Division of Medicinal Chemistry

Scientific Abstracts

for the

237th Spring National Meeting and Exposition

March 22-26, 2009

Salt Lake City, UT

Publication date: February 6, 2009

A note from the Secretary of the Division:

The Executive Committee has made revisions to its bylaws, and the revised bylaws document is now available for members to view at the following link:

http://www.acsmedchem.org/MEDI_Draft_Bylaws_Jan_2009.pdf

A vote to ratify the revised bylaws will be held at the annual Division business meeting at the Salt Lake City ACS meeting. The meeting will begin at 6:15 pm. on Sunday, March 22, 2009, just before the Poster Session and Social Hour. The room number has yet to be assigned, but it will be near the poster session, and signs will be available to direct you to the correct room. On behalf of the Executive Committee, I hope to see many of you at the business meeting.

Sincerely,

Patrick M. Woster, Ph.D.
Secretary and Public Relations Chair
Division of Medicinal Chemistry

The program at a glance:

Sunday, March 22, 2009

MORNING

9:00 AM-11:20 AM
Nano Meets Neuro: Novel Challenges for Nanoscience in Probing Brain Chemistry Division of Analytical Chemistry, Division of Biological Chemistry, Division of Colloid & Surface Chemistry, and Nanoscience: Challenges for the Future‡
Section C Salt Palace Convention Center -- Ballroom A

9:00 AM-11:55 AM
Metabolic Syndrome
Section A Salt Palace Convention Center -- Ballroom H

9:00 AM-12:20 PM
General Oral Session
Section B Salt Palace Convention Center -- Combo Ballrooms C&E

AFTERNOON

1:00 PM-3:40 PM
Nano Meets Neuro: Novel Challenges for Nanoscience in Probing Brain Chemistry Division of Analytical Chemistry, Division of Biological Chemistry, Division of Colloid & Surface Chemistry, and Nanoscience: Challenges for the Future‡
Section A Salt Palace Convention Center -- Ballroom H

1:30 PM-5:00 PM
First Time Disclosure of Clinical Candidates
Section B Salt Palace Convention Center -- Combo Ballrooms C&E

EVENING

7:00 PM-9:00 PM
General Poster Session
Section A Salt Palace Convention Center -- Hall 5

Monday, March 23, 2009

MORNING

9:00 AM-12:15 PM
Smissman Award Symposium
Section A Salt Palace Convention Center -- Combo Ballrooms C&E

AFTERNOON

1:30 PM-4:50 PM
Recent Developments in Metalloprotease Inhibitors
Section B Salt Palace Convention Center -- Ballrooms H&J

1:30 PM-5:35 PM
Latest Developments in Glutamate Receptors
Section A Salt Palace Convention Center -- Combo Ballrooms C&E

Tuesday, March 24, 2009

MORNING

9:00 AM-12:20 PM
Novel Targets for the Treatment of Alzheimer's Disease
Section A Salt Palace Convention Center -- Combo Ballrooms C&E

Small Molecule Strategies for Inhibiting Human Viral Infections
Section B Salt Palace Convention Center -- Ballrooms H&J

AFTERNOON

2:00 PM-5:15 PM
General Oral Session
Section B Salt Palace Convention Center -- Ballrooms H&J

2:00 PM-5:45 PM
Novel Antibiotics: Strategies for Discovery of Novel Antibacterial Targets and Inhibitors
Section A Salt Palace Convention Center -- Combo Ballrooms C&E

Wednesday, March 25, 2009

MORNING

9:00 AM-12:15 PM
From Poor to Rich: Optimization of Oral Bioavailability from Nonbioavailable Leads
Section A Salt Palace Convention Center -- Combo Ballrooms C&E

9:00 AM-12:35 PM
Targeting the Hedgehog Signaling Pathway for Therapeutic Opportunities in Cancer and Dermatology
Section B Salt Palace Convention Center -- Ballrooms H&J

AFTERNOON

1:30 PM-4:50 PM
Importance and Utility of Screening Collections
Section A Salt Palace Convention Center -- Combo Ballrooms C&E

1:30 PM-5:10 PM
Optimizing the Stability of Clinical Candidates During Drug Discovery
Section B Salt Palace Convention Center -- Ballrooms H&J

EVENING

7:00 PM-9:00 PM
General Poster Session
Section A Salt Palace Convention Center -- Hall 1

Thursday, March 26, 2009

MORNING

9:00 AM-12:20 PM
General Oral Session
Section B Salt Palace Convention Center -- Ballroom H

Ion Channel Inhibitors for Pain and Atrial Fibrillation
Section A Salt Palace Convention Center -- Ballroom C

AFTERNOON

1:30 PM-4:50 PM
General Oral Session
Section A Salt Palace Convention Center -- Ballroom C

MEDI 1

Targeting genomic (FXR) and nongenomic (TGR5) bile acids receptor pathways for metabolic disorders: Discovery, S.A.R. and molecular modeling of potent and selective bile acids derivatives

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It has been discovered in recent years that bile acids (BAs) are not only lipid solubilizers and simple regulators of bile-acid homeostasis, but that they are also complex metabolic integrators and signaling factors of a number of genomic and nongenomic pathways. They are the endogenous ligands, in particular, for FXR and TGR5, a nuclear and a membrane G-protein coupled receptor, respectively, that represent novel, attractive therapeutic targets for metabolic disorders. Accordingly, this presentation will cover the FXR and TGR5 mediated actions of (BAs) and our recent results in the discovery, S.A.R., molecular modeling of a number of potent and selective BA derivatives and their pre-clinical and clinical profile towards metabolic disorders such as T2D, obesity, hypertriglyceridaemia and atherosclerosis.

MEDI 2

DGAT-1 Inhibitors as novel therapeutics for dyslipidemia

Andrew J. Souers[1], *Andrew.Souers@abbott.com, Andrew J. King*[1], *Scott Mittelstadt*[1], *Gang Zhao*[2], *Andrew S. Judd*[1], *Brian D. Dayton*[3], *Jason A. Segreti*[1], *Kelly Larson*[1], *Martin Voorback*[1], *Regina M. Reilly*[1], *Michael Brune*[4], *Philip R. Kym*[1], *Christine A. Collins*[1], *and Bryan F. Cox*[1]. *(1) Pharmaceutical Discovery, Abbott Laboratories, Global Pharmaceutical Research Division, 100 Abbott Park Rd, Abbott Park, IL 60064, Fax: 847-935-5165, (2) Process Research, Abbott Laboratories, Global Pharmaceutical Research Division, Abbott Park, IL 60064, (3) Exploratory Pharmacokinetics, Abbott Laboratories, Global Pharmaceutical Research Division, Abbott Park, IL 60064, (4) Global Operations, Abbott Laboratories, Global Pharmaceutical Research Division, Abbott Park, IL 60064*

DGAT-1 is one of two DGAT enzymes that catalyze the final and only committed step in triglyceride synthesis, the acylation of the 3'-OH group of diacylglycerol from a fatty acyl-CoA donor. DGAT-1 knockout mice have substantially reduced postprandial triglyceride levels, have improved insulin sensitivity and are

protected from diet-induced obesity. This and other data substantiate the hypothesis that inhibition of triglyceride synthesis will prevent excess triglyceride accumulation in adipose tissue, leading to body weight loss and improved insulin sensitivity. Furthermore, as a large body of research indicates that postprandial hyperlipidemia underlies much of the atherosclerosis burden, inhibition of DGAT-1 has the potential to significantly reduce atherosclerosis and exert beneficial metabolic effects that would ultimately reduce cardiovascular risk. In order to provide pre-clinical validation for DGAT-1 inhibition in these settings, we identified a potent and orally bioavailable small molecule. This compound was profiled extensively in acute and semi-chronic models of in vivo efficacy, and showed good oral activity across these assays. The results of these in vivo experiments will be reported.

MEDI 3

Piperazine sulfonamides as potent, selective, and orally bioavaliable 11-beta-HSD1 inhibitors for the treatment of Type II diabetes and obesity

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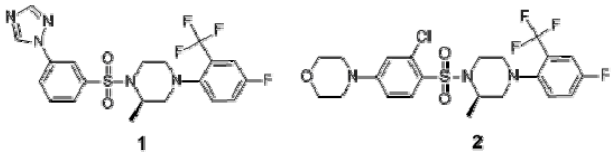
Intracellular amplification of glucocorticoid signaling, through the reduction of cortisone to cortisol by 11-beta-hydroxysteroid dehydrogenase Type I (11-beta-HSD1), is rapidly emerging as an important mechanism in metabolic homeostasis. Mice lacking 11-beta-HSD1 are resistant to diet- and stress-induced obesity and demonstrate improved insulin sensitivity and lipid and lipoprotein profiles. Adipose specific over-expression of 11beta-HSD1 in mice leads to several metabolic abnormalities such as visceral obesity, insulin resistance, aberrant lipid and cholesterol metabolism and hypertension. Inhibition of 11beta-HSD1 is therefore an attractive approach to the resolution of metabolic disorders such as Type II Diabetes. We have discovered a novel class of piperazine sulfonamides as selective 11beta-HSD1 inhibitors. Through extensive SAR study, we improved both potency and metabolic stability of the series. We report herein analogs such as 1 and 2 with good pharmacokinetic profile and strong ex-vivo inhibition in both liver and adipose tissue.



1 2

MEDI 4

Potent and orally bioavailable stearoyl-CoA desaturase (SCD) inhibitors for the potential treatment of obesity and diabetes

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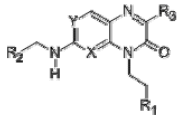
Based on studies with knockout mice, antisence oligonucleotides, and small molecule inhibitors, stearoyl-CoA desaturase (SCD) has recently emerged as a therapeutic target for the potential treatment of obesity, metabolic syndrome, and diabetes. SCD has been linked to a number of metabolic functions including: regulation of body weight, energy balance, plasma and liver triglyceride levels, glucose production, and peripheral insulin resistance. We discovered a series of structurally unique SCD inhibitors from independent screen of a large compound collection. Hit compound 1 provided the starting point (HEPG2 IC50 410 nM, F = 10%). We pursued optimization of potency by changing substituents and scaffolds. Success at optimizing potency often came at the expense of bioavailability. For example, compound 2 had HEPG2 IC50 81 nM and F = 2.2% while compound 3 three had sub-nanomolar potency (HEPG2 IC50 0.1 nM) and no detectible plasma levels after PO dosing. In order to overcome this problem, we experimented with some dramatic structural changes. Our efforts resulted in a compound with HEPG2 IC50 6 nM and F = 78%. The structure of this compound and its in vivo properties, along with the highlights of our optimization efforts, will be discussed in the presentation.



1 R_1 = NHAc, R_2 = 3,4-di-Cl-Ph, R_3 = 4-PhOMe, X = N, Y = N
2 R_1 = NHAc, R_2 = 3,4-di-Cl-Ph, R_3 = 4-PhOMe, X = N, Y = CH
3 R_1 = NHAc, R_2 = 3-CF_3-4-Cl-Ph, R_3 = 4-PhOMe, X = CH, Y = CH

MEDI 5

Semicarbazide-sensitive amine oxidase (SSAO): A potential target for the treatment of diabetes and its complications

Peter Matyus[1], *Petra Dunkel*[2], *Eva Toth-Sarudy*[2], *Gyorgy Turos*[2], *Marjo Pihlavisto*[3], *Kalman Magyar*[4], *Zsuzsa Soltesz*[4], *and Christian Carpene*[5]. *(1) Faculty of Pharmacy, Semmelweis University, H-1092, Budapest, Hungary, (2) Department of Organic Chemistry, Semmelweis University, 1092 Budapest, (3) Biotie Therapies Corp, Turku FIN-20520, (4) Department of Pharmacodynamics, Semmelweis University, 1089 Budapest, (5) INSERM U858, Universiter Toulouse III, Toulouse, France*

Growing attention has recently been focused on semicarbazide-sensitive amine oxidase (SSAO) [EC 1.4.3.6.] and its possible role in the pathology of diabetes. SSAO is involved in the metabolism of biogenic and xenobiotic amines. Its major sources are limited to the endothelial cells, smooth muscle cells and adipocytes. Moreover, there is a sequence identity between vascular adhesion protein-1 (VAP-1) and membrane-bound SSAO. VAP-1 has a role in the adhesion of lymphocytes to endothelial cells.

Elevated SSAO levels have been observed in diabetes, markedly in the presence of diabetic complications. Products of SSAO may be involved in formation of advanced-glycation end products, may contribute to oxidative stress and damage to the vascular wall (therefore to diabetes complications).

On the other hand, SSAO-mediated deamination causes several insulin-like effects in glucose transport, adipocyte differentiation and lipid metabolism. Therefore, SSAO substrates potentially may be used to modulate glucose transport and lipolysis in adipose tissue, their effects partially or totally reproducing insulin actions.

Our goal is to develop novel, effective compounds in both areas.

We have recently synthesized several new inhibitors exhibiting remarkable SSAO inhibitory and in vivo antiinflammatory effects.

In the field of SSAO substrates, antilipolytic effect of the compounds was studied in rat, human and mouse adipocytes. Some compounds completely blocked isoprenaline stimulation and even lowered the lipolytic activity below basal level and activated H2O2 production in human adipose tissue and stimulated glucose transport. Potential antidiabetic properties of these compounds are suggested.

MEDI 6

Progress toward an α-hemolysin heptamerization inhibitor

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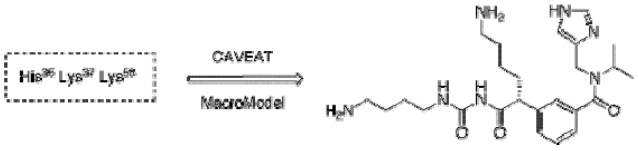
α-Hemolysin (α-HL) is a 33 kDa protein toxin that has been identified as a major virulence factor of methicillin-resistant Staphylococcus aureus (MRSA). The structure of the α-HL heptameric pore complex has been solved by X-ray crystallography and served to identify the residues that are important to heptamer formation and stability. We have used the CAVEAT software package along with the MacroModel molecular modeling suite to generate synthetically viable small molecule targets that would mimic important residues of an α-HL monomer. The design and initial synthetic studies will be discussed.



MEDI 7

Identification of nonsulfonylurea P2Y12 inhibitors as a follow-up series to PRT060128

***Shawn M. Bauer**[1], sbauer@portola.com, Mukund M. Mehrotra[1], Meenakshi Venkataraman[1], Pamela B Conley[2], Marzena Jurek[2], Athiwat Hutchaleelaha[3], Christine Ye[3], Stanley Hollenbach[2], Robert Scarborough[1], and Anjali Pandey[1]. (1) Department of Chemistry, Portola Pharmaceuticals, Inc, 270 East Grand Avenue, South San Francisco, CA 94080, Fax: 650-246-7776, (2) Department of Biology, Portola Pharmaceuticals, Inc, South San Francisco, CA 94080, (3) Department of DMPK, Portola Pharmaceuticals, Inc, South San Francisco, CA 94080*

The discovery and clinical use of the irreversible P2Y12 antagonist clopidogrel (Plavix) has confirmed the clinical utility of inhibiting this target. Despite its status as a clinically effective orally administered anti-platelet therapy, clopidogrel's irreversible mechanism of action, CYP-dependant conversion to the active form, and suboptimal inhibition of platelet aggregation in 20 – 40% of patients provides opportunity for improved efficacy and safety. Our discovery efforts have resulted in the identification of a competitive, reversible, non-purine inhibitor, PRT060128, which is currently undergoing phase II clinical evaluation. This presentation details our efforts toward the identification of a second-generation inhibitor. During this investigation we discovered a replacement for the sulfonylurea moiety previously deemed necessary during our earlier studies, resulting in a series of inhibitors with similar potency and pharmacokinetic (PK) properties. Investigations toward optimizing the potency and PK properties by, followed by

evaluation of the chiral materials in platelet aggregometry, collagen induced thrombosis in a perfusion chamber assay, and PK studies in three animal species will be presented.

MEDI 8

Design, synthesis, and biological evaluation of nonpeptidic, cell-permeable bivalent Smac mimetics as potent inhibitors of XIAP

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The resistance to apoptosis in cancer cells is a major problem in most of current cancer therapies. The X-linked inhibitor of apoptosis protein (XIAP) inhibits apoptosis by directly binding to and potently inhibition of both caspase-9 via its BIR (Baculovirus IAP Repeat) 3 domain, and caspase-3/7 via its linker region between BIR 1 and BIR 2. Smac, released from mitochondria, functions as an endogenous inhibitor of XIAP and other IAPs. Mature Smac protein binds a well-defined surface groove of XIAP via its AVPI tetrapeptide binding motif, while dimeric Smac proteins interact with both XIAP BIR 2 and BIR 3 domains. In the work presented here, we developed a series of bivalent Smac mimetics using our potent monovalent variants. These bivalent Smac mimetics bind XIAP linker-BIR2-BIR3 proteins with low nanomolar affinities as tested using our fluorescence polarization assay, and effectively induce apoptosis in human cancer cell lines, while showing no or little toxicity to normal cells. These bivalent Smac mimetics, 100 to 1000 times more potent than their relative monovalent variants, are promising lead compounds for the development of a new class of anticancer therapy.

MEDI 9

Community-based small molecule collaborative drug discovery for neglected infectious diseases and cancer

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Case studies from medicinal chemists and biologists working in secure collaborative groups to rapidly develop drug candidates for commercial and humanitarian markets will be presented. The first case study involves overcoming drug resistance which is the major problem for malaria. New approaches that allow scientists working together to develop new drugs faster are desperately needed. The discovery of alternatives to Verapamil, a known chemosensitizer to overcome both tumor and malaria resistance, will be presented using novel collaborative drug discovery technologies to help specialists work together in a global network. A detailed example showing how chemosensitizers addressing chloroquine resistance can be identified combining results from the University of Cape Town (South Africa) with structurally related compounds from the University of California at San Francisco (USA) and similar FDA/Orphan (courtesy Dr. Lipinski) approved drug compounds will be presented. This new collaborative technology allows researchers to build up networks of technical experts around therapeutic or target areas thus facilitating discovery of new drug candidates. Other case studies will presented including: a Malaria Computational and Experimental around large set of historical small molecule animal SAR data case study (UNC, St. Jude), a Malaria UGI-4CC Open Collaboration case study (Drexel-Indiana-UCSF), a Tuberculosis Public Private Partnership case study (TAACF, Lilly, Cornell), and a GPCR gene-family wide Ki community project (PDSP, UNC). The community-based platform is currently being used openly to help develop new treatments for neglected infectious diseases such as malaria, Chagas Disease, and African Sleeping Sickness and securely against commercial cancer targets.

MEDI 10

Biomimetic simulation of reactions postulated to occur during inhibition of ribonucleotide reductases by 2'-azido-2'-deoxynucleotides

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Mechanism-based inhibitors of ribonucleotide reductases (RNRs) such as 2'-azido-2'-deoxyuridine-5'-diphosphate (N_3UDP) have provided insight into the mechanism of reduction of the natural nucleotides into 2'-deoxynucleotides. Experiments with ^{13}C, ^{15}N and ^{17}O labeled N_3UDP established a mechanism which proposed an azide loss from the initial C3' radical to generate 2'-deoxy-3'-ketonucleotide. Addition of the nitrogen-centered radical (formed from the reaction of HN_3 with Cys225-based thiyl radical) to 3'-keto group provided the first evidence for the trapping of 2'-deoxy-3'-ketonucleotides in the reduction process (JACS 2005, 127, 7729). Synthesis of 3'-azido-3'-deoxynucleosides bearing a cysteinyl or vicinal dithiol substituent attached to C2' or C5' and a

biomimetic and theoretical simulations of the reactions between thiyl radicals and azido group, postulated to occur during inhibition of RNR, will be discussed. The 2,2'-azobis-(2-methyl-2-propionamidine) dihydrochloride has been used as a source of carbon radical to generate thiyl radicals at physiological pH in H_2O at 45 ^{o}C.

MEDI 11

Aleglitazar, a potent and balanced dual PPAR alpha/gamma agonist for the treatment of type II diabetes and dyslipidemia

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Recently, the ligand-dependent transcription factors Peroxisome Proliferator Activated Receptor-α (PPARα) and -γ (PPARγ) have been identified as primary molecular targets for the antidiabetic thiazolidinediones (γ) and the lipid lowering fibrates (α), respectively. This has provided new opportunities for the treatment of type 2 diabetes (T2D) and associated co-morbidities. The profile of a dual PPARα/γ agonist appears well-suited for addressing both hyperglycaemia and dyslipidemia in one drug and lowering as well the enhanced cardiovascular risk of diabetic patients. Capitalizing on X-ray structural data obtained with known PPARα- and γ-selective compounds as well as relying on detailed molecular modeling studies in combination with chemical intuition, novel PPAR ligands have been designed and synthesized.

A novel, highly promising class of dual PPARα/γ agonists, α-alkoxy-benzothiophenyl-propionic acids, has been discovered. In depth evaluation of this compound class led to the identification of Aleglitazar (R1439). Aleglitazar interacts as balanced coagonist with similar low nanomolar IC50 and EC50 values with human PPARγ and human PPARα receptors in vitro, while showing only marginal functional activity at the PPARδ receptor. In the db/db mouse and the fa/fa rat model, Aleglitazar by far exceeds the antidiabetic effects seen with Rosiglitazone.The potency of Aleglitazar on plasma lipid modulation in high fat rats and in human Apo-AI transgenic mice, however, is less impressive, but fully in line with the reduced activity seen in its interaction with rodent PPARα receptors.

Conclusion:

The in vitro and in vivo profile of Aleglitazar, together with the excellent drug-likeness of the compound and the absence of off-target effects, rendered this molecule an ideal candidate for clinical development. Phase II clinical trials with Aleglitazar have been successfully completed in 2008.

MEDI 12

Design and optimization of renin inhibitors: Orally bioavailable alkyl amines

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Renin is an attractive target for antihypertensive drugs. Application of a proprietary structure-based drug design methodology led to the identification of low MW alkylamine renin inhibitors with a novel scaffold. Optimization around this scaffold afforded a lead compound with a MW of 508 and IC50 of 0.47 nM against purified human renin. This compound was effective in an animal model of hypertension when administered orally.

MEDI 13

Discovery and pharmacological evaluation of dual FMS/Kit inhibitors

Prabha N. Ibrahim[1]*, pibrahim@plexxikon.com, Jiazhong Zhang*[2]*, Marika Nespi*[2]*, Ryan Bremer*[2]*, Betsy Burton*[3]*, Bernice Wong*[2]*, Ben Powell*[4]*, D. Rick Artis*[5]*, Kam Zhang*[6]*, Brain West*[7]*, bwest@plexxikon.com, Paul Lin*[4]*, Chao Zhang*[8]*, Gaston Habets*[9]*, Greg Tesch*[10]*, Gideon Bollag*[11]*, and Peter Hirth*[4]*. (1) Department of Chemistry, Plexxikon Inc, 91 Bolivar Drive, Berkeley, CA 94710, Fax: 510-647-4048, (2) Plexxikon Inc, Berkeley, CA 94710, (3) Discovery Biology, Plexxikon, Inc, Berkeley, CA 94710, (4) Plexxikon, Inc, Berkeley, CA 94710, (5) Plexxikon, Inc, Berkeley, CA 94706, (6) Department of Structural Biology, Plexxikon Inc, Berkeley, CA 94710, (7) Department of Molecular Biology, Plexxikon Inc, Berkeley, CA 94710, (8) Department of Informatics, Plexxikon Inc, Berkeley, CA 94710, (9) Department of Assay Development and Screening, Plexxikon Inc, berkeley, CA 94710, (10) Monash Medical Centre, Clayton, Australia, (11) Discovery Biology, Plexxikon Inc, Berkeley, CA 94710*

Fms and Kit, receptor tyrosine kinases, are key regulators of macrophages and mast cells respectively. Macrophage survival and proliferation are mediated by the cytokine CSF-1, through Fms (CSF-1R), whereas, mast cells are regulated by SCF, via Kit. These receptors control autoimmune processes involved in many diseases, including rheumatoid arthritis (RA) and multiple sclerosis (MS). We have identified a series of potent inhibitors of Fms and Kit with demonstrated efficacy in in-vivo models of RA, acute mouse model of renal inflammation (UUO) and MS. Further efforts, guided by co-crystallography of lead compounds in both Fms and Kit, have led to a portfolio of lead compounds with varying Fms/Kit activity profiles. This presentation will describe the efficacy of lead compound in a mouse model of RA, UUO, MS, as well as, the activities of follow on compounds in biochemical and cell-based assays for Fms and Kit.

MEDI 14

Discovery of NA808: A novel host targeting anti-HCV agent

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Chronic hepatitis C continues to be the most important cause of chronic liver disease. The current standard of care for HCV infection is the treatment with pegylated interferon alpha in combination with ribavirin, however, its side effects and limited response rate are creating need for enhanced treatment options. There are new anti-HCV drugs in development which target viral enzymes, but direct anti-virals have possibility to develop viral resistance.

Using HCV replicon system, we identified a lead compound, NA255 from natural screening sources, and found its target was a host protein, serine palmytoyltransferase. Optimization of NA255 resulted in the identification of NA808 as a development candidate, which showed strong anti-replicon activity and significant reduction of HCV RNA level in human chimeric liver mice model.

In this presentation, its mode of action and optimization of the lead compound along with a profile of NA808, which is currently in clinical trials, will be detailed.

MEDI 15

Phenol-pyrazole inhibitors of mutant B-raf

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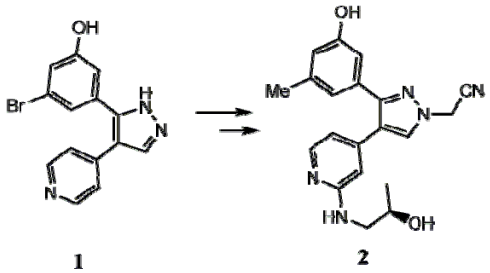
B-Raf is mutated in number of human cancers mainly melanoma, thyroid and colorectal. Raf is a key kinase in the Ras/Raf/Mek pathway, thus making mutant B-Raf an attractive oncology target. Discussed herein is the medicinal chemistry effort done at Pfizer directed at developing a potent mutant B-raf inhibitor for cancer therapy starting from an efficient phenol-pyrazole lead, compound 1. By adhering to basic medicinal chemistry principles of focusing on ligand efficiency and controlling lipophilicity, a 3-vector SAR was developed leading to a very potent mutant B-raf inhibitor, compound 2. As common to phenolic compounds, compound 2 suffered from secondary metabolism, especially glucuronidation. Also discussed are three general strategies to overcome glucuronidation in phenolic compounds.



MEDI 16

Quantum dot technologies for elucidating brain chemical signaling

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Molecular/genomic technologies of the past two decades have allowed investigators to make major advances in identifying and altering the expression of neural signaling molecules that are critical to regulating healthy brain function. However, better tools are needed to further elucidate the functional role of identified signaling molecules. Nanotechnology can offer new capabilities that will

allow investigators to probe the function of key neural molecules using multiple modalities, at the scale of single molecules, in live cells. Here I will present three main quantum dot-based technologies that our laboratory has developed to investigate neural function: 1) neurotrophin-QD imaging probes for activating neural growth signaling, 2) QD imaging probes for imaging protein trafficking and endocytic events in neural cells, and 3) ultrasensitive QD assays for measuring specific protein-protein interactions in neural cells. These QD-based technologies offer investigators a means to probe specific inter-molecular interactions with significantly improved sensitivity and to relate these interactions with high-resolution in real-time, in live neurons at the scale of single molecules.

MEDI 17

Probing the distribution and behavior of individual serotonin receptors in primary hippocampal neurons using quantum dots

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Drugs targeting the serotonergic system are used in a large panel of psychiatric disorders. For example, serotonergic receptors are often the target of anxiety- and depression-based medications. Current therapeutics are widely-used but produce a myriad of debilitating side-effects and their mechanism of action is still largely unclear. In order to better understand the action of serotonergic modulators, their native behaviors must first be elucidated. Here, we exploit quantum dots as single-molecule probes of serotonin receptors. The use of QD-receptor conjugates permits high resolution and quantitative imaging of individual receptors. Currently-used technologies are limited by their ability to measure only average receptor behavior. Additionally, these techniques leave out important details of molecular dynamics, because each receptor molecule is in a different fraction of its lifetime at the time of measurement. Because of their photostability and brightness, QD-conjugates allow the visualization and measurement of molecular dynamics, such as receptor recycling. These experiments reveal exquisite, previously undemonstrated, detail of the “life and times” of a serotonin receptor. Understanding these dynamics under normal physiological conditions will lead to a fuller understanding of how therapeutic agents affect the behavior of these receptors, and ultimately better treatments for patients suffering from mood-based disorders.

MEDI 18

Drug-conjugated nanocrystal labeling and single protein tracking of the serotonin transporter protein

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Neurotransmitters, such as serotonin, control critical behaviors including mood, sleep, appetite, and aggression. Imbalances in these neurotransmitters are related to mental illnesses. Transporter proteins are responsible for the efficient clearance of neurotransmitters from the extracellular space following release. Transporters are among the most widely and successfully targeted proteins for medication development, most notably the serotonin transporter (SERT) selective reuptake inhibitors (SSRIs), typified by Prozac. We have developed a non-isotopic labeling strategy based on drug-conjugated nanocrystals that enables the real time visualization of the trafficking of SERT in oocytes, mammalian cells, and neurons.

MEDI 19

Strategies for optical voltage-sensing in neuronal networks

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High signal-to-noise optical sensing of fast changes in membrane potential remains an elusive holy grail of neuroscience. Chimeras of voltage-gated ion channels and fluorescent proteins initially seemed promising as tools, but are plagued with low expression levels and often complete lack of delivery to the plasma membrane. Entirely new approaches to dye-based or genetically-encoded voltage sensors are needed. In this talk, we present several possible constructs that have showed initial promise. The first is a hybrid of a quantum dot (QD) and the voltage-sensitive dye di-1-ANEPIA, which uses fluorescence resonance energy transfer to amplify the dye's sensitivity. The second approach uses electron rather than energy transfer, in an entirely genetically-encoded construct where the electron donor is embedded in the plasma membrane and a fluorescent protein is attached to its terminus. Finally, we present a strategy for directed evolution of fluorescent proteins with the aim of sensing membrane potential.

MEDI 20

A biomolecular photodiode for imaging of cell membrane potential

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We have created a biomolecular photodiode consisting of a membrane-bound cytochrome c protein fused with a GFP (green fluorescent protein) variant. A similar assembly has been shown to produce unidirectional photocurrent in vitro with the cytochrome acting as an electron acceptor from the FP upon visible light excitation. Electron transfer between the cytochrome and the FP is a highly voltage dependent process. By embedding this assembly in the membrane of living cells, it is subjected to the membrane potential. As this potential changes over ~100 mV, as in an action potential, the extent of electron transfer should vary significantly, manifesting as a change in fluorescence intensity of the FP donor. The feasibility of the sensor is investigated in several ways, including modeling, electrophysiology, and direct application of current to purified membrane fragments.

MEDI 21

In search of brain nanobiosensors: Small-molecule recognition and biomolecule capture as critical first steps

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To explore interneuronal signaling in the central nervous system at length and time scales pertinent to its intrinsically encoded information, and to relate this information to complex behavior, as well as brain disorders and new treatment and prevention strategies, chemically specific in vivo nanobiosensors are needed that approach the sizes of synapses (ca. 20 nm) and respond in milliseconds. Using highly specific functionalization chemistries and nanoscale self-assembly and patterning strategies, we demonstrate that large biomolecules, including antibodies or membrane-associated receptor proteins with high affinity for serotonin or dopamine, can be selectively captured from solution by tethered small-molecule neurotransmitters or closely related molecules with minimal nonspecific binding. We are using neurotransmitter-functionalized surfaces to capture and to identify high-affinity molecular-recognition elements for future use with semiconductor nanowire or carbon nanotube platforms to create ultrasmall,

multiplexed sensing devices to revolutionize in vivo sensing and functionally directed proteomics.

MEDI 22

Enabling direct electrochemical and biological studies in living cells with multifunctional nanoscale needle probes

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Nanoscale electrode probes capable of probing microenvironments provide exciting new opportunities for fundamental and applied studies in cell biology and neuron science. We report the fabrication and characterization of long and straight needle nanoprobes for electrochemistry, and the study of their applicability and behavior in microenvironments. The needle nanoprobe, with a nanoscale ring-shaped Au electrode (~ 1000 nm2 in area) at the tip of the needle serving as the active electrode, was used, with another metal-coated nanowire as a reference electrode, for local electrochemical sensing inside isolated microdroplets having volumes down to a few picoliters for the first time. It was further used to non-intrusively pierce through cell membrane and to mechanochemically deliver a minute amount of single quantum dots and biomolecules into specific compartments in living cells. The combination of those unique capabilities makes such needle nanoprobes powerful tools for studying single living cells or single synapses of neurons.

MEDI 23

Single-walled carbon nanotube multimodal optical biosensors for genotoxin detection and identification

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Single-walled carbon nanotubes (SWNT) offer unique advantages for biosensing such as photostable near-infrared (n-IR) emission for prolonged detection through biological media, and single-molecule sensitivity.

We demonstrate carbon nanotube complexes that detect and identify six genotoxic analytes, including chemotherapeutic drugs and reactive oxygen species (ROS), which are spectroscopically differentiated into four distinct

classes. A pair of single-walled carbon nanotubes provides four optical modes that are modulated to uniquely fingerprint agents by the degree to which they alter either the emission band intensity or wavelength. Binding of the analytes to the sensor complex induces charge transfer events or solvatochromic shifts of two SWNT bands, whose response differs by analyte.

We employ our sensing and fingerprinting method of these analytes in real time within live mammalian cells, demonstrating the first multiplexed optical detection from a nanoscale biosensor and the first label-free tool to optically discriminate between genotoxins.

MEDI 24

Nanoscale strategies to improve the reliability of chronic neural recordings

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Recent advances in neural prosthetics demonstrate the feasibility for restoring movement through neural signals recorded from intra-cortical microelectrodes in paralyzed persons. However, widespread clinical application of this technology is hampered by a lack of reliability in chronic neural recordings. Our laboratory has recently proposed a novel hypothesis that suggests that unreliability of chronic recordings is partially dependent on the local tissue response, which in turn is marked by chronic inflammation and associated local neurodegeneration. Therefore, in order to preserve the network connectivity of target neurons, it is important to manage the chronic inflammatory response to microelectrodes. We present our work on two potential approaches to minimize chronic inflammation surrounding microelectrodes and improve chronic recording reliability: 1) nanoscale coatings and 2) nanoscale electrodes. Nanoscale coatings are advantageous because they contribute minimally to the electrical impedance of the electrode and introduce negligible distance between the recording sites and target neurons. We have investigated two strategies for controlling inflammation by engineering coatings that: 1) are inherently anti-inflammatory and 2) facilitate sustained local release of anti-inflammatory proteins/drugs. Alternately, nanoscale electrodes have the potential to minimize inflammation by decreasing vasculature damage during insertion. Current challenges associated with both of the above approaches will be discussed.

MEDI 25

Brain tissue responses to implanted analytical devices: Microdialysis probes and voltammetric microelectrodes

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Microdialysis and voltammetry facilitate simultaneous measurements of dopamine in brain extracellular space. Simultaneous measurements produce highly disparate results. Both techniques involve penetration of tissue with a device: this disrupts the tissue. We employ fluorescence and transmission electron microscopy to evaluate tissue responses to the implants. Microdialysis probes (~200 μm) cause millimeter-sized wounds due to a suppression of blood flow, which we image by labeling blood vessels with fluorescent nanobeads and antibodies against endothelial cells. The wound activates glial cells, the brain's immune system. Voltammetric microelectrodes (~10 μm) trigger neither ischemia nor the immune response. According to electron microscopy, microelectrode-induced disruption is confined to a distance of 3 μm from the electrode. A key physical attribute of the microelectrodes is that their dimensions are smaller than the spacing of brain blood vessels, supporting the concept of critical diameters of implanted sensors.

MEDI 26

Microchip analysis of neuronal secretions by immunoaffinity capillary electrophoresis

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The influence of inflammatory cytokines on the function of brain astrocytes has been of great interest to immunologists and neurobiologists, alike. Previous work by our group has demonstrated the release of immune regulators by astrocytes during stimulation with the pro-inflammatory neuropeptide, vasoactive intestinal peptide. (Brenneman, et al. Neuropeptides, 2003, 37, 111) The present studies describe the application of a microdialysis-sampling microchamber capable of culturing 5-10 neuronal cells. Over time, the secretion by-products of the cells can be sampled by the microdialysis probe, during the culture. Studies were performed to investigate the effects of various doses of known inflammatory cytokines and other biomarkers on the activity of the cultured cells. The microdialysis samples were collected in a microfraction collector and analyzed for

the presence of neuropeptides and other neuronal secretory products by chip-based immunoaffinity capillary electrophoresis (ICE).

MEDI 27

Discovery of BMS-708163: A potent and selective gamma-secretase inhibitor which lowers CSF beta-amyloid in humans

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The β-amyloid hypothesis of Alzheimer's Disease (AD) is supported by pathology data, analysis of familial AD mutations, and numerous preclinical studies. The formation of Aβ peptides is a result of cleavage of the amyloid precursor protein (APP) by γ-secretase and thus, γ-secretase inhibitors (GSI) are an attractive therapeutic approach for treating and/or preventing AD. However, γ-secretase also cleaves other proteins, including Notch. γ-Secretase mediated cleavage of Notch is required to control cell fate decisions in several tissues, including the gastrointestinal tract and spleen. Thus, the need for GSIs with selectivity towards Notch cleavage is paramount. In this presentation, we will discuss the optimization of a series of γ-secretase inhibitors for potency, Notch selectivity, brain penetrance, and desirable pharmacokinetic properties. These efforts resulted in the discovery of BMS-708163, a potent GSI (APP IC50 = 300 pM) that is selective against Notch (190-fold), and significantly reduces Aβ in preclinical animal models. Furthermore, we will summarize results from Phase I clinical trials which demonstrate the pharmacokinetics, tolerability, and effect of BMS-708163 on reducing CSF Aβ levels in humans.

MEDI 28

Discovery of a novel, orally bioavailable CGRP receptor antagonist for the treatment of migraine

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Calcitonin gene-related peptide (CGRP) is believed to play a key role in migraine pathogenesis. Phase II clinical trials provided proof of concept for the acute treatment of migraine with the intravenously administered CGRP receptor

antagonist olcegepant. Our program to develop orally bioavailable CGRP receptor antagonists began with a benzodiazepine-containing HTS lead of micromolar potency and high molecular weight. Initial optimization of this benzodiazepine led to the identification of the advanced clinical compound telcagepant. In a complementary approach, a rapid analogue synthesis strategy was employed to diversify the lead structures and identify alternatives to the benzodiazepine. This approach afforded a diverse set of spirohydantoin-based leads that combined a significant reduction in molecular weight with improved potency relative to the HTS lead. Modification of such structures gave highly potent antagonists which possessed modest oral bioavailability. Polar functionality was incorporated in order to modulate metabolism and improve aqueous solubility, thereby increasing oral bioavailability. This strategy led to the identification of a highly potent and selective CGRP receptor antagonist. The promising pharmacological attributes of this compound are being evaluated in clinical studies.

MEDI 29

Discovery of AMG 221: An 11β-HSD1 inhibitor in the clinic for type 2 diabetes

Christopher Fotsch[1], *Jeffrey Adams*[2], *Michael Bartberger*[3], *Eric A. Bercot*[2], *Lynn Cai*[1], *Victor M. Castro*[4], *Michelle Chen*[5], *Rod Cupples*[5], *Maurice Emery*[6], *Jenne Fretland*[6], *Anil Guram*[2], *Sonja Gustafsson*[4], *Andrew Hague*[2], *Clarence Hale*[5], *Nianhe Han*[1], *Michael Hayashi*[6], *Martin Henriksson*[4], *Dean Hickman*[6], *Evert Homan*[4], *Randall W. Hungate*[1], *Lars Johansson*[4], *Steven Jordan*[3], *Christina Kaiser*[4], *Renee Komorowski*[5], *Aiwen Li*[1], *Qingyian Liu*[1], *Guy Matsumoto*[6], *Kenneth McRae*[2], *George Moniz*[2], *Gunnar Palm*[4], *David Pyring*[4], *David J. St. Jean Jr.*[1], *Yaxiong Sun*[3], *Mona Sydow-Bäckman*[4], *Lars Tedenborg*[4], *Hua Tu*[5], *Stephania Ursa*[5], *Murielle Véniant*[5], *Meredith Williams*[4], *Giufen Xu*[6], *Qiuping Ye*[6], *Chester Yuan*[1], *Jiandong Zhang*[3], *Xiping Zhang*[6], *and Minghan Wang*[5]. *(1) Department of Chemistry Research and Discovery, Amgen, Inc, One Amgen Center Drive, Thousand Oaks, CA 91320, (2) Chemical Process R&D, Amgen, Inc, Thousand Oaks, CA 91320, (3) Department of Molecular Structure, Amgen, Inc, Thousand Oaks, CA 91320, (4) Biovitrum AB, Stockholm, Sweden, (5) Department of Metabolic Disorders, Amgen, Inc, Thousand Oaks, CA 91320, (6) Department of Pharmacokinetics and Drug Metabolism, Amgen, Inc, Thousand Oaks, CA 91320*

11β-Hydroxysteroid dehydrogenase type 1 (11β-HSD1) regulates glucocorticoid action by converting cortisone to cortisol at the tissue level. Both genetic and pharmacologic studies suggest that 11β-HSD1 inhibition is a viable therapeutic strategy for the treatment of type 2 diabetes and the metabolic syndrome. Early 11β-HSD1 inhibitors were identified from the extract of the licorice root, e.g., glycyrrhetinic acid. Further derivatization of this compound led to carbenoxolone,

which was identified as a potent inhibitor of 11β-HSD1 and was shown to be efficacious in improving insulin sensitivity in humans. One drawback of carbenoxolone is that it also inhibited 11β-HSD2, an enzyme which plays a role in electrolyte balance. In an effort to identify potent and selective inhibitors of 11β-HSD1, we screened our compound collections and identified compounds with a thiazolone core. In this presentation, we will describe structure activity studies that led to the discovery of our clinical candidate, AMG 221. In addition, we will describe our work to identify a back-up clinical candidate.

MEDI 30

Discovery of PF-2413873: A nonsteroidal progesterone receptor antagonist for the treatment of endometriosis

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Steroidal progesterone receptor antagonists, such as mifepristone (RU486) have demonstrated efficacy in reducing the symptoms of endometriosis in clinical trials. We have taken a non-steroidal approach to our PR antagonist program. This presentation will highlight the discovery and optimisation of an aryl-pyrazole ether series from the initial high throughput screening hits, showing how the challenges of lipophilic, neutral drug space have impacted upon this program and the strategies employed to overcome them. We will disclose the structure, in vitro and in vivo pharmacological profile of PF-2413873, currently in Phase 1 clinical trials for the treatment of endometriosis. Finally, pharmacokinetic data from Phase 1 clinical trials in male volunteers will be presented.

MEDI 31

Physicochemical properties approach to the identification of a histamine H3 receptor antagonist for the treatment of ADHD

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Histamine plays a key role in attention, learning/memory, and wakefulness. Histamine H3 receptors are inhibitory auto/hetero-receptors that regulate the release of histamine, acetylcholine and other neurotransmitters. PF-03654746 is a novel, potent and highly selective H3 receptor antagonist in vitro and in vivo with optimal physicochemical properties. Pre-clinical data with H3 receptor antagonists suggest that they may have utility in the treatment of disorders involving attention, learning/memory and vigilance such as ADHD, schizophrenia, Alzheimers Disease and narcolepsy. PF-03654746 is a useful tool to evaluate the role of H3 receptors in these disorders. The structure of the clinical candidate PF-03654746 along with its' preclinical rational, Phase I single dose PK and POM biomarker will be disclosed.

MEDI 32

The discovery and development of selective androgen receptor modulator MK-0773

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Androgens such as testosterone and dihydrotestosterone are therapeutically effective muscle anabolic agents, but their use is limited by their adverse effects, including the promotion of hirsutism in women and prostate growth in men. The selective androgen receptor modulator (SARM) MK-0773 has been developed to offer beneficial myoanabolic effects with a significantly reduced risk of adverse effects. The discovery, development, and early clinical profile of MK-0773 will be described

MEDI 33

Advances in medium pressure liquid chromatography

***Jack E. Silver**, jsilver@teledyne.com, Nancy Fowler, Paul Bellinghausen, and Candice Scanlon, Teledyne Isco, 4700 Superior Street, Lincoln, NE 68504, Fax: 402-465-3091*

Advances in medium pressure liquid chromatography (MPLC) column design and particle morphology allow higher loading capacities and higher thoughput as well as increased compound purity in both normal and reverse phase chromatography.

Example purifications will be presented with comparisons to currently existing MPLC columns.

MEDI 34

Si-containing hydroxyapatite coating on titanium for implant application

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Synthesis of chemically modified or ion substituted hydroxyapatite has drawn many scientist's interest since major component of biological tissues such as bone, teeth and some invertebrate skeletons are composed of hydroxyapatite containing various kinds of inorganic substances. Especially, incorporation of silicon ion into hydroxyapatite structure is of great interest since Si plays an important role in developing artificial bone.

In this study, Si-containing hydroxyapatite coating on titanium substrate was studied using a Si-containing calcium phosphate sol. In sol-gel coating of Si-HA onto titanium substrate, the adhesion to substrates is closely related to substrate surface compositions and surface roughness.

The bioactivity of the Si-HA on titanium substrate was tested by soaking into a simulated body fluid and in vitro cellular culture. The results of bioactivity experiments suggest that the Si-HA coated titanium substrate has a good biocompatibility and can be the useful materials for implants and bone augmentation.

MEDI 35

Synthesis and biological evaluation of potential RXR selective agonists: Novel bexarotene analogs

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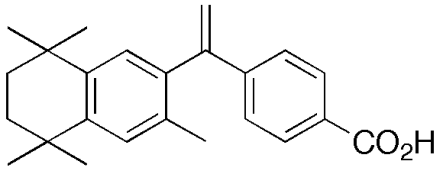
Bexarotene (Targretin®) is an FDA approved drug used in the treatment of cutaneous T-cell lymphoma (CTL). Bexarotene is a selective agonist for the retinoid X receptor (RXR) that induces RXR homodimer formation at low concentrations. While bexarotene has proved to be an efficient treatment for CTL, there can be side effects such as hypothyroidism and raised triglycerides in treated patients. Such side effects are presumed to arise from unintended interaction of RXR with other nuclear receptors. Our studies have focused on creating several novel bexarotene analogs that differ from bexarotene by the substitution of a chemical group or a single atom. The novel bexarotene analogs have been evaluated for RXR binding in an RXR mammalian-2-hybrid assay, and those analogs that bind to RXR have been tested for potency in an RXRE-mediated transcriptional assay. Possible mutagenic and toxic activity of the RXR analogs has been evaluated with Saccharomyces cerevisiae.



Bexarotene

MEDI 36

SiliaSep HP flash cartridges: High performance separation tools

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High performance SiliaSep HP Flash cartridges are new separation tools that can often be a good alternative to the preparative HPLC when the standard flash chromatography did not show satisfying results. Made with UltraPure small particle size silica gel and using an innovative packing technology, SiliaSep HP have turned out to be very successful in cases where standard flash chromatography has hardly failed. Not only do they offer a great resolution, they can be used to purified multi grams at the same time.

Results presented will highlight specific cases of organic synthesis where the standard flash chromatography did not show satisfying results and where the SiliaSep HP has turned out to be a very efficient solution for the purification of the desired molecules.

MEDI 37

Comparative methods for analysis of protein covalent modification by electrophilic quinoids formed from xenobiotics

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Conjugation of biotin and fluorophore tags is useful for assaying covalent protein modification. Oxidative bioactivation of selective estrogen receptor modulators (SERMs) yields electrophilic quinoids that covalently modify proteins. Identification of the protein targets of reactive metabolites is of general important for xenobiotics. Four methodologies, using SERM derivatives and different biotin/fluorophore tags, were compared for purification and quantification in this study. Comparison showed: the azidoTag/Staudinger method was sensitive but nonspecific; the azidoTag/click method had low sensitivity; the dansylTag failed to detect modified proteins in hepatocytes. The COATag (covert oxidatively activated tags, SERM conjugated to biotin) was adjudged superior, detecting 5 ng of modified protein in vitro and identifying protein targets in hepatocytes. In metabolism studies, the azide group was metabolically labile, and in highly oxidative environments required for bioactivation, azidoTag methodologies are disfavored. For study of protein targets of electrophilic metabolites formed by in situ oxidative bioactivation, the COATag is both sensitive and specific, and shows cell permeability.

MEDI 38

Design and synthesis small molecule inhibitors of alpha-synuclein and amyloid-beta fiber formation

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We designed and synthesized novel boronic acid and chromene based small molecule library. We tested their in vitro activity against alpha-Synuclein and A-beta by examining the effect on the aggregation process. The aggregation was monitored using the amyloid specific Thioflavin T fluorescence, as well as by native gel electrophoresis, and transmission electron microscopy. We observed that some compounds were effective at stabilizing the initial species, while others appear to stabilize a ring-like oligomeric intermediate as observed by electron microscopy. Furthermore, some compounds were able to promote the formation of amyloid fibers. Together these results serve as a foundation for future designs of small molecule inhibitors and diagnostic agents (PET-agents) of amyloid fiber formation, but also provide insight into the mechanism of aggregation in many neurodegenerative diseases.

MEDI 39

Salicylamides as positive allosteric modulators of nAChR-alpha7

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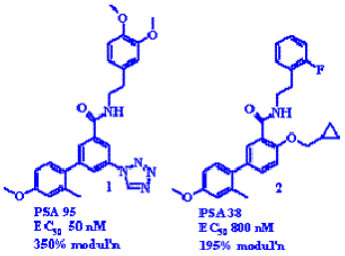
Lead Identification in CNS The improvement of cognitive function is a critical medical need for Alzheimer's disease and late-stage Parkinson's patients. Nicotinic agonists have been shown preclinically to improve memory and cognition. Enhancing endogenous cholinergic neurotransmission by positive modulation of the selective alpha7 nicotinic acetylcholine receptor (nAChR-α7) is one of the options being explored as a possible treatment. An HTS campaign identified a series of 3,5-disubstituted benzamides (e.g. **1**) acting as positive modulators at nAChR-α7. The series was optimized with the goal of improving CNS penetration leading to salicylamides (e.g. **2**), characterized by a reduced polar surface area. The design, synthesis, and evaluation of a novel salicylamide series that act as positive modulators at the human alpha7 nAChR will be presented.



MEDI 40

Monocyclic β-lactams as neuroprotective agents

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High doses of glutamate in the synapse, often induced by stress, can lead to nervous cell damage and cell death (excitotoxicity). Neuronal damage due to excess of glutamate is associated with diseases such as Parkinson's, Alzheimer's, with depressive-like behaviors and possibly major depressive disorder (MDD), stroke, etc. Our current work focuses on the assesment of the generalization of the previously reported neuroprotective effects of β-lactam antibiotics to the monocyclic β-lactams synthesized in our laboratories. In addition to expanding the class of compounds that may be important as neuroprotective agents, this study will provide insight into structure/activity relationships (SAR) that will aid our understanding of the mechanisms responsible for their neuroprotective effects.

MEDI 41

Synthesis of inhibitors of the N-acetyl-L-ornithine transcarbamylase in Stenotrophomonas maltophilia

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Stenotrophomonas maltophilia is a gram-negative bacterium responsible for various nosocomial infections, predominantly affecting patients with cystic fibrosis, immunosuppression, organ transplantation and urinary tract infection. It is highly resistant to most antibiotics, increasing the time spent in the intensive care unit. Mortality rates of 30% have been reported. S. maltophilia utilizes a

novel enzyme, N-acetyl-L-ornithine transcarbamylase (AOTCase), in arginine biosynthesis, which is the only metabolic pathway for this particular α-amino acid available to the organism. The synthesis of potential inhibitors of AOTCase will be presented.

MEDI 42

Monocyclic β-lactams as anti-Moraxella agents

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The design, synthesis and structure/activity relationships (SAR) of novel compounds that have demonstrated antimicrobial activity against clinical isolates of the bacteria Moraxella catarrhalis will be presented. This microorganism is a significant cause of ear aches in children and a cause of sinus and lung infections in adults, with estimated associated cost of these types of infections of $2 billion each year.

MEDI 43

Use of nitric oxide to enhance the efficacy of silver sulfadiazine as an antibacterial agent

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Although penicillin was hailed as a miracle cure only 65 years ago, widespread resistance soon followed. In fact, cases of resistance to all contemporary antibiotics are well documented. Hence, novel approaches to battle infection are highly sought after. Nitric oxide (NO), a diatomic free radical endogenously produced by the immune system in response to invading pathogens, possesses broad-spectrum antimicrobial action. Lipid peroxidation, one antibacterial mechanism ascribed to NO, disrupts the bacterial membrane, thereby increasing cell permeability. Therefore, we hypothesized that synergistic activity may be elicited by the combination of NO and a second antimicrobial agent with inherently limited membrane permeability (due to size and/or chemical structure).

The concerted effect of NO, delivered via a small molecule NO donor, and silver sulfadiazine, a topical biocide, was evaluated by determining the fractional bactericidal concentration after 120 min (FBC120). Synergistic action against a number of pathogenic species was observed, particularly against Gram-positive bacteria.

MEDI 44

Rational design of novel bacterial enzyme inhibitors

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Antibiotics remain one of the most effective ways of controlling and eradicating bacterial infections; however many species of bacteria have developed a resistance to current antibiotic drugs. This is why it is crucial that new molecules are designed to keep up with the constantly adapting bacteria.

A number of bacterial enzymes that are crucial for growth and survival have been identified through gene deletion experiments. In the absence of these genes, no bacterial growth was observed. We are designing inhibitors for these enzymes using non-reactive substrate analogues as potential lead compounds. Our next step is to test these compounds for inhibitory activity using existing published assays to these enzymes. A lead compound will be identified from these tests and will be optimized for more effectiveness in enzyme inhibition.

MEDI 45

Antibiotic activity of *Echinacea* herb in cultures of *Escherichia coli* and *Staphylococcus aureus*

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Three *Echinacea* samples were tested for antibiotic properties on *Escherichia coli* and *Staphylococcus aureus*. The aqueous extract of *E. angustifolia* roots and *E. purpurea* foliage created halos of dead *S. aureus*. While aqueous root extracts of *E. purpurea* were antibiotically inactive, methanol extracts revealed antibiotic activity. Conversely, methanol extracts of *E. angustifolia* roots and *E. purpurea* foliage showed no activity. GC-MS analysis of methanol extracts revealed two common compounds with m/z ratios of 256.3 and 284.3. *E. purpurea* root extracts contained higher concentrations of these compounds than the other

samples, potentially indicating concentration-dependent activity. Possibly one or both of these compounds is responsible for the antibiotic activity. The GC-MS analyses revealed various phenolic structures in these components, which may be related to a known group of phenolic compounds within *Echinacea*. Further characterization of these phenolic compounds will be presented.

MEDI 46

Development of a novel activity assay describing the structure-activity-relationship of tetrabutylammonium counter-anions as antimicrobial agents

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Due to the rising number of strains of drug-resistant bacteria, the development of new antimicrobials has become increasingly important. The antibacterial abilities of quaternary amines and their derivatives have been well known and documented for many years against both gram-positive and gram-negative bacteria. By monitoring the Zone of Inhibition of various concentrations of tetrabutylammonium salts, a comparison of the counter-anions can be observed. This is the first time that an encompassing study emphasizing the role of the counter-anion on activity has been reported. Activity is reported as $ZI_{max}max/K_{ZI}$ which has been shown to be an excellent method of determining efficacy of these salts. Support for this assay was performed using Minimum-Inhibition-Concentration (MIC), which validated the trend observed.

MEDI 47

New classes of novel gram-positive specific antimicrobials: Inhibitors of *E. coli*, *S. aureus*, and surrogates of the causative agents of methicillin-resistant *S. aureus*, tuberculosis and anthrax

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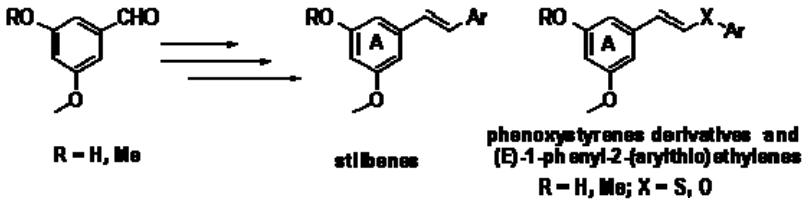
The antimicrobial phenolic stilbene [(*E*)-3-hydroxy, 5-methoxystilbene] was isolated from the leaves of *Comptonia peregrina* (L) by Monte et. al[1]., and tested against a series of Gram-positive bacteria[2]. This compound was inhibitory against drug-resistant Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (**MRSA**) and surrogates of the causative agents of **anthrax** and **tuberculosis**. These results prompted the design and synthesis of two new classes of compounds [functionalized phenoxystyrenes and (*E*)-1-phenyl-2-(arylthio)ethylenes], in addition to various functionalized stilbenes. The antimicrobial activity of the natural product (*E*)-3-hydroxy-5-methoxystilbene and eighty of its synthetic analogs including the stilbenes and the antimicrobial scaffolds (phenoxystyrenes and phenothiostyrenes) were tested against clinically significant Gram-positive bacteria, using minimum inhibitory concentration assays with either pathogenic or non-pathogenic surrogates/species. Analysis of the results indicated a loss of antimicrobial activity in the absence of at least one phenolic moiety in ring **A**. Compounds with more than one phenolic group were also active against Gram-negative bacteria such as *Escherichia coli* **ATCC 29522**. The incorporation of a benzothiophene moiety was shown to enhance activity. One benzothiophene derivative was four times more potent than the parent compound against *Bacillus anthracis* (Sterne strain) and eight times more potent against *Staphylococcus aureus* **ATCC 29213**, a non-pathogenic surrogate of **MRSA**. Additional evaluations will be performed as new analogs are synthesized with the aim of increasing both the spectrum and potency of antimicrobial activity. Recent results will be published.



MEDI 48

Compounds targeting Lipid A as antibacterial agents

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***Walter A. Szarek**, szarekw@chem.queensu.ca, Department of Chemistry, Queen's University, Kingston, ON K7L 3N6, Canada, Fax: 613-533-6532*

The Lipid A portion of LPS consists of 4 to 7 acyl chains and two phosphorylated glucosamines and is primarily responsible for the immune responses triggered by LPS. We have determined that bivalent tetrazolium salts can form a high-affinity complex with Lipid A and thus have antibacterial properties. Employing compounds such as Tetrazolium Blue Chloride (TB), Nitrotetrazolium Blue Chloride (NTB) and Tetranitroblue Tetrazolium Chloride (TNBT), we have determined that increased nitro content is correlated with the ability of the compounds to competitively inhibit the binding of SYBR-Green I to LPS in solution. TNBT has a relative affinity for LPS that equals or exceeds that seen for the endotoxin scavenger, polymyxin B. Further, TNBT was bactericidal with low micromolar MIC values when added to cultures of multi-drug resistant P. aeruginosa, E. coli, K. pneumoniae , E. cloacae, P. mirabilis, M. morganii, C. freundii, S. marcescens and Salmonella spp.

MEDI 49

Synthesis and evaluation of inhibitors selective for mycobacterial vs. human proteasomes

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Previous research in our labs has shown that certain oxathiazol-2-ones act as selective suicide-substrate inhibitors of the Mycobacterium tuberculosis (Mtb) proteasomes by cyclo-carbonylating its active site threonine to form an oxazolidin-2-one. We now report an improved procedure for the preparation of oxathiazol-2-ones that has enabled the generation of a focused library of compounds designed to specifically target the Mtb proteasome. The structure-activity relationship and selectivity for the Mtb proteasome of these compounds is also presented.

MEDI 50

Inhibition of Sortase A in *Staphylococcus aureus*: A novel antibacterial target

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Staphylococci are responsible for more than a million hospital-acquired bacterial infections every year. In an effort to identify new antibacterial agents against S. aureus that act through novel mechanisms we have pursued inhibitors of the bacterial surface enzyme S. aureus Sortase A (SrtA). SrtA plays a crucial role in pathogenesis of Gram-positive bacteria by modulating the ability of bacterium to adhere to host tissue via a covalent anchoring of surface proteins to cell wall peptidoglycan. SrtA cleaves the amide bond between the threonine and glycine of the LPXTG motif of surface proteins during the surface anchoring. Genetic knockout experiments have shown that mutants of Gram-positive bacteria lacking SrtA fail to display surface proteins and are defective in establishing infection in animal models. Thus, inhibitors of SrtA are promising candidates for treatment and prevention of Gram-positive bacterial infections. High resolution crystal structures of recombinant S. aureus SrtA∆59, a fully active variant of SrtA and its complex with its substrate LPETG has recently been determined. Utilizing the crystal structure of SrtA∆59 we have initiated structure based inhibitor design studies. In our preliminary studies, we have identified low micromolar inhibitors of the enzyme by using virtual screening of commercial compound libraries against the SrtA∆59 active site and testing the activity of the inhibitors in vitro using a fluorescence resonance energy transfer (FRET) activity assay. Results of the SAR studies on our lead inhibitor will be presented.

MEDI 51

Nonconventional antibiotic strategies: Suppression of virulence via QseC antagonism

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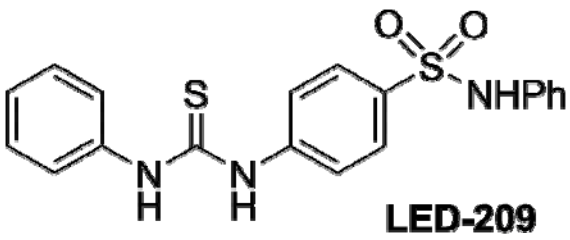
QseC is a conserved, membrane-embedded sensor histidine kinase present in at least 25 important human and plant pathogens. Activation of QseC by either autoinducer-3 (AI-3), a bacterial-derived quorum sensor, or by host adrenergic signals, initiates a complex regulatory cascade resulting in transcription of key bacterial virulence genes. We have identified a small molecule, LED209, which inhibits the binding of signals to QseC and consequently blocks QseC-mediated activation of virulence gene expression. LED209 is not toxic and markedly inhibits the virulence of several pathogens in vitro at 5 pM and in vivo at

20mg/kg. Unlike conventional antibiotics, LED209 does not directly influence bacterial growth and may obviate the development of bacterial resistance.



LED-209

MEDI 52

Improving the potency of novel membrane targeted antibiotics by solution phase combinatorial chemistry

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The enormous success of antibiotics is seriously threatened by the development of resistance to most of the drugs available on the market. Thus, novel antibiotics are needed that are less prone to bacterial resistance and directed toward novel biological targets. Recently, our lab discovered a novel set of compounds that are active against methicillin-resistant and vancomycin-resistant S. aureus. Microbial studies revealed that these agents displayed excellent kill kinetics with no observed regrowth. These novel compounds have mode of action similar to daptomycin, in that they target the membrane and cause disruption of the membrane potential of the bacteria. The potent compound has a MIC value of 0.5 mg/L against MRSA, which is comparable to vancomycin in-vitro. An in-vivo study revealed that our compound was able to cure mice with a MRSA infection when given at a dose of 50 mg/kg. SAR studies have revealed the tail as a critical region of the molecule, and as an important moderator of the activity. To improve the potency of these molecules, we have conducted a solution phase mixture synthesis using 20 different amines in the tail region. Preliminary evidence suggests that members of the library display greater potency than the parent compound. This poster will report on the details of these studies.

MEDI 53

MIF is a novel target for drug discovery in autoimmune and inflammatory diseases

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MIF is a potent pro-inflammatory cytokine implicated in the pathogenesis of numerous autoimmune and inflammatory diseases (e.g. sepsis and type 1 diabetes). X-ray crystallographic studies have shown that MIF crystal structure possesses a pocket at the interface between the adjacent subunits. Therefore, we reasoned that molecules that targeted this site could be useful to inhibit MIF actions. Indeed, ISO-1 was specifically designed to fit into the pocket of MIF, an interaction confirmed by the crystal structure of the MIF complex with ISO-1(1). Administration of ISO-1 improves survival during sepsis (2) and treat diabetes (3). ISO-1 is the first small molecule inhibitor of MIF with therapeutic implications and indicates the potential of the MIF pocket as a novel target for therapeutic interventions in human diseases. We will present our recent studies that generated new potent inhibitors with an IC50 of 100 nM, a 200-fold more potent than ISO-1(4, 5).

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MEDI 54

Discovery of highly selective matrix metalloproteinase-13 inhibitors for the treatment of osteoarthritis

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Osteoarthritis (OA) is a degenerative joint disease in which breakdown of the articular cartilage results in chronic joint pain and reduced physical function. Matrix metalloproteinase-13 (MMP-13), one of a family of zinc-dependent proteases, is responsible for the cleavage of type II collagen, the major structural protein in articular cartilage, and is found to be elevated in osteoarthritic joints. Therefore inhibition of MMP-13 may offer the promise of halting the progression of joint deterioration in OA. Broad-spectrum MMP inhibitors however have faced significant clinical development challenges. Our efforts have focused on the identification of highly selective MMP-13 inhibitors which bind though the S1' active site pocket and are not dependent on inhibitor binding to the catalytic zinc. Through high-throughput screening and scaffold-hopping strategies, lead optimization has provided a series of potent, highly selective (> 1,000 fold), and orally bioavailable MMP-13 inhibitors. A representative lead compound has demonstrated cartilage protection in preclinical animal models.

MEDI 55

Protective anti-inflammatory drugs containing NSAID esters with alkyl-aryl carbonate linkers

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A new pro-drug series based on bifunctional ester-carbonates of classic non-steroidal anti-inflammatory drugs (NSAIDs) has been shown to be effective topically in inhibition of inflammation following chemical challenge by either chloroethyl ethyl sulfide (CEES) or 12-O-tetradecanoylphorbol-13-acetate (TPA or phorbol ester). The compounds are unsymmetrical alkyl-aryl carbonates which have the dual property of inhibiting acetylcholinesterase and releasing naproxen, ibuprofen, indomethacin, or diclofenac upon hydrolysis. Four different synthetic approaches to the class were developed. Stability of the members of this drug family, their efficacy in blocking CEES or TPA edema, and structure-activity relationships in the class will be presented.

MEDI 56

Synthesis and study of anti-inflammatory D-series resolvins

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Several oxygenated metabolites of docosahexaenoic acid (DHA) and other omega-3 fatty acids were recently shown to exhibit potent anti-inflammatory and pro-resolution properties, that may help explain their long-known health benefits. These novel lipid mediators, termed resolvins, are formed via stereochemically defined enzymatic routes, and behave as endogenous regulators of the inflammatory response. Herein, we report the total synthesis and biological investigation of several D-series (DHA-derived)resolvins which were synthesized in a stereochemically pure form via a convergent approach.

MEDI 57

Kv1.3 blockers for treatment of autoimmune diseases

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The voltage-gated potassium channel Kv1.3 represents a promising target for the treatment of autoimmune diseases, e.g. multiple sclerosis, due to its dominant role in the proliferation of disease associated activated effector memory T-cells. Applying virtual high throughput screening (vHTS) based on docking procedures into homology models generated from the crystal structures of the bacterial KcsA and the mammalian Kv1.2 as well as on pharmacophore alignment on reference blockers of Kv1.3, four structurally significantly different classes of inhibitors have been identified and evaluated. These classes display submicromolar levels of affinity, including two lead classes with IC50 values on the Kv1.3 even down to 40 nM, EC50 values in a second-line assay down to 130 nM and good oral bioavailability.

MEDI 58

Discovery and synthesis of selective androgen receptor modulator MK-0773

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Androgens such as testosterone and dihydrotestosterone are therapeutically effective muscle anabolic agents, but their use is limited by their adverse effects, including the promotion of hirsutism in women and prostate growth in men. The selective androgen receptor modulator (SARM) MK-0773 has been developed to offer beneficial myoanabolic effects with a significantly reduced risk of adverse effects. The structure-activity relationships in the structural series containing MK-0773, as well as the synthetic approaches to the class, will be described.

MEDI 59

Cartilage biopolymers: Self-assembly and load-bearing properties.

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Chemically, cartilage is a highly nonuniform tissue. In the course of disease both tissue structure and composition change. The generally accepted concept is that cartilage derives its resistance to mechanical loading from a fibrous network mainly consisting of collagen type II, which is prestressed due to the osmotic swelling pressure exerted by negatively charged proteoglycan aggregates. Changes in the relative amounts of these components due to disease will change the macroscopic properties of cartilage. Previous findings indicate that osteoarthritic cartilage not only contains more water but also binds it with greater avidity. We intend to determine how the interactions of the major biochemical constituents of articular cartilage influence its osmotic and mechanical behavior. We combine osmotic swelling pressure measurements, elastic modulus measurements made by the AFM, and small-angle X-ray and neutron scattering measurements to investigate the structure of cartilage polymers and their assemblies over a broad range of length scales.

MEDI 60

2-Aminopyrimidine agonists of the Wnt beta-catenin cellular messaging system 1: Lead optimization studies toward the discovery of WAY-262611

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The Wnt beta-catenin cellular messaging system has been implicated in several biological processes such as cancer, neurodegeneration and bone homeostasis. Wnt beta-catenin deactivation at the cell surface occurs through binding of Dkk-1 to co-receptors Kremen-1/2 and LRP5/6. Certain LRP5 gain-of-function mutations in humans enable the receptor to recognize and bind to the natural agonist Wnt but not to the natural antagonist Dkk-1. The result is a high bone mass phenotype in humans suggesting potential efficacy in osteoporosis if the same phenotype could be observed through pharmacological regulation. To this end, a functional assay was devised where Wnt-3a and Dkk-1 were overexpressed in an osteosarcoma cell line (U2OS cells) with a TCF-response element luciferase reporter system and used for a high throughput screen of the corporate collection of small molecules. A weak agonist, with a 2-aminopyrimidine core structure, was discovered and served as a lead for optimization. Structure activity relationship and selectivity studies led to an optimized lead compound, WAY-262611, with low micromolar cellular activity that was devoid of kinase activity, an important factor for minimizing false positives due to inhibition of glycogen synthase kinase 3 (GSK3 alpha/beta) and other kinases.

MEDI 61

2-Aminopyrimidine agonists of the Wnt beta-catenin cellular messaging system 2: Additional lead optimization and in vivo studies on WAY-262611

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Targeting pharmacological activation of the Wnt beta-catenin cellular messaging system is a potential novel approach to achieving anabolic bone growth for the prevention of osteoporosis induced fractures. A small molecule with a 2-aminopyrimidine core structure, WAY-262611, was shown in the accompanying poster, via cell based functional assay, to be a selective agonist of this system and devoid of kinase inhibition (IC50 >> 10 micromolar in 28 kinase assays). Effects of the compound on bone formation rate in a mouse calvaria model using wild type mice as well as conditional Dkk-1 knockout mice will be shown. In addition, WAY-262611 was used as a template for further structure activity relationship studies in an attempt to find new molecules with more potent activity in the primary functional assay.

MEDI 62

Synthesis of potent and selective nonzinc binding matrix metalloproteinase-13 inhibitors

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Matrix metalloproteinase-13 (MMP-13) has been implicated in osteoarthritis (OA) because of its ability to irreversibly cleave type II collagen, the major structural protein in articular cartilage. Several broad-spectrum MMP inhibitors have undergone clinical studies, but they have encountered safety limitations for chronic administration. It is hypothesized that a highly selective MMP-13 inhibitor could suppress cartilage degradation and stop the progression of disease in OA patients while overcoming the safety hurdles observed with broad-spectrum agents. Our efforts have focused on the identification of highly selective MMP-13 inhibitors which bind through the S1' active site pocket and are not dependent on inhibitor binding to the catalytic zinc. The optimization of a novel chemical template to provided potent, highly selective (> 1,000 fold), and orally bioavailable MMP-13 inhibitors will be presented.

MEDI 63

Synthesis and biological evaluation of 2,4-diamino-6-(arylaminomethyl)pyrido[2,3-*d*]pyrimidines as inhibitors of *Pneumocystis jirovecii* and *Toxoplasma gondii* dihydrofolate reductase

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Opportunistic infections like *Pneumocystis* pneumonia and toxoplasmosis are a major cause of mortality in AIDS patients. Current therapies suffer from disadvantages of coadministered sulfonamides, side effects, high cost, variable effectiveness and lack of selectivity. In an attempt to develop single agents which are potent and selective against dihydrofolate reductase from *P. jirovecii* (pjDHFR) or *T. gondii* (tgDHFR), a series of 2,4-diamino-6-(arylaminomethyl)pyrido[2,3-*d*]pyrimidines were developed. Initial structure activity studies at the aryl side chain indicated that electron withdrawing groups were conducive for *P. carinii* DHFR (pcDHFR) activity and afforded up to 16-fold selectivity for pcDHFR over mammalian DHFR. The compounds were synthesized by reductive amination of the common intermediate 2,4-diamino-pyrido[2,3-*d*]pyrimidine-6-carbonitrile. A series of compounds with modifications in the aryl side chain was designed to further improve the selectivity and potency against pjDHFR and/or tgDHFR over mammalian DHFR. The design, synthesis and evaluation of these compounds will be presented in this report.

MEDI 64

Synthesis of classical 6-substituted pyrrolo[2,3-*d*]pyrimidines as GARFTase inhibitors with folate receptor (FR) specificity and antitumor activity

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Glycinamide ribonucleotide formyltransferase (GARFTase) is the first of two folate-dependent enzymes in the *de novo* purine biosynthetic pathway. Because of its role in *de novo* synthesis, it is recognized as a target for cancer chemotherapy. As part of a continuing effort in our laboratory to develop novel classical antifolates as GARFTase inhibitors and as antitumor agents, Gangjee et al. recently reported the potent GARFTase inhibitory activity of a series of classical 6-substituted pyrrolo[2,3-*d*]pyrimidine analogues with FR specificity. In the present series, we have synthesized the side chain furan analogues of our lead pyrrolo[2,3-*d*]pyrimidines. The synthesis and potent GARFTase, FR specific and antitumor activities of these analogues will be reported and discussed.

MEDI 65

The importance of the glutamate moiety for folate receptor targeting and GARFT ase inhibitory activity in classical pyrrolo[2,3-d]pyrimidine antifolates

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We have recently reported a series of pyrrolo[2,3-*d*]pyrimidine classical antifolates that are specifically taken up by the folate receptor (FR) and inhibit FR expressing tumor cells (KB and IGROV1) at nanomolar IC_{50} values. In addition, these analogs are not transported via the reduced folate carrier (RFC) into normal cells. Glycinamide ribonucleotide formyl transferase (GARFTase) was confirmed as the target. To further investigate the structural requirements of antifolates with respect to FR substrate activity, a series of analogs with variations in the glutamate moiety were designed and synthesized. The synthesis and FR substrate and antitumor activity of these analogs will be presented.

MEDI 66

Design, synthesis, evaluation of orally active small-molecule Smac mimetics as new anticancer drugs

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Smac/DIABLO is a protein released from mitochondria into the cytosol in response to apoptotic stimuli. Smac promotes apoptosis at least in part through antagonizing inhibitor of apoptosis proteins (IAPs), including XIAP, cIAP-1, and cIAP-2. Smac interacts with these IAPs via its N-terminal AVPI binding motif. There has been an enormous interest in academic laboratories and pharmaceutical companies in the design of small-molecule Smac mimetics as potential anticancer agents. This task is particularly challenging because it involves targeting protein-protein interactions. Herein, we report our design, synthesis and evaluation of a novel class of small-molecule Smac mimetics. Our most promising Smac mimetics bind to XIAP, cIAP-1 and cIAp-2 with low nanomolar affinities (Ki = 1-5 nM) and potently inhibit cell growth in a number of cancer cell lines. Furthermore, they achieve an excellent oral bioavailability and are highly effective in inhibition of tumor growth in xenografts models of human cancer. The design, synthesis, biochemical, biological and pharmacological evaluations of this class of novel Smac mimetics will be described.

MEDI 67

Design and synthesis of potent, specific and orally active small-molecule inhibitors of the MDM2-p53 interaction

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Reactivation of p53 through blocking the p53-MDM2 protein-protein interaction using small-molecule inhibitors is an attractive cancer therapeutic strategy. Recently, we have reported the discovery and design of spiro-oxindoles as a new class of potent, selective, non-peptide small-molecule inhibitors of the MDM2-p53 interaction. Herein, we describe our further optimization efforts, which yielded potent, specific and orally active small-molecule inhibitors of the MDM2-p53 interaction. Our most potent lead compounds have binding affinities 1000-times

more potent than the natural p53 peptide and are highly selective for blocking the MDM2-p53 interaction over other protein-protein interactions. They achieve oral bioavailability of 50% in animals and are highly effective in inhibition of tumor growth in xenograft models of human cancer with wild-type p53 and show no or little toxicity to animals. These compounds are promising leads for preclinical and clinical development as a new class of anticancer drugs.

MEDI 68

Synthesis and evaluation of a novel, potent and selective, orally bioavailable melanocortin-4 receptor antagonist for the treatment of cancer cachexia

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Cancer cachexia, a severe form of muscle wasting, is a consequence of a decrease of appetite and a loss of lean body mass as response to a chronic inflammation, which cannot be compensated by increased nutrient intake.

Currently no treatment is available for cachexia patients. Based on their recently demonstrated effects on feeding behavior and energy homeostasis in rodent models, Melanocortin-4 receptor (MC4-R) antagonists are perceived as a promising, novel approach for the treatment of cancer cachexia by increasing appetite and reducing energy expenditure.

We report on the discovery of a novel chemical series of potent and selective MC4-R antagonists. In vivo efficacy upon oral administration of the lead compound in animal models for food intake and cancer cachexia as well as pharmacokinetic data will be disclosed. The data presented here suggest further investigations on this novel class of MC4-R antagonists bear the potential to indentify a development candidate.

MEDI 69

The design, synthesis and biological evaluation of conformationally constrained Hsp90 inhibitors

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The 90 kDa class of heat shock proteins (Hsp90) has rapidly evolved into a target of great interest for chemotherapy against various cancers and neurodegenerative diseases. Recently, we disclosed chimeric analogues based on important hydrogen bonding interactions of two natural products, geldanamycin (GDA), and radicicol (RDC), with Hsp90. Recent studies have reported that the bent conformation in which Hsp90 binds ligands in the N-terminal nucleotide binding pocket produces an entropic barrier that must be surpassed for efficient binding. We have hypothesized that designing conformationally constrained analogues will minimize the entropic penalty upon binding and increase hydrogen bonding interactions, therefore increasing binding affinity to Hsp90. We have developed and tested a series of conformationally constrained cis-amide chimeric Hsp90 inhibitors and will report the syntheses and biological evaluation of these compounds.008-->

MEDI 70

Exploring binding of HDAC isoforms with inhibitors by photoaffinity probes

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Histone deacetylases (HDACs) are a family of enzymes that regulate chromatin remodeling and gene transcription. They consequently control critical cellular processes, including cell growth, cell cycle regulation, DNA repair, differentiation,

proliferation, and apoptosis. Since many cancers are associated with aberrant transcriptional activity, and the HDACs can affect transcription factors and gene regulation, these enzymes have been identified as attractive targets for cancer therapy. Here we propose a method to visualize the binding modes of the ligands in different HDAC isoforms by small molecule photoaffinity probes (PAPs). A PAP consists of an HDAC ligand, an aromatic azide group for photo-crosslinking with the protein, and an aliphatic azide group for attaching a tag for detection in vitro and in cells. In this study we 1) evaluate inhibitory activity of the PAPs against class I and II HDACs, 2) perform photoaffinity experiments with PAPs and HDAC3 and HDAC8 proteins in vitro, label the former with a biotin tag, and visualize the resulting adduct by Western blotting, 3） perform photoaffinity experiments in whole cells, label the PAPs with a fluorescent tag, and visualize the resulting adduct using confocal microscopy.

MEDI 71

Efficient synthesis of cruentaren A and preparation of analogs for the investigation of structure-activity relationships

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Cruentaren A, isolated from the myxobacterium byssovorax cruenta, is a salicylate containing macrolide and selective inhibitor of mitochondrial F1Fo-ATP synthase with no inhibitory activity at Na+/K+ or V-ATPases. Due to the subnanomolar cytotoxicity of this natural product against a variety of human cancer cell lines (e.g. IC50 values of 0.3 ng/mL in KB-3-1 and 0.6 ng/mL in K-562), cruentaren A represents a promising lead compound for further investigation for potential us as a cancer chemotherapeutic. Preliminary structure-activity relationships have been reported for cruentaren A, however, a route of total synthesis that allows for the development of new analogs for biological testing is desired. Toward this goal, a formal synthesis of cruentaren A has been accomplished utilizing Myers's pseudoephedrine chiral auxiliaries and an optimized propargylic Grignard addition. The synthetic strategy, results, and analogue preparation will be reported.

MEDI 72

Mechanistic studies on interaction of NiCR and NiCR-2H with DNA

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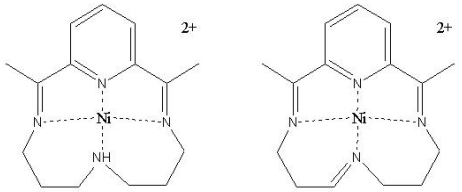
NiCR has been extensively investigated as a DNA damaging agent and nucleic acid probe for many years. A recent study suggests that NiCR-2H exhibits better cytotoxicity towards MCF7 human breast adenocarcinoma cells than NiCR in the absence of oxidants despite the fact that they possess ‘similar' structures. However, the mechanism behind these observed results remains unclear. Here we report the systematic investigation on the interaction of NiCR and NiCR-2H with DNA and the antiproliferative activity against cancer cell lines other than MCF7. Our spectrometric and NMR results show that there is production of NiCR-2H from the oxidation of NiCR in the presence of lower molar ratios of oxidant (oxone). NiCR-2H has much better H/D exchange rate on the methyl groups than NiCR. Both ligands most likely coordinate at N7-position of 5'-dGMP and are groove binders. These observations suggest that NiCR-2H may be an important intermediate in the DNA cleavage mechanism of NiCR.



MEDI 73

Targeting the TNF-alpha/TNFR interaction with small molecule mimetics

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Abnormal production of tumor necrosis factor-alpha (TNF-alpha) has been implicated in autoimmune disorders, including Crohn's disease which causes inflammation of the gastrointestinal tract. Current therapies of Crohn's disease have limited efficacy and more efficient, drug-like therapeutics are needed. The binding event of TNF-alpha with its 55 kd receptor (TNF-R55) is a part of a signal cascade that leads to inflammation. The crystal structure of a closely related cytokine, TNF-alpha bound to the extracellular, soluble domain of TNF-R55 (sTNF-R55) has been used to create a homology model of the TNF-alpha/sTNF-R55 interaction. The design and synthesis of small molecule mimetics of TNF-R55 as potential TNF-apha/TNF-R55 interaction inhibitors will be presented.

MEDI 74

Synthesis and biological evaluation of novel estradiol-platinum(II) hybrid molecules designed for site-specific treatment of female cancers

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Chemotherapy is an effective treatment for several types of cancer. However, the toxic side effects limit its full potential for a cure. The development of site-specific anticancer therapy is a subject of intense research. Several strategies can be used to target cancer cells. For instance, the use of a carrier molecule being able to recognize a specific receptor in the cell is a tactic of choice used by several researchers. We have developed estradiol-platinum(II) (E2-Pt(II)) hybrid molecules in order to target the estrogen receptor (ER).

The hybrids were synthesized in 8 chemical steps with 21% overall yield. All hybrids present high affinity for the ERs. MTT assays revealed that the hybrids decreased the viability of cancer cells more efficiently than cisplatin itself in vitro. The most promising hybrid derivative possesses enhanced anticancer activity compared to cisplatin and is able to specifically target hormone-dependent tumors in an in vivo xenografts model.

MEDI 75

Investigation of new neo-tanshinlactone analogs as potent and selective anti breast cancer clinical trials candidates

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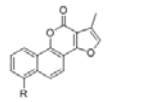
Neo-tanshinlactone (1) is a potent and selective in vitro anti-breast cancer agent. To explore structure-activity relationships of 1 and develop new lead compounds, novel analogs with various substituents and different skeletons were synthesized and evaluated for in vitro activity against a human tumor cell line panel. Several compounds showed potent and selective cytotoxic activity against breast cancer cell lines. In particular, analogs 2 and 3 demonstrated potent cytotoxicity against ZR-75-1 (IC50 = 0.2 and 0.3 μg/mL, respectively). Moreover, these two compounds displayed unique selectivity, with 12-fold greater activity against SK-BR-3 than MCF-7 and 10-fold greater activity against ZR-75-1 than SK-BR-3, respectively. The synthesis, anti-breast cancer activities and SAR exploration of 1-analogs will be presented. (Supported by NIH grant CA 17625 awarded to K. H. Lee)



1: R = Me, Neo-tanshinlactone
2: R = Pr
3: R = /Pr

MEDI 76

Synthesis, tubulin polymerization assays and cytotoxicity of D-seco paclitaxel analogs

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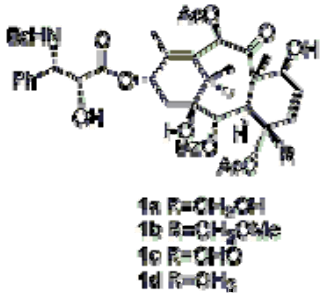
Synthesis, Tubulin Polymerization Assays and Cytotoxicity of D-seco Paclitaxel Analogs

It has been quite long that people think the oxygen atom in oxetane D-ring is crucial to the binding of paclitaxel to its main target microtubule, as well as its potent cytotoxicity. However, it was recently found that some D-seco paclitaxel analogs exhibited tubulin polymerization promotion ability comparable to that of paclitaxel, but lacked cytotoxicity against tumor cells¡£ We¡¯re interested to understand the structural factors controlling the differentiation between tubulin pertubuation ability and cytotoxicity, so we design and synthesize D-seco paclitaxel analogs **1a-d**. Initial efforts for the multistep synthesis of **1** starting from 10-deacetyl baccatin III failed. Instead, starting from paclitaxel, we were able to prepare D-seco paclitaxel analogs successfully. All these analogs are currently under biological evaluations.



1a R=CH_2OH
1b R=CH_2OMe
1c R=CHO
1d R=CH_2

MEDI 77

Discovery of CYT997, a potent vascular disrupting agent and inhibitor of tubulin polymerization

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Microtubules play an essential role in cell division, intracellular transport and cellular motility. Disruption of the assembly or collapse of the microtubular network is a well validated mechanism of action for a number of clinically important classes of anti-cancer drugs including the taxanes and the vinca alkaloids.

CYT997 was optimized from a lead obtained from a large-scale cell-based screen for small molecule antiproliferative agents. CYT997 is an orally active small molecule inhibitor of tubulin polymerization, is active (low nM) against a large panel of cancer cell lines, and shows potent antitumor efficacy in xenograft models.

Importantly, CYT997 is not a substrate for the multi-drug resistance efflux pump Pgp and also possesses potent vascular disrupting activity in vivo at doses well below its MTD. CYT997 is currently in Phase I/II clinical trials. This poster will describe the SAR of the series of compounds that led to the discovery of CYT997 and biological data obtained in support of its selection for development.

MEDI 78

Green tea polyphenols block the anticancer effects of boronic acid-based proteasome inhibitors

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The anticancer effects of green tea and its constituent polyphenol natural products, such as epigallocatechin gallate (EGCG), have been the subject of several investigations, while green tea and EGCG are often recommended as healthy supplements. However, we report herein that combining green tea polyphenols with certain chemotherapy agents can effectively block their actions with potential adverse effects on cancer treatment. In particular, we have found that polyphenols such as EGCG effectively inactivate boronic acid-based proteasome inhibitors, such as Bortezomib (Velcade®) a first in class agent approved for the treatment multiple myeloma. Herein, we will present the experimental evidence for this type of inactivation, and provide a rationale for its molecular basis which is supported by structural and spectroscopic studies.

MEDI 79

Discovery of 1-benzoyl-3-cyanopyrrolo[1,2-*a*]quinolines as a new series of apoptosis inducers using a cell- and caspased-based high-throughput screening assay: Structure-activity relationships of the 4-, 5-, 6-, 7-, and 8-positions

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We recently reported the discovery of 1-benzoyl-3-cyanopyrrolo[1,2-*a*]quinoline (**1a**) as a potent apoptosis inducer using our Anti-cancer Screening Apoptosis Program (ASAP), and the SAR of the 1- and 3-positions (Kemnitzer, W. *et al. Bioorg. Med. Chem. Lett.* **2008,** In press). These compounds were found to be active in the caspase activation assay and the cell growth inhibition assay with low nanomolar EC_{50} and GI_{50} values in T47D, HCT116 and SNU398 cells. In this presentation, we will describe the SAR and the chemistry of the 4-, 5-, 6-, 7-, and 8-positions of 1-benzoyl-3-cyanopyrrolo[1,2-*a*]quinolines.

MEDI 80

Synthesis and evaluation of γ-lactam derived small molecules as anticancer agents

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β-Hydroxy-γ-carboxy-γ-lactams and fused bicyclic γ-lactam-β-lactones are extremely important pharmacophores found in several biologically active natural products such as lactacystin, omuralide, salinosporamide, cinnabaramides etc. We have recently developed a simple protocol for the synthesis of functionalized γ-carboxy-γ-lactam molecules via tandem Baylis-Hillman reaction - Schiff base alkylation chemistry. We have extended this methodology for the efficient and short synthesis of several β-hydroxy-γ-carboxy-γ-lactams and fused bicyclic γ-lactam-β-lactones via allylic hydroxylation and dihydroxylation procedures. All the synthesized molecules have been evaluated for their anti-cancer activity on multiple myeloma (RPMI 8226) cancer cell lines. The synthesis and biological evaluation of these molecules as potential anticancer agents will be presented.

MEDI 81

Discovery of novel angiogenesis inhibitors using transgenic zebrafish as a high-throughput phenotypic screening model

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Angiogenesis plays a significant role in tumor progression and metastasis of the great majority of human solid tumors. In previous work, we described compound library screening and identification of indirubin-3'-monoxime (IRO) as a novel and potent antiangiogenic agent utilizing an automated, quantitative *in vivo* zebrafish assay developed in collaboration with Zygogen, LLC. For further investigation of IRO, a small focused library was constructed by chemical modification and a ligand-based substructure search around the IRO structure. These small focused libraries were screened in the *in vivo* transgenic zebrafish assay to identify two novel compounds, 7-methylindirubin-3'-oxime and 2,4,7-trichloro-9-fluorenone oxime. Both exhibit significant antiangiogenic activity in zebrafish embryos. Each of the two classes of compounds shows dose-dependent antiangiogenic activity with submicromolar IC_{50} values in zebrafish. Further biological activity for novel

indirubins and fluoren-9-one oximes derived from a human endothelial cell-based angiogenesis assay will be presented.

MEDI 82

Investigation of indoloazepine as an adjuvant drug for cancer through chemoprotection

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Cancer cells are often treated with radiation therapy involving the use of high energy x-rays. The induction of DNA damage is used to induce cell death for cancerous cells, however, healthy cells are more sensitive to DNA damage than the cancerous cells. As a result, the healthy tissue damage that occurs during the ionizing radiation (IR) treatment is often the limiting factor of the therapy. It is possible to minimize healthy tissue damage caused by chemotherapeutics and IR by inhibiting checkpoint kinases, such as checkpoint kinase 2, with inhibitors. Chk2 responds to DNA damage and is activated in the presence of double strand breaks (DSBs) and other forms of DNA damage which can be caused by IR. Upon activation, Chk2 is thought to activate p53, a tumor suppressing protein, and cause inhibition of cell growth allowing for cellular repair. Since p53 is mutated in 50% of all cancers, it can be hypothesized that an indirect abrogation of this pathway, through Chk2 inhibition, would give healthy cells a chance to repair the damage caused by radiation and lessen the harmful effects of therapy. Although there are few known potent Chk2 inhibitors, one that shows promise in being able to provide chemoprotection following IR is indoloazepine.

MEDI 83

Structure activity relationship of dual acting histone deacetylase-topoisomerase II inhibitors

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Several preclinical reports have shown that HDAC inhibitors (HDACi) act synergistically with topoisomerase II (topoII) inhibitor such as anthracyclines to enhance apoptosis. The HDACi-induced structural changes of chromatin may render the DNA more accessible and HDACi may therefore be used to potentiate DNA damaging agents such as topo II inhibitors. However such combination therapies are often sequence and dose dependent, complicated by inherent pharmacokinetic disadvantages of individual drugs. Therefore development of single molecule containing “combination therapy” potential will harness the positive attributes of multiple drug therapy while eliminating or minimizing its shortcomings. At this front, we previously reported dual topoII-HDAC inhibitors. Here, we report in vitro HDAC inhibition, topoII inhibition, and whole cell activity data which verify complementary nature of topoII-HDAC inhibitors. Flow cytometry experiments indicate that these agents act across various stages of cancer thereby targeting larger population of cells. The SAR studies of these inhibitors will be presented.

MEDI 84

Synthesis and evaluation of ether-linked dimers of epipodophyllotoxin

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Numerous analogs of epi-podophyllotoxin, bearing amine and ether substituents at C4 have been reported. Several of these semi-synthetic drugs derived from podophyllotoxin, including etoposide and teniposide, are used clinically in cancer therapy.

The mechanism of these analogs involves an increase in topoisomerase II-mediated DNA breaks, and inhibition of topoisomerase II's ability to ligate the cleaved DNA. Activity depends on one molecule of etoposide binding on each strand of DNA, requiring two drugs per event. Evidence suggests that the two drugs act independently of each other. One implication for drug design, is that linked dimers of epi-podophyllotoxin analogs may have increased activity over the monomers.

Although many C4 substituted epi-podophyllotoxins have been reported, there are few reports of dimers. The syntheses and evaluation of several ether and amine-linked dimers are reported here; including assays for topoisomerase II binding and DNA adduct formation. These covalently linked analogs of epi-podophyllotoxin should provide further insight into the two-drug model and potentially provide novel antitumor agents.

MEDI 85

Design, synthesis, and biological evaluation of indole-derived mitotic spindle poisons based on colchicine

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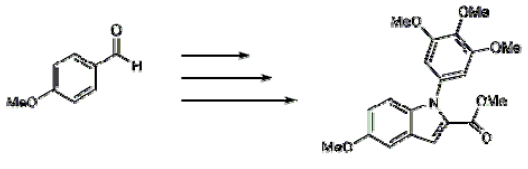
Colchicine, a natural product found in the autumn crocus plant and a very old FDA approved drug for the treatment of gout, is the first mitotic spindle poison discovered. Its high cyto-toxicity, however, hampers its use as a therapeutic agent for cancer. Chemical agents, that have a strong binding affinity for tubulin and induce cell-cycle arrest, have a tremendous potential in the area of cancer research and are being pursued fervently by researchers in the field. Aryl derivatives of indole are known to have a highly desirable profile in exhibiting anti-mitotic properties. Our efforts are focused on synthesizing a small library of these N-arylated indole derivatives and evaluating their activities against a variety of cancer cell lines. The synthetic scheme will utilize 3 to 4 steps of high yielding reactions thus furnishing the target compounds with high efficiency. The parent indole derivative prepared thus far has shown to mimic the bio-activity of colchicine in inducing cellular necrosis.



Target Compound

MEDI 86

Discovery and optimization of a selective inhibitor of oncogenic B-Raf

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B-Raf is an important protein kinase that mediates growth factor and cytokine signaling in driving proliferation and preventing apoptosis. The discovery of oncogenic B-Raf mutations in a majority of patients with metastatic melanoma, and in many tumors from patients with colorectal cancer and other cancers, presents the opportunity to develop oncogene-selective inhibitors with a favorable safety profile. By using a structure-guided approach, we have designed a family of kinase inhibitors that are selective for the V600E oncogenic B-Raf allele over wild type B-Raf. These compounds show a marked selectivity for B-RafV600E verses wild-type in both biochemical and cellular assays. In melanoma models, cell cycle arrest and apoptosis is observed exclusively in B-RafV600E-positive cells. In B-Raf V600E-dependent tumor xenograft models, oral dosing causes significant tumor growth delays, including tumor regressions, without evidence of toxicity. PLX4032, a member of this class of B-RafV600E selective inhibitors, is currently in Phase I clinical trials.

MEDI 87

Targeted photodynamic therapy of cancer using novel photosensitizer derivatives based on pyropheophorbide-a (PPa)

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Potent and effective photosensitizers in combination with visible light can destroy tumors by photodynamic therapy, a process which has many advantages over conventional treatments. However, slow blood clearance, lack of selective targeting and poor delivery has stifled the advance of PDT.

PPa, a chlorophyll derivative has been chemically modified to improve its aqueous solubility, hydrophobic aggregation and undesirable non-covalent binding to biomolecules. These modifications include the addition of a conjugation site for covalent coupling onto lysine side chains of antibody fragments. The resulting photo-immunoconjugates can target tumor cells selectively and upon PDT bring about cell death with high efficacy.

We report on the synthesis and characterization of these PPa derivatives and the resulting anti-tumor immuno-conjugates including tumor targeting in a murine human tumor xenograft model of cancer.

MEDI 88

Discovery of pf-4217903-a highly potent and exquisitely selective c-met inhibitor

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c-Met/HGF signaling plays an important role in human oncogenesis and tumor progression, and is thus an attractive target for oncology therapeutics. 6-[1,2,3]Triazolo[4,5-b]pyrazin-1-ylmethyl-quinolines have been identified as a class of potent and exquisitely selective c-Met inhibitors at Pfizer. To improve PK properties along with potency, an extensive lead optimization program was conducted. Due to a disconnection between in vitro metabolic stability and in vivo rat clearance, an appropriate logD range was discovered to obtain good in vivo PK properties. The result of this investigation lead to PF-4217903, 2-[4-(3-quinolin-6-ylmethyl-3H-[1,2,3]triazolo[4,5-b]pyrazin-5-yl)-pyrazol-1-yl]-ethanol, was discovered as a highly potent and exquisitely selective c-Met inhibitor with good PK properties. PF-4217903 demonstrated over 1000-fold selectivity against a diverse array of >150 different tyrosine and serine-threonine kinases.

MEDI 89

Synthesis of c-glycoside of tumor antigen Tn

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Tumor cells usually have abnormally amount of certain oligosaccharides that not found, not much less in health cells, making it an ideal component for anti-cancer vaccine. Tn is tumor-associated carbohydrate antigens. Reports of the glycoconjugate of Tn and carrier protein KLH (Tn-KLH) can induce high median IgM and IgG titers against Tn, when used to vaccinate mice. However, this O-linked glycoconjugate of Tn and carrier protein is very labile to chemical and enzymatic hydrolysis in vitro, and by neuramidase in vivo, therefore hindered it potential use in cancer treatment. Our strategy was to replace the O-linked motif to C-linked motif to improve the stability and “foreigness”. The key step of our synthesis was the construction of (S)-alpha amino acid linked to glucosamine

through the utilization of asymmetric Strecker reaction. The determination of the absolute stereochemistry of the chiral center is also discussed.

MEDI 90

Discovery and in vivo efficacy of a novel, selective, and orally bioavailable Melanocortin-4 receptor antagonist for the treatment of cancer cachexia

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Cancer cachexia represents a complex syndrome caused by an interaction between tumor and host. It includes several major metabolic abnormalities and maladaptations: Energy intake is reduced, resting energy expenditure is increased and catabolism is accelerated. Despite high medical need, no effective treatments are available.

Melanocortin-4 receptor (MC4-R) antagonists are among the most promising drug candidates for the treatment of cachexia.

We will present our efforts in the design, synthesis, and in vivo evaluation of a novel MC4-R selective antagonist lead for the treatment of cancer cachexia. The non-peptide small molecule is orally bioavailable and penetrates the blood brain barrier. In healthy mice, the compound increases food intake upon oral administration. In a 2-week study with mice implanted with C26 adenocarcinoma, once daily oral dosing significantly inhibited the development of cachexia.

The data presented here suggest that this class of novel MC4-R antagonists bears the potential to deliver a development candidate.

MEDI 91

Enhancing the antitumor activity of antibody-maytansinoid conjugates with hydrophilic linkers

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Antibody-maytansinoid conjugates are anticancer agents composed of highly cytotoxic maytansinoids, a tumor-targeting monoclonal antibody and a linker that stably connects the two. Thiol-bearing maytansinoids can be covalently linked via either a reducible disulfide bond, or a non-reducible thioether bond. Linkers bearing hydrophilic moieties have been developed that enable a higher concentration of the cell-killing maytansinoid to be delivered to the target cell resulting in improved anti-tumor activity of the conjugates in human tumor xenografts models. Conjugates bearing these hydrophilic linkers also showed superior activity compared to traditional linkers against multi-drug resistant cancer cell lines in vitro and tumor models in vivo derived from these cell lines. The design and synthesis of these linkers and the biological evaluation of antibody-maytansinoid conjugates bearing these linkers will be presented.

MEDI 92

Photodynamic therapy for prostate cancer

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Photodynamic therapy (PDT) has emerged as a noninvasive regimen for cancers treatment which is based on the generation of reactive oxygen species (ROS) formed by light activation of a photosensitizer (PS). PS for PDT are often fluorescent dyes, such as porphyrinic pigments. This key cytotoxic species generate singlet oxygen upon photoirradiation and cause localized oxidative cell damage and death. We have focused our efforts on developing an agent to target delivering the PS of prostate cancer cells for PDT applications. Specifically, we have designed chemical agents that bind to the cell surface prostate cancer biomarker, prostate-specific membrane antigen (PSMA). Recently, our group demonstrated that phosphoramidate peptidomimetic PSMA inhibitors are capable of both cell-surface labeling of prostate cancer cells and intracellular delivery. We have now developed a “photodrug” which consists of a PS linked to peptidomimetic inhibitors of PSMA. In this presentation, we described the synthesis of high affinity, small-molecule inhibitors of PSMA outfitted with a porphyrinic pigment, and demonstrated their capability to selectively kill prostate cancer cells in vitro.

MEDI 93

Synthesis of 2-methyl-4-oxo-benzo[4,5]thieno[2,3-*d*]pyrimidines as TS inhibitor

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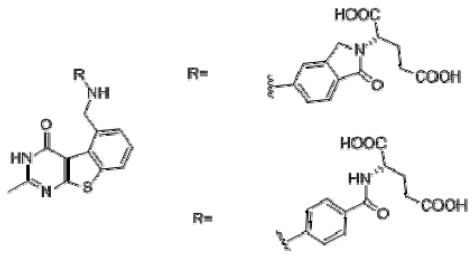
The only de novo pathway for the synthesis of dTMP is catalyzed by thymidylate synthase (TS) via the reductive methylation of dUMP to dTMP. Inhibition of TS has long been targeted as a useful mechanism for cancer chemotherapy, due to its crucial role in dTMP and DNA synthesis. Tricyclic TS inhibitor, OSI 7904 is a potent noncompetitive TS inhibitor that also inhibits the translation of TS mRNA to TS enzyme. In an effort to further explore the SAR of tricyclic TS inhibitors, we designed some additional tricyclic analogs with the 2-methyl-4-oxo-benzo[4,5]thieno[2,3-*d*]pyrimidine scaffold. Molecular modeling using human TS crystal structures suggested that the benzene ring in the molecular has hydrophobic interaction with Trp109, which should afford potent inhibition of human TS. The synthesis and biological activities of the target compounds will be reported and discussed.



MEDI 94

Design, synthesis and biological evaluation of 2-desamino-4-alkyl-5-[(substituted phenyl) ethyl]-7-substituted pyrrolo[2,3-d]pyrimidines as antitumor antimitoic agents

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Microtubules are cytoskeletal protein polymers and they play a crucial role in many biological processes, including mitosis and cell division, and have been a

target for the development of a number of new anticancer drugs. We recently published a series of 7-benzyl-4-methyl-5-[(2-substituted phenyl)ethyl]-7*H*-pyrrolo[2,3-*d*]-pyrimidin-2-amines that demonstrated potent antimitotic and antitumor activities against antimitotic-sensitive as well as resistant tumor cells. Here, we report the design and synthesis of a series of 2-desamino-4-alkyl-5-[(substituted phenyl) ethyl-7-substituted pyrrolo [2, 3-*d*]pyrimidines as potential antimitoic agents to optimize our parent compounds and to add to the SAR. The synthesis for the 4-chloro-5-iodo-7-substituted pyrrolo[2,3-*d*]pyrimidine involved common intermediates that were coupled with appropriate acetylene synthons at the 5-position (Sonogashira coupling) and methyl/ethyl synthons at the 4-position (palladium catalyzed cross-coupling). This was followed by a reduction of the triple bond to obtain the target compounds. This report will present the design, synthesis and evaluation of the title compounds.

MEDI 95

Classical and nonclassical 2-amino-4-oxo-5-arylthio-substituted-6-isopropyl thieno[2,3-*d*]pyrimidine antifolates as potent thymidylate synthase inhibitors

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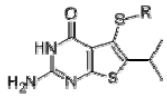
The only de novo pathway for the synthesis of dTMP is catalyzed by thymidylate synthase (TS) via the reductive methylation of dUMP to dTMP. Inhibition of human TS has long been considered as a useful mechanism for cancer chemotherapy. Gangjee et al. recently discovered the potent TS inhibitory activity of a series of 2-amino-4-oxo-5-arylthio-substituted-6-methylthieno[2,3-*d*]pyrimidine analogues. In the present series, we have designed and synthesized classical and nonclassical 6-isopropyl substituted thieno[2,3-*d*]pyrimidines as homologues of our previous compounds. The synthesis and biological activities against TS of these analogs will be reported and discussed.



R = 4-C_6H_4-CO-L-Glu
R = Ph
R = 4-NO_2-Ph
R = 3,4-di-Cl-Ph
R = 1-Naphthyl
R = 2-Naphthyl
R = 4-F-Ph
R = 4-OMe-Ph
R = 4-Cl-Ph
R = 4-Br-Ph

MEDI 96

The stereospecific interactions of 3-deoxy-PI derivatives with the PTEN phosphatase domain

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The PTEN gene is a tumor suppressor known to play important roles in controlling the processes of embryonic development, cell migration and apoptosis, and as such is an important target for cancer therapy. Although recently biochemical studies show significant variability in activity among a class of PTEN inhibitors based on the 1D-3-deoxy-phosphatidylinositol and its derivatives, the detailed protein-ligand interactions and the catalytic mechanism has not been well studied. In this work, docking calculations and molecular dynamics simulations were used to explore the interactions of six of the above inhibitors with the PTEN protein and reveal the likely binding modes and their relationship to the observed activities. We characterized the structures of the PTEN-ligand complexes by analyzing the interaction energies and also computed the relative binding free energies within the MM-GBSA approximation to qualify inhibitor activity.

MEDI 97

Synthesis and structure activity relationship of D-homo cyclopamine analogs: A-ring fused heterocyclic analogs

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Aberrant Hedgehog signaling pathway has been implicated in several types of cancer. Cyclopamine, a plant *Veratrum* alkaloid natural product, is an antagonist of the Hedgehog pathway and has shown promising anticancer activity. A 7-membered D-ring semi-synthetic analog of cyclopamine, IPI-269609, was shown to have greater acid stability and better aqueous solubility relative to cyclopamine while also having equivalent biological activity in the Hedgehog pathway. Efforts to improve the biological activity and properties of this novel D-homo cyclopamine scaffold utilized the 3-ketone as a handle for synthetic manipulations. These efforts resulted in the discovery of novel A-ring fused heterocyclic analogs with a 10 fold improvement in biological activity relative to

cyclopamine. The synthetic transformations that resulted in this potent series as well as the structure activity relationship of the products will be reported.

MEDI 98

Synthesis and structure activity relationship of D-homo cyclopamine Hedgehog antagonists: 7-Membered A-ring lactam analogs

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Recent evidence suggests that blocking aberrant Hedgehog pathway signaling may be a potential therapeutic strategy for the treatment of several types of cancer. Cyclopamine, a plant *Veratrum* alkaloid natural product, is an antagonist of the Hedgehog pathway and was used as a starting point for the development of improved Hedgehog pathway antagonists. A 7-membered D-ring semi-synthetic analog of cyclopamine, IPI-269609, was shown to have greater acid stability and better aqueous solubility relative to cyclopamine while also having equivalent biological activity in the Hedgehog pathway. Further synthetic manipulations of the A-ring provided a novel series of analogs that potently inhibit the hedgehog pathway. Synthetic transformations of the A-ring into various lactams resulted in the discovery of novel 7-membered ring lactam analogs with a 10 fold improvement in biological activity relative to cyclopamine. The synthetic transformations that resulted in this potent series as well as the structure activity relationship of the products will be reported.

MEDI 99

Synthesis and structure activity relationship of D-homo cyclopamine analogs: 3-Substituted analogs

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There is increasing evidence suggesting that blocking aberrant Hedgehog pathway signaling can be a very promising and novel therapeutic avenue for the treatment of cancer. Cyclopamine, a plant *Veratrum* alkaloid natural product, is an antagonist of the Hedgehog pathway and was used as a starting point for the development of new Hedgehog pathway antagonists. A 7-membered D-ring semi-synthetic analog of cyclopamine, IPI-269609, was previously shown to have greater acid stability and better aqueous solubility relative to cyclopamine. The stereoselective reduction of the enone of IPI-269609 to the cis-decalone provides analogs with a 10-fold increase in potency relative to cyclopamine. Further synthetic manipulations of the resulting 3-ketone provided a novel series of analogs that potently inhibit the Hedgehog pathway. Synthetic transformations of the 3-ketone as well as the structure activity relationship of the products will be reported. This work resulted in the discovery of IPI-926, a systemic Hedgehog antagonist currently under clinical evaluation.

MEDI 100

Discovery of piperidine-4-carboxamides as potent chemokine receptor CCR2b antagonists, Part II: Reduction of hERG ion channel affinity and CYP450 liability

***Pradyumna Mohanty**, pmohanty@epixpharma.com, Steffi Koerner, Rosa Melendez, Jian Lin, jlin@epixpharma.com, Dongli Chen, Merav Fichman, Efrat Ben-Zeev, Dilara McCauley, Andrew Kolodziej, Christine Kitsos, Vincent Jacques, Qing Deng, Biplab Das, Sharon Shacham, Simon Jones, Shomir Ghosh, and Sheila Dewitt, EPIX Pharmaceuticals, 4 Maguire road, Lexington, MA 02421, Fax: 781-761-7632*

Poster abstract for 237th ACS National Meeting & Exposition March 22-26, 2009, Medicinal Chemistry Division

Presenter: Pradyumna Mohanty

Discovery of piperidine-4-carboxamides as potent chemokine receptor CCR2b antagonists. Part II: reduction of hERG ion channel affinity and CYP450 liability

Pradyumna Mohanty; Steffi Koerner; Rosa Melendez; Jian Lin; Dongli Chen; Merav Fichman; Efrat Ben-Zeev; Dilara McCauley; Andrew Kolodziej; Christine Kitsos; Vincent Jacques; Qing Deng; Biplab Das; Sharon Shacham; Simon Jones; Shomir Ghosh; Sheila Dewitt.

EPIX Pharmaceuticals, Inc.

4 Maguire Road, Lexington, MA 02421

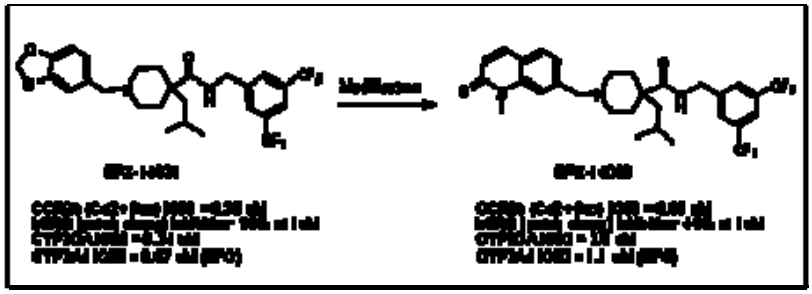
Abstract

A series of piperidine-4-carboxamide derivatives were discovered as potent antagonists of CCR2b. However, CYP inhibition and poor selectivity against hERG channel were observed as liabilities for early analogues in this series. Replacement of the 4-hydroxy-3-methoxy phenyl or 3,4-methylenedioxy phenyl moiety in the R3 subunit played an important role in improving selectivity. We will discuss key SAR findings that allowed for separation of CCR2 antagonist activity from undesirable hERG ion channel interactions while reducing CYP inhibition and retaining potency.

The outline of this poster:

1. A brief introduction of problematic issues of hERG from biological point of views
2. hERG and CYPs liability issues of EPX-14031 and 14047
3. Rational design of compounds to address the issues (Phenol isosteres)
4. Chemistry (synthetic scheme)
5. SAR discussion.
6. Conclusion

Only disclose the structures of 6-membered core



MEDI 101

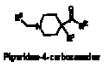
Discovery of piperidine-4-carboxamides as potent chemokine receptor CCR2b antagonists, Part I: Structure-based design and structure-activity relationship studies

Jian Lin*, jlin@epixpharma.com, Rosa Melendez, Pradyumna Mohanty, pmohanty@epixpharma.com, Steffi Koerner, Merav Fichman, Efrat Ben-Zeev, Dilara McCauley, Andrew Kolodziej, Christine Kitsos, Vincent Jacques, Qing Deng, Dongli Chen, Biplab Das, Sharon Shacham, Simon Jones, and Yael*

Marantz, EPIX Pharmaceuticals, Inc, 4 Maguire Road, Lexington, MA 02421, Fax: 781-761-7632

Abstract

We describe the structure-based design, synthesis, and biological evaluation of a new series of piperidine-4-carboxamide derivatives as CCR2b antagonists. SAR studies in the hit to lead phase on Compound **1** led to the discovery of several potent CCR2b antagonists. Compound **2** displayed potent functional activity in a calcium mobilization assay with an IC_{50} of 82 nM. It also inhibited MCP-1 induced human monocyte chemotaxis (IC_{50} = 490 nM). ADME and selectivity profiling of representative compounds will also be discussed.



Piperidine-4-carboxamide

MEDI 102

Efficient syntheses of 8-substituted xanthine adenosine receptor antagonists

*Dong Ma[1], ma.d@neu.edu, Graham B. Jones[1], and **Amy E Kallmerten**[2], kallmerten.a@neu.edu. (1) Department of Chemistry and Chemical Biology, Northeastern University, Boston, MA 02115, (2) Department of Chemistry & Chemical Biology, Northeastern University, 360 Huntington Ave. 102HT, Boston, MA 02115, Fax: 617-373-8795*

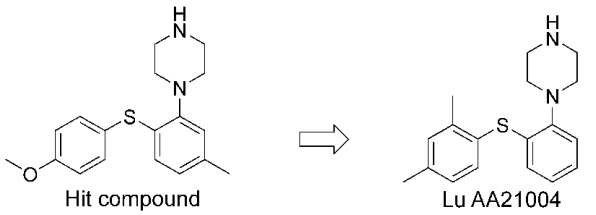
A2A Adenosine receptor antagonists have become major targets in CNS drug discovery due to pathway interactions between A2A and D2 dopamine receptors. A number of lead compounds have emerged based on the xanthine skeleton, including the chlorostyryl caffeine CSC, the thienylated xanthine DMPTX, and the dimethoxystyryl xanthine KW-6002. The latter, now referred to as istradefylline, is a clinical candidate for Parkinson's disease based on promising results obtained with co-administration of levodopa. In this presentation a new one-pot route to 8-substituted xanthines from 5,6-diaminouracils and carboxaldehydes will be presented. The process, promoted by (bromodimethyl)sulfonium bromide, is mild and efficient and eliminates the need for external oxidants. Preparation of a new analog of the antagonist KW-6002 is presented, and in situ bromination of aryl substituted products demonstrated. Synthesis of analogues featuring built in functionality for facile radiolabeling for positron emission tomography and single photon emission computed tomography will be detailed.

MEDI 103

Discovery of Lu AA21004: A novel compound for the treatment of mood disorders

Benny Bang-Andersen*, ban@lundbeck.com, Thomas Ruhland, Garrick Smith, Morten Jørgensen, Berith Bjørnholm, Kim Andersen, Ejner K. Moltzen, Arne Mørk, Lise T. Brennum, Klaus G. Jensen, Tine B. Stensbøl, and Sandra Hogg, Lundbeck Research Denmark, H. Lundbeck A/S, 9 Ottiliavej, DK-2500 Copenhagen-Valby, Denmark*

Significant unmet needs in the treatment of depression and anxiety remain, despite the existence of several treatment options, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs). It is known that the therapeutic effect of an SSRI can be augmented by compounds with other mechanisms of action, particularly compounds that interact with serotonin (5-HT) receptor subtypes. We report the structure-activity relationship for a series of phenylsulfanyl amines, leading to the discovery of Lu AA21004, a novel 5-HT(3) receptor antagonist, 5-HT(1A) receptor agonist, and 5-HT enhancer. The administration of Lu AA21004 to rats leads to enhanced levels of brain 5-HT as compared to SSRIs. Lu AA21004 is currently undergoing clinical phase III evaluation for the treatment of patients with mood disorders.



MEDI 104

Conformationally restricted tryptamine sulfonamides as novel and selective 5-HT6 receptor antagonists

Jagadishbabu Konda*, kjagadish@suven.com, Rama Sastry Kambhampati, krsastri@suven.com, Prabhakar Kothmirkar, Trinath Reddy Bandyala, Sivasekhar N. K. Yarra, Sobhanadri Arepalli, M. Abdul Rasheed, Anil K. Shinde, anilshinde@suven.com, and Ramakrishna Nirogi, Discovery Research - Medicinal Chemistry, Suven Life Sciences Ltd, Serene Chambers, Road-5, Avenue-7, Banjara Hills, Hyderabad 500034, India*

Cognitive dysfunction is one of the primary manifestations of several serious neurological and psychiatric disorders. Hitherto available abundant pre-clinical literature data supports the use of serotonin 5-HT6 receptor antagonism as a promising mechanism for treating cognitive impairment and obesity and is expected to provide significant benefits to patient populations. Our continuing

efforts towards discovery and synthesis of selective 5-HT6 receptor antagonists, with the desirable pharmacokinetic properties necessary for the CNS agents, have lead to the identification of novel and potent conformationally restricted tryptamine sulfonamide derivatives, with Ki in the range of 1 - 5 nM, when tested by the in-vitro radio-ligand binding techniques. The lead compound from this series is found to be active in animal models of cognition, like water maze and NORT at 1 mg/kg and 3 mg/kg (p.o). Details of synthesis, physicochemical properties, in-vitro binding data along with SAR and in-vivo animal data will be presented.

MEDI 105

Identification of a potent, noncovalent series of fatty acid amide hydrolase (FAAH) inhibitors

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Fatty acid amide hydrolase (FAAH) plays a central role in regulating anandamide signaling and has therefore attracted considerable interest as potential therapeutic target for the treatment of pain, inflammation and other central nervous system (CNS) disorders in recent years. To date, nearly all FAAH inhibitors reported appear to rely on covalent modification of the active site serine (S-241). Herein we describe the rational design and identification of a novel, potent and selective series of FAAH inhibitors. Based on crystallographic and kinetic studies the compounds described constitute the first series of potent, reversible, non-covalent FAAH inhibitors to date. The synthesis, SAR and binding mode of the series will be presented.

MEDI 106

Design, synthesis and evaluation of heterocyclic peptide ketoamides as calpain inhibitors

Asli Ovat*, Zhao Zhao Li, and James C. Powers, School of Chemistry and Biochemistry, Georgia Institute of Technology, Atlanta, GA 30332*

Calpains are calcium-dependent cysteine proteases which are widely distributed in mammalian cells. Calpains are involved in a wide range of cellular calcium-

regulated functions, including signal transduction, cell proliferation and differentiation, and apoptosis. Moreover, altered calpain activity has been observed in several human diseases. Specific calpain inhibitors hold promise for the treatment of neuromuscular and neurodegenerative diseases in which calpains have been shown to be upregulated (e.g. Parkinson's, Alzheimer's diseases, ALS and multiple sclerosis). Peptidyl ketoamides are transition-state inhibitors and reversibly inhibit calpain possibly due to hemithioacetal formation with the thiol group of the active site cysteine. Heterocyclic peptide ketoamides have the potential to cross the blood-brain barrier and the potency of the inhibitors have been successfully increased by incorporating small hydrophobic groups on the heterocyclic ring. ->

MEDI 107

Novel aryl sulfonamides: A new chemical class of selective 5-HT6 receptor antagonists

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5-hydroxytryptamine6 (5-HT6) receptor is almost exclusively expressed in the CNS, particularly in areas associated with learning and memory. Various reports supported the use of 5-HT6 receptor antagonism as a promising mechanism for treating cognitive dysfunction, obesity and associated metabolic disorders. As a part of ongoing programme at Suven for the synthesis of selective 5-HT6 ligands we have identified compounds based on N-(piperidinylamino aryl) sulfonamide scaffold which are highly potent (Ki = 0.5 to 15 nM), selective and orally active in animal model of cognition like NORT and Water Maze. Pharmacokinetic profile on the lead compound in Wister rats showed that they are highly brain penetrant with Cbrain/Cplasma ratio > 0.5. Synthesis, physicochemical properties, in-vitro binding data along with pharmacological data will be presented.

MEDI 108

Development of $GABA_A$ subtype selective agents for the treatment of alcohol abuse

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Behavioral Biology, New England Primate Research Center, Harvard Medical School, Southborough, MA, (3) Division of Behavioral Biology, Johns Hopkins Bayview Medical Center, Baltimore, MD, (4) School of Medicine, University of Maryland, Baltimore, MD

To elucidate the role of specific $GABA_A$/benzodiazepine receptor subtypes in regulating alcohol reinforcement, a number of active β-carbolines have been synthesized and evaluated. Recently, a study with the benzodiazepine receptor antagonists, 3-propoxy-β-carboline (3-PβC) and β-carboline-3-carboxylic acid *t*-butyl ester (βCCt), was carried out to examine the role of α_1 receptor subtypes within the ventral pallidum (VP) on alcohol self-administration. Examination of the data indicated a reduced rate in alcohol self-administration in rats as well as reduced alcohol consumption and increased latency to gain access to alcohol in baboons. Studies on 3-PβC indicated that it was active against alcohol craving as well. The synthesis of analogs of βCCt and 3-PβC, as well as binding affinities of these new β-carbolines will be presented, along with the effects of 3-PβC and βCCt on rats and baboons. These results provide a new avenue for the design of clinically safe and effective drugs for treatment of alcoholism.

MEDI 109

Lipoamino acid structure-anticonvulsant activity relationships of the systemically-active galanin analogs

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A combination of lipoamino acid(LAA) and cationization introduced to the truncated galanin yielded systemically–active anticonvulsant analogs: the most active analog, Gal–B2, contained the –Lys–Lys–Lys(Palmitoyl)–Lys–NH_2 motif. To study LAA structure–anticonvulsant activity relationships, orthogonally–protected LAA were synthesized in which Lys side chain was coupled to either fatty acids varying in length from C_8 to C_{18} or to a monodispersed PEG4. Six new Gal-B2 analogs were synthesized and characterized in the receptor binding assay, *in vitro* serum stability, lipophilicity (logD), circular dichroism, and in the 6 Hz model of epilepsy. The presence of various lipoamino acids or the Lys(PEG4) did not affect the receptor binding properties, but the anticonvulsant activity substantially varied between the analogs, and was generally correlated with the lipophilicity. Our results suggest that an optimized lipoamino acid adjacent to positively-charged amino acid residues may significantly improve the antiepileptic activity of galanin analogs following systemic administration.

MEDI 110

Synthesis of potential negative modulators of the dopamine D_2 receptor based on Pro-Leu-Gly-NH_2

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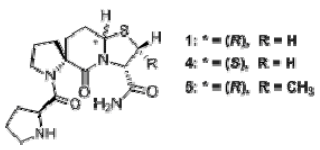
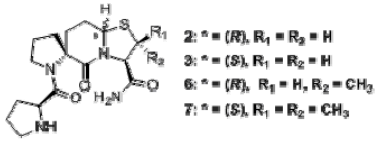
Two diastereomeric peptidomimetics (**2** and **3**) based on Pro-Leu-Gly-NH_2, a naturally occurring positive dopamine D_2 receptor modulator, were previously found to exhibit *opposite* modulatory activities. On the basis of molecular modeling studies, we hypothesize that differential orientation of the thiazolidine β-methylene carbons of **2** and **3** is responsible for the opposite behavior of the two modulators at the allosteric regulatory site. Through substitutions at the thiazolidine β-methylene carbons, we designed **4–6** to convert the positive modulators **1** and **2** into negative modulators and designed **7** to enhance the negative modulatory activity of **3**.





MEDI 111

Exploration of the complex hydrogen-bonding network in the D1 dopamine receptor: Synthesis and evaluation of bicyclic catechol-containing dopamine analogs

***Lisa A. Bonner**, lbonner@pharmacy.purdue.edu, Benjamin R. Chemel, Uros Laban, Jose I. Juncosa, Val J. Watts, and David E. Nichols, Department of Medicinal Chemistry and Molecular Pharmacology, Purdue University, 575 Stadium Mall Drive, West Lafayette, IN 47907-2091, Fax: 765-494-1414*

Dopamine pathways in the brain play important roles in reward circuitry, memory consolidation, and locomotion. We are engaged in the design of agonist ligands selective for the D1-like family of dopamine receptors. Our work involves the design of rigid ligands, coupled with biological assays and homology modeling. We previously determined that a series of 2-substituted 7,8-dihydroxy-4-aminomethylchromans were inactive at D1 receptors, but showed unexpected D2 potency. The compounds were designed as analogues of highly D1-selective

isochromans reported by Abbott laboratories. To explain our results, we hypothesized that an intramolecular hydrogen bond in the chroman molecules disrupts the complex hydrogen-bonding network required for agonist activation of the D1 receptor, but has a less consequential effect in the D2 receptor. To test this hypothesis, carbocyclic analogues of these two series of compounds were synthesized and pharmacologically evaluated. The results support our hypothesis, and the new compounds proved to be selective D1 agonists.

MEDI 112

Antiviral drug design using computational chemistry

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The goal of this research was to identify a compound or family of compounds that would allow effective treatment of the influenza virus without unnecessary risks and side-effects. Protein crystal structures of an influenza virus were obtained from the Protein Data Bank. Using a docking program, different compounds were fitted into various target sites on the protein to identify possible high-affinity inhibitors.

MEDI 113

Predicting UDP-glucuronosyltransferase of new structures

***Kurt Enslein**, kenslein@enres.com, Enslein Research, Inc, 183 East Main Street, Rochester, NY 14604, Fax: 585-232-8620, and Robert Fraczkiewicz, Simulations Plus, Inc, Lancaster, CA 93534*

We have developed classification QSAR models for UGT isozymes useful for Phase II drug metabolism, i.e., UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9 and UGT2B7, using literature data. These models determine whether a compound can be glucuronidated by specific isozymes. The models were developed using Artificial Neural Network Ensemble (ANNE) methodology and molecular descriptors implemented in ADMET PredictorTM 3.0. Independent test compounds were used for evaluation. For example, the UGT1A4 database consisted of 128 compounds of which 10%, 15%, or 20% were selected for evaluation by the Kohonen algorithm. 96%-92% were accurately predicted, while model fit was 92-95%. The more important descriptors used for the UGT1A4 models, typical also of those appearing in the other models, consisted of Huckel pi atomic charges, Fukui indices, E-state indices, and structural descriptors. These models can be used in the study of pharmaceuticals, subsequent to

Phase I metabolism and those compounds metabolized directly by Phase II enzymes.

MEDI 114

Molecular docking and 3-D-QSAR studies of ranitidine analogs as acetylcholinesterase inhibitors in the treatment of Alzheimer's disease

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Alzheimer's disease is the most common form of dementia and is increasing in prevalence in our aging society. Improvement of CNS cholinergic neurotransmission is the major mechanism of action for the drugs currently used for this disease. To date, this has been largely accomplished through the inhibition of the hydrolytic enzyme acetylcholinesterase (AChE). The histamine H2 antagonist, ranitidine, has been shown to be a moderately potent inhibitor of human acetylcholinesterase. In an attempt to develop more potent AChE inhibitors, molecular docking and 3D-QSAR methods were applied to a novel set of ranitidine analogs. The binding modes of these compounds at both the catalytic site and the peripheral binding site were explored and the various hydrophobic and hydrogen bonding interactions were determined between the inhibitors and AChE. A primary QSAR model will be reported which will provide future direction for the further development of ranitidine analogs as multitargeted therapeutic agents.

MEDI 115

QSAR models of 5-HT2B receptor ligands and their application to predicting compounds that could cause valvulopathy.

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Biological screening against 5-HT2B receptor has identified several marketed drugs that could cause the fatal condition of valvulopathy. To provide an efficient tool for eliminating such high risk compounds at early stages of drug discovery, we have developed statistically validated and externally predictive combi-QSAR models that can be used to virtually screen chemical databases for possible 5-HT2B ligands. Our models are generated in a two-tier approach: first, to discriminate 5-HT2B binders from non-binders, and second, to categorize binders as agonists or antagonists. Predictive models with classification accuracies as high as 0.80 and 0.83 respectively, as estimated on external validation sets, were obtained. The models were used for virtual screening of the World Drug Index and several dozen putative binders, some of which were predicted to be agonists with potential valvulopathic risks have been identified. The predicted agonists were found to belong to several therapeutic groups, and were submitted for experimental testing.

MEDI 116

File enhancement: "Bench to Bedside" with '"Iterative Efficiency"

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Abstract: This poster introduces the concept of ‘Iterative Efficiency' (IE) advocating select multi-component reactions (MCRs) as tools to enhance corporate decks. It is founded on the central tenet of efficiency in medicinal chemistry ~ increased ‘iterative speed' around the ‘hypothesis–synthesis–screening' loop and reduced numbers of iterations for expedited value chain progression. The latter is commonly addressed via ‘knowledge-based' front loading approaches. The poster details MCR strategies that deliver libraries with desirable properties that also enable downstream ultra-high iterative speeds. This combination equates to libraries with ‘high iterative efficiency potential' and qualitative measures of this are discussed. Successful MCR studies by several companies (hit to clinic) with no intermediate ‘scaffold hopping' will be portrayed. Such examples may be viewed as the original ‘holy grail' of combinatorial chemistry, now being witnessed as facilitated by the exponentially increasing ‘chemical diversity space' made accessible by MCR methodologies in the last decade.

MEDI 117

Molecular structure, inhibition, and docking studies of a family of polyaromatic hydrocarbons

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Cytochrome P450 enzymes are involved in the metabolism of environmental pollutants through a detoxification process. However, these P450s have been shown to oxidize PAHs to carcinogenic species that bind DNA and lead to cancer formation. It has been shown that some arylacetylenes can function as mechanism-based inhibitors of P450 enzymes involved in carcinogenesis and possibly prevent the initiation of cancer. In an effort to study the SARs for a family of pyrene derivatives, we have determined the X-ray crystal structures and performed in vitro inhibition assays on P450s 1A1, 1A2, 2A6, and 2B1. Studies show that these molecules dock into the narrow regions of the active site pockets with the aromatic planes of the molecules situated parallel to the heme plane. The active site pocket can accommodate the acetylene groups in different docking poses. The correlation between the inhibition results and the docking conformations will be presented. NIH/MBRS-SCORE (S06GM 08008 and SC1GM084722) support is gratefully acknowledged.

MEDI 118

Theoretical study of HIV-1 integrase inhibitors' tautomerism and their chelating complexes with two magnesium ions

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The tautomerism and corresponding transition states of authentic HIV-1 integrase inhibitors, including α,γ-diketo acid, α,γ-diketotriazole, dihydroxypyrimidine carboxamide, and 4-quinolone-3-carboxylic acid were investigated at the B3LYP/6-311++G(d,p) level in gas phase and aqueous solution using the PCM model in Gaussian 03. We describe the most stable states found in gas phase and solution. We also investigate changes, in either environment, in the most stable structure found when acid moieties are

deprotonated. To study how these tautomers may chelate two magnesium ions, we modeled an assembly of three formic acids (substituting for Asp 64, Asp 116 and Glu 152), four water molecules, and two magnesium ions. They were arranged according to the coordinates of Tn5 Transposase, a relative of integrase, to partly mimic the binding site of integrase. The calculations also employed B3LYP/6-311++G(d,p) level both in gas phase and in water. Initial results in the aqueous model show that, when the –OH group in á position deprotonates (in the α,γ-diketo acid, the carboxylic acid also deprotonates), the two magnesium ions can form the most stable complex, with each ion being in the center of a hexacoordinated octahedral complex. When a water molecule in the complex was replaced by a methanol, which mimics the terminal 3'-OH of viral DNA, a good chelating complex was still formed. This may indicate that, in the binding site of integrase, the terminal 3'-OH of viral DNA interacts with one magnesium ion via a chelating bond.

MEDI 119

Identification of ligand features essential for TACE inhibitors by pharmacophore modeling

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A five point pharmacophore with two hydrogen bond acceptors (A), one hydrogen bond donor (D), and two aromatic rings (R) as pharmacophoric features was developed for Tumor necrosis-á converting enzyme (TACE) from known inhibitors using PHASE. The pharmacophore hypothesis yielded a statistically significant 3D-QSAR model, with a correlation coefficient of r2=0.923 for training set molecules. The model generated showed excellent predictive power, with a correlation coefficient Q2=0.601 for an external test set of molecules. The pharmacophore proposed here was then utilised for the successful retrieval of active molecules with diverse chemotypes from search of the ASINEX database, thus validating the developed model. The geometry and features of pharmacophore are expected to be useful for the design of TACE inhibitors.

MEDI 120

Computational correlation studies toward inactivation of O6-alkylguanine-DNA alkyltransferase by O6-benzylguanine analogs

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O6-alkylguanine-DNA alkyltransferase (AGT) is a DNA repair protein that acts in a single step to restore DNA with O6-Alkylguanine adducts, and thus prevents mutations and apoptosis arising from alkylated guanines. AGT irreversibly transfers the alkyl group to an active site cystine in the acceptor site and provides resistance to alkylating therapeutic agents. So various analogs of benzyl guanine were synthesized and tested for activity as potential inhibitors. The nature and position of the substitutions -methyl and -aminomethyl profoundly affected their activity. Molecular modeling of their interactions with alkyltransferase provided a molecular explanation for these

results. The square of the correlation coefficient (R2) obtained between E-model scores (obtained from GLIDE XP/QPLD docking calculations) vs. log(ED50) values via a linear regression analysis was 0.96. The models indicate that the ortho- substitution causes a steric clash interfering with binding whereas the meta- aminomethyl substitution allows an interaction of the amino group to generate an additional hydrogen bond with the protein.

MEDI 121

Ligand-based molecular modeling study on DNA G-quadruplex mediated telomerase inhibitors: 3-D-QSAR CoMFA/CoMSIA approach

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Small molecules based on acridine platform are a new class of G-quadruplex binding telomerase inhibitors. CoMFA and CoMSIA were employed to study 3D-QSAR on substituted acridines as telomerase inhibitors. QSAR models were derived from a training set of 58 molecules. An external test set consisting of 21 molecules were used to validate the CoMFA and CoMSIA models. All molecules were superimposed on the template structure by combination of centroid and atom-base alignment. The statistical quality of the QSAR models was assessed using the parameters r2conv, r2cv, and r2pred. A highly significant CoMFA model was obtained using both steric and electrostatic fields with good conventional r2 and cross-validated r2 values up to 0.933 and 0.460 respectively. This model also showed best test set prediction for 21 compounds with predictive r2 value of 0.648. CoMSIA model developed with steric, hydrophobic, H-bond acceptor and H-bond donors fields displayed r2cv 0.467, r2conv 0.925 and r2pred 0.634. 3D contour maps were analyzed and emphasize the importance of the substituents on acridines, which may play essential role in overall anti-telomerase activity. The results help us to provide guidelines to design novel and potent G-quadruplex DNA binding telomerase inhibitors.

MEDI 122

Discovering potent molecules with human embryonic stem cells to treat heart disease

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Heart disease is the leading cause of death in the United States, claiming hundreds of thousands of lives each year. To address treatment of this disease, we are creating technology for cardiac tissue repair derived from stem cells. Accordingly, a commercially available library (14,000 compounds) was screened for cardiogenesis differentiation agents in a high content cell-based assay using mouse embryonic stem cells. The screens provided four structurally distinct “hits” that were potent and reproducible in assays of cardiogenic differentiation. Each “hit” appeared to promote cardiomyogenesis at a different time point in the differentiation cascade. Herein, we describe the synthesis and SAR of two of the ”hits” as well as the results of our strategy to optimize the ”hits” into drug-like lead candidates. This work was supported by CIRM SEED grant number RS1-00169-1 (JC) in collaboration with the Burnham Institute for Medical Research CIRM grant number RC1-00132-1 (MM).

MEDI 123

Antioxidant activities of some potential drugs used in hypertension

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Lately, we have directed our efforts to investigate the effects of antioxidants on blood pressure and membrane fluidity of hypertensive rats. In this study, we are reporting our in-vitro investigation of a number of antioxidants for radical scavenging activities using DPPH (1,1-diphenyl-2-picrylhydrazyl) and spectroscopic method. The antioxidants used in this study were vitamin E, probucol, 9-hydroxyxanthene, flaxseed oil, and chlorthalidone. The antioxidant activity was evaluated by measuring the decrease in absorbance of DPPH detected at 515 nm and the color change from purple to yellow. The DPPH radical scavenging effects of the antioxidants used in this study will be compared with that of Trolox, our control, and the IC50 (concentrations required for 50% inhibition) of DPPH radicals will be reported for these antioxidants.

MEDI 124

17,18-Epoxyeicosatetraenoic acid, a potent antiarrhythmic EPA metabolite: SAR and stable analogs

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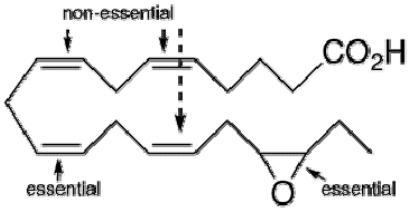
17,18-Epoxyeicosatetraenoic acid (17,18-EETeTr), a cytochrome P450 epoxygenase metabolite of eicosapentaenoic acid (EPA), exerts negative chronotropic effects and protects against Ca2+-overload arrhythmia in neonatal rat cardiomyocytes with an EC50 ~1 nM. Structure-activity-studies revealed the cis-Δ8,9-olefin and 17,18-epoxide are minimal structural elements for agonist activity. Several chemically and metabolically robust agonist analogs show promise as potential clinical candidates.



17,18-EETeTr

MEDI 125

Beneficial role of inducible nitric oxide synthase in thrombosis

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Nitric oxide (NO) is an important vasoactive molecule produced by three NO synthase (NOS) enzymes: neuronal (nNOS), inducible (iNOS) and endothelial NOS (eNOS). While eNOS contributes to vasodilation and prevents hypertension, iNOS is implicated in many disease states. We have previously demonstrated that iNOS-derived NO leads to protein-bound 3-nitrotyrosine formation in atherosclerotic lesions and certain organs during atherosclerosis. In this study, we sought to determine the role of iNOS in a murine model of thrombosis. Blood flow was measured in the carotid arteries of wild-type mice versus iNOS-deficient mice (iNOS-null) following ferric chloride-induced thrombosis. The iNOS-null mice demonstrated increased susceptibility to thrombotic occlusion, which may be due to increased levels of thromboxane, a potent vasoconstrictor and platelet aggregator. Thus, while iNOS may cause potentially damaging reactions during atherosclerosis, therapies aimed at iNOS inhibition would need to consider its potentially beneficial role during stroke.

MEDI 126

Effects of flax oil on membrane fluidity and blood pressure of hypertensive and normotensive rats

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Systemic hypertension is known to be the major risk factor for coronary heart disease. Membrane fluidity of erythrocytes and cardiac muscle tissue were studied in spontaneously hypertensive (SHR) and Wistar-Kyoto (WKY) rats using the spin labeling technique and EPR spectroscopy. The rats were administrated flaxseed oil 0.1 mL/100 g, 3 days/week for 4 weeks and blood pressure was measured once weekly, using tail-cuff method. The values of the maximum splitting parameter for a fatty acid spin-label (5-SASL) incorporated in erythrocyte and cardiac membranes from both SHR and WKY rats were compared. Our preliminary results suggest an increase in membrane fluidity and a decrease in blood pressure of SHR rats.

MEDI 127

Novel inhibitors of Nav1.5 late current

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Ranexa®, approved by the FDA for the treatment of chronic stable angina pectoris, is a novel selective inhibitor of the Nav1.5 late current relative to peak sodium channel current. The inhibition of the Nav1.5 late current may decrease sodium-dependent intracellular calcium overload during ischemia and reperfusion. Herein, we describe the SAR on the inhibition of the Nav1.5 late current for two unique classes that bear no structural resemblance to Ranexa®. Compound 1, initially described by Allergan as a topical anesthetic, was found in our hands to inhibit Nav1.5 late current by 45% with moderate hERG inhibition of 49% (both assays performed at 10 uM on PatchXpress using hNav1.5/ HEK293 cells). We have varied the polar linker and aromatic regions of 1 to enhance the inhibition of the Nav1.5 late current while diminishing the hERG inhibition. The second class is based on the well-known L-type calcium channel blockers, dihydropyridines (DHP), using compound 2 as a starting point. After a series of structural modifications, we obtained the non-symmetrical DHP 3, a potent inhibitor of Nav1.5 late current with low hERG and calcium channel inhibition. The synthesis and SAR of these two series will be presented along with a discussion of hypothetical binding modes based on Nav1.5 homology molecular modeling.

MEDI 128

Inhibition models for cytochrome P450 1A2, 2C9, 2D6, and 3A4

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Inhibition of cytochrome P450 is important in drug toxicities and drug-drug interactions. We developed Artificial Neural Network Ensemble models using ADMET Predictor™, including classification models for CYP450-1A2, -2C9, -2D6, and -3A4 inhibition, and two regression models for CYP450-3A4 substrate-specific inhibition in Human Liver Microsomes (HLM) with midazolam and recombinant-expressed CYP450-3A4 with testosterone. The concordances of the classification models on the external set are 89.7%, 80.0%, 80.4%, 76.9%, 88.8%, and 100%, respectively. The regression models predict logarithm of substrate-specific inhibition constant (Ki). Determination coefficients (R2) on the external test sets were 0.655 and 0.716, and root-mean-squared errors (RMSE) were 0.460 and 0.528 respectively Descriptor sensitivity analysis showed aromatic carbons strongly affect the inhibition constant Ki. We also tested the ability of each model to estimate the Ki value of the molecules in the opposite dataset. Predicting the “testosterone” dataset with the midazolam inhibition model yielded RMSE=1.11 with R2=0.097. Predicting the “midazolam” dataset with the testosterone metabolism model yielded RMSE=1.09 and R2=0.223. The two models appear to distinguish modes of interaction with CYP3A4 for midazolam and testosterone.

MEDI 129

Sansalvamide A binds to HSP90 and disrupts IP6K2 binding

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Sansalvamide A is a cytotoxic molecule that works via binding to heat shock protein (HSP90), selectively disrupting a key protein-protein interaction between HSP90 and inositol hexakisphosphate kinase 2 (IP6K2). Hsp90 is an anti-apoptotic protein that is up regulated in a majority of cancers. IP6K2 is in a family of enzymes that generates inositol pyrophosphate 7 (IP7), which mediates apoptosis. Hsp90 binds to IP6K2 in cells preventing it from causing apoptosis. Thus, San A has the ability to bind to Hsp90, allowing the release of active

IP6K2, which initiates apoptosis. This makes San A an excellent lead for further development of chemotherapeutics that interact with this novel protein-protein interaction.

MEDI 130

New therapies for treating cancer and inflammation

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The combined efforts of chemists, pharmacologists and biochemists at Emory have successfully resulted in the development of novel and selective preclinical and clinical agents of biomedical interest. I will briefly describe several recent projects involving collaborations with Emory University School of Medicine faculty that have resulted in the identification of novel small molecules targeted to proteins of high biomedical interest. These include CXCR4 antagonists and synthetic curcumin analogs.

MEDI 131

Design and synthesis of thrombin receptor antagonists

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Cardiovascular disease, especially heart attack and stroke, remains a major cause of mortality in the United States and Western Europe. In most cases, the cause of death is the presence of a thrombus in a major artery, a result of inappropriate activation of the coagulation pathway. The enzyme thrombin plays a central role in this process by cleaving fibrinogen to fibrin, and by activating platelets, which contribute to arterial thrombus formation. In a process unique to the protease-activated receptor (PAR) family, thrombin cleaves the N-terminus of the thrombin receptor (PAR-1) present on these cells, creating a tethered ligand which activates the receptor. Antagonists of PAR-1 are of high interest as potential agents for the prevention of arterial thrombosis, especially since they may lack the bleeding liability of other antithrombotic drugs (e.g thrombin and Factor Xa inhibitors). Starting from a modestly-potent lead derived from the natural product himbacine, we have discovered several series of potent, orally bioavailable PAR-1 antagonists which block thrombin-induced activation of

platelets. The design, synthesis and structure-activity relationships of these antagonists will be discussed

MEDI 132

Design, synthesis, and evaluation of fatty acid amide hydrolase inhibitors

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A summary of studies leading to the discovery of potent and selective inhibitors of fatty acid amide hydrolase (FAAH) will be described. FAAH degrades (hydrolyzes) the endogenous fatty acid amide signaling molecules including anandamide and oleamide terminating their neuromodulatory effects providing a new therapeutic target for a range of potential clinical disorders.

MEDI 133

Adventures in drug discovery: Enzyme inhibitors, receptor antagonists … and more

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During my 35-year career in the pharmaceutical industry as a drug hunter, I have encountered many therapeutic targets and many clinical candidates. Under the old drug discovery paradigm of phenotypic assessment, I discovered TOPAMAX (topiramate), a blockbuster drug that is marketed worldwide for treating epilepsy and migraine headache. Its mechanisms of action are still not fully understood. Hoping to make another substantial impact on medicine, my research group has pursued diverse enzyme inhibitors and receptor antagonists. We have sought inhibitors of serine proteases involved in thrombosis and inflammatory diseases by applying structure-based drug design, and antagonists of peptide-based receptors within the GPCR and integrin superfamilies by a variety of tools. This lecture will be comprised of vignettes that reflect on the diversity of this drug discovery research. [Recent literature of interest: Maryanoff, B. E. J. Med. Chem. 2004, 47, 769-787; Maryanoff, B. E. Acc. Chem. Res. 2006, 39, 831-840; Maryanoff, B. E.; Zhang, H.-C. ARKIVOC 2007, 7-35.]

MEDI 134

20 Years of metabotropic glutamate receptor drug development.: An historical perspective on the discovery of the compounds which have been critical to our understanding of the physio-pathological involvement of these receptors

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The existence of metabotropic glutamate receptors (mGluRs) was demonstrated more than 20 years ago. This discovery initiated a race for the development of selective molecules acting at these receptors which was dramatically fuelled by the cloning of the various subtypes of the mGluR family in the early 90s. The successive efforts of university laboratories and the pharmaceutical industry provided a variety of more and more selective tools which allowed unravelling of the physiological role of these receptor subtypes and their possible involvement in various pathological states. The difficulties associated with the development of molecules highly selective for specific receptor subtypes even led to the successful exploration of alternative pharmacology like the allosteric modulation. The combination of these efforts in the pharmaceutical industry finally recently delivered several clinically efficacious drugs showing the enormous potential of this receptor family as a source of first in class drugs

MEDI 135

Group II metabotropic glutamate receptors (mGluRs): Design and synthesis of small molecule modulators

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Group II metabotropic glutamate receptors(mGluR2 and mGluR3) are found both pre- and postsynaptically (Schoepp 2001) and couple to Gi and Go-proteins to negatively regulate the activity of adenylyl cyclase. In particular, Group II mGluRs function as glutamate autoreceptors that modulate presynaptic glutamate release (Conn and Pin 1997; Anwyl 1999; Cartmell and Schoepp 2000). Thus, modulation of Group II mGluRs by small molecules represents a promising approach for the treatment of diseases caused by aberrant glutamatergic transmission such as schizophrenia, anxiety or drug addiction. We recently initiated a program focused on the design, synthesis and in vitro and in vivo evaluation of small molecule modulators of Group II mGluRs. This presentation will provide an update on our progress towards new potent and selective mGluR2 modulators and their characterization in relevant tests, including rat models of aspects of cocaine dependence.

MEDI 136

A novel series of group III metabotropic glutamate receptor (mGluR) agonists

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Presynaptic Group III mGlu receptors and specifically subtype 4 have been shown to be potential therapeutic targets for several CNS pathologies such as Parkinson disease, anxiety or pain. However only a limited number of ligands have yet been disclosed preventing in depth investigation. We thus initiated a program aiming at the discovery of agonists of these receptors. In a virtual high throughput screening of the mGlu4 receptor binding site, we identified (R)-PCEP (3-amino-3-carboxyPropyl-2'-CarboxyEthyl Phosphinic acid as the best hit. The S isomer proved to be more potent and was optimized in a series of derivatives. While it had been difficult in the past to find new orthosteric ligands of group III mGlu receptors, a large number of these new compounds were able to activate these receptors. Among them LSP1-2111 revealed a marked preference for subtype 4 versus 8, the two most homologous group III subtypes. LSP1-2111 was then further evaluated at native receptors and in an animal model of Parkinson disease. Most interestingly, LSP1-2111 produced antiparkinsonian effects at 10 fold lower doses than with previously known agonists (e.g. L-AP4, ACPT-I, (1S,2R)-APCPr).

MEDI 137

Allosteric mGluR5 antagonists: From discovery to clinical development

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mGluRs have been the target(s) of drug discovery efforts aimed at modulating dysregulation of glutamatergic transmission in a wide range of neurological and

psychiatric disorders. In particular, we have focussed on inhibition of the postsynaptically-located mGluR5 subtype in order to reduce excessive glutamatergic transmission as a therapeutic approach. Discovery of the first selective, potent allosteric antagonist, MPEP, opened the way to exploring the potential of mGluR5 antagonism in a variety of animal models of disease as well as for optimisation and derivation of the MPEP structure to produce mGlu5 antagonists with drug like properties. The future challenge in the field is to identify which diseases in man are amenable to mGlu5 antagonist therapy and bring them to the patient.

MEDI 138

The discovery and function of sweet taste enhancers

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The human sweet taste receptor is composed of two proteins, T1R2 and T1R3. These proteins are members of the C-class G protein-coupled receptor (GPCR) family. Cells expressing T1R2 and T1R3 respond to virtually all sweeteners. Using a high-throughput screening assay for the human sweet receptor and chemistry optimization we discovered a number compounds that shift the dose response to sweeteners in the receptor assay and enhance sweetness in taste tests. Unlike receptor modulators for other C-class GPCRs, which act via the Transmembrane Domain, these sweet enhancers function via the Venus Flytrap Domain of T1R2. Sweet enhancers have a number of potential uses including the ability to enhance the nutritional profile of foods and beverages by significantly reducing the levels of carbohydrate sweeteners yet maintaining sweet taste. My talk will focus on our progress toward the discovery and development of these novel ingredients.

MEDI 139

Discovery, SAR and antiparkinsonian effect of novel positive allosteric modulators (PAMs) and ago-potentiators of metabotropic glutamate receptor subtype 4 (mGluR4)

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The metabotropic glutamate receptors (mGluRs) are members of the GPCR family C, characterized by a large extracellular amino-terminal agonist binding domain. The Group III mGluRs are the least explored and characterized of the

mGluRs, but despite this fact, mGluR4 has garnered a great deal of attention as a therapeutic target for Parkinson's disease. Dominated by (-)-PHCCC, the first mGluR4 PAM, the field moved slowly due to the potency and physiochemical properties of (-)-PHCCC. This talk will concern the discovery and development of three novel series of mGluR4 PAMs and ago-potentiators, VU0155041, VU0080241 and VU001171, which are more potent, efficacious and possess improved properties relative to (-)-PHCCC. VU0155041 displayed significant efficacy in Parkinsonian models, further validating the therapeutic role of mGluR4 activation in PD.

MEDI 140

Metzincin clan of metalloproteinases as therapeutic targets

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Metalloproteinases or metalloendopeptidases are zinc-dependent hydrolytic enzymes (zincins), with HEXXH sequence in which two histidines acting as ligands of the catalytic zinc and the glutamate as the general base. A subclass of zincins is called metzincins, which have HEXXHXXGXXH/D sequence with conserved glycine and a third zinc-binding histidine or aspartate, and a methionine-turn under the enzyme active site. Metzincins include astacins, matrixins (matrix metalloproteinases; MMPs), adamalysins (ADAMs), serralysins, snapalysins, and leishmanolysins. Many members of metzincin clan are potential therapeutic targets. For instance, MMPs play essential roles in angiogenesis, stroke, cardiovascular diseases, inflammation, multiple sclerosis, chronic obstructive pulmonary disease, adipogenesis, and cancer invasion and metastasis; ADAMs and ADAMTSs are also implicated in cancer progression and arthritis. The development of selective metalloproteinase inhibitors may lead to new therapies for many diseases. Our effort in developing novel MMP inhibitors will be discussed.

MEDI 141

Aggrecanase inhibitors

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Osteoarthritis is a debilitating disease that causes pain and lack of function. Current therapeutic options offer only symptomatic relief and do not target disease modification. Aggrecan, a highly glycosylated protein, is a major component of articular cartilage that provides elasticity and compressibility to the joint. ADAMTS-4 (aggrecanase-1) and ADAMTS-5 (aggrecanase-2), members of the ADAM-TS family of enzymes (A Disintegrin And Metalloprotease with Thrombospondin motifs) are key mediators of aggrecan degradation throughout the osteoarthritis disease process. Murine knock-out studies have shown that ADAMTS-5, but not ADAMTS-4, are responsible for cartilage degradation in animal models of arthritis. However, the relative contribution of ADAMTS-4 and ADAMTS-5 in human disease is not clear. ADAMTS-4 and ADAMTS-5 double knockout mice are phenotypically normal and are protected from developing osteoarthritis. Therefore, targeting both aggrecanases represents a reasonable strategy for developing disease-modifying therapeutics. An overview of aggrecanases as targets and the preliminary results of our development of selective aggrecanase inhibitors will be discussed.

MEDI 142

Methionine aminopeptidases as drug targets

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Methionine aminopeptidases (MetAP) are evolutionarily highly conserved enzymes that catalyze the co-translational removal of N-terminal initiator methionine. Although this family of enzymes have been shown to be essential for both bacterial and yeast, each isoform of the enzyme appears to have evolved tissue- and cell type-specific function in multicellular organisms. Thus, MetAP2 was identified as the target for the fumagillin family of natural products that potently inhibit endothelial cell proliferation, hence angiogenesis. In contrast, MetAP1 was recently found to play an important role in the timely progression of tumor cells in the G2/M phase of cell cycle and in the survival of both leukemia and lymphoma cells. As a result, both MetAP1 and MetAP2 are promising targets for developing novel anti-angiogenic and anticancer drugs. In this presentation,

some recent advances in our understanding of the cellular functions of MetAP1/2 and in the identification of novel inhibitors for these enzymes will be reported.

MEDI 143

Screening for exosite-targeting inhibitors of the anthrax lethal factor metalloproteinase

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The low success rate of antibiotic therapy for inhalational anthrax has prompted efforts towards the discovery of therapeutic agents targeting the bacteria's deadly toxin. A critical component of anthrax toxin is lethal factor (LF), a metalloproteinase that cleaves mitogen activated protein kinase kinases (MKKs) in host cells. We have used peptide library screening to design substrates for high throughput screening and substrate analog inhibitors. Such active site-directed inhibitors, however, can cross-react with host metalloproteinases. We have taken an alternative approach to identify LF inhibitors that do not bind to the enzyme active site. Efficient cleavage of MKKs by LF depends on an exosite interaction between the substrate and protease. We have developed a high throughput screening strategy based on cleavage of a full length MKK to identify exosite-binding inhibitors. In addition to constituting novel types of LF inhibitors, hits can be used as structural probes to map exosite interactions.

MEDI 144

Bicyclic heterocycles as orally active and specific matrix metalloproteinase-13 inhibitors for the treatment of osteoarthritis

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Quinazolinones and pyrido[3,4-d]pyrimidin-4-ones as orally active and specific matrix metalloproteinase-13 inhibitors were discovered for the treatment of osteoarthritis. Starting from a high-through-put screening (HTS) hit thizolopyrimidin-dione (I), the authors obtained two chemotypes, using computer-aided drug design (CADD) and methodical structure-activity relationship (SAR) studies. They occupy the unique S1'-specificity pocket and do not bind to the Zn2+ ion. Some pyrido[3,4-d]pyrimidin-4-ones, such as (II), possess favorable absorption, distribution, metab., and elimination (ADME) and safety profiles. The compd. II effectively prevents cartilage damage in rabbit animal models of

osteoarthritis without inducing musculoskeletal side effects when given at extremely high doses to rats.

MEDI 145

Design of highly selective matrix metalloproteinase-13 inhibitors for the treatment of osteoarthritis

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Matrix metalloproteinase-13 (MMP-13) is a zinc-dependent protease responsible for the cleavage of type II collagen, the major structural protein in articular cartilage. Degradation of this cartilage matrix is a characteristic feature in the development of osteoarthritis (OA) which leads to chronic joint pain and reduced physical function for millions of Americans. Because of the critical role MMP-13 plays in the pathology of this disease, inhibition of the enzyme offers the potential to halt the progression of disease in OA patients. Due to the multifaceted role metalloprotienases play and the structural similarities among the family, the discovery of an MMP-13 selective agent has been a critical need and a scientific challenge for drug discovery. This presentation will describe our efforts to optimize a novel chemical series which binds at the S1' active site pocket and is not dependent on inhibitor binding to the catalytic zinc. Innovative strategies in pharmacokinetic optimization and the use of cartilage degradation biomarkers coupled with insight from structure-based drug design has allowed for the identification of preclinical candidates which are orally bioavailable, potent inhibitors of MMP-13 with exquisite selectivity (>5000 fold over 20 metalloprotienases tested) and demonstrate cartilage protection in preclinical animal models.

MEDI 146

Novel targets for the treatment of Alzheimer's disease

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The decline in FDA-approved new drug candidates in recent years suggests that the “low-hanging fruit” has mostly been harvested. Fortunately, there are several examples for the utility of compounds or drug mixtures that act on multiple additive or synergistic targets. To exploit this approach could require the willingness to consider that drug targets might be addressed by molecules of rather low specificity and moderate potency. Multi-functional compounds might be designed with the ability to (1) offer both palliative and disease modifying actions; (2) act on targets that produce additive or synergistic therapeutic responses; (3) simultaneously evoke a therapeutic response at the desired target and prevent an undesired response mediated off-target; (4) allow one component to promote the drugable characteristics (e.g., brain penetration) of the therapeutic component; and (5) prolong the duration of effectiveness of one compound by contributing the pharmacodynamic actions of another. Salient examples will be presented.

MEDI 147

Metabolism of amyloid beta peptide and pathogenesis of Alzheimer's disease

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The conversion of normal brain aging to Alzheimer's disease (AD) via a transition state, i.e. mild cognitive impairment (MCI), appears to consist of chronic processes caused primarily by accumulation of amyloid β peptide (Aβ). This notion give us a hope that, by manipulating the Aβ levels in the brain, we may be able not only to prevent and cure the disease but also to partially control some very significant aspects of brain aging. Aβ is constantly produced from its precursor and immediately catabolized under normal conditions, whereas dysmetabolism of Aβ seems to lead to pathological deposition. We have focused our attention on elucidation of the unresolved mechanism of Aβ catabolism in the brain because there has been no consistent evidence for increased anabolism prior to deposition in sporadic AD (SAD) unlike familial AD (FAD). SAD accounts for 99% or more of all AD cases. We found that a neutral endopeptidase, neprilysin, degrades monomeric and oligomeric forms of Aβ under both physiologic and pathologic conditions, resulting in recovery of sypnaptic plasticity and cognitive function in a mouse model of AD. We also found that Aβ3(pE: pyroglutamate)-42 (generated from Aβ1-42) and calpain (cytoplasmic calcium-activated cysteine protease) are involved in neurodegeneration in vivo, suggesting that inhibitors specific to glutamyl cyclase and calpain activities could become anti-AD medications. I anticipate that optimized cocktails based on these and other strategies shall help us preserve our human dignities in our later lives.

Combination of presymptomatic diagnosis with preventive medicine seems to be the most pragmatic in both medical and socio-economical terms.

Key words: aging, Alzheimer's disease (AD), mild cognitive impairment (MCI), amyloid β peptide (Aβ), metabolism, proteolysis, neprilysin, pyroglutamate, calpain.

MEDI 148

Development of Hsp90 inhibitors as novel therapeutics for AD

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Both malignant transformation and neurodegeneration, as it occurs in Alzheimer's disease, are complex and lengthy multistep processes characterized by abnormal expression, post-translational modification, and processing of certain proteins. To maintain and allow the accumulation of these dysregulated processes, and to facilitate the step-wise evolution of the disease phenotype, cells must co-opt a compensatory regulatory mechanism. In cancer, this role has been attributed to heat shock protein 90 (Hsp90), a molecular chaperone that maintains the functional conformation of multiple proteins involved in cell-specific oncogenic processes. In this sense, at the phenotypic level, Hsp90 appears to serve as a biochemical buffer for the numerous cancer-specific lesions that are characteristic of diverse tumors. We proposes a similar role for Hsp90 in neurodegeneration, and present data suggesting that Hsp90 can act as a regulator of pathogenic changes leading to the neurodegenerative phenotype in Alzheimer's disease. We also present our efforts towards the development of Hsp90 inhibitors as possible therapeutic interventions in Alzheimer's disease.

MEDI 149

NADPH oxidase as a therapeutic target in Alzheimer's disease

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Microglia, the resident innate immune cells in the brain, are strongly implicated in both the pathology and progressive nature of Alzheimer's disease (AD). Microglia are activated in response to both beta amyloid and neuronal damage, and can become a chronic source of neurotoxic cytokines and reactive oxygen species (ROS). NADPH oxidase is a multi-subunit enzyme complex responsible for the production of both extracellular and intracellular ROS in microglia. Importantly, NADPH oxidase expression is upregulated in AD and is implicated as a key mechanism of microglia-mediated beta amyloid neurotoxicity. Our research has shown that activation of microglial NADPH oxidase causes neurotoxicity through two mechanisms: 1) extracellular ROS produced by microglia are directly toxic to neurons; 2) intracellular ROS function as a signaling mechanism in microglia to amplify the production of several pro-inflammatory and neurotoxic cytokines. Here, we describe how targeting NADPH oxidase can reduce a broad spectrum of toxic factors (for example, cytokines, ROS, and reactive nitrogen species) to result in inhibition of neuronal damage.

MEDI 150

Alzheimer's disease drug discovery targeted to the nonamyloidogenic path of APP mRNA translation linked to Alpha-secretase (ADAM-17) expression

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Intracellular levels of the Alzheimer's (AD) Amyloid Precursor Protein (APP) are closely regulated at the translational level by interleukin-1 (IL-1) and iron responsive domains in the 146 base 5 untranslated region of APP mRNA. We found IL-1 and the m-1 muscaric agonist AF102B induced the non-amyoidogenic metabolic pathway by co-activating astrocytic APP translation and alpha sectretase ADAM-17 gene transcription, perhaps via poly-C binding protein-1 binding sites in the 5'UTR of APP mRNA and the ADAM-17 gene. As proof-of concept, paroxetine (SSRI) suppressed APP 5UTR driven luciferase reporter translation in neuroblastoma transfectants and effectively suppressed Abeta-peptide in vivo. We high throughput screened and identified13 leads that limited APP 5'UTR translation, including an APP 5'UTR intercalator (JTR-0009). JTR-009 is a benzimidazole based compound that limited APP translation. To gain

anti-amyloid efficacy, we will optimize our screened APP 5'UTR inhibitors to access structures that co-activate ADAM-17 while limiting APP translation.

MEDI 151

Inhibiting human papillomavirus infections

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Human papillomavirus (HPV) infection is the most common sexually transmitted disease and represents the etiologic basis for the development of cervical cancer. HPV encodes two critical oncogenes, E6 and E7, that not only function in the initiation of cancer, but also in the maintenance of the malignant cell phenotype. Since these two oncogenes are required for the continued proliferation of tumor cells, they provide an ideal target for the design of small molecule “anti-cancer” drugs. HPV-transformed cells have known sensitivity to several classes of anti-neoplastic agents and the basis for their activity will be discussed, as well as ongoing attempts to develop new and highly specific molecules to interfere with the function of the E6 and E7 proteins.

MEDI 152

Discovery and development of nitazoxanide, a novel drug for the therapy of hepatitis B and hepatitis C virus infections

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Nitazoxanide (NTZ, Alinia®) is a first-in-class, broad spectrum, thialozide anti-infective currently in clinical development for the treatment of chronic hepatitis C virus (HCV) infection. Recent clinical trials of NTZ plus peginterferon and ribavirin demonstrated SVR rates of approximately 80% with no enhancement of adverse side effects. Current data indicate that tizoxanide (TIZ), the active metabolite of NTZ, target host cell pathways rather than directly interfering with viral functions. NTZ and TIZ are potent inhibitors of HCV replication (genotypes 1a [H77], 1b [CON1] replicons; genotype 2a [JFH-1, infectious virus] in cell culture (EC50 ca.0.15uM; EC90, ca.0.9uM). Combinations of TIZ with interferon alfa-2b produced synergistic interactions against HCV replication. Combinations of TIZ and compounds targeting anti-HCV proteins (2'C-methyl cytidine (nucleoside, NS5B), HCV-796 (non-nucleoside, NS5B), telepravir (VX-950) and BILN2061 (NS3) also displayed synergistic interactions against HCV replication with no apparent changes in relative cytotoxicity. Combination treatments with additional

clinically-relevant small molecule HCV inhibitors are in progress. The addition of ribavirin did not affect the relative potency of combinations of TIZ and interferon, indicating no interference between ribavirin and TIZ. TIZ monotherapy was equally effective in inhibiting several clinically relevant drug-resistant mutants (NS5b S282T, genotypes 1a and 1b; NS3 A156V/T, genotype 1b; NS3 R155K, genotype 1a). While it was possible to select HCV replicon-containing cell lines that were resistant to 10uM NTZ or TIZ (10X EC90), it was not possible to transfer the TIZ-resistant phenotype to naive Huh7.5 cells by transfection of HCV RNA from these lines, indicating that primary resistance was conferred by changes in the host, not the virus. NTZ and TIZ are also active against hepatitis B virus replication in cell culture models, are equipotent against several clinically-relevant drug-resistant HBV mutants, and display synergistic interactions with several licensed anti-HBV nucleosides and nucleotides.

MEDI 153

Small molecule strategies for inhibiting human viral infections

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Medicinal plants have long been an excellent source of pharmaceutical agents. Accordingly, the author's Natural Products Research Laboratories (NPRL) uses medicinal chemistry by combining chemistry and biology to discover and design new chemotherapeutic agents based on plant-derived compound leads. Research approaches include bioactivity- or mechanism of action-directed isolation and characterization of active compounds, rational drug design-based modification and analog synthesis, as well as structure-activity relationship and mechanism of action studies. Anti-AIDS research in the NPRL has led to the extremely potent anti-HIV agent dimethyl succinyl betulinic acid (renamed Bevirimat by its licensee Panacos Pharmaceuticals Inc.), which was developed from the natural triterpene lead betulinic acid. Bevirimat succeeded in anti-AIDS Phase IIa clinical trials, is currently in Phase IIb trials, and will soon be placed in Phase III trials. Bevirimat is also the first in a new class of HIV drug candidates called “maturation inhibitors”. The discovery and development of Bevirimat and many other classes of natural products, including DCK and DCP, which are currently in preclinical development as clinical trials candidates for treating AIDS, will be discussed. (Aided by NIH grants AI-33066 and AI-77417).

MEDI 154

SAR studies on a series of inhibitors of human cytomegalovirus

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Infection by human cytomegalovirus (hCMV) remains a significant threat to susceptible people throughout the world. We have discovered a series of imidazolyl-pyrimidine compounds, which were found to be irreversible inhibitors of the hCMV UL70 primase based on results from radiolabeling and SAR studies. Analogs are described that rival ganciclovir and cidofovir in antiviral potency and possess improved cytotoxicity profiles

MEDI 155

Discovery of GS-9131, an oral prodrug of a novel nucleoside phosphonate HIV reverse transcriptase (RT) inhibitor

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A broad ranging study of nucleoside phosphonate RT inhibitors (NtRTI) allowed the determination of key structural features that typically result in potent RT inhibition. Unsaturated 2',3'-dideoxy-2',3'-didehydro (d4) analogs displayed high potency and in some cases favorable resistance profiles toward clinically relevant resistant RT mutants. The optimal phosphonate inhibitor, GS-9148 (2'-Fd4AP) also included a 2'-fluorine substitution which was rationally designed to eliminate mitochondrial toxicity effects.

The design of amidate prodrugs, cleaved intracellularly by cathepsin A, proved effective in oral delivery of GS-9148 and subsequent generation of active metabolite (GS-9148 diphosphate) in lymphatic PBMC cells. Prodrug GS-9131 upon oral administration in dogs, resulted in a PBMC GS-9148 diphosphate Cmax = 9.2 micromolar, and a long (>24 h) intracellular half life suggesting the potential for QD dosing. In summary, GS-9131 is a novel, rationally designed NtRTI prodrug with an excellent resistance and toxicity profile, currently in clinical development for the treatment of HIV.

MEDI 156

New drugs for bad bugs: Strategies for addressing the challenges of antibacterial drug discovery

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The need for new antibiotics is undisputed with many reports emphasizing the paucity of antibiotics in the current industry pipeline. Although sequencing of the bacterial genomes have identified a large number of potential new targets, high-throughput screens of these targets have yielded few tractable leads. Our experience likely mirrors the industry as a whole, resulting in the bulk of new antibiotics in development across industry being focused on improving the spectrum of existing classes. Our group is addressing these challenges by creating a broad discovery platform consisting of programs focused on novel targets coupled with partnerships with biotech companies having transformational technologies. These combined efforts are directed at addressing the key unmet needs for this area which include: oral/iv agents for MRSA, iv agents for hospital acquired gram negative infections and new agents to tackle multi-drug resistant RTI pathogens such as S.pneumoniae. Furthermore, we have created industry leading partnerships with the Defense Threat Reduction Agency (US Department of Defense) and the Wellcome Trust which provide funding that has enabled us to direct one of our internal antibacterial drug discovery programs at hospital gram negative and biothreat pathogens. The current talk will concentrate on the unique issues facing novel antibacterial drug discovery and how new strategies are needed to create a new generation of antibiotics.

MEDI 157

Molecular machines that assemble biological membranes

***Daniel E. Kahne**, kahne@chemistry.harvard.edu, Department of Chemistry and Chemical Biology, Harvard University, 12 Oxford Street, Cambridge, MA 02138*

Integral ß-barrel proteins are characteristically found in the outer membranes of mitochondria, chloroplasts, and Gram-negative bacteria. The cellular machine that assembles these proteins is conserved and contains as its principal component an integral membrane protein, called YaeT in E. coli, which has one or more polypeptide transport associated (POTRA) domains. I will talk about the structure of a periplasmic fragment of YaeT comprising four POTRA domains, one of which is unique in containing a site that binds extended peptides. We propose that this POTRA domain facilitates the assembly of ß-barrel proteins in the outer membrane by a mechanism involving ß-strand augmentation.

MEDI 158

Novel DNA gyrase inhibitors: Fragment-based NMR screening to antibacterial agents

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DNA gyrase, consisting of the subunits GyrA and GyrB, is a member of the type II family of topoisomerases that control the topological state of DNA in cells. Through ATP hydrolysis, GyrB provides the energy required for breaking and resealing DNA that is needed for negative supercoiling by DNA gyrase. ParE is the ATPase subunit of the closely related enzyme, topoisomerase IV, which is involved in the separation of linked closed circular bacterial chromosomes. Both enzymes are essential across bacterial species and inhibition of either function in bacteria results in a disruption of DNA synthesis and cell death. The pyrrolamides are a novel class of antibacterial agents that target DNA gyrase. This series was discovered at AstraZeneca through a fragment-based lead generation (FBLG) effort using NMR to identify low molecular weight compounds that bind to the ATP pocket of GyrB. A focused library of compounds was synthesized based on selected fragment hits and the resulting pyrrolamide series was selected for further investigation. Compounds in this series are potent inhibitors of DNA gyrase and topoisomerase IV through competitive displacement of ATP in the GyrB subunit, as demonstrated by enzyme kinetics and protein crystallography. In addition, these compounds display promising antibacterial activity against a broad spectrum of important human pathogens, including strains that are resistant to current drugs. Representatives of the class are bactericidal, demonstrate a low frequency of spontaneous resistance and are efficacious against S. pneumoniae in mouse infection models. Therefore, the pyrrolamides demonstrate promise as a novel class of antibacterial agents for the treatment of hospital and community-acquired infections.

MEDI 159

Structural, mechanistic and inhibitory analysis of the transpeptidation/glycosyltransfer steps of peptidoglycan synthesis in MRSA

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Peptidoglycan glycosyltransferases (GTs) catalyze the polymerization step of cell-wall biosynthesis, are membrane-bound, and are highly conserved across all bacteria. Long considered the "holy grail" of antibiotic research, they represent an essential and easily accessible drug target for antibiotic-resistant bacteria, including methicillin-resistant Staphylococcus aureus. We have determined the 2.8 angstrom structure of a bifunctional cell-wall cross-linking enzyme, including its transpeptidase and GT domains, both unliganded and complexed with the substrate analog moenomycin. The peptidoglycan GTs adopt a fold distinct from those of other GT classes. The structures give insight into critical features of the catalytic mechanism and key interactions required for enzyme inhibition.

MEDI 160

The discovery of potent and selective inhibitors of undecaprenyl pyrophosphate synthase

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Undecaprenyl pyrophosphate synthase (UPPS) is cis-prenyl transferase which is essential for bacterial viability. It catalyzes the sequential condensations of eight isopentenyl pyrophosphate molecules with farnesyl pyrophosphate to form C55 undecaprenyl pyrophosphate, which is the lipid carrier for bacterial cell wall peptidoglycan assembly. The critical biological function makes UPPS an attractive target for the discovery of novel antibacterial agents. In a high throughput screening campaign, hits with a tetramic acid core structure were identified as specific inhibitors of UPPS. Subsequent medicinal chemistry effort generated analogs with potent enzyme and whole-cell inhibitory activities.

MEDI 161

Rational drug design of antiviral agents against influenza, HCV and HIV virus

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Influenza neuraminidase, HCV protease and HIV integrase are well defined targets for structure based rational drug design. Case studies of the design of a number of highly potent inhibitors of these targets will be presented. The studies will include the utilization of X-ray crystal structures, in vitro SAR and in vivo results in the design of the potent inhibitors.

MEDI 162

Discovery of an allosteric activator of glucokinase

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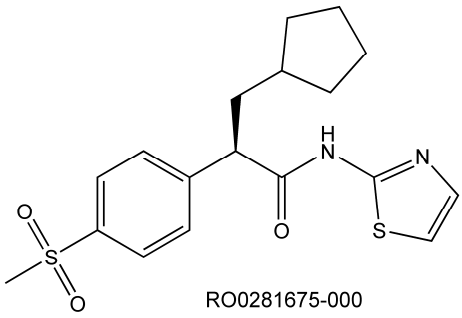
Glucokinase (GK) plays a key role in whole-body glucose homeostasis by catalyzing the phosphorylation of glucose in cells that express this enzyme, such as pancreatic beta cells and hepatocytes. A class of antidiabetic agents that act as nonessential mixed-type GK activators (GKAs) by increasing the glucose affinity and maximum velocity (Vmax) of GK have been identified. This presentation will provide detailed SAR surrounding the phenylacetamide class of GKAs demonstrating the progression from a HTS hit to a clinical lead compound, RO0281675-000, which is the first glucokinase activator to progress to the clinic. Dose response data in an OGTT in humans will be shown.



RO0281675-000

MEDI 163

Discovery of BMS-754807, a small molecule inhibitor of IGF-1R in clinical development

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Considerable attention has been focused on understanding the role of insulin-like growth factor I receptor (IGF-1R) signaling in stimulating mitogenesis, transformation to the oncogenic phenotype, and the anti-apoptotic effects observed in malignant cells. Inhibition of IGF-1R signaling results in blockade of two important pathways for tumor growth the RAS/Raf/MAP Kinase, pathway primarily responsible for mitogensis, and the PI-3 kinase pathway which has an anti-apototic role. Epidemiological studies have also highlighted the importance of IGF-1R in key tumor types by correlating elevated IGF-I levels with increased risk of developing colon, breast, prostate, and lung tumors. As monoclonal antibodies targeting the extra-cellular binding domain of IGF-1R have advanced in the clinic, the potential of this target has been demonstrated and the interest in small molecules inhibitors of IGF-1R has intensified. Recently, several small molecule inhibitors of IGF-1R have entered the clinic including pyrroloprimidines (NVP-AEW-541), imidazopyrazines (OSI-906), 2-4-diaminopyrimidines (XL-228), and podophylotoxin derivatives (AXL-1717). This presentation will disclose for the first time the discovery and development of a novel class of IGF-1R inhibitors leading to the clinical candidate, BMS-754807.

MEDI 164

EP-3 Receptor antagonists for Prostaglandin E-2 are novel potent antiplatelet agents that do not prolong bleeding

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The platelet EP-3 receptor belongs to the family of GPCR's. It facilitates platelet aggregation in response to multiple agonists. Similar to the P2Y12 receptor for

adenosine diphosphate (ADP), the target of clopidogrel and prasugrel, EP3 regulates cAMP synthesis through the inhibitory G(i) pathway to reduce adenylyl cyclase activity. Current evidence suggests that EP-3 antagonists represent a novel class of anti-platelet agents, useful in addressing PGE-2 facilitated inflammatory risk of atherothrombosis in cardiovascular disease. We used a ligand-based design strategy to develop multiple classes of potent and selective EP-3 antagonists. Following optimization of our lead series, we have identified the clinical compound DG-041. It inhibits PGE-2 facilitation of platelet aggregation in vitro and ex vivo. DG-041 potentially has a superior safety profile to P(2)Y(12) antagonists as it does not affect bleeding times. Both discovery funnel and therapeutic window for DG041 will be discussed.

MEDI 165

Development of a CNS multiparameter optimization design tool increasing the probability of a compound survival by aligning metabolism, permeability, and safety properties in one molecule

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As the cost to develop pharmaceutical drugs increases and the regulatory environment for the industry becomes more conservative it is imperative that clinical candidates are designed with an improved probability of success. CNS MPO provides a prospective holistic assessment of a compound's attributes with respect to metabolism, permeability, safety, and drug-likeness. The CNS MPO algorithm was designed by incorporating knowledge from CNS drug space, general medicinal chemistry expertise, and safety and ADME analyses. Six physicochemical properties were selected to be the foundation of the CNS MPO algorithm. Looking at the in-vitro metabolism, permeability, and efflux, data from thousands of compounds and in-vivo safety data from CNS candidates, the CNS MPO has improved the probability of aligning and optimizing these parameters in one molecule. The overall MPO score defines the CNS drug space and correlates with Pfizer CNS clinical candidate survival. The power of this MPO is that it is prospective, expands drug design space versus hard property cut-offs, and can predict probability of outcomes prior to compound synthesis.

MEDI 166

Nonpeptide orally bioavailable glucagon receptor antagonists

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Glucagon is a 29 amino acid peptide secreted from the alpha-cells in responds to low plasma levels of glucose. Glucagon is a timely and potent activator of hepatic glucose production, whereas the role of insulin in the liver is to inhibit hepatic glucose production and induce hepatic glucose utilisation and storage. Inappropriately high glucose production from the liver is believed to be an important contributor to the development of hyperglycemia in type 2 diabetes. This is presumably a result of hepatic insulin resistance in combination with lack of suppression of glucagon secretion from the alpha-cells in response to elevated glucose. In type 2 diabetes the glucagon level is elevated relative to the blood glucose and insulin levels. Therefore, new therapeutic agents, capable of blocking the effect of glucagon on hepatic glucose production has attracted attention for treatment of hyperglycemia in type 2 diabetes.

This talk presents the optimization of a new series of small molecule human glucagon receptor (hGluR) antagonists. In the process of optimizing glucagon receptor antagonists we counter-screened against the closely related human GIP receptor (hGIPR) and through structure activity analysis we obtained compounds with low nanomolar affinities that were selective towards the hGluR in comparison to the hGIPR and the human GLP-1 receptor (hGLP-1R). In the best cases we obtained a >50 fold selectivity for the hGluR over the hGIPR and a >1000 fold selectivity over the hGLP-1R. A potent and selective glucagon receptor antagonist was demonstrated to inhibit glucagon-induced glycogenolysis in primary rat hepatocytes as well as to lower glucagon-induced hyperglycemia in Sprague Dawley rats. Furthermore, the compound was shown to lower blood glucose in the ob/ob mouse after oral dosing.

MEDI 167

Identification of potent, orally bioavailable nonnucleoside HCV RNA polymerase inhibitors

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Chronic hepatitis C virus (HCV) infection afflicts more than 170 million people worldwide and is a major cause of serious liver disease. Current HCV therapies, combinations of pegylated interferon and ribavirin, are associated with inadequate cure rates (particularly in patients infected with genotype 1 HCV) and significant side effects thus necessitating the identification of more effective anti-HCV agents. The HCV RNA-dependent RNA polymerase (NS5B) is an attractive target for the development of novel HCV treatments due to its essential role in the HCV replication cycle. We previously disclosed the identification of several potent, non-nucleoside NS5B inhibitors which bind to the “palm” site of the NS5B protein. Many of these molecules exhibited poor pharmacokinetic properties following oral administration to animals. We now describe new modifications to these inhibitors that significantly improve the oral bioavailability properties of the resulting compounds without sacrificing other desirable biological attributes. An optimized example is a potent inhibitor of the NS5B enzyme (genotype 1b IC_{50} <0.010 uM) and exhibits robust antiviral activity in cell culture (genotype 1b replicon EC_{50} = 0.017 uM). This molecule also displays favorable in vitro DMPK characteristics (solubility, microsome $t_{1/2}$, and Caco-2 P_{app}) as well as improved oral bioavailability properties in monkeys relative to earlier compounds studied. Importantly, the plasma concentrations of the optimized compound in monkeys 12 h after administration of a single 1 mg/kg oral dose were >10-fold higher than the corresponding antiviral EC_{50} value.

MEDI 168

6, 9-Disubstituted purines as potent dual Src/Abl tyrosine kinase inhibitors targeting the “inactive” conformation

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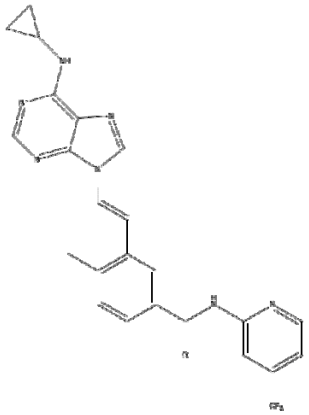
Abstract: Dual Src/Abl kinase inhibitors have demonstrated great potential in the treatment of both solid and hematologic malignancies. We have discovered a novel series of potent dual Src/Abl inhibitors based on a 9-(arenethenyl)purine scaffold. These novel inhibitors bind to the inactive, DFG-out conformation of both kinases and several display favorable pharmacokinetic profiles. Once-daily

oral administration of inhibitor A was found to significantly increase the survival of mice injected intravenously with Ba/F3 cells expressing wild-type Bcr-Abl and in addition elicited dose-dependent tumor shrinkage in mice bearing Src Y527F xenografts. Several compounds in this series also demonstrated potent activity against a panel of imatinib resistant mutations including the T315I variant which represents 15-20% of clinically observed mutants and is resistant to approved agents, including imatinib, dasatinib, and nilotinib.



MEDI 169

Discovery of 3-carboxamide isoxazoles as TRPV1 antagonists for the treatment of pain

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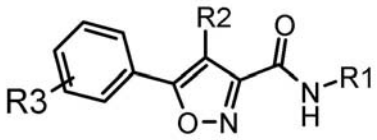
Transient Receptor Potential Vanilloid 1 (TRPV1) is a Ca2+ permeant non-selective cation channel expressed in a subpopulation of primary afferent neurons. TRPV1 is located (both in the periphery and spinal cord) on a subset of Aä and C fibres, the afferents commonly associated with nociception. In addition to mediating the effects of exogenous capsaicin, primary afferent TRPV1 receptors are thought to mediate the actions of heat (> 43 °C), and protons (pH < 6.8) and are modulated by a variety of endogenous lipid mediators including arachidonoic acid metabolites. Consequently, TRPV1 is believed to act as an integrator of nociceptive responses to both chemical and thermal noxious stimuli and TRPV1 antagonists should have utility in the management of acute and chronic nociceptive pain. High throughput screening of the PCOP compound library followed by hit optimisation led to a lead candidate that shows potent, competitive inhibition of capsaicin-induced Ca2+ influx in vitro, and potent antinociception in vivo. A lead optimisation program was initiated focusing on improving bio-activity, selectivity, and solubility with the aim to develop novel orally active TRPV1 antagonists, suitable for once or twice daily dosing for the treatment of both acute and chronic pain. The focus of this presentation will detail

SAR developed within the 3-carboxamide isoxazole series and explore the challenges involved in improving both the pharmacological and physicochemical properties. In vivo data will also be disclosed for a selection of compounds showing effective analgesia.



MEDI 170

Discovery of orally active Bace-1 inhibitors for the treatment of Alzheimer's disease

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Alzheimer's disease is a devastating neurodegenerative disorder for which no efficacious treatment is currently available. The disease is characterized by the progressive formation of insoluble amyloid plaques and neurofibrillary tangles in the brain. BACE-1 is an aspartyl protease which plays a key role in the formation of these plaques and inhibition of this enzyme represents one of the most attractive areas of research in the quest to provide an effective therapy for sufferers of Alzheimer's disease.

Our strategy for the design of BACE-1 inhibitors has been based on the transition-state mimetic concept, an approach that has been used successfully to design inhibitors of other aspartyl proteases, most notably HIV protease. This approach typically relies on replacement of the scissile amide bond of an appropriate substrate with a stable mimetic of the putative transition-state structure.

This presentation will describe how, during our lead generation effort, the support of X-ray crystallography at an early stage allowed the rapid discovery of a key inhibitor-enzyme interaction. Further crystallographic studies led to the identification of five different binding modes and enabled the design of new and more potent inhibitors. The information gained from these studies allowed inhibitors with nanomolar potency to be developed from our initial micromolar

hits. This work culminated in the discovery of the first BACE-1 inhibitor with efficacy in animal models of neurodegeneration following oral dosing. Further modifications led to a second generation of inhibitors of similar potency and with improved oral bioavailability. The in vivo efficacy of such inhibitors is currently under investigation.

MEDI 171

If it's not one thing, it's another: Improving the Phase 1 and Phase 2 metabolic stability of a series of pyrazole-containing gamma-secretase inhibitors

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A series of de novo designed, pyrazole-containing molecules was explored during a lead finding effort for our gamma-secretase inhibitor program. We found that these molecules exhibited good potency and selectivity towards inhibition of gamma-secretase. However, in vitro assays indicated a high rate of clearance by both oxidative and conjugative metabolic pathways. Numerous avenues were explored in an attempt to improve the metabolic stability of the series and specific modifications were found that allowed for continued development. Both successful and unsuccessful strategies will be discussed.

MEDI 172

Discovery of orally available aldosterone synthase (CYP11B2) inhibitors

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Aldosterone synthase (CYP11B2) is a mitochondrial cytochrome P450 enzyme which is expressed in the adrenal cortex, where it catalyzes the three-step conversion of 11-deoxycorticosterone to aldosterone. Elevated aldosterone levels are implicated in various medical conditions, including hypertension,

congestive heart failure, cardiac, vascular and renal fibrosis. The inhibition of aldosterone synthase is expected to offer a useful therapeutic strategy to treat disorders mediated by aldosterone. The discovery of series of aldosterone synthase inhibitors which demonstrated in vivo efficacy following oral administration in a rat model will be presented. The lecture will highlight how an early focus on in vitro metabolic clearance data, along with a combination of in vitro and in vivo metabolite identification studies led to compounds with good oral bioavailability.

MEDI 173

Optimization of oral pharmacokinetics in the discovery of clinical candidates for the treatment of sexual dysfunction

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Uprima™ (apomorphine sublingual) is a non-selective dopamine agonist with clinical efficacy in Male Erectile Dysfunction and with case reports of efficacy in the treatment of Female Sexual Dysfunction FSD. Apomorphine has side effects which include nausea, vomiting and hypotension. Our hypothesis is that both D2 and D3 agonism are involved in prosexual pathways, but only D2 is implicated in the dose-limiting side effects. To prove this a series of D3 selective agonists were discovered. The early stages of the project through to FIM are described, including the discovery of a clinical candidate which demonstrated >1000 fold functional selectivity for D3 receptor mediated agonism. Whilst this agent possesses an excellent pharmacological profile to test the hypothesis, it is subject to high systemic clearance. First-pass hepatic extraction for this agent can be defeated in humans through dosing of the agent via the intranasal route. As an alternative solution to this issue we sought to identify an agent with the pharmacological profile of the intranasal agent, but with a pharmacokinetic profile suitable for oral dosing. The presentation will describe the discovery and synthesis of such as agent. Furthermore, the presentation will describe additional examples of optimisation of oral pharmacokinetics in the discovery of agents designed for the treatment of Sexual Dysfunction.

MEDI 174

Challenges in the development of orally bioavailable antagonists of the calcitonin gene-related peptide receptor, a family B GPCR: Discovery of telcagepant (MK-0974) for the treatment of migraine

***Chris Burgey**, christopher_burgey@merck.com, Department of Medicinal Chemistry, Merck Research Laboratories, WP14-2, 770 Sumneytown Pike, P.O. Box 4, West Point, PA 19486*

Calcitonin gene-related peptide (CGRP) is a neuropeptide that is believed to be involved in the pathogenesis of migraine headache and CGRP receptor antagonists represent a promising new approach for the treatment of migraine. Since CGRP receptor antagonists lack direct vasoconstrictor activity, this approach may offer advantages over current 5–HT1B/1D receptor agonists (triptans), which are contraindicated for use in patients with cardiovascular disease. Our strategy to develop orally bioavailable antagonists for this Family B GPCR, a class of receptors for which it has been notably difficult to do so, will be discussed. Elements of design and optimization leading to telcagepant (MK-0974), an orally bioavailable CGRP receptor antagonist currently in Phase III clinical trials, and the backup MK-2918 will be presented.

MEDI 175

Hedgehog pathway antagonists: New mechanisms and targets

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Inappropriate activation of the Hedgehog (Hh) signaling pathway has been implicated in a diverse spectrum of tumors, including those of the skin, brain, lung, pancreas, and prostate. Pharmacological blockade of the Hh pathway has emerged as a therapeutic strategy, and antagonists of the Hh signaling protein Smoothened (Smo) have exhibited anti-tumor activities in both animal models and human clinical trials. Since inhibitors of this transmembrane protein have limited efficacy against Hh pathway activation that is initiated downstream of the Hh receptor Patched1 (Ptch1), small molecules that target other Hh pathway regulators could remediate a broader range of Hh pathway-dependent cancers. We report here several Hh pathway inhibitors that are epistatic to Smo, each of which has a unique mechanism of action. We further demonstrate the ability of certain compounds to block cell proliferation and neoplastic transformation promoted by an oncogenic form of Smo. These novel pathway antagonists will be

valuable probes for elucidating downstream Hh signaling mechanisms and for developing new chemotherapies against Hh pathway-dependent tumors.

MEDI 176

GLI transcription factors as pharmacological targets

***Rune Toftgård**, rune.toftgard@ki.se and Matthias Lauth, Center for Biosciences, Karolinska Institutet, Novum, SE-141 57 Huddinge, Sweden*

The Hedgehog (Hh) signaling pathway ending with activation of the GLI transcription factors is of key importance for normal embryonic development, tissue maintenance, regeneration and for development of several forms of cancer including skin, brain, pancreas and breast cancer. Of particular interest is the apparent role of Hh-signaling in the control of proliferation and maintenance of adult stem cell populations and cancer initiating cells as examplified by active Hh-signaling in a skin stem cell population marked by Lgr5 expression. In addition to ligand- and receptor-induced signaling a number of downstream activation mechanisms resulting in GLI activation exist. We have identified small molecule inhibitors of GLI-mediated transcription that block tumor cell growth in vitro and in a xenograft model. By targeting the final effector step in the Hh-pathway such inhibitors have the advantage of blocking Hh signaling irrespective of the activation mechanism.

MEDI 177

Discovery of the Hedgehog antagonist GDC-0449 for the treatment of solid tumors

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Cellular pathways involved in cell differentiation and embryonic development have recently been implicated in cancer. In particular, the hedgehog pathway has been shown to be activated in BCC (basal cell carcinoma), some medublastomas, and a number of other epithelial cancers. Hedgehog ligands bind to the trans-membrane protein Patched (PTCH) which releases Smoothened (SMO) to transmit signals to the nucleus, resulting in the transcription of a number of proteins including the transcription factor Gli. Organic compounds, such as the plant derived cyclopamine, have been shown to block this signal transduction cascade by binding to SMO. Herein we report the discovery of a potent and efficacious small molecule inhibitor of the hedgehog pathway, identified via a systematic structure-activity process with an emphasis on superior pharmaceutical properties. The compound, GDC-0449, is currently

being developed by Genentech as a novel cancer therapeutic and has advanced to Phase II clinical trials in patients with colorectal and ovarian cancers.

MEDI 178

Discovery of IPI-926, a semisynthetic clinical candidate that targets the Hedgehog pathway

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Recent evidence suggests that blocking aberrant Hedgehog pathway signaling may be a potential therapeutic strategy for the treatment of several types of cancer. Cyclopamine, a plant *Veratrum* alkaloid, is a natural product antagonist of the Hedgehog pathway. However, cyclopamine has poor pharmaceutical properties and is a weak inhibitor of the pathway. Recently, our group reported the synthesis of D-homo cyclopamine analogs by an unprecedented sequence of synthetic transformations on the natural product: chemoselective cyclopropanation followed by stereoselective acid-catalyzed rearrangement. These D-homo analogs are more stable to acid-catalyzed degradation than the natural product. Further elaboration of the A-ring generated three new series of analogs with improved potency and/or solubility. Lead compounds from each series were characterized *in vitro* and evaluated *in vivo* for biological activity and pharmacokinetic properties. These studies led to the discovery of IPI-926, a novel semi-synthetic cyclopamine analog as a clinical candidate with improved pharmaceutical properties and potency, and a superior plasma pharmacokinetic profile relative to cyclopamine.

MEDI 179

Inhibiting smoothened from inside: Rationally designed nanomolar inhibitors of the Hedgehog pathway

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Smoothened, a critical component of the Hedgehog (HH) pathway is a seven transmembrane domain protein with three intracellular loops. Peptides corresponding to the highly conserved intracellular loops of Smoothened inhibit the HH pathway and cancer cell growth (J. Med. Chem, 50: 4534, 2007). CD and NMR spectroscopy studies have shown that anchoring peptide inhibitors to the cell membrane through lipidation facilitates folding of even short, otherwise unfolded peptides into stable structures. Lipidation enhances the potency of inhibitors by several orders of magnitude via three mechanisms: 1) stabilization of peptide tertiary structure, 2) enhancement of cell permeability and 3) increasing the local concentration of the compounds in the membrane. The inhibitors described here are stable in serum and can be delivered either topically or intravenously. Derivatives of the second intracellular loop inhibit growth of HH pathway-dependent cancer cells with GI50 values in the subnanomolar range. These agents are promising drug candidates for the treatment of many tumor types.

MEDI 180

Evolution and utility of a corporate screening collection against CNS targets

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The view of what a screening collection should contain has changed over the past decade. After the technological innovations that allowed high throughput screening in the early 1990's came a push to increase the size of corporate screening collections. There was no precedent of how to build a corporate screening collection and many companies followed a “bigger is better” philosophy with the primary success criterion being the hit-rate of the assay. The concept of hit-rate as the only metric of success has given way to success criteria including chemical scope, compound quality and time spent in the lead generation. In this presentation, we will outline learning based on over thirty lead generation

campaigns against CNS targets. This knowledge has helped us to better define how to expand and utilize our corporate collection for emerging targets.

MEDI 181

Evolution of Eli Lilly screening collection

***Richard J. Loncharich**, Discovery Operations, Eli Lilly and Company, Building 87/2, 307 E McCarty Street, Indianapolis, IN 46285, Fax: 317-433-0552*

Over the last few decades a number of rules-based methods have been established to increase success rates of Lead Generation efforts. As a part of this learning, knowledge-based library design is a major component of Lilly's strategy for building its sample screening collection. An overview about Lilly's approach to enrich its sample collection will be discussed.

MEDI 182

Approaches to front loading: Optimizing success with synthesis

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This talk will discuss strategies that address the growth of corporate compound collections. A historical perspective on paradigms will be briefly detailed leading into modern practices of front loading libraries with desirable properties with extensive biological annotation. Segmentation of collections into smaller sets, encompassing target family, diversity oriented, fragment, lead-like, drug-like sets + others will be highlighted. Anecdotes from industry and hierarchical mis-perceptions of phrases ‘easy chemistry' and ‘chemistry driven' will be discussed and coupled with the growth of research in enabling chemistries that includes one and two step methodologies employing multi-component reactions. Following the mantra of buying non-exclusive compound sets without assessment of chemical tractability or more importantly ‘iterative efficiency' and following a ‘rear-view mirror' approach in designing target family libraries, with or without the balance of a strategic, proprietary, chemo-centric, diversity-oriented in house efforts, will be discussed.

MEDI 183

Building the NIH MLSMR screening collection for discovery of biological probes

***Timothy G. Lease**, Tim.Lease@glpg.com, BioFocus DPI, South San Francisco, CA 94080*

The nine HTS centers comprising the NIH Molecular Libraries Probe Production Centers Network (MLPCN), part of the NIH Roadmap Initiative, conduct high throughput screens on assays submitted to NIH from biologists around the globe. MLPCN's goal is not drug discovery but generation of probe compounds useful for elucidating biological pathways. Since 2005, NIH's Molecular Libraries Small Molecule Repository (MLSMR) has built a collection of over 300,000 compounds to facilitate MLPCN's objective. The MLSMR compound collection comprises subsets of known biologically active compounds, natural products, targeted libraries, and compounds from academicians, as well as a large diversity collection. How is the MLSMR collection different from one designed for drug discovery? What is NIH's strategy for building the MLSMR collection, and how will the collection evolve?

MEDI 184

Construction of a fragment-based screening collection

***Christopher W. Murray**, c.murray@astex-therapeutics.com, Computational Chemistry and Informatics, Astex Therapeutics, 436 Cambridge Science Park, Milton Road, Cambridge CB4 0QA, United Kingdom*

Fragment-based screening offers an alternative to high throughput screening for the generation of lead molecules. Fragment-based approaches use low molecular weight starting points which typically form a small number of high quality interactions. The small number of interactions means that fragments have weak affinity for typical target classes but the presence of high quality interactions means they have high potencies relative to their size (i.e., high ligand efficiency). The weak affinity of fragments often necessitates screening approaches (e.g., xray, NMR) which can detect millimolar binding and such screening methods are lower throughput compared to traditional assays. Fortunately the size of a fragment library required to sample chemical space is much smaller than that needed with a library of drug-like compounds and the reasons for this are discussed. The evolution of Astex screening collections over several generations is also outlined and in particular, an approach we adopted to enrich our screening collection with specifically synthesised proprietary compounds is presented. The talk will include some examples of how the output from the fragment library has inputted into successful lead generation campaigns.

MEDI 185

Metabolic stability challenges in drug discovery

***Li Di**, Chemical and Screening Sciences, Wyeth Research, CN 8000, Princeton, NJ 08543*

Metabolic stability plays an important role in pharmacokinetics of drug candidates. It affects clearance, oral bioavailability and overall in vivo exposure of compounds. Metabolic clearance influences how much and how often a drug should be dosed. Screening of metabolic stability has been moved to much earlier in the drug discovery process to provide earlier alert to potential liabilities for chemotypes, guide structural modifications, triage compounds for vivo studies and diagnose in vivo PK. Multiple animal species are typically applied to provide guidance on in vivo studies using different animal models, due to species dependence of metabolizing enzymes. In vitro and in vivo correlations are critical to develop confidence in using in vitro models. Other factors can also have significant impact on in vivo clearance, such as efflux transporters (Pgp, MRPs), biliary clearance, plasma stability, plasma protein binding and red blood cell partitioning. Real-world drug discovery examples and case studies will be discussed.

MEDI 186

Inhibitors of respiratory syncytial virus fusion: Optimization from screening leads to potent, orally active compounds

***Nicholas A. Meanwell**, Nicholas.Meanwell@bms.com, Department of Chemistry, Bristol-Myers Squibb Research and Development, 5 Research Parkway, Wallingford, CT 06492*

Respiratory syncytial virus (RSV) is a leading cause of respiratory tract infection that infects virtually all children in the first 2 years of life. Although typically restricted to the upper respiratory tract, in those who are immunosuppressed or have underlying cardiopulmonary problems, RSV can infect the lower respiratory tract, causing significant morbidity and mortality. RSV is also an underestimated pathogen in the elderly, where it is frequently misdiagnosed as influenza.

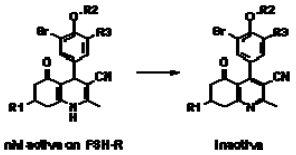
We identified a series of benzimidazole derivatives with potent and selective RSV fusion-inhibiting activity using a tissue cell culture screen. Structure-activity studies that focused on maintaining potency whilst optimizing the balance between metabolic stability and membrane permeability produced compounds with oral bioavailability in animals and antiviral activity in models of RSV infection. BMS-433771 emerged from this work as a potent, orally bioavailable inhibitor of RSV fusion that binds to the F protein amino terminus heptad repeats.

MEDI 187

PK/PD optimization of dihydropyridine allosteric FSH-receptor agonists

***CM. Timmers**, marco.timmers@spcorp.com, Department of Medicinal Chemistry Oss, Schering-Plough Research Institute, Molenstraat 110, Oss 5342 CC, Netherlands, Fax: + 31 412 662546*

Gonadotropins (FSH, LH and hCG) are natural glycoprotein hormones that act as key regulators in mammalian sexual maturation and reproduction. In females, FSH is responsible for follicular growth during the first half of the menstrual cycle. A distorted balance of endogenous FSH plasma levels, one of the causes of female infertility, may be counteracted by supplying exogenous FSH. Since FSH has to be administered parenterally, there is a need for orally active LMW FSH receptor agonists.



HTS and subsequent optimization activities have gained allosteric LMW agonists for the FSH receptor with a dihydropyridine (DHP) core structure. Metabolite identification studies have revealed various metabolically labile sites on the parent structure, such as oxidation to the pyridine analog. This presentation will highlight several approaches to improve the metabolic stability of the DHP core structure. Also the effect of metabolic stabilization on the PK/PD relationship for follicle stimulation will be discussed in more detail.

MEDI 188

Minimizing metabolic activation at the lead optimization stage: Challenges and solutions

***Jean-François Lévesque**, jeanfrancois_levesque@merck.com, Pre-clinical DMPK, Merck Frosst Centre for Therapeutic Research, 16711 Transcanada Hwy, Kirkland, QC H9H 3L1, Canada, Fax: 514-428-4900*

It is now well established that the metabolism of small molecules drug candidates can lead to the formation of reactive intermediates that have the potential to covalently bind to macromolecules. These reactive intermediates are believed to be the initiators of clinical adverse events, including target organ toxicities, and immune system mediated idiosyncratic reactions. There are therefore on-going efforts at a drug discovery stage to assess the metabolic activation potential of

lead molecules and to abrogate this potential liability through informed structure-metabolism-relationship (SMR). Several case studies, in particular from the DP1 antagonist program, will be presented to illustrate the impact of metabolic activation on drug discovery programs and some of the approaches that can be utilized to minimize the formation of reactive intermediates.

MEDI 189

The more we know the harder it seems: Past, present and future in metabolism optimization in drug discovery

***Dennis A. Smith**, dennis.a.smith@pfizer.com, Global Research & Development, Pfizer, Sandwich Laboratories, Sandwich, Kent, United Kingdom*

Examples of the attempt to optimize the metabolism of compounds selected as clinical candidates and for drugs will be presented

MEDI 190

An artificial neural network model for prediction of logD

***Marvin Waldman**, marv@simulations-plus.com, Robert Fraczkiewicz, and Walter S. Woltosz, walt@simulations-plus.com, Simulations Plus, Inc, 42505 10th Street West, Lancaster, CA 93534, Fax: 661-723-5524*

Lipophilicity is a critical physicochemical property for understanding the absorption, distribution, and pharmacokinetics of drugs. logP, logarithm of the octanol-water partition coefficient, is generally used to measure lipophilicity. However, for compounds containing acidic or basic groups, ionization can significantly alter their lipophilic characteristics. The distribution coefficient, which measures the partitioning of all ionized and neutral forms into octanol, is a more appropriate measure of lipophilicity at a given pH. We describe a neural network ensemble model for prediction of logD as a function of molecular structure and pH. The model is trained on several thousand logD measurements at various pH values. We compare its performance to simpler approaches, such as assuming zero partitioning of ionized species or ion partitioning based on simple scaling rules, and also its performance on an external test set not used for training. Analysis of the descriptors used and their influence on logD is also presented.

MEDI 191

Derivatives of fluoroquinolones: Synthesis and biological evaluation as potential antitumor agents

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Fluoroquinolones, a well-known class of broad-spectrum antimicrobial agents, are among the most attractive drugs in the antiinfective chemotherapy field. This class of antibacterial agents targets DNA gyrase and topoisomerase IV, two enzymes belonging to the type II topoisomerase family. Mammalian topoisomerase II possesses a mechanism of action similar to that of DNA gyrase/topoisomerase IV. Several fluoroquinolones have been shown to have antiproliferative and apoptotic activity against several cancer cells and to inhibit growth of transitional bladder carcinoma cell lines but few SAR have been done in the field of antitumor quinolones.

The fact that this class of drugs shows topoisomerase II inhibitory activity has given rationality to quinolone-based drug design in the search for novel antitumor agents. We have initiated a screening programme to search for new derivatives of fluoroquinolones as antitumor agents. We describe the synthesis and antiproliferative properties on human cancer cell lines of ciprofloxacin and levofloxacin derivatives.

MEDI 192

Genetic and biochemical analysis of MTA/SAH nucleosidase as a target for antibiotic development

Ken Cornell[1]*, kencornell@boisestate.edu, Jacob Jones[1], Matt Wolter[1], Maria Martinez[1], Tony Martinez[1], and Nikhat Parveen[2]. (1) Department of Chemistry and Biochemistry, Boise State University, 1910 University Dr, Boise, ID 83725-1520, (2) UMDNJ-New Jersey Medical School, Newark, NJ 07103*

5' Methylthioadenosine / S-adenosylhomocysteine nucleosidase (MTN) is a bacterial enzyme central to the salvage the purine and methionine components of S-adenosylmethionine that are consumed in a host of metabolic reactions involved in polyamine and biotin synthesis, autoinducer formation, and methylation reactions. Inhibition or loss of MTN activity in a variety of bacterial species through pharmacologic interruption with MTA analogs or gene knock-out leads to changes in carbon utilization and growth profiles, interruption of autoinducer II production, and decreased biotin and biofilm synthesis. These phenotypic alterations could be rescued by introduction of additional MTN gene copies, or culture supplementation with polyamines or biotin. The results of

biochemical and in vitro studies suggest that MTN inhibitors are potential chemotherapeutics that may function best as adjunctive therapies to improve the activity of standard antibiotics.

MEDI 193

Discovery and structure-activity relationship investigations of 4-arylethynyldihydrocinnamic acid agonists of the antidiabetic target free fatty acid receptor 1

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The receptor FFA1 (GPR40) is highly expressed in pancreatic beta-cells and responds to physiological concentrations of long-chain free fatty acids to enhance glucose-stimulated insulin secretion, and is currently receiving attention as a new potential target for treatment of type 2 diabetes. We recently discovered a series of 4-arylethynyldihydrocinnamic acid agonists of the FFA1 receptor. Here, we describe the discovery and preliminary structure-activity relationships of this compound series. Representative compounds enhance glucose-stimulated insulin secretion from rat INS-1E cells and from isolated mouse islets, and thus have the potential to serve as tools in the further exploration of the receptor and as leads of drug discovery on the receptor.

MEDI 194

Design and synthesis of azabicyclo octane derivatives as dipeptidyl peptidase IV inhibitors

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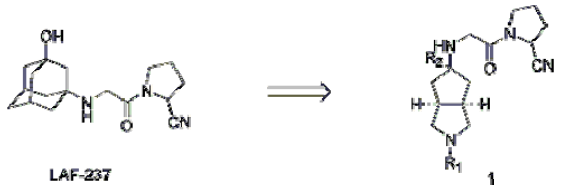
Dipeptidyl peptidase IV(DPP-IV) inhibitors are emerging as a new class of therapetutic agents for the treatment of type 2 diabetes. The catalytic action of DPP-IV is the principle means of degradation of glucagons-like peptide-1, a key mediator of glucose-stimulated insulin secretion, and DPP-IV inhibition shows clinical benefit as a novel mechanism for the treatment of type 2 diabetes. A novel series of azabicyclo octane derivatives represented by general formula (1) was synthesized and evaluated as inhibitors of DPP-IV. These compounds exhibit excellent in vitro activities and selectivities and in vivo efficacies. The design, synthesis and inhibitory activities of these compounds will be discussed.



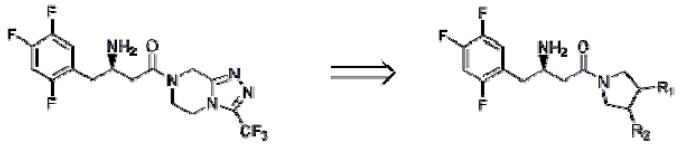
LAF-237 1

MEDI 195

Design and synthesis of pyrrolidine amino amides as dipeptidyl peptidase IV inhibitors

*TANG Peng Cho, tangpc@shhrp.com, **YANG Fang Long**, yangfl@shhrp.com, ZHANG Lei, SHEN Guang Yuan, LUO Jing Jing, and LI Xin, Shanghai Hengrui Pharmaceuticals Co. Ltd, 279 Wenjing Road, Shanghai 200245, China*

Dipeptidyl peptidase IV(DPP-IV) inhibitors are emerging as a new class of therapeutic agents for the treatment of type 2 diabetes. The catalytic action of DPP-IV is the principle means of degradation of glucagons-like peptide-1, a key mediator of glucose-stimulated insulin secretion, and DPP-IV inhibition shows clinical benefit as a novel mechanism for the treatment of type 2 diabetes. A novel series of cyclopyrrolidine amino amides were synthesized and evaluated as inhibitors of DPP-IV. The design, synthesis and inhibitory activities of these compounds will be discussed.



MK-0431

MEDI 196

Discovery of DNP-60502, a novel, potent AMPK activator for the treatment of metabolic syndrome

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AMP-activated protein kinase (AMPK) plays a key role as a master regulator of cellular energy homeostasis. The kinase is activated in response to cellular ATP depletion. The AMPK activation exerts important effects on glucose and lipid metabolism such as glucose uptake and fatty acid oxidation in skeletal muscle. Therefore the activator of AMPK is attractive as treatment of diabetes and other metabolic disorders. Reported here is a series of novel AMPK activators. The syntheses and SAR studies of this class of compounds will be presented. DNP-60502, one of the lead molecules in this series, displays potent AMPK activation in vitro and is effective in several animal models.

MEDI 197

Discovery of (4,4-difluoro-1,2,3,4-tetrahydro-5*H*-1-benzazepin-5-ylidene)acetamide derivatives as novel arginine vasopressin V_2 receptor agonists

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Arginine vasopressin (AVP) is a cyclic nonapeptide that is produced and secreted by the hypothalamo-neurohypophysial system. Stimulation of the V_2 receptor with AVP causes water reabsorption in the kidney via an increase in cAMP with subsequent activation of the aquaporin-2 water channel, which results in a lower urine volume. This implies that the V_2 receptor agonist can be used as a drug for the treatment of diseases such as central diabetes insipidus and nocturia. Here we illustrate the discovery of a novel series of (4,4-difluoro-1,2,3,4-tetrahydro-5*H*-1-benzazepine-5-ylidene)acetamide derivatives used as arginine vasopressin V_2 receptor agonists. Some representative compounds obtained in this study were found to decrease urine volume in water-loaded rats.

MEDI 198

Pharmacological characterization of AX-9657, a potent and selective neutrophil elastase inhibitor with good lung distribution

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Neutrophil elastase (NE) is a serine protease, expressed mainly by neutrophils, that is capable of degrading a variety of structural proteins of the extracellular matrix. Infiltration of activated neutrophils and excessive NE activity have been implicated in several lung diseases, including acute lung injury, cystic fibrosis, pulmonary fibrosis and COPD. Thus a NE inhibitor targeting excessive NE activity in lung tissue could have good therapeutic potential. In the search for a novel NE inhibitor, we have found AX-9657, a potent, selective, and water-soluble human NE (HNE) inhibitor. A distinct feature of AX-9657 is a high exposure level in lung tissue, enabling it to inhibit lung NE activity released from infiltrated neutrophils under inflammatory conditions. AX-9657 inhibited HNE-induced lung hemorrhage and edema induced by intratracheal administration of LPS. These results suggest that AX-9657 may be effective for the treatment of lung diseases through inhibition of excessive NE activity in lung tissue.

MEDI 199

Synthesis and optimization of 2-pyridin-3-yl-benzo[d][1,3]oxazin-4-one based inhibitors of human neutrophil elastase

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The hit to lead optimization of a 61 nM HNE inhibitor, 5-methyl-2-(2-phenoxy-pyridin-3-yl)-benzo[d][1,3]oxazin-4-one, is described. A structure-activity relationship study focused on the 5 and 7 benzoxazinone positions yielded the optimized 5-ethyl-7-methoxy-benzo[d][1,3]oxazin-4-one core structure. 2-[2-(4-methyl-piperazin-1-yl)-pyridin-3-yl] derivatives of this core were shown to yield HNE inhibitors of similar potency with significantly different stabilities in rat plasma.

MEDI 200

Vitamin D receptor antagonists from agonists: An unexpected discovery

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Vitamin D receptor agonists have been extensively studied for applications in cancer and other hyperproliferative disorders. In contrast, only a very small number of vitamin D receptor antagonists have been reported. In studying a variety of molecules which combine vitamin D receptor agonism and histone deacetylase inhibition, we have found that relatively minor variations in structure can turn a VDR agonist into a VDR antagonist. This paper will discuss the synthesis and biochemical characterization of a vitamin D receptor antagonist. Computational studies to investigate the mechanism of antagonism will be reported.

MEDI 201

Aromatic analogs of geranyl- and digeranylbisphosphonate

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Bisphosphonates represent an important class of biologically active compounds. Their clinical use as drugs to treat diseases associated with bone resorption is well documented, and the activity of the nitrogenous bisphosphonates is now known to result from impact on isoprenoid biosynthesis. Our labs have developed specific inhibitors of geranylgeranyl diphosphate synthase based upon a geranylbisphosphonate core. Here we will discuss the synthesis and biological evaluation of a series of mono- and dialkylbisphosphonates that possess an aromatic substructure. This substructure limits the conformational flexibility of the isoprenoid chain and affects selectivity towards specific enzymes of isoprenoid biosynthesis.

MEDI 202

Design and synthesis of new inhibitors for protein Farnesyltransferase and Geranylgeranyltransferase type-I

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Ras proteins are found constitutively activated (due to point mutations) in about 30% of all human cancers, resulting in uncontrolled proliferation and tumor cell survival. The interest in farnesyltransferase and geranylgeranyltransferase was heightened when it was discovered that Ras requires farnesylation and geranylgeranylation for its cancer-causing activity. This prompted many researchers to design and synthesize farnesyltransferase inhibitors (FTIs) and geranylgeranyltransferase inhibitors (GGTIs) as potential anticancer drugs. More recently FTIs have been shown to be potent inhibitors of tumor growth in several animal models. The only disadvantage is that these inhibitors show some toxicity in preclinical trials. The objective of our project is to synthesize new FTIs and GGTIs, which may show high selectivity and less toxicity to human body. We cloned and purified these two enzymes using various different methods. In the mean time, the design and synthesis of new FTIs and GGTIs are in progress through two major approaches: (1) rational design of CAAX peptidomimetics; (2) FPP/CAAX bisubstrate transition state analogs.

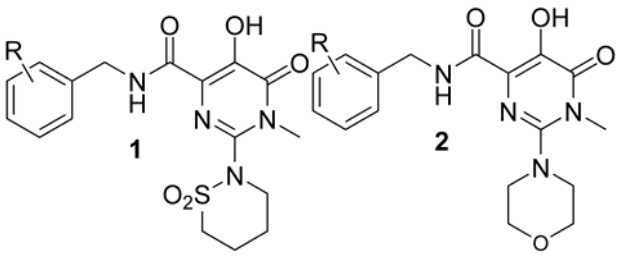
MEDI 203

C2 N-Linked heterocyclic derivatives of the dihydroxypyrimidione-4-carboxamide HIV integrase inhibitor template

Michael A. Walker[1], *Jacques Banville*[1], *Roger Remillard*[1], *Serge Plamondon*[1], *Gilles Bouthillier*[1], *Alain Martel*[1], *Yasu Ueda*[1], *Timothy Connolly*[1], *John Matiskella*[1], *Belgin Gulgeze*[1], *Albert Torri*[2], *Margaret Casperson*[2], *Sagarika Bollini*[2], *Brian Terry*[2], *Zeyu Lin*[2], *Himadri Samanta*[2], *Ira Dicker*[2], *Mark Krystal*[2], *and Nicholas A. Meanwell*[1]. *(1) Discovery Chemistry, Bristol-Myers Squibb, Wallingford, CT, (2) Virology, Bristol-Myers Squibb*

The dihydroxypyrimidinone-4-carboxamide heterocycle is very useful as a template for inhibiting HIV-1 integrase. Both potency and PK can be modulated by varying the substituent attached to the C2-site of the pyrimidine. In contrast to previous studies where C-linked substituents were examined, the current

approach looks at N-linked derivatives. The N-linkage to the core provides a means to modulate the electronic properties of the Mg^{+2}-binding domain of the template. SAR studies led to two series (**1** and **2**) of potent inhibitors having either a sultam or morpholino group attached to C2.

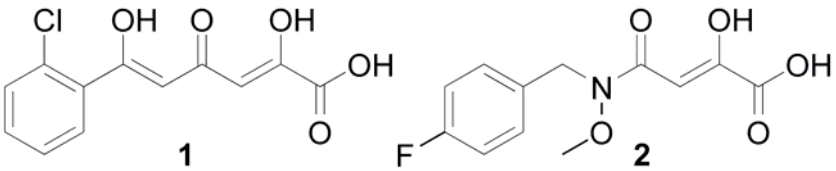


MEDI 204

Optimization of compound efficiency in the context of discovering an amide ketoacid based HIV-integrase inhibitor with oral antiviral activity

Michael A. Walker[1], *Jacques Banville*[2], *Timothy Johnson*[1], *Zhuping Ma*[3], *Roger Remillard*[1], *Serge Plamondon*[1], *Gilles Bouthillier*[1], *Alain Martel*[1], *Albert F Torri*[4], *Margaret Casperson*[5], *Sagarika Bollini*[4], *Brian J Terry*[4], *Zeyu Lin*[6], *Himadri Samanta*[4], *Mark Krystal*[5], *Ming Zheng*[7], *and Nicholas A Meanwell*[3]. *(1) Discovery Chemistry, Bristol-Myers Squibb Co, 5 Research Parkway, Wallingford, CT 06492, (2) Discovery Chemistry, Bristol-Myers Squibb, Wallingford, CT 06492, (3) Virology Chemistry, Bristol-Myers Squibb Research and Development, Wallingford, CT 06492, (4) Virology, Bristol-Myers Squibb Co, (5) Virology, Bristol-Myers Squibb Research and Development, (6) Virology, Bristol-Myers Squibb, Wallingford, CT, (7) Metabolism and Pharmacokinetics*

In the current study we demonstrate a hit-to-clinical candidate pathway that resulted in 50- and 2000-fold improvements in enzyme-inhibition and antiviral activity without an increase in molecular weight or change in molecular topology. The original hit , **1** (mw = 268) was optimized in a stepwise manner. Potential covalent protein-binding moieties were removed by reducing the number of the ketone groups. High enzyme inhibition activity was achieved by optimizing the aryl-portion of the molecule. Protein binding was reduced by replacing the standard amide by the corresponding methyl-hydroxamide. This eventually led to the discovery of compound **2** (mw = 269) a highly efficient inhibitor and antiviral agent.



MEDI 205

Design, synthesis and HIV-1 integrase inhibitory activity of N-benzyl-4-hydroxy-5-oxo-2,5-dihydro-1H-pyrrole-3-carboxamides.

B. Narasimhulu Naidu[1], *Jacques Banville*[1], *Sagarika Bollini*[2], *Gilles Bouthillier*[3], *Hatice Belgin Gulgeze*[3], *Timothy Johnson*[3], *Mark Krystal*[2], *Zeyu Lin*[4], *Alain Martel*[3], *Nicholas A. Meanwell*[1], *Dawn D Parker*[5], *Serge Plamondon*[3], *Roger Remillard*[3], *Himadri Samanta*[2], *Margaret E. Sorenson*[3], *Brian J Terry*[2], *Albert F Torri*[2], *Michael A. Walker*[3], *Ming Zheng*[5], *and Ma Zupping*[3]*. (1) Discovery Chemistry, Bristol-Myers Squibb, CT, (2) Virology, Bristol-Myers Squibb Co, (3) Discovery Chemistry, Bristol-Myers Squibb Co, Wallingford, CT 06492, (4) Virology, Bristol-Myers Squibb, Wallingford, CT, (5) Pharmaceutical Candidate Optimization, Bristol Myers Squibb Co, Wallingford, CT 06422*

Integrase is one of the three key enzymes required for the successful replication of human immunodeficiency virus type 1 (HIV-1). This enzyme catalyzes the insertion of double stranded viral DNA into the host genome. This occurs through a multi-step process involving formation of pre-integration complexes followed by 3'-processing and strand transfer reactions. N-Benzyl-4-hydroxy-5-oxo-2,5-dihydro-1H-pyrrole-3-carboxamides were found to inhibit the strand transfer step of the integration process. In this presentation, the design, synthesis, HIV-1 integrase inhibitory activity and animal pharmacokinetics of N-benzyl-4-hydroxy-5-oxo-2,5-dihydro-1H-pyrrole-3-carboxamides will be discussed.

MEDI 206

Binding to FKBP partitions a bifunctional HIV-1 protease inhibitor into blood cells and prolongs its lifetime in vivo

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HIV protease inhibitors are a key component of anti-retroviral therapy, but their susceptibility to cytochrome P450 metabolism reduces their systemic availability and necessitates repetitive dosing. Importantly, failure to maintain adequate inhibitor levels is believed to provide an opportunity for resistance to emerge; thus, new approaches to prolong the lifetime of these drugs are needed. Using a strategy inspired by the natural product FK506, we have synthetically modified an HIV protease inhibitor such that it acquires high affinity for the abundant, cytoplasmic chaperone FKBP. This modified protease inhibitor maintains activity against HIV-1 protease (IC50 = 19 nM) and is partitioned into the cellular

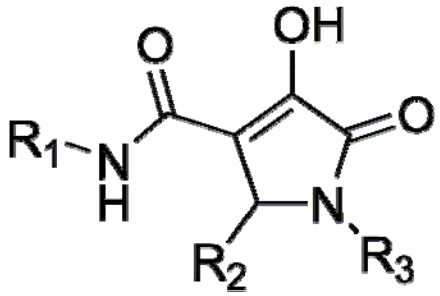
component of whole blood via binding to FKBP, improving its half-life in mice by almost 20-fold compared to the unmodified compound. Based on these findings, we propose that addition of FKBP-binding groups might partially overcome the poor pharmacokinetic properties of existing HIV protease inhibitors and, potentially, other drug classes.

MEDI 207

Solid phase synthesis of novel pyrrolidinedione analogs as potent HIV integrase inhibitors

Annapurna Pendri[1], *Timothy L. Troyer*[1], *Samuel W. Gerritz*[1], *Michael J Sofia*[1], *Michael A. Walker*[2], *B. Narasimhulu Naidu*[2], *Jacques Banville*[2], *Nicholas A. Meanwell*[2], *Zeyu Lin*[3], *and Mark R. Krystal*[3]. *(1) Early Discovery Chemistry, Bristol-Myers Squibb, Wallingford, CT 06492, (2) Discovery Chemistry, Bristol-Myers Squibb, Wallingford, CT, (3) Virology, Bristol-Myers Squibb, Wallingford, CT*

Chronic HIV infection and the emergence of drug resistant virus with HAART requires continual addition to the armamentarium of anti-HIV agents. HIV integrase is an enzyme involved in the integration of reverse-transcribed viral DNA into host cell DNA, and is essential for viral replication. Inhibitors of HIV integrase have proven to be an effective and exciting addition to antiretroviral treatments. In an effort to prepare heterocyclic variants of diketoacid inhibitors, a pyrrolidinedione scaffold was identified as a template for the synthesis of promising HIV integrase inhibitors. In this presentation, a solid-phase route to prepare pyrrolidinedione amides, which facilitates the simultaneous variation of R1, R2 and R3 on the template, will be described along with the HIV-1 integrase inhibitory activity of the resultant compounds.

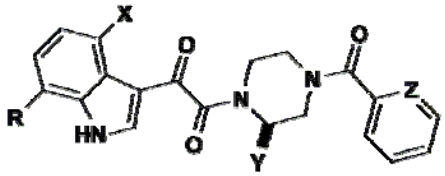


MEDI 208

C7-Heteroaryl-indoles as potent and orally bioavailable inhibitors of HIV attachment

Kap-Sun Yeung[1]*, kapsun.yeung@bms.com, Zhilei Qiu*[1]*, Haiquan Fang*[1]*, Zhiwei Yin*[1]*, Michelle E. Farkas*[1]*, Ashok Trehan*[1]*, Bradley Pearce*[1]*, J. J. Kim Wright*[1]*, Keith Ricarrdi*[1]*, Timothy P. Spicer*[1]*, Pei-Yong Shi*[1]*, Yi-Fei Gong*[1]*, Richard J. Colonno*[1]*, Zheng Yang*[1]*, Lisa Zadjura*[1]*, Celia J. D'Arienzo*[1]*, Marc R. Browning*[1]*, Steven Hansel*[1]*, Kenneth Santone*[1]*, Jonathan Barker*[2]*, Malcolm Taylor*[2]*, Richard Coxhead*[2]*, Russell Thomas*[2]*, Thomas Coulter*[2]*, Ping-Fan Lin*[1]*, Nicholas A. Meanwell*[1]*, and John F. Kadow*[1]*. (1) Bristol-Myers Squibb R&D, 5 Reaearch Parkway, P.O. Box 5100, Wallingford, CT 06492, Fax: 203-677-7702, (2) Evotec (UK) Ltd, Abingdon, Oxfordshire OX14 4SA, United Kingdom*

An early step in the process of HIV entry into host cells is the attachment of the viral envelope glycoprotein gp120 to the host cell receptor CD4. This step can be inhibited by a class of indole- or azaindole-oxoacetic piperazinyl benzamides that act by binding to the CD4 binding site in gp120. Clinical candidate BMS-488043 achieved proof-of-concept for this inhibition mechanism in HIV-infected patients. As part of the SAR development, the substitution on the indole C7 position of the early lead compound, 4-fluoroindole BMS-705, with various 5- and 6-membered heteroaryl moieties was explored. Highly potent inhibitors exhibiting pM potency in the primary cell-based assay using pseudotyped virus expressing JRFL envelope were identified. One such analog also provided superior animal pharmacokinetic properties compared to the initial clinical candidate BMS-378806, while maintaining good activity against viruses in cell culture. In this presentation, various aspects of the SAR and in vitro profiles of the C7 heteroaryl series, as well as animal pharmacokinetic properties of key compounds will be presented, and results discussed.



R = 5- or 6-Membered Heterocycles

MEDI 209

The development of a PSMA targeted imaging agent for prostate cancer.

Jessie Byers*, byerjess@gmail.com, Clifford Berkman, cberkman@wsu.edu, Paul Benny, bennyp@wsu.edu, and Tom Porter, trporter@wsu.edu, Department of Chemistry, Washington State University, Mail Stop 4630, Pullman, WA 99164*

Accurate and reliable imaging techniques for prostate cancer remain a challenge but encouraging results have been made in targeting the prostate cancer biomarker, PSMA (prostate-specific membrane antigen). Based on the enzymatic activity of PSMA, we have developed a library of high-affinity, small-molecule inhibitors of PSMA that can be conscripted as a targeting element for prostate

cancer cells. In these designs, alterations to the inhibitor core allows for convenient attachment radio-imaging and radio-therapeutic agents. In this study, we have focused on both improvements to the inhibitor cores for enhanced affinity for PSMA and the conjugation of various chelating groups for binding of imaging and therapeutic radionuclides. It is anticipated that the development of imaging agents for prostate cancer will allow for the detection of prostate cancer from early to late stages. In addition, the modular construction of these compounds hold the promise of being later translated into radiotherapeutic agents for the treatment of prostate cancer.

MEDI 210

Synthesis of a Gd(III)DOTA-lysine dendron specific contrast agent for cell receptor imaging by MR

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In this work we describe the synthesis of a small lysine-based dendron consisting of eight individual GdDOTA units. The dendron was covalently attached to a peptoid that binds with high specificity and affinity to the vascular endothelial growth factor receptor 2 (VEGFR-2) important in tumor metastasis. The r1 of the Gd8-dendron-peptoid conjugate was 15.1 ± 0.2 mM-1s-1 (37°C, pH 7, 23 MHz) per Gd3+ corresponding to a molecular r1 of 120 mM-1s-1 per targeted agent. T1-weighted images of Porcine aortic endothelial cells overexpressing the human VEGFR-2 (2.5x105 receptors/cell) exposed to the conjugate agent showed a significant contrast enhancement when compared to non-exposed cells, cells without the receptor or cell exposed only to the Gd8-dendron. The local concentration of bound agent in the VEGFR-2 expressing cells was ~700 nM. These data demonstrate it is possible to detect highly overexpressed cell receptors by using low molecular weight targeted Gd3+-based agents.

MEDI 211

Synthesis and evaluation of methoxy-substituted deschloromazindols as potential PET radioligands for imaging the norepinephrine transporter

***Kuo-Shyan Lin**, kuoshyan@yahoo.com, Guo-Feng Huang, and Chester A. Mathis, mathisca@upmc.edu, Department of Radiology, University of Pittsburgh, 200 Lothrop Street, B-938, Pittsburgh, PA 15213, Fax: 412-647-0700*

5-(4-Chlorophenyl)-2,3-dihydro-5-hydroxy-5H-imidazo[2,1-a]isoindole (Mazindol) is currently one of the most potent ligands to the norepinephrine transporter (NET). However, mazindol did not catch much attention as a candidate for the development of NET selective PET radioligand due to its poor binding selectivity over dopamine transporter and serotonin transporter (DAT and SERT), as well as the lack of suitable positions for labeling with C-11. Houlihan and co-workers (J Med Chem 2002; 45: 4097-4109) reported that (1) the deschloro analog of mazindol (deschloromazindol) preserves high binding affinity to NET but substantially decreases binding affinity to DAT and SERT; (2) 6-, 7- and 9-methoxy-substituted mazindols increase the binding affinity to NET but greatly decrease the binding affinity to SERT. Based on this observation, we have synthesized a series of methoxy-substituted deschloromazindols as NET-selective ligands. The design, synthesis, binding affinities to NET, SERT and DAT, and their potential as PET radioligands will be presented.

MEDI 212

Expeditious synthesis of labeled contrast agents for multimode cns imaging

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The advent of multi-mode in vivo imaging methods (PET, SPECT, MRI) has placed renewed emphasis on the need for efficient methodologies for radiomedicinal chemistry. In this presentation we will outline the capabilities of the new Center for Translational and Neuroimaging at Northeastern University and provide examples of newly developed labeling procedures based on microwave mediated processes. Specific CNS targeting agents will be discussed including methods for radioiodination for SPECT imaging and fluorination for PET imaging. Applications of multi-mode imaging in CNS mapping and behavioral neuroscience will also be outlined.

MEDI 213

Synthesis of new carbon-11 labeled celecoxib derivatives as PET radioligands to image inflammation

***Mingzhang Gao**, migao@iupui.edu, Min Wang, wang1@iupui.edu, Gary D. Hutchins, and Qi-Huang Zheng, qzheng@iupui.edu, Department of Radiology, Indiana University School of Medicine, 1345 West 16th Street, L3-202, Indianapolis, IN 46202, Fax: 317-278-9711*

Cyclooxygenases (COX-1/COX-2) catalyse the biosynthesis of prostaglandins and thromboxanes from arachidonic acid. COX-1 is present in most tissues and associated with homeostasis. COX-2 is expressed during inflammation and implicated in various pathological processes such as Alzheimer's disease and Parkinson's disease. Celecoxib is a selective COX-2 inhibitor. A novel series of celecoxib derivatives have been recently developed as more potent anti-inflammatory agents. New carbon-11 labeled celecoxib derivatives were designed and synthesized as radioligands for biomedical imaging technique positron emission tomography (PET) to image inflammation. Unlabeled celecoxib derivatives (precursors and standards) were synthesized from substituted phenylethanones in multiple steps with moderate to excellent yields. The target tracers [^{11}C]methyl 2-(4-(5-p-tolyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenylsulfonamidooxy)acetate, [^{11}C]methyl 2-methyl-2-(4-(5-p-tolyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenylsulfonamidooxy)propanoate, [^{11}C]methyl 2-(4-(5-(4-methoxyphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenylsulfonamidooxy)acetate and [^{11}C]methyl 2-methyl-2-(4-(5-(4-methoxyphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenylsulfonamidooxy)propanoate were prepared from their corresponding precursors 2-(4-(5-p-tolyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenylsulfonamidooxy)acetic acid, 2-methyl-2-(4-(5-p-tolyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenylsulfonamidooxy)propanoic acid, 2-(4-(5-(4-methoxyphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenylsulfonamidooxy)acetic acid and 2-methyl-2-(4-(5-(4-methoxyphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenylsulfonamidooxy)propanoic acid with [^{11}C]CH_3OTf under basic condition through *O*-[^{11}C]methylation and isolated by solid-phase extraction (SPE) method in 50-60% radiochemical yields.

MEDI 214

Synthesis of [^{11}C]PBR28 as a PET radioligand for peripheral benzodiazepine receptors

***Min Wang**, wang1@iupui.edu, Mingzhang Gao, migao@iupui.edu, Barbara E. Glick-Wilson, Bruce H. Mock, bmock@iupui.edu, Gary D. Hutchins, and Qi-Huang Zheng, qzheng@iupui.edu, Department of Radiology, Indiana University School of Medicine, 1345 West 16th Street, L3-202, Indianapolis, IN 46202, Fax: 317-278-9711*

Peripheral benzodiazepine receptor (PBR) has become a clinical biomarker of neuroinflammation and tumor progression. It also provides an attractive target for

the development of receptor-based PET radioligands to study brain and cancer diseases. [^{11}C]PBR28 (*N*-(2-[^{11}C]methoxybenzyl)-*N*-(4-phenoxypyridin-3-yl)acetamide) has been developed as a clinically useful PET tracer for characterizing PBR. Although a few papers dealing with the synthesis of [^{11}C]PBR28 have appeared, there are gaps in synthetic detail among them, and certain key steps gave poor yields or were difficult to repeat in our hands. Consequently, we investigated an improved synthesis of [^{11}C]PBR28. The precursor *N*-(2-hydroxybenzyl)-*N*-(4-phenoxypyridin-3-yl)acetamide and the authentic standard PBR28 (*N*-(2-methoxybenzyl)-*N*-(4-phenoxypyridin-3-yl)acetamide) were synthesized from 4-chloro-3-nitropyridine and *o*-salicylaldehyde or *o*-anisaldehyde, respectively, in 4 steps with moderate to excellent yields. The direct methylation of the precursor also provided PBR28. [^{11}C]PBR28 was prepared by *O*-[^{11}C]methylation of the precursor with [^{11}C]CH_3OTf under basic condition (NaH) and isolated by HPLC method in 70-80% radiochemical yields.

MEDI 215

Synthesis of new carbon-11 labeled dual aromatase-steroid sulfatase inhibitors for PET imaging of aromatase and sulfatase in breast cancer

***Min Wang**, wang1@iupui.edu, Mingzhang Gao, migao@iupui.edu, Gary D. Hutchins, and Qi-Huang Zheng, qzheng@iupui.edu, Department of Radiology, Indiana University School of Medicine, 1345 West 16th Street, L3-202, Indianapolis, IN 46202, Fax: 317-278-9711*

Aromatase and steroid sulfatase are particularly attractive targets in the treatment of estrogen receptor positive breast cancer and the development of enzyme-based cancer imaging agents for biomedical imaging technique positron emission tomography (PET). A novel series of sulfamate derivatives have been recently developed as dual aromatase-steroid sulfatase inhibitors (DASIs). New carbon-11 labeled sulfamate derivatives were designed and synthesized as potential PET DASI radiotracers for imaging of aromatase and sulfatase in breast cancer. Unlabeled sulfamate derivatives and their desmethylated precursors were synthesized from substituted benzaldehydes in multiple steps with moderate to excellent yields. The target tracers 5-(((4-cyanophenyl)(4*H*-1,2,4-triazol-4-yl)amino)methyl)-2-[^{11}C]methoxyphenyl sulfamate and 4-(((4-cyanophenyl)(4*H*-1,2,4-triazol-4-yl)amino)methyl)-2-[^{11}C]methoxyphenyl sulfamate were prepared from their corresponding precursors 5-(((4-cyanophenyl)(4*H*-1,2,4-triazol-4-yl)amino)methyl)-2-hydroxyphenyl sulfamate and 4-(((4-cyanophenyl)(4*H*-1,2,4-triazol-4-yl)amino)methyl)-2-hydroxyphenyl sulfamate with [^{11}C]CH_3OTf under basic condition through *O*-[^{11}C]methylation and isolated by high pressure liquid chromatography (HPLC) method in 30-45% radiochemical yields.

MEDI 216

Structural activity relationship of imidazoline-based scaffolds as small molecules inhibitors of proinflammatory transcription factor NF-κB

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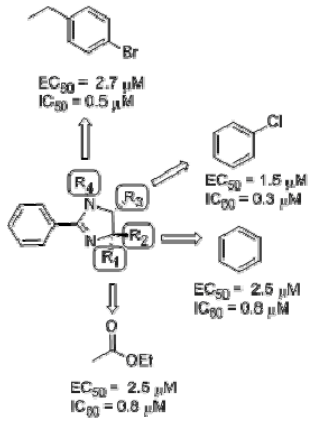
NF-&kappaB, a ubiquitous mammalian transcription factor, regulates the transcription of numerous genes including those responsible for inflammatory response, such as interleukin-6 (IL-6) and tumor necrosis factor &alpha (TNF-&alpha). Therefore, inhibition of NF-&kappaB represents a viable molecular target for the development of anti-inflammatory therapies. We describe the synthesis and biological evaluation of a series of imidazoline-based compounds as potent inhibitors of NF-&kappaB mediated gene transcription in TNF-&alpha stimulated cell culture (EC50 ~ 2.5 – 5 &muM) in addition to being inhibitors of IL-6 production in IL-1&beta stimulated human blood (IC50 ~ 0.3-0.5 &muM).



MEDI 217

Discovery of selective inhibitors of mutant b-raf

Judith G. Deal*, judy.deal@pfizer.com, Cynthia L Palmer, William H Romines, Julie Y Park, Lisa C Guo, Luke Zehnder, Tami J. Marrone, Michele McTigue, Dorothy DeLisle, James Solowiej, Xiao-Hong Yu, and Shubha Bagrodia, Pfizer Global Research & Development - La Jolla, 10770 Science Center Dr, San Diego, CA 92121*

B-Raf is mutated in a number of human cancers, mainly melanoma, thyroid and colorectal. Raf is a key kinase in the Ras/Raf/Mek pathway, thus making mutant B-Raf an attractive oncology target. There are no therapeutic agents currently on the market targeting exclusively mutant B-Raf. Our aim was to discover selective agents to better understand the role of mutant B-Raf and its inhibition in oncology. Designing selective kinase inhibitors can be challenging due to the inherent binding site homology of many kinases. This poster describes the synthetic efforts which led to a novel series of diaminothiazoles as potent and selective mutant B-Raf inhibitors originating from a high throughput screening hit which exhibited dual VEGFR/mutant B-Raf inhibition.

MEDI 218

Small molecule inhibitors of Janus kinases

John Feutrill*, john.feutrill@cytopia.com.au, Laura Andrau, David G. Bourke, Xianyong Bu, Patricia Bukczynska, Christopher Burns, Naomi Court, Andrew Donohue, Emmanuelle Fantino, Michelle Farrugia, Max Joffe, Marcel Kling, Margarita Kurek, Tracy Nero, Thao Nguyen, James T. Palmer, Harrison Sikanyika, Herbert Treutlein, Soo San Wan, Andrew Wilks, and Jun Zeng, Cytopia, 576 Swan Street, Richmond Victoria 3121, Australia*

The Janus kinases (JAKs) are an important family of cytoplasmic tyrosine kinases that play an essential role in cytokine signal transduction. The recent identification that an activating mutation of JAK2 (V617F) is present in a significant proportion of patients diagnosed with myeloproliferative diseases (MPDs) including >95% of patients with Polycythemia Vera (PV) and >50% of Essential Thrombocythemia (ET) patients, has initiated much interest in the discovery and development of selective JAK2 inhibitors as a potential treatment for this patient population.

Cytopia has undertaken a medicinal chemistry program to optimize a series of weakly active JAK2 inhibitors. This program has led to the identification of CYT387, a novel small molecule inhibitor of JAK2 with good potency, selectivity, and oral bioavailability. CYT387 has shown cellular efficacy in MPD patient derived samples and in vivo efficacy in a murine model of PV, supporting Cytopia's progression of this compound into clinical trials for the treatment of MPDs.

MEDI 219

Novel N4-phenyl substituted tricyclic indeno[1, 2-d]pyrimidines as tyrosine kinase inhibitors and antiangiogenic agents

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Angiogenesis plays a key role in the growth and metastasis of solid tumors. Abrogation of angiogenesis via RTK inhibition provides a new paradigm for the treatment of cancer. Since angiogenic pathways are redundant, the most successful RTK inhibitors in cancer chemotherapy are those with multiple, rather than single RTKs inhibition.

Gangjee *et al.* designed and synthesized *N*4-(4-chlorophenyl)-9*H*-indeno[2,1-*d*]pyrimidine-2,4-diamine with dual cytostatic and cytotoxic activities as an antitumor agent. The regio isomer of this scaffold is *N*4-phenyl-5*H*-indeno[1,2-*d*]pyrimidine-2,4-diamine of general structure **1.** These compounds also showed potent cytotoxicity against the growth of EGFR overexpressing A431 tumor cells in culture compared to a standard. The design, synthesis and RTK inhibitory activities of these compounds will be presented and discussed.

MEDI 220

Evolution of a series of potent and efficacious PI3 kinase inhibitors

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The well documented deregulation of the PI3K/AKT/mTOR pathway in numerous tumor types has established a significant desire for PI3K inhibitors with drug-like properties. Our program directed toward identifying potent and orally available molecules that inhibit PI3 kinase has previously disclosed GDC-0941. This poster will discuss the evolution of our thienopyrimidine series of PI3 kinase inhibitors. Topics highlighted will include structure-guided design to improve binding affinity,

broad evaluation of solvent-exposed functionality, and modification of the bicyclic core. The impact of these changes on potency, in vitro metabolic stability, and in vivo PK will be presented. One outcome of these studies was the identification of a molecule of interest whose efficacy in a PI3 kinase-driven tumor model will be shown.

MEDI 221

Discovery and development of novel furano-pyrimidine analogs as Aurora kinase inhibitors

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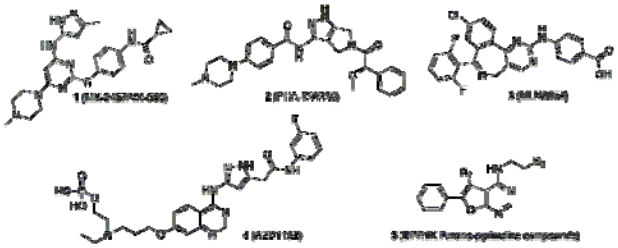
Inhibition of Aurora kinase, a member of serine/threonine kinase involved in the regulation of cell division is emerging as a new molecular targeted cancer treatment option. Three isoforms of Aurora kinase, A, B and C are known. Both Aurora A and B are over expressed in many human cancers and are linked to chromosome instability, oncogenic transformation, tumour progression and development of chemoresistance. Inhibitors of Aurora kinase such as MK-0457/VX-680 (**1**), PHA-739358 (**2**), MLN8054 (**3**) and AZD1152 (**4**), in various animal models had shown tumor regression and are now in different stages of clinical development for various cancers.



Based on the current success of Aurora kinase inhibitors in the development of kinase-based cancer therapy, we have initiated an in house compound library screening program for the identification of novel Aurora kinase inhibitors. This led to the identification of furano-pyrimidine compound (**5**) BPR1K224 as an Aurora kinase A inhibitor with an IC_{50} of ~400 nM. Over 300 analogs of the lead compounds were rapidly synthesized and screened for Aurora kinase activity to identify 2nd generation lead compounds. X-ray co-crystal structure of the lead compounds in complex with Aurora A protein revealed that the back pocket of Aurora protein is unoccupied. Based on this insight, rationale modification of one the 2nd generation lead had led to the identification of potent Aurora kinase A

inhibitor BPR1K432 (IC_{50} ~50 nM), which possessed anti-proliferative activity in HCT-116 cell line (IC_{50} ~400 nM). Additional structural refinement led to the synthesis of several potent analogs.

MEDI 222

Synthesis and biological evaluation of potential EGFR Tyrosine kinase inhibitors: Aryl, benzyl and styryl coumarins

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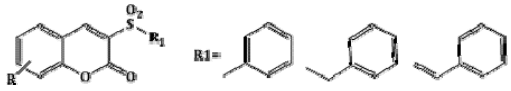
Epidermal Growth Factor Receptor (EGFR) (also known as erb-B1 or HER-1) and the related Human Epidermal Growth Factor Receptor-2 HER-2 (also known as erbB-2) are among the growth factor receptor kinases that have been implicated as being important in cancer. Over-expression of these receptors is found in a number of cancers (e.g., breast, ovarian, colon, prostate) and has been associated with poor prognosis in patients. In addition, signaling through the EGFR promotes tumor neovascularization and induces resistance to cytotoxic chemotherapy. Based on these multiple impacts on cancer cell physiology, the EGFR tyrosine kinase has been recognized as an attractive molecular target for selective treatment of solid tumors with increased EGFR expression levels. Small molecule TK inhibitors are a class of promising new anticancer drugs and several chemical series such as 4-anilinoquinazolines, 4-anilinopyrido[d]pyrimidines, 4-anilinopyrazolo[3,4-d]pyrimidines and dianilinophthalimides have been reported as EGFR inhibitors. Here we wish to present the synthesis, structure activity relationship and biological activity of some novel EGFR inhibitors, aryl, benzyl and styryl sulfonyl coumarins.



MEDI 223

5-Bicyclic heteroaryl-3-pyridinecarbonitriles as PKC-theta inhibitors

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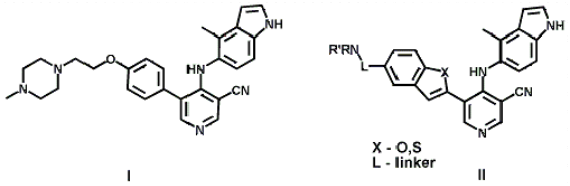
Wyeth Research, 401 North Middletown Road, Pearl River, NY 10965, (2) Inflammation, Wyeth Research, Cambridge, MA 02140

Protein kinases are critical regulators of cellular processes in normal and disease states. The protein kinase C family is a group of serine/threonine kinases comprised of twelve isoenzymes that share sequence and structural homology. These enzymes are expressed in a wide range of tissues and cell types. PKC-theta is found predominantly in T cells and skeletal muscle and has been implicated in the signaling of T cell activation, proliferation, and cytokine production. Thus an inhibitor of PKC-theta may be of therapeutic importance in treating autoimmune and inflammatory diseases where T cells play a pivotal role. We previously reported that a 3-pyridinecarbonitrile analog with a phenyl substituent at C-5 and a 4-methyl-5-indolylamine substituent at C-4 (I) was a potent inhibitor of PKC-theta. Replacement of the C-5 phenyl ring of I with bicyclic heteroaryl rings, provided compounds exemplified by II. The routes to these analogs and their PKC-theta inhibitory activity will be discussed.



I II

MEDI 224

Hit to lead campaign of a series of cyclobutenediones as MAPKAP kinase 2 inhibitors for the treatment of inflammatory diseases

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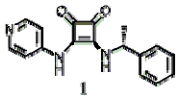
MAPKAP Kinase 2 (MK2) plays a crucial role in the regulation of tumor necrosis factor-A (TNF-A) production. TNF-A is a pro-inflammatory cytokine that is associated with various inflammatory diseases including rheumatoid arthritis, psoriasis, and inflammatory bowel disease. It is postulated that an inhibitor of MK2 could decrease TNF-A production and therefore serve as a therapy for inflammatory diseases. In a search for MK2 inhibitors, a high throughput screen of our compound library led to the identification of cyclobutenedione 1. Follow-up

characterization of this compound indicated that it inhibits MK2 with an IC50 of 8.9 μM, binds to MK2 with a Ki of 14.5 μM, and is ATP competitive. Utilizing information from an x-ray co-crystal of compound 1 with MK2, new cyclobutenediones with improved MK2 inhibition were designed. A description of the structure activity relationships of the cyclobutenedione series in the early stages of the MK2 project will be given.



1

MEDI 225

New fluorescence-based binding assay for identification and characterization of kinase inhibitors

***Upinder Singh**, upinder.singh@invitrogen.com, Connie Lebakken, Steve Riddle, William J. Frazee, Hildegard C. Eliason, Jill K. Wolken, Yi Gao, Laurie Reichling, Bryan D. Marks, and Kurt W. Vogel, Invitrogen Discovery Sciences, 501 Charmany Drive, Madison, WI 53719, Fax: 608-204-5200*

Activity-based kinase assays have limitations in terms of breadth of target coverage and the type information they can provide about compounds. Because activity assays measure signal from an active kinase, they are not well suited to characterize compounds which bind preferentially to the non-activated form of a kinase, as observed for several important kinase inhibitors such as imatinib or sorafenib. Another increasingly common theme among effective kinase inhibitors is slow binding or slow off rates, which are not easily observed using traditional activity assays. To overcome these limitations, we have developed a kinase binding assay platform based on the use of Alexa Fluor® 647 conjugated to kinase inhibitor scaffolds. Data will be presented demonstrating application to this technology to interrogate both active and non-activated kinase preparations, to easily examine compounds with slow binding kinetics, and to assess compound potency.

MEDI 226

Design, synthesis and evaluation of 5-chloro-N4-substituted phenyl-9H-pyrimido[4,5-b]indole-2,4-diamines as potential inhibitors of multiple receptor tyrosine kinases

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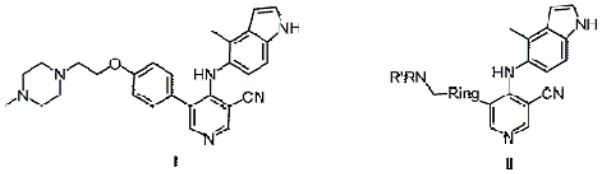
Inhibition of receptor tyrosine kinase (RTK) signaling pathways has become an important area for the development of novel anticancer agents. Recent studies suggest that the multifactorial mechanisms by which cancer cells proliferate demands the development of multi RTK targeted agents. In an effort to develop ATP-competitive multi-RTK inhibitors the 5-chloro-*N*^{4}-substituted phenyl-9*H*-pyrimido[4,5-*b*]indole-2,4-diamine scaffold was designed. It was proposed that the 2-amino group in these compounds, not only provides additional binding in the RTK hinge region, but also enables additional binding modes in other RTK active sites. This perhaps allows inhibition of an increased spectrum of RTKs. The synthesis of the target compounds involved *N*-(4,5-dichloro-9*H*-pyrimido[4,5-*b*]indol-2-yl)-2,2-dimethylpropanamide) as a common intermediate. A nucleophilic displacement of the 4-chloro group of the common intermediate by appropriately substituted anilines afforded the target compounds. Biological evaluation indicated that some of these compounds exhibited multi-RTK inhibition.

MEDI 227

C-5 Substituted phenyl and monocyclic heteroaryl 3-pyridinecarbonitriles as PKC-theta inhibitors

Joan Chen[1]*, chenj12@wyeth.com, Daniel Wang*[1]*, Biqi Wu*[1]*, Chuan Niu*[1]*, Diane H. Boschelli*[1]*, Julie Lee*[2]*, Xiaoke Yang*[2]*, Agnes Brennan*[2]*, and Divya Chaudhary*[2]*. (1) Chemical & Screening Sciences, Wyeth Research, 401 N. Middletown Road, Pearl River, NY 10965, (2) Inflammation, Wyeth Research, Cambridge, MA 02140*

The protein kinase Cs (PKCs) are a family of serine-threonine kinases that vary in their expression and mode of activation with the theta isoform playing a key role in T cell signaling. PKC-theta deficient mice are resistant to the development of several T cell mediated diseases including asthma, arthritis, multiple sclerosis and inflammatory bowel disease. Therefore, small molecule inhibitors of this kinase may be efficacious in treating a variety of diseases. We earlier reported that the 3-pyridinecarbonitriile I was an ATP competitive inhibitor of PKC-theta. Keeping the group at C-4 of the pyridine core constant, we varied the substituents on the phenyl ring at C-5 and then replaced the C-5 phenyl ring with several monocyclic heteroaryl rings, including furan, thiophene and pyridine. The preparation of these new analogs (II) and their PKC-theta inhibitory activity will be discussed.



MEDI 228

Leishmanial choline kinase as a new therapeutic target

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Leishmaniasis is a zoonotic disease caused by the genus Leishmania spread in tropical and subtropical regions. Current drugs such as pentavalent antimonials exhibit high toxicity for humans with increasing parasite drug resistance, as well as high cost. New successful drugs are needed and characterization of new molecular targets must be completed. Here we describe, at the molecular and biochemical level, the choline kinase of Leishmania infantum and propose it as target for leishmaniasis treatment. A 1900bp PCR fragment was cloned into the BamHI-HindIII restriction sites of the pET45b vector (Novagen) and expressed in ArcticExpress RIL® cells (Stratagene). The His-tagged protein was purified using a Co2+ resin. Kinetic analysis was performed using the radioisotope assay described by Gee and Kent (2003). Purified enzyme displayed choline kinase activity in vitro, facilitating inhibition assays with synthetic compounds. Compounds showing inhibition activity against the enzyme will be tested in cultured parasites. Funded: Universidad de Antioquia (Colombia).

MEDI 229

Reversed chloroquines: Molecules that overcome malaria's resistance to chloroquine

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Chloroquine (CQ) was the drug of choice to treat malaria for nearly half a century, but widespread resistance has severely reduced its effectiveness. Reversal agents (chemosensitizers) can reverse the effects of chloroquine resistance, but high dosages raise questions about their clinical viability. We hypothesized that covalently attaching a reversal agent moiety to a chloroquine-like moiety would give a "reversed chloroquine" (RCQ) able to overcome the effects of resistance with a much reduced reversal agent dose. These RCQs exhibit lower IC50 values than CQ against even D6, a chloroquine-sensitive strain of P. falciparum malaria, and reduced the IC50 against various chloroquine-resistant strains typically by 2- to 3- orders-of-magnitude relative to CQ. Thus, the RCQ-approach may be viable in the struggle against malaria, as well as open a route toward new therapies for other diseases that have drug resistance mechanisms similar to malaria.

MEDI 230

Development of novel chemotypes for negative allosteric modulation of mGluR5

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Metabotropic glutamate receptors (mGluRs) are G-protein couple receptors that bind glutamate and modulate neurotransmitter release in the central nervous system. Dysfunction of these receptors has been implicated in a variety of disease states, including Parkinson's disease, schizophrenia, drug addiction, anxiety and other cognitive disorders. Eight mGluR subtypes have been identified, but selective targeting of the individual receptors has proven challenging due to the high degree of homology in their orthosteric active sites. Allosteric modulation of these receptors at novel binding sites that are spatially distinct from the traditionally targeted orthosteric site has proven to be a successful strategy. A variety of allosteric modulators of the mGlur5 subtype have been identified, including MPEP and MTEP, which bind to the transmembrane regions of the receptor. Herein we disclose the development and biological examination of novel chemotypes for the selective negative allosteric modulation of mGluR5.

MEDI 231

Hit-to-lead optimization of 3,5-disubstituted-oxadiazoles as novel noncompetitive mGlu5 receptor antagonists

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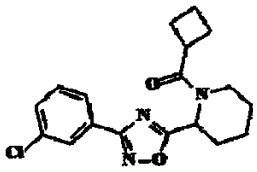
Recent findings pointed out an important role of the mGlu5 receptor in anxiolysis. mGluR5 could therefore be considered as a promising drug target for anxiolytics without no benzodiazepine-like side effects. Literature data suggest that the first selective non-competitive mGluR5 antagonist compound, 2-methyl-6-(phenylethynyl)pyridine (MPEP)[1] has a very broad and potent anxiolytic-like activity in rodent models of anxiety with short onset of action and without potential to induce sedation or psychotomimetic effects.

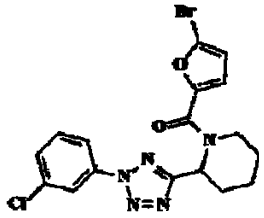
The high throughput screening (HTS) of our corporate compound deck resulted in several clusters including carbamoyl-oximes[2] and 3,5-disubstituted-oxadiazoles.

On this poster we are going to present the hit-to-lead optimization of the HTS hits represented by compound **1** leading to promising compounds that meet the requirements of our *chemical lead* definition.[3]



1

rK_i: 205 nM



2

rK_i: 55 nM

1. Novartis AG. *WO 9902497* (11. 07. 1997).

2. Gedeon Richter PLC. *PCT/HU06/00117* (19. 12. 2006).

3. Gedeon Richter PLC. *PCT/HU06/00087; PCT/HU06/00088* (10. 05. 2006).

MEDI 232

5-Hydroxytryptophan-functionalized self-assembled monolayers capture native membrane-associated serotonin receptors

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Departments of Chemistry and Physics, The Pennsylvania State University, University Park, PA 16802, Anne M. Andrews, ama11@psu.edu, Huck Institutes of the Life Sciences, Pennsylvania State University, University Park, PA 16801, and Mitchell J. Shuster, mjs648@psu.edu, Department of Chemistry and Physics, Pennsylvania State University, University Park, PA 16802

1,2Amit Vaish,3 Mitchell J. Shuster, 2,4Paul S. Weiss and 2,4,5Anne M. Andrews

1Department of Bioengineering, 2Huck Institute of the Life Sciences, 3Department of Physics, 4Department of Chemistry and 5Department of Veterinary & Biomedical Sciences

We have developed methods to tether small molecules to self-assembled monolayers (SAMs) at necessarily low surface coverages so as to retain sufficient chemical functionality for recognition by large biomolecules. We chose the neurotransmitter serotonin as a prototypical small molecule because of its importance in psychiatric disorders. The amino acid precursor of serotonin, 5-hydroxytryptophan (5-HTP) was covalently bound to oligoethyleneglycol alkanethiol SAMs by carbodiimide coupling chemistry. Surface chemistry was analyzed by X-ray photoelectron spectroscopy and Fourier transform infrared spectroscopy. Using quartz crystal microgravimetry, we demonstrate that 5-HTP-functionalized surfaces show low nonspecific binding. They selectively capture anti-5-HTP antibodies or recombinant receptors that natively recognize free serotonin vs. receptors for other neurotransmitters with similar structures. Previously studied serotonin-functionalized surfaces fail to show binding of membrane-associated serotonin receptors. Our findings suggest that the lack of recognition of tethered serotonin itself is due to masking of primary amines by the tethering chemistry.

MEDI 233

Measuring serotonin transporter function in rhesus peripheral blood lymphocytes using boron-doped diamond electrodes

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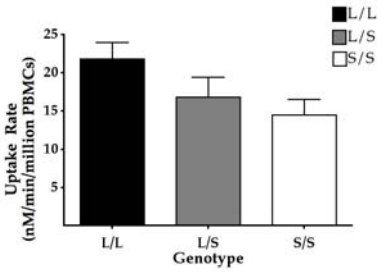
Altered serotonin neurotransmission plays a role in the etiology and treatment of mood and anxiety disorders. Commonly prescribed antidepressants inhibit

serotonin transporters (SERT) thereby changing serotonin signaling. The same gene encodes SERT centrally and peripherally, thus, we are investigating whether peripheral blood cells, which express SERT, can be used to non-invasively study alterations in SERT function. Boron-doped diamond microelectrodes (BDDs), lacking polar carbon-oxygen functional groups, show low background currents and fouling when exposed to high serotonin concentrations and cell suspensions demonstrating better performance when determining serotonin uptake rates compared to carbon fiber microelectrodes. Preliminary results using BDDs show a gene-associated decrease in serotonin uptake concomitant with the short allele of the rh5-HTTLPR, a promoter polymorphism related to the human 5-HTTLPR that correlates with anxiety-related personality traits and susceptibility to stress-associated depression. Fabrication of nanoscale BDDs will be important for future use of these materials in vivo.



MEDI 234

Improved resolution of closely related organic compounds with Reveleris™ flash cartridges

Romulus Gaita[1]*, romulus.gaita@grace.com, Scott Anderson*[2]*, and Kathy Lawrence*[2]*, kathy.lawrence@grace.com. (1) TCS, Grace Davison Discovery Sciences, 2051 Waukegan Rd, Deerfield, IL 60015, (2) Grace Davison Discovery Sciences, Deerfield, IL 60015*

The need for high purity compounds in drug discovery continues to expand as higher throughput purification techniques encourage better ways to discover new drugs and other materials. Flash chromatography is one well-accepted purification technique, which can produce high purity compounds. The silica packed in Reveleris™ cartridges is specifically designed to increase cartridge efficiency and therefore resolution of closely eluting compounds, in some cases greater than two times better resolving power over typical packings. Greater efficiency enables more peaks to be baseline resolved and results in increased sample purity and decrease fraction volumes. Additionally, by increasing sample loads on a given cartridge size and elevated pressure capability, sample throughputs and yields increase and overall purification costs are lowered.

MEDI 235

Novel dual detection flash instrument improves sample purity and productivity

Romulus Gaita[1]*, romulus.gaita@grace.com, Scott Anderson*[2]*, and Kathy Lawrence*[2]*, kathy.lawrence@grace.com. (1) TCS, Grace Davison Discovery Sciences, 2051 Waukegan Rd, Deerfield, IL 60015, (2) Grace Davison Discovery Sciences, Deerfield, IL 60015*

Flash chromatography is predominantly a crude purification technique used by synthetic organic chemists to purify synthesized crude reaction mixtures. The present instrumentation employed for flash chromatography may be inadequate to result in efficient or quantitiave purifications due to their limitation of requiring the mixture components to absorb UV light. This paper will focus on a novel flash instrument using a unique combined detection technique whereby improved compound purity and compound recovery is efficiently achieved. This novel combined and patent pending detection technique incorporates multiple detectors and enables difficult to detect impurities to be identified and removed quickly and cleanly. By detecting more and ultimately collecting less, the combined detection maximizes sample recovery, eliminates repeated runs, and avoids excessive time-wasting post-purification workup on undesirable components. Consequently, flash purifications are made simpler, cleaner, more reliable, and more efficient allowing the synthetic chemist to be more confident and productive.

MEDI 236

Sulfonamides and sulfones as secondary pharmacophores in soluble epoxide hydrolase inhibitors

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Soluble epoxide hydrolase (sEH) has generated interest as a potential pharmaceutical target in a number of disease indications including hypertension, stroke, end organ protection, inflammation, and metabolic syndrome. Human sEH is distributed in various tissues with the highest levels in liver, kidney, thymus, and heart. Epoxyeicosatrienoic acids or (EETs), formed by the action of cytochrome P450 epoxygenase, have been shown to produce vasodilation in various vascular beds such as renal, coronary, intestinal and cerebral circulation, and to have anti-inflammatory properties in vivo. However, the dihydroxyeicosatrienoic acids (DHETs), the sEH hydrolysis products of EETs,

have reduced biological activity. A general SAR model for soluble epoxide hydrolase inhibitors involves a primary pharmacophore connected to a secondary pharmacophore 5-7 Å distant by a lipophilic spacer. Urea and amide functionalities have been identified as the primary pharmacophores affording the most potency in sEH inhibitors with ester, amide, ether, alcohol, and ketone moieties all serving as a secondary pharmacophore. In continuation of our efforts to identify novel and potent sEH inhibitors, we have explored other secondary pharmacophores in combination with the urea primary pharmacophore. This poster summarizes our recent work incorporating sulfone and sulfonamide functionality as a secondary pharmacophore in soluble epoxide hydrolase inhibitors.

MEDI 237

Discovery of a novel, potent and highly selective β_3-adrenergic receptor agonist, SM-350300, for the treatment of overactive bladder syndrome

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β_3-Adrenergic receptor (β_3-AR) is an attractive target for the treatment of obesity, diabetes and overactive bladder (OAB). Clinical trials of early β_3-AR agonists, however, have been discontinued due to insufficient efficacy, poor pharmacokinetics or inadequate selectivity versus other β-ARs. The selectivity is of especially critical importance because the poor selectivity causes adverse events such as tachycardia and muscle tremor. Therefore, our strategy for exploring β_3-AR agonist focused on improving potency and selectivity compared to those of AJ-9677, a formerly-developed compound. We synthesized a series of indol-7-yloxy derivatives and found SM-296067 which showed a good biological activity with high selectivity against β-ARs. Furthermore, SM-350300, a prodrug of SM-296067, exhibited improved bioavailability and ameliorated pathological conditions in several rodent OAB models. The design, synthesis, structure-activity relationship and pharmacological profiles of these compounds will be described.

MEDI 238

Discovery of α-arylamino hydroxamic acids as novel anthrax lethal factor inhibitors

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Lethal factor (LF), a Zn^{2+}-dependent metalloprotease, is the key virulence factor of anthrax which continues to pose a widespread threat as a biowarfare and bioterrorism agent. Mounting evidence supports the idea that inhibition of lethal factor may offer a promising therapeutic approach for treating anthrax, particularly in late stage infection. We now report on our discovery of α-arylamino hydroxamic acids as novel anthrax lethal factor inhibitors. The design, synthesis, and SAR analysis of these compounds will be presented.

MEDI 239

Design, synthesis, biophysical and biological studies of fluorescent Hoechst-polyamide hybrid molecules

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Polyamides are non-fluorescent imidazole and pyrrole-containing analogs of distamycin. They bind to specific sequences of DNA via the minor groove and have the capacity to regulate gene expression. Polyamides are potential useful for the treatment of genetic or gene derived diseases, including cancer. Continuing efforts in the polyamide field are aimed at the design and development of new polyamide structures that have greater base pair specificity, higher binding strength, and improved cellular uptake. Specific efforts taken in the authors' laboratories are centered on the design and development of polyamide molecules that contain fluorescent heterocyclic entities. The fluorophore offers a versatile probe for investigating the dynamics of how polyamides interact with DNA, and also for physically following the molecules as they travel inside a cell and eventually reaching the nucleus. In our studies the fluorescent heterocyclic moiety is designed to be an integral component of the DNA base pair recognition element of the molecules. Accordingly, two fluorescent bisbenzimide (Hoechst)-polyamide hybrid molecules were designed

and synthesized. Synthetic results along with the DNA binding and cell penetration properties of the hybrid molecules will be presented.

MEDI 240

New polymeric sorbents for postsynthesis reaction cleanup

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PoraPak Rxn sorbents are polymer-based chromatography products designed for cleanup of synthetic reactions. Two chemistries are available; PoraPak Rxn CX, a strong cation-exchange sorbent and PoraPak Rxn RP, a reversed-phase sorbent. Synthetic chemists are familiar with silica-based chromatographic products for reaction cleanup. However, silica will dissolve at high pH while bonded-phases are susceptible to hydrolysis at low pH. Both conditions can result in the introduction of sorbent related contaminants into the purified product fractions. The polymeric nature or PoraPak Rxn sorbents eliminates these potential problems. The sorbents exhibit good mechanical stability across a wide range of solvents and pH. The products can be used with gravity flow or with the assistance of vacuum or pressure. We will present examples of the cleanup of two common types of reactions used in medicinal synthesis. The first example, using PoraPak Rxn CX, demonstrates the cleanup of reductive amination reaction. The second example, demonstrates the cleanup of an amide coupling reaction using PoraPak Rxn RP.

MEDI 241

Laser induced autofluorescence and anti-Stokes fluorescence spectroscopy in breast, colon and lung human biopsies

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Spectroscopy based cancer diagnosis techniques have been studied intensively mainly because of the clean experimental tools used, their big variety, and the simplification of the biopsies histological study that they provide. These techniques are popular also because of their adopting feasibility to clinical practice and in vivo diagnosis. Among them, laser induced autofluorescence (LIA) has been recently surfaced because it may provide a significant ‘contrast' between cancerous (CA) and grossly (GU) uninvolved samples. We employed LIA using 488 and 532 nm excitation wavelengths on Breast, Colon and Lung

paired biopsy samples of CA and GU tissues in both Stokes and anti-Stokes fluorescence (ASF) configurations. The ASF spectroscopy has led to another way of discriminating CA/GU tissues. LIA and ASF respond to two different physical phenomena, and their investigation may deepen our understanding of laser-tissue interaction.

MEDI 242

Characterization of novel inhibitors of the enzyme N5-CAIR synthetase

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One promising but unexplored area in antimicrobial drug design is de novo purine biosynthesis. Recent biochemical studies have shown that de novo purine biosynthesis is different in microbes than in vertebrates. The differences in the pathways are centered on the synthesis of 4-carboxyaminoimidazoleribonucleotide (CAIR) which requires the enzyme N-carboxyaminoimidazoleribonucleotide synthetase (N5-CAIR synthetase). Vertebrates do not require this enzyme and sequence analysis reveals that vertebrates have no homolog for this enzyme. Genetic studies have shown that microorganisms deficient in this enzyme are unable to grow in minimal media or human serum and inactivation of this enzyme render microbes nonpathogenic. Despite this biochemical rational, no studies aimed at identifying small molecule inhibitors of N5-CAIR synthetase have been published. To remedy this problem we have conducted high-throughput screening (HTS) against E. Coli N5-CAIR synthetase using a highly reproducible phosphate assay. HTS was done with 48000 compounds and we found 14 that inhibited the enzyme. None of these compounds have been identified as inhibitors against any other assay reported in the PubChem data base. The14 compounds could be classified into 3 different classes according to chemical structure. The Michelis-menten kinetics for 5 compounds, representing each of three classes was determined. Kinetic and analytical studies revealed that class I inhibitors decomposed to ninhydrin which then reacted with the substrate of the reaction. Class II inhibitors are noncompetitive with both AIR and ATP suggesting that these agents bind to a site distal from the active site. Finally 2 compounds representing class III were found to be competitive with either AIR or ATP respectively. Antimicrobial studies

revealed that two of the agents inhibited the growth of E Coli. Growth was reversible upon addition of adenine indicating that the purine pathway was the site of action for these agents.

MEDI 243

Design, synthesis and structural activity relationship of 1,3,6-trisubstituted-4-oxo-1,4,-dihydroquinoline-2-carboxylic acid as selective ET-A antagonists for prevention of preterm labor

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Endothelin-1 (ET-1) is a member of novel family of vasoconstrictors, which consists of 21 amino acid residues with two intra-chain disulphide linkages. It is involved with variety of pathological coniditons including systemic and pulmonary hypertension, congestive heart failure, renal failure, cancer, preterm labor (PTL) and cerebrovascular disease. ET-1 exerts its biological effects through the stimulation of 2 subtypes of receptors, endothelin receptor subtype A (ETA) and endothelin receptor subtype B (ETB) receptors. ETA receptors mediate most of the actions of ET-1 associated with these pathological conditions suggesting a selective ETA receptor antagonist would be useful as a therapeutic agent for chronic treatment of these pathological conditions. Previously we synthesized and reported a series of 6-alkoxy substituted-3-carboxybenzyl-N-benzyl-quinol-4-ones as potential ETA selective inhibitors. Preliminary in vitro studies of these compounds showed 6-n-propoxy analog to be potent (IC50 = 0.11nM) ETA antagonists with selectivity of 8300 for ETA over ETB receptors. Herein we report the in vivo pharmacological and toxicity studies of these compounds. Based on these results, another series of compounds were also synthesized with different N-1 substitution on the 4-oxo-1,4-dihydroquinoline ring. Results of the biological testing will be discussed in terms of structure activity relationship related to the binding affinity of these compounds to ETA and ED50 to prevent PTL.

MEDI 244

Improved oral absorption of salmon calcitonin with AT-1002 peptide

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Increased systemic availability of Salmon calcitonin (sCT) after intra-duodenal delivery with AT-1002, a 6-amino acid peptide that enhances paracellular permeability was investigated. The permeability enhancement effect of AT-1002 was assessed in vitro on Caco-2 monolayers on transwell plates. There was a significant (6-fold) increase in the net flux of the total sCT in the presence of AT-1002. Systemic availability of sCT after intra-duodenal administration was measured using jugular vein cannulated rats randomly receiving treatments of sCT w/o AT-1002. The plasma concentration of sCT was significantly increased (2-fold) when sCT was co-administered with 10 mg/kg of AT-1002 vs. sCT alone. The pharmacokinetic profile displayed an increase in the rate and extent of absorption for a period of 90 min. These results demonstrate enhanced absorption of sCT in vitro and in vivo in the presence of AT-1002. This technology might be useful for drug delivery of peptides and therapeutic agents.

MEDI 245

The structure activity relationship studies of 3-(biaryl)-8-oxabicyclo[3.2.1]octane-2-carboxylic acid methyl esters

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Structure activity relationship studies of five series of 3-(biaryl)-8-oxabicyclo[3.2.1]oct-2-ene-2-carboxylic acid methyl esters and their corresponding SmI2 reduction products were investigated. The affinities for DAT and SERT of these compounds were determined in competition studies using [3H]-3ƒ"-(4-fluorophenyl)tropane-2ƒ"-carboxylic acid methyl ester (WIN 35,438). Each compound was tested 2-5 times in brain tissue of monkey. The 3-biaryloctenes manifest binding potently and selectively to DAT versus SERT. The nature of the 3-aryl system in the oxatropane series studied is crucial for preferred interaction with DAT. Thus, the benzofuran, benzothiophene, benzoxazole, benzimidazole and indole groups (series IV) have the strongest interaction with the binding site of DAT as compared to the other biaryl substituens (series II, III and V). Within this series sulfure hetereoatom seems to

have biggest influence on inhibition of WIN 35,438 with a remarkable DAT selectivity over SERT. The most potent analogues compound at DAT is benzthiophen derivative with an IC50 value of 13 nm for DAT and 177-fold selectivity over SERT (SERT: IC50 2,300 nm). Indole (DAT: IC50 336; SERT: IC50 17,000, 50-fold selectivity) and benzofuran (O-2551) (DAT: IC50 349; SERT: IC50 35,000, 100-fold selectivity) derivatives are also notably potent at and selective for DAT. Potency among the SmI2 reduction products is the highest with the chair diastereomer of benzthiophen substituent with a less pronounced DAT selectivity DAT: IC50 9; SERT: IC50 10). On the other hand, the corresponding boat diastereomer manifests DAT selectivity (DAT: IC50 18, SERT: IC50 79).

MEDI 246

Redox-active liposome delivery agents as "smart" drug excipients

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The overall goal of this research is the development of redox-active liposome delivery agents with highly controllable stimuli-responsive behavior for primary application as "smart" liposome-based chemotherapeutic excipients. Currently marketed liposome delivery vehicles rely on non-specific degradation for passive release of drug contents, resulting in leaky systems that both lower the amount of drug reaching the diseased site and increase harmful side effects due to systemic exposure. Our research investigates an active release mechanism via redox-induced liposome rupture by exploiting NAD(P)H:quinone oxidoreductase (NQO1), which is over-expressed in a variety of cancer cell lines. Our unique approach provides a way to adjust the rate of the liposome opening by altering the reduction potential of the electrochemically active quinone-trigger. Combined with the inherent structural specificity of NQO1 for quinone substrates, this electronic control will also allow the tuning of these triggerable liposomes toward NQO1, thus providing a means for site-specific and selective drug delivery.

MEDI 247

Investigation of protein resistance on controlled triblock copolymers

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Biocompatible nonfouling surfaces are extremely important for many applications in biomedical diagnostics, tissue engineering, drug delivery, and marine coating. In this work, we report a study of protein adsorption/resistance on the triblock copolymers of poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) (PEO-b-PPO-b-PEO) and poly(ethylene oxide)- Poly(å-caprolactone) - poly(ethylene oxide) (PEO-b-PCL-b-PEO). Both (PEO-b-PPO-b-PEO) and (PEO-b-PCL-b-PEO) consisting of hydrophilic PEO units and hydrophobic PPO or PCL units are first synthesized. Those triblock copolymers are then grafted on the CH3-terminated SAMs to obtain brush and stable conformation with high surface density, which is required for nonfouling properties. The molecular weight, hydrophilic/hydrophobic ratio, and operating conditions (temperature and solvent) are also turned in order to achieve optimal surface chemistry and density for preventing protein adsorption. Polymer surfaces are carefully characterized by contact angle X-ray photoelectron spectroscopy, transmission electron microscopy, atomic force microscope, and Fourier transform infrared spectroscopy before protein adsorption. Polymers interactions with lysozyme and fibrinogen are measured and evaluated by surface plasmon resonance (SPR) biosensor for their ability of protein resistance. The SPR experiments show that total nonspecific protein adsorption on well controlled triblock copolymers is very low, demonstrating that the triblock copolymers are very reliable, sensitive platform as nonfouling surfaces.

MEDI 248

Metabolic supplementing, sacrifice compensation and associated energy cooperation: Science in Chinese herb medicine

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Plants herb medicines are major sources of Chinese traditional medicine. Chinese traditional medicine is empirically based methodology which has been proved to be quite effective for some chronic disease. Chinese traditional medicine is also good at prevention and for healthcare and rehabilitation. However, lacking understanding of the mechanism prevent its acceptance and application worldwide. Here we proposed a general mechanism: (1) Metabolic supplement, Traditional Chinese compound medicine provides indispensable components for restoring the biochemical metabolic process in diseased body. (2) Sacrifice compensation, Traditional Chinese medicine has ingredients which serve as free radical scavenger, antioxidants and other possible targets, so it

protects our body from harm by sacrifice metabolism of these ingredients. (3) Associated energy cooperation, Combination and coordination of effective components in Traditional Chinese medicine provide different energy bands source which is key to restore series of tandem catalytic cycles and process in diseased body.

MEDI 249

Acylcholine derivatives based on enantioenriched aminocyclanols

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Our laboratory is interested in the medicinal chemistry of nicotinic acetylcholine receptors. Recently we have begun a study of constrained choline derivatives based on enantioenriched aminocyclanols, available through Jacobsen ring opening of the corresponding *meso*-epoxides with azidotrimethylsilane. Through this process we are systematically evaluating the effect of ring size and chirality to investigate the optimal dihedral angle for subtype selectivity of this series. The preparation of the *trans*-cholines in the 4- to 6-membered ring series and preliminary biological results will be discussed.

MEDI 250

The discovery of indeglitazar through scaffold based drug discover approach

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PPARs (Peroxisome Proliferator Activated Receptors –a, g,and d) are members of the nuclear hormone receptor super family and known for their ability to regulate lipid and glucose metabolism. Our approach to a pan PPAR agonist is to provide an effective therapy for treating insulin resistance (from PPARg) and homeostasis and catabolism of dietary lipids (through PPARa and PPARd) associated with type II diabetes and metabolic syndrome. Through our Scaffold Based Drug Discovery™ approach, we have been able to identify a novel PPAR Pan Agonist, Indeglitazar, with has partial agonism in PPARg and PPARd within a period of six months. In vivo assessment of Indeglitazar demonstrated a good efficacious response in reduction of glucose and triglyceride, and elevation of cholesterol, with no side effects observed in comparison to Pioglitazar in both rodent and primate models. Toxicity assessment also confirmed the safety profile, when SD rats and Cynomolgus monkeys were treated at high dose for a 28 day period. Indeglitazar was chosen to move forward in clinical assessment.

MEDI 251

Discovery of pyrrolopyridazines as novel DGAT1 inhibitors

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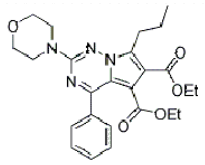
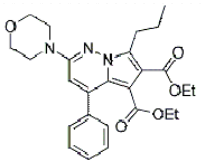
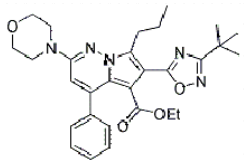
Disorders or imbalances in triglyceride metabolism are implicated in the development of obesity, insulin resistance syndrome, type II diabetes and coronary heart disease. DGAT1 is a microsomal enzyme that catalyzes the final step in triglyceride synthesis. DGAT1 plays a major role in the absorption of triglyceride from the intestine and deposition of triglyceride into adipose tissue. DGAT1-/- mice have reduced adiposity, are resistant to diet-induced obesity and have increased insulin and leptin sensitivity. A high-throughput screen of our small molecule library resulted in the discovery of pyrrolotriazine 1 as a moderately potent DGAT1 inhibitor. Focusing our structure-activity studies first on the core structure of 1 resulted in the discovery of pyrrolopyridazine 2 possessing increased DGAT1 inhibitory activity and increased ACAT1 selectivity. An investigation of the sidechains at C2, C4, C6 and C7 resulted in compounds with increased DGAT1 IC50 values, including 3, where the ester at C6 is replaced by an oxadiazole.



1
DGAT1 IC_{50} = 0.22 μM
ACAT1 IC_{50} = 0.50 μM



2
DGAT1 IC_{50} = 0.11 μM
ACAT1 IC_{50} = 1.30 μM



3
DGAT1 IC_{50} = 0.048 μM

MEDI 252

Discovery of S-2367: A potent and selective NPY Y5 antagonist for the treatment of obesity

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Neuropeptide Y (NPY) is a 36-amino acid peptide neurotransmitter that is widely distributed in the mammalian central and peripheral nervous systems. So far five distinct subtypes of G protein-coupled NPY receptors, Y1, Y2, Y4, Y5, and y6, are known. Among them, the Y5 receptor subtype is thought to play a role in meal initiation and the regulation of energy balance. Therefore, antagonist of NPY Y5 receptors is considered to have a potential as an anti-obesity drug.

In this presentation, we will describe how we successfully found a novel, potent and selective orally available NPY Y5 antagonist, S-2367, starting from the HTS hit, benzanilide analogue. During the lead optimization stage, the PK profile was improved by introducing less lipophilic amine fragment to give orally available Y5 antagonists, which was found to be effective in reducing weight in DIO mice model. S-2367 is now under clinical trial, and was already proved to be an agent that has a significant effect on the weight loss in Phase IIa clinical trial, suggesting a potential of promising anti-obesity drug. The synthesis and the details of the structure-activity relationships will be also presented.

MEDI 253

Discovery of novel diarylpyrazolyl thiadiazoles as cannabinoid CB1 receptor antagonists

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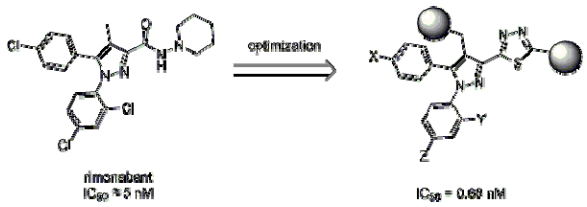
Since the CB1 receptor antagonist SR141716 (rimonabant) was previously reported to modulate food intake, CB1 antagonism has been considered as a new therapeutic target for the treatment of obesity. In the present study, various derivatives based on diarylpyrazole coupled with 1,3,4-thiadiazole were synthesized and tested for CB1 receptor binding affinity. Further SAR studies were carried out to optimize the substituents of 1,3,4-thiadiazole ring. These SAR studies introduced several novel CB1 antagonists with $IC_{50} \approx 1$ nM for the CB1 receptor binding. Based on these results, more potent compounds with $IC_{50} \leq 1$ nM could be prepared. Additional studies on CB2 binding affinity (CB1/CB2 selectivity), *in vivo* efficacy study and preliminary toxicological test were carried out to choose the best-in-class compound, being the candidate for development of CB1 receptor antagonist for the treatment of obesity.



MEDI 254

Novel adamantyl cannabinoids

Ganesh A. Thakur*, gathakur@gmail.com, Center for Drug Discovery, Department of Pharmaceutical Sciences, Northeastern University, 116 Mugar Life Sciences Building, 360 Huntington Avenue, Boston, MA 02115, Shama Bajaj, bajaj.s@neu.edu, Department of Chemistry and Chemical Biology, Center for Drug Discovery, Northeastern University, Boston, MA 02115, Carol Paronis, Department of Pharmaceutical Sciences, Northeastern University, Boston, MA 02115, Yan Peng, Center for Drug Discovery, Northeastern University, Boston, MA 02115, and Alexandros Makriyannis, a.makriyannis@neu.edu, Center for Drug Discovery, Northeastern University, Boston, MA 02115*

The endocannabinoid system encompasses three key components, the CB1 and CB2 cannabinoid receptors, their endogenous cannabinoids (endocannabinoids) and enzymes, proteins and transporters involved in endocannabinoid formation and inactivation. The endocannabinoid system is involved in an ever increasing number of pathological conditions including pain, immunosupression and appetite enhancement or suppression and has become an important target for the development of novel medications. Earlier, we reported a novel class of cannabinergic ligands with classical tricyclic skeleton bearing adamantyl side chains. From these, 1-adamanyl side chain was shown to impart both improved

affinity and selectivity for CB1 receptor. Our present work involves refining other structural features within the tricyclic ring to further improve CB1 affinity, selectivity and potency. Variations in the NAH (Northern Aliphatic Hydroxyl) region of the molecule were carried out to optimize its interaction with CB1 receptor. This work has identified AM4054 as a very potent and highly efficacious CB1-selective ligand. Details of synthesis, structure-activity relationships for CB1/CB2 receptors and in vitro as well as in vivo data for these compounds will be presented.

MEDI 255

Novel CB2 selective cannabinoids

Ganesh A. Thakur, *gathakur@gmail.com, Center for Drug Discovery, Department of Pharmaceutical Sciences, Northeastern University, 116 Mugar Life Sciences Building, 360 Huntington Avenue, Boston, MA 02115, Vidyanand Shukla, v.shukla@neu.edu, Department of Pharmaceutical Sciences, Center for Drug Discovery, Northeastern University, Boston, MA 02115, and Alexandros Makriyannis, a.makriyannis@neu.edu, Center for Drug Discovery, Northeastern University, Boston, MA 02115*

Cannabinoids elicit their biochemical and pharmacological effects primarily by interacting with two well-characterized receptors, designated as CB1 and CB2. Research from our and other laboratories has shown that CB2-selective cannabinoids are very effective against neuropathic and inflammatory pain without any undesirable CNS effects. Our continued effort to find a better CB2 ligand led to the discovery of bicyclic keto cannabinoids bearing substituted benzophenone side chain. A number of analogs were synthesized and evaluated for their biological activity at both CB receptors. Details of their synthesis and CB1 and CB2 receptors structure-activity relationships will be presented.

MEDI 256

Discovery and optimization of oxazole based diacylglycerol acyltransferase 1 inhibitors for the treatment of obesity

Weiya Yun[1], *David R. Bolin*[1], *Shiming Li*[2], *Mushtaq Ahmad*[1], *Stanley J. Wertheimer*[3], *Karin Conde-Knape*[3], *Yingsi Chen*[4], *and Sonja Kazmer*[3]. *(1) Discovery Chemistry, Hoffmann-La Roche Inc, 340 Kingsland Street, Nutley, NJ 07110, (2) WellGen, Inc, North Brunswick, NJ 08902, (3) Metabolic Diseases, Hoffmann-La Roche Inc, Nutley, NJ 07110, (4) Department of Discovery Technologies, Hoffmann-La Roche Inc, Nutley, NJ 07110*

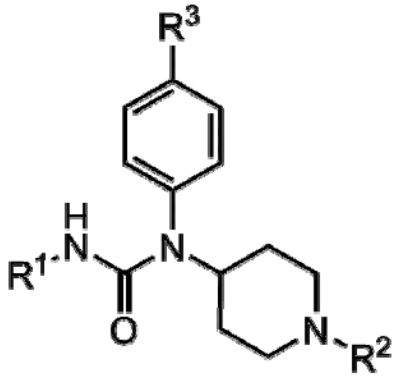
Obesity is largely due to excessive accumulation of triacylglycerides. Diacylglycerol O-acyltransferase 1 (DGAT1) is a key enzyme that catalyzes the final and rate-limiting step in triacylglyceride synthesis. DGAT1-deficient mice are lean, have increased energy expenditure and are resistant to diet-induced obesity. Consequently, DGAT1 inhibition would be expected to be a feasible therapeutic strategy for human obesity and obesity-associated complications, such as type 2 diabetes. Via high throughput screening and early lead optimization effort, we have identified a series of hydrazide based DGAT inhibitors. Through bioisosteric replacement of the acyl-hydrazide scaffold with an oxazole, metabolically more stable and more efficacious DGAT inhibitors were identified. This presentation will describe the synthesis and structure-activity relationship studies of these oxazole based DGAT1 inhibitors. Their pharmacokinetic and in vivo efficacy evaluations will also be presented.

MEDI 257

Reduction of hERG inhibitory activity in the N-[piperidin-4-yl]urea series of H3 antagonists

Michael Berlin[1]*, michael.berlin@spcorp.com, Yoon Joo Lee*[1]*, Christopher Boyce*[1]*, Yi Wang*[1]*, Kevin McCormick*[1]*, Robert Aslanian*[1]*, and Steve Sorota*[2]*. (1) Department of Chemical Research, Schering-Plough Research Institute, 2015 Galloping Hill Rd, Kenilworth, NJ 07033, Fax: 908-740-7152, (2) Department of Cardiovascular Pharmacology, Schering-Plough Research Institute, Kenilworth, NJ 07033*

Structural features of the substituted 4-piperidinyl urea analogs 1, responsible for the H3 antagonist activity, have been identified. Structure-activity relationship of the H3 receptor affinity, hERG ion channel inhibitory activity and their separation is described. Preliminary pharmacokinetic evaluation of the compounds of the series is addressed.



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MEDI 258

Indole amines as novel, potent, and selective antagonists of the human histamine type 3 receptor

William R. Solvibile[1]*, Ji-In Kim*[1]*, kimj1@wyeth.com, Adedayo Adedoyin*[2]*, Suzan Aschmies*[3]*, Julie Brennan*[3]*, Thomas Comery*[3]*, Mark Day*[3]*, Li Di*[1]*, Jeannette Golembieski*[3]*, Steve Grauer*[3]*, Julia Heinrich*[3]*, Warren D. Hirst*[3]*, Cody Kelley*[3]*, Katie Kubek*[3]*, Karen Marquis*[3]*, Rachel Navarra*[3]*, Xiaoping Ning*[3]*, Mark Pausch*[3]*, Gregory J. Tawa*[1]*, tawag@wyeth.com, Sharon Rosenzweig-Lipson*[3]*, Marla J. Williams*[1]*, Gouming Zhang*[3]*, Jonathan Gross*[1]*, grossj@wyeth.com, Nicholas Brandon*[3]*, and Albert J. Robichaud*[4]*, robicha@wyeth.com. (1) Chemical and Screening Sciences, Wyeth Research, CN 8000, Princeton, NJ 08543, Fax: 732-274-4505, (2) Drug Safety and Metabolism, Wyeth Research, Collegeville, PA 19426, (3) Discovery Neuroscience, Wyeth Research, Princeton, NJ 08543, (4) Chemical Sciences, Wyeth Research, Princeton, NJ 08543*

Novel Indole amines were designed and synthesized as small molecule antagonists of the Histamine Receptor Type 3 (H3). Analogs discovered are potent and selective for the human H3 receptor, and demonstrate *in vivo* efficacy in rodent behavioral models of cognition. The design, synthesis, SAR, molecular modeling and pharmacological profile of these new analogs as potential treatments for cognitive dysfunction will be described.

MEDI 259

Azacyclamine derivatives as Histamine-3 (H3) receptor antagonists

Marla J. Williams[1]*, Jonathan L. Gross*[1]*, Adedayo Adedoyin*[2]*, Suzan Aschmies*[3]*, Julie Brennan*[3]*, Mark Day*[3]*, Li Di*[1]*, Jeannette Golembieski*[3]*, Steve Grauer*[3]*, Warren D. Hirst*[3]*, Cody Kelley*[3]*, Ji-In Kim*[1]*, Katie Kubek*[3]*, Karen Marquis*[3]*, Rachel Navarra*[3]*, Mark Pausch*[3]*, William R. Solvibile*[1]*, Guo Ming Zhang*[3]*, Nicholas Brandon*[3]*, Thomas Comery*[3]*, and Albert J Robichaud*[4]*. (1) Chemical and Screening Sciences, Wyeth Research, CN 8000, Princeton, NJ 08543, (2) Drug Safety and Metabolism, Wyeth Research, Collegeville, PA 19426, (3) Discovery Neuroscience, Wyeth Research, Princeton, NJ 08543, (4) Chemical Sciences, Wyeth Research, Princeton, NJ 08543*

The histamine-3 (H3) receptor is a G-protein coupled receptor (GPCR) predominantly expressed in the CNS. In addition to its function as a pre-synaptic auto-receptor, modulating histaminergic tone, the H3 receptor also serves as a hetero-receptor, and H3 receptor activation inhibits the release of several important neurotransmitters. H3 receptor expression localization in brain regions such as the cortex and hippocampus in addition to its ability to modulate

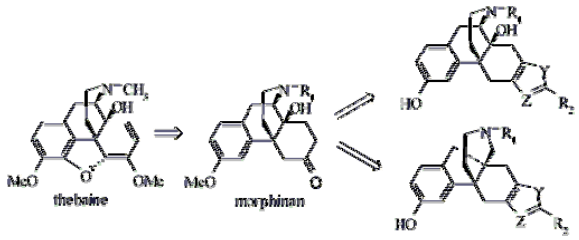
neurotransmitter systems important to memory and cognition make the H3 receptor a potentially important therapeutic target for the treatment of cognitive dysfunction. The design, synthesis, SAR, and pharmacological profile of a novel series of azacyclylamines as antagonists of the H3 receptor will be described.

MEDI 260

Developing novel morphinanoids with dual actions at opioid receptors

Fuying Li, Synthetic Organic & Medicinal Chemistry Laboratory, Shanghai Institute of Materia Medica, Xin Xie, National Center for Drug Screening, Shanghai Institute of Materia Medica, and ***Ao Zhang****, aozhang@mail.shcnc.ac.cn, Synthetic Organic & Medicinal Chemistry Laboratory, Shanghai Institute of Materia Medica, 555 Zuchongzhi Rd, Shanghai 201203, China, Fax: 86-21-50806035*

Analogs of opioids, such as morphine, codeine, thebaine, and levorphanol, are of current interest due to their utilities as analgesics and as potential therapeutic agents for the treatment of drug abuse. In our approach toward the identification of novel opioid ligands as potential treatment of drug abuse, we recently developed several series of morphinanoids with a heterocycle fused to the morphinan template. Interestingly, compounds with a heterocycle fused to the right-side of the morphinan molecule yielded an improvement of binding at the delta opioid and/or mu receptors. A series of rearranged morphinan heterocycles were also prepared.



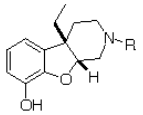
MEDI 261

Probes for narcotic receptor mediated phenomena: Binding studies on racemic cis benzofuro[2,3-c]pyridin-8-ols

Malliga R. Iyer[1]*, iyerma@mail.nih.gov, Christina M. Dersch*[2]*, Richard B. Rothman*[2]*, Jeffrey R. Deschamps*[3]*, Arthur E. Jacobson*[1]*, aej@helix.nih.gov, and Kenner C. Rice*[1]*, kr21f@nih.gov. (1) Drug Design and Synthesis Section, Chemical Biology Research Branch, National Institute on Drug Abuse and the National Institute on Alcohol Abuse and Alcoholism, NIH, DHHS, 5625 Fishers Lane, Room 4N03, MSC 9415, Rockville, MD 20852, Fax: 301-402-0589, (2)*

Clinical Psychopharmacology Section, NIDA-IRP, NIH, DHHS, Baltimore, MD 21224, (3) Naval Research Laboratory, Washington, DC 20375

Cis-1,2,3,4,4a,9a-Hexahydrobenzofuro[2,3-c]pyridin-6-ols with suitable substitution on the nitrogen have been shown to have potent affinity for opioid receptor subtypes (mu, delta, kappa). A similar study involving racemic cis-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-c]pyridin-8-ols was undertaken. Benzofuro[2,3-c]pyridin-8-ols with varied substitution pattern was synthesized using well documented chemistry. Additionally, a shorter and efficient route was developed for the synthesis of racemic 4a-ethyl-2-methyl-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-c]pyridin-8-ol. The opioid receptor binding affinities of these compounds were also determined. The presentation will detail the chemistry and pharmacology of the new opioid derivatives.

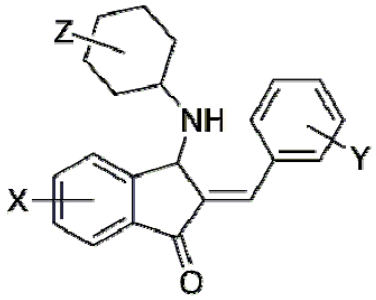


MEDI 262

Identification and structure-activity relationship of an allosteric inhibitor of the dual specificity phosphatase Dusp6

Vasiliy N. Korotchenko[1]*, vak19@pitt.edu, Weixiang Dai*[1]*, Karl T. Debiec*[2]*, Kristina A. Greene*[2]*, Gabriela Molina*[3]*, Ahmet Bakan*[4]*, Ivet Bahar*[4]*, bahar@pitt.edu, Michael Tsang*[3]*, and Billy W. Day*[5]*, bday@pitt.edu. (1) Department of Pharmaceutical Sciences, University of Pittsburgh, 3501 Fifth Ave, BST3-10030, Pittsburgh, PA 15261, (2) Department of Chemistry, University of Pittsburgh, (3) Departments of Microbiology and Molecular Genetics, University of Pittsburgh, (4) Department of Computational Biology, University of Pittsburgh, (5) Departments of Pharmaceutical Sciences and of Chemistry, University of Pittsburgh, Pittsburgh, PA 15213*

The dual specificity phosphatase Dusp6 is a mitogen-activated protein kinase (MAPK) phosphatase, also known as MKP3, that functions as a feedback regulator of fibroblast growth factor (FGF) signaling to limit the activities of the extracellular regulated kinase ERK2. We have identified a small molecule inhibitor of Dusp6, (E)-2-benzylidene-3-(cyclohexylamino)indan-1-one (BCI), from a zebrafish chemical screen. Treatment with BCI blocked Dusp6 activity and expanded FGF target gene expression in the embryo as visualized with green fluorescent protein-labeled gene products. Herein, we report the design, synthesis, biological activity and SAR of BCI analogs. Syntheses of affinity versions of BCI will be disclosed.



BCI: X, Y, Z = H

MEDI 263

Gold(I)-based inhibitors of protein tyrosine phosphatases

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The protein tyrosine phosphatases (PTPs) are a family of enzymes that have been implicated in a number of disease states ranging from autoimmunity to cancer. These enzymes are thus emerging targets of drug design and the development PTP inhibitors have attracted much attention as potential therapeutics for these ailments. A significant challenge associated with this has been achieving selectivity for a PTP of interest. Towards this end, we have developed a series of gold(I)-complexes as PTP inhibitors. In addition, inhibition studies in vitro indicate selectivity for certain members of the PTP family that are involved in T cell signaling. Finally, we have also examined the cellular effects of these inhibitors on these enzymes in T cells in detail.

MEDI 264

Identifying protein tyrosine phosphatase inhibitors using a novel comparative screening approach

Rhushikesh A. Kulkarni, *r.kulkarni@utah.edu, Department of Medicinal Chemistry, University of Utah, 30 South 2000 East, SKH 311, Salt Lake City, UT 84112, and Amy M. Barrios, amy.barrios@utah.edu, Deparment of Medicinal Chemistry, University of Utah, Salt Lake City, UT 84112*

Lymphoid specific tyrosine phosphatase (LYP), a protein tyrosine phosphatase (PTP), is known to negatively regulate T-cell signaling by lowering the phosphorylation levels of the signaling proteins. A gain-of-function mutation in LYP is implicated in the development of autoimmune disorders like rheumatoid arthritis. Therefore, inhibition of LYP provides an attractive strategy for treatment of these disorders. However, finding selective inhibitors of LYP is challenging owing to the highly conserved catalytic domain of PTPs. Traditionally, inhibition of PTPs has been studied by measuring the dephosphorylation of a small molecule phosphotyrosine mimic such as difluoromethylumbelliferone phosphate (DiFMUP), which interacts with limited residues in catalytic domain of PTPs. We have designed fluorogenic, peptide-based substrates that show extended interactions with PTP catalytic domains for use in high-throughput screening for novel PTP inhibitors. We hypothesize that using a peptide-based substrate in PTP inhibitor screens will help to minimize the number of false positive and false negative hits as compared to the traditional screening method. Here, we report the results from screening of small molecules against LYP using both a small molecule substrate and a peptidic substrate with the aims of finding selective inhibitors of LYP and testing our hypothesis that the peptidic substrate is a superior screening tool compared to traditional small molecule substrates.

MEDI 265

Selective PTP inhibitors with therapeutic potential

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Protein tyrosine phosphatases (PTPs) are enzymes that help regulate cell signaling pathways. Lyp is a PTP present in T cells and is a logistical target for therapeutics because it has been linked to a variety of autoimmune diseases. Unfortunately, effective PTP-targeted therapeutics cannot be developed until a better understanding of PTP substrate and inhibitor selectivity is achieved. Our aim is to obtain Lyp selective peptide substrates using peptide libraries containing a fluorogenic phosphotyrosine mimic (pCAP). From these Lyp-selective peptide substrate sequences, selective peptide inhibitors can be developed. This poster will present the preliminary results of our novel substrate selectivity approach to PTP-selective inhibitor design.

MEDI 266

Development of a cellular assay for evaluating the permeability of novel neutrophil elastase inhibitors

***Emme CK Lin**, emmel@activx.com, Lingling Du, Eric S Okerberg, Yi Hu, Allister S Fraser, Lan M Pham, Julia Cajica, Christopher M Amantea, Heidi E Brown, John Kozarich, and Kevin R Shreder, ActivX Biosciences, La Jolla, CA 92037*

Human neutrophil elastase (HNE), the primary protease in neutrophils, is thought to be causally responsible for the tissue damage in inflammatory respiratory diseases. Due to very high concentrations of HNE in neutrophils and the fact that HNE is stored in an active form, one approach to target this enzyme is to inactivate it while it is still intracellular. We developed an assay using ActivX serine hydrolase activity-based probe technology to measure the cell permeability of novel HNE small molecule inhibitors for this specific purpose. The HL-60 human cell line exhibited HNE characteristics most similar to neutrophils and allowed for the evaluation of compound permeability across live cellular membranes and a pH differential, challenges not replicated by an in vitro PAMPA assay. The assay was highly valuable in the development of potent, benzoxazinone-derived HNE inhibitors which were shown to exhibit a wide range of cell permeabilities depending on their structure.

MEDI 267

Assembly of a metal-binding fragment library to identify new chelators for inhibitors targeting metalloenzymes

***Jennifer Andrene Jacobsen**, j3jacobs@ucsd.edu, Melissa T. Miller, melissa-miller@ucsd.edu, and Seth M. Cohen, scohen@ucsd.edu, Department of Chemistry and Biochemistry, University of California, San Diego, La Jolla, CA 92093-0358*

A metal-binding fragment library was assembled to find new chelators for use as anchors in inhibitors of metalloenzymes. Low molecular weight (<230g/mol) fragments that bind to metals through two to four donor atoms were explored in this library. Cyclic compounds were chosen as the main focus for this library owing to their enhanced chelation effects due to limited rotation and to their improved stability toward cleavage associated with peptide proteolysis. The fragment library was screened against various metalloenzymes including MMPs -2 and -9 and anthrax lethal factor in high concentration assays. Hydroxypyrothiones, hydroxypyridinethiones, and other previously studied N-donor chelators were confirmed as hits against MMPs. New metal-binding fragments discovered in this library offer the ability to develop novel metalloenzyme inhibitors.

MEDI 268

Novel method for screening EGFR inhibitors using enzyme fragment complementation

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The epidermal growth factor receptor (EGFR) is a cell membrane protein whose downstream signaling pathways lead to DNA synthesis and cell proliferation. Over-expression of EGFR has been associated with a number of cancers and as such serves as an attractive target for cancer therapies. In the present study, a novel competitive binding assay for screening EGFR inhibitors has been developed using &beta-Galactosidase Enzyme Fragment Complementation (EFC). EFC technology is based on splitting the E. coli &beta-galactosidase (&beta-gal) into two fragments, a large protein fragment (enzyme acceptor, EA) and a small peptide fragment (enzyme donor, ED). These fragments are inactive separately, but in solution, they rapidly recombine to form an active enzyme that hydrolyzes luminescent or fluorescent substrates to produce an easily detectable signal.

Tarceva is a potent inhibitor of EGFR and has been well accepted as an anti-cancer drug. Herein, Tarceva was chemically conjugated to ED (enzyme donor fragment of &beta-galactosidase (&beta-gal). The conjugated ED-Tarceva exhibited its capability to form an active &beta-galactosidase (&beta-gal) enzyme and generate a signal. In the presence of EGFR kinase however, the signal was reduced indicating successful binding of the ED-Tarceva towards EGFR Kinase. The conjugated ED-Tarceva was then allowed to compete with free Tarceva for EGFR kinase binding site. A reversal of the signal with the free Tarceva suggested a competition between ED-Tarceva and Tarceva for EGFR binding pocket. Tarceva-ED conjugate binding affinity and its capability to get competed by free Tarceva thus forms a basis to screen novel candidates as inhibitors for receptor tyrosine kinases such as EGFR for future drug discovery and development.

MEDI 269

Endophytic analysis of tropical plants yields a platform for drug discovery

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Endophytic analysis of tropical plants remains a largely unexplored source of novel bioactive small molecules and natural product chemistry. The internal microorganisms of parasitic plant species provide a method of selection optimized by evolution of unique survival traits, aided by positive exchange of defensive compounds between microorganism and plant. Two endophytic organisms – one fungal and one bacterial – were isolated from the living tissues of a single structural parasite collected in the Ecuadorian Amazon. The two strains were identified using morphological and genetic methods, then screened for anti-fungal, anti-bacterial, and anti-herbivory activity using multiple assay methods. Strongly selective antibiotic activity was seen in both strains of endophytic organisms. Extracts derived from biologically active organisms were analyzed using bioactivity-guided fractionation, resulting in natural products possessing compelling biological activity. This research demonstrates the extraordinary potential of endophytic analysis as a source of novel natural products with bioactivity relevant to the pharmaceutical industries.

MEDI 270

A new collaborative web-based database architecture for community-based pharmaceutical research

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We have developed a novel, collaborative web-based database architecture (Collaborative Drug Discovery (CDD)) to archive and mine a broad range of heterogeneous low- and high-throughput biological data and chemical structures. Such data can be selectively and securely shared among colleagues or even openly shared on the Internet in both proprietary and open-access formats, which makes this a valuable tool for sharing data between or within academic and pharmaceutical organizations. An application of CDD involves overcoming drug resistance to chloroquine, used to treat malaria. We have discovered alternatives to the known chemosensitizer verapamil using the CDD database to foster collaborations in a global network by combining compounds from UCSF, known FDA/Orphan approved drug compounds (collated by Dr. Chris Lipinski) and experimental results from the University of Cape Town, South Africa. This community-based collaborative approach provides networks of technical experts with the platform to speed development of new treatments for neglected infectious diseases.

Research into neglected infectious diseases has been shown to benefit from a novel collaborative web-based database architecture (Collaborative Drug

Discovery), enabling networks of technical experts to speed development of new treatments.

MEDI 271

Multicomponent reactions for the generation of biologically active small molecules

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As high throughput screening has become a more prominent technique in academic laboratories, there has been a need to develop reactions that are both facile and are amenable to probing chemical space. Multicomponent reactions (MCR's) provide a way of generating a large variety of substitution patterns on a core structure thus expanding the chemical spaced probed. The Passerini reaction, the Ugi reaction, the Biginelli reaction, the Hantzsch reaction, or various other reactions have been particularly useful for synthesizing peptoids and/or heterocylces. Our progress on the use of these reactions to synthesize functionalized molecules with the ability to modulate heat shock protein 70 activity will be discussed.

MEDI 272

The pharmacodynamic screening of novel vinflunine derivatives

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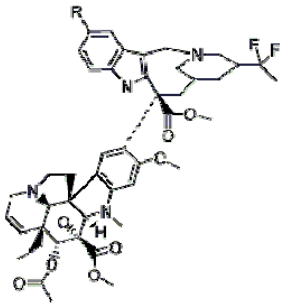
Cyano and alkynyl substituted Vinflunine derivative compounds were evaluated in human NSCLC A549 nude mice-transplanted tumors model. The two compounds showed significant tumor growth inhibition in a dose-dependented manner as compared to ®Vinflunine.



R= H ; alkynyl; CN

MEDI 273

Pro-apoptotic screening of novel aza triterpenoids through structure-activity relationship investigation

Ali Koohang, *akoohang@advancedlifesciences.com, Aye Aye Mar, Erika L. Szotek, David A. Eiznhamer, Ze-Qi Xu, and Michael T. Flavin, Drug Discovery, Advanced Life Sciences, 1440 Davey Rd, Woodridge, IL 60517*

Apoptosis is a highly regulated process by which excessive cells are eliminated in order to maintain normal cell development and tissue homeostasis. It is proposed that resistance to apoptosis often contributes to failure in cancer prevention and treatment. Apoptotic cell death regulators are considered important targets for discovery and development of new therapeutic agents in oncology research. We have designed and synthesized a triterpenoid-based library of new compounds and investigated their activity in an efficient cell-based assay to identify potential hits capable of modulating the process of intrinsic pathway of apoptosis. Our approach involves screening of new molecules for in vitro cytotoxicity, induction of early to mid apoptosis and activation of selective caspases as well as the release of cytochrome c in cell death signaling. We will present the synthesis and potent activity of a novel class of aza triterpenoids in a panel of cancer cell lines with the ability to induce apoptosis through activation of caspases.

MEDI 274

A high throughput screening FRET assay for identification of novel anthrax toxin lethal factor inhibitors

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A high throughput screening fluorescence resonance energy transfer (FRET) assay was used to identify novel inhibitors of the anthrax toxin lethal factor (LF). Large-scale virtual screening of approximately thirty-five million non-redundant compounds in silico for potential activity against LF resulted in dozens of potential lead compounds. These potential leads were selected for an experimental HTS FRET assay using a consensus sequence peptide substrate (List Biological Laboratories). This kinetic assay was performed in a multiwell (384) plate-based format with low nanomolar concentration (20 nM) of LF and a low micromolar concentration (7.5 μM) of oAbz/Dnp substrate with short incubation time (15 min). The time-dependent increase in fluorescence intensity was monitored at 37 °C every 60 sec for 30 min using excitation and emission wavelengths of 320 and 420 nm, respectively. The IC50 values were obtained by dose response measurements. Experimental screening resulted in 17 hit compounds with at least micromolar inhibition against LF, twelve of which exhibited IC50 values less than 50 μM. The three most active compounds from this set were compounds with IC50 values less than 4 μM. This in vitro assay has been found to be suitable for large-scale HTS screening to identify potential lead and/or probe scaffolds to further investigate LF inhibition.

MEDI 275

Design and synthesis of thallium-sensitive fluorescent probes for FLIPR assay of potassium channels

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Potassium channels are important targets for a large number of therapeutic indications as well as for safety profiling of new drugs. The ability to use a high throughput functional assay for the detection and characterization of small molecule modulators of potassium channels is a current theme in medicinal chemistry research. The assay principle is essentially based on the fact that thallium ions (Tl+) can act as a surrogate of potassium ions, and hence are permeable through potassium channels. The influx of Tl+ into a cell through its potassium-specific channels is thus a measure of the channel activity. We have designed and synthesized a series of fluorescent probes based on a BAPTA-coumarin core structure. The synthesis of the probes as well as their utility in high throughput assay of potassium channels will be presented.

MEDI 276

Design, synthesis, biochemical and biological evaluations of novel and potent small-molecule inhibitors of STAT3.

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Constitutive activation of the Signal Transducers and Activators of Transcription 3 (STAT3) is frequently detected in human cancer specimens from patients with advanced diseases and cancer cell lines, but not in normal epithelial cells. Persistent activation of STAT3 signaling has been demonstrated to directly contribute to oncogenesis by stimulating cell proliferation and preventing apoptosis in human cancer cells. STAT3 activation may not only provide a growth advantage, allowing accumulation of tumor cells, but also confer resistance to conventional therapies that rely on apoptotic machinery to eliminate tumor cells. STAT3 represents an important and specific molecular target for designing an entirely new molecularly targeted therapy for human cancer with constitutively active STAT3 with potentially low toxicity to the normal cells without constitutive STAT3 signaling.

STAT3 is recruited from cytosol and makes specific interactions through its SH2 domain with different cytokine receptor with phosphotyrosine docking sites on the receptors. STAT3 then becomes phosphorylated on a carbonyl terminal tyrosine (Tyr705). Tyrosine physphorylation of

STAT3 causes it to dimerize and translocate to the nucleus and bind to specific promoter sequences on its target genes. Dimerization of STAT3 is a decisive event for its activation. Thereby, blocking the dimerization of STAT3 using a small molecule antagonist is a very attractive therapeutic approach for developing a molecularly targeted therapy for the treatment of human cancer in which STAT3 is constitutively activated. Herein, we wish to report the design, synthesis, biochemical and biological evaluations of novel and potent small-molecule inhibitors of STAT3. Our most potent inhibitors bind to Stat-3 with low nanomolar affinities and display excellent selectivity over Stat-1 and Stat-5. These compounds are excellent biochemical and pharmacological tools to further elucidate the role of Stat-3 in cancer and promising lead compounds for the development of potent and specific Stat-3 inhibitors for the treatment of human cancer.

MEDI 277

Synthesis of dihydroquinoline derivatives as novel STAT3 inhibitors

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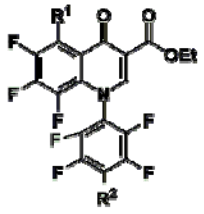
The JAK-STAT3 pathway regulates genes that are important in cell proliferation thus is a promising target for cancer therapy. A high throughput screening (HTS) campaign using an Apo-ONE Homogenous Caspase 3/7 assay in U266 cells identified 4-oxo-1-phenyl-1,4-dihydroquinoline-3-carboxylic acid ethyl ester **1** as a potential STAT3 pathway inhibitor. Optimization of this HTS hit led to the identification of the 7-cyano analog **2** which inhibited STAT3-Y705 phosphorylation with an EC_{50} of 170 nM. Compound **2** inhibited activation of JAKs but did not inhibit JAK1, JAK2, and JAK3 enzyme activity in in vitro kinase assay. The specificity of compound **2** for inhibition of the JAK-STAT3 pathway was further tested in K562 cells where STAT5 is constitutively activated by a different signaling pathway, the oncogene BCR-ABL. In contrast to a control Src kinase inhibitor, compound **2** did not inhibit STAT5-Y694/699 phosphorylation. Biochemical evidence suggests compound **2** was selective for the JAK-STAT pathway and it inhibited many STAT3 target genes.



1: (R^1 = F, R^2 = F), STAT3-P, EC_{50} = 4.9 μM
2: (R^1 = H, R^2 = CN), STAT3-P, EC_{50} = 170 nM

MEDI 278

Two synthetic approaches to 6'-deaminocarbocyclic sinefungin

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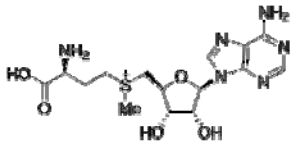
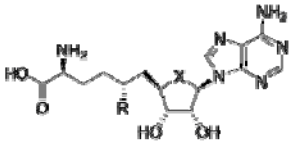
The significant antiviral properties of sinefungin (**2**), a structural analogue of AdoMet (*S*-adenosyl-L-methionine, **1**), have been attributed to its potent inhibition of viral mRNA methyltranferases. 6'-Deaminosinefungin (**3**), a simplified sinefungin analogue, has been found to be another efficient cofactor inhibitor of biomethylations. In the rational design of derivatives of **3**, as a means to improve upon its antiviral scope and reduce its associated cytotoxicity, 6'-deaminocarbocyclic sinefungin (**4**) was sought in our laboratories at Auburn. Two synthetic approaches to this compound and their comparison will be presented. This research was supported by funds from DHHS (AI 56540).



1



2, X=O, R=NH_2
3, X=O, R=H
4, X=CH_2, R=H

MEDI 279

Synthesis of open-chain epothilones

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Macrolactone natural products, epothilones are anti-mitotic agents with a mechanism of action analogous to that of the clinically used anticancer drug paclitaxel. They are microtubule stabilizing agents that exert their antiproliferative activity by the disruption of microtubule dynamics, leading to arrest of cell division at G2/M phase and inducing apoptosis. However, in contrast to paclitaxel, epothilones are effective against multiple drug resistant cell lines.

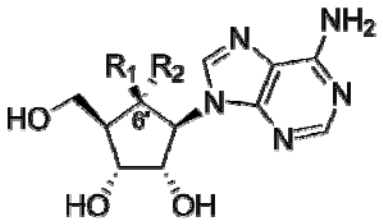
We have designed and synthesized a new class of open-chain epothilone analogues that retain some of the key structural elements known to be crucial for the biological activity of epothilones. The biologically important C1-C8 fragment of epothilone structure was retained unchanged. Changes were effected in the aromatic side chain while maintaining the minimum structural requirements, necessary for biological activity. The synthesis of these open-chain epothilone analogues for SAR studies will be presented.

MEDI 280

A practical synthesis of 6'-fluoroaristeromycins

***Chong Liu**, liuchon@auburn.edu and Stewart W. Schneller, schnest@auburn.edu, Department of Chemistry and Biochemistry, Auburn University, 179 Chemistry Building, Auburn, AL 36849, Fax: 334-844-0239*

Aristeromycin (**1**), a naturally occurring carbocyclic nucleoside, has been known to be one of the most potent inhibitors of *S*-adenosyl-L-homocysteine hydrolase (SAH), an enzyme of relevance in biomethylations. Structural modification at its C-6' site offers a center for the design of new SAH inhibitors not available in the more common ribofuranosyl based nucleosides. In that regard, the C-6' substituted aristeromycin series is receiving increasing attention. Because of the antiviral potential of 6'-α and 6'-β-fluoroaristeromycins (**2** and **3**), a practical synthesis of these derivatives was sought. The results of these investigations will be presented. This research was supported by funds from DHHS (AI 56540).



1, R_1=H, R_2=H
2, R_1=H, R_2=F
3, R_1=F, R_2=H

MEDI 281

Design and synthesis of 3-deazaaristeromycin derivatives

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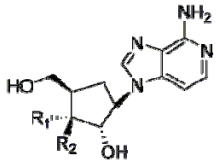
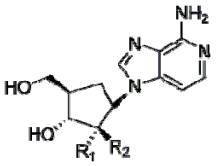
Nucleoside analogs based on the 3-deazaaristeromycin (**1**) framework have found promise in antiviral agent design and biochemical investigations as AdoHcy hydrolase inhibitors. Also, it is noteworthy that placement of a fluorine atom can have significant effects on a biological molecule due to imparting increased lipophilicity, powerful electronic effects and altered metabolic properties. In our efforts to build upon the 3-deazaaristeromycin platform for new bio-agent design, we have investigated the synthesis and biological properties of the 3'-fluoro-3'-deoxy- and 2'-fluoro-2'-deoxyaristeromycin derivative **2**, **3**, **5** and **6**. The 3'-deoxy- and 2'-deoxyaristeromycin derivatives **4** and **7** arose driving these studies and will also be described. This research is supported by funds from the Department of Health and Human Services (AI56540)



1: R1 = OH, R2 = H
2: R1 = F, R2 =H
3: R1 = H, R2 =F
4: R1= H, R2 = H



5: R1 = F, R2 =H
6: R1 = H, R2 =F
7: R1= H, R2 = H

MEDI 282

Synthesis of resveratrol using palladium catalyzed bond formation

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Resveratrol has received much interest in the popular press recently due to its positive biological activity including its use as an anticancer compound, an anti-obesity compound, antioxidant, and potential preventer of cardiovascular disease. The current synthetic routes utilizing Wittig chemistry or Grignard addition are efficient but are not stereospecific as both the cis and trans isomers are formed. The preparation of an arylacetylene from the corresponding aldehyde via Corey-Fuchs methodology followed by elimination and Sonogashira coupling of the resulting alkyne to an aryl halide would lead to dehydroresveratrol. Stereoselective reduction (hydrogenation on Lindlar's catalyst or metal-ammonia reduction) would give rise individually to each of the possible stereoisomers.

MEDI 283

Hexachloroethane: A highly efficient reagent for the synthesis of chlorosilane from hydrosilane

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Chlorosilanes are important in organic synthesis such as using as protecting group for highly reactive hydroxyl and amino functional groups or using as a reagent for Mukaiyama aldol condensation. Generally, chlorosilanes are mainly prepared by reacting alkyl or ally chlorides with CuCl2, NiCl2, PdCl2, Pd/C as a catalyst. However, most methods have certain limitation such as high temperature, long reaction time, and expensive and toxic chlorinating agents which is hard to handle. In this presentation, the new efficient methodology for

preparing chlorosilanes is developed using chlorinating agent in combination with PdCl2 as a catalyst under mild conditions to give a quantitaive yield of the desired product. The effects of type and amount of chlorinating agents were investigated to optimize the reaction conditions. Cl3CCCl3 appeared to be a highly reactive reagent for preparing the corresponding chlorosilane under mild conditions.

MEDI 284

Nucleophilic selectivity in reactions of 3-chloromethylisoxazole-4,5-dicarboxylate

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A collection of ninety-one 3-(arylthiomethyl)isoxazole-4,5-dicarboxamides were prepared starting from dimethyl 3-(chloromethyl)isoxazole-4,5-dicarboxylate. The thioether moieties in these compounds were subsequently oxidized to give the corresponding 3-(arylsulfonylmethyl)isoxazole-4,5-dicarboxamides. The yields for these transformations are excellent. By carefully controlling stoichiometry and reaction conditions, the C4 and C5 carboxyamides could be differentially diversified. The total of 182-member library is reported and most compounds are tested for bio-activities and also are deposited at the National Institutes of Health molecular repository.

MEDI 285

Fragment based drug design toward novel metalloprotein inhibitors

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The presented study focuses on the synthesis of a library of N-hydroxypyridinone and N-hydroxypyridinethione fragments and their potency against zinc endopeptidases - matrix metalloproteases (MMPs) and anthrax lethal factor (LF). The entire library of 96 compounds was synthesized via a microwave-assisted procedure developed in the lab. The in vitro potency (% inhibition) of each compound at 50 uM was measured using a fluorescence based assay against

both MMPs and LF. Fragments that generated 95%-100% inhibition were selected for molecular docking studies and computational modeling to aid in fragment based drug design toward more potent and selective inhibitors. Overall, the O,S metal binding N-hydroxypyridinethiones were more potent than the O,O metal binding N-hydroxypyridinones against both zinc enzymes.

MEDI 286

Synthesis and in vitro biological evaluation of ring B abeosterols as novel inhibitors of Mycobacterium tuberculosis

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A series of 3β-hydroxy steroid analogues possessing a contracted cyclopentane B-ring were prepared based on the initial activity screening of a recently reported naturally occurring marine 5(6→7)abeo-sterol against Mycobacterium tuberculosis. All of the novel ring B abeo-sterols synthesized showed good inhibitory activity, whereas none of the starting steroids based on the common 3β-hydroxy- Δ^5-cholestane nucleus, proved to be active. Therefore, the 5(6→7)abeo-sterol nucleus present in compounds **3**, **5**, **7**,**9**, and **11** represents a novel scaffold for the development of new antitubercular agents.

MEDI 287

Synthesis and antitubercular activity of 4,6-diamino-1,3,5-triazine derivatives

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A series of 2,4-Diamino-1,3,5-triazine analogs have been explored as a novel class of antitubercular agents. In the course of this study, we have developed an efficient methods to construct a chemical library of 1,3,5-triazine by microwave-assisted reactions. The biological activity of the library was evaluated against M. tuberculosis (H37Rv) as well as other bacterial strains. In this study, we wish to

report the design, synthesis and biological activity of the libraries as potential antitubercular agents.

MEDI 288

Photodynamic inactivation with Mycobacterium smegmatis

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Efforts to control Tuberculosis (TB), a highly infectious disease, have been hampered by the increasing rise of multiple-drug resistant strains. Herein, we explore the feasibility of photodynamic inactivation (PDI) as an alternative approach to the current antibiotic-based treatments. *Mycobacterium smegmatis* was employed as a model for *Mycobacterium tuberculosis* and the reduction in colony forming units (CFU) was examined as function of the photosensitzer (PS) concentration and the light dose used. The most promising results were achieved using cationic tetrakis(1-methyl-4-pyridinio)porphyrin (146 nM), resulting in a 99.99% reduction of CFU after illumination under medically achievable conditions. Further, studies employing a range of PS (porphyrins, phthalocyanines, bactericlorins) and a comparison to E. coli, will be presented. The data show that mycobacteria can be photodynamically inactivated with cationic PS in very high efficency at nanomolar conentration, suggesting that PDI may be an attractive treatment option for drug-resistant TB.

MEDI 289

Novel pyridopyrimidine derivatives as inhibitors of STa induced cGMP synthesis

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Escherichia coli enterotoxin, heat-stable enterotoxin (STa), induces diarrhea when it binds to intestinal epithelial cell membrane receptor, guanylyl cyclase type C (GC-C). This activates the enzyme to convert guanosine triphosphate (GMP) to cyclic guanosine 3',5'-monophosphate (cGMP), causing intracellular levels of cGMP to spike. This in turn induces activation of a cGMP-dependent protein kinase and chloride-ion channel, cystic fibrosis transmembrane conductance regulator (CFTR). Activation of CFTR triggers the influx chloride

ions into the intestinal lumen and the accumulation of water and sodium ions, thus causing diarrhea. In an effort to develop a novel approach to the treatment of acute diarrhea based on inhibition of stimulated cyclic nucleotide synthesis, several compounds were screened from which 5-(3-bromophenyl)-1,3-dimethyl-5,11-dihydro-1H-indeno-[2',1':5,6]pyrido[2,3-d]pyrimidine-2,3,6-trione (BPIPP), was identified as a promising lead. Through SAR studies we have identified three new potent derivatives. Their structures, activities and chemistry for their synthesis will be presented.

MEDI 290

Design, synthesis and diversification on cyclohexen-1,4-dione libraries

***Eric A. Tanifum**, eatanifu@utmb.edu, Adijah M. Nyong, and Scott R. Gilbertson, srgilber@utmb.edu, Department of Pharmacology and Toxicology, The University of Texas Medical Branch, 301 University Boulevard BSB 3.330, Galveston, TX 77555*

The diverse biological activities of compounds containing quinone and dihydroquinone functional groups suggest that the cyclohexen-1,4-dione scaffold could be a potential source for interesting biological activity as well. A search of PubChem revealed that such compounds are not represented in that database. As part of a project to synthesize pilot-scale libraries for high-throughput screening for the NIH Small-Molecule Repository, we have designed and synthesized a diverse library of cyclic enediones. Representative members from this library as well as the chemistry used to prepare them will be presented.

MEDI 291

Novel 2-aminoalkylethers for the treatment of atrial fibrillation: Discovery of vernakalant

***Gregory N. Beatch**, gbeatch@cardiome.com, Cardiome Pharma Corp, 6190 Agronomy Road, 6th Floor, Vancouver, BC V6T 1Z3, Canada*

A series of 2-aminoalkylethers were evaluated as potential atrial selective antiarrhythmic drugs for the treatment of atrial fibrillation. These compounds displayed varying degrees of potency for block of sodium and potassium ion channels and antiarrhythmic activity in in vivo models. Structure-activity studies were designed to select compounds with enhanced potency in fibrillating atria and reduced potency in the normal ventricle, as well as an optimized safety margin for extra-cardiac effects. These studies led to the identification of vernakalant, 3 pyrrolidinol, 1-[(1R,2R) –2-[2-(3,4 dimethoxyphenyl) ethoxy]cyclohexyl]-, hydrochloride, (3R)-, which was selected for clinical

development based on its in vivo safety and efficacy profile. An NDA for vernakalant (injection) is currently under review by the FDA, while Phase 2 clinical studies have been completed with its oral formulation.

MEDI 292

Evaluation of potent and selective T-Type calcium channel antagonists in models of pain and insomnia

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T-type calcium channels are low-voltage activated ion channels that play an important role in regulating a variety of biological processes, both peripherally and in the CNS. Indeed, T-type calcium channels have been proposed as therapeutic targets for diverse diseases such as hypertension, absence epilepsy, sleep disorders, and pain. Several compounds including mibefradil, ethosuximide, and pimozide have been reported to inhibit T-type calcium channels; however, their wide spectrum of activity makes it difficult to conclusively determine the consequences of T-type calcium channel inhibition. Here, we report two classes of potent and selective T-type calcium channel antagonists derived from 1,4-substituted piperidines and aryl acetamides. Promising leads in each of these classes were identified through a high-throughput screen and each series was optimized for potency as well as selectivity against other ion channels. Many compounds in both series are orally bioavailable and exhibit good brain penetration which makes them useful tools for in vivo exploration of the central effects of T-type calcium channel inhibition. We will present our results from evaluation of T-type antagonists in rodent models of inflammatory and neuropathic pain. Further, we utilized EEG as an additional marker for central activity and observed robust, dose-dependent changes in sleep architecture in rats.

MEDI 293

Discovery and pharmacological evaluation of potent, selective blockers of the $Na_v1.8$ sodium channel with efficacy in models of neuropathic pain

***Michael E. Kort**, michael.e.kort@abbott.com, Global Pharmaceutical Research and Development, Abbott Laboratories, 100 Abbott Park Rd, Abbott Park, IL 60064-6100*

Non-selective inhibitors of voltage-gated sodium channels (VGSCs), originally developed as local anesthetics, antidepressants, and anticonvulsants, are efficacious in many painful human neuropathies. A growing body of evidence suggests that the peripherally expressed, tetrodotoxin resistant VGSC $Na_v1.8$ (PN3) plays a key role in the pathophysiology of certain pain states. It was envisioned that selective blockade of this sodium channel isoform might offer effective analgesia with a reduction in the adverse events typically associated with non-selective therapeutic agents. Herein we describe the discovery of potent (IC_{50} <10 nM) furfuramide-based $Na_v1.8$ blockers with >100-fold selectivity versus human $Na_v1.2$, $Na_v1.5$ (hH1), and hERG channels. We discuss the further elaboration of this chemical series to provide orally bioavailable molecules and characterize the in vivo pharmacology of selected compounds in rodent pain models.

MEDI 294

Discovery, SAR and pharmacology of sodium channel Nav1.8 selective quinazolines

WITHDRAWN

MEDI 295

Novel dihydropyridines as inhibitors of Nav1.5 late current

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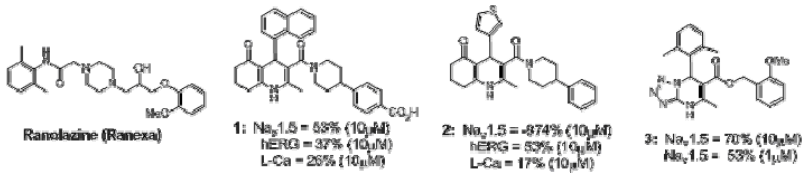
Ranexa® is a novel selective inhibitor of the Nav1.5 late current relative to peak sodium channel current that is approved by the FDA for the treatment of chronic stable angina pectoris. The inhibition of the Nav1.5 late current may decrease sodium-dependent intracellular calcium overload during ischemia and reperfusion. To discover new inhibitors of the Nav1.5 late current, we hypothesized that we may be able to convert through structural modification the known L-type calcium channel (L-Ca) inhibitors of the dihydropyridine (DHP) class into inhibitors of the persistent sodium current with low to no calcium channel inhibition. We achieved some success with compound 1 that was found to inhibit Nav1.5 late current by 53% (10 μM on PatchXpress using hNav1.5/ HEK293 cells) with moderate L-Ca inhibition of 37% (10 uM on fluoresent plate assay). Small structural changes in 1 afforded compound 2 that was found to actually dramatically increase the Nav1.5 late current. This observation is

consistent with this class of compounds binding to the Nav1.5 channel in a mode that may stabilize the hydrophobic inactivation gate docking, thereby preventing a leaky sodium current, or greatly destabilize the inactivation gate docking. We further modified the DHP aromatic rings to look more like ranolazine, as in compound 3, and this enhanced the inhibition of the Nav1.5 late current. The synthesis and SAR of the DHP series will be presented.



MEDI 296

Self-assembled quadruplex-DNA ligand

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The development of ligands for G-quadruplex DNA (QDNA) that bind with high selectivity and affinity remains a challenge that must be overcome if QDNA is to become a viable target for pharmacological intervention. Recently, we reported on a hydrophilic 8-aryl-2'-deoxyguanosine derivative, mAGcat, that self-assembles in aqueous environments to form a discrete supramolecule of nanoscopic dimensions. Such supramolecule shows excellent size, shape and charge complementarity to the surface at the interface between a dimeric QDNA ([(TTAGGG)4]2) resulting in a sandwich-like complex. We will present NMR spectroscopic evidence indicating the key features of the structure of the complex and its thermal stability. This strategy is attractive due to the ease of synthesis of the monomers and their self-assembly into a large but discrete structure, which leads to the selective binding to QDNA. We expect that this and related ligands will enable the development of novel drugs and biological probes.

MEDI 297

DNA-encoded libraries: A new resource for innovative hit identification

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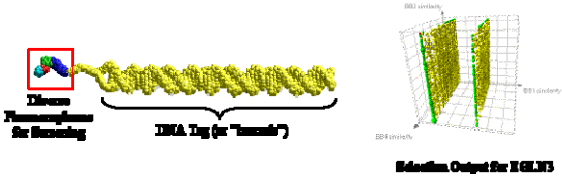
Encoded Library Technology (ELT) enables 1) efficient preparation of libraries containing millions to billions of DNA-tagged pharmacophores, and 2) a simple screening and deconvolution method that quickly identifies pharmacophores that have binding affinity to molecular targets of interest. A growing DNA-encoded “compound collection,” now in excess of 12 billion members, enables the technology. This presentation will describe what a DNA-encoded library is, how a library is prepared, and how libraries are screened by “selection” on the basis of target affinity. The presentation will also illustrate how SAR information embedded in the “selection” output enabled chemists to rapidly identify novel binding pharmacophores and subsequently submicromolar DNA-free inhibitors for prolylhydroxylases EGLN1 and EGLN3. With knowledge of active-site residues, chemists quickly improved physical properties and inhibitor potency by more than 10-fold. X-ray co-crystallography confirmed the specific nature of the interaction and the predicted binding mode of the inhibitors to EGLN1.



MEDI 298

Prostate-specific membrane antigen-targeted imaging, diagnosis, and therapy of prostate cancer

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Prostate cancer (PCa) is a major cause of mortality and morbidity in the US. Current methods for detecting PCa are limited, leaving early malignancies undiagnosed and sites of metastasis disease undetected. Major deficiencies also exist in treatment of PCa, especially metastatic disease. In an effort to improve both diagnosis and therapy of PCa, we have developed a PSMA-targeted ligand that delivers attached imaging and therapeutic agents selectively to PCa cells. The PSMA-targeted radioimaging agent is shown to localize almost exclusively in human PCa tumor xenografts, and a PSMA-targeted chemotherapeutic agent is demonstrated to promote complete elimination of the same xenografts with no toxicity to normal tissues. The PSMA-targeted fluorophore is shown to selectively label CTCs in blood samples from PCa patients. Tandem use of the imaging and

therapeutic agent targeted to the same receptor should allow detection, staging, monitoring, and selecting/ treatment of PCa patients with improved accuracy and efficacy.

MEDI 299

Retinoids, a new strategy for proteasome inhibition

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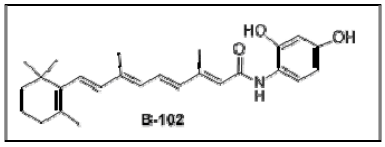
The proteasome is the major cytoplasmic and nuclear proteolytic system in eukaryotes. Its activity is required for numerous cellular processes and many human diseases have been associated with dysfunctional proteasome. Malignant cells are especially sensitive to proteasome inhibition. Though many proteasome inhibitors have been developed in the past and Bortezomib/Valcade was the first FDA approved drug in 2003 as a chemotherapeuticum still there is dire need to develop novel proteasome inhibitors with different specificity or less side effects. Here we describe the design, synthesis and biochemical analysis of a retinoid derivative as a novel proteasome inhibitor. Based on previous reports that retinoids effect proteasome activity, we constructed a small library of retinoid compounds and tested their ability to inhibit proteasomal activity in an in vitro assay. We found that compound B-102 efficiently inhibited the chymotryptic activity of the proteasome and will be the lead compound for future inhibitor development.



MEDI 300

Identification of a novel retinamide derivative that regulates cardiovascular development, using forward chemical genetic screen in zebrafish embryos

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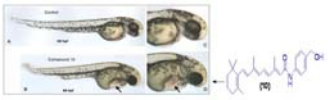
It is well documented that biological pathways governing embryonic development continue to be used for controlling adult physiology, and are disease targets. Therefore, small molecule modulators of gene networks active in early development can lead to a better understanding of signal pathways and the design of novel therapeutic and diagnostic agents for adult diseases. For this purpose, we describe a chemical genetic approach by interfacing libraries of small molecules with developing embryos. We focus on retinoid signaling pathways, as these play key roles in patterning the body axis and in the formation of many organ systems. We synthesized a small library of novel retinoic acid analogues and tested their activity by evaluating phenotypic changes caused in developing zebrafish embryos. We showed that related compounds significantly affect development. Distinct phenotypes are generated depending on time of exposure, and we demonstrated that compound 10 produces specific cardiovascular defects when added after 1 day. Experiments are in progress to isolate the targets responsible for causing these phenotypic changes.



MEDI 301

Design, synthesis and evaluation of bivalent conformationally constrained Smac mimetics as inhibitors of IAP family proteins

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A series of non-peptidic, cell-permeable, bivalent small-molecule second mitochondria-derived activator of caspase mimetics (bi-valent Smac mimetics) have been designed, synthesized and evaluated. These Smac mimetics bind to XIAP, cIAP-1 and cIAP-2 with low nano-molar affinities and inhibit cell growth with IC50 values between low nanomolar and sub-micromolar. The most potent

bivalent Smac mimetics are capable of inducing of robust apoptosis in a subset of cancer cell lines at concentrations as low as 1 nM and effectively inhibit tumor growth in the MDA-MB-231 xenograft model.

MEDI 302

Predicting kinetic parameters for substrates of human cytochrome P450

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Michaelis-Menten constant and maximum metabolic rate are two important kinetic parameters for human physiological pharmacokinetic/pharmacodynamic (PK/PD) models. We developed human CYP450 kinetic parameter models for the hydroxylation reaction catalyzed by five CYP P450 enzymes: 1A2, 2C9, 2C19, 2D6, and 3A4. Models were developed using Artificial Neural Network Ensemble methodology and molecular descriptors as implemented in the software ADMET PredictorTM. The dataset contained 40~70 substrates for each enzyme, with kinetic parameters measured from in-vitro metabolic studies on cloned virus-infected cells expressing human enzyme-specific microsomes. For the five logKm models, squared correlation coefficient, R2, was in the range of 0.6~0.9 and root-mean-squared error (RMSE) was in the range of 0.3~0.5 log units; Q2 and RMSE for the external test sets were in the range of 0.4~0.9 and 0.4~0.5 log units, respectively. For the five logVmax models, R2 was in the range of 0.6~0.7 and RMSE was in the range of 0.4~0.7 log units; Q2 and RMSE of the external test sets were in the range of 0.3~0.8 and 0.3~0.6 log units, respectively. Predicted parameter values from these models are expected to be used in early human PK models for purposes of risk assessment and to support decision-making in drug discovery.

MEDI 303

Probing the mechanism of pseudopterosins

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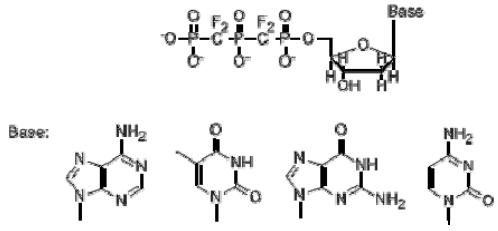
To explore the role of the O-glycoside linkage in the expression of PsA biological activity, the Suzuki-Miyaura cross-coupling protocol was applied to the synthesis of the C-glycoside analogue of PsA methyl ether. Its activity profile resembled that of PsA and PsA O-methyl ether when assayed for its anti-inflammatory activity and its ability to inhibit phagocytosis. We conclude that the intact structure is present when a pseudopterosin expresses its anti-inflammatory and phagocytosis inhibitory properties and that they are not likely to be prodrugs. To test our hypothesis that the pseudopterosins undergo oxidation to form a cation radical intermediate, and that the cyclization and ring opening constitute the conformational change that triggers the alteration in the conformation of the receptor that ultimately leads to the downstream expression of bioactivity, the cyclic voltammogram of the model catechol glycoside under neutral conditions was obtained. The keto ketal of pseudopterosins that ought to be convertible to its pseudopterosin was synthesized.

MEDI 304

Synthesis of bis(difluoromethylene)triphosphonic acid and nonhydrolyzable nucleotide analogs

Mikhail Zibinsky[1]*, zibinsky@gmail.com, Rehana Ismail*[1]*, G. K. Surya Prakash*[1]*, gprakash@usc.edu, Thomas G. Upton*[2]*, tupton@usc.edu, Boris A. Kashemirov*[2]*, and Charles E. McKenna*[2]*. (1) Loker Hydrocarbon Research Institute and Department of Chemistry, University of Southern California, 837 Bloom Walk LHI 101, Los Angeles, CA 90089-1661, (2) Department of Chemistry, University of Southern California, Los Angeles, CA 90089*

A simple procedure for the preparation of the previously unknown (difluoromethylene)triphosphonic acid was developed. Bis(difluoromethylene)triphosphonic acid was used in the synthesis of non-hydrolyzable nucleotide analogs for the first time. Several new deoxynucleotide analogs were prepared. All these novel compounds mimic natural substrates for many different enzymes leading to the greater understanding of such enzyme structure, dynamics and functions.



MEDI 305

Investigation of early steps in the pradimicin A biosynthetic pathway

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The early biosynthetic steps of pradimicin A were investigated through combinatorial biosynthesis approach. A key pentangular intermediate JX116 was biosynthesized in a heterologous Streptomyces host, catalyzed by minimal PKS (PdmABC), three cyclases (PdmDKL), a monooxygenase (PdmH) and a ketoreductase (PdmG). The formation of the five-ring aglycon of pradimicin A requires the synergistic actions of PdmH, PdmK and PdmL. C-6 reduction by PdmG is not necessary for the formation of the pentagular structure, removal of which yielded a new five-ring polyphenol JX111a. Biosynthesis of JX134 revealed the function of PdmJ as the C-5 hydroxylase, responsible for the stereo-selective introduction of the 5S-OH. Another important tailoring enzyme, PdmN, was characterized as the first amide synthase found in type II polyketide biosynthetic pathway. With relatively relaxed substrate specificity, this enzyme can introduce D-alanine and D-serine to JX116, producing two new pradimicin derivatives JX137a and JX137s, respectively.

MEDI 306

Design of hybrids with vitamin D receptor agonism and histone deacetylase inhibition as anticancer agents

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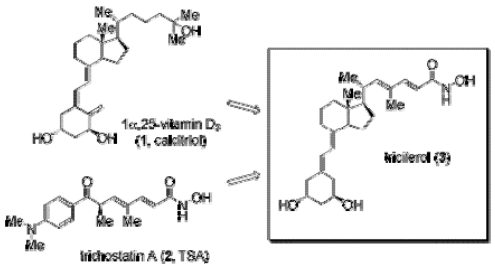
1,25-Dihydroxyvitamin D3 and its analogs have been investigated as potential therapies for cancer treatment. However, due to problems of low potency and side effects such as hypercalcemia, advancement in clinical trials has been limited. We have found that incorporating histone deacetylase inhibitory activity into vitamin D-like structures greatly increases their effectiveness against several cancer cell lines. These hybrid molecules have been shown to bind two biological targets of vastly different structure and function, the vitamin D receptor, a nuclear receptor, and histone deacetylase, a zinc metalloenzyme. This talk will discuss the design, synthesis and evaluation of a series of hybrid ligands. The effect of

hybrid structure on HDAC isozyme selectivity and resulting effects on cell survival and cell morphology will be highlighted.



MEDI 307

Synthesis and biological evaluation of novel vitamin D3 derivatives

Wei Li[1]*, wli@utmem.edu, Michal A. Zmijewski*[2]*, Jianjun Chen*[3]*, Zorica Janjetovic*[2]*, Jordan K. Zjawiony*[4]*, Trevor Sweatman*[5]*, Duane D. Miller*[1]*, dmiller@utmem.edu, and Andrzej T. Slominski*[2]*. (1) College of Pharmacy, University of Tennessee Health Science Center, Memphis, TN 38163, Fax: 901-448-6828, (2) Department of Pathology and Laboratory Medicine, University of Tennessee Health Science Center, Memphis, TN 38163, (3) Department of Pharmaceutical Sciences, University of Tennessee Health Science Center, Memphis, TN 38163, (4) Department of Pharmacognosy and National Center for Natural Products Research, School of Pharmacy, University of Mississippi, University, MS 38677, (5) Department of Pharmacology, University of Tennessee, Memphis, TN 38163*

Calcitriol is a powerful oncostatic form of vitamin D3 that is of limited clinical utility due to hypercalcemic (toxic) effects. The removal of the side chain has been shown to reduce the calcemic activity of vitamin D3, therefore, secosteroidal compounds lacking or with a shortened side chain are potential candidates for anti-cancer drugs. In this report a series of androsta and pregna-5,7-dienes was synthesized from their respective 3-acetylated 5-en precursors. These compounds were subjected to UVB irradiation to generate vitamin D-like structures. Additional products with tachysterol-like (T-like) or lumisterol-like (L-like) structures were also produced. The distribution of these products was UVB dose dependent. At low doses, previtamin D-, T- or L-like compounds were formed as the main products, while higher doses induced further isomerization, with formation of potentially oxidized derivatives. Biological evaluation of these newly synthesized compounds using cultured normal and malignant skin cells revealed anti-proliferative activity and identified some of them as candidate(s) for further testing as potential therapeutic drugs for treatment of hyperproliferative diseases including cancer.

MEDI 308

Synthesis, antibacterial activity, and new applications of aminoglycosides

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Antibiotic resistance represents stringent problems for the global health. Development of new antibiotic is urgent. Utilizing synthetic methodologies (glycodiversification), we have synthesized libraries of neomycin and kanamycin classes of aminoglycosides. Novel aminoglycosides with prominent antibacterial activity against a panel of resistant bacteria including Pseudomonas aeruginosa, mecilline-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant enterococci (VRE) have been identified. In addition, we have also discovered new applications of aminoglycosides. These include antifungal, antiviral and potential therapeutic for neural disease.

MEDI 309

Inhibition of aquaporin-4 by estrogen receptor modulators

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Aquaporin-4 (AQP4) is a water specific member of the aquaporin family of neutral solute transporters, and is the primary water transporter in the human brain. Inhibitors of its water transport properties have been proposed as therapeutics for conditions giving rise to cytotoxic edema, such as cerebral ischemia. Recently, our laboratory has identified a number compounds that inhibit AQP4 in vitro, several of which were known to lessen neurological damage following an ischemic insult. Tamoxifen, an estrogen receptor (ER) modulator, was identified from virtual screening and was found to reversibly inhibit AQP4 water transport. The efficacy of this compound in reducing post-ischemic neurological damage led us to consider the potential effect of other ER modulators on AQP4 function. Our presentation will focus on studies into the AQP4 inhibitory effect of tamoxifen and other ER modulators. Support by the Ministry for Education, Culture, Sports, Science and Technology (Japan).

MEDI 310

Addressing metabolism and toxicity in early drug discovery with rapid estimates of quantum mechanical descriptors

Robert Fraczkiewicz[1], *Marvin Waldman*[1], *marv@simulations-plus.com, John C. Crison*[2], *and Walter S. Woltosz*[1], *walt@simulations-plus.com. (1) Simulations Plus, Inc, 42505 10th Street West, Lancaster, CA 93534, Fax: (661) 723-5524, (2) Life Sciences Department, Simulations Plus, Inc, Lancaster, CA 93534*

It has been shown that quantum mechanical descriptors of molecules are particularly suitable for modeling their metabolism and toxicity in biological systems. We have overcome inherently long CPU times of quantum methods by creating ultra-fast (i.e., >200,000 molecules/hour) empirical estimates of certain quantum mechanical descriptors (sigma and pi partial atomic charges, pi system HOMO/LUMO energies, chemical hardness and electronegativity, and Fukui reactivity indices) at the atomic and molecular level by fitting high quality ab initio electron densities calculated for a dataset of almost 700 organic molecules. This dataset, containing neutral as well as formally-charged molecules, was composed with maximum diversity of individual atomic environments in mind. All molecular geometries were optimized at the B3LYP/6-311G** level, followed by extraction of approximately 13,000 sigma and pi partial atomic charges with the aid of the NPA and Natural Bond Orbital (NBO) schemes. One part of the data set (11,000) was used to train a new empirical model for very fast estimation of the atomic charges; the remainder (2,000) was sequestered as an external validation set. Two separate empirical models, both using only 2D molecular structures as input, were created: one for sigma, the other for pi subsystems. Sigma and pi electron densities on atoms were estimated with excellent results: for both models the root-mean-square-error (RMSE) on the external test set was close to 0.05 electron units.

The importance and usefulness of thus-derived estimated quantum mechanical descriptors were subsequently demonstrated on a wide array of predictive models related to metabolism and toxicity built by our group.

MEDI 311

The multistrategy for design of dopamine D1 and serotonin 5-HT1A receptor ligands

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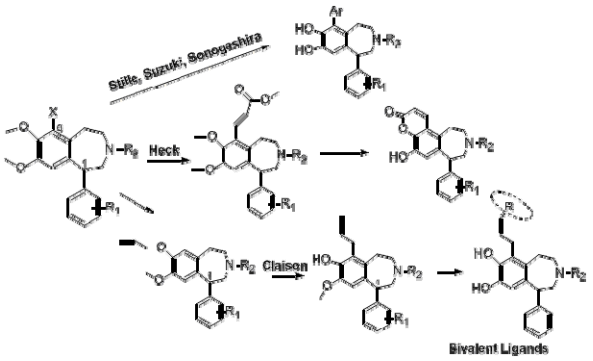
Dopamine D1 receptor agonists are potential anti-parkinsonian agents, but serious dyskinesia side effects are generally accompanied. Recently, several serotonin 5-HT1A receptor agonists are reported capable of attenuating L-DOPA-induced dyskinesia. In this regard, a dopamine D1 agonist mixed with 5-HT1A receptor agonism would be an optimal pharmacological profile for promising anti-PD treatment. By docking a D1 receptor agonist SKF-83959 into the predicted 5-HT1A receptor binding model, a potential lipophilic pocket for 5-HT1A receptor binding on the D1 agonist structure is identified. Several drug design and discovery strategies were used to develop dopamine D1 and serotonin 5-HT1A receptor bisfunctional ligands by introducing different functional groups to the D1 receptor agonist core structure. Binding assays of these new compounds indicated that a C6-aryl substituent generally potentiates the binding on the D1 receptor, while an appropriate functional group on the N-side chain leads the compound active at 5-HT1A receptor. Compound SOMCL-621 possessing high potency at D1, and full inhibition of binding at 5-HT1A was selected for further evaluation for its anti-PD potentials.



MEDI 312

Crystal structure of the naturally occurring Baeyer-Villiger monooxygenase MtmOIV

Miranda Beam*, miranda.beam@berea.edu, Department of Chemistry, Berea College, CPO 2191, Berea College, Berea, KY 40404, Fax: 859-985-3303, Nicholas Noinaj, University of Kentucky, and Jürgen Rohr, College of Pharmacy, University of Kentucky, Lexington, KY 40536*

Combinatorial biosynthesis of natural products has yielded new and exciting drugs. Mithramycin oxygenase OIV (MtmOIV) from the biosynthetic pathway of the aureolic acid anticancer drug mithramycin (MTM) is a key enzyme with novel functionality, and may be significant for future MTM analogue design through combinatorial biosynthesis. Here we present the three-dimensional structure of MtmOIV, a characterized BVMO, determined by X-ray crystallography using molecular replacement to resolution of 2.9Å. MtmOIV is a 56 kD homo-dimeric FAD and NADPH dependent monooxygenase responsible for the key step of

mithramycin biosynthesis. The structure and function of this important enzyme could pave the way for the generation of a new generation of aureolic acid type anticancer drugs.

MEDI 313

Structural and thermodynamic characterization and comparison of RNA single mismatches

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The tertiary structural arrangement of RNA is often dictated by its secondary structure, especially by non-canonical regions. The focus of this project is to investigate the thermodynamic contribution and tertiary structures of RNA single mismatches by comparing optical melting data to structural data found in RNA structures deposited in the Protein Data Bank (PDB). The PDB has been searched for RNA single mismatches, which were then classified and described based on several structural features. The features of identical and similar single mismatches were compared and analyzed for structural patterns. The resulting patterns are then compared to available thermodynamic data to help understand the relationship between stability and structure. Such a database and comparison may allow researchers to predict structural features of unstudied sequences and quickly look-up studied sequences, which would be especially beneficial for those designing therapeutics to target RNA or those that use RNA as the targeting agent.

MEDI 314

Folate and antifolate synergism with nucleoside analogs

***Anthony R Vortherms**, arvorthe@syr.edu, Chemistry, Syracuse University, Syracuse, NY 13244, and Robert Patrick Doyle, rpdoyle@syr.edu, Department of Chemistry, Syracuse University, Syracuse, NY 13244-4100*

Conjugates of folate and methotrexate (MTX) and the nucleoside analogs 3-azidodeoxythymidine (AZT), iododeoxyuridine (IUdR) and dideoxycytidine (ddC) linked using poly(ethyleneglycol) are presented. In vitro cytotoxicity assays of the conjugates against drug resistant ovarian cell line A2780/AD are preformed and comparisons made to such assays performed unconjugated (cocktail) systems. The toxicity of the conjugates is shown to be enhanced with the MTX and nucleoside analogs working with a complementary mode of action. Combining the two most cytotoxic conjugates (those based on MTX with IUdR and AZT)

results in a system with low micromolar activity over 24 hours, a significant result compared to cocktails of the same components at the same time point. In vivo dose-related studies in mice reveal tumor suppression or complete tumor regression.

MEDI 315

Optimization of anthranilimide based glycogen phosphorylase inhibitors

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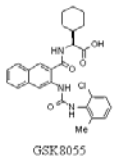
Hepatic glucose output is elevated in Type 2 diabetic patients, and evidence suggests that drugs which lower hepatic glucose output are effective antihyperglycemic agents. Glycogenolysis, which is the release of monomeric glucose from its polymeric storage form called glycogen, is a key contributor to hepatic glucose output. Glycogen Phosphorylase is the enzyme that catalyzes this process. The optimization of lead glycogen phosphorylase inhibitor anthranilimide GSK8055 will be presented.



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