatment of cancer in both animal models as well as in clinical trials. Intriguingly, a guanine-rich nuclease hypersensitive element (NHE) was identified in the proximal promoter region of the PDGFR-β gene. This region was found to be crucial for basal transcription levels and forms multiple G-quadruplex structures. There is evidence that formation/stabilization of these G-quadruplexes downregulates transcription. Using NMR spectroscopy, we have determined the fold of the most thermodynamically stable and thus the most likely biologically relevant structure, the Mid-5' G-quadruplex. This structure has three stacked G-tetrads, and is primarily parallel-stranded with a broken-ended strand resolved in a snap-back structure. Potential capping interactions with the 5' flanking sequence as well as the 5-nucleotide loop are unique features that can be

exploited as prospective targets for drug interactions. Currently, the screening and identification of Mid-5' PDGFR-β G-quadruplex interactive molecules are underway.

MEDI 191

Highly sensitive and rapid detection of carbon nanotube-based biosensors using immune binding reaction

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The field effect transistor (FET) based on a network of single-walled carbon nanotubes (SWCNTs) that can perform sensitive and selective real-time monitoring of target analytes are tremendously valuable for various sensing applications. Here carbon nanotube–field effect transistors (CNT–FETs) were functionalized with antibody-binding fragments as a receptor, and the binding event of specific target antigen onto the fragments was detected by monitoring the gating effect caused by the charges of the target antigen. We were able to lower the detection limit to a protein concentration of 100 ng/mL, without cutting antibody or labeling the target proteins. Our results show that there is good correlation between the two platforms with respect to detecting analytes.

MEDI 192

Synthesis and characterization of isoquinolines

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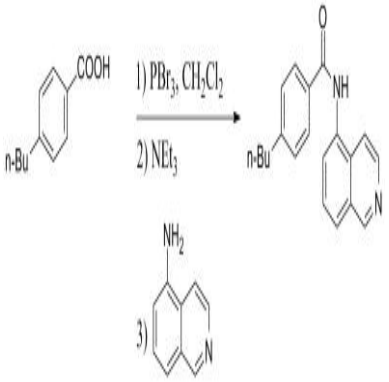

Researches on prostate cancer have shown that increased levels of androgens are the primary reason for being prostate cancer. In this respect, hormone therapy is generally preferred to treat prostate cancer, because inhibition of the target enzyme might be resulting in the total blockage of androgen biosynthesis in adrenal glands and testes. Many studies have indicated that CYP-17 enzyme catalyzes the last step of the androgen production; therefore, CYP-17 enzyme was selected as the primary target enzyme for the treatment of prostate carcinoma. In this project, synthesis of isoquinoline derivatives as part of larger drug molecules potentially active against prostate cancer was targeted. All transformations of isoquinoline derivatives were verified with NMR data.

MEDI 193

Effects of Ranitidine on insulin and lime: Induced gastric secretion in Wistar albino rats

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The effect of a relative H_2 – receptor blocker, ranitidine on insulin and lime - induced gastric acid secretion was evaluated in selected wistar Albino rats (male and female). The rats were divided into three groups of lime juice, insulin and control and were analyzed using Gosh and Schild method. In this study, the first group was perfused with lime solution (25% v/v, 50% v/v, 75% v/v and 95% v/v) and was used to modify the secretory rates of the parietal cells. The mean basal secretion was increased from 22.80 ± 5.14 mMol/L/hr to 54.34 ± 5.14 mMol/L/hr while Ranitidine (zantac) injected intramuscularly decreased mean secretion from 54.34mMol/L/hr to 35.53±5.14 mMol/L/hr. Insulin (40 IU/kg) was administered intravenously to the second group of rats, the mean basal secretion increased from 8.01 ± 0.67mMol/L/hr to 9.98± 0.6mMol. Ranitidine was administered intramuscularly and that caused a significant decrease in the mean secretion from 9.98 ± 0.6mMol/L/hr to 8.49 ± 0.42mMol/L/hr. Generally, results obtained from this study indicated, a higher insulin inhibition for ranitidine over

lime and was statistically significant. Lime and insulin are gastric acid agonists as opposed to ranitidine; hence, Ranitidine could pose a good candidate for ulcer treatment. Sex differences and implications are also underscored.

MEDI 194

Enzymes to control bacterial biofilm formation

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Biofilms on medical devices cause more than 65 % of the hospital-acquired infections. Moreover, in biofilm mode of growth, bacteria resist the conventional antimicrobial treatments. The ability of the pathogens to invade, overcome defense mechanisms, cause infection and biofilm formation is controlled by a regulatory mechanism known as quorum sensing (QS). Small hormone-like molecules called autoinducers (AIs) regulate the QS. Consequently, modulation of these QS signals has emerged as a potential strategy for prevention of biofilm formation and bacterial virulence. In this study, the degradation of QS signals and extracellular polymer substances (EPS) from the biofilms was evaluated. The degradation kinetics of model and biofilm-extracted AIs and EPS was determined in the presence of quorum-quenching and EPS-degrading enzymes (acylase, lactonase and oxidoreductas, α-amylase and proteases). These enzymes efficiently decreased the biofilm formation of several medically relevant bacterial species, such as *P. aeruginosa, B. subtilis, S. aureus* and *E. coli.*

MEDI 195

Metabolomics study of antistasis effects of dragon's blood based on GC-MS

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Metabonomics was more and more concerned in pharmacy studies, especially the traditional Chinese medicine which is also a holistic approach. Dragon's blood is a famous traditional Chinese medicine (TCM) since ancient time. The most important usage of the drug is in the treatment of blood stasis syndrome which is a common pathological syndrome in the elderly. Blood stasis syndrome is a significant pathological syndrome in TCM treatment theory. In the present work, an acute stasis rat model was established and confirmed by hemorheological examination. Then a metabolomic approach was applied to study the influence of dragon's blood on metabolic changes of the acute stasis rats. PLS-DA of the serum GC-MS fingerprints allowed discrimination of the controlled, stasis model, and stasis rats after administration of dragon' blood. And several significantly difference metabolites were found and identified including lactic acid, pyroglutamic acid, citric acid, glutamic acid, creatinine.etc.

MEDI 196

Overview of the nitric oxide pathway in drug discovery in the CNS and periphery

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NO signaling can be cGMP-dependent or cGMP independent, the latter not involving activation of soluble (or NO-sensitive) guanylyl cyclase (sGC). NO signaling in drug discovery has been dominated by the early association of NO and nitrovasodilators with smooth muscle relaxation in the vasculature and hence cardiovascular, cardiopulmonary, and coronary indications. The prostaglandin-like effects of NO in the GI tract have also infiltrated mainstream thinking for gastroprotective prodrugs. Similarly, NO toxicity resulting from upregulation of inducible nitric oxide synthase (NOS2) and neurotoxicity putatively caused by the corybantic interplay of glutamate and NOS1 have influenced thinking on whether to inhibit or supplement NO in therapy. Firstly, examples will be presented on the use of NO-donor drugs in the less studied vista of NO/cGMP in the CNS: 1) NO-chimeras that reduce levels of neurotoxic amyloid-β (Aβ) and restore cognition in Alzheimer's animal models; 2) hybird nitrate NO-SSRI's that speculatively may have no therapeutic lag; 3) hybrid NO-flurbils that stimulate Aβ clearance; and 4) neuroprotective peptidomimetic furoxans. Stimulation of NOS3 by estrogens will be compared with NO-SERMs, chimeric selective estrogen receptor modulators that are procognitive and anti-thrombotic even in the presence of attenuated NOS3 function associated with aging. Secondly, comparison will be made between NO-donor strategies and the use of novel, brain-bioavailable, NO-independent sGC activators and inhibitors in the CNS. Finally, we will remind ourselves that NO-donor bioactivation and bioactivity remains poorly understood, by reference to the biology and forgotten chemistry of aspirin hybrid nitrates that have been pursued in cancer therapy and chemoprevention.

MEDI 197

Selective inhibitors of neuronal nitric oxide synthase

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Nitric oxide synthase (NOS) is a family of homodimeric enzymes that catalyzes the oxidation of *L*-arginine to *L*-citrulline and nitric oxide (NO). The constitutive endothelial isozyme (eNOS) produces NO involved in the regulation of smooth muscle relaxation and blood pressure and in the inhibition of platelet aggregation. A second constitutive isozyme, neuronal NOS (nNOS), makes NO that is important for neurotransmission. A third isozyme, inducible NOS (iNOS), is located in activated macrophage cells and acts as a cytotoxic agent in normal immune responses.

NO overproduction by nNOS has been associated with neurodegenerative diseases, such as Parkinson's, Huntington's, and Alzheimer's diseases, stroke, and cerebral palsy. Compounds that inhibit nNOS decrease the production of NO in the brain. However, because of the importance of NO to physiological functioning, potent as well as nNOS-selective inhibitors are essential. This lecture describes the design of potent and highly dual-selective nNOS inhibitors and their modification for enhanced potency, selectivity, and lipophilicity.

MEDI 198

Therapeutic potential of targeting endogenous inhibitors of nitric oxide synthesis

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Asymmetric dimethylarginine (ADMA) — a naturally occurring amino acid that is a product of protein breakdown — is released into the cytoplasm following the post-translational methylation of arginine residues within proteins and the subsequent proteolysis of these arginine-methylated proteins. ADMA inhibits all three isoforms of nitric oxide synthase and therefore has the potential to produce diverse biological effects, particularly in the cardiovascular system. In addition to its renal clearance, endogenously produced ADMA is metabolized to !-citrulline and dimethylamine by the dimethylarginine dimethylaminohydrolase (DDAH) enzymes. Pharmacological modification of DDAH has therefore been proposed as a mechanism for manipulating endogenous ADMA concentrations and regulating the production of nitric oxide in situations where alterations in nitric oxide signalling have been shown to contribute to pathophysiology. In this presentation I will describe the biology of ADMA and the potential therapeutic utility of inhibiting DDAH activity in disease states where excessive nitric oxide synthesis contributes to pathology.

MEDI 199

Discovery of nitric oxide-donating prostaglandin F2α analogs for the treatment of glaucoma

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Nitric Oxide (NO) plays an important role in modulating intraocular pressure (IOP), a major risk factor for glaucoma. Constitutive NOS are found in many ocular tissues including those regulating inflow and outflow. Administration of compounds stimulating the NO-cGMP pathway or overexpression of eNOS lead to increases of outflow resulting in IOP lowering.

Currently, there are no IOP lowering drugs acting through the NO-cGMP pathway. Data suggests that NO-donors may decrease IOP through the conventional outflow route complementary to the uveoscleral pathway used by PGF 2α analogs. We designed new

compounds targeting both NO donation and activation of PGF 2α (FP) receptors. Herein, I present synthetic efforts on latanoprost isopropylester (Xalatan) analogs where the isopropyl moiety was replaced with linkers bearing one or two nitrates. The compounds were tested in glaucoma models. BOL-303259-X showed potent IOP lowering in phase 2 studies. Nicox's partner Bausch + Lomb is advancing BOL-303259-X into phase 3.

MEDI 200

Nitric oxide donating angiotensin II receptor antagonists for the treatment of hypertension

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Angiotensin II receptor antagonists (ARBs) are widely used antihypertensive agents with excellent tolerability and evidence for reduction of the risk of fatal and non-fatal stroke. Nitric oxide (NO) has many vascular actions and commercially available nitrates (e.g. isosorbide mononitrate) are indicated for the treatment of angina but not for blood pressure (BP) control despite being effective in lowering BP, particularly systolic BP. A potential for additive or synergistic effect of the two agents is supported by preclinical and clinical studies suggesting the involvement of the angiotensin II type 1 receptor (AT1-R) in endothelial dysfunction and interactions between RAAS and NO signaling pathways. As part of a joint research program with NicOx, we have sought to demonstrate that linking of NO donors to ARBs will deliver superior BP lowering and may also impart the many beneficial cardiovascular (CV) effects of NO leading to greater CV event reduction. This presentation will cover the design, synthesis and biological evaluation of a novel series of NO-ARBs.

MEDI 201

Soluble guanylate cyclase (sGC) stimulators as an emerging treatment for cardiopulmonary disease

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Nitric oxide (NO) is a key signaling molecule that is involved in the regulation of a variety of biological and physiological processes in mammals. Organic nitrates (such as glyceryl trinitrate) and other NO-donor or nitrovasodilator drugs that release NO by spontaneous decomposition or bioconversion activate soluble guanylate cyclase (sGC) which converts guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP). Such drugs have a long and distinguished heritage in the treatment of cardiovascular disease. However, they have a number of limitations and innovative approaches are needed to realize the full potential of the NO/sGC/cGMP -signaling pathway.

Recently a novel drug class, sGC stimulators, has been discovered. sGC stimulators share a dual mode of action, they stimulate sGC directly and enhance sensitivity of sGC to low levels of bioavailable NO. The clinically most advanced compound in this class, riociguat, underwent Ph III clinical trials for pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH). The lead discovery and optimization history of riociguat and the structural activity relationship within this class are presented.

MEDI 202

Gene expression changes in tumor xenografts by Py-Im polyamides

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Many human diseases are caused by dysregulated gene expression. Py-Im polyamides are synthetic molecules programmed to read the minor groove of the DNA double helix by a set of simple chemical principles. Hairpin oligomers achieve affinities and specificities comparable to transcription factors, alter the structure of the DNA and disrupt protein-DNA interactions. Recent investigations demonstrate that cell permeable hairpin Py-Im polyamides possess favorable pharmacokinetics and controllable toxicity in mice. Current research efforts are focused on understanding how these molecules modulate gene expression pathways in both cell culture and xenograft tumor models.

MEDI 203

Progress towards small-molecule, non-phosphorylated STAT3 inhibitors

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Stat3 is a nuclear transcription factor required for regulating genes involved in proliferation, apoptosis, angiogenesis and invasion, in addition to genes encoding cytokines, chemokines and growth factors. In contrast to the transient nature of Stat3 activation in normal cells, many human cancers harbor constitutive Stat3 activity. Stat3 downstream target genes are critical to the dysregulated biological processes that promote tumor cell growth, survival and induce chemoresistance, thus targeting Stat3 signaling represents an important therapeutic target in cancer therapy.

We have rationally designed and developed Stat3 inhibitors that disrupt transcriptionaly active Stat3–Stat3 homo-dimers, suppress Stat3 activation (phosphorylation), inhibit Stat3-target gene expression (c-Myc, Bcl-xL, survivin) and potently induce apoptosis in brain tumor cells harboring aberrant Stat3 activity. Moreover, lead compound SH-4-54, a non-phosphorylated small molecule, demonstrated in vivo blood-brain barrier

permeability, potent inhibition of Stat3 phosphorylation in vivo and induced strong anti-tumor effects against the most aggressive and lethal glioblastomas.

MEDI 204

Small molecule modulators of transcriptional activator-coactivator complexes

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Most essential cellular functions are accomplished by dynamic macromolecular assemblies comprised of least one enzymatic component surrounded by non-enzymatic moieties that enforce timing, location and specificity. In the case of transcription, transcriptional activators direct the assembly of the RNA polymerase II holoenzyme at specific gene promoters at particular time points; once the polymerase is engaged, the complex disassembles as transcription initiates. This is accomplished through protein-protein interactions (PPIs) that are dynamic and often short-lived. Mis-regulation of activator-transcriptional machinery assembly events is at the heart of many human diseases and the PPIs that direct these dynamic processes are critical for probe development and for therapeutic targeting. Nonetheless, activator-transcriptional machinery PPIs have historically been all but impossible for small molecule modulation. We will discuss two new strategies for the discovery of small molecule modulators of activator-transcriptional machinery PPIs, strategies that have produced molecules with unique potency and specificity profiles.

MEDI 205

Control of gene expression with engineered zinc finger proteins

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Improper regulation of gene expression underlies a considerable proportion of human disease, yet the majority of therapeutic interventions only target proteins amenable to “small-molecule” or antibody-based inhibition. To extend our therapeutic arsenal to the complete universe of known disease targets requires methodology that can function independently of the nature of the molecular target – a potential promise of tackling disease at the DNA level. Here, we show that control over human genes implicated in disease can be achieved by using an engineered zinc finger protein-based DNA binding domain specific for the gene of interest and a relevant functional domain. Such designed ZFPs exhibit single-gene specificity in the context of the human genome, and function to evoke therapeutic gene control (via the activation, repression, knockout or correction of the targeted gene) in cellular and animal models of disease.

MEDI 206

Efficient inhibition of c-Myc by the naturally-occurring triterpenoid celastrol and its analogs

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The bHLH-ZIP transcription factor c-Myc is de-regulated in human cancers and is required for the proliferation/survival of cancer cells. We have identified small molecules that disrupt the association between c-Myc and is bHLH-ZIP heterodimerization partner, Max. However, these molecules bind Myc with low affinities, exhibit poor *in vivo* behaviors and have minimal anti-tumor activity. We found the naturally-occurring triterpenoid quinone methide celastrol to be a potent Myc inhibitor. The removal of a reactive quinone methide group, which promiscuously forms Michael adducts with sulfur-containing nucleophiles and limits the therapeutic appeal of celastrol, did not affect its inhibition of c-Myc. The mechanism of action of celastrol appears to involve the binding of c-Myc at or close to two bHLH-ZIP sites previously shown to bind other small molecules. Celastrol-like analogs with reduced target promiscuity may represent a new class of c-Myc inhibitors with pharmacologic profiles superior to those of previously identified c-Myc inhibitors.

MEDI 207

Understanding and overcoming resistance of MDM2 and Bcl-2/Bcl-xL small-molecule inhibitors in human cancer

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Targeting apoptosis pathways through the design of small-molecule inhibitors are being pursued as novel cancer therapeutic approaches. A number of classes of small-molecule inhibitors designed to directly target key apoptosis regulators, including Bcl-2/Bcl-xL inhibitors, MDM2 inhibitors and IAP inhibitors, are now in clinical development. Preclinical and clinical studies have shown that both de novo and acquired resistance to these novel agents is common. Therefore, understanding the underlying molecular mechanism of action for drug resistance is critical for the successful development of these novel agents. Herein, we will present our recent findings using both in vitro and in vivo models. Our data have provided novel insights into the mechanism of drug resistance and effective strategies to overcome such resistance.

MEDI 208

Resistance is useless: Structure-activity and mechanistic studies of small molecules that induce collateral sensitivity in multidrug-resistant cancer cells

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Multidrug resistance (MDR) is a major obstacle to chemotherapeutic cancer treatments. MDR is often a result of up-regulation of ATP-binding cassette (ABC) transporters following chemotherapy, one example being the multidrug pump P-glycoprotein (P-gp). We have been exploring the phenomenon of collateral sensitivity (CS) – the ability of some compounds to selectively kill MDR cancer cells over non-MDR cancer cells. Three topics will be discussed. (1) The isatin-β-thiosemicarbazone NSC73306 was shown to selectively kill P-gp expressing cells. Structure-activity studies have revealed the key pharmacophore required for activity. (2) The orphan drug tiopronin was unexpectedly found to mediate CS, but in a non-P-gp dependent manner. We have determined that the CS activity of tiopronin is mediated by generation of reactive oxygen species (ROS), achieved by inhibition of the enzyme glutathione peroxidase (GPx). (3) A high-throughput screen has been developed, and identified several new CS leads.

MEDI 209

Rebastinib and DCC-2701: Targeting of resistance mechanisms in cancer treatment

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Rebastinib is a clinical stage inhibitor of BCR-ABL and TIE2 kinases, designed using Deciphera Pharmaceuticals' switch pocket technology [Cancer Cell (2011) 19: 556]. Preclinical and clinical data summarizing its utility in the treatment of refractory chronic myeloid leukemia will be presented. In addition to inhibition of BCR-ABL, rebastinib is 50-times more potent at inhibition of TIE2 kinase, increasingly implicated in stromal mechanisms of cancer drug resistance. Clinical treatment of solid tumors by radiation or chemotherapy often leads to initial clinical response, followed by resistance and disease progression caused by recruitment of bone marrow derived TIE2-expressing monocytes (TEMs) that re-establish tumor vasculature and invasiveness. Rebastinib potently blocks this mechanism. DCC-2701, an inhibitor of TIE2, VEGFR2, and MET kinases, is also being developed to target therapy-induced resistance by blocking major stromal pathways. Preclinical data will be presented for both rebastinib and DCC-2701, along with summary Phase 1 clinical data on rebastinib.

MEDI 210

Topoisomerase IIα mediated drug resistance in metastatic cancer: An old target with new tricks

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Prior to metastasis tumor cells undergo epithelial-mesenchymal transition (EMT), resulting in increased invasive potential and drug resistance. We have identified human TopoIIα as an enhancer protein required for TCF/Lef/β-catenin (TCF) transcription, implicated in 80% of sporadic colorectal cancer (CRC), and familial adenomatous polyposis (FAP). This presentation will discuss our recent research demonstrating that when TopoIIα participates in protein-complexes, binding sites accommodating TopoIIα poisons are hindered/altered causing drug resistance. An Achilles heel to this mechanism of drug resistance is the requirement of ATP for TopoIIα complex formations. Using innovative 3D-models of metastatic cancer we identified neoamphimedine (neo), a marine alkaloid that can revert/suppress the metastatic phenotype through ATP-competitive inhibition of TopoIIα, ultimately blocking aberrant TCF-transcription and subsequent invasive potential. Finally, we will discuss the development of neo as an anti-metastatic agent with the potential to eradicate mortality due to metastasis and increase the quality of life by decreasing adverse side effects.

MEDI 211

Anticancer drug candidate against drug resistance in leukemia and its mechanisms of action

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Drug resistance is a serious challenge in cancer treatment and cancer cells can acquire resistance through multiple mechanisms. We have developed CXL017, which reveals selective cytotoxicity towards multi-drug resistant cancer cell lines. Drug resistant cancer cells, HL60/MX2, also failed to acquire resistance to CXL017 and surprisingly regained sensitivity towards standard therapies. We have investigated the mechanisms responsible for HL60/MX2 cells' resistance to standard therapies and the molecular bases for its re-sensitization upon chronic CXL017 exposure – Mcl-1 over-expression, at least partially resulted from its improved stability vie ERK1/2 activation, is a critical determinant for cross-resistance to standard therapies, while topo IIβ confers resistance specifically to mitoxantrone mainly via gene expression down-regulation. Structure-activity relationship studies leading to more potent CXL candidates will also be discussed.

MEDI 212

Current status and future directions of disease modifying therapy in multiple sclerosis

***Benjamin M Segal**, bmsegal@umich.edu. Neurology, University of Michigan, Ann Arbor, Michigan 48109, United States*

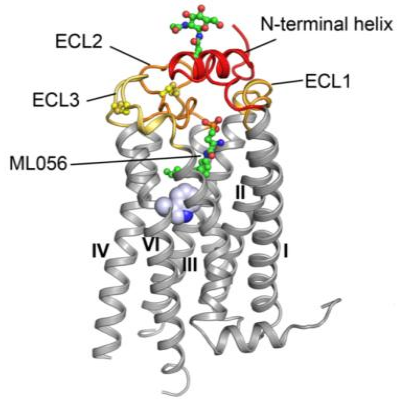
The last decade has witnessed unprecedented advances in the treatment of multiple sclerosis (MS). Nine drugs have been approved by the Food and Drug Administration (FDA) for the management of relapsing remitting (RR) MS. A number of other promising agents are currently under review or are being tested in Phase 3 trials. These disease modifying therapies (DMTs) have been shown to prevent clinical exacerbations and new MRI lesion formation with varying degrees of efficacy. Each is designed to alter or suppress the autoimmune response that is believed to drive MS pathogenesis. While the introduction of DMT has improved the clinical outlook for patients in the RR phase of disease, significant challenges remain. Future priorities include the development of effective DMT for individuals with progressive disease, the introduction of neuroprotective and neuroregenerating agents and the discovery of biomarkers that facilitate customized therapy.

MEDI 213

Integrated chemical and structural biology of S1P1 therapeutics

***Hugh Rosen**[1], hrosen@scripps.edu, Edward Roberts[2], Pedro J Gonzalez-Cabrera[1], M. Germana Sanna[1], Steven Brown[1]. (1) Department of Chemical Physiology, The Scripps Research Institute, United States (2) Department of Chemistry, The Scripps Research Institute, United States*

The sphingosine 1-phosphate (S1P) receptor signaling system has biological and medical importance, especially in the treatment of multiple sclerosis. S1P1 was the first lipid G protein-coupled receptor to be solved at 2.8A resolution



. This lysophospholipid ligand binds to five high-affinity G protein-coupled receptors to generate multiple downstream signals that directly modulate homeostasis and

pathology. ranging from vascular development, endothelial integrity, the control of cardiac rhythm, to treating multiple sclerosis. Understanding this integrated biochemical system has exemplified the impact of chemistry, genetics, and now structural biology. The S1P receptors have a novel N-terminal cap occluding access to the binding pocket from the extracellular environment. Good evidence for alternate binding mode and even allosteric agonists now exist, and the basis of sub-type selectivity is better understood. In addition, fluorescence-tagged receptor knock-in mice are now used to analyse integrated receptor function in physiology and pathology, and model pharmacodynamics. Causal relationships between protein expression, signal, and control points in physiology and pathology can now be directly understood.

MEDI 214

Discovery of highly potent $S1P_1$ receptor antagonists with in vivo efficacy

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Multiple sclerosis (MS) is a chronic autoimmune disorder of the central nervous system (CNS) that is characterized by inflammation leading to astrogliosis, demyelination, and loss of oligodendrocytes and neurons. Recently, the first oral disease-modifying therapy Fingolimod/FTY720 (Gilenya®) was approved in patients with relapsing forms of MS. In addition to direct effects on neural cells, this first-in-class sphingosine 1-phosphate (S1P) receptor modulator reduces CNS damage by interfering with lymphocyte recruitment which is critically regulated by the Sphingosine-1-phosphate receptor-1 ($S1P_1$). This G-protein coupled receptor has been identified as promising therapeutic target in autoimmune diseases, after recognizing that S1P receptor agonists down-regulate the $S1P_1$ receptor on T-cells and prevent lymphocyte egress from lymphoid organs. This "*functional antagonism*" provided a strong rationale for $S1P_1$ receptor blockade in autoimmune diseases. Herein we present the identification of a novel $S1P_1$ receptor antagonist scaffold by HTS, followed by a successful optimization to afford single digit nanomolar tool compounds for subcutaneous administration. First *in vivo* studies in rats confirmed the immunomodulatory properties, kicking-off a broad strategy to address the scaffold inherent bioavailability issues. These efforts ultimately led via a prodrug approach to the discovery of NIBR-0213. Oral administration of this highly potent and selective $S1P_1$ receptor antagonist induces long lasting reduction of peripheral blood lymphocyte counts leading to efficacy in relevant animal models of autoimmune diseases.

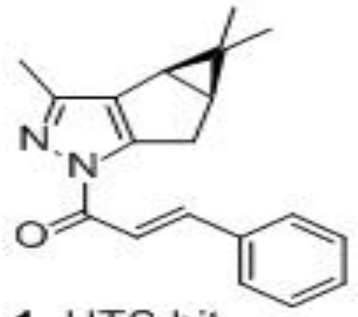
MEDI 215

Toward the discovery of novel, orally active $S1P_1$-selective receptor agonists

***Martin H Bolli**, martin.bolli@actelion.com, Magdalena Birker, Stephan Buchmann, Patrick Hess, Christopher Kohl, Cyrille Lescop, Boris Mathys, Claus Müller, Oliver Nayler, Markus Rey, Michael Scherz, Beat Steiner, Jörg Velker, Thomas Weller. Department of Drug Discovery, Actelion Pharmaceuticals Ltd, Allschwil, Switzerland*

S1P receptor agonists lead to sequestration of circulating lymphocytes to lymphoid organs and prevent these immune cells from causing inflammation and tissue damage. S1P receptor agonists therefore have great therapeutic potential to treat autoimmune diseases such as multiple sclerosis, rheumatoid arthritis or psoriasis. Indeed, a pro-drug of a non selective S1P receptor agonist, FTY720 (Gilenya^{TM}) is an approved treatment for relapsing remitting multiple sclerosis. Attention has focused on dissecting the pharmacological effects conveyed by the five known S1P receptors. Experiments with $S1P_1$ receptor knock-out mice and $S1P_1$ selective agonists demonstrated that targeting $S1P_1$ is necessary and sufficient to cause lymphocyte sequestration to lymphoid organs. $S1P_5$ agonism maintains immunoquiescence in the brain and may contribute to remyelination, whereas activation of the $S1P_3$ pathway has been reported to cause heart rate reduction, vaso- and bronchoconstriction, and pulmonary epithelial leakage.

To date, a number of selective $S1P_1$ and $S1P_{1/5}$ receptor agonists are in clinical development for multiple sclerosis and other diseases. Despite being selective against $S1P_3$, several of these compounds have been reported to cause first dose effects on heart rate in humans.



1, HTS hit

Here, we will present our efforts to evolve the structure of our HTS hit **1** into a compound suitable for clinical development. Key questions driving our drug discovery program were the compounds' stability, their S1P receptor selectivity profile as well as means to avoid the first dose effect on heart rate.

MEDI 216

Preclinical and clinical evaluation of alemtuzumab in multiple sclerosis

***William Siders**, bill.siders@genzyme.com. Neuroimmunology, Genzyme Corporation, Framingham, MA 01701, United States*

Alemtuzumab is a humanized monoclonal antibody that selectively targets CD52 to deplete circulating T and B lymphocytes, thought to be critical mediators of MS inflammatory processes. Alemtuzumab has shown efficacy superior to subcutaneous interferon beta-1a in two phase III clinical trials conducted in relapsing-remitting MS patients. Following alemtuzumab treatment, a distinctive pattern of T and B cell repopulation begins within weeks, potentially leading to a rebalancing of the immune system. To explore the mechanism of action of alemtuzumab, human CD52 transgenic mice were used to evaluate alemtuzumab-mediated depletion and repopulation of lymphocytes in circulation as well as within lymphoid tissues. In addition, the impact of alemtuzumab on the immune status of treated mice was also examined. To expand our understanding of anti-CD52 therapy in the context of disease, an antibody against murine CD52 was generated and its activity was evaluated in an EAE mouse model of multiple sclerosis.

MEDI 217

Discovery and development of Lipitor: Would anyone make this molecule today?

Bruce D Roth*, roth.bruce@gene.com. Discovery Chemistry, Genentech, South San Francisco, CA 94080, United States*

The HMG-CoA reductase inhibitor Lipitor (atorvastatin calcium), the largest selling drug in the history of the pharmaceutical industry, was designed and synthesized in 1985 at a time when medicinal chemistry was dominated by QSAR analyses and the emerging discipline of structure-based drug design. This was prior to the dramatic change in the practice of medicinal chemistry caused by the publication of Lipinski's Rule of 5, which caused the industry to focus on property-based drug design as a way of controlling ADMET properties. Despite this, one of the key aspects of the selection of Lipitor as a development candidate was development of the relationship between lipophilicity and differential drug distribution to liver and peripheral tissues. This talk will explore the development of the understanding of the tissue selectivity of atorvastatin and other HMG-CoA reductase inhibitors in relationship to physicochemical drug properties and place this work in the context of the current practice of medicinal chemistry.

MEDI 218

Controlling stem cell fate decisions with chemistry

Laura L. Kiessling*, kiessling@chem.wisc.edu. Departments of Chemistry and Biochemistry, University of Wisconsin, United States*

Human pluripotent stem cells (human embryonic stem cells and induced pluripotent stem cells) are valuable because they can be expanded and then differentiated into any desired cell type. Selective differentiation largely remains a black box, however, because the repertoire of signals known to direct the propagation or differentiation of human pluripotent stem (hPS) cells is limited. The undefined culture conditions used

typically makes it challenging to determine the signaling pathways that must be activated or suppressed. Our goal is to control hPS cell self-renewal and differentiation using conditions that are chemically defined. In physiological settings, the cellular microenvironment transmits information through three types of components: soluble molecules, neighboring cells, and the collection of secreted proteins and glycans that is termed the extracellular matrix. In seeking conditions for hPS cell culture and differentiation, researchers have focused on identifying soluble signals. To augment this approach, we are devising combinations of small molecules and defined synthetic surfaces that can be used to deliver signals that direct cell decisions. To mine this molecular space, we synthesized arrays of chemically defined surfaces composed of self-assembled monolayers. From these arrays, we identified surfaces with surprising assets: They not only permit hPS cell differentiation to specific lineages but even *instruct*them to do so. Our findings highlight the dramatic effects of both soluble and insoluble chemical cues on stem cell pluripotency and differentiation.

MEDI 219

Studies in natural product synthesis

***Phil S Baran**, pbaran@scripps.edu. Department of Chemistry, The Scripps Research Institute, La Jolla, California 92037, United States*

This talk will focus on advances in chemistry made as a consequence of preparing complex natural products in a scalable fashion. The advantages of aiming for the “ideal” synthesis, harnessing innate reactivity, and embracing the logic of C–H functionalization will be demonstrated in this context. A direct consequence of aiming for practical syntheses is the invention of reactions with broad utility for the largest body of practicing organic chemists: those in the pharmaceutical industry.

MEDI 220

Award Address (E.B. Hershberg Award for Important Discoveries in Medicinally Active Substances sponsored by Merck Research Laboratories). Seeking new drugs via unconventional drug discovery projects

***Bruce E. Maryanoff**, bmaryano@scripps.edu, Luke J. Leman, Yannan Zhao, Tomohiro Imura, M. Reza Ghadiri. Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, La Jolla, CA 92037, United States*

At Johnson & Johnson, my research group employed distinctly different approaches to discover new medicines. While we applied structure-based drug design to find potent enzyme inhibitors [*J. Med. Chem.* **2004** , *47*, 769], sought antagonist ligands for various cell-surface receptors [*Acc*. *Chem*. *Res*. **2006** , *39*, 831], and used phenotypic assessment [*J*. *Med*. *Chem*. **2009** , *52*, 3431], we also traveled less conventional roads. Thus, we explored peptide derivatives in supramolecular modalities to seek potential drugs. One project involved collagen-model peptides that self-assembled to produce

functional collagen-like materials. We designed and synthesized 32-mer peptides, $(GPO)_{10}$ end-capped with aromatic amino acids, which formed triple-helical structures that self-assembled into micron-size, fibrillar, collagen-like materials [*PNAS* **2008** , *105*, 8525]. Two 32-mers exhibited robust biofunctionality, as gauged by their induction of platelet aggregation in vitro. Another project involved mimetics of apolipoprotein A-I to produce reconstituted high-density lipoproteins for combating atherosclerosis. This research is now being pursued at Scripps-La Jolla in the laboratory of Prof. M. Reza Ghadiri. We designed, synthesized, and characterized novel, multivalent apoA-I mimetics and studied HDL-like nanoparticles generated from them. Our mimetics are based on molecular scaffolds bearing multiple, amphiphilic, alpha-helical peptides, the sequence of which was excerpted from apoA-I. The trimer construct (3 x 23-mers) was remarkably stable to proteolysis and had a prolonged half-life in mouse plasma in vivo. Phospholipid nanoparticles containing this substance functioned in vitro and in vivo to remodel mature HDL into nascent HDL and promote cellular cholesterol efflux. In LDL receptor-deficient mice, fed a high-fat diet, this nanomaterial robustly inhibited atherosclerosis in a 10-week, i.p.-dosing study.

MEDI 221

Discovery of BMS-741672, a potent, selective, and orally bioavailable antagonist of CC Chemokine Receptor 2 (CCR2)

Percy H Carter, *percy.carter@bms.com, Michael G Yang, Zili Xiao, Robert J Cherney, Douglas G Batt, Gregory D Brown, Jing Chen, Mary Ellen Cvijic, George V De Lucca, John V Duncia, Gregory Ford, Daniel S Gardner, Kathleen Gillooly, Soo S Ko, Sandhya Mandlekar, Punit Marathe, Murray McKinnon, Kim Mcintyre, Judith Murray, Jian Pang, Timothy P Reilly, Ruowei Mo, Anne Rose, Luisa Salter-Cid, Joseph B Santella, Ding Ren Shen, Qing Shi, Anurag Srivastava, Andrew J Tebben, Jenny Xie, Songmei Xu, Qihong Zhao, Joel C Barrish. Research & Development, Bristol-Myers Squibb Company, Princeton, NJ 08540, United States*

We describe the development of the structure-activity relationships in a series of lactam-conjugated tri-substituted cyclohexanes as CCR2 antagonists. This work culminated in the discovery of BMS-741672 as a potent, selective, and orally bioavailable CCR2 antagonist that was moved into clinical development.

MEDI 222

Discovery of LDK378, a potent and selective anaplastic lymphoma kinase (ALK) inhibitor for the treatment of ALK-driven cancers currently in Phase 1 and 2 clinical trials

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*Richmond[6], Jonathan Chang[6], Todd Groessl[6], You-Qun He[6], Bo Liu[6], Andrew Phimister[10], Badry Bursulaya[7], Christian Lee[7], Jennifer Harris[8], **Pierre-Yves Michellys**[1], pmichellys@gnf.org. (1) Medicinal Chemistry, Genomics Institute of the Novartis Research Foundation, San Diego, CA 92121, United States (2) Drug Discovery Oncology, Genomics Institute of the Novartis Research Foundation, San Diego, CA 92121, United States (3) Cellular Profiling, Genomics Institute of the Novartis Research Foundation, San Diego, CA 92121, United States (4) Oncology Pharmacology, Genomics Institute of the Novartis Research Foundation, San Diego, CA 92121, United States (5) CVM Pharmacology, Genomics Institute of the Novartis Research Foundation, San Diego, CA 92121, United States (6) Pharmacokinetics, Genomics Institute of the Novartis Research Foundation, San Diego, CA 92121, United States (7) Structural Biology, Genomics Institute of the Novartis Research Foundation, San Diego, CA 92121, United States (8) Drug Discovery Biology, Genomics Institute of the Novartis Research Foundation, San Diego, CA 92121, United States (9) Pharmacokinetics, Novartis Pharmaceuticals Corporation, East Hanover, NJ 07936-1080, United States (10) Toxicology, Novartis Vaccines and Diagnostics, Inc., Emeryville, CA 94608, United States (11) Pharmacology, Sanofi Adventis, Cambridge, MA 02139, United States*

Anaplastic lymphoma kinase (ALK) is a receptor tyrosine kinase belonging to the insulin receptor superfamily. Expression of ALK in normal human tissues is only found in a subset of neural cells, however it is involved in the genesis of several cancers through genetic aberrations involving translocation of the kinase domain with multiple fusion partners (e.g. NPM-ALK in ALCL or EML4-ALK in NSCLC) or activating mutations in the full-length receptor resulting in ligand-independent constitutive activation (e.g neuroblastoma). Presented is the discovery of the novel and selective anaplastic lymphoma kinase inhibitor LDK378. Synthesis, preliminary structure activity relationships (SAR) pre-clinical profile and in vivo efficacy in rat xenograft models are described as well as the medicinal chemistry rational design strategy employed to overcome the development deficiencies of the first generation clinical candidate TAE684. LDK378 is currently ongoing Phase 1 and 2 clinical trials and has shown promising preliminary signs of efficacy.

MEDI 223

Identification of substituted 2-thio-6-oxo-1,6-dihydropyrimidines as inhibitors of human lactate dehydrogenase

Peter Dragovich[1]*, dragovich.peter@gene.com, Benjamin Fauber[1], Laura Corson[1], Charles Ding[2], Charles Eigenbrot[1], HongXiu Ge[2], Anthony Giannetti[1], Thomas Hunsaker[1], Sharada Labadie[1], Yichin Liu[1], Shiva Malek[1], Borlan Pan[1], David Peterson[1], Keith Pitts[1], Hans Purkey[1], Steve Sideris[1], Mark Ultsch[1], Erica VanderPorten[1], BinQing Wei[1], Qing Xu[2], Ivana Yen[1], Qin Yue[1], Huihui Zhang[2], Xuying Zhang[2]. (1) Genentech, Inc., South San Francisco, CA 94080, United States (2) WuXi AppTec, Shanghai, Waigaoqiao Free Trade Zone 200131, China*

Lactate dehydrogenase A (LDHA) is a homotetrameric enzyme which catalyzes the cytosolic conversion of pyruvate to lactate in the final step of glycolysis. Elevated LDHA levels are prevalent and associated with poor survival in many cancer indications, and shRNA-mediated LDHA knockdown in glycolytic cancer cell lines results in significant inhibition of tumor growth. A novel 2-thio-6-oxo-1,6-dihydropyrimidine-containing inhibitor of human LDHA was identified by high-throughput screening of the Genentech and Roche chemical archives (IC_{50} = 8.1 uM). Biochemical, surface plasmon resonance, and saturation transfer difference NMR experiments indicated that the compound specifically associated with human LDHA in a manner that required simultaneous binding of the NADH co-factor. Structural variation of the screening hit resulted in significant improvements in LDHA biochemical inhibition activity (best IC_{50} = 0.48 uM). A crystal structure of an optimized compound bound to human LDHA was obtained and explained many of the observed structure-activity relationships.

MEDI 224

Fragment targeting of protein-protein interactions and allosteric modulation

***Tom D Heightman**, tom.heightman@astx.com. Astex Pharmaceuticals, Cambridge, Cambridgeshire CB4 0QA, United Kingdom*

Recently, fragment-based methods have successfully delivered clinical candidates for targets considered untractable using traditional methods.

At Astex, fragment based discovery is driven by a combination of high-throughput crystallographic screening and biophysical methods. This methodology is binding site agnostic, allowing the identification of ligands at potential allosteric as well as orthosteric sites. In addition, the detailed structural insights provided by crystallographic screening and structure-guided optimization allow parsimonious building of affinity, which provides drug candidates with enhanced ligand efficiency likely to minimize attrition in development.

The talk will describe the application of fragment based methods to the discovery of (i) a novel chemotype disrupting protein-protein interactions in the Inhibitor of Apoptosis Protein (IAP) family with potent in vivo anti-tumor activity, and (ii) potent antiviral allosteric inhibitors of the full length hepatitis-C virus NS3/4a enzyme, which stabilize the interaction between the protease and helicase domains, leading to an auto-inhibited conformation of the holoprotein.

MEDI 225

Targeted covalent-reversible inhibitors for the treatment of autoimmune and inflammatory disease: Application to Bruton's tyrosine kinase

***Mark Schnute**[1], mark.e.schnute@pfizer.com, John Springer[1], Shaun Selness[1], Robert Hughes[1], Jeff Ohren[2], Nicole Caspers[2], Seungil Han[2], Nelson Huang[1], Kieran*

Geoghegan[2], Li Xing[1], Margaret Grapperhaus[1], Thomas Owen[1], Michelle Schmidt[1], Balekudru Devadas[1], Susan Hockerman[1], D. Joseph Rogier[1], Christoph Zapf[1], Rajeev Hotchandani[1], Yuchuan Wu[1], Ingrid Buchler[1], Kyung-Hee Kim[1], Adrian Huang[1], Eva Chenail[1], Eddine Saiah[1], Zhao-Kui Wan[1], John Trujillo[2], Mihir Parikh[2], Arthur Wittwer[3], Evelyn Li[3], Erica Liu[3], Erin McCarthy[3], Joy Miyashiro[3], Shashi Mohan[3], Nancy Wood[3], Jason Edmonds[3], Wenyan Miao[3], Nilufer Seth[3], David Beidler[3], Pratap Singh[3], Dean Messing[3], Sarah Soucy[3], Christopher Wrocklage[3], Tatyana Andrey[3], Andrew Rankin[3], Martin Hegen[3], Cheryl Nutter[3], John Douhan[3], Kyri Dunussi-Joannopoulos[3], Suvit Thaisrivongs[1]. (1) Department of Biotherapeutics Chemistry, Pfizer, Cambridge, MA 02140, United States (2) Department of Medicinal Chemistry, Pfizer, Groton, CT 06340, United States (3) Department of Immunology and Autoimmunity, Pfizer, Cambridge, MA 02140, United States

Targeting of non-catalytic cysteine residues with covalent inhibitors is a powerful strategy for optimizing pharmacologic potency and selectivity on challenging targets such as the protein kinases. Nonetheless, concerns over off-target modification of proteins by irreversible covalent inhibitors leading to idiosyncratic toxicity has led to caution in applying this strategy to chronic diseases such as inflammation and autoimmune indication even though these events are rare. The utilization of covalent inhibitors that reversibly form an adduct with the protein cysteine is attractive as they may provide the pharmacodynamic and selectivity benefit with less propensity to form long-lived protein adducts. Herein we describe a strategy to design, optimize and characterize covalent, reversible inhibitors targeting Bruton's Tyrosine Kinase (Btk) and demonstrate their potential utility towards the treatment of inflammatory and autoimmune diseases. Structure-based drug design was utilized to optimize non-covalent inhibitor contacts within the kinase and guide placement of the covalent reactive group. Subsequent tuning of the reactivity and specificity of the electrophile resulted in the discovery of a class of highly selective Btk inhibitors within the cysteine homolog family. Through this strategy, we identified an orally bioavailable, potent and selective small molecule inhibitor of Btk which forms a covalent but reversible adduct with the enzyme as confirmed through enzymology, co-crystal structure analysis and mass spectroscopic characterization. The Btk inhibitor has been shown to be efficacious in several preclinical animal models of arthritis and autoimmune disease. This compound represents a new class of covalent Btk inhibitors which offers promise as a clinical candidate for the treatment of autoimmune and inflammatory diseases.

MEDI 226

Fragment screening and structure-based drug design with G protein-coupled receptors

***Steve P Andrews**, steve.andrews@heptares.com.Heptares Therapeutics, Welwyn Garden City, Hertfordshire AL7 3AX, United Kingdom*

Recent advances in understanding the structures and functions of GPCRs are having an enormous impact on the medicinal chemistry community. Indeed, the 2012 Nobel Prize for chemistry was awarded to pioneers of the GPCR field.

Stabilized GPCRs (StaRs®) can be crystallized in activated and ground-state conformations during 'live' medicinal chemistry campaigns. Results of some of the first examples of achieving this will be presented, along with structure-based drug design case studies. For example, crystal structures of β1 adrenergic receptor were solved in co-complex with fragment-sized molecules and used to guide the optimization of potent, efficient and novel ligands.

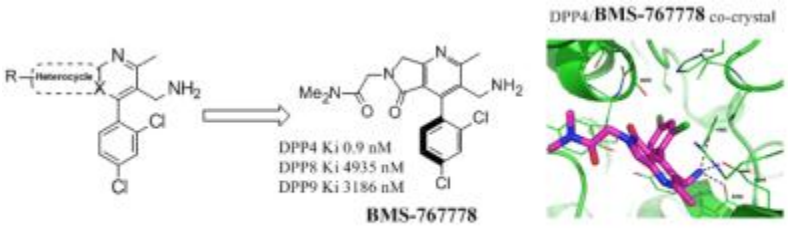
For several GPCRs, efficient leads with good drug-like properties have been identified following virtual or fragment screening. In three cases, these have been progressed to a candidate drug in less than 2 years.

The process for generating StaRs® will be described, along with their use in fragment and biophysical screening.

MEDI 227

Discovery of BMS-767778, a highly potent and selective DPP4 inhibitor for the treatment of diabetes mellitus

Pratik Devasthale*, pratik.devasthale@bms.com.Metabolic Diseases Chemistry, Bristol-Myers Squibb, Hopewell, NJ 085343, United States*



[figure1]

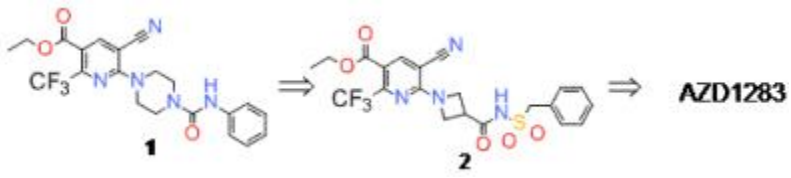
Mitigation of hERG and CYP liabilities in the 5-oxopyrrolopyridine series via exploitation of the solvent-exposed region of the active site of DPP4 yielded BMS-767778 with an overall activity, selectivity, efficacy, PK, and developability profile suitable for progression into the clinic. Stucture-Activity relationships in the series as well as characterization of BMS-767778 is described.

MEDI 228

Lead optimization of a new chemical class of $P2Y_{12}$ inhibitors leading to the identification of the Clinical Candidate AZD1283

***Fredrik R Zetterberg**, fredrik.zetterberg@astrazeneca.com.CVGI iMED Chemistry, AstraZeneca R&D, Mölndal, Sweden*

Antiplatelet drugs decrease platelet aggregation and inhibit thrombus formation. The important role of the $P2Y_{12}$ receptor in platelet function makes it an attractive target for the development of novel antiplatelet therapies. The first class of compounds to show clinical efficacy were the thienopyridine pro-drugs including ticlopidine and clopidogrel, whose active metabolite binds irreversibly to the receptor. However, preclinical data suggested that antagonists that bind reversibly to the $P2Y_{12}$ receptor would not only give a faster off-set of effect, but also improve the separation of anti-thrombotic effect and bleeding risk.



In our search for $P2Y_{12}$ antagonists we have previously reported on the generation of a series of acyl sulphonamides of the type **2** starting from urea compounds of the type **1** .[i] We herein present the lead optimization program leading to the selection of the clinical candidate AZD1283. The presentation will cover the Medicinal Chemistry story discussing how we improved on a number of parameters, for example solubility and metabolic stability. A special focus will be given esters and ester replacements. We will also discuss the selection criteria, risk management, dose predictions and the fate of the clinical candidate AZD1283. The presentation will also contain synthesis highlights and large scale preparatory routes.

i Peter Bach, Jonas Boström, Kay Brickmann, J.J.J. van Giezen, Ragnar Hovland, Annika U. Petersson, Asim Ray, Fredrik Zetterberg *Bioorg. Med. Chem Lett.* **2011** , 21 (2011) 2877

MEDI 229

Pharmaceutical research and development: Past and present realities and future aspirations

***Paul L. Feldman**, paul.l.feldman@gsk.com. GlaxoSmithKline Pharmaceuticals, United States*

The pharmaceutical industry's (pharma's) endeavor to discover, develop, and provide access to therapeutic agents has had a significant and lasting impact on society. As an example, pharma's rapid response to the AIDS crisis has enabled many HIV positive patients to turn this fatal disease to one that can be managed chronically with proper adherence to medications. Additionally, significant philanthropic endeavors continue to

be undertaken by pharma to treat underdeveloped world maladies. However, it has not all been good news for pharma with significant well-publicized drug withdrawals and recent settlements that have tarnished its reputation. These setbacks have also been coupled with lower output (fewer drugs approved with a larger investment) from pharma's research and development organizations. Despite these recent challenges there remain significant reasons for optimism for pharmas role to play in supporting the future of healthcare. High unmet medical needs remain to be addressed and this is coupled with advances in science that provide great opportunity to discover and develop valuable medications that will be part of our unmet medical needs solution. Chemists are central to healthcare and pharma success. Improving our success rate of molecules reaching the market is critically dependent upon chemistry (reducing attrition) as well as how chemists translate some of the exciting scientific discoveries into therapeutics. Chemists can take a leadership role helping pharma through these recent challenges and I will proffer some opportunities that chemists are well-positioned to address.

MEDI 230

Award Address (Earle B. Barnes Award for Leadership in Chemical Research Management sponsored by The Dow Chemical Company Foundation). Setting a course for biomedical innovation in the 21stcentury

***Alan Palkowitz**, palkowitz_alan_d@lilly.com. Department of Discovery Chemistry Research and Technologies, Eli Lilly & Company, United States*

The pharmaceutical industry is in a period of significant transformation. The success of the enterprise during the last century in extending life expectancy and improving the quality of human health with novel therapies is unparalleled and has set the benchmark for future innovation. While scientific, business and regulatory challenges have limited the productivity of the industry during the past several years, key learnings are providing new paths to future discoveries that will reverse these trends and yield breakthrough medicines to address unmet patient needs. Organizations that will contribute to this future will be distinguished by their ability to engage disease complexity with diverse strategies and technologies that are enabled by a talent base capable of solving difficult challenges at the interface of multiple scientific disciplines. Key to this future will also be unique models for collaboration that bring together scientific expertise and capabilities from around the globe in a coordinated and focused effort. As in the past, chemists will remain at the core of future biomedical innovation. In this lecture, a perspective on the future of drug discovery and the opportunities for scientific leadership will be shared.

MEDI 231

Therapeutic intervention in neurological diseases of matrix

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Damage to the brain in certain diseases, such as traumatic brain injury (TBI) and stroke, is accompanied by remodeling of the extracellular matrix in attempts at recovery. Unfortunately, the repair mechanisms often cannot meet the physiological needs of the brain in time, which leads to a series of events resulting in tissue death in the affected areas. These effects manifest themselves within hours to days from the initial insult and provide a window of opportunity for therapeutic intervention. Currently, there are no therapeutics that rescue or protect the affected areas of the brain. I will disclose a class of molecules that are permeable through the blood-brain barrier and intervene in the disease progression in animal models of neurological diseases.

MEDI 232

Discovery and development of both intranasally and orally administered CGRP (calcitonin gene-related peptide) receptor antagonists for the treatment of migraine

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Antagonists of the CGRP (calcitonin gene-related peptide) receptor, a Class B GPCR (G-protein coupled receptor), have been shown to be clinically effective in the acute treatment of migraine headaches. Four compounds have already achieved Proof-of-Concept in human migraine trials. In this seminar, the discovery of a series of CGRP receptor antagonists will be presented. Specifically, the discovery of an intranasally bioavailable, picomolar potent CGRP receptor antagonist (BMS-742413) and an orally bioavailable picomolar CGRP receptor antagonist (BMS-927711) will be detailed. A complete characterization of both compounds will be presented, and clinical results for BMS-927711 will also be presented.

MEDI 233

Rational design of selective inhibitors for β-catenin/t-cell factor protein-protein interactions

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We are developing new techniques to rationally design selective inhibitors specific for one protein-protein interface. The aberrant formation of the β-catenin/T-cell factor (Tcf) complex in the canonical Wnt signaling pathway has been recognized as the major driving force for many cancers, including colorectal and hepatocellular carcinomas, and pulmonary fibrosis. Crystallographic and biochemical analyses reveal that the binding modes of Tcf, E-cadherin and adenomatous polyposis coli (APC) with β-catenin are identical. The design of small-molecule inhibitors that selectively disrupt the β-catenin/Tcf complex while leaving the β-catenin/cadherin and β-catenin/APC interactions unaffected is critical but challenging. By using a new strategy we are

developing, we successfully designed and synthesized new nanomolar inhibitors for β-catenin/Tcf interactions with more than 1000-fold selectivities for β-catenin/Tcf over β-catenin/E-cadherin and β-catenin/APC interactions. The binding modes of the inhibitors were validated by the site-directed mutagenesis and structure-activity relationship studies. Various cell-based studies demonstrated that the newly discovered inhibitors significantly attenuated canonical Wnt signaling in cancer cells, inhibited cancer proliferation and induced cancer apoptosis.

MEDI 234

$Ca_V1.3$-selective L-type calcium channel antagonists, novel therapeutics to slow the progression of Parkinson's disease

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L-Type calcium channels (LTCCs) expressed in the brain are heterogeneous. The predominant class of LTCC has a $Ca_V1.2$ pore-forming subunit. LTCCs with a $Ca_V1.3$ pore-forming subunit are much less abundant, but have been implicated in the generation of mitochondrial oxidant stress underlying pathogenesis in Parkinson's disease (PD). Thus, selectively antagonizing $Ca_V1.3$ LTCCs could provide a means of diminishing cell loss in PD without producing side effects accompanying general antagonism of LTCCs. To fill this gap, high-throughput screening of commercial and 'in-house' chemical libraries and modification of promising hits was carried out. Pyrimidine-2,4,6-triones were identified as a potential scaffold; structure-activity relationship-based modification of this scaffold led to a potent and highly selective (>600-fold) $Ca_V1.3$ LTCC antagonist. The biological relevance was confirmed by whole-cell patch-clamp electrophysiology. Homology modeling and computer modeling were used to enhance the potency and selectivity. Studies directed at the mechanism of action of these compounds are being carried out. These are the first highly selective $Ca_V1.3$ LTCC antagonists and point to a novel therapeutic strategy for PD that slows the progression of the disease rather than just treats the symptoms.

MEDI 235

New probes for the kappa opioid receptor: Screening, chemistry, and pharmacology

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One goal of our laboratories is to provide probes to explore the kappa opioid receptor (KOR) and its possible role in addiction. Screening of chemical libraries carried out in collaboration with the Psychoactive Drug Screening Program and the Molecular Libraries Probe Production Centers Network has resulted in the identification of five chemotypes that selectively bind to the KOR. The results of this work will be described along with investigations into the pharmacological action of selected compounds.

MEDI 236

Selective orexin receptor antagonists for the treatment of CNS disorders

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The orexin neuropeptides (orexin-A and orexin-B) project widely throughout the brain and play a major role in various neurobiological processes including the regulation of vigilance and wakefulness. Anatomical and functional evidence also suggest an important interaction of the orexin system with rewards pathways of the brain. Orexins mediate their effect by stimulating two closely related G protein-coupled receptors, orexin-1 (OX1R) and orexin-2 (OX2R). Pharmacological blockade by the dual OX1/2R antagonists Almorexant and Suvorexant has been shown to promote sleep in animals and humans during their active period. Preclinical data indicate that selective blockade of OX2 receptor is sufficient to initiate and prolong sleep. Conversely, using less than optimal pharmacological tools several studies suggest that transmission at the OX1 receptor plays an important role in the reinstatement of extinguished cocaine-seeking behaviors in rodents. Presented here will be the discovery, synthetic methods, and SAR associated with novel selective orexin receptor antagonists.

MEDI 237

Neurotensin receptors and substance abuse

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The National Institute on Drug Abuse (NIDA) has declared the development of medications for treating methamphetamine addiction as one of its primary goals. They identified the two GPCR neurotensin receptors, NTR1 and NTR2, as relatively unexplored targets with the potential to significantly impact drug addiction. There are two principal reasons for such interest. One is the demonstrated ability of the peptide neurotensin, acting at these two receptors, to regulate dopamine flow in the key areas of the brain associated with methamphetamine addiction. The second reason follows from the ability of these receptors to mediate non-opioid analgesia as this may provide a non-addictive alternative to current opioid-based pain medications. This presentation will highlight recent advances in this area as well as contributions from our laboratory toward the discovery of novel small-molecule compounds active at the neurotensin receptors.

MEDI 238

Characterization of 70 human melanocortin-4 receptor polymorphisms and the lessons learned

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Our research has focused upon the *in vitro* pharmacological characterization of 70 human melanocortin-4 receptor (hMC4R) single nucleotide polymorphisms (SNPs) to determine the potential molecular mechanism(s) that might associate a particular SNP with obesity. These include decreased cell surface expression and changes in endogenous agonist/antagonist ligand molecular recognition and potency/efficacy. Experimental approaches include the discovery of agonists (peptide and small molecule) that can functionally rescue hMC4R SNPs that do not respond normally to endogenous agonists using both a targeted design approach and a combinatorial screening approach. Our progress towards these efforts and the lessons we have learned will be presented.

MEDI 239

Development of novel tools to study the neuropeptide S system in models of substance abuse.

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Neuropeptide S is a 20-amino acid peptide that functions as an agonist through activation of its cognate GPCR receptor system. Modulation of the Neuropeptide S (NPS) receptor has been associated with a variety of disease states including anxiety, panic disorder, narcolepsy, PTSD, and importantly substance abuse. Through comprehensive chemical modification and analog synthesis we have now defined a comprehensive NPS antagonist pharmacophore using traditional medicinal chemistry and computational/scaffold hopping approaches. The compounds developed in our laboratory are highly potent at blocking NPS receptors in vitro using a calcium mobilization functional assay and are also active in rodent models of cocaine self-administration, stress induced, cue induced, and drug induced reinstatement. Further modification and testing of these analogs will be of significant value in determining the comprehensive role of NPS in modulating substance abuse behaviors.

MEDI 240

Lipid biochemistry, mass spectrometry, and lipidomics: A journey in five decades

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There has been a long relationship between advances made in mass spectrometry and application of this technique to lipid biochemistry. Some of our earlier understandings of electron ionization mass spectrometry came from the fundamental studies of Professors Fred McLafferty, Ragnar Ryhage, and Einar Stenhagen with the mass spectral behavior of fatty acid methyl esters. Advances in lipid biochemistry have also benefitted from the ability of mass spectrometry to provide detailed information not only of structures, but also quantitative analysis of lipids and lipid metabolites. The initial discovery of the chemical structures of metabolites of arachidonic acid came from the pioneering studies of Samuelsson and co-workers characterizing novel metabolites as prostaglandins and thromboxane. The newer methods of electrospray ionization and matrix assisted laser desorption ionization (MALDI) has opened almost unlimited applications of mass spectrometry to lipid biochemistry. Specific examples from our laboratory have included understanding basic biochemical events within cells that lead to arachidonic acid remodeling and the important role of lysophospholipid acyltransferases in this process. The characterization of these enzymes can be carried out in a multiple choice assay to reveal the potential of these enzymes, in making different phospholipid molecular species using multiple reaction monitoring on a triple quadrupole mass spectrometer. Many lipids are synthesized in cells as complex mixtures of closely related molecular species (glycerolipids, glycerophospholipids, and sphingolipids) and powerful strategies have been developed with the enormous quantity of data that must be generated to define the lipidomic composition of a cell. Neutral lipids have been a challenging area to investigate and a specific example is the analysis of over fifty oxidized cholesteryl ester molecular species that accumulate in the plaque of humans during the progression of

atherosclerosis. Such studies would not have been possible, even in the past several years, without technological advances in mass spectrometry.

MEDI 241

Secreted phospholipases A2: Role in asthma and arthritis

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We have been studying the role of secreted phospholipases A2 in asthma and arthritis using mouse models and active site directed inhibitors. Genetic deletion of group X secreted phospholipase A2 leads to a dramatic reduction of airway inflammation in a mouse model of allergic asthma. The enzyme is highly expressed in airway epithelial cells, and we provide data that it is involved in airway eicosanoid production. We also designed a specific inhibitor of this enzyme using the x-ray structure of related enzyme-inhibitor complexes, and we showed that this inhibitor recapitulates what we see in the genetic knockout. Mice lacking group IIA secreted phospholipase A2 show greatly reduced joint inflammation in a mouse model of rheumatoid arthritis. We are trying to determine the membrane target for this enzyme in the synovium. We have also been successful in making a group IIA phospholipase A2 specific inhibitor, and biochemical studies show that it displays a novel mode of binding to the active site.

MEDI 242

Sphingosine kinase 1: A key role in inflammation and cancer

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The sphingolipid metabolite sphingosine-1-phosphate (S1P) and the kinases that produce it have emerged as critical regulators of numerous fundamental biological processes important for inflammation and cancer. Activation of sphingosine kinases (SphKs) by a variety of agonists increases intracellular S1P. S1P can be secreted out of cells and bind to and signal through five specific G protein-coupled receptors, designated S1PR1-5. It is now well established that this "inside-out" signaling by S1P is important for many human diseases. The roles of the S1PRs in cell and organismal physiology will be discussed in detail and particularly their roles in chronic intestinal inflammation and colitis-associated cancer (CAC). Focus will be on activation of SphK1 and how the SphK1-S1P-S1PR1 axis is at the nexus between NF-κB and Stat3 and connects chronic inflammation and CAC. The development of inhibitors of SphK1 and small molecules that target specific subtypes of S1P receptors will also be discussed. The effectiveness of the pro-drug FTY720 (known as Fingolimod or Gilenya), approved

for the treatment of multiple sclerosis, has become the gold standard for S1P-centric drugs, and will be used to illustrate the therapeutic value of modulating SphK1 and S1P receptor functions which holds great therapeutic promise.

Supported by NIH grants R37GM043880, R01CA61774, and U19 AI077435.

MEDI 243

Chemoproteomic approaches for targeting endocannabinoid signaling networks

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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 244

Role of phosphatidic acid in human disease

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Phosphatidic acid (PtdOH) is a lipid second messenger and essential intermediate in the biosynthesis of glycerophospholipids. PtdOH has been demonstrated to be involved in binding cell signaling components such that it serves to nucleate signaling centers as well as playing a role in the formation of intracellular vesicles and trafficking. PtdOH is generated from multiple sources including lipid biosynthetic pathways as well as the result of signaling processes downstream of G protein couple receptors (GPCR) and tyrosine kinase receptors (TKR). Presumably these distinct sources provide differential pools of PtdOH in cells and understanding the origins of these various pools is essential to optimize drug discovery endeavors. We have developed isoenzymes selective inhibitors of phospholipase D and characterized the effects of these small molecules as potential therapeutic tools in the treatment of human brain cancers and infectious

disease. The targets are validated using siRNA approaches to knockdown the isoenzymes selectively as well as exploitation of a transphosphatidylation reaction that is a molecular signature of phospholipase D. Detailed mass spectrometry based metabolomic analysis shows the consequences of blocking selective pathways on the cellular lipid composition and bioenergetic pathways, including braches that are defective in disease states. Recent findings demonstrate the potential benefits and therapeutic application of targeting phospholipase D.

MEDI 245

Reversible covalent inhibition: An optimal approach to achieve highly potent, selective and durable inhibitors of cysteine containing targets

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Drug discovery has traditionally focused on identification of potent and selective inhibitors that have been optimized to achieve efficacious drug exposure at the lowest possible dose. Methodology to achieve exposure driven durable inhibition inevitably results in surplus exposure with concomitant safety liabilities. A better strategy for drug design is to create potent and selective inhibitors that have been optimized for durable residence time on targets at the lowest possible dose. While the design of drug candidates with slow off rate kinetics has long been desired, no general methodology has existed to enable the optimization of residence time across target classes. This seminar will highlight Principia Biopharma's reversible covalent methodology which enables the design of potent, selective and durable inhibitors for targets containing cysteine residues in their binding pockets. Specific examples of orally bioavailable inhibitors with relevant activities in pharmacodynamic assays will be presented.

MEDI 246

Targeting drug resistance with covalent inhibitors

***Daniel Rauh**, daniel.rauh@tu-dortmund.de. Chemische Biologie, Technische Universität Dortmund, Dortmund, Germany*

The discovery of mutations in the epidermal growth factor receptor (EGFR) has marked a dramatic change in the treatment of non-small cell lung cancer. Patients with EGFR-mutant lung carcinoma receiving EGFR inhibitors have a median overall survival of more than 2 years, contrasting with the survival of unselected patients receiving chemotherapy. Acquired resistance to these targeted drugs is in 50% of the cases mediated by a secondary point mutation in the kinase domain of EGFR the gatekeeper position (T790M). The particular size and physicochemical properties of the amino acid found at this position are critical determinants for kinase inhibitor affinity and selectivity. Gatekeeper mutations affect the thermodynamic and kinetic binding characteristics of all 4-amino-quinazoline-based inhibitors (originally developed to target wild-type EGFR).

The impact of current and next generation covalent kinase inhibitors to overcome this T790M drug resistance in mutant EGFR will be highlighted.

MEDI 247

Chemoproteomic probes that target lysine and cysteine: Interrogating Src-family kinases and beyond

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Src-family tyrosine kinases play pivotal roles in human physiology and disease, and several drugs that target members of this family are in clinical use. None of these drugs appear to discriminate among closely related kinases. However, assessing their selectivity toward endogenous kinases in living cells remains a significant challenge. Here, I will discuss the design of two kinase-directed chemical probes, each consisting of a nucleoside scaffold with a 5'-electrophile. A 5'-fluorosulfonylbenzoate reacts with the conserved catalytic lysine (Lys295) and shows little discrimination among related kinases. By contrast, a 5'-vinylsulfonate reacts with a poorly conserved, proximal cysteine (Cys277) found in three Src-family and six unrelated kinases. Both probes bear an alkyne tag and efficiently label endogenous kinases in living cells. These and other kinase-directed probes have provided new insights into the selectivity of kinase inhibitor drugs, as well as new potential targets for treating disease.

MEDI 248

Discovery of highly potent and selective covalent reversible cathepsin S inhibitors

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Cathepsin S (CatS) is a cysteine protease involved in the antigen presentation process and in extra cellular matrix degradation. Dysregulated CatS activity is a driver for chronic inflammation, destructive proteolysis, arterial calcification and increased neoangiogenesis. Therefore CatS is an interesting target for several indications such as autoimmune diseases, cancer or cardio vascular diseases. One approach to inhibit the proteolytic activity of CatS is to block its active site with covalent reversible inhibitors which react with the cysteine present in the catalytic triad. This presentation will focus

on the identification and optimization of covalent reversible CatS inhibitors via X-ray structure elucidation and molecular modeling to improve potency, selectivity, reversibility, and ADME properties.

MEDI 249

Towards optimized utility of proteasome inhibitors with peptide epoxyketones

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The ubiquitin/proteasome pathway is the primary means by which intracellular protein degradation occurs. As such, the proteasome plays a central role in regulating most facets of cell physiology and has been the target of drug discovery programs in cancer and inflammatory diseases. Cleavage of target proteins occurs via 3 distinct proteolytic activities within the 20S core particle of the 26S proteasome. There are 2 forms of the 20S core, the constitutive proteasome and the immunoproteasome, distinguished by their active site subunits. These active sites, defined in part by their substrate specificity, make up a unique class of proteases in that the catalytic nucleophile is an N-terminal threonine residue. Several distinct classes of proteasome inhibitors have been described, with multiple compounds having entered clinical trials, and 2 drugs, bortezomib (a peptide boronate) and carfilzomib (a peptide epoxyketone), achieving marketing approval for the treatment of multiple myeloma. Peptide epoxyketones are distinguished by formation of a dual-covalent, morpholino adduct formed by reaction with the side chain hydroxyl and free amine of the catalytic threonine. This distinct chemical mechanism has enabled improved selectivity against other classes of proteases. The resulting elimination of off-target activity enabled the exploration of dose intensive therapy with carfilzomib in clinical trials, which translated to increased response rates and activity in patients resistant to bortezomib. Through a pharmacology driven medicinal chemistry effort, we designed an orally bioavailable analog of carfilzomib, oprozomib, which displays similar levels of proteasome inhibition and biodistribution. Another focus of our research is subunit selective inhibitors. Our discovery of subunit selective peptide epoxyketones has helped elucidate distinct roles for both the immunoproteasome and constitutive proteasome in immune cell biology. Immunoproteasome selective inhibitors are highly efficacious in mouse models of autoimmunity and represent a new class of therapeutics for the treatment of inflammatory diseases.

MEDI 250

Biology of covalent BTK inhibitor PCI-32765 (Ibrutinib): From bench to bedside

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PCI-32765 (ibrutinib) is an orally administered, potent and specific covalent inhibitor of Bruton's tyrosine kinase (BTK) in Phase 3 clinical development for the treatment of B cell lymphoproliferative diseases. PCI-32765 binds covalently to Cys481 of BTK, and inhibits Btk activity (IC50= 0.5 nM) in biochemical assays, and suppresses B-cell receptor (BCR) activation of primary B lymphocytes (EC50=10 nM). PCI-32765 treatments inhibit the phosphorylation of key kinases involved in the BCR signaling pathway via BTK inhibition, including PLCg, ERK and JNK (Honigberg, 2010[a]). In malignant B cells, PCI-32765 suppresses BCR and chemokine (CXCL12, CXCL13) activated adhesion and migration and inhibits migration of CLL, MCL and FL cells underneath stromal cells in co-culture. In addition, PCI-32765 inhibits chemokine release (CCL3, CCL4, CCL22 and CXCL13) from CLL/MCL cells in co-culture (Chang, 2011[b]). In vivo PK/PD studies in humans and animals demonstrate rapid covalent binding of drug to BTK. The binding remained 24 hours post drug dose despite rapid elimination of drug which results in a unique approach to improve selectivity for BTK in vivo relative to reversibly inhibited off target kinases (Advani, 2012[c]). Clinical results from Phase I/II studies show promising single agent activity of PCI-32765 across several NHL histologies including CLL, MCL and DLBCL (Advani, 2012[c]). Mechanistically, lymphocyte mobilization into the peripheral blood is notable from most patients in response to treatment with PCI-32765. Malignant B cells were decreased in Ki67, CD38 and pErk expression. This effect is likely to be related to PCI-32765 suppression of BTK activation which results in inhibition of B lymphoma chemotaxis, adherence and pseudoemperipoleisis. We propose that BTK is essential for the homing of lymphoma cells into secondary lymphoid organs, and that its inhibition results in peripheral blood compartment shift. PCI-32765 is a first-in-class covalent BTK inhibitor with demonstrated efficacies in B cell malignancies.

MEDI 251

Discovery and development of telaprevir- a covalent HCV protease inhibitor recently approved for the treatment of people with chronic genotype 1 HCV infection

***Ann D Kwong**, anndkwong@yahoo.com.InnovaTID, Cambridge, MA 02138, United States*

The active site of the HCV protease domain is extremely hydrophobic, flat, and solvent-exposed, with few pockets to increase the affinity for an inhibitor to bind. Given the chemical nature of the substrate-binding site, it is not surprising that no suitable HTS leads were identified. Peptide inhibitor truncation studies revealed that the affinity for binding was spread over a wide area. To increase the interaction of a small molecule with the protease active site, Robert Perni and co-workers introduced a covalent, reversible electrophilic alpha-ketoamide “warhead” into the inhibitor design to increase the half-life of binding to the protease. The increased half-life had a surprising and significant impact when the biological properties non-covalent and covalent HCV protease inhibitors were compared. Interestingly, both of the first HCV protease inhibitors (telaprevir, INCIVEK; boceprevir, VICTRELIS) approved for use in

combination with pegylated interferon alfa-2a and ribavirin are covalent ketoamide inhibitors.

MEDI 252

Properties and applications of some selectively fluorinated rings and things

***David O'Hagan**, do1@st-andrews.ac.uk. Chemistry, University of St Andrews, St Andrews, Fife KY15 5EA, United Kingdom*

The presentation will highlight recent work on the synthesis and properties of acyclic and cyclic hydrocarbon motifs carrying multiple vicinal C-F bonds (~CHFCHFCHFCHF~) of defined stereochemistry and will also explore aspects of the CF_2 group when incorporated into an aliphatic chain or ring. In each case a particular emphasis will be placed on the stereoelectronic influence of these substituents including geometry, conformation and polarity and how the introduction of fluorine, and control of stereochemistry, impacts of the behaviour and properties of such motifs.

Enzymatic formation of the C-F bond from fluoride ion, using the fluorinase enzyme from Streptomyces cattleya, will also be described, particularly employing it as a catalyst for the preparation of [^{18}F]-5-fluoro-5-deoxyribose ([^{18}F]-FDR), which has potential as an efficient bioconjugation tool for labelling bioactive peptides and proteins with the short lived fluorine-18 isotope, for positron emission tomography (PET) imaging applications.

MEDI 253

Catalytic methods for nucleophilic fluorination

***Abigail G. Doyle**, agdoyle@princeton.edu. Department of Chemistry, Princeton University, Princeton, NJ 08544, United States*

Fluorine-containing organic molecules are important in nearly every facet of the chemical industry, and as such, mild, selective, and efficient methods for carbon–fluorine (C–F) bond formation are in high demand. This talk will describe my group's recent efforts to develop catalytic methods for aliphatic C–F bond formation using nucleophilic fluoride sources, including the design of Pd(0)-catalyzed asymmetric allylic fluorination and Co-catalyzed enantioselective hydrofluorination reactions. Pertinent mechanistic studies will also be described; in one case, these studies have enabled the identification of a rapid, functional group- and moisture-tolerant procedure for the incorporation of [18F]fluoride ion into organic electrophiles.

MEDI 254

Synthesis and applications of fluorine-18 labeled radiopharmaceuticals

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Radiopharmaceuticals labeled with fluorine-18 (half-life = 109.77 min) find widespread use in non-invasive positron emission tomography (PET) imaging of biochemical processes in living human subjects. This presentation will introduce PET imaging and showcase strategies for radiolabeling bioactive molecules with fluorine-18 (including strategies for nucleophilic aromatic fluorination reactions, radio-click chemistry, as well as new unconventional approaches to radiochemistry). Imaging applications of fluorine-18 labeled radiopharmaceuticals in personalized medicine (e.g. in neurology, cardiology and oncology) and drug discovery (e.g. receptor occupancy studies, and monitoring patient response to therapy) will also be highlighted.

MEDI 255

Gamma-secretase modulators: Aligning potency, clearance, and brain penetration through strategic use of fluorine

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Incorporation of fluorine atom(s) is a common tactic in medicinal chemistry to improve potency and to address ADME issues. Strategic use of fluorine within the gamma-secretase modulator (GSM) program afforded increased potency, and improved pharmacokinetic properties by blocking metabolic soft spots guided by Met ID studies. Gamma-secretase modulators (GSMs) have emerged as a potential disease modifying treatment for Alzheimer's disease, but as an intra-membrane cleaving aspartyl protease, gamma-secretase represents a challenging drug target leading to compounds that often push the boundaries for acceptable CNS physicochemical property space. An analysis of the Pfizer MDR efflux ratio data set demonstrated that an increase in molecular weight due to introduction of one or more fluorine atoms has negligible impact on P-gp mediated efflux. Application of these concepts to the GSM program has allowed alignment of potency and ADME while maintaining excellent brain penetration.

MEDI 256

Fluorine substitution in allosteric modulator programs of cell surface receptors

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Among the top 200 marketed drugs over half are eliminated by the cytochrome P450 class of drug metabolizing enzymes (DMEs). P450-mediated oxidation of a pharmacophore can result in pharmacological deactivation or bioactivation of the drug candidate, the later of which is becoming an increasingly important challenge for allosteric modulator programs targeting G-protein coupled receptors (GPCRs) wherein metabolite-ligands may present unanticipated pharmacology, including mechanism based toxicity. By virtue of its increased resistance to metabolism and impact on modulating drug cell permeability, the carbon-fluorine bond is extensively employed in lead optimization campaigns, including allosteric modulator programs. The use of fluorine substitution in metabotropic and muscarinic GPCR allosteric modulator ligands and its impact in addressing challenges associated with primary target activity/SAR (e.g. 'molecular switches'), receptor family selectivity, CNS penetration, and metabolite-ligand formation will be presented.

MEDI 257

Big changes from a small atom: Effects of fluorine substitution on small molecule MET inhibitors

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The introduction of fluorine atoms to medicinal compounds can have dramatic effects on pharmaceutical properties such as potency, selectivity, and metabolism as well as physicochemical properties such as solubility and lipophilicity. During the course of our efforts to develop inhibitors of the MET receptor tyrosine kinase, mono and bis-fluorine substitutions were strategically incorporated onto an amino piperidine ring to alter the pKa of the ring nitrogen. These changes had little effect on MET potency and efficacy in animal models yet had the expected effects on PK parameters, solubility, and hERG inhibition. Additionally, several unexpected changes in kinase selectivity and toxicity improvements were uncovered that could be prospectively explained by examining bound co-crystal structures and PK in tissues, respectively. These results, in addition to the synthesis of these complex compounds, will be discussed.

MEDI 258

Discovery of 1,3,8-triazaspiro[4.5]decane-2,4-diones as efficacious pan-inhibitors of hypoxia-inducible factor prolyl hydroxylase 1-3 (HIF PHD1-3) for the treatment of anemia

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The discovery of 1,3,8-triazaspiro[4.5]decane-2,4-diones (spirohydantoins) as a structurally novel class of pan-inhibitors of the prolyl hydroxylase (PHD) family of enzymes for the treatment of anemia is described. The initial hit class, spirooxindoles, was identified through Affinity Selection Mass Spectrometry (AS-MS) and optimized for PHD2 inhibition and desired PK/PD profile (efficacious, short-acting PHD1-3 inhibitors). Derived from the spirooxindole hit, spirohydantoins provided a modest enhancement of the ADME properties but their further optimization was initially impeded by chemical intractability. A new set of general conditions for C-N coupling, developed using high throughput experimentation (HTE) technique, enabled a full SAR analysis of the spirohydantoin pharmacophore. This optimization resulted in the first reported examples of hydantoin derivatives with good PK in preclinical species for any indication. Observed potassium channel off target activity (hERG) was successfully mitigated through the systematic introduction of acidic functionality to the molecular structure. Undesired upregulation of alanine aminotransferese (ALT) liver enzymes was preclinically derisked by achieving a comfortable on/off-target margin. Optimized spirohydantoins represent a class of highly efficacious, short-acting, small molecule PHD1-3 inhibitors causing a robust erythropoietin (EPO) upregulation in vivo in multiple preclinical species. This profile deems spirohydantoins as attractive short-acting PHD1-3 inhibitors with the potential for treatment of anemia.

MEDI 259

Cracking the histone code: Developing inhibitors of bromodomain-acetyl-lysine interactions

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Histones, the core proteins around which DNA is wound, are susceptible to multiple post-translational modifications, combinations of which are proposed to form a 'histone code' that is involved in regulating gene expression. One such PTM, lysine acetylation, influences recruitment of transcriptional regulators through interaction with bromodomain-containing proteins (BCPs), which 'read' lysine acetylation state. There are 61 bromodomains, found within 46 proteins; these modules are emerging important therapeutic targets and the protein-protein interactions they mediate are druggable. To develop tools that enable elucidation of cellular bromodomain function, we have designed and synthesized small molecules capable of preventing the bromodomain-acetyl-lysine interaction. Herein, the design, synthesis and application of two different acetyl-lysine mimics will be described. The optimisation of these moieties to provide potent and selective ligands for the CREB binding protein (CREBBP) and the bromodomain and extra terminal domain (BET) family of BCPs will be discussed.

MEDI 260

Discovery of highly potent, selective, and brain-penetrable LRRK2 inhibitors

***Anthony A Estrada**, estrada.anthony@gene.com. Department of Discovery Chemistry, Genentech, South San Francisco, CA 94080, United States*

Elevated LRRK2 activity has been identified as a risk factor for the development of Parkinson's disease (PD). There is a high demand for potent, selective and brain-penetrable LRRK2 inhibitors to test whether inhibition of LRRK2 kinase activity will reduce the rate of disease progression in PD patients or animal models of PD. Starting from ligand efficient aminopyrimidine LRRK2 inhibitors, a thorough lead optimization process using property and structure-based drug design was executed. High throughput in vivo pharmacokinetic profiling enabled rapid validation of in vitro permeability and metabolic stability predictions. Guided by this data, optimal physicochemical parameters were established. Effective incorporation of these guidelines into our molecular design process resulted in the rapid discovery of inhibitors possessing an ideal balance of LRRK2 cellular potency, broad kinase selectivity, metabolic stability, and brain penetration across multiple species. Details of these efforts, as well as pharmacodynamic effects of the lead compound, will be presented.

MEDI 261

Structures and function of cytochrome P450 17A1: Drug target for metastatic prostate cancer

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Prostate cancer is a leading cause of cancer mortality in U.S. men. Cytochrome P450 17A1 (CYP17A1) is a key multifunctional enzyme in the synthesis of steroid androgens responsible for prostate cancer proliferation. Specifically, CYP17A1 first accomplishes a 17α-hydroxylation essential for androgen and glucocorticoid production. Subsequently the enzyme also performs a second, mechanistically-distinct lyase reaction cleaving the 17-acyl group from 17α-hydroxypregnenolone that is required only to generate androgens. The first FDA-approved CYP17A1 inhibitor inhibits both reactions, thus obliterating androgen production, but also disrupting glucocorticoid and mineralocorticoid levels. However distinct mechanisms for CYP17A1 hydroxylation and lyase reactions raise the potential to inhibit just the latter androgen-producing capability. Recent structures of CYP17A1 provided the opportunity to examine ligand interactions with the enzyme, suggesting key structural and chemical features of the protein, substrates, and inhibitors. Structures with steroidal CYP17A1 inhibitors currently in use and in development suggest the structural basis of potentially problematic promiscuous inhibitor binding to the androgen receptor. Comparison of CYP17A1 complexes with inhibitors that alter both enzymatic reactions versus CYP17A1 complexes with inhibitors that decimate only the lyase reaction suggest critical residues in a hydrogen bonding network likely to control enzyme reactivities. Site-directed mutagenesis of active site residues and those in the putative cytochrome b_5 binding site, and analysis of naturally-occurring mutations from patients with steroidogenic disease have provided orthogonal routes to dissect the structural and functional interactions that control the two disparate

reactions within the single CYP17A1 active site. This information is expected to inform the design of inhibitors that are not only selective for CYP17A1 over other enzymes in the steroidogenic pathway, but are also selective inhibitors of the enzyme's lyase reaction. Such enzyme-selective and reaction-selective inhibitors would be optimal for the treatment of metastatic prostate cancer with reduced off-target and off-pathway side effects.

MEDI 262

Discovery of a potent dual neurokinin 1 receptor antagonist and serotonin transporter inhibitor for the treatment of depression

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Current treatments of depression are associated with a number of undesirable side effects. Neurokinin 1 (NK1) antagonists have demonstrated the ability to potentiate the antidepressant effects of serotonin-selective reuptake inhibitors (SSRIs) in multiple animal models. A drug which incorporated both activities may offer important tolerability improvements over the current standard of care. Medicinal chemistry efforts identified a novel, dual-acting biphenyl chemotype which suffered from significant ion channel inhibition and extensive protein binding. Cues in the structure-activity relationship were pursued to identify heterocyclic replacements which reduced ion channel blockade, protein binding, and molecular weight. Optimization of this series led to the identification of compounds that achieved the desired target profile and were active in a preclinical model of depression. Scale-up of the lead compound for toxicological evaluation required the development of an unprecedented heterocycle-directed asymmetric hydrogenation to afford the product in excellent chemical yield and high optical purity.

MEDI 263

Using small molecules to engineer and explore human immunity

***David A. Spiegel**, david.spiegel@yale.edu.Yale University, United States*

Antibody-based therapeutics have become critical instruments in treating diseases ranging from rheumatoid arthritis to cancer in recent years. However, antibodies and other therapeutic proteins are limited in therapeutic applications by their chemical structures: because they are peptide-based, they require intravenous administration, are often highly immunogenic or allergenic, and treatment regimens are often very costly.

This talk describe recent research efforts in our laboratories toward the design, chemical synthesis, and biological characterization of small molecule antibody recruiting therapeutics against prostate cancer, *Staphylococcus aureus*, and the human immunodeficiency virus (HIV). These are bifunctional small molecules designed to

redirect antibodies already present in the human bloodstream to the surfaces of pathogenic cells, such as cancer cells, bacteria, and virus particles. The ternary complex formed between these agents, endogenous antibodies, and target cells will lead to immune-mediated pathogen destruction. In theory, this strategy would exploit many of the advantages of biologics, while circumventing the disadvantages, by capitalizing on the chemical properties of small molecules (e.g., high oral bioavailability, facile synthesis, and low cost).

It is our hope that this small molecule-based strategy will serve as starting point toward entirely novel scientific insights and therapeutic approaches relevant to a wide range of disease states.

MEDI 264

Marinopyrrole derivatives as potential antibiotic and anticancer agents

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The marine natural products, Marinopyrroles, were first reported to have antibiotic activity against methicillin-resistant *Staphylococcus aureus* (MRSA) in 2008. Due to their novel class of molecular structures and promising biological properties, they have attracted considerable attention. After we reported the first total synthesis of "symmetrical" marinopyrrole A along with a dozen derivatives in 2010, we revealed the synthesis of a novel series of "asymmetrical" marinopyrrole derivatives with superior antibiotic activities against MRSA. We also discovered that marinopyrrole A is a novel Mcl-1 inhibitor that overcomes ABT-737 resistance by binding to and targeting Mcl-1 for proteasomal degradation. In this talk, the design, synthesis, optimization and SARs of these potential antibiotic and anticancer agents from both "symmetrical" and "asymmetrical" series of marinopyrroles will be presented.

MEDI 265

Targeting the glucose regulated protein 78 in cancer therapy

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Glucose regulated protein 78 (GRP78) is a chaperone protein constitutively expressed in almost all cell types and contains multiple cellular functions, including regulating

protein folding events in the lumen of the endoplasmic reticulum (ER).[1] In the absence of normal GRP78 signaling activity, the accumulation of unfolded proteins in the ER induces cellular stress conditions which ultimately lead to programmed cell death. In cancer cells, GRP78 overexpression generates cell-surface GRP78 which prevents cancer cell apoptosis during stress conditions.[2] Thus, targeting and down-regulating cancer-cell surface GRP78 expression may function as an ideal method for selectively inducing cancer cell death. Our work describes the design, synthesis and characterization of GRP78 receptor cancer targeting ligands for the delivery of chemotherapeutic agents in cancer cells. Our methodology is proposed to overcome the devastating side-effects related to non-specific chemotherapy, and facilitate the targeted delivery of tumor killing agents directly into cancer cells to conquer the disease.

1. Lee, A.S. *Methods* **2005** , *35*, 373-381.
2. Li, J.; Lee, A.S. *Curr. Mol. Med.* **2006** , *6*, 45-54.

MEDI 266

Novel small-molecule suppressors of cytokine-induced beta-cell apoptosis for the treatment of type 1 diabetes

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Type-1 diabetes (T1D) is characterized by autoimmune destruction of pancreatic beta cells resulting in decreased insulin production. The secretion of inflammatory cytokines by infiltrating macrophages in the pancreatic islets of Langerhans triggers an intracellular signaling cascade leading to beta-cell apoptosis. The development of small molecules that prevent immune system-mediated death of beta cells may have therapeutic potential to augment traditional insulin replacement therapy for the treatment of T1D.

At the Broad Institute, we developed a phenotypic assay using the rat INS-1E beta-cell line to measure cell viability when treated with small molecules in the presence of the cytokines: tumor necrosis factor-alpha, interleukin-1beta, and interferon-gamma. Subsequently, a high-throughput screen (HTS) identified several small-molecule “hits” that suppressed beta-cell apoptosis. Here, we report the discovery, medicinal chemistry optimization, and mechanism-of-action studies of diversity-oriented synthesis (DOS)-generated small molecules that protect beta cells from the deleterious effects of cytokines.

MEDI 267

Thromboxane (A_2) receptor antagonists as potential candidates for Alzheimer's disease

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Recent studies identified a role for the thromboxane A_2 prostanoid (TP) receptor, a G protein-coupled receptor, in modulating the production of amyloid β (Aβ) peptide, which is involved in the pathogenesis of senile plaques in Alzheimer's disease (AD). This observation led to the hypothesis that TP receptor antagonists may be therapeutically useful for AD treatment. However, the majority of existing TP receptor antagonists exhibit poor blood-brain barrier (BBB) permeability. This lack of brain-penetration is likely caused in part by the presence in these molecules of a carboxylic acid moiety, which is believed to be important for receptor interaction, but that could hamper passive diffusion across the BBB. Thus, to identify brain-penetrant candidates, we designed, synthesized and evaluated series of analogues of known TP-receptor antagonists wherein the carboxylic acid moiety was replaced by a range of known and novel bio-isosteres. This effort led to the identification of candidate compounds derived from known TP receptor antagonists that exhibit low nM binding affinity for the TP receptor and that can readily cross the BBB.

MEDI 268

Design and development of Nexturastat A, a potent and selective inhibitor of HDAC6

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Modulation of the epigenome is understood to be carefully orchestrated by a variety of enzymes, classically describedas a balance of histone acetyltransferases (HATs) and histone deacetylases (HDACs) which act in a state of opposite activity on both histone and non-histone substrates. Widespread inhibition of HDACs, of which there are 11 isoforms comprised of three Zn^{2+} classes, can have vast cellular consequences. The role of HDACs are currently being elucidated and individual isoforms are being found to possess unique roles within the cell, as such, there is high interest for the development of isoform-specific HDAC inhibitors (HDACi). Herein we report the development and SAR of branched urea linkers as part of the canonical HDACi scaffold that led to Nexturastat A, a potent and selective HDAC6 inhibitor. Nexturastat A increases acetyl-tubulin levels and interestingly inhibits the growth of melanoma cells.

MEDI 269

Regiospecific synthesis of isoindolinones as MDM2 inhibitors

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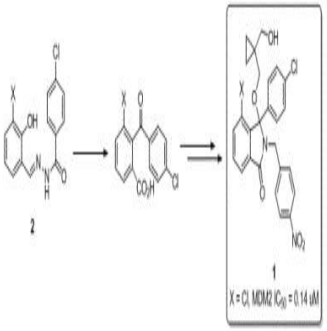
Inhibition of the MDM2-p53 protein-protein interaction is an important approach to cancer therapy. MDM2-p53 inhibitors, e.g isoindolinones **1** , reactivate p53 in MDM2 amplified cell-lines, inducing growth inhibition or apoptosis (*Bio. Med. Chem. Letts*, 2011, 54, 5916). Previous isoindolinone syntheses were hampered by difficult separation of A-ring regioisomers. A versatile, regioselective synthesis of 4-substituted isoindolinones e.g. **1** was achieved using a lead-mediated rearrangement of *N*-acylhydrazone **2** . A small-series of 4-substitutions was investigated, demonstrating the optimal properties of chlorine at this position.



MEDI 270

Inhibitors of Ras carboxyl methyltransferase as potential treatments for pancreatic cancer

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Mutant K-Ras proteins are key drivers in ~90% of human pancreatic carcinomas. K-Ras is modified post-translationally via prenylation, proteolysis, and α-carboxyl methylation. Both prenylation and methylation are necessary for the proper localization and biological function of K-Ras. Thus, there is great interest in blocking the methylation of K-Ras by human isoprenylcysteine carboxyl methyltransferase (hIcmt) as a route to

block its activity in tumor cells. We have developed a readily-synthesized class of nanomolar hIcmt inhibitors based on the substrate *N*-acetyl-farnesyl cysteine (AFC). Elaboration of the structure-function relationships around these compounds led to our current lead compound, sTAB-F_3-Diol, which has a K_i of approximately 50 nM against hIcmt. sTAB-F_3-Diol also blocked cellular Ras activation, interfered with Ras signaling through Erk, and exhibited nanomolar to low micromolar GI_{50} values versus pancreatic tumor cells *in vitro*. We are currently further optimizing the biochemical activity and drug-like characteristics of this potent and promising agent.

MEDI 271

Taxoid-based tumor-targeting chemotherapeutic agents bearing an imaging module

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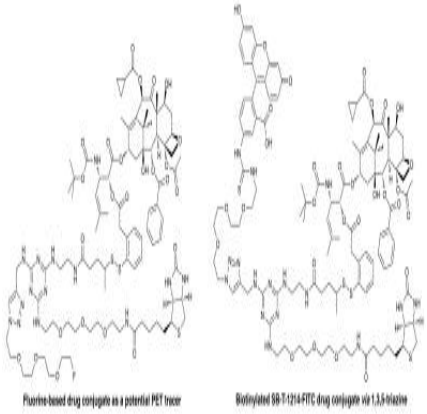
Novel taxoid-based, tumor-targeting drug conjugates bearing a single imaging agent were designed and synthesized. Biotin receptors are overexpressed in a variety of human cancers. Thus, biotin has been selected as a tumor-targeting module (TTM) in the following drug conjugates. Second-generation taxoid, SB-T-1214, exhibiting orders of magnitude greater potency than paclitaxel in various cell lines, was selected as the cytotoxic agent. Each molecule is connected *via* a 1,3,5-triazine splitter by a water-solubilizing polyethylene glycol spacer and a glutathione-triggered self-immolative disulfide linker, respectively. Bearing a terminal acetylene allows for rapid conjugation to various imaging agents. To assess *in vivo* biodistribution, a fluorine-labeled drug conjugate was prepared as a potential PET tracer by rapid “click” conjugation of a fluorinated prosthetic. The cytotoxicity was evaluated on various cancer cell lines. Furthermore, a fluorescein isothiocyanate (FITC) analog was prepared to verify the internalization of the biotinylated drug-scaffold by means of flow cytometry. This mechanism-based tumor-targeting drug delivery system will find a wide range of applications including dual-TTM and dual-drug delivery. The syntheses and biological evaluation of these novel drug conjugates will be presented.



MEDI 272

Amidine-based sphingosine kinase inhibitors: Optimization and pharmacokinetics

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The sphingosine kinases (SphKs) have been identified as a driving force in cancer progression. The two isoforms, SphK1 and SphK2, control the production of the potent growth signaling molecule sphingosine 1-phosphate (S1P), shown to be elevated in a variety of cancers. SphK inhibitors may prove effective as targeted cancer therapies and help to further elucidate the role of the SphKs in disease. Amidine-based SphK1 inhibitors have been some of the most potent and most selective of their type in the chemical literature to date. First generation amidine-based SphK inhibitors have a low half-life presumably due to a metabolically labile amide bond. Replacement of the amide with oxadiazole isosteres has proven to be effective at increasing the half-life while maintaining potency and selectivity at the recombinant enzyme. The optimization, *ex vivo* and *in vivo* biological activity and pharmacokinetic properties of these inhibitors will be described.

MEDI 273

Development of streptolysin S inhibitors as anti-virulence drugs

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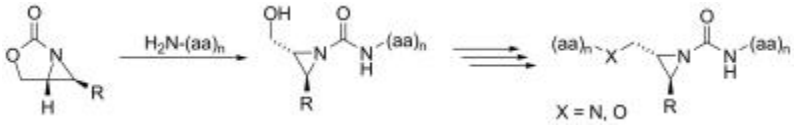
Cork, Cork, Ireland (4) Alimentary Pharmabiotic Centre, Cork, Ireland (5) Teagasc, Moorepark Food Research Centre, Fermoy, County Cork, Ireland (6) Department of Microbiology, University of Illinois at Urbana-Champaign, Urbana, Illinois 61801, United States (7) Institute for Genomic Biology, University of Illinois at Urbana-Champaign, Urbana, Illinois 61801, United States

Targeting bacterial virulence is an alternative strategy for producing drugs that circumvent traditional antibiotic resistance. One approach is to inhibit the production of crucial toxins, providing a means of directly reducing pathogenicity. The production of streptolysin S (SLS), a posttranslationally modified ribosomal peptide cytolysin produced by *S. pyogenes*, was found to be inhibited by cpd1, a known protease inhibitor. A photoactivatible crosslinking derivative of cpd1 was synthesized and is being used to identify the cpd1 biological target by affinity purification and mass spectrometry. Inhibition of the production of a related toxin in *L. monocytogenes* was shown, demonstrating the potential of cpd1 to be used against other pathogens. Derivatization to determine structure-activity relationships for cpd1 resulted in a compound with a 6-fold increase in potency, and this compound is being used in efforts to determine the efficacy of SLS inhibition as an anti-virulence strategy in a mouse infection model.

MEDI 274

Synthesis of N-acyl aziridine containing peptidomimetics

***Greggory M Wells**, gw352301@ohio.edu, Stephen C Bergmeier. Department of Chemistry and Biochemistry, Ohio University, Athens, Ohio 45701, United States*



Peptidomimetics have demonstrated biological activity toward a broad range of medicinal targets. Although aziridine containing peptidomimetics have been reported, there are no examples of *N*-acyl aziridines. We have recently shown that fused ring aziridines can be converted to aziridinyl ureas by reaction with amine nucleophiles. We will present new examples of this reaction using amino acids and peptides as the nucleophile to generate peptidomimetics containing an aziridinyl urea. Structural and biological studies with these novel peptidomimetics will also be presented.

MEDI 275

New PET and SPECT imaging agents for the translocator protein (18 kDa)

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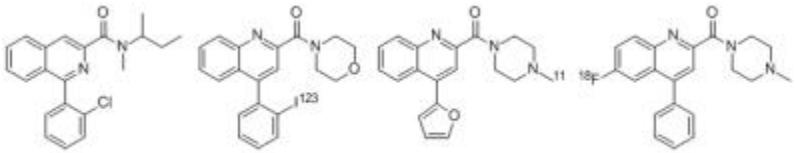
The Translocator Protein (18 kDa) (TSPO) has been implicated in microglial activation within the central nervous system, and expression is upregulated when neuronal inflammation/degeneration occurs. This, therefore, offers an attractive target for PET and SPECT imaging of a range of diseases. PK11195 **1** , a TSPO imaging agent, has excellent binding affinity but poor bioavailability and non-specific binding. A research program has been initiated focusing on the preparation of novel PK11195 analogues with improved physicochemical properties for imaging TSPO. The synthetic chemistry utilised, along with physicochemical properties and biological binding data will be presented.



PK11195 **1**

MEDI 276

Discovery and preclinical pharmacology of BMS-906024, a pan-Notch inhibitor for the treatment of cancer

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Deregulation of the Notch pathway has been shown to be oncogenic in numerous tissue types including breast cancer, lung cancer, and colorectal carcinoma. Notch signal activation can cause uncontrolled proliferation, restrict differentiation leading to increased self-renewal capacity, evasion of apoptosis, and enhancement of angiogenesis and metastasis. There is increasing evidence that Notch plays a role in the maintenance and survival of cancer stem cells. Gamma-Secretase mediates the Notch signaling pathway by releasing the Notch intracellular domain which translocates to the nucleus and binds to the transcription factor CSL to activate transcription of various target genes. This presentation will summarize structure-activity relationship in a series of inhibitors of gamma-secretase mediated Notch signaling that culminated in identification of BMS-906024 as the clinical candidate. In vivo evaluation of the clinical candidate will be described in relevant tumor xenograft models. BMS-906024 is currently in Phase I clinical trials for the treatment of cancer.

MEDI 277

Discovery of LGX818: A potent, selective RAF kinase inhibitor for treatment of BRAFV600E-positive melanoma

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The RAF serine-threonine kinases—in particular the BRAF and CRAF isoforms— are key components of the mitogen-activated protein kinase (MAPK) signal transduction pathway, which regulates proliferation, differentiation, and apoptosis in mammalian cells. Activating mutations of BRAF, especially V600E BRAF, are found in multiple cancers, most notably in melanoma, where approximately 40% of cases are BRAF-V600E positive. Selective RAF inhibitors have demonstrated significant efficacy in melanoma patients with tumors harboring the BRAF-V600E mutation. Presented is LGX818, a selective small molecule mutant-BRAF kinase inhibitor that suppresses the RAF-MEK-ERK pathway in tumor cells expressing activating BRAF-V600 mutations. In rodent BRAF-V600 tumor xenograft models, LGX818 induces sustained tumor regression at low doses and is well-tolerated. LGX818 has shown an excellent preclinical safety profile. Multiple clinical trials are underway with LGX818 in patients harboring mutant-BRAF solid tumors.

MEDI 278

Discovery of AZD5423, a potent and selective non-steroidal glucocorticoid receptor modulator for the inhaled treatment of respiratory diseases

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Inhaled glucocorticoids are very potent anti-inflammatory drugs that alone or in combination with bronchodilators are the mainstay of inhaled therapy for respiratory diseases such as chronic obstructive pulmonary disease (COPD) and Asthma. However there is still a large unmet clinical need in both of these diseases. The presentation will describe the identification and properties of AZD5423, a novel, highly selective and efficacious inhaled GR-modulator currently in clinical phase II studies. This includes the successful integration of structural chemistry and computational chemistry to resolve both genotoxicity and efficacy issues leading to the identification of novel indazole ether GR modulators. This series was amenable to parallel synthesis, resulting in a rapid exploration of the scope of the series and providing the project with highly potent ligands, often with a cellular potency in pM range. The best compounds were progressed into a series of well-established models for respiratory diseases, from which AZD5423 was selected. The presentation will also describe the rational application of inhalation compound properties to obtain the desired lung PK.

MEDI 279

Discovery of TL32711 (Birinapant): A novel bivalent Smac mimetic and antagonist of the inhibitor of apoptosis proteins for the treatment of cancer

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Birinapant (TL32711) is a novel bivalent Smac mimetic or antagonist of cIAP1, cIAP2, ML-IAP and XIAP, members of the inhibitor of apoptosis (IAP) family of proteins, which is currently undergoing clinical development for the treatment of cancer. The IAPs regulate apoptosis by controlling the activation of specific caspase enzymes. Like other reported Smac mimetics, birinapant was designed to interact with the BIR3 domains of IAP proteins. Birinapant selectively triggers the ubiquitylation and proteasomal degradation of cIAP1 and cIAP2, key components of the TNFα-receptor I complex, resulting in the inhibition of canonical NF-κB-mediated transcription and activation of the extrinsic apoptotic pathway. In primary xenograft mouse models, birinapant effectively inhibits the growth of tumors. In preclinical toxicology studies, birinapant was well-

tolerated compared with less selective bivalent Smac mimetics. In clinical studies, across a broad dose range, birinapant has been safe as a single agent and when combined with multiple standard-of-care chemotherapies.

MEDI 280

Discovery and development of MGL-3196, a liver-directed thyroid hormone beta agonist for the treatment of hypercholesterolemia/dyslipidemia and hypertriglyceridemia

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Thyroid hormone receptors are members of the nuclear hormone receptor family. Thyroid hormone (T3) is known to have a positive effect on levels of cholesterol and triglycerides, primarily through its action at the thyroid hormone receptor beta (THR-β) in the liver. Many of the adverse effects of hyperthyroidism, including cardiac effects, are mediated by thyroid hormone receptor alpha (THR-α). We report the discovery and SAR of a series of selective THR-β agonists. This series was optimized for THR-β selectivity and minimal THR-α activity, lack of activity in a micronucleus test, high liver exposure and absence of cardiotoxicity, leading to the identification of MGL-3196. Dosed orally, MGL-3196 exhibits beneficial effects on cholesterol and liver triglycerides while maintaining normal levels of thyroid hormones and TSH in preclinical models. MGL-3196 is currently in clinical development for the treatment of hypercholesterolemia/dyslipidemia and hypertriglyceridemia. The PK and lipid results from Phase I studies will be presented.

MEDI 281

Chemical subtleties in small-molecule modulation of peptide receptor function: The case of CXCR3 biaryl-type ligands

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The G protein-coupled chemokine receptor CXCR3 plays a role in numerous inflammatory events. The endogenous ligands for the chemokine receptors are peptides, but in this study we describe small-molecule ligands that are able to activate CXCR3. A class of biaryl-type compounds that is assembled by convenient synthetic routes is described as a new class of CXCR3 agonists. Intriguingly, SAR and SFR

studies reveal that subtle chemical modifications on the outer aryl ring (e.g. either the size or position of a halogen atom) results in a full spectrum of agonist efficacy on CXCR3. QM calculations and NOESY NMR studies suggest that the biaryl dihedral angle and the electronic nature of *ortho*-substituents play an important role in determining agonist efficacies. Compounds VUF11222 and VUF11418 are the first non-peptidomimetic agonists on CXCR3, rendering them highly useful chemical tools for detailed assessment of CXCR3 activation as well as for studying downstream CXCR3 signaling.

MEDI 282

Design, synthesis, and structure-activity relationships of dual PDE3/4-inhibitory fused bicyclic heteroaromatic-4,4-dimethylpyrazolones

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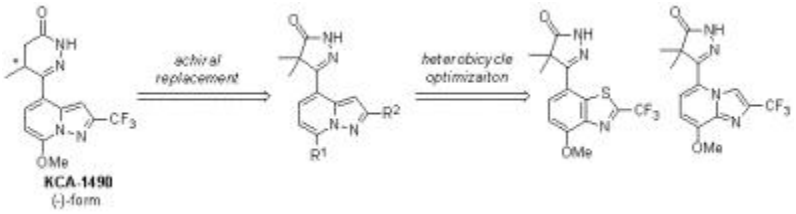
(–)-6-(7-Methoxy-2-trifluoromethylpyrazolo[1,5-*a*]pyridin-4-yl)-5-methyl-4,5-dihydro-3-(*2H*)-pyridazinone (KCA-1490) is a dual PDE3/4 inhibitor that exhibits potent combined bronchodilatory and anti-inflammatory activity. Here we show that a 4,4-dimethyl-pyrazolone subunit serves as an effective surrogate for the 5-methyl-4,5-dihydropyridazin-3(2*H*)-one ring of KCA-1490. The 2- and 7-substituents in the pyrazolo[1,5-*a*]pyridine subunit markedly influence the PDE-inhibitory profile. Moreover, a survey of bicyclic heteroaromatic replacements for the pyrazolo[1,5-*a*]pyridine allowed further refinement of the inhibitory profile and identified imidazo[1,2-*a*]pyridine-4,4-dimethylpyrazolone derivative as an orally active, achiral KCA-1490 analog with well-balanced dual PDE3/4-inhibitory activity.



MEDI 283

Structure-activity relationships in human toll-like receptor 8-active 2,3-diamino-furo[2,3-c]pyridines

***Deepak B Salunke**, deepsalunke@gmail.com, Euna Yoo, Nikunj M Shukla, Rajalakshmi Balakrishna, Subbalakshmi S Malladi, Katelyn J Serafin, Victor W Day, Xinkun B Wang, Sunil A David. Department of Medicinal Chemsitry, University of Kansas, Lawrence, KS 66047, United States*

In our ongoing search toward identifying novel and synthetically simpler candidate vaccine adjuvants, we hypothesized that the imidazo[1,2-*a*]pyrazines, readily accessible via the Groebke−Blackburn−Bienaymé multicomponent reaction, would possess sufficient structural similarity with TLR7/8-agonistic imidazoquinolines. With pyridoxal as the aldehyde component, furo[2,3-c]pyridines, rather than the expected imidazo[1,2-*a*]pyridines, were obtained, which were characterized by NMR spectroscopy and crystallography. Several analogues were found to activate TLR8-dependent NF-kB signaling. In a focused library of furo[2,3-*c*]pyridines, a distinct SAR was observed with varying substituents at C2. In human PBMCs, none of the furo[2,3-*c*]pyridines showed any proinflammatory cytokine induction but upregulated several chemokine ligand genes. In immunization studies in rabbits, the most active compound showed prominent adjuvantic effects. The complete lack of proinflammatory cytokine induction coupled with strong adjuvantic activity of the novel furo[2,3-*c*]pyridines render this hitherto unknown chemotype an attractive class of compounds which are expected to be devoid of local or systemic reactogenicity.

MEDI 284

Ligand-based design, synthesis, and biological evaluation of a novel series of RAGE (Receptor for Advanced Glycation End Products) inhibitors

Young Taek Han[1], Gyeong-In Choi[1], Do-Hyun Son[2], Nam-Jung Kim[1], Hwayoung Yun[1], Sunjin Lee[1], Dong Jo Chang[1], Hyun-Seok Hong[3], Kyeojin Kim[1], Tae Woo Kim[1], ***Changjin Lim**[1], Koryoi@snu.ac.kr, Hyun-Ju Park[2], Jeewoo Lee[1], Young-Ger Suh[1]. (1) College of Pharmacy, Seoul Nat'l Univ., Seoul, Republic of Korea (2) School of Pharmacy, Sungkyunkwan University, Suwon, Republic of Korea (3) Medifron DBT, Sandanro 349, Ansan-City, Gyeonggi-Do 425-839, Republic of Korea*

Alzheimer's disease (AD) is well known as one of the most common neurodegenerative disease in elderly individuals. According to “b-amyloid (Ab) hypothesis”, Ab peptide is central to the pathological cascade involved in the pathogenesis of AD. Ab is produced mostly in somatic cells through the proteolysis of amyloid precursor protein (APP), and the entry of Ab into the brain and subsequent accumulation is essential for the pathogenesis of AD. Receptor for advanced glycation end products (RAGE)-Ab interaction not only promotes the transport of Ab into the brain, but also activates NF-kB, a transcription factor that plays a crucial role in various inflammatory responses. In this context, the inhibition of the RAGE-Ab interaction has been recognized as more preclusive and curative AD treatment strategy.

In connection with the development of novel RAGE inhibitors as potential AD therapeutics, we designed and synthesized on the structural basis of a monomeric

advance glycation end product (AGE). Subsequently, we identified a novel scaffold for RAGE-inhibitory activity. We also established the structure-activity relationship of the inhibitors based on the *in vitro* RAGE inhibition. In particular, one of the analogs resulted in the significant inhibition of Ab accumulation in the brain and in a noticeable improvement in cognitive function in AD model mice after oral administration. The mechanism of the RAGE inhibitory activities was partly elucidated by SPR analysis, the results of which supported the hypothesis that the direct binding of the inhibitorwith RAGE contributed to its RAGE-inhibitory activities. In addition, the binding mode of the inhibitors with RAGE was predicted by a docking study of the inhibitors on the RAGE V-domain.

MEDI 285

Synthesis and biological evaluation of clovamide analogs for anti-inflammatory activities

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Clovamide, discovered in red clover and in cocoa, attracted attention due to its anti inflammatory, antioxidant and neuroprotective effects. For the purpose of discovering the compound possessing the anti-inflammatory effect, a series of clovamide analogues, where the caffeic acid moiety was replaced with various fluorinated moieties, were synthesized and tested on anti-inflammatory assays in BV2 cells. Among the synthesized compounds, the compound in which the dihydroxy group in the phenyl ring was substituted with a trifluoromethyl group at the meta-position and the double bond was reduced to a single bond, showed good anti-inflammatory activities with suppression of NO production in lipopolysaccharide-induced BV2 cells. The syntheses and biological evaluations of various analogues will be discussed in detail.

MEDI 286

Syk inhibitors for medical applications

Xianchang Gong*, xianchang@gmail.com, Taiyou Hu, Zhengzheng Wang. Department of Chemistry, Jinan Saiwen Pharmtech Inc., Jinan, Shandong Province 250100, China*

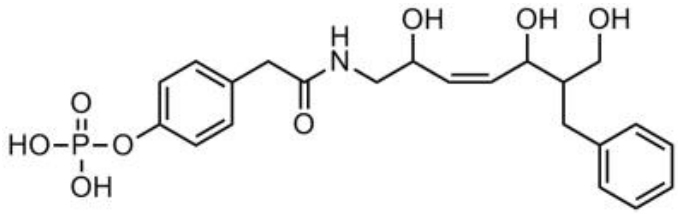
Spleen tyrosine kinase is a member of the Syk family of Tyrosine kinases. Syk inhibitors are current in clinical trials for the treatment of rheumatoid arthritis. A lead series of potent Syk inhibitors has been discovered and studied.

MEDI 287

Design and synthesis of novel Lck SH2 domain ligands bearing a stereodiversified molecular scaffold

***Christine Marian**, cmarian@purdue.edu, Richard F Borch. Department of Medicinal Chemistry and Molecular Pharmacology, Purdue University, West Lafayette, Indiana 47907, United States*

As an important modulator of protein tyrosine kinase signaling, the Src homology-2 (SH2) domain has emerged as an attractive drug target. However, SH2 domain inhibitors often suffer proteolytic cleavage, cellular impermeability, and poor potency. Using a structure-based approach, we have designed a novel series of Lck kinase SH2 domain ligands incorporating a *cis*-enediol scaffold. These non-peptidic ligands offer increased conformational rigidity and a stereodiversified core, and can be delivered intracellularly using prodrug chemistry previously developed in our laboratory.



MEDI 288

Identification of the first non-secosteroid antagonist for the vitamin D receptor

***Kelly A Teske**, kateske@uwm.edu, Leggy Arnold. Department of Chemistry and Biochemistry, University of Wisconsin-Milwaukee, Milwaukee, Wi 53211, United States*

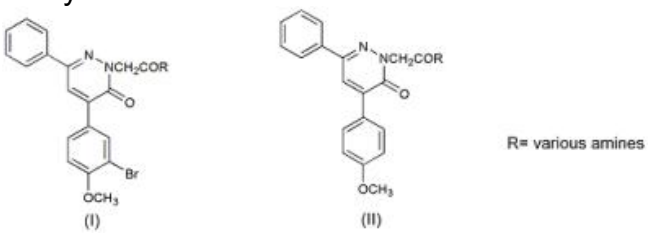
The vitamin D receptor is a nuclear hormone receptor that regulates cell proliferation, cell differentiation, and calcium homeostasis. The receptor is activated by 1,25-dihydroxyvitamin D_3, which induces transcription regulated by coactivator binding. Thousands of VDR agonists have been synthesized but most of them induce hypercalcemia *in vivo* or exhibit poor selectively among other nuclear receptors. Herein, we report the first non-secosteroid antagonist for VDR, which has great potential as anti-allergic and as a cure for diseases caused by hypercalcemia such as crohn's disease and sarcoidosis. The compounds presented here were derived from GW0742, a known selective agonist of the nuclear receptor Peroxisome Proliferator-Activated Receptor δ (PPARδ). GW0742 was identified as a VDR antagonist during a screening campaign with the NIH chemical and genomics center (NCGC) and is currently used as a scaffold to develop highly selective modulators for VDR.

MEDI 289

Synthesis and pharmacological evaluation of a series of 4,6-diaryl substituted 3(2*H*)-pyridazinones as safer anti-inflammatory agents

***Deepika Sharma**, d_sharma84@yahoo.com, Ranju Bansal. University Institute of Pharmaceutical Sciences, Panjab University, Chandigarh, Chandigarh 160014, India*

A new series of 3(2*H*)-pyridazinone based NSAIDs with 4,6-diaryl substitution have been designed and synthesized in order to find better anti-inflammatory agents. The structures of synthesized derivatives have been established by IR, NMR and elemental analysis.



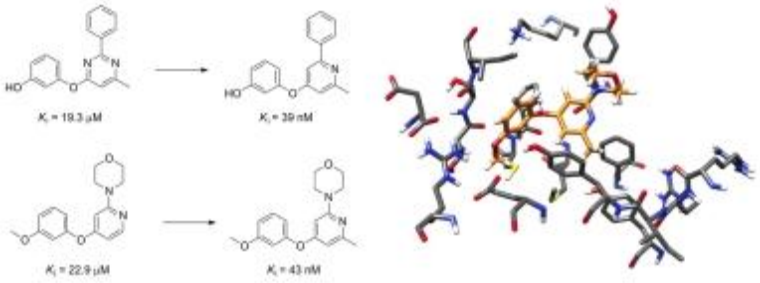
Anti-inflammatory activity of synthesized compounds (20 mg/Kg and 40 mg/kg) was studied using carrageenan-induced rat paw edema model. All compounds exhibited potent anti-inflammatory activity and superior gastrointestinal safety profile than indomethacin. Interestingly bromo unsubstituted derivatives (II) displayed better potency in comparison to substituted counterparts (I).

MEDI 290

Small ligand modifications induce large structure changes in the Plasmodium falciparum macrophage migratory inhibitory factor tautomerase active site

***Markus K. Dahlgren**, markus.dahlgren@yale.edu, Julian Tirado-Rives, William L. Jorgensen. Department of Chemistry, Yale University, New Haven, CT 06520-8107, United States*

We have previously developed potent and selective inhibitors of the tautomerase activity of *Plasmodium falciparum* macrophage migratory inhibitory factor (*J. Med. Chem*. ASAP, doi: 10.1021/jm301269s). For some cases, small ligand modifications led to large enhancements (400-500 times) in K_i values. Insights are provided here into the origins of the variations through molecular dynamics simulation of protein-ligand complexes.

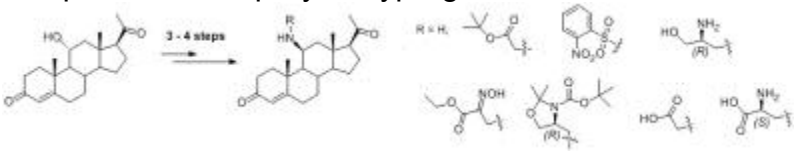


MEDI 291

Facile stereoselective synthesis of a new family of aminosteroids: 11β-aminoprogesterone and its derivatives

***Keyur Pandya**, kpandya@ualberta.ca, John C. Vederas. Department of Chemistry, University of Alberta, Edmonton, Alberta T6G2G2, Canada*

Aminosteroids and C-11 substituted steroids have attracted long lasting interest due to their numerous pharmacological properties. The 10β, 11α and 12β-aminoprogesterones have been reported with their biological activity, but 11β-aminoprogesterone still remains unknown. Stereoselective C-11β functionalization of steroids imposes sever steric hindrance due to the C-18 and C-19 angular methyl groups. Here, we disclose a facile synthesis of new aminosteroids: 11β-aminoprogesterone and its derivatives, such that their biological activities can be compared with 11β-hydroxyprogesterone and other aminosteroid conjugates.



MEDI 292

Discovery of novel trisubstituted cyclohexane derivatives as potent and bioavailable CCR2 antagonists

***Robert J Cherney**, robert.cherney@bms.com, Ruowei Mo, Michael G Yang, Zili Xiao, Dayton T Meyer, Qihong Zhao, Sandhya Mandlekar, Yvonne C Lo, Gengjie Yang, Persymphonie B Miller, Peggy A Scherle, Zelda R Wasserman, Heather Jezak, Kimberly A Solomon, Andrew J Tebben, Mary Ellen Cvijic, Joel C Barrish, Carl P Decicco, Percy H Carter. Research and Development, Bristol-Myers Squibb Company, Princeton, New Jersey 08543-4000, United States*

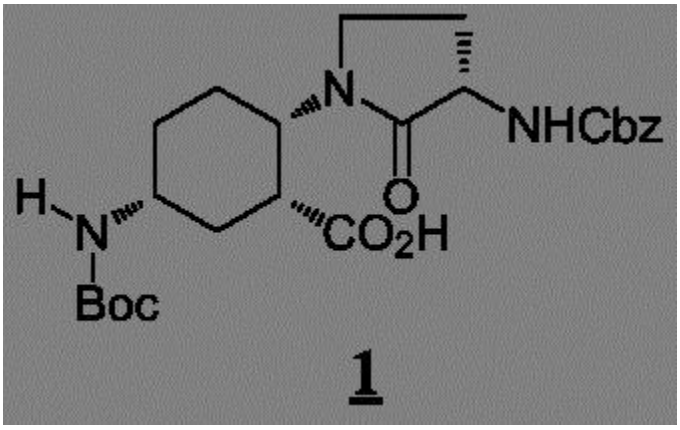
Chemokines are endogenous proteins that are involved in the migration of leukocytes to points of inflammation. We have been interested in the chemokine, monocyte chemoattractant protein-1 (MCP-1 or CCL2), as it is overexpressed in many autoimmune and inflammatory conditions. MCP-1 induces its functional response via its cell surface-expressed receptor, CC chemokine receptor 2 (CCR2), which is a G protein-coupled receptor. It is thought that antagonism of this pair (CCR2/MCP-1) could hold promise as a potential therapeutic for a host of diseases, including rheumatoid arthritis, atherosclerosis, multiple sclerosis, and diabetes. In this disclosure, we describe novel, potent, and bioavailable trisubstituted cyclohexane derivatives as CCR2 antagonists.

MEDI 293

Design and synthesis of 2-substituted cyclohexylaminobenzamide-derived inhibitors of CC Chemokine Receptor 2 (CCR2)

Michael G Yang*, michael.yang@bms.com, Joel C Barrish, Douglas G Batt, Gregory Brown, Bang-Chi Chen, Robert J Cherney, MaryEllen Cvijic, George V Delucca, John V Duncia, Daniel S Gardner, Joseph B Santella, Qing Shi, Anurag Srivastava, Bei Wang, Zili Xiao, Qihong Zhao, Rulin Zhao, Percy H Carter.Bristol-Myers Squibb Company, Princeton, NJ 08543, United States*

CCR2 is critically involved in the migration of inflammatory monocytes and has been implicated in the pathogenesis of a number of inflammatory diseases. In our own efforts to develop selective small molecule antagonists of this receptor, we previously developed SAR from intermediate 1. Presently, we describe our continued advancement of these SAR efforts through the Curtius rearrangement of 1, leading to the discovery of clinical candidate BMS-741672. The first generation synthesis of BMS-741672 will be described in detail.



1

MEDI 294

Design and synthesis of anti-inflammatory steroids with improved therapeutic index: Disovery of an inhaled dissociated steroid

Purakkattle Biju[1]*, purakkattle.biju@merck.com, Kevin McCormick*[1]*, Robert Aslanian*[1]*, Michael Berlin*[1]*, Richard Chapman*[1]*, Robbie McLeod*[2]*, Daniel Prelusky*[3]*, Stephen Eckel*[2]*, George Kelly*[2]*, Michelle Natiello*[2]*, Aileen House*[2]*, Xiomara Fernandez*[2]*, Rema Bitar*[1]*, Jonathan Phillips*[2]*, John Anthes*[2]*. (1) Department of Medicinal Chemistry, MRL, Merck & Co., Kenilworth, New Jersey 07033-1300, United States (2) Department of Allergy and Immunology, MRL, Merck & Co., Kenilworth, New Jersey 07033-1300, United States (3) Department of Drug Metabolism and Pharmacokinetics, MRL, Merck & Co., Kenilworth, New Jersey 07033-1300, United States*

Glucocorticoids (anti-inflammatory steroids) have been on the market for more than 60 years and represent the most effective therapy for both acute and chronic inflammatory conditions[1] including allergic and non allergic diseases such as asthma, COPD, rheumatoid arthritis and many more. Mechanistically, glucocorticoids are involved in two major gene transcription pathways, transrepression and transactivation. Broadly speaking, transrepression is the interaction of the glucocorticoid receptor-steroid monomer complex with the transcription factors such as AP-1 and NFκ-B, which is believed to be the major contributor of the antiinflammory activity of glucocorticoids. However, most of the systemic side effects are due to the interaction of glucocorticoid receptor-steroid dimer complex with DNA, which brings increased transcription called transactivation. The transactivation of genes by GR is suggested to be key in determining the metabolic side effects of glucocorticoids. The major side effects such as decreased bone density skin thinning, HPA axis suppression and diabetes are hypothesized to be due to the genomic events as a result of the interaction of glucocorticoid receptor-steroid dimer complex with DNA. Hence, a glucocorticoid that can separate transactivation from transrepression may display an improved safety profile and is called a dissociated steroid or selective glucocorticoid receptor modulator. Herein, we report our SAR efforts towards the discovery of an inhaled candidate **1** that demonstrated dissociated profile both *in vitro* and *in vivo*

MEDI 295

Stereocontrolled synthesis and biological actions of DHA-derived lipid mediators

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The many beneficial health effects of the omega-3 fatty acid docosahexaenoic acid (DHA) have been attributed to the endogenous production of novel anti-inflammatory lipid mediators, generated during the inflammatory response. The most potent of these oxygenated metabolites of DHA are produced enzymatically in enantiomerically pure form, and feature distinct stereochemical features. Herein, we report the concise and stereocontrolled total synthesis of DHA-derived lipid mediators with unique biological actions involving the regulation of inflammation and infection.

MEDI 296

MIF as a therapeutic target: Recent developments and future possibilities

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Macrophage migration inhibitory factor (MIF) is a potent pro-inflammatory cytokine implicated in the pathogenesis of numerous autoimmune and inflammatory diseases (e.g. sepsis, asthma, arthritis, cancer, multiple sclerosis, and diabetes). X-ray crystallographic studies have shown that MIF is homotrimeric with a catalytic pocket formed between each adjacent subunit. We therefore reasoned that compounds targeting this site could be useful to inhibit MIF activity. Our group developed ISO-1, one of the first MIF inhibitors to bind the enzymatically-active hydrophobic pocket of MIF. This inhibitor and others have shown efficacy in various models of inflammatory disease where enhanced MIF levels have been reported. Administration of ISO-1 improved survival during sepsis, ameliorated diabetes, and reduced the size of tumor in animal models (for review see (Al-Abed, 2011, Future Medicinal Chemistry)). The success of these studies has led to the continued development and screening of small molecules which can block MIF pro-inflammatory activities by targeting the unique enzymatically-active hydrophobic pocket. Recently, we have uncovered thyroxine (T4) as a potential endogenous inhibitor of MIF activity (Al-Abed, PNAS, 2011). These results may have implications for Euthyroid Sick Syndrome (ESS), a condition resulting in low thyroid hormone levels (T3, T4) and high pro-inflammatory cytokine levels, which can result from sepsis, starvation, surgery, trauma, chronic degenerative disease, myocardial infarction, bone marrow transplantation, or other severe systemic illness. We found that both L (biologically active) and D isoforms of T4 could inhibit the enzymatic (tautomerase) *(in-vitro*) and biologic (*in-vivo*) activities of MIF. Current studies focus on developing and testing new analogues that inhibit MIF activity and could potentially be used for the treatment of sepsis and other inflammatory diseases, autoimmune disease, and cancer.

MEDI 297

Design and development of selective Pim1 kinase inhibitors

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The Pim1 gene was initially identified as a proviral integration site in Moloney murine leukemia virus-induced mouse T-cell lymphomas. Pim kinases are implicated in the development of solid tumors. DNA microarray analyses showed the overexpression of Pim1 in human prostate cancer in relation to the grade of the prostate cancer. Pim

protein's role in human cancers such as prostate, pancreatic, colon, chronic lymphocytic leukemia, non-Hodgkin's lymphoma and multiple myeloma is well established. It has been found that the knockout of *Pim1* in mice is not lethal and its absence does not induce any immediately obvious phenotype. This makes Pim1 an attractive target for chemotherapy. Our search for small molecules as kinase inhibitors, lead us to quinazolines and anthraquinones. Polyhydroxy-1,2,3,4-tetrahydroanthracene-9,10-diones were found to selectively inhibit Pim1, Pim3 and CSNK1d kinases. Docking studies revealed the binding orientation of these molecules and provided critical insights for further development of these compounds towards improving their potency while maintaining their selectivity profile. The synthesis of the designed anthracenedione derivatves and the bioassay of these compounds are presented.

MEDI 298

Kinase-focused library: Design and synthesis of pyrimidines derivatives bearing amino substituents using high throughput parallel synthesis

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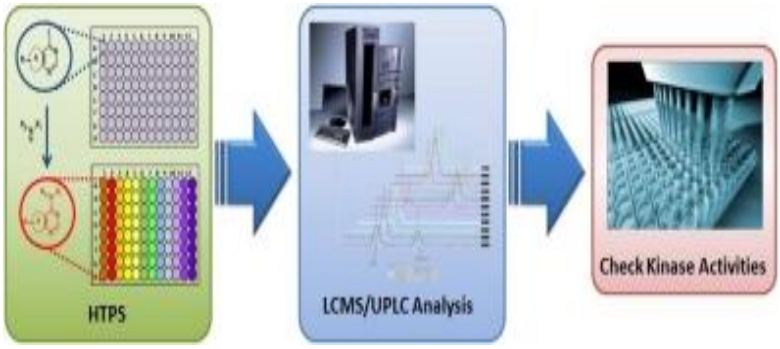
Pyrimidine derivatives bearing amino substituents have been of multifold biological and pharmacological interest. In order to speed up lead identification for drug discovery, the application of high throughput parallel synthesis (HTPS) has become an important target. It is also well known that S_NAr reaction has become a useful and efficient synthetic protocol.

Herein, a focused library of pyrimidine derivatives was rapidly synthesized in parallel reactor via S_NAr displacement and progress of all reactions was monitored by UPLC and LCMS. All library compounds were further screened for kinase activities leading to the identification of interest hit.



MEDI 299

Development drug candidate targeting EGFR kinase: DBPR112

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Lung cancer is the major cause of cancer death in the world while non small cell lung cancer (NSCLC) accounts approximately 85% of all lung cancer diagnosis. EGFR mutations, found in 10–30% of patients with NSCLC characterize a subpopulation with exquisite sensitivity to EGFR tyrosine kinase inhibitors (EGFR-TKIs). However, the clinical benefits of first-generation TKIs (like gefitinib) can be further improved because of the development of drug-acquired resistance within 10–14 months in patients who initially respond to the treatment. Therefore, there is a need to discover next generation medicines as EGFR-TKIs for NSCLC patients.

Currently, we had identified DBPR112 as a potent EGFR-TKI with oral *in vivo* activity in a mouse model for lung adenocarcinoma. DBPR112 showed IC_{50} of 2 nM in HCC827 cells and potent $EGFR^{Wild\text{-}Type}$ (IC_{50}: 10 nM) and $EGFR^{L858R/T790M}$ (IC_{50}: 70 nM) kinase inhibition which are better than gefitinib and similar to that of BIBW2992 (afatinib, developed by Boehringer Ingelheim) that is currently under phase III clinical trial. DBPR112 was orally administered against the growth of human lung HCC827 tumors subcutaneously xenografted in nude mice. A dramatic reduction of the tumor size was noted in the tumors treated with DBPR112 without significant loss of body weights in the nude mice. In addition, the pharmacokinetics properties of DBPR112 are superior to those of BIBW2992. These results demonstrate the potential of DBPR112 as a therapeutic candidate for the treatment of lung adenocarcinoma with EGFR mutations.

MEDI 300

BPR000K, a novel Aurora kinase inhibitor

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Aurora kinases A, B, and C, members of sereine/threonine kinase, are key mitotic regulators involved in maintaining the genomic integrity of daughter cells. Because over-expression of Aurora A and Aurora B is frequently associated with tumor genesis, these molecules have been targeted for cancer therapy. Here we describe the profile of BPR000K, a specific and potent small molecule inhibitor discovered by the Institutes of Biotechnology and Pharmaceutical Research, National Health Research Institutes, targeting the Aurora kinase.

BPR000K showed potent *in vitro* Aurora kinase A inhibition (IC_{50}: 41 nM) and caused 4N-DNA accumulation at low concentration (26 nM). Moreover, BPR000K exhibited anticancer activity against a broad spectrum of cancer cells (IC_{50}: 10~500 nM against Colo205, TW039, HCT-116, MOLM-13 and MIA Paca-2). In HCT-116 xenograft model, BPR000K suppressed tumor growth up to 90% at 20 mg/kg twice a day for 10-day treatment by IV administration, and showed better antitumoral activity than the reference agent (VX-680 at 50 mg/kg). The body weight loss is less than 10% during the dosing period. BPR000K also exhibited significant tumor regression *in vivo* by IV administration at 50 mg/kg once a day for 10-day treatment in Colo205 and MIA Paca-2 xenograft models. BPR000K suppressed tumor growth up to 90% at 50 mg/kg twice a day for 10-day treatment by IV administration in pencreative cancer xenograft models.

MEDI 301

Design and synthesis of Aurora kinase inhibitors as anticancer agents

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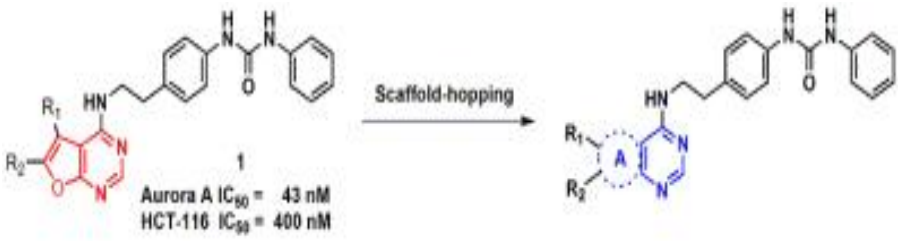
In our preliminary result, compound **1** , which contained the urea side chain and di-substituted furanopyrimidine core structure, possessed Aurora A kinase inhibition with an IC_{50} of 43 nM and anti-proliferation against HCT-116 with an IC_{50} of 400 nM. In the present work, we applied the scaffold-hopping strategy to explore the structure-activity relationship of this series of kinase inhibitors. Based on the bioisosterism, various five-member heterocyclic-fused pyrimidine cores with a variety of substitutents were synthesized to replace the furanopyrimidine moiety, such as thiopheno-, oxazolo-, imidazolo-, pyrrolo-pyrimidine and quinazoline. It is noted that the inhibitors containing thienopyrimidine or quinazoline as core structure revealed the remarkable antiproliferative activity with the low IC_{50} value of 21 nM and 20 nM, respectively. After introducing the solubilizing group into quinazoline core, the final compound showed significant *in vivo* antiproliferative activity in HCT-116 tumor xenograft model.



MEDI 302

Design, synthesis, and biological evaluation of novel estrone analogs targeting MAPK pathway for the treatment of melanoma

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Melanoma is the most lethal type among skin cancers, causing about 75 % of all skin cancer deaths. B-Raf mutations show high incidence in melanoma. Inhibition of MEK can induce apoptosis. Inhibition of the MAPK signaling at any level can assist in the treatment of melanoma. A synthetic scheme for assembling a side chain possessing an α,β-unsaturated ketone at C17 of ring D of estrone was executed, followed by thiol Michael addition. Molecular docking study revealed the synthesized estrone analogs are competing with the ATP binding pocket at MEK. However, slight structural modifications on the estrone skeleton will lead to better binding affinity towards the non-ATP binding pocket. The first generation of the estrone analogs showed IC_{50} on A-375 cell lines, ranging from 19.70 to 31.84 μM. This prompted us to design the second generation of estrone analogs with a modification at C9 and C11 to be further evaluated in-vitro using MTT, ELISA, and ATP binding assays.

MEDI 303

Design and development of glyceollin derived anti-cancer agents

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Breast cancer is one of the most prominent and fatal malignancies affecting women today. Multiple types of this malignancy exist with the most common form expressing estrogen receptors (ERs) which promote tumor growth. Selective estrogen receptor modulators (SERMs) have utility as an adjuvant therapy for breast cancer and are of interest because they can elicit different agonistic and antagonistic effects on ERs alpha and beta. Glyceollins (GLYs) are natural, phytoalexin products that have anti-estrogenic properties. This project focuses on the design, synthesis and characterization of GLY analogues that we hope will have SERM-like properties. They are designed using a GLY scaffold coupled with pharmacophores from known SERMs and anti-cancer agents on the market. After synthesis, target analogues are tested using growth inhibition assays on human cancer cell lines. Molecular modeling provides additional data to form structure activity relationships that guide future target design.

MEDI 304

Design, synthesis, and biological evaluation of 7-benzyl-4-alkyl-5-substituted-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-amines as potential antimitotic agents that also reverse tumor resistance

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The crucial involvement of microtubules in mitosis makes them a target for antitumor agents. Despite the unprecedented success of these agents in cancer chemotherapy, multidrug resistance is a major limitation. Previously, we reported the discovery of a novel series of 7-benzyl-4-methyl-5-[(2-substituted phenyl)ethyl]-7*H*-pyrrolo[2,3-*d*]-pyrimidin-2-amines, which demonstrated antimitotic and antitumor activities against both antimitotic-sensitive as well as resistant tumor cells. Based on these findings, a series of 7-benzyl-4-alkyl-5-substituted-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-amines were designed and synthesized as potential antitumor antimitotic agents to further the SAR study. The design and synthesis of the title compounds will be presented herein. The evaluation of these compounds is currently underway and will be reported and discussed.

MEDI 305

Nanoparticle platform for combination therapy of metastatic prostate cancer

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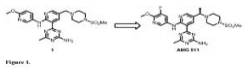
Castration-Resistant Prostate cancer (CRPC) is one of the most prevalent and deadly forms of cancer affecting men in the United States. Currently, chemotherapy is the only form of cancer therapy that has shown to improve the survival of those with CRPC. However, chemotherapeutic agents do not help to relieve many of the symptoms related with CRPC, such as chronic inflammation and bone metastases. Nanotechnology has recently emerged as a promising method for the delivery and tumor accumulation of multiple drugs with high efficiency. FDA approved polymeric nanoparticles (NPs), such as those composed of poly(lactide-*co*-glycolide) (PLGA) and poly(ethyleneglycol) (PEG), have shown exceptional ability to enter tumor tissues through the enhanced permeability and retention effect (EPR) and release therapeutics in a controlled fashion. Here, we present a controlled-release, highly functionalized NP platform with the capabilities to deliver synergistic combination of chemotherapeutics, anti-inflammatory agents, and bone resorption inhibitors for the treatment of CRPC.

MEDI 306

Identification of AMG 511 as a selective class I phosphoinositide 3-kinase inhibitor

Ryan P. Wurz[1], *rwurz@amgen.com, Kristin L. Andrews*[2], *Yunxin Y. Bo*[1], *Shon K. Booker*[1], *Sean Caenepeel*[3], *Victor J. Cee*[1], *D'Angelo D. Noel*[1], *Daniel J. Freeman*[3], *Bradley J. Herberich*[1], *Fang-Tsao Hong*[1], *Claire L. M. Jackson*[1], *Jian Jiang*[5], *Brian A. Lanman*[1], *Longbin Liu*[1], *John D. McCarter*[4], *Erin L. Mullady*[4], *Nobuko Nishimura*[1], *Liping H. Pettus*[1], *Anthony B. Reed*[1], *Tisha San Miguel*[4], *Adrian L. Smith*[1], *Markian M. Stec*[1], *Seifu Tadesse*[1], *Andrew S. Tasker*[1], *Divesh Aidasani*[5], *Xiaochun Zhu*[5], *Raju Subramanian*[5], *Nuria A. Tamayo*[1], *Ling Wang*[3], *Douglas A. Whittington*[6], *Bin Wu*[1], *Tian Wu*[7], *Kevin Yang*[1], *Leeanne Zalameda*[4], *Nancy Zhang*[3], *Paul E. Hughes*[3], *Mark H. Norman*[1]. *(1) Medicinal Chemistry, Amgen Inc., Thousand Oaks, CA 91320, United States (2) Molecular Structure, Amgen Inc., Thousand Oaks, CA 91320, United States (3) Oncology Research, Amgen Inc., Thousand Oaks, CA 91320, United States (4) High-Throughput Screening/Molecular Pharmacology, Amgen Inc., Thousand Oaks, CA 91320, United States (5) Pharmacokinetics and Drug Metabolism, Amgen Inc., Thousand Oaks, CA 91320, United States (6) Molecular Structure, Amgen Inc., Cambridge, MA 02142, United States (7) Pharmaceutics, Amgen Inc., Thousand Oaks, CA 91320, United States*

Phosphoinositide 3-kinase (PI3K) dependent signaling is frequently activated in human cancers. Herein, we describe our efforts to develop PI3K inhibitors as potential cancer therapeutics. Optimization of pyridyltriazine **1** led to clinical candidate AMG 511 (Figure 1), a potent pan inhibitor of class I PI3Ks with a superior pharmacokinetic profile. AMG 511 was shown to potently block the targeted PI3K pathway in a mouse liver pharmacodynamic model and inhibit tumor growth in a U87 xenograft model.



MEDI 307

Two-photon active coumarins for high contrast imaging of cancer cells

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A series of anti-tumor and two-photon (TP) active 4-*N,N'*-dimethylcinnamoyl coumarins were synthesized that exhibit red shifted, enhanced absorption and emission spectra with enormous Stokes shift in comparison to the parent coumarin. These compounds are relatively non-toxic as no adverse effects of coumarin have been reported. Apart from being biologically active, these synthesized C-6 and C-8 substituted cinnamoyl coumarins also poses excellent optical properties e.g. higher molar extinction coefficient, large quantum efficiency of fluorescence,and emission in the visible spectrum region. These compounds also exhibit large value of TP absorption cross-sections. A correlation between the structure and TPA behavior was established. TPA confocal microscopy revealed that these coumarin derivatives can be internalized by the cells rendering them a potential candidate as a bio-marker in TP confocal imaging and drug delivary system.

MEDI 308

Towards the optimization of c-Myc inhibitor JY-3-094

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c-Myc is a basic helix-loop-helix leucine zipper (bHLH-LZ) transcription factor that is important for cell proliferation, differentiation and survival. Heterodimerization of c-Myc with Max is an obligatory requirement for c-Myc to become transcriptionally functional. Importantly, overexpression and/or dysregulation of c-Myc has been associated with tumorigenesis, contributing to the development and progression of a wide variety of human cancers, including lung, breast, pancreatic and colorectal cancers. Inactivation of c-Myc results in cell cycle arrest, apoptosis and tumor regression. Hence, inhibition of c-Myc with small-molecules is an attractive goal towards the development of novel, and urgently-needed, anti-cancer agents. We have recently disclosed the novel small-molecule c-Myc inhibitor JY-3-094, which selectively inhibits c-Myc–Max dimerization with an IC_{50} of 33 μM (Max–Max: IC_{50} > 100 μM). However, JY-3-094 exhibits poor cytotoxicity in c-Myc-overexpressing cell lines. Our efforts to optimize the in vitro and cellular c-Myc inhibitory activities of JY-3-094 will be presented.

MEDI 309

Towards selective Mcl-1 and pan-Bcl-2 antagonists: Structure–activity relationships of side-chain substitutions of synthetic α–helix mimetics

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Bcl-x_L and Mcl-1 are anti-apoptotic proteins of the B-cell lymphoma (Bcl-2) family localized in the outer mitochondrial membrane that are over-expressed in a wide range of human cancers, and contribute to resistance to conventional chemotherapy drugs. These proteins exert their anti-apoptotic functions through sequestering pro-apoptotic Bcl-2 family members, which include Bak and Bim. More particularly, this protein–protein interaction is mediated by a hydrophobic groove on the surface of the anti-apoptotic protein and the BH3 α–helix of the pro-apoptotic protein. Although small-molecule mimicry of the BH3 α–helix has afforded potent Bcl-x_L inhibitors, the likewise inhibition of Mcl-1 has not been forthcoming. Thus, in an effort to develop potent and selective Mcl-1 inhibitors, as well as pan-Bcl-2 inhibitors, we have translated the recent findings of saturation mutagenesis studies of the Bim-BH3 α–helix into our synthetic α–helix mimetics, and we will present the outcomes of our research.

MEDI 310

Discovery, structure-guided design, and validation of WEHI-539, a novel, potent, and selective inhibitor of the pro-survival BCL-2 family member BCL-X_L

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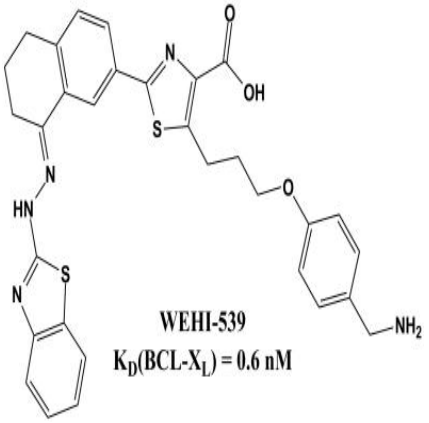
Pro-survival BCL-2-family proteins are often over-expressed in tumours and essential for their sustained expansion. Moreover, the pro-survival BCL-2 family member BCL-X_L renders malignant tumour cells resistant to diverse anti-cancer therapeutics. Hence, enhancing apoptotic responses by inhibiting BCL-X_L is likely to have widespread utility in cancer treatment and, compared to inhibiting multiple pro-survival BCL-2 family members, a BCL-X_L-selective inhibitor would be expected to minimize the toxicity to normal tissues. Here, we describe the discovery by a high throughput screen of a novel series of small molecules targeting BCL-X_L and their structure-guided development by medicinal chemistry. The optimized compound, **WEHI-539** , has high affinity (sub-nM) and selectivity for BCL-X_L and potently kills cells by selectively antagonizing the pro-survival activity of BCL-X_L. **WEHI-539** will be an invaluable *in vitro* tool for distinguishing the roles of BCL-X_L from those of its pro-survival relatives, both in normal cells and

crucially in malignant tumor cells, many of which may prove to rely upon BCL-X_L for their sustained growth.



MEDI 311

Rationally-designed small-molecule inhibitors of c-Myc–Max dimerization

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c-Myc is a nuclear oncoprotein of the basic helix-loop-helix leucine zipper (bHLH-LZ) family that is required for the transcription of genes involved in the regulation of the cell cycle, cell proliferation, differentiation, metabolism and survival. In order for c-Myc to become transcriptionally active, it must first heterodimerize with Max, forming a coiled coil structure. Overexpression and/or dysregulation of c-Myc is responsible for the development and progression of a variety of human cancers. Accordingly, the development of c-Myc inhibitors represents a highly targeted, and now validated, approach towards the expansion of the antineoplastic drug arsenal. Through consideration of the c-Myc–Max/DNA crystal structure, we have designed novel α-helix mimetics intended to perturb the structure of the c-Myc–Max heterodimer through disruption of the helix–helix interface. Our most potent compounds inhibit c-Myc–Max dimerization with single-digit micromolar IC_{50} values in vitro and in c-Myc-overexpressing cell lines.

MEDI 312

Two-photon-fluorescence microscopy as a promising noninvasive optical biopsy tool for early detection of human tumor colonic mucosa

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Endoscopic identification of tumor colonic mucosa often provides serious challenges because of the reduced resolution, elimination of benign lesion and high risk of perforation. Several optical biopsy techniques such as optical tomography, laser induced fluorescence spectroscopy and second harmonic generation has been proposed to address this issue. Here, we hypothesize a noninvasive optical biopsy technique namely Two-Photon-Fluorescence Microscopy (TPFM) for high contrast real time imaging of a large number of endoscopically visible lesions. TPFM is a nonlinear imaging technique depending on intrinsic tissue emission and provide several advantages over the conventional spectroscopy techniques such as deeper penetration, less photodamage, less photobleaching and high transparency. It can be used to selectively remove the malignant lesion and provide higher contrast. A prototype two-photon endoscope has also been described.

MEDI 313

Evaluation of the biological binding abilities of synthesized anti-tumor aminoacridines

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Previously m-amsacrine has shown promise in its use as an anti-tumor agent however, due to its short half-life and the formation of dangerous byproducts through breakdown, the interest in the formation of new agents is of interest. Progress on the design and synthesis of additional 9-aminoacridine derivatives are investigated later. The synthesized 9-aminoacridines contain potential hydrogen bonding sites in hope to prevent hydrolysis at physiological pH and increase binding in spite of poor sequence specificity. The target compounds were synthesized, purified, and evaluated on genomic DNA for their ability to intercalate as identified through thermal denaturation studies and viscosity titrations. The results of the evaluation will be presented.

MEDI 314

Targeted delivery of doxorubicin to renal carcinoma cells via peptide-based bionanoconjugates

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In this study, short peptide sequences are used in conjunction with gold nanoparticles to improve both the specific delivery and controlled release of small molecules into clear cell renal cell carcinoma (ccRCC) cells. The bionanoconjugates described here are defined by the synergy between metal nanoparticles, targeting biomolecules, and self-assembling biomaterials. We wanted to examine the ability of short peptide sequences to deliver small molecules to specific tissues, while at the same time overcoming the limitations often discussed in the literature. This was accomplished by building both structural and functional features into the peptide sequence, including; [1] selective targeting, [2] cellular uptake and [3] controlled drug release. Targeting peptides derived from phage display specific to the Caki-2 ccRCC cell line, self-assembling peptides, and BSA fragments were conjugated to gold nanoparticles to form the complete bionanoconjugate. The chemotherapy agent doxorubicin was incubated with the bionanoconjugate to allow for embedding into the self-assembled peptide layer. Cytotoxicity assays were performed on both Caki-2 and Primary Renal Mixed Epithelial Cells with drug-loaded and non-loaded bionanoconjugates to determine if a) the delivery vehicle itself is cytotoxic and b) if increased cell death is seen in cancerous cells compared to normal cells. Examination of these features will permit us to enhance our understanding of peptide-based bionanoconjugates and facilitate the convergence of these technologies on directed therapeutics.

MEDI 315

Efforts toward finding small molecule molecular probes to test a new approach to leukemia treatment: Blocking the Rin1/Abl protein-protein interaction

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Most common forms of leukemia are causally linked to the expression of the Philadelphia chromosome, which leads to production of the uncontrollably active tyrosine kinase Bcr-Abl, which in turn allows for overproduction of leukocytes, a hallmark of leukemia. Patients carrying the Philadelphia chromosome now take inhibitors of Bcr-Abl, such as Gleevec®, to curb the effects of the disease or even to prevent its onset. Mutations in Bcr-Abl can unfortunately confer drug resistance, so 2nd generation analogs that are effective against many mutant forms have been advanced. In an alternative but perhaps complimentary approach, we have targeted an upstream regulator of native Abl (and also of mutant Bcr-Abl): the allosteric activator protein Rin1. Leukocyte proliferation is halted in the absence of Rin1 activation. Here we present early results of an uHTS-derived effort, within the NIH's Molecular Libraries Probe

Center Network (MLPCN), to find small molecules that block the Rin1-Abl interaction. We show results of a screening campaign using the NIH collection (~360,000 small molecules), confirmation of hits, selection of multiple lead series for possible chemistry follow-up, and early SAR to augment potency and verify mechanism of action.

MEDI 316

Design and synthesis of a novel taxoid for radiolabeling studies of tumor-targeted drug conjugates

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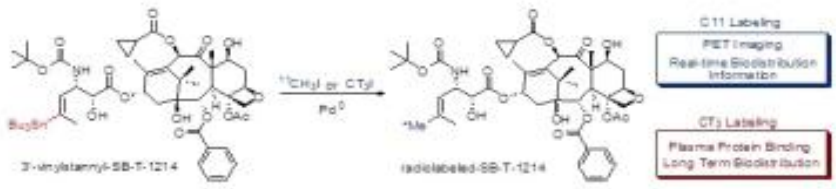
Next generation taxoid SB-T-1214 has shown outstanding efficacy in vitro and in vivo in numerous paclitaxel-resistant tumor cell lines. Accordingly, it has been used as the cytotoxic warhead for numerous tumor-targeted drug conjugates including those with polyunsaturated fatty acids, vitamins, monoclonal antibodies, and other biological macromolecules. In order to facilitate the preclinical development of conjugates bearing SB-T-1214 as an active agent, information pertaining to their protein binding and/or biodistribution *in vivo* is essential. Thus, an analogue of SB-T-1214, bearing a distal vinyl stannane at the C3' position was designed and synthesized to facilitate the incorporation of radionucleotides including ^{11}C for PET imaging and tritium for long-term biodistribution analysis. The synthesis of this compound and radiolabeling studies will be presented.



MEDI 317

Synthesis of soy phytoalexins having anti-cancer properties

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Breast cancer is one of the leading causes of cancer deaths in women worldwide. Inhibition of estrogen receptors is an important strategy toward the treatment of estrogen dependent breast cancer. Estrogen mimicking plant compounds called

phytoestrogens, can bind to estrogen receptors and exert estrogenic effects. They also serve to block the effects of endogenous estrogens, hence acting as antiestrogens. Thus, these phytoestrogens have the ability to act as natural, selective estrogen receptor modulators or SERMs. The glyceollins are 6a-hydroxypterocarpan phytoalexins that are produced as a mixture having three members when soybean plants are stressed by either biotic or abiotic elicitors. They exhibit antiestrogenic activity and have the potential to act as natural SERMs. This presentation will convey our attempts to synthesize Glyceollin III using a novel synthetic route in order to test its activity against various cancer cell lines.

MEDI 318

Synthesis and structure-activity relationship studies of the cytotoxic anhydrophytosphingosine Jaspine B

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Jaspine B has been isolated from the marine sponges *Pachastrissa and Jaspis sp*, and exhibited sub-micromolar cytotoxicity ($IC_{50} \leq 0.5$ μM) against various cancer cell lines. Studies have indicated that interference with ceramide metabolism via inhibition of sphingomyelin synthase is most probably responsible for the cytotoxic effects. The present research is aimed at the development of a flexible total synthetic route to Jaspine B, and its further application in SAR investigations. In a chiral pool approach, starting from the L-serine-derived lactone **1** , a stereocontrolled synthesis of the *cis*-fused bicyclic lactone **2** was achieved in a one-pot reaction. Conversion of the lactone **2** to the tetrahydrofuran derivative **3** , and its subsequent transformation to enantiopure Jaspine B, and variously modified analogs thereof were accomplished efficiently. Details of the synthesis and biological studies will be presented.

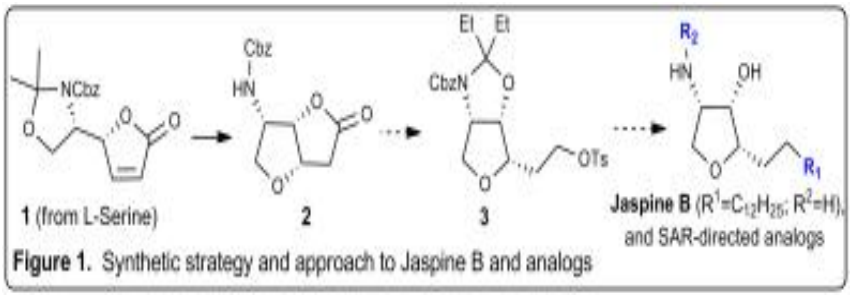

Figure 1. Synthetic strategy and approach to Jaspine B and analogs

MEDI 319

Towards novel, benzodiazepine-based α-helix mimetics as specific inhibitors of the Mcl-1 oncoprotein

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Mcl-1 (myeloid cell leukemia-1) is an anti-apoptotic protein that belongs to the Bcl-2 (B-cell lymphoma 2) protein family, and is frequently overexpressed in many different human cancers. In recent years, it has been demonstrated that high levels of Mcl-1 are also associated with resistance to conventional chemotherapeutics. Thus, Mcl-1 is a promising target for the development of novel, and potentially synergistic, antineoplastics. Currently, there are no potent and selective Mcl-1 inhibitors in the literature. The surface of Mcl-1 presents a hydrophobic crevice that engages the α-helical BH3 “death” domain of pro-apoptotic proteins, such as Bak and Bim, thereby inhibiting the cell-killing functions of those proteins. By analogy with the validated approach towards the inhibition of the related anti-apoptotic protein Bcl-x_L, we have developed, using molecular modeling as our guide, novel, benzodiazepine-based, low-molecular-weight compounds that mimic both faces of the pro-apoptotic BH3 α-helix as potential selective inhibitors of Mcl-1.

MEDI 320

Targeting the vascular endothelial growth factor receptor-2 (VEFGR2) with peptoid-inspired ligands

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Activation of Vascular Endothelial Grown Factor Recpetors (VEGFRs) has been identified as one of the key players in various angiogenesis-related pathological conditions including age related macular degeneration and cancers involving growth and metastasis of solid tumors. Current therapeutic strategies to antagonize this process either utilize receptor tyrosine kinase inhibitors targeting the intracellular kinase domain of these receptors, or VEGF-neutralizing monoclonal antibodies. As an alternative to these, we sought to target the extra-cellular domain of the VEGFR2 receptor by developing synthetic antibody surrogates generated by submonomer synthesis of peptoid-inspired oligomers. Previously, a one-bead one-compound peptoid library was screened and a hit from this screen, named GU40C, was found to bind the extra-cellular domain of VEGFR2 with modest affinity. The medicinal chemistry efforts to improve the binding of this peptoid hit were focused on positional scanning of the GU40C backbone with various heterocyclic building blocks. Three halomethyl carboxylic acid derivatives containing the thiazole, furan and pyrazine scaffolds were used in solid phase synthesis of backbone modified GU40C analogs. These analogs were evaluated in a ligand displacement assay with immobilized extra-cellular domain of VEGFR2 on an ELISA platform. This experiment revealed certain positions that were more tolerant to

heterocyclic modifications than others, and generated several analogs with a higher affinity as compared to the original GU40C lead. Synthesis, structure-activity relationships and pharmacological characterization of these synthetic antibody surrogates derived from backbone modified GU40C analogs will be presented in this poster.

MEDI 321

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 322

Anticancer and antituberculosis activity of benzyloxylated benzaldehydes and 2-aryl-2-imidazolines

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Chronic pulmonary tuberculosis is a disease which continues to spread scare particularly to people in developing countries. With consideration to the seriousness of this pandemic health problem, the need to explore and develop new compounds that may exhibit novel inhibitory mechanism is timely in TB drug discovery research. In accord to our growing interest in preparing derivatives with potent antituberculosis

activity, we hereby disclose the synthesis and evaluation of benzyloxylated ketoaryls and 2-arylimidolines as promising inhibitors of *M. tuberculosis* H_{37}Rv *in vitro*. Benzyloxy)benzaldehydes were prepared through Williamson ether synthesis between benzylic halides and aromatic hydroxyaldehydes. The antitubercular activities were evaluated against *M. tuberculosis* H_{37}Rv using the colorimetric microplate Alamar blue assay (MABA). In addition, the low-oxygen-recovery assay (LORA) was also carried out to determine inhibitory activity of the derivatives against *M. tb*'s in a non-replicating persistent (NRP) state. An improved activity was observed when the aldehyde functionality was transformed into a 2-imidazoline platform (MIC up to 3 mg/mL). Noteworthy, the derivative which features a *trans*-4,5-diphenyl configuration and 2,6-dichloro substitution showed the lowest MIC value. When other bioactive derivatives were transformed to a 1,3-diazacyclopentene moiety, significant improvement of inhibition was also observed. It seemed that halogenated and hydrophobic characters are relevant for activity against *M. tb.* In addition, MIC values against slow-replicating *M. tb.* based on the LORA assay (up to 2.8 mg/mL) suggested high activity for chlorinated and non-polar derivatives.

MEDI 323

New ferrocenecarboxylate derivatives: Synthesis, characterization, and in vitro antitumor activity study on human colon carcinoma cells (HT-29) and human breast cancer cells (MCF-7)

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New ferrocenecarboxylate derivatives were synthesized and biologically examined in vitro with colon cancer cells (HT-29) and breast cancer cells (MCF-7). Ferrocenecarboxylic acid was first activated with oxalyl chloride. The acyl chloride formed was added dropwise into a solution containing different phenolic compounds to form the ester. After extraction, the compound was purified by column chromatography using silica as stationary phase and eluted with dichloromethane (same solvent used in most stages of the reaction). The esters were characterized by FTIR spectroscopy, NMR spectroscopy and X-Ray Crystallography. The cytotoxicity studies were performed by the MTT biological assay using HT-29 and MCF-7 cell lines. Ferrocene has no significant cytotoxicity, but as moiety in organic molecules, it that can be transported into the cell having anti proliferative effect by its well known redox properties. Recent results show promising candidates for anti-cancer drug development.

MEDI 324

Rational design and construction of HER2 targeting recombinant human serum albumin

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HER2 is a receptor over-expressed in approximately 30% of human breast cancers. Human serum albumin (HSA) is the main protein in plasma and its biophysical and biochemical properties make it an ideal candidate for drug delivery. The overall purpose of this study is to develop an HSA-based drug delivery system capable of targeting HER2 to enhance tumor drug delivery. HER2 binding sequences derived from trastuzumab, pertuzumab and ZHER2 screened by phage display were integrated into HSA, respectively. The recombinant albumins were expressed and purified. Biochemical and cellular assays confirmed the binding affinity of the recombinant HSAs to HER2. It is expected that this recombinant albumin can serve as 1) a scaffold to produce highly specific, targeted proteins, and 2) an approach to create bi-specific proteins capable of promoting a synergistic effect on the inhibition of cancer cell growth when combined with chemotherapeutic agents.

MEDI 325

Development of novel esterase activated matrix metalloproteinase proinhibitors

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Matrix metalloproteinases (MMPs) are a family of over 20 zinc-dependent endopeptidases that collectively are capable of degrading all components of the extracellular matrix. Overexpression of MMPs has been associated with a number of pathologies including tumor cell invasion and metastasis. The activity of MMPs can be controlled with inhibitors that bind to the catalytic metal via a metal binding group (MBG). Inhibitors have been developed, but have been largely unsuccessful during clinical trials due to systemic inhibition. To address this problem, the prodrug approach offers a viable way to eliminate undesired effects. Proinhibitors can be developed, by blocking the MBG with a stimulus-responsive protecting group. In the presence of a desired stimulus, the proinhibitor will cleave to expose the active MBG. This work explores the development of inactive MMP proinhibitors (proMMPi) that can become activated, releasing a metal binding group (MBG), after deprotection by esterase.

MEDI 326

Nitrogen-based heterocycles in sphingosine kinase inhibitors

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Cancer has been of concern in the biomedical community for sometime; however, there is still much that is not understood about the disease. There are many different pathways cancer cells use to survive, which can be oncogene or non-oncogene addictions. The pathway our laboratory is most concerned about is the Sphingolipid Rheostat. Sphingosine 1-phosphate, S1P is an endogenous signaling molecule that regulates many cellular processes, including cell growth, survival, and movement, upon binding to $S1P_{1-5}$. Some cancer cells use this pathway to proliferate, leading to non-oncogene addiction.

Our laboratory is synthesizing inhibitors of the sphingosine kinases, SphK1 and SphK2, in order to regulate the cellular production of S1P. Interesting biological data has been obtained from N,O heterocyclic inhibitors, and so, synthesis of N-based heterocyclic inhibitors makes for an interesting comparison. The synthesis of these N-based heterocyclic inhibitors is described and the biological data compared to our previous SphK inhibitors.

MEDI 327

Multitarget-directed drug design strategy: Novel 1,4-naphthoquinone derivatives designed as multifunctional small molecules to target non-small cell lung cancer

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Single compounds that interact simultaneously with many targets either directly or following metabolism have shown significant promise in drug discovery. Novel 1,4-naphthoquinone-based compounds designed in this study have the potential to induce cancer cell death by inhibiting the epidermal growth factor receptor (EGFR) implicated in the development and progression of non-small cell lung cancer (NSCLC) and bio-reduction to DNA-damaging metabolites by the enzyme DT-diaphorase (DTD), a reductase overexpressed in NSCLC. The design, molecular docking studies, multistep synthesis and biological evaluation of the target compounds will be presented.

MEDI 328

Development of imidazole-based compounds for selective Grp94 inhibition

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Glucose regulated protein (Grp94), the ER isoform of the Hsp90 chaperone family, plays an important role in cellular communication and adhesion. As such, the development of isoform-selective inhibitors will be significant for the elucidation of isoform-dependent biological processes as well as potentially address toxicity issues observed in clinical trials for current Hsp90 inhibitors. To date, however, the development of Hsp90 isoform-selective inhibitors has been limited. Previous work took advantage of a secondary hydrophobic pocket by radamide analogues in which the *cis*-amide conformation played a critical role for Grp94 inhibition. Therefore, compounds that mimick the *cis*-amide conformation of radamide could potentially lead to more selective Grp94 inhibitors. Towards this objective, a series of imidazole linked analogues, in which the conformation is locked into a predisposed *cis*-amide conformation, was synthesized and evaluated for their inhibitory effect on Grp94 and Hsp90. The results from such studies will be presented.

MEDI 329

Development of radamide analogs as inhibitors of Grp94

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Heat shock protein 90 (Hsp90) is a promising therapeutic target for the treatment of cancer and other diseases. The Hsp90 inhibitors in clinical trials exhibit *pan*-Hsp90 inhibition as they simultaneously disrupt all four Hsp90 isoforms, and this property may be responsible for some of the unfortunate results obtained thus far (off-target effects and toxicities were observed). The chimeric Hsp90 inhibitor, radamide, bound to both yeast Hsp90 and the Grp94 isoform revealed a unique binding interaction that results from a five amino-acid insertion into the binding site which specifically alters the quinone binding region. This alteration produced a hydrophobic pocket for Grp94 inhibitors that can be exploited by modifications to the quinone ring of radamide. Using a structure-based approach, a series of radamide analogues was synthesized and their effect on Grp94 and Hsp90α/β inhibition will be presented.

MEDI 330

Rapid screening of a click-based library for G-quadruplex selective photocleavage agents

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DNA containing repeating G-rich sequences can adopt higher-order structures known as a G-quadruplexes (G4). These structures are believed to form at telomeres and

within the promoter regions of some genes, particularly in a number of proto-oncogenes, where they may play a role in regulating transcription. Alternatively, G4 DNA may act as a barrier to replication. In order to investigate these potential biological roles, probes that combine highly selective G4 DNA targeting with photocleavage activity can allow temporal detection of G4 DNA, providing opportunities to obtain novel insights. Towards this end, we have designed a library of potential photoactive probes using “click” chemistry to join known G4 DNA interactive groups with moieties known to facilitate photocleavage of DNA . This library is screened using our recently described FRET-based assay for G4 DNA photocleavage activity and preference as well as binding selectivity for G4 DNA.

MEDI 331

Reverse engineering tricyclic neuroleptics as anticancer therapeutics

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FoxO1, a transcription factor and tumor suppressor, is phosphorylated and rendered inactive by cytoplasmic sequestration by the PI3K-AKT and RAS-MAPK oncogenic kinase pathways. A chemical biological screen for modulators of FoxO1 localization revealed that the tricyclic neuroleptics (chlorpromazine, trifluoperazine) restore FoxO1 to the nucleus. Unfortunately, their CNS effects are severely dose-limiting, precluding their clinical use in cancer therapy.

In redesigning the tricyclics, a key insight was that the CNS and anti-cancer pharmacophores did not coincide. Synthesis of a library of phenothiazines with nitrogen modifications (amides, sulfonamides vs. neuroleptic Me_2N) retained anti-proliferative properties. These compounds, however, lack a basic amine and do not bind CNS receptors, abrogating the CNS pharmacology.

Subsequent medicinal chemistry focused on dibenzazepines. These compounds demonstrated anti-proliferative activities in lung cancer cell lines and induced tumor regression in in vivo transgenic and xenograft mouse models. Further work using these leads discovered that these effects are a consequence of the disrupted activation of AKT and ERK.

MEDI 332

Synthesis and biological evaluation of conjugated acridines

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Telomerase [1] is a reverse transcriptase enzyme found in both healthy and tumor cells, that synthesizes TTAGGG repeats on the ends of chromosomes. These repeats protect chromosomes from degradation and make the cell immortal, a key feature of cancer. It has been found that nearly every type of cancer exhibits increased telomerase activity, which makes it a novel target for anti-cancer drug development. [2]

Some acridines have shown promising results in inhibiting the enzyme telomerase. There is experimental evidence that acridine moieties intercalate with the G- quadruplex structure of telomere and therefore they disrupt the telomerase activity.[3] We have developed synthetic procedures for preparation of wide variety of diverse acridine based anticancer libraries. We will present our results toward library preparation of those libraries along with their biological data for selected acridine derivatives.

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MEDI 333

Voltage gated sodium channels: A novel target for breast cancer metastasis therapy

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Currently, there is no therapeutic strategy for metastasis prevention or targeting and current treatments rarely lead to long-term survival of patients without disease recurrence. Fortunately, our increasing understanding of the metastatic process has resulted in the discovery of several potential drug targets to prevent metastasis. One such target is the voltage-gated sodium channels (VGSC). Recently, it has been recognized that VGSCs are over expressed and functional in a variety of aggressive,

metastatic human cancer cells, including metastatic breast cancer. Literature reports, and our own preliminary studies, strongly support the necessity of sodium channel function in breast cancer cell invasiveness. We have used a 3D-QSAR Comparative Molecular Field Analysis (CoMFA) model to design a number of VGSC blockers with activities in nM range. We showed that selected VGSC blockers with activity against nNav1.5, the subtype overexpressed in aggressive breast cancer, inhibited the invasion of MDA-MB-231 breast cancer cells at nM concentrations.

MEDI 334

Evaluation of Fusarochromanone: A potent anticancer agent

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Fusarochromanone (FC101) is a small molecule with a host of interesting biological functions, including very potent anti-angiogenic and direct anti-cancer activity. Herein, we report our progress towards the chemical synthesis of parent FC101 and a number of structural isomers of FC101. We report our successful synthesis of parent FC101 based on our novel synthetic methodology which utilizes the Sonogashira cross-coupling. We will also present the evidence of the structural elucidation of the synthetic FC101 by both ^{1}H and ^{13}C-NMR. We also report our progress towards the assessment of biological properties of the parent FC101. We have shown that FC101 exhibits very potent *in-vitro* growth inhibitory effect. FC101 induced apoptosis and an increase in proportion of cells in the sub-G1 phase in both HaCat and P9-WT cell lines as evidenced by cell cycle profile analysis. Thus we view FC101 as an excellent lead candidate, a small molecule anti-cancer agent that affects tumor signal transduction, and apoptosis.

MEDI 335

Inactivation of boronic acid proteasome inhibitors by dietary polyphenols

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The FDA approval of the proteasome inhibitor Bortezomib (Velcade®) for the treatment of multiple myeloma and lymphoma demonstrated the viability of boron-based

therapeutics, and led to additional drug candidates of this type. The incorporation of a boronic acid or boronate functionality in these agents provides a unique approach for protease-type inhibition. At the same time, however, these types of molecules are also susceptible to interaction and inactivation by dietary polyphenols, including flavonoids natural products with notable biological activity such as epigallocatechin gallate (EGCG), a key ingredient of green tea. In our earlier studies we have shown the inactivation of Bortezomib by EGCG, which can block the drug's actions and limit the therapeutic benefits for patients. Herein, we present our spectroscopic and structural studies of Bortezomib in combination with a variety of phenolic molecules. Our results show that there are significant differences on the inactivation of the boronic acid moiety based on the nature of the phenol or polyphenol used.

MEDI 336

Structure-based design of novel inhibitors of dUTPase as potential anticancer agents

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Among the most widely used anticancer therapeutics are agents that target DNA synthesis and repair, such as 5-fluorouracil (5-FU), that causes cell death through irreversible inhibition of thymidylate synthase (TS). In many patients with resistant cancers, however, 5-FU and other TS inhibitors become ineffective as a result of the over-expression of dUTPase, an enzyme responsible for the conversion of the deoxyuridine triphosphate (dUTP) to deoxyuridine monophosphate (dUMP). Herein, we report new types of potential anticancer agents based on the inhibition of dUTPase. The structure-based design, synthesis, optimization, and growth inhibition data are presented. Through the use of phenotypic assays with our inhibitors alone and in combination with TS inhibitors, we demonstrate the potential therapeutic benefits of this approach.

MEDI 337

Probe the effect of B ring mobility in taxane on the microtubule binding and cytotoxicity

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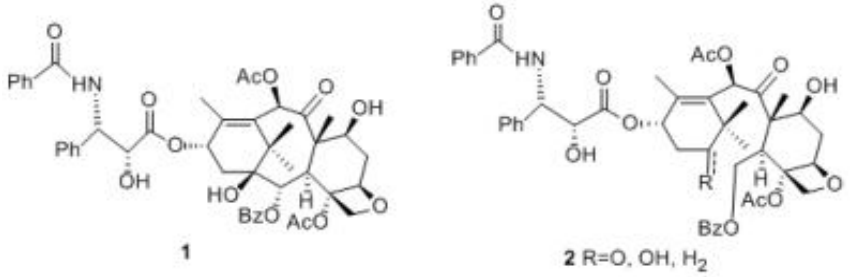
Taxane is a tricyclic triterpene skeleton originally discovered in *Taxus* sp. One of such triterpenoid, paclitaxel (Taxol, **1**), is renowned as an antitumor drug extensively used in

clinics. The rigid tricyclic core structure has been known to provide 2/3 of free energy contributions when Taxol binds to microtubules (MTs), and also shown differential binding affinity to different tubulin isotypes (e.g. beta-I vs. beta-III). A-seco and C-seco taxanes have been synthesized, and are poorly active in drug sensitive cancer cells, which may be related to their low binding affinity to beta-I isotype tubulin in MTs. However, C-seco taxanes have shown better cytotoxicity against drug resistant tumor cells with high beta-III expression level, which was attributed to their enhanced binding to beta-III isotype tubulin *in silico*. In this study, we designed and synthesized some B-seco paclitaxel and its analgs (**2, 3**), and tested their MT binding and cytotoxicity in drug sensitive and resistant tumor cells. The effect of B ring mobility on the MT binding and cytotoxicity has been explored through this study, which may provide an alternative way to enhance the binding to both beta-I and beta-III isotype tubulins, and improve the activity in both drug sensitive and drug resistant tumors.



MEDI 338

Control of the human DBf4 gene by a small pyrrole and imidazole-containing polyamide (f-IPI) andnot its H-pin analog (f-IPI^2)

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Pyrrole- and imidazole polyamides are analogs of distamycin. They can be designed to target and bind in the minor groove of any DNA sequence. In this study, two polyamides that bind 5'-ACGCGT-3' were designed: one is **f-IPI** which binds as a side-by-side, antiparallel stacked dimer. The other is **f-IPI^2** , which is a covalently linked H-pin dimer of **f-IPI** . The two **f-IPI** units are joined at the N1-position of the two corresponding pyrriole units through an ethyleneglycol linker. 5'-ACGCGT-3' is the MluI cell cycle box (MCB), which is a transcriptiona; factor binding site that activates the expression of the HuCdc7/Dbf4 core gene in mammalian cells. Dbf4 is the regulatory subunit of Cdc7 kinase, which is essential for the initiation of DNA replication throughout S-phase. In this study, the DNA binding properties of **f-IPI** and **f-IPI^2** will be presented as well as their ability to affect the expression of the Dbf4 gene in human cells. The effects of these

polyamides on cell growth and apopotosis of cancer cells in culture will also be presented.

MEDI 339

Development of potent inhibitors of DNA-dependent protein kinase (DNA-PK)

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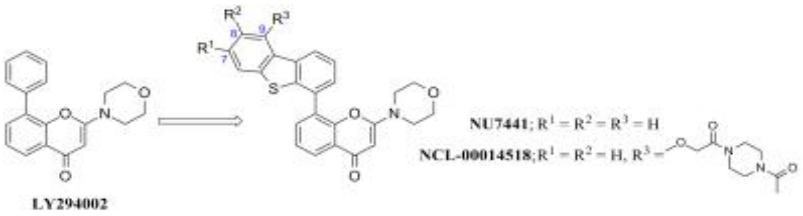
DNA-dependent protein kinase (DNA-PK) is involved in the non-homologous end-joining pathway of DNA double strand breaks (DSBs). DSBs can be initiated by ionising radiation or chemotherapy.[1] ATP-competitive inhibitors of DNA-PK could potentiate the effects of these cancer therapies. Inhibitor design was guided by the non-selective PIKK inhibitor, LY294002. Lead compound NU7441 was hampered by sub-optimal pharmaceutical properties.[2] Synthesis of 7-, 8- and 9-substituted dibenzothiophene inhibitors provided water-soluble compounds with retained potency.



References

1. *Nature*, 2001, **411** , 366.
2. *J. Med. Chem.,* 2005, **48** , 7829.

MEDI 340

Design, synthesis, and biological evaluation of novel Largazole analogs with modified surface recognition cap groups targeting histone deacetylases

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Epigenetic regulation by altering gene expression without changing DNA sequences is a promising new strategy in developing anticancer agents. As histone deacetylases (HDAC) play an important role in gene expression, HDAC inhibitors have become an increasingly popular class of agents for targeting epigenetic regulation. Isoform and class-selective HDAC inhibitors are being developed to reduce the undesirable side effects resulting from non-selective HDAC inhibitory activity. Largazole is a potent and class I selective HDAC inhibitor isolated from a marine cyanobacterium of the genus *Symploca*. The depsipeptide ring of largazole constitutes the surface recognition cap group that interacts with the less conserved hydrophobic rim of the HDAC active site. In order to investigate the effect of the nature of this group on isoform and class selectivity, we have designed and synthesized largazole analogues with structural alterations in the depsipeptide ring. The synthesis and biological activity of these novel largazole analogues will be presented.

MEDI 341

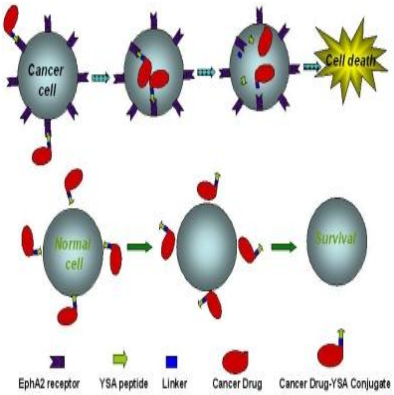
WITHDRAWN

MEDI 342

Target EphA2 receptor for cancer therapy

***Si Wang**, siwang@burnham.org, John Stebbins, Roberta Noberini, Ziming Zhang, Maurizio Pellecchia, Elena Pasquale, Shinichi Kitada, Paul Fisher.Cancer Center, Sanford-Burnham Medical Research Institute, La Jolla, CA 92130, United States*

A high proportion of cancers express high levels of the EphA2 receptor. We identified that several peptides selectively bind to EphA2 receptor by phage display and combinatorial chemistry approaches. Conjugating the EphA2 binding peptides to pacliaxel may keep their EphA2 binding affinity and antitumor activity. What's more, these conjugates have demonstrated much more effective than paclitaxel at inhibiting tumor growth *in vivo* and efficiently control PC-3 metastases. The EphA2 binding peptide-paclitaxel conjugates possess a remarkable anticancer activity, not only showing selectivity between tumor tissues and non-tumor tissues but also being able to penetrate tumor tissues and maximizing drug activity.



The use of the EphA2 binding peptides for cancer drug delivery can overcome two major drawbacks of cancer drugs: poor selectivity and poor penetration. As a result, these novel EphA2 targeting agents may enhance antitumor activity of cancer drug and reduce their side effects, and finally improve therapeutic index.

MEDI 343

Halogen bonding-based scaffold decoration: Data mining the PDB

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As a rather new type of non-covalent interaction between ligand and protein, halogen bonding is slowly being integrated into molecular modeling and the drug design process. Aromatic halogenated molecules can theoretically form halogen bonds with any electron donor. Based on quantum chemical calculations, we evaluated the interaction energies between several halobenzenes and the oxygen of N-methylacetamide, representing the carbonyl-function of the protein backbone. In a ligand-protein complex very rarely optimal interaction geometries are observed. In order to assess all spatial dependencies of the halogen bond with regards to deviations from optimal geometries, our calculatios include variations in distance and bond angles. On the basis of these calculations we developed a tool for scaffold decoration applicable to any crystal structure. For every unsubstituted aromatic atom in a ligand the tool determines if halogenation of this position leads to a favorable halogen bonding interaction with the binding site (taking clashes into account).

MEDI 344

Exploiting solvent effects in drug design and optimization

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Upon ligand binding, solvent molecules around the binding pocket and theligand become displaced or rearranged. These desolvation energies can be asignificant portion of the total binding energy, and thus representopportunities for ligand design. Computing desolvation energetics typicallyrequires lengthy simulations, but this talk presents a fast and easy-to-usemethod (3D-RISM) which computes desolvation energies in minutes, withoutusing explicit simulations. Application to ligand optimization isdemonstrated using case studies.

MEDI 345

MOE in education: A pedagogical tool for the chemical sciences

***Petrina Kamya**, pkamya@chemcomp.com. Chemical Computing Group, Montreal, Quebec H3A2R7, Canada*

Molecular modeling is fast becoming a fundamental research and teaching aide in academia. One of the most predominant molecular modeling suites in industry today is MOE, Molecular Operating Environment. Here we introduce the wide range of MOE applications available to academics, and demonstrate how MOE has been used as a teaching aide in the life sciences, including Computational and Medicinal Chemistry, Pharmacology, and Biology.

Chemical Computing Group has a solid history of supporting research and pedagogic programmes in academia through sponsored initiatives and awards including the CCG Excellence Awards at the ACS. MOE's comprehensive, integrated platform, and open-source code provides a variety of scientific researchers with an all in one drug discovery tool that is easily integrated, customizable and a fundamental research and teaching aide.

MEDI 346

Rationalizing non-standard interactions in ligand design: The duality of halogens

***Alain Ajamian**, aajamian@chemcomp.com. Chemical Computing Group, Montreal, QC H3A 2R7, Canada*

Non-standard intermolecular interactions such as CH donors, halogen bonds, close sulfur contacts and cation-π interactions have recently been recognized as significant factors in protein-ligand binding. However, exploiting these interactions in structure-based drug design projects (SBDD) has been difficult, because they are inadequately modeled using MM force-field based methods. Atom-centered charges typically used in force-fields cannot capture the anisotropic charge distributions responsible for some non-standard interactions. To address these challenges, a model of intermolecular interactions based on Extended Hückel Theory (EHT) is proposed, which accounts for the effect of electron delocalization and geometry on interaction strength. The qualitative and semi-quantitative accuracy of the model is demonstrated using case

studies that highlight the importance of non-standard interactions in a number of systems, including native ligands of the thyroid hormone receptor.

MEDI 347

Scaffold replacement and 3D ligand optimization applied to the discovery of tyrosine kinase inhibitors

***Nels Thorsteinson**, nthorsteinson@chemcomp.com. Chemical Computing Group, Montreal, Quebec H3A 2R7, Canada*

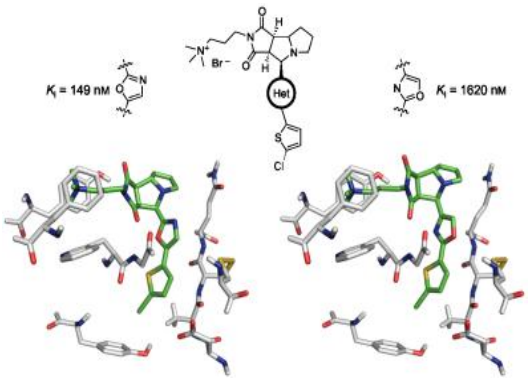
Point mutations within the BRC-ABL tyrosine kinase domain give rise to imatinib-resistant mutants. Designing next generation ligands to counteract TK inhibitor resistance remains a challenging problem. Scaffold replacement is applied to the imatinib framework where the 2-amino-pyrimidine fragment is exchanged through a scaffold screen to produce a number of related congeneric series. 3D ligand optimization is subsequently performed on one of the hits yielding a structurally related isomer of ponatinib, a known selective high affinity tyrosine kinase inhibitor.

MEDI 348

Systematic investigation of amide stacking

***Michael Harder**[1], harder@org.chem.ethz.ch, Bernd Kuhn[2], François Diederich[1]. (1) Department of Chemistry and Applied Biosciences, ETH Zurich, Zurich, Switzerland (2) Pharma Research and Early Development, F. Hoffmann-La Roche, Basel, Switzerland*

Earlier studies of our research group on the enzyme factor Xa yielded two oxazole containing inhibitors.[1] The 11-fold difference in binding affinity was surprising since X-ray co-crystal analysis showed almost identical binding modes (Figure: PDB codes 2Y5G and 2Y5H).



Noncovalent interactions between π–systems are important in molecular recognition and routinely used in rational drug design.[2] Amide groups are exposed in many enzyme active sites. We used quantum chemical calculations to systematically study the stacking of aromatic molecules on planar amide fragments.

[1] L. M. Salonen, M. C. Holland, P. S. J. Kaib, W. Haap, J. Benz, J. L. Mary, O. Kuster, W. B. Schweizer, D. W. Banner, F. Diederich, *Chem. Eur. J.* **2012** , *18*, 213–222.

[2] L. M. Salonen, M. Ellermann, F. Diederich, *Ang. Chem. Int. Ed*. **2011** , *50*, 4808–4842.

MEDI 349

3D QSAR CoMFA and CoMSIA studies for design of potent human steroid 5α-reductase inhibitors

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Testosterone is converted to its more active metabolite dihydrotestosterone by NADPH dependent, microsomal human 5α-reductase (5α-R) (EC 1.3.99.5) enzyme, which is an important target for various androgen dependent diseases. 3D-QSAR CoMFA and CoMSIA studies were performed on a set of fifty two, 4-azasteroidal human steroid 5α-reductase inhibitors. The models developed using maximum common substructure based alignment, were found to be reliable and significant with good predictive r^2 value. CoMSIA model developed using combination of steric, electrostatic, hydrophobic, hydrogen bond donor and hydrogen bond acceptor features has shown r^2cv= 0.564 with 6 optimum components, r^2ncv = 0.945, F-value = 101.196, r^2Pred= 0.693 and SEE= 0.209. The contour plots obtained has shown a favourable effect of bulkier groups at C-17 position. The study further gave insight into important interactions occurring between receptor active site and ligands which helps in design of potent inhibitors of the enzyme.

MEDI 350

Quantifying desolvation of varying protein-drug complexes using the quartz crystal microbalance and dual polarization interferometer

***Andrea Diaz**, aed02011@mymail.pomona.edu, Cynthia Selassie, Malkiat Johal. Department of Chemistry, Pomona College, Claremont, CA 91711, United States*

In the field of drug design, predicting interactions between a drug and its target-binding site is essential when evaluating drug candidates. However, in order to have an accurate prediction of these interactions, it is important to consider the role of water involved. Past studies have shown that the difference in hydration sensitivity between the quartz crystal microbalance and the dual polarization interferometer allows the instruments to be used in tandem to investigate changes in hydration states of protein-

drug complexes. We sought to use this technique to understand and create a profile on how drugs of varying hydrophobicities alter the hydration state of bovine serum albumin. The degree of desolvation of drugs of varying hydrophobicities including Trifluprom azine, Indomethacin, Procaine, and Labetalol was investigated. In general, drugs with higher hydrophobicities were shown to bind more tightly to their target site and displace more water molecules than hydrophilic drugs.

MEDI 351

Novel ligand attachment for targeted in vivo polymer conjugate siRNA delivery based on substituted 2,3-maleamic acids

Jeffrey Carlson*, jeffrey.carlson@arrowres.com, Jonathan Benson, Collin Hagen, Vladimir Trubetskoy, David Rozema, Andrei Blokhin. Arrowhead Research Corporation, Madison, Wisconsi 53711, United States*

RNA interference (RNAi) promises to be a new therapeutic modality for the treatment of numerous diseases via selective gene silencing; however, targeted in vivo delivery of the agent of silencing, short interfering RNA (siRNA), remains a challenge. One strategy of delivery is by conjugation of the nucleic acid to membranolytic polymers. The siRNA-polymer conjugates are reversibly masked using both shielding agents, to inhibit non-specific interactions, and targeting ligands to elicit cell specificity. The ligand attachments, sensitive to latent physiological triggers, are designed to release from the polymer within the target cells, restoring membrane activity and allowing for siRNA escape via endosomolysis. As previously developed within our group, reversibility of ligand attachment in the acidic intracellular endosome is conferred by a pH-labile maleamate bond, which is formed by the reaction of a primary amine with a maleic anhydride.

Presented here are a series of novel maleamic acid based cleavable linkers, sensitive to the acidic environment of the endosome, with the desired properties of ligand attachment: extracellular stability and acid lability. Through use of various electron withdrawing groups at the alkene moiety the rate of deacylation was altered correlating to the relative adjustment of the effective maleamic acid pKa. Biological properties of siRNA-polymer conjugates prepared with the new ligands revealed extended periods of circulation without compromising biological activity. Rational design and synthetic approaches to the new compounds will be discussed.

MEDI 352

Cyclic peptide-capped gold nanoparticles for enhanced siRNA delivery

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Department of Cell and Molecular Biology, University of Rhode Island, Kingston, Rhode Island 02881, United States

We have previously reported homochiral L-cyclic peptides and their corresponding peptide-capped gold nanoparticles for the nuclear targeting delivery of anti-HIV drugs and biomolecules. Herein, $[WR]_5$ and $[WR]_5$-AuNPs were tested for intracellular delivery of small RNA interfering molecules (siRNA). Microscopy was used to observe the delivery of the fluorescence-labeled siRNA. Next, transfections were performed with siRNAs targeting Fanconi Anemia proteins. Knockdown of these proteins was monitored using Western blotting. Microscopy shows $[WR]_5$ and $[WR]_5$-AuNPs (25 μM) delivered copious amounts of siRNA (200 nM) into the cells significantly higher than that of siRNA alone after 24 h incubation in HeLa cells at 37 °C. However, the peptides were capable of only modest knockdown of the FA proteins, presumably because of limited release of the siRNA carriers or the nuclear localization of the complex bypassing the cytoplasmic target. Further investigations are needed to improve the release and/or targeting of peptide carrier-siRNA complex.

MEDI 353

Exploring the basis for stable oligonucleotide interactions and their relevance in regulating gene expression

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Silencing gene expression by small interfering RNAs (siRNAs), ribozymes and antisense DNA form the basis of gene therapy, which aims to treat genetic disorders, cancers and other infectious diseases. At the heart of their efficacy *in-vivo*, is an exquisite selectivity, in which gene targets are regulated by base-pairing interactions with the complementary oligonucleotide strand. Therefore, insight into the optimal oligonucleotide hybridization conditions is a necessary requirement to improve the regulatory activity of oligonucleotides in gene therapy applications. Towards this effect, the influence of the length, sequence, and chemical composition of the antisense strand in selected buffer conditions on RNA binding affinity and specificity is described in this presentation. The structural and bio-physical properties of the oligonucleotide complexes were investigated by PAGE, thermal denaturation and CD spectroscopy to assess their relevance in RNA binding and regulation.

MEDI 354

Information rich flash chromatography I: Mass directed fractionation

***Jack E Silver**, Jack.Silver@teledyne.com, Ronald L Lewis. Teledyne ISCO, Lincoln, NE 68504, United States*

Mass spectrometers (MS) have long been used for detection when coupled with HPLC. Nearly universal detection of compounds is achieved when MS is combined with UV detection. The introduction of lower-cost mass spectrometers allows automated flash chromatography to enjoy the advantages of mass directed purification. These include collection of only the desired product utilizing a targeted molecular weight as a trigger. For natural products, known compounds can be identified and ignored during purification allowing the chemist to isolate only those materials with molecular weights that would suggest they are novel. Selection of ionizing agents become critical to successful generation of an unambiguous molecular ion in flash chromatography and is described in this poster. Mass-directed purification of synthesized compounds is also demonstrated.

MEDI 355

Information rich flash cromatography II: All-wavelength collection and purity measurement

Jack E Silver*, Jack.Silver@Teledyne.com, Ronald L Lewis. Teledyne ISCO, Lincoln, NE 68504, United States*

UV-visible detectors have been used on flash chromatography systems for several years to control the fraction collector. The purity measurements were limited to ratio measurements that required *a priori* knowledge of the spectra of the compound and impurities so that the correct wavelengths could be used both to collect peaks and determine purity.

All-Wavelength Collection is a technique that monitors all detector wavelengths in a user-defined range. A change of absorbance within that range is treated as another peak and triggers collection or peak cutting by the fraction collector. All-Wavelength Collection also can be employed to determine peak purity over the entire spectral range chosen by the chemist with solvent background suppression.

Examples from synthesized compounds and natural products will be presented.

MEDI 356

New wide pore C18 phase for fast and efficient purification of peptides by flash chromatography

Melissa J Wilcox*, melissa.wilcox@grace.com, Chitra Sundararajan, Bopanna N.K., Kimberly Wolfson, David Crowshaw. Grace Discovery Sciences, Deerfield, IL 60015, United States*

Peptides and proteins are becoming increasingly popular for their potential use as therapeutic drugs. To earn and maintain a share in the fast-growing peptide market, peptide researchers and manufacturers are constantly trying to improve and optimize

the various steps in peptide synthesis. One of the main bottlenecks in peptide synthesis is the purification step. Techniques such as FPLC and Preparative HPLC are limited by small loading amounts, long separation times, poor recoveries and high costs.

Here, we demonstrate that flash chromatography can be a powerful tool in the fast and efficient purification of a diverse range of peptides. A new wide pore C18 phase expands flash purification capabilities to larger sized peptides, while providing better resolution. We present data to show the benefits of higher loading and faster peptide purifications. This rapid purification technique ensures less degradation of peptides and provides better recovery, yields and purity.

MEDI 357

Synthesis and evaluation of a folate targeted, acid activated dye

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The folate receptor (FR) has emerged as an attractive target for both in vitro and in vivo imaging applications. Specifically, FR levels are elevated in numerous malignant tissues and diseases associated with inflammation (e.g. atherosclerosis, infection) and thus FA serves as a useful targeting moiety for the diagnosis and detection of these diseases. We describe the synthesis and assessment of a folate conjugate developed using the acid sensitive dye pHRhodo. The conjugate was readily taken up by FR+ L1210 leukemia cells as demonstrated via fluorescence microscopy. More importantly, uptake was blocked by excess folic acid and only observed during endocytosis. Given that the dye only fluoresces bright red in an acidic environment, this imaging agent should prove advantageous for assessing cells/tissues undergoing FR mediated endocytosis.

MEDI 358

Evaluating the chromatographic behavior of HCP: A tool for rap id process development

***Xiaofeng Bao**, baoxiaofeng@mail.njust.edu.cn, Xiaolu Liu, Yanyan Jin. Department of Biochemical Engineering,Xiaolinwei 200, Nanjing University of Science & Technology, Nanjing, Jiangsu 210094, China*

Objectives: We recently synthesized a series of novel non-imidazole analogues based on our previously radiolabeled [^{18}F]-XB-1 structure motif as prospective standard compounds and radiolabeling agents as PET tracers for further study and elevation of histamine H_3 receptor radioligands in animals.

Methods: We developed accessible synthetic routes to prepare histamine H_3 receptor radioligand precursors 5b, 5d and references 5a, 5d according to the synthetic protocol

developed by Bao xiaofeng et al [1]

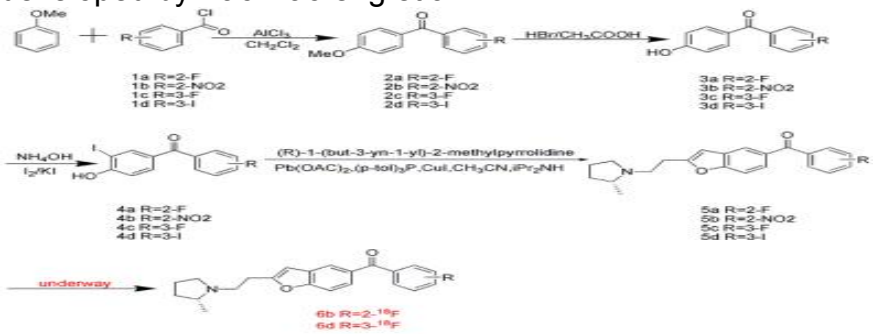

Figure 1: Synthesis of precursors and references of histamine H3 receptor radioligands

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Results: Chemically pure (>98%) 5a, 5b, 5c, 5d were prepared and on Pharmacological Screening.

Conclusions: Precursors and reference compounds based the non-imidazole 2-aminoethyl benzofuran derivatives have been synthesized. Radiosynthesis and evaluation of the ^{18}F-labeled PET radioligand for brain histamine subtye-3 receptors in animals are currently underway.

Research Support: This research was supported by Jiangsu Science Foundation BK2011704, NJUST Research Funding NO.2011ZDJH08.

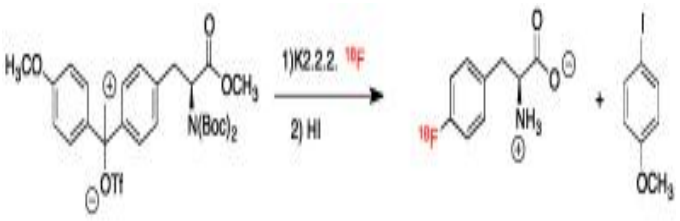
References: [1] Xiaofeng Bao.et al. (2012) J. Med. Chem., 55, 2406−2415.

MEDI 359

Highly efficient synthesis of no-carrier-added [^{18}F]-4-fluoro-L-phenylalanine

Katelyenn S. Glaspy[2]*, katelynnsglaspy@student.cofo.edu, Kiel D. Neumann*[1]*, Jerry C. Easdon*[2]*, Stephen G. DiMagno*[1]*. (1) Department of Chemistry, University of Nebraska-Lincoln, Lincoln, Nebraska 68588, United States (2) Department of Chemistry, College of the Ozarks, Point Lookout, Missouri 65726, United States*

A novel preparation of the radiotracer [^{18}F]4-fluoro-L-phenylalanine, a potential PET imaging agent for the detection of gliomas, is reported. The goal of this project was to further demonstrate the utility of diaryliodonium salt intermediates in the synthesis of high specific activity [^{18}F]fluorinated amino acids using (n.c.a.) [^{18}F]fluoride. The diaryliodonium salt **1** precursor was synthesized in high yield from commercially available L-phenylalanine according to previously reported methods.[1] Fluorination of **1** with Kryptofix potassium [^{18}F]fluoride, followed by a rapid deprotection with HI, provided the radiotracer in good yield.



1

Preliminary radiofluorination reactions employing the precursor **1** provided a 25% RCY (unoptimized, EOB) of n.c.a-[^{18}F]-4-fluoro-L-phenylalanine (determined by radio-HPLC).

References: [1]Wang, B; Qin, L; Neumann, K D; Uppaluri, S; Cerny, R L; DiMagno, S G; *Org. Lett.* **2010,** *12,*3352-3355.

MEDI 360

Synthesis and evaluation of a new positron emission tomography (PET) radioligands for 5-HT$_4$ imaging in nonhuman primate: [^{18}F]MNI-698

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In the central nervous system, 5-HT$_4$ receptors are primarily localized in the limbic and nigro-striatal pathways implicate in learning and memory. Preclinical evidence have shown that 5-HT$_4$ agonists increase acetylcholine release in these brain regions resulting in cognitive improvement in animal model of Alzheimer's disease (AD). Moreover, a decrease in 5-HT$_4$ receptors in the hippocampus was observed, post mortem, in Alzheimer's disease patients. These findings emphasize the need for non-invasive scintigraphic methods for assessing new drug targeting 5-HT$_4$ receptors and elucidating their pathophysiological changes in AD patients. We present the radiosynthesis, *in vitro* and *in vivo* evaluation of a novel [^{18}F]fluorinated benzodioxane derivatives [^{18}F]MNI-698, analogue of the selective antagonist SB204070. [^{18}F]MNI-698 was obtained following a two steps radiolabelling procedure with a 4±1% radiochemical yield and a radiochemical purity above 98%. Brain distribution of [^{18}F]MNI-698 by PET imaging in non human primates were in accordance with reported distribution of 5-HT$_4$. [^{18}F]MNI-698 shows the highest brain uptake in the striatum (7 SUV), follow by the hippocampus and substantia nigra (5.5 and 5 SUV respectively). Blockade study using SB204070 demonstrates the specificity of the signal, suggesting that [^{18}F]MNI-698 is a promising candidate for human imaging of 5-HT$_4$ receptors.

MEDI 361

T3P: Novel synthetic applications of this green reagent

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n-Propane Phosphonic Acid Cyclic Anhydride (T3P®) is an exceptional reagent for amide/peptide bond formation. T3P® has previously demonstrated its efficacy in the commercial scale manufacture of numerous APIs. More recently, esterifications, the formation of nitriles, hydroxamic acids, Weinreb amides and isonitriles have been achieved with T3P®, chemoselectively and in uniformly high yield. Further, T3P® has demonstrated utility in facilitating both the Curtius and Lossen rearrangements. Oxidation of alcohols to the corresponding aldehydes or ketones has been achieved under mild conditions with T3P®. Ease of use, mild reaction conditions, excellent selectivity, low epimerization and high yields are the hallmarks of these T3P® facilitated transformations. The desired product can be isolated by simple liquid/liquid extraction. Because of its superior performance in coupling reactions, hazardous additives such as explosive HOBt, are not required.

Numerous examples of these novel applications will be presented, wherein the inherent advantages of T3P® will be highlighted.

MEDI 362

Allylic oxidation of Δ^5-steroids at the C-7 position

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There has been renewed interest in 7-oxo-steroids in recent years due to their role in protecting neural cells from damage.[1-3] Allylic oxidation reactions using Cr(VI) species and N-hydroxyphthalimide represent an important synthetic method of introducing a carbonyl group into the the allylic positions of Δ^5-steroids in the presence of a sensitive 3β-substituent group.[4]The feasibility and efficiency to effect the oxidation of the allylic C-7 position in derivatives of dehydroepiandrosterone, testosterone and pregnenolone were investigated. For the reactions, various oxidants such as sodium dichromate, sodium chromate(VI), ammonium dichromate, sodium tungstate, sodium vanadate, sodium molybdate and ceric ammonium nitrate were used in combination with N-hydroxyphthalimide or N-hydroxysuccinimide as carrier.

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2. A. K. Pringle, W. Schmidt, J. K. Deans, E. Wulfert, K.G. Reymann, L. E. Sundstrom. Eur. J. Neurosci., 2003, 18, 117-124.

3. B. Dudas, I. Hanin, M. Rose, E. Wulfert. Neurobiol. Dis., 2004, 15, 262-268.

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MEDI 363

Direct synthesis of 3,3-difluorooxindoles from indoles via electrophilic fluorination

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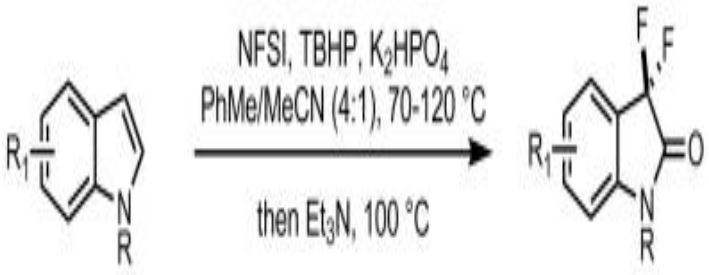
The introduction of fluorine(s) into bioactive molecules typically increases their metabolic stability, lipophilicity, bioavailability, permeability and binding affinity of bioactive molecules. An estimated 30-40% of all agrochemicals and 20% of pharmaceuticals contain fluorine.

Oxindole derivatives are useful synthetic intermediates for the preparation of biologically active molecules. The replacement of the keto carbonyl in isatinswith the isosteric *gem*-difluoro moiety leads to 3,3-difluoroxindole, a useful analogue for biological studies. This is often synthesized directly by nucleophilic fluorination of isatinsusing the thermally unstable diaminosulfur trifluoride (DAST), or more recently, bis(methoxyethyl)-aminosulfur trifluoride (Deoxofluor) and 4-*tert*-butyl-2,6-dimethylphenylsulfur trifluoride (Fluolead). Yet, there has been no report on the direct conversion of broadly available indoles to 3,3-difluoroxindoles to-date. Herein, a convenient one-pot method for the synthesis of 3,3-difluorooxindoles from readily available indoles *via* electrophilic fluorination has been developed.



MEDI 364

Synthesis of chemical probes using microwave assisted [2+2+2] cyclotrimerization of alkynes with the potential to target biological pathways

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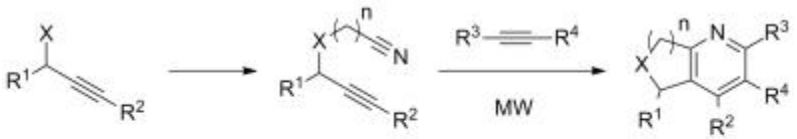
[2+2+2] cycloadditions of alkynes catalyzed by transition metals appear as a convergent approach to the synthesis of polysubstituted carbon-heterocyclic ring systems. This work applies the concept of Diversity Oriented Synthesis (DOS) to assemble various compounds, in which the key step (pairing step) was performed using microwave assisted [2+2+2] cyclotrimerization of alkynes (Scheme 1). The synthetic intermediates generated in the study will form the basis for the generation of small molecules that will be used to probe biological pathways.



X=OH, NHNs
R^1=Me, Ph
R^2=H, $Si(OEt)_3$
n=0,1

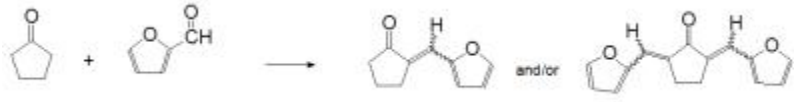
Scheme 1

MEDI 365

Furfurylidene compounds from Aldol reactions of cycloalkanones and furfural

Zach J Easdon[1]*, easdonz@william.jewell.edu, Jerry C Easdon*[2]*. (1) Department of Chemistry, William Jewell College, Liberty, MO 64068, United States (2) Department of Chemistry, College of the Ozarks, Pt. Lookout, MO 65726, United States*

The pharmacophore group furfurylidene is present in a variety of molecules possessing anti-inflammatory, antibiotic, antifungal, analgesic or hypnotic activity. The Aldol condensation reaction of cycloalkanone with furfural produces mono and bis fufurylidene substituted cycloalkanones. We have explored conditions to selectively produce either the mono or bis substituted compounds. Additionally the stereochemistry of the resulting alkenyl products has been determined.



MEDI 366

Green-based synthetic approaches for cannabinoid analogs

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Most pharmacotherapeutic and psychoactive effects of marijuana are attributed to a small subset of the ~60 known plant cannabinoids, namely delta-1-tetrahydrocannabinol (THC). An exogenous CB_1 and/or CB_2 cannabinoid receptor agonist, THC is believed to mediate central nervous (CNS) disorders, pain, inflammation, digestive disorders, and immune responses. Because chronic pain often requires a combination of pharmaceutical agents for effective management, past studies suggest cannabinoids are a potential addition to the arsenal of treatment options for patients with varied diseases. Symptoms associated with diseases, which are characterized by morphological, pathological, and clinical determinants, require a search for pharmacological agents that can broaden new targeted therapeutic options. This promising feature of Cannabinoids can be exploited as a potential approach to pain management with a novel therapeutic target and mechanism; however processes of synthesizing cannabinoid analogues can be both costly and environmentally damaging. To address this problem, cost effective methods to facilitate the synthesis of cannabinoid analogues that ameliorates the process of drug discovery is investigated through an environmentally safe lens. Preliminary data supports the environmental benefits of using green-based solvents and catalytic agents as a reliable direction to eliminate the inherent toxicity due to the synthesizing process.

MEDI 367

Computational directed synthesis of cannabinoid analogs

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Cannabinoids have long been shown to have theraputic properties as analgesics, muscle relaxants, and apepitite stimulants. There interest to develop novel approaches to synthesize cannabinoids that contain the theraputic properties while devoid of its psychoactivity. The endogenous psychoactive form Δ^9 –THC (Tetrahydrocannabinol) and the non-psychoactive Δ^0 –THC differ by the presence of a double bond present at the Δ^9 position of the psychoactive form. There is obvious interest in the role this double bond plays in the reactivity of this compound. Computational simulations of various chemical reactions are used to compare the relative thermodynamic energies when using either Δ^9 –THC or Δ^0 –THC. These calculated differences in energy are predictors of the synthetic success of the various reactions simulated. I aim to show a positive correlation between the differences in the calculated thermodynamic energies of the two fairly similar compounds leads to the relative success of a chemical reaction; with success defined as the formation of a the desired product.

MEDI 368

Towards efficient and process-scale syntheses of selected bicyclo[1.1.1] pentane derivatives with potential applications in drug discovery and agrochemistry

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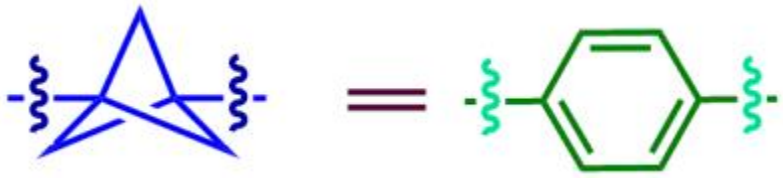
Phenyl and other six-membered aromatic moieties are major constituents of several bioactive molecules. The use of these molecular functions is often accompanied by complications with biopharmaceutical properties such as lipophilicity and metabolic stability. Customary tactics to counter these issues often lead to an obese lead compound. An exit from this rather unproductive cycle would be possible with the application of an appropriate bioisostere. The use of a bicyclo[1.1.1]pentane motif as a replacement for an aryl/phenyl group has been demonstrated in the literature. Unfortunately, the use of these unusual phenyl/aryl bioisoteres in medicinal chemistry endeavors is discouraged by their limited commercial availability and long low-yielding synthetic sequences to secure these compounds.

We have recently embarked on a program that is aimed at investigating new and scalable routes to phenyl isosteres with applications in medicinal chemistry. As a part of this study, we have successfully synthesized a class of bicyclo[1.1.1]pentane-aryl systems. In collaboration with our process chemistry unit, efforts are also underway to implement this chemistry at a kilo-lab scale. Apart from the synthetic studies, we are also keen in understanding the analogy, if any, of the interactions between aryl and bicyclo[1.1.1]pentane derivatives and their biological targets. In this presentation we intend to narrate a general overview of our approach along with its current progress and future perspectives.



MEDI 369

Automated optimization of chemical reactions in flow for early phase drug discovery

***Richard Jones**, flowchemistry@thalesnano.com, Ildiko Kovacs, Ferenc Darvas. ThalesNano Inc., Budapest, Hungary*

The major objective of the early phase drug discovery is to present widevariety of novel chemical structures in a cost and time effective manner.Flow chemistry with the

extended parameter space and enhanced heat/masstransfer readily contributes to this effort. There has been significantprogress in the development of miniaturized in-line monitoring techniquesfor the rapid analysis and optimisation of flow syntheses includingin-line IR, MS and recently NMR spectroscopy. Furthermore, flow technologycombined with in-line analysis can be used to automatically optimizereaction conditions. Experiment design algorithms (such as Simplex™) coulddecide which parameters to adjust, thus, the process can be self-optimizeduntil the desired conversion, selectivity achieved. In the presentationoxidations, N-alkylation, heterocyclic ring formation reactions areinvestigated in flow for automatic optimization connecting IR (FlowIR™)and miniaturized NMR into the flow line providing feedback to adjust thekey parameters of the flow reactors (H-Cube Pro ™).

MEDI 370

Substrate activity screening methodology for protein tyrosine kinases

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Greater than 99% of kinase inhibitors target the highly conserved ATP binding site. These compounds often potently inhibit multiple kinases which complicates their use as biological probes. Recently, attention has turned towards targeting less conserved sites such as the protein substrate binding site. We aim to develop general methodology for the discovery of substrate-competitive kinase inhibitors. Substrate activity screening identifies *substrates* of an enzyme instead of inhibitors, and then the reactive portion of the substrate is modified to convert it into an inhibitor. Using an ADP-based detection assay, we identified small molecule substrates of the protein tyrosine kinase c-Src. Through the incorporation of multiple fluorines, we have converted a substrate into an inhibitor. Our optimized inhibitor has greater than 60-fold selectivity over the highly similar kinase c-Abl, and Lineweaver-Burk plots have confirmed a substrate-competitive, ATP-noncompetitive binding mode.

MEDI 371

Synthesis of benzodiazepines active against neuropathic pain as well as schizophrenia

Michael M Poe[1]*, mmpoe@uwm.edu, Zhi-jian Wang*[1]*, Alessandra Di Lio*[2]*, Sundari R Rallapalli*[1]*, Rahul Edwankar*[1]*, James M Cook*[1]*, Hanns Ulrich Zeilhofer*[2]*. (1) Department of Chemistry and Biochemistry, University of Wisconsin - Milwaukee, Milwaukee, WI 53211, United States (2) Institute of Parmacology and Toxicology, University of Zurich, Zurich, Switzerland*

Recently we have designed a series of subtype selective GABA(A)-ergic ligands that are active as nonsedating anxiolytics in rodents and primates. These GABAergic/BzR agonists are nearly silent at α1 and α5β2γ2 subtypes; consequently, tolerance does not develop to the anxiolytic, anticonvulsant, or antihyper-algesic effects. Based on available literature these agents will exhibit little or no abuse potential in contrast to the well known tranquilizers (Valium, Xanax and Librium). Because they do not develop tolerance and do not cause amnesia, ataxia nor sedation, they are targeted for treatment of neuropathic and inflammatory pain. Also, another series of ligands has been synthesized that target α5β2γ2 subtypes while staying silent at α1 which can used to target treatment of schizophrenia. Analogs of the lead compound can be synthesized and quickly screening using transiently transfected cells assayed with an automated-patchclamp instrument. Again, these non toxic agents do not develop tolerance.

MEDI 372

Design and synthesis of novel N-phenyl-N-(piperidin-4-yl) propionamide derivatives and their use as opioid receptor ligands

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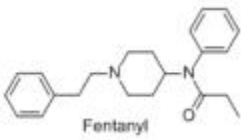
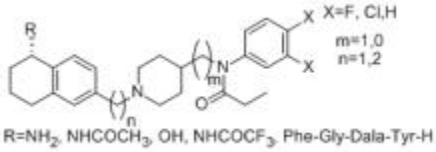
Opioid receptors are important class of GPCRs which deal with the analgesic effects in humans. Opioid analgesics are widely used in the managemet of neuropathic pain. The clinical use of opioids is limited by serious side effects. μ receptors are the most important receptor target for almost all commercially available potent opioid agonist.

Compound	R	n	m	X	K_i [^{3}H]DAMGO (nM	K_i[^{3}H]DPDPE (nM)
DS-90	OH	1	1	H	190	7800
DS-106	NH_2	1	1	H	580	6000
DS-109	$NHCOCH_3$	1	1	H	460	10000
DS-118	Tyr-DAla-Gly-Phe	1	1	H	10	320
DS-125	NH_2	1	0	H	44	10000
DS-126	$NHCOCH_3$	1	0	H	49	10000





Here we designed and synthesized novel μ-selective opioid ligands of N-phenyl-N-(piperidin-4-yl) proionamide derivatives which contain the (5-amino/hydroxyl tetrahydronaphthalen-2yl) methyl group. Basically our designs are based on fentanyl the well known potent μ-agonist in which we replaced the phenethyl group with the tetrahydronaphthalen-2yl methyl moiety with amino, and hydroxyl and opioid peptide analog substitution at the 5thposition.

1. Supported by USPHS, NIDA

2. WO00/71518A2, WO2009/077584

3. *Expert Opin. Drug. Discov.* **2010** , *5*, 10

MEDI 373

Design, synthesis, and evaluation of selected 1,4-dihydropyridine type acetylcholinesterase inhibitors

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Pharmacophore mapping and docking studies were carried out to develop optimized leads for the design of 1,4-dihydropyridines as acetylcholinesterase inhibitors. Theoretical ADME analysis was also carried out. Based on correlating results, selective 1,4-dihydropyridines were synthesized by a novel green catalyst based approach. Structures and purity of newly synthesized compounds were confirmed by using LCMS and NMR. Biological evaluation of these molecules showed 5 compounds to be potent acetylcholinesterase inhibitors with IC(50) (hAChE) in the nanomolar range. Molecular modeling investigation supports dual AChE inhibitory profile for all the compounds, binding simultaneously at the catalytic active and at peripheral anionic sites of the enzyme. These compounds are being carried forward as promising leads in the treatment of Alzheimer's disease.

MEDI 374

Synthesis and evaluation of quinoline analogs as potential drugs in Alzheimer's disease

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Virtual screening was carried out on a set of 2 million molecules using a pharmacophore mapped from a set of 74 potent acetylcholinesterase inhibitors selected from extensive literature search of published articles. Refinement of the hits obtained led to the selection of a quinoline derivative as an acetylcholinesterase inhibitor. Theoretical ADME analysis and docking studies led us to the development of a series of quinoline derivatives with potent acetylcholinesterase activity in the nanomolar range. Structures and purity of newly synthesized compounds were confirmed by using LCMS and NMR. Further liposomes were also synthesized to increase the invivo activity in mice and reduce the toxicity for 2 selected leads with better activity and reduced toxicity. These compounds are being further tested as promising leads in the treatment of dementia.

MEDI 375

γ-Secretase modulators with reduced lipophilicity and reduced liver toxicity

Tongfei Wu, Frederik J. R. Rombouts, Francois P. Bischoff, Didier Berthelot, Daniel Oehlrich, Michel A. J. De Cleyn, Adriana I. Velter, Michel Surkyn, Sven Van Brandt, Andrés A. Trabanco, Marc Mercken, ***Harrie J. M. Gijsen****, hgijsen@its.jnj.com. Department of Neuroscience, Janssen Research and Development, Division of Janssen Pharmaceutica NV, Beerse, Belgium*

Alzheimer's disease (AD) represents one of the principal unmet medical needs, being the third highest cause of death after cancer and heart disease. With an increasingly ageing population worldwide, AD represents a huge burden to society. Gamma secretase modulation has been proposed as a potential disease modifying approach to AD. Gamma secretase modulators (GSMs) act by reducing the production of the toxic Aβ42 peptides and biasing the APP processing towards shorter length Aβ peptides. Since the termination of the GSM tarenfurbil in 2008 due to negative phase III trial results, considerable progress has been made towards more potent and better brain penetrable compounds. Most of the potency gain has been achieved by adding lipophilicity, resulting in compounds with low ligand lipophilicity efficiency (LLE). The suboptimal drug-like properties have translated into side effects for several of these compounds, such as liver toxicity. In continuation of our work on conformationally restricted amino-pyridones, which led to potent but lipophilic GSMs,[1] we now disclose the evolution of a simple amide series. Bioisosteric replacement of the amide linker by an imidazole or 1,2,4-triazole heterocycle, followed by conformational restriction into 1,2,4-triazolopiperidines gave potent compounds with reduced molecular weight and aromaticity compared to our previous series. Subsequent replacement of key carbon-atoms with hetero-atoms resulted into compounds with reduced lipophilicity, as well as reduced liver toxicity.

1)F. Bischoff, D. Berthelot, M. De Cleyn, G. Macdonald, G. Minne, D. Oehlrich, S. Pieters, M. Surkyn, A. A. Trabanco, G. Tresadern, S. Van Brandt, I. Velter, M. Zaja, H. Borghys, C. Masungi, M. Mercken, and H. J. M. Gijsen *J. Med. Chem.,* DOI: 10.1021/jm201710f, 2012.

MEDI 376

Development of potent azaindazole LRRK2 inhibitors with a key intramolecular hydrogen bond

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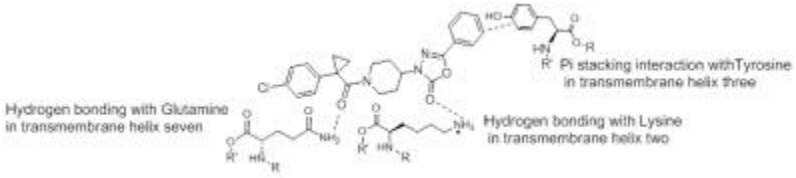
The discovery of disease-modifying therapies for Parkinson's disease represents a critical need in neurodegenerative medicine. Genetic mutations in LRRK2 have been suggested as risk factors for the development of PD and some of these mutations have been linked to increased LRRK2 kinase activity and neuronal toxicity in cellular and animal models. As such, research towards brain-permeable kinase inhibitors of LRRK2 has received much attention. During our efforts to this end, a 5-azaindazole series was optimized for potency, metabolic stability and brain penetration. A key design element involved the incorporation of an intramolecular hydrogen bond to increase permeability and potency against LRRK2. This poster will outline the structure-activity relationships of a “matched pair” series including the challenge of obtaining a desirable balance between metabolic stability and brain penetration.

MEDI 377

Exploration and maximization of GPR55 antagonists using synthetically diversified ligands

Mary A Lingerfelt[1]*, malinger@uncg.edu, Haleli Sharir*[2]*, Dow P Hurst*[1]*, Mary H Abood*[2]*, Patricia H Reggio*[1]*, Mitch P Croatt*[1]*. (1) Department of Chemistry and Biochemistry, University of North Carolina at Greensboro, Greensboro, North Carolina 27402-6170, United States (2) Department of Anatomy and Cell Biology, Temple University School of Medicine, Philadelphia, Pennsylvania 19140, United States*

The research presented involves the synthetic diversification and biological evaluation of a parent chemotype of an antagonist of the recently de-orphanized cannabinoid-like G-protein coupled receptor, GPR55. The parent molecular scaffold is a compound that selectively antagonizes GPR55, displaying no activity at any of the other similarly structured cannabinoids. By rationally varying substituents to maximize the various interactions between the binding pocket and the ligand, the efficacy and the selectivity of ligands for GPR55 can be modified.

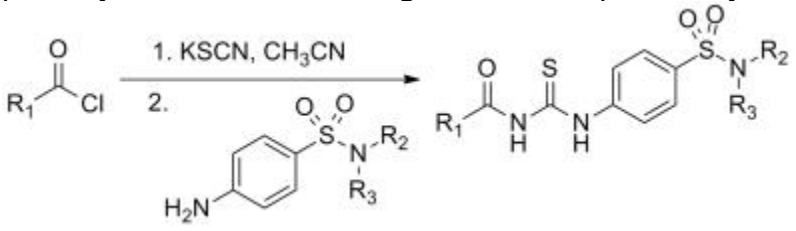


MEDI 378

Synthesis and biological evaluation of GPR55 agonists

Lara Fakhouri*, lialfakh@uncg.edu, Haleli Sharir, Dow Hurst, Mary Abood, Patricia Reggio, Mitch Croatt. Department of chemistry and biochemistry, university of north carolina at greensboro, greensboro, north carolina 27402-6170, United States*

The recently de-orphanized GPCR55 has been established to have a role in inflammatory and neuropathic pain. HTS presented four agonistic hits, from which the most potent and selective one was chosen as a lead. Synthesis of diverse analogues of the lead, which were designed based on a computer model of the target receptor, was done to optimize the potency and selectivity. This is crucial to accurately determine the potency and kinetics of antagonists which potentially have therapeutic applications.



MEDI 379

Development of cannabinoid and T type calcium channel ligands for treatment of pain

Steven W McDaniel[1], *steven.mcdaniel@umontana.edu, Ravil R Petrov*[1], *Haitao You*[2], *Vinicius M Gadotti*[2], *Chris Bladen*[2], *Gerald W Zamponi*[2], *Philippe Diaz*[1]. *(1) Department of Bio-medical Science, University of Montana, Missoula, Montana 59801, United States (2) Department of Physiology and Pharmacology, University of Calgary, Calgary, Alberta, Canada*

Neuropathic pain effects 8% of population worldwide and is among the most challenging types of chronic pain to treat. Both T-type calcium channels and cannabinoid receptors modulate signaling in the primary afferent pain pathway. It has been shown that several endocannabinoids and phytocannabinoids can directly block T-type calcium channels with potencies in the high nanomolar and low micromolar range, and can trigger analgesia in animals. Based on these discoveries we sought to develop mixed T-type calcium channel and cannabinoid CB_2 modulators along with selective T-type calcium channel blockers. We synthesized and pharmacologically characterized a series of novel dual T-type channel and cannabinoid receptor ligands, then tested their analgesic effects using an in vivo model of inflammatory pain. Our data show that mixed T-type/CB_2 ligands and selective T-type antagonist may provide new strategies for developing effective pain therapeutics. We will report details of the synthesis, *in vitro* characterization, and *in vivo* testing of these novel compounds.

MEDI 380

Development of small chalcone and chalcone-likeorganic molecules for apolipoprotein E (apoE) modulation throughstructure-activity relationship (SAR) study

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Apolipoprotein E (apoE) is a prominent transport
lipoprotein in the body and brain that helps distribute cholesterol and
triglycerides between organs in the human body.
Genetic variance in apoE alleles has been shown to increase the
probability of developing Alzheimer's disease.
We have previously screened a small library of small molecules that identified
two structurally diverse scaffolds. Specific chalcones have previously shown
the ability to modulate the production of apoE in ELISA assays. This presentation aims
at describing our

efforts with further structure-activity relationship (SAR) studies in an attempt to improve efficacy and develop drug-likeness.

MEDI 381

Synthesis of kappa opioid receptor agonist/antagonist chemotypes to treat drug addiction

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Drug addiction is a serious issue that affects millions of people in the US. Illicit drugs create high levels of dopamine in the body, which causes users to experience a state of euphoria. Dopamine is regulated by what are known as Kappa Opioid Receptors inside of a human cell. When KOR's are bound with agonist chemotypes they are activated and prevent the release of dopamine in the body. Currently the most used form of drug addiction treatment is rehabilitation, in which addicts go through a period of counseling in a drug free environment. With this sudden halt of drug use addicts experience a dramatic decrease of dopamine levels in the body, which can cause drug relapse, depression, anxiety, chronic pain, and other negative side effects. The overall objective of this project is to synthesize small molecules that can serve as KOR partial agonists/antagonists. These small molecules can lead to the creation of new treatments that can help regulate the amount of dopamine released in the body, which can be used to treat drug addiction and other psychiatric disorders. The methods used and results of the synthesis will be presented.

MEDI 382

Synthesis of heterocyclic cannabinoids

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Since the discovery of the cannabinoid receptors (CB_1 and CB_2), cannabinoids have evolved from classification as a recreational drug to compounds evidenced to affect a plethora of diseases. The location of these receptors range from the CNS to peripheral tissues and therefore ligands can be designed to target diseases that act through the CNS and PNS. Here we present research that focuses on the synthesis of cannabinoid analogues designed to mimic the CB1 affinity of phytocannabinoids, yet alter the hydrogen-bond donating and accepting ability of the molecule relative to the putative THC-CB_1 model. The reported synthesis substitutes the olivitol-based C-ring of THC with a nitrogen-containing heterocycle. The substitution of the olivitol-based C-ring is done in a cost effective and high yielding manner. Computational studies of drug-ligand interactions show that the synthesized heterocycles mirror or surpass THC binding

affinities; thus showing the compounds potential to be used as phytocannabinoid alternatives.

MEDI 383

Synthesis and SAR of aryl-naloxamides targeting truncated exon 11-associated mu opioid receptor (MOR-1) splice variants as non addicting and non-abusable analgesics

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3-Iodobenzoylnaltrexamide ***1*** (IBNtxA) is a potent analgesic acting through a novel receptor target that lack many side-effects of traditional opiates composed, in part, of exon 11-associated truncated six transmembrane domain MOR-1 (6TM/E11) splice variants. To better understand the SAR of this drug target, a number of 4,5-epoxymorphinan analogs were synthesized. Results show the importance of a free 3-phenolic group, a phenyl ring at the 6 position, an iodine at the 3'or 4' position of the phenyl ring and an N-allyl or c-propylmethyl group to maintain high 6TM/E11 affinity and activity. 3-Iodobenzoylnaloxamide ***15*** (IBNalA) with a N-allyl group displayed lower delta opioid receptor affinity than its naltrexamine analog, was 10-fold more potent an analgesic than morphine, elicited no respiratory depression or physical dependence and only limited inhibition of gastrointestinal transit. Thus, the aryl-naloxamide scaffold can generate a potent analgesic acting through the 6TM/E11 sites with advantageous side-effect profile and greater selectivity.

MEDI 384

New class TRPM8 antagonist, voacangine is the first natural competitive antagonist for menthol receptor, TRPM8

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TRPM8 is activated by cold temperature and cooling compounds, menthol and icilin. TRPM8 is involved in cold allodynia and pain in urological and respiratory disorders. TRPM8 blocking drugs are being developed energetically as a new therapy for these disorders. Because only a few natural TRPM8 antagonists have been reported, the

finding of new compounds having different structures from known antagonists could lead to develop new type of blockers.

We are searching for TRP channel-effective substances from natural sources for TRP channel-target medicines. Here we found that voacangine from *Voacanga africana* having iboga structure is a novel strong TRPM8 antagonist.

Mouse TRPM8-expressing HEK cells were used. Receptor responses were evaluated as increases of intracellular Ca^{2+} by using a microplate reader and a fluorescent microscope.

Voacangine attenuated menthol- or icilin-induced TRPM8 activation in a concentration-dependent manner. Schild plot analysis showed that voacangine competitively inhibits menthol (pA_2 = 5.07 ± 0.12, K_B =8.50 ± 0.76 μM, slope = 1.1 ± 0.0), but non-competitively antagonizes against icilin. The IC_{50} values of voacangine were 9 μM for menthol and 7 μM for icilin. Voacangine showed much stronger potency than capsazepine and any other natural ones, but a little weaker than BCTC against both menthol and icilin. Up to 30 μM, voacangine did not block cold-induced TRPM8 activation.

Voacangine is the first natural competitive antagonist for TRPM8 with high potency and the first alkaloid antagonist for TRPM8. Since most of known TRPM8 antagonists are non-competitive, voacangine could contribute to develop new class of TRPM8 blocker.

MEDI 385

Application of bioisosterism approach in the design, synthesis, and biological evaluation of nitrofurazone derivatives as antichagasic candidates

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Chagas disease, caused by the parasite *Trypanosoma cruzi,* affects 10 to 14 million people and provokes 21 million deaths, still lacks satisfactory treatment, especially in the chronic form. Based on the activity of nitrofurazone in cruzain, the major cysteine protease in the parasite, we designed and synthesized aromatic semicarbazone-derived compounds using bioisosterism. All compounds showed significant lower IC_{50} values in amastigotes, ranging from 0.65 to 1.3 μM, when compared to the reference drug benznidazol (5.1 μM). Permeability studies *in vitro* through Caco-2 cells membranes showed that all compounds presented high permeability (Papp > 10 x 10^{-6} cm/s).

Cytotoxicity studies in human HepG2 cells revealed selectivity index (IC_{50} cytotox/IC_{50} parasite) greater than 50. Docking studies also suggested a complementary relationship between the semicarbazone-derived moieties and the Cys25 in the active site. This study makes us strongly believe that those molecules have an excellent potential as leads for future antichagasic agents.

MEDI 386

Inhibitors of AddAB and RecBCD bacterial DNA repair enzymes: A novel class of antibiotics identified through molecular probe development efforts

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AddAB and RecBCD are related bacterial helicase/nuclease enzymes responsible for DNA repair and genetic recombination. They unwind and then hydrolyze DNA, making sequence-specific endonucleolytic scissions, and are critically important for repairing DNA double strand breaks. Mutant bacteria lacking functional helicase/nucleases are not viable in infecting mammalian hosts. Inhibitors of these enzymes may therefore be effective as antibacterial drugs, preventing DNA damage by reactive oxygen species that follow infection. No potent and selective drug-like small molecules inhibitors of AddAB and RecBCD are known, however. We herein report results of a probe development effort, within the NIH's Molecular Libraries Probe Center Network (MLPCN), to find inhibitors of AddAB and RecBCD. We discuss the uHTS results from the NIH collection (then 326,000 small molecules), hit confirmation, lead selection, and finally structural optimization to augment potency and define mechanism of action. We show two structure classes with AddAB / RecBCD activity, with SAR studies for each series. Molecular probes inhibiting AddAB and/or RecBCD will be useful tools in evaluating the therapeutic potential of selective and potent small molecule inhibition of bacterial helicase/nucleases.

MEDI 387

3-Aryl-4(1H)-quinolones with broad range in vivo antimalarial activity

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Malaria is devastating parasitic diseases of man with approximately 1 million deaths per year. Recent reevaluation and optimization studies of 4(*1H*)-quinolones and close analogues lead to new antimalarial leads with *in vitro* erythrocytic stage activity and improved physicochemical properties. Despite a large number of potent compounds emerged from these recent studies, only few have been reported to have been studied in *in vivo* models. Herein, we report our efforts to develop orally bioavailable 3-phenyl-substituted 4(*1H*)-quinolones (P4Qs). Preliminary data suggests that P4Qs with atropisomeric character possess improved *in vivo* antimalarial efficacy in a *P. berghei* infected mouse model, and activity against gametocytes. The atropisomeric character of selected P4Qs has been studied using quantum mechanics torsion profile calculations to determine rotation barrier. Furthermore, the relative flexibility of C-H vectors was monitored by ^{13}C T_1 spin-lattice relaxation experiments in which shorter relaxation times are indicative of relatively slower segmental motion or flexibility.

MEDI 388

Synthesis and evaluation of 4(1*H*)-quinolone prodrugs targeting multi-drug resistance *P. falciparum* malaria

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4(*1H*)-Quinolones and 1,2,3,4-tetrahydroacridones (THAs) are known to possess causal prophylactic activity and potent erythrocytic stage inhibition in avian malaria models, but not against malaria parasites in mammals. Recently, the Manetsch laboratory has synthesized and identified 4(*1H*)-quinolones and THAs displaying excellent *in vitro* activity against *P. falciparum* and adequate *in vivo* activity in *P. berghei* infected mice. Subsequent pharmacokinetic studies with lead quinolone compounds suggests the aqueous solubility is the major reason for poor bioavailability and moderate *in vivo* activity. Herein, we describe the development of a prodrug approach to circumvent the observed bioavailability issues. 4(*1H*)-quinolones have been derivatized via esterification, alkylation, alkyloxycarbonyloxymethylation or phosphorylation. Prepared prodrugs have then been tested for chemical stability at different pHs, aqueous solubility as well as regeneration of active parent compound *in vitro*. A selected set of prodrugs has been shown to possess improved *in vivo* antimalarial efficacy in a *P. berghei* infected mouse model.

MEDI 389

Synthesis, antimalarial activity, and physicochemical properties of 7-(2-phenoxyethoxy)-4(1H)-quinolones

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Malaria has become one of the most widespread infection diseases. There are a few antimalarial classes which possess activity against blood stages of malaria. However, very few compound classes have been shown to be active against the liver, blood, and gametocyte stages of the parasite's life cycle. It has been reported that quinolone ester ICI56,780 is active in eradicating dormant exoerythrocytic parasites in *Plasmodium cynomologi* infected rhesus monkeys. This discovery was stalled due to the rapid resistance induction that appeared. Because of recent advances in preclinical efficacy models and ease of assessing physicochemical properties, this class of compounds, which was worked on more than 20 years ago, has been revisited. Herein, structure-activity relationship and structure-property relationship studies of ICI56,780 analogues are discussed. The results suggest that ICI56,780 and analogues thereof have potential for the development of a novel chemotype to treat multidrug resistant malaria, to kill EE stages, to block transmission, and to eradicate malaria.

MEDI 390

Design, synthesis, and SAR studies on a new class of antimycobacterials

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Tuberculosis (TB) is a bacterial infection causes more deaths than any other infectious disease. It is estimated that 9 million people are infected with tuberculosis annually leading to an estimated 1.5 million deaths per year. Novel acrylic acid ethyl ester derivatives were synthesized and evaluated as potential agents against Mycobacterium species. Minimum inhibitory concentration (MIC) assays indicated that compounds 3 and 4 have in vitro activity against *Mycobacterium smegmatis*. When tested against *Mycobacterium tuberculosis* and other Mycobacterium strains compounds 3 and 4 were found to have variable activity and SAR studies were started on this line of compounds. Based on these studies two compounds were identified as potential leads, compounds 5 and 6 were found to have MICs of 8 µg/mL against *Mycobacterium tuberculosis*. SAR studies are ongoing and many derivatives of 5 and 6 are currently being tested for activity.

MEDI 391

Design and synthesis of a new class of antibacterials with activity against mycobacteria and gram-positive bacteria

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Drug-resistant strains of bacteria are an ever present threat to modern healthcare and the need for new treatments is growing. The discovery of novel stilbene compounds with activity against a number of gram-positive bacteria as well as mycobacterium has led to a potentially new class of antibacterials that show great promise against drug-resistant strains of bacteria. SAR studies along with the development of a simple 1-step synthesis of diverse stilbene analogs has led to compounds with minimum inhibitory concentrations (MIC's) in the range of 1-10 μg/mL against a number of gram-positive bacterial species including Methicillin resistant *Staphylococcus aureus* (MRSA) and mycobacterium species including surrogates of *Mycobacterium tuberculosis* (MTB). A pharmacophore model has also been constructed to aid in designing new compounds and to further our understanding of the mode of action of these novel small molecules.

MEDI 392

Design, 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 cell division protein that 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 a promising target for the drug discovery of broad-spectrum antibacterial agents against various bacterial pathogens. Based on rational drug design, we have synthesized libraries of 2,5,6-trisubstituted benzimidazoles, bearing ether and sulfide substituents at the 6-position and their antibacterial activities screened. We will present the design and synthesis of those novel 2,5,6-trisubstituted benzimidazoles and their biological activities against *Mtb* and *M.smegmatis* strains.

MEDI 393

Synthesis and biological evaluation of novel antitubercular trisubstituted benzimidazoles targeting FtsZ

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FtsZ, a vital cell division protein in prokaryotes, polymerizes upon binding to GTP and forms the 'Z ring'. Interference of the assembly-disassembly of this essential protein has been shown to affect the cell division processes, leading to inhibition of septation. We have synthesized libraries of novel trisubstituted benzimidazoles and identified compounds which target Mtb FtsZ protein and exhibit excellent activity against drug-sensitive and resistant Mtb strains. Based on rational drug design the lead compounds have been optimized to improve ADME properties and efficacy. Herein we will present the synthesis, in vitro and in vivo evaluation of selected compounds against Mtb strains.

MEDI 394

Design, synthesis, and biochemical characterization of bisubstrate adenylation inhibitors of biotin protein ligase from *Mycobacterium tuberculosis* resistant to cyclonuclesoide formation

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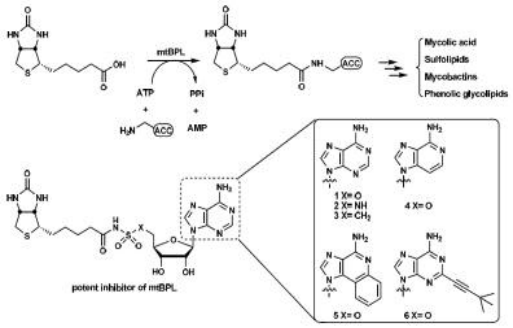
Mycobacterium tuberculosis (*Mtb*) the etiological agent of tuberculosis is the leading cause of infectious disease mortality from a bacterial pathogen. The lack of new antibiotics for *Mtb,* along with the increased prevalence of multidrug resistant strains

demands the development of new drugs, ideally with novel mechanisms of action. The mycobacterial biotin protein ligase (*Mt*BPL) globally regulates lipid metabolism in *Mtb* through the posttranslational biotinylation of acyl coenzyme A carboxylases (ACCs) involved in lipid biosynthesis and is essential for *Mtb* survival. We developed a rationally designed, bisubstrate inhibitor (**2**) of *Mt*BPL that displays potent subnanomolar enzyme inhibition and antitubercular activity against multidrug resistant and extensively drug resistant *Mtb* strains. Here we present the design, synthesis and evaluation of a focused series of analogs of **2** that are resistant to cyclonucleoside formation, a key decomposition pathway of our initial compound **1** , which is caused by intramolecular nucleophilic attack of the N-3 adenine on C-5'. Improved chemical stability is realized through replacement of the N-3 and C-5' oxygen atoms with carbon as well as incorporation of bulky group on the nucleobase to prevent the required *syn*-conformation necessary for proper alignment of N-3 with C-5'.



MEDI 395

Synthesis and antibacterial evaluation of novel 4-chromanone and chalcone analogs

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The development of novel antibacterial agents is urgently needed due to emergence and spread of drug resistant bacterial pathogens. Olympicin A was recently isolated and reported to show potent antibacterial activity especially against multi-drug resistant *Staphylococcus aureus* (MRSA) strains, with MICs values ranging from 0.5 to 1 µg/mL. Inspired by olympicin A, as well as recently described abyssinone II antibacterial lead, a panel of 4-chromanone and chalcone derivatives bearing aromatic, aliphatic, bicyclic, and spiro motifs were designed. Subsequently, an efficient synthesis was developed using a sealed pressure tube; and several series of diverse 4-chromanone and

chalcone structural analogues were synthesized by reacting substituted 2-hydroxyacetophenone with appropriate aldehydes in the presence of pyrrolidine in ethanol. Whole cell antimicrobial assessment was performed against *M. tuberculosis* and a select panel of Gram-positive and -negative bacterial pathogens. Some compounds showed good to potent anti-Gram-positive activities, among them, the chalcone derivative displaying an allyloxyphenyl or a myrtenal moiety demonstrated the best activity against MRSA (MIC 0.39 and 1.56 µg/mL, respectively). Detailed structural activity relationships and preliminary mode of action studies will also be presented.

MEDI 396

Synthesis of siderophore conjugated Lactivicin compounds with activity against gram-negative pathogens

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Novel siderophore conjugated analogs of the natural product, lactivicin, were designed, guided by X-ray crystallography of a covalent complex of a lactivicin derivative with *Pseudomonas aeruginosa* (Pae) Penicillin Binding Protein 3 (PBP3). Analogs bearing a variety of sideophore mimicking groups extending into open regions of the active site were synthesized and evaluated. The targeted analogs exhibited Minimum Inhibitory Concentrations (MIC) against pathogenic Gram-negative organisms: Pae (0.5 - 32 µg/mL), *Klebsiella pneumoniae* (0.5 – 32 µg/ mL), *Acinetobacter baumaunii* (0.06 – 32 µg/mL), and *Escherichia coli* (0.25 – 2 µg/mL) and potent inhibition of Pae PBP1a, 1b and PBP3 (IC_{50} 0.03 – 2.5 µM). A lead compound employing a novel siderophore mimic, 3,4-dihydroxyphthalimide, displayed enhanced Gram-negative inhibition and useful pharmacokinetics in rat.

MEDI 397

New polymyxin analogs for the treatment of multidrug-resistant gram-negative nosocomial pathogens

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Multidrug-resistant Gram-negative bacteria (Acinetobacter baumannii, Pseudomonas aeruginosa, and Klebsiella pneumoniae) are a serious threat to human health. The polymyxin class of antibiotics is one of the last lines of defense for treating infections caused by these pathogens. We have synthesized novel Dap-3 polymyxin analogs that exhibit greater potency against polymyxin resistant recent clinical isolates without losing activity against susceptible strains.

MEDI 398

Development of 2,4-diaminoquinazolines with in vivo antileishmanial activity

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N^2,N^4-disubstituted quinazoline-2,4-diamines were found to display activity against *Leishmania donovani* and *L. amazonensis*. SAR studies suggested the most potent activities were obtained with quinazoline-2,4-diamine scaffolds bearing N^2-benzyl-N^4-alkyl/phenyl or N^2-isopropyl-N^4-furfuryl substituent combination. Substitution of the benzenoid ring has been identified to play a secondary role for efficacy with improved selectivity indices. Assessment of key physicochemical properties confirmed that the aqueous solubility, distribution coefficient, and passive transcellular permeability were in acceptable ranges. Subsequently, three selected lead compounds were tested in an *in vivo* murine visceral leishmaniasis model. While two compounds did not have activity translate from *in vitro* to *in vivo*, the third quinazoline reduced parasitemia by 37% when 15 mg/kg/day were given via the intraperitoneal route for five consecutive days. Therefore, we think that the observed potencies of frontrunner compounds in conjunction with favorable physicochemical and pharmacokinetic properties make N^2,N^4-disubstituted quinazoline-2,4-diamines a suitable platform for the future development of antileishmanial agents.

MEDI 399

Non-microbicidal inhibition and dispersion of mucoid *Pseudomonas aeruginosa* biofilm by polyol-derivatized hydrocarbons

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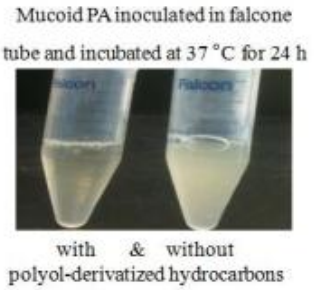
Pseudomonas aeruginosa (PA) is the prevalent pathogen in the lungs of chronic Cystic fibrosis (CF) patients. Over time PA strain in CF patients mutates to mucoid strain that overproduce alginate and form biofilm with increased antibiotic resistance. Here we report, a nontoxic polyol-derivatized hydrocarbons that inhibits biofilm formation and disperses 3-day old already formed biofilm of wild type and mucoid PA strains. Polyol-derivatized hydrocarbons also reduced the extra polymeric substances secreted by mucoid PA as shown in figure



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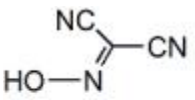
MEDI 400

Light-insensitive silver(I) cyanoximates as antimicrobial agents

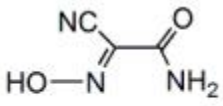
*Mark Whited[1], Korey Still[2], Shalaka R Lotlikar[2], Marianna A. Patrauchan[2], **Nikolay N. Gerasimchuk**[1], NNGerasimchuk@MissouriState.edu. (1) Department of Chemistry, Missouri State University, Springfield, Missouri 65897, United States (2) Department of Microbiology and Molecular Genetics, Oklahoma State University, Stillwater, Oklahoma 74078-3020, United States*

We have reported earlier synthesis and characterization of a series of remarkably light stable silver(I) complexes of cyanoximes [1,2]. These represent new class of ampolydentate ligands of NC-C(R)=NOH composition that readily form sparingly water soluble and thermally stable complexes of Ag(I) that also have shown promising antimicrobial activity [3]. To assess the bactericidal effect of the complexes on the ability of pathogenic bacteria to form a biofilm, a quantitative 96-well plate assay was used. Selected for studies Ag(ACO), Ag(BCO), Ag(CCO) compounds (ligands shown in Figure 1) were embedded into the polymeric light-curable acrylamide composite commonly used in dental practice, and applied onto the surface of the wells. Four human pathogens *Pseudomonas aeruginosa* strains PAO1 and FRD1, *Streptococcus mutans* strain UA159, and *Staphylococcus aureus* strain ST228, representing different infection profiles, were selected. The preliminary measurements showed at least 34 fold reduction in the growth of *P. aeruginosa* PAO1 in the presence of Ag(ACO) versus the

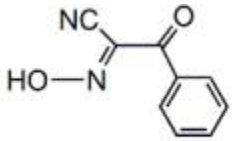
growth in the presence of the composite alone. Several practical bio-medical applications of studied silver(I) cyanoximates are reviewed and discussed.



H(CCO)



H(ACO)



H(BCO)

1. Gerasimchuk, N.; Esaulenko, A.N.; Dalley, K.N.; Moore, C. *Dalton Trans.* **2010** , *39*, 749-764.

2. Glower, G.; Gerasimchuk, N.; Biagioni, R.; Domasevitch, K.V. *Inorg. Chem.* **2009** , *48* (6), 2371-2382.

3. Gerasimchuk, N.; Gamian, A.; Glover, G.; Szponar, B. *Inorg. Chem.* **2010** , *49* (21), 9863-9874.

MEDI 401

Discovery of a novel class of potent HCV NS4B inhibitors: Identification and optimization of piperazinone derivatives

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Hepatitis C virus (HCV) infection is a major health problem that leads to chronic liver disease, such as cirrhosis and hepatocellular carcinoma. HCV infects a substantial number of individuals, estimated to be 2-15% of the world's population. The approved Standard of Care (SOC) involves the combination of a protease inhibitor with pegylated-interferon (PEG-IFN) and the oral nucleoside ribavirin (RBV) but it is limited clinical benefit for HCV Genotype 2, 3, 4, 5 and 6 infected patients. The sustained virologic response (SVR or undetectable HCV RNA in serum at the end of treatment) rate for most–difficult-to-treat genotype-1 HCV patients with approved drugs boceprevir and telaprevir is about 70% with the protease inhibitor, RBV, and PEG-IFN combination and produces undesired side effects. Moreover, there is no established vaccine for HCV. Consequently, there is an urgent need for improved therapeutic agents that effectively combat chronic HCV infection in all genotypes.

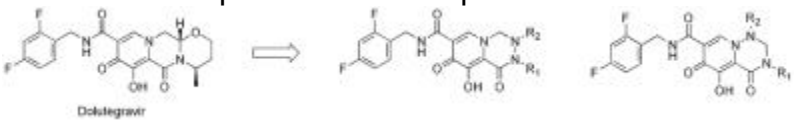
A number of potential HCV molecular targets for which anti-HCV therapeutics have now been in clinical trials include, but are not limited to, NS3/4A protease, NS5A replication factor and the NS5B polymerase. Another HCV auxiliary protein is NS4B. NS4B is relatively poorly characterized and believed to be associates with a number of additional non-structural proteins that permit formation of the so-called "membranous web" structure that facilitates HCV replication. In an effort to improve treatment of HCV, it remains of vital interest to identify compounds capable of inhibiting the action of the NS4B protein of HCV. Herein, we report the identification and SAR development studies of potent piperazinone derivatives as a novel class of HCV NS4B inhibitors.

MEDI 402

Discovery of novel HIV integrase inhibitors part 1: Molecular design and SAR of azabicyclic carbamoyl pyridone inhibitors

Yoshiyuki Taoda[1]*, yoshiyuki.taoda@shionogi.co.jp, Brian A. Johns*[2]*, Toshiyuki Akiyama*[1]*, Hiroshi Yoshida*[1]*, Teruhiko Taishi*[1]*, Takashi Kawasuji*[1]*, Hitoshi Murai*[1]*, Tomokazu Yoshinaga*[1]*, Akihiko Sato*[1]*, Tamio Fujiwara*[1]*. (1) Shionogi & Co., Ltd., Osaka, Japan (2) GlaxoSmithKline, Research Triangle Park, NC, United States*

We discovered two azabicyclic scaffolds designed based on the integrase inhibitor dolutegravir (DTG) which is currently in late state clinical evaluation. These new scaffolds were pursued in an effort to back-up the lead asset with a novel chemotype while maintaining the favorable drug attributes that have manifested in DTG. Optimization of the new series resulted in low nM antiviral activity with outstanding resistance and pharmacokinetic profiles.



Molecular design concepts, synthetic approaches and SAR of the series will be presented.

MEDI 403

Discovery of novel HIV integrase inhibitors part 2: Selection and evaluation of an azabicyclic carbamoyl pyridone inhibitor as a pre–clinical candidate

Toshiyuki Akiyama[1]*, toshiyuki.akiyama@shionogi.co.jp, Brian A. Johns*[2]*, Yoshiyuki Taoda*[1]*, Hiroshi Yoshida*[1]*, Teruhiko Taishi*[1]*, Takashi Kawasuji*[1]*, Hitoshi Murai*[1]*, Tomokazu Yoshinaga*[1]*, Akihiko Sato*[1]*, Tamio Fujiwara*[1]*. (1) Shionogi & Co., Ltd., Osaka, Japan (2) GlaxoSmithKline, Research Triangle Park, NC, United States*

Evolving structure-activity studies using an azabicyclic carbamoyl pyridone series resulted several leads with promising antiviral properties. Potency against a panel of

clinically relevant resistant mutants derived from first generation HIV integrase inhibitor experience (raltegravir and elvitegravir) and drug concentration at 24 hours after dosing (C24) were key criteria in our evaluation. These favorable antiviral data along data suggestive of a lack of cross-resistance to existing agents and a pharmacokinetic profile predictive of once daily (qd) dosing without pk boosting agents resulted in the selection of Shionogi/GSK1362867 as a pre-clinical candidate. The lead optimization and selection strategy to balance antiviral, pharmacokinetic and physicochemical properties used for the discovery and pre-clinical data of Shionogi/GSK1362867 will be the subject of this presentation. This work has led to a suitable back-up to the late stage clinical asset dolutegravir.

MEDI 404

Synthesis of β-diketoacid dihydropyrimidine derivatives targeting HIV integrase

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Among the different enzymes involved in HIV replication cycle, viral integrase (IN-HIV) appear as an emerging therapeutic target for the treatment of AIDS. Herein, we report the synthesis of dihydropyrimidine scaffolds library, bearing a β-diketoacid moiety. The inhibition effects of all synthesized compounds were measured by HIV-1 integrase 3'-Processing and strand transfer activity assay. Among these compounds, some of them exhibit sub-micromolar IC_{50} values.

MEDI 405

Identification of novel PPAR-gamma/delta agonists

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The peroxisome proliferator-activated receptors (PPARs-α, β/δand γ) are ligand-regulated transcription factors that play a critical physiological role in lipid sensing and homoeostasis. Synthetic PPAR-γ (thiazolidinediones) ligands have been used in the treatment of diabetes. A joint computational and experimental study has been carried

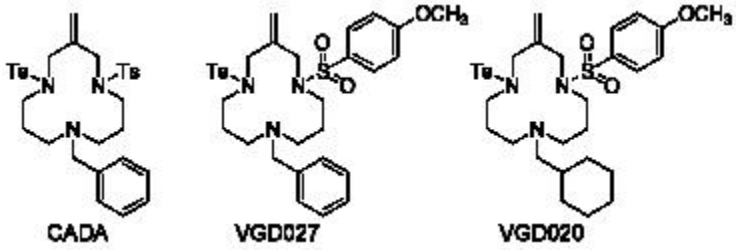
out to develop PPAR-γ/δ agonists. Twenty-three compounds have been designed, synthesized and evaluated as potential agonists. Of the compounds studied, AutoDock Vina docking simulations predicted compound 9 to possess the highest binding affinity in both PPAR-γ and PPAR-δ. A detailed analysis of the binding pockets found 9 occupied the Y-shaped active site and adopted a position predicted by the popularly reported pharmacophoric model of the PPAR ligands. Luciferase assays show 9 inhibits PPAR-γ but activates PPAR-δ. Interestingly, it elevated the expression of genes associated with fatty acid oxidation and insulin sensitivity. Further it attenuated rosiglitazone mediated lipid accumulation in adipocytes.

MEDI 406

Synthesis of electron-rich cyclotriazadisulfonamide (CADA) analogs as anti-HIV and human CD4 receptor down-modulating agents

Chiraphorn Khan[1], Nicholas C. Pflug[1], Dominique Schols[2], Kurt Vermeire[2], ***Thomas W. Bell****[1], twb@unr.edu. (1) Department of Chemistry, University of Nevada, Reno, NV 89557-0216, United States (2) Rega Institute for Medical Research, Katholieke Universiteit Leuven, Leuven, Belgium*

Cyclotriazadisulfonamide (CADA, figure) potently inhibits human immunodeficiency virus (HIV) entry and replication by specifically down-modulating the main HIV receptor, CD4. The specific biomolecular target is unknown, but CADA apparently inhibits translocation of nascent CD4 across the membrane of the endoplasmic reticulum. Previous structure-activity relationship (SAR) studies revealed that unsymmetrical CADA analogs bearing one electron-rich substituted benzenesulfonyl side arm are among the most potent (figure). For example, VGD027 (IC_{50} 0.30 μM) and VGD020 (IC_{50} 0.046 μM) with one 4-methoxybenesulfonyl side arm are both more potent than CADA (IC_{50} 0.56 μM) for CD4 receptor down-modulation in CD4-transfected cells (*J. Med. Chem.* **2011** , *54*, 5712). The current study probes the effect of many additional electron-rich arenesulfonyl side arms on CD4 down-modulation and anti-HIV potency. Syntheses and SAR studies are reported for the new compounds, which display a wide range of potency.



MEDI 407

Towards the synthesis of novel 1,3-azaborines as potential HIV-1 protease inhibitors

***Kristín Sigurjonsson**, sigurjonssonk@gmail.com, **Michael D. Frank**, frankm@cwu.edu, John D. Schreiber, Julia J. Jennings, Andrea L. Faulkner, Levente Fabry-Asztalos. Department of Chemistry, Central Washington University, Ellensburg, Washington 98926-7539, United States*

Exponential growth of organoboron chemistry in recent years is a testament to the wide range of possible utility for boron containing compounds. Boron possesses unique chemical properties which make it valuable in the search for better pharmaceuticals. The borinic acid target compounds of this research include a chiral 1,3-azaborine, with nitrogen beta to boron. We are synthesizing novel boronates that are designed as compounds with potential dual-mode, both competitive and associative, inhibitory action of HIV-1 protease. The first known 1,3-azaborine cyclic structure has only been recently elucidated by the Lui group from the University of Oregon. Due to the specifics of our target compound our synthetic approach differs from the first methods to produce the 1,3-azaborine structure. By incorporating a chiral 1,3-azaborine into a transition state peptide mimic we hope to produce a medicinally useful compound. The cyclic boronates, due to their structural rigidity, are expected to be better inhibitors than their straight chain analogs. These novel structures will also serve to expand molecular diversity and organoboron chemistry.

MEDI 408

Bicyclic pyridines as novel SIRT1 activators: Use of increasing saturation to improve physiochemical properties of SIRT1 activators

***Pui Yee Ng**, Pui-Yee.2.Ng@gsk.com, Lauren M McPherson, Charles A Blum, Jeremy S Disch, Chi B Vu, Thomas A Considine, Andrew B Haser, Siva Lavu, Meghan L Davis, Elden O Lainez, Marie E Yeager, Robert B Perni. Department of Medicinal Chemistry, Sirtris, A GSK Company, Cambridge, MA 02139, United States*

SIRT1, a member of the sirtuin family, is a NAD^+-dependent protein deacylase that has been implicated as a regulator of key metabolic and inflammatory pathways through deacetylation of several protein substrates, including PGC-1α, NFκb, and FOXO. In recent years, SIRT1 has increasingly gained relevance as a potential small molecule drug target and recently reported activators of SIRT1 represent significant advances in drug-like small molecule SIRT1 activators over resveratrol and its analogs. Nevertheless, there remains much room for improvement in their physiochemical properties. In this poster, we report recent progress using the strategy of core structure saturation and addition of chiral centers resulting in SIRT1 activators with improved physiochemical properties. These properties include f(sp3), solubility, ligand efficiency, and LogD. The relationship of physiochemical properties to the SAR of bicyclic pyridine SIRT1 activators will also be discussed.

MEDI 409

Novel beta-adrenergic agonists for treatment of diabetic retinopathy

jayaprakash pagadala[1]*, pagadalajp@gmail.com, Youde jiang*[2]*, Quihua Zhang*[2]*, Kimberly Williams-Guy*[2]*, Jena J Steinle*[2]*, Duane D Miller*[1]*. (1) pharmacutical sciences, University of Tennessee Health Science Center, memphis, TN 38163, United States (2) Ophthalmology, University of Tennessee Health SCience Center, memphis, tn 38163, United States*

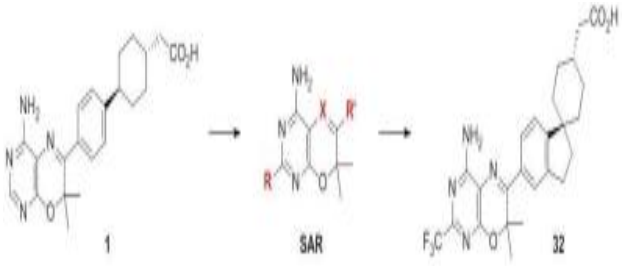
Diabetic retinopathy is the leading cause of blindness in working-age adults. Complications of diabetic retinopathy include pericyte loss, basement membrane thickening of capillaries, microaneurysm formation, and an increase in inflammatory marker levels. We have shown that retinal endothelial cells (REC) and Müller cells responded to increased glucose concentrations with an increase in inflammatory markers and apoptosis, which is reduced following treatment with b-adrenergic receptor agonists. In our previous publication, we have evaluated the ability of optically active *R*-(-)-isoproterenol, *S*- (+)-isoproterenol, and the racemic mixture of (±)-isoproterenol, a non-selective b-adrenergic receptor agonist, to reduce the cleavage of caspase 3 and TNFa levels. We observed *R*- (-)-isoproterenol is more effective than *S*- (+)-isoproterenol. Thus we are reporting on a new series of isoproterenol adrenergic analogs that we have prepared, possessing a higher selectivity and they are more effective than isoproterenol in preventing REC apoptosis through increasing PKA and IGFBP3 levels, which are reduced in response to hyperglycemia. One of the compound **1** [(R)-4-(1-hydroxy-2-((3,4,5-trimethoxyphenethyl)amino)ethyl)benzene-1,2-diol hydrochloride], has been shown to be a promising candidate for treatment of diabetic retinopathy. Compound **1** increases PKA–IGFBP-3 signaling which appears to be quite significant in inhibiting diabetic retinopathy in pathophysiologic models and this new agent could possibly be considered for use in the treatment of diabetic retinopathy.

MEDI 410

Discovery of novel, conformationally restricted, and orally efficacious DGAT1 inhibitors

Kexue Li[1]*, kli@amgen.com, Brian Fox*[1]*, Jian Zhang*[1]*, Kiyosei Iio*[3]*, Masahiro Suzuki*[3]*, Ito Soichiro*[3]*, Hidekazu Ozeki*[3]*, Akio Kobayashi*[3]*, Ji Ma*[1]*, Alan Hao*[1]*, Marc Labelle*[1]*, Dustin McMinn*[1]*, Marie Smith*[1]*, Shoichi Sagawa*[3]*, Noboru Furukawa*[3]*, Takashi Inaba*[3]*, Mutsuyoshi Matsushita*[3]*, Takuya Matsui*[3]*, Nobuya Ogawa*[3]*, Chihiro Okuma*[3]*, Kazuyuki Sugimoto*[3]*, Masahiro Tanaka*[3]*, Atsuhito Yoshida*[3]*, Yukihito Ishii*[3]*, Daisuke Tomimoto*[3]*, Simon Jackson*[2]*, Rebekah Choi*[2]*, Bei Shan*[2]*, Ajit Srivastava*[2]*, Frank Kayser*[1]*. (1) Department of Medicinal Chemistry, Amgen, Inc., South San Francisco, CA 94080, United States (2) Department of Metabolic Disorders, Amgen, Inc., South San Francisco, CA 94080, United States (3) Central Pharmaceutical Research Institute, Japan Tobacco, Osaka, Japan*

The diacylglycerol acyltransferase DGAT-1 is one of two known DGAT enzymes that catalyze the final step in the synthesis of triacylglycerols in tissues such as adipose and the small intestine, where this enzyme is highly expressed. Inhibition of DGAT-1 is therefore expected to reduce triglyceride accumulation in adipose tissue and delay triglyceride absorption in the small intestine. Studies have suggested inhibition of DGAT-1 *in vivo* as a target for the treatment of not only obesity and dyslipedemia but also for diabetes in humans. Compound **1** was identified earlier on as our 1st generation DGAT1 inhibitor for preclinical development. However, acute liver toxicity was observed in high single dose study in cynomolgus monkey. Here, the identification of our 2nd generation DGAT-1 inhibitors, is being described. For example, compound **32** has excellent selectivity and good pharmacokinetic properties across species. It has improved potency both *in vitro* and *in vivo* and has been shown to be more efficacious compared with compound **1** . In this poster, the SAR and the synthesis of this series of novel DGAT-1 inhibitors will be presented.

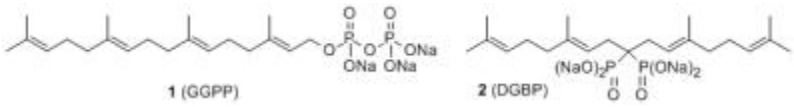


MEDI 411

Inhibitors of geranylgeranyl diphosphate synthase

Xiang Zhou[1]*, xiang-zhou@uiowa.edu, Jacqueline E. Reilly*[3]*, Craig H. Kuder*[2]*, Raymond J. Hohl*[2,3]*, David F. Wiemer*[1,3]*. (1) Department of Chemistry, University of Iowa, Iowa City, IA 52242-1294, United States (2) Department of Internal Medicine, University of Iowa, Iowa City, IA 52242, United States (3) Department of Pharmacology, University of Iowa, Iowa City, IA 52242, United States*

Geranylgeranyl diphosphate (**1** , GGPP) is a linear isoprenoid that is prepared biosynthetically from the 15-carbon isoprenoid farnesyl pyrophosphate (FPP) through the enzyme GGPP synthase. We have shown that digeranyl bisphosphonate (**2** ,DGBP) is an inhibitor of this enzyme and that DGBP is competitive with FPP, while others have suggested that it is effective because of a V-like shape. We have prepared a number of new analogues designed to preserve this shape but demonstrate increased potency. The synthesis of these new compounds as well as the bioassays that establish their biological activity will be presented.



MEDI 412

Exploring the chemical space of GPR40 and GPR120 with small molecules

Hugo Tremblay[1]*, hugo.tremblay3@usherbrooke.ca, Takafumi Hara*[2]*, Akira Hirasawa*[2]*, Gozoh Tsujimoto*[2]*,* ***Eric Marsault***[1]*, eric.marsault@usherbrooke.ca. (1) Institut de Pharmacologie de Sherbrooke, Université de Sherbrooke, Sherbrooke, Quebec J1H 5N4, Canada (2) School of Pharmaceutical Sciences, Kyoto University, Kyoto, Japan*

GPR40 (FFAR1) and GPR120 are both G protein-coupled receptors activated by long chain fatty acids. While GPR40 is predominantly expressed on the beta cells of the pancreas, GPR120 is expressed on intestinal L cells, adipocytes and macrophages. While the main role of GPR40 is to elicit fatty acid-mediated potentiation of insulin in the presence of glucose, the roles of GPR120 are broader and involve the release of the incretin GLP-1 as well as key steps in adipocyte inflammation. Collectively, the activation of GPR40 and GPR120 has the potential to address the two main deficiencies of type 2 diabetes deficient insulin secretion and insulin resistance.

GPR40 and GPR120 share very little homology, yet they are both activated by long chain fatty acids and so far, synthetic ligands bear some similarities. In this presentation, we will present our efforts in the optimization of small molecules to better understand the ligand-receptor interactions between the two receptors, with the goal to optimize bi-functional agonists of GPR40 and GPR120.

MEDI 413

New matriptase inhibitors as a potential treatment against influenza

Eloic Colombo[1]*, eloic.colombo@usherbrooke.ca, Dominic Duchêne*[1]*, Antoine Désilets*[1]*, Alexandre Beaulieu*[2]*, Émilie Gravel*[2]*, Rafael Najmanovich*[1]*, Martin Richter*[2]*, Richard Leduc*[1]*,* ***Eric Marsault***[1]*, eric.marsault@usherbrooke.ca. (1) Institut de Pharmacologie de Sherbrooke, Université de Sherbrooke, Sherbrooke, Québec J1H 5N4, Canada (2) Centre de Recherche Clinique Étienne le Bel, Université de Sherbrooke, Sherbrooke, Quebec J1H 5N4, Canada*

Matriptase belongs to the family of type 2 serine proteases and is widely expressed on epithelial tissues, including the lung. Recent studies have demonstrated the ability of matriptase to proteolytically activate th hemagglutinin precursor HA0 into HA1, an obligatory step performed by enzymes of the host in order to initiate the replication of the influenza virus. This obligatory step presents an opportunity for the development of new treatments targeting the host and not the highly mutable virus, with the goal to

provide an approach which will escape the high levels of resistance encountered by current anti-influenza treatments.

We report herein new peptidomimetic inhibitors of matriptase in the form of slow, tight-binding inhibitors. The design, synthesis, selectivity and activity of this new class of inhibitors against the influenza H1N1 virus in vitro will be presented, as well as a molecular model of the inhibitor docked into the enzyme active site.

MEDI 414

Design and synthesis of conformationally rigid macrocyclic tissue factor-factor VIIa inhibitors

Peter W Glunz[1]*, peter.glunz@bms.com, Xiaojun Zhang*[1]*, Nicholas Wurtz*[1]*, Yan Zou*[1]*, Inda Delucca*[1]*, Brandon Parkhurst*[1]*, Daniel Cheney*[2]*, Luciano Mueller*[3]*, Anzhi Wei*[4]*, Joseph M Luettgen*[5]*, Robert M Knabb*[5]*, Timothy Harper*[6]*, Pancras C Wong*[5]*, Ruth R Wexler*[1]*, E Scott Priestley*[1]*. (1) Discovery Chemistry, Bristol-Myers Squibb, Princeton, NJ 08543, United States (2) CADD, Bristol-Myers Squibb, Princeton, NJ 08543, United States (3) Mechanistic Biochemistry, Bristol-Myers Squibb, Princeton, NJ 08543, United States (4) Protein Science and Structure, Bristol-Myers Squibb, Princeton, NJ 08543, United States (5) Discovery Biology, Bristol-Myers Squibb, Princeton, NJ 08543, United States (6) PCO MAP, Bristol-Myers Squibb, Princeton, NJ 08543, United States*

Inhibitors of the tissue factor-Factor VIIa serine protease complex (TF-FVIIa) have shown strong antithrombotic efficacy in animal models with minimal bleeding liability, suggesting the TF-FVIIa complex is an important therapeutic target for the treatment of thrombotic disorders. We have discovered a macrocyclic, phenylglycine amide-based inhibitor of TF-FVIIa. Further optimization of this chemotype was complicated by the observation of atropisomerism upon substitution of the P2 phenyl group of that macrocycle. Based upon NMR studies of the exchange of these atropisomers and molecular modeling of stabilizing strategies, we identified linker substitution that rigidified the desired atropisomer and significantly improved potency.

MEDI 415

Biarylmethyl indoline and indole analogs as potent and selective inhibitors of Factor XIa

Joanne M Smallheer*, joanne.smallheer@bms.com, Shuaige Wang, Karen A Rossi, Alan Rendina, Paul E Morin, Anzhi Wei, Ge Zhang, Pancras C Wong, Dietmar Seiffert, Ruth R Wexler, Mimi L Quan. Department of Research and Development, Bristol-Myers Squibb Co, Princeton, NJ 08534, United States*

Elevated levels of factor XI in humans has been identified as a risk factor for thromboembolic disease. In contrast, factor XI deficient mice are protected in multiple

thrombosis models. Furthermore, normal haemostasis is maintained in mice deficient in factor XI, and prolonged provoked bleeding times are not observed in these animals. Likewise, in cases of human factor XI deficiency (Hemophilia C) only a mild bleeding diathesis is present. This combined evidence supports the hypothesis that intervention with a factor XIa inhibitor may provide efficacy in the treatment of thromboembolic diseases with minimal bleeding liability. Based on this, we have focused on the discovery of novel factor XIa inhibitors. Using a pharmacophore model developed from a subset of hits identified from high throughput screening against factor XIa, a novel series of potent biphenylmethyl indoline and indole factor XIa inhibitors were designed and synthesized. Further optimization of the initial lead compounds provided selective, subnanomolar factor XIa inhibitors.

MEDI 416

Carvedilol protects H9c2 rat cardiomyocytes from cell death in a thiol oxidative stress model

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2-acetylamino-3-[4-(2-acetylamino-2-carboxyethylsulfanylthiocarbonylamino)phenylthiocarbamoylsulfanyl]propionic acid (2-AAPA), a glutathione reductase inhibitor, is currently being developed as a model of thiol oxidative stress in H9c2 rat cardiomyocytes. 2-AAPA increased oxidized glutathione (GSSG), protein disulfides and S-glutathionylation in H9c2 cells, which was associated with decreased mitochondrial membrane potential, release of cytochrome c as well as increased reactive oxygen species (ROS) production and apoptosis. Carvedilol (10 μM), a β-blocker with antioxidant ability, significantly increased the viability of 2-AAPA (100 μM) treated cells from 33% to 71% compared to control by 2 hours pretreatment followed with a 48 hours post treatment. Carvedilol also inhibited 2-AAPA induced mitochondrial membrane potential loss and apoptosis. However, carvedilol unexpectedly increased cellular GSSG leading to an even lower GSH/GSSG ratio than that of 2-AAPA alone. Further studies on the protective mechanism of carvedilol in the thiol oxidative stress model are in progress.

MEDI 417

High-density lipoprotein-based theranostic nanoparticle platform for atherosclerosis

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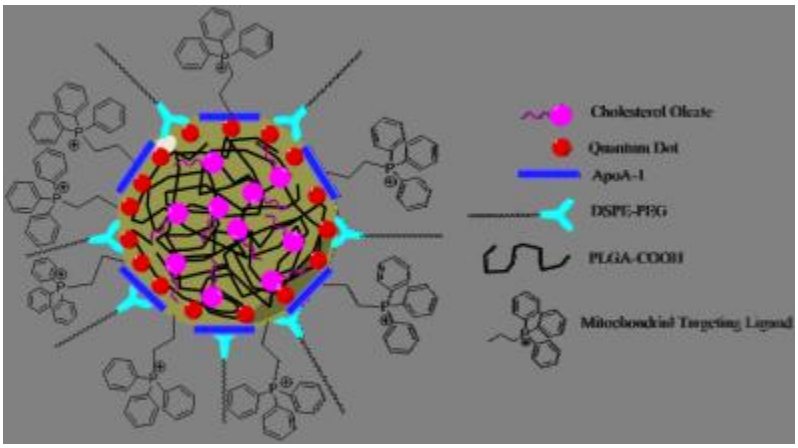
Atherosclerosis continues to be one of the leading causes of death in the United States despite numerous advances in treatment and prevention. There is growing interest in

the early identification and treatment of vulnerable plaques, which are at high risk of disruption followed by thrombosis. However, there is no accepted method for the early detection of such plaques. Here we present a high-density lipoprotein (HDL)-mimicking nanoparticle (NP) for the detection of apoptotic macrophages in vulnerable plaques by targeting the mitochondrial membrane collapse that occurs during apoptosis. These HDL-mimicking NPs demonstrate excellent biocompatibility, serum stability, physicochemical, and non-immunogenic properties, which prove to be promising for future clinical imaging of apoptosis in vulnerable plaque for its early diagnosis. They are also potentially suitable for rerouting cholesterol away from plaque macrophages to help prevent or slow the progression of vulnerable plaque. In vitro sensing as well as in vivo biodistribution and pharmacokinetics will be discussed.



MEDI 418

Chinese herb extract for anti-hypertension applications

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A chinese herb has been studied and one compound has been isolated from the extracts.

This compound has been tested for anti-hypertension applications. Compared to other anti-hypertention drugs in the market, the mechanisms of this compound is noval. kg of this compound has been isolated with purity>99.5%. We are in the process to prepare an IND to SFDA.

MEDI 419

Novel anticancer agents: Design and synthesis of Boron-based small molecule inhibitors of nicotinamide phosphoribosyltranferase (Nampt)

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NAD^+ is involved in cell signaling, cellular respiration, transcription regulation, and post-translational protein modification, and Nampt is an essential enzyme for its synthesis.Compared to normal cells, tumor cells depend on a higher rate of NAD^+ turnover, and thus Nampt activity is found to be up-regulated in tumors. A potent and selective small molecule inhibitor of Nampt, drug FK866, induces thrombocytopenia, mild fatigue, lymphopenia, anemia, and liver function abnormalities in patients. To increase its efficacy and reduce side effects, we have prepared a series of FK866 analogs by replacing its benzoylpiperidine group with various boron clusters (neutral: *o*-, *m*-, and *p*-$[C_2B_{10}H_{12}]$; and anionic: *nido*-$[C_2B_9H_{12}]^-$, and *closo*-$[B_{12}H_{12}]^{2-}$). In addition, we varied the length of alkyl chain, and the distance between the amido and pyridine groups using *trans*-3-(3'-pyridyl)acrylic, 3-pyridinepropionic, or nicotinic acids. For comparison, we have prepared FK866 analogs, where the benzoylpiperidine moiety was absent or replaced with adamantane, or phenyl groups.