American Chemical Society

Division of Medicinal Chemistry
ABSTRACTS

228th ACS National Meeting

Philadelphia, PA
August 22-26, 2004 **D. L. Flynn, Program Chair**

SUNDAY MORNING

- **Amino Acid Neurotransporters**

W. J. Porter, Organizer Papers 1-5

- **General Oral Session I**

B. S. J. Blagg, Presiding Papers 6-16

SUNDAY AFTERNOON

- **Transporters in Drug Discovery**

M. R. Myers, Organizer Papers 17-21

- **Nicotinic ACH Receptors**

S. Ananthan, Organizer Papers 22-27

SUNDAY EVENING

- **Poster Session I**

D. L. Flynn, Presiding Papers 28-152

MONDAY MORNING

- **Alfred Burger Award Symposium - Recent Advances Towards Novel Cardiovascular Therapeutics**

R. R. Wexler, Organizer, Presiding; K. A. Jacobson, Presiding Papers 153-157

MONDAY AFTERNOON

- **Diversity and Chemogenomics**

P. Wipf, Organizer Papers 158-162

- **Conventional and Non-Conventional Nucleosides**

V. E. Marquez, Organizer Papers 163-167

MONDAY EVENING

- **Sci-Mix Session**

D. L. Flynn, Presiding Papers 11, 33, 35, 62, 68, 74-75, 87-88, 96, 102-103, 108, 129-131, 150, 173, 216, 220, 225, 232, 236, 241, 244, 249, 253, 258, 266, 274-275, 281, 299, 301-302, 304-305, 312, 327, 329, 333

TUESDAY MORNING

- **Graduate Student Award Symposium**

K. A. Jacobson, Presiding Papers 168-172

- **General Oral Session II**

D. Rotella, Presiding Papers 173-182

TUESDAY AFTERNOON

- **David Robertson Memorial Symposium**

B. K. Trivedi, Organizer Papers 183-187

WEDNESDAY MORNING

- **Inflammation Part I, Emerging Small Molecule Inhibitors for Treatment of Autoimmune and Inflammatory Diseases**

J. Kozlowski, Organizer Papers 188-192

- **Anti-Obesity Therapy**

M. J. Bishop, Presiding — Papers 193-197

WEDNESDAY AFTERNOON

- **Inflammation Part II, Emerging Small Molecule Inhibitors for Treatment of Autoimmune and Inflammatory Diseases**

L. McQuire, Organizer; R. J. Cherney, Presiding — Papers 198-203

- **Dipeptidyl Peptidase IV Inhibitors**

A. E. Weber, Presiding — Papers 204-208

WEDNESDAY EVENING

- **Poster Session II**

D. L. Flynn, Presiding — Papers 209-308, 309-323

THURSDAY MORNING

- **General Oral Session III**

D. L. Flynn, Presiding — Papers 324-333

- **Gamma-Secretase Inhibitors, Sponsored by Eli Lilly & Company**

D. G. Brown, Organizer; M. S. Wolfe, Presiding — Papers 334-338

DIVISION OF MEDICINAL CHEMISTRY

1.

AMINO ACID TRANSPORTERS AS TARGETS FOR THERAPEUTIC INTERVENTION. ***Beth J. Hoffman**, Neurscience Discovery Research, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285, Fax: 317-433-7741, hoffman_beth@lilly.com*

Amino acid transporters are critical for the tight regulation and recycling of amino acids as evidenced by redundant systems of low and high affinity, multiple gene families and gene products, for glutamate, GABA, glycine, proline, D-serine, aspartate and taurine. Recent studies have provided insight into the biology of amino acid transporters, suggesting that they may be attractive targets for therapeutic intervention. Following a review of gene families and associated proteins, this presentation will focus on high affinity transporters. Aspects of transporter biology and regulation will be exemplified using data from cellular localization, structure-function studies, mechanisms of regulation, transport kinetics and genetic manipulation in vivo. An overview of our current understanding of the role of amino acid transporters in regulating neurotransmission will be used to highlight those aspects of biology that remain to be elucidated. Identification of potent, selective pharmacological tools should aid in focusing on the most promising therapeutic targets.

2.

COMBINING FLUORESCENCE AND ELECTROPHYSIOLOGY TO PROBE GLUTAMATE TRANSPORTER STRUCTURE AND FUNCTION. ***G. Leary**, J.B. Ross, and M.P. Kavanaugh, NIH COBRE Center for Structural and Functional Neuroscience, University of Montana, Missoula, MT 59803, Fax: 406-342-5228, michael.kavanaugh@umontana.edu*

Although there is little direct evidence, most models of neurotransmitter transporter function postulate a cyclical gating scheme with mutually exclusive states for internal and external substrate binding. A conformational transition between these states needs to occur every time a transmitter molecule is transported across the membrane. Charge movements across the membrane may occur during this conformational switch and/or during binding and unbinding of transmitter and cotransported ions. In order to test the idea of a conformational transition linked to a charge moving transport cycle, we constructed neuronal glutamate transporter mutants that could be covalently labeled at the mouth of the transporter pore with a fluorescent probe to allow simultaneous monitoring of fluorescence and currents under voltage clamp. GFP-fusion constructs were also analyzed. The data show that fluorescence photometry and lifetime analysis represents a novel and useful approach to monitor glutamate transporter structure and function. Support Contributed By: NCRR P20RR15583and NS33270

3.

PHARMACOPHORE DEVELOPMENT FOR THE GLUTAMATE VESICULAR TRANSPORTER (VGLUT1). ***Charles M. Thompson**[1], Richard J. Bridges[1], and John M. Gerdes[2]. (1) Center for Structural and Functional Neuroscience, University of Montana, Dept of Biomedical and Pharmaceutical Sciences, Missoula, MT 59812, Fax: 406-243-4643, charles.thompson@umontana.edu, (2) Center for Structural and Functional Neuroscience, Department of Chemistry, University of Montana*

L-Glutamate is transported into presynaptic vesicles in an ATP-dependent manner by the glutamate vesicular transporter (VGLUT). VGLUT is a specific transporter for glutamate but it is low affinity (Km = 1 to 3 mM), which is in contrast to the excitatory amino acid transporters (EAATs; Km = 5-50 ìM). VGLUT is an integral membrane protein but, until recently, very little was known about its structure, binding and pharmacology. This presentation will briefly review the features of VGLUT-mediated uptake of glutamate, advances in the pharmacology, known and optimized substrate and inhibitor structures, our

4.

DISCOVERY AND SAR OF SELECTIVE INHIBITORS OF THE HGLYT-1B TRANSPORTER. ***Samuel Gibson**[1], Robert Gilfillan[1], David Jaap[1], David Miller[1], Glenn Walker[2], and Grant Wishart[1]. (1) Department of Medicinal Chemistry, Organon Research, Newhouse, United Kingdom, s.gibson@organon.co.uk, (2) Department of Pharmacology, Organon Research*

Alteration of glycine levels in the mammalian central nervous system may influence inhibitory activity mediated by the strychnine-sensitive glycine receptor (SSGR)or excitatory neurotransmission through the glycine site on the NMDA complex. SSGR's are located in the spinal cord and brainstem and are closely associated with the neuronal GlyT-2 transporter whereas GlyT-1 is distributed more widely in the CNS and may play a role in controlling concentrations of the co-agonist glycine in the vicinity of NMDA receptors. This affords an opportunity for inhibition of the transporter to enhance NMDA receptor function through elevated concentrations of the co-agonist glycine. This mechanism may have relevance in addressing hypoglutaminergic function associated with psychosis. We describe here three series of selective GlyT-1b inhibitors. In vitro SAR is discussed for all three series,together with some conclusions concerning the interactions of these ligands with the transporter.

5.

SYNTHESIS AND STRUCTURE ACTIVITY RELATIONSHIP OF NOVEL CHIRAL LIGANDS FOR THE GLYCINE-REUPTAKE TRANSPORTER TYPE-2 (GLYT-2). ***Methvin Isaac**, Medicinal Chemistry, NPS Pharmaceuticals Inc, 6850 Goreway Drive, Mississauga, ON L4V 1V7, Canada, Fax: 905-677-9595, misaac@npsp.com*

The amino acid glycine is a major neurotransmitter in the mammalian central nervous system (CNS) functioning at both inhibitory and excitatory synapses. Two distinct glycine transporters, GlyT-1 and GlyT-2, have been recently cloned and share 50% identity at both the nucleotide and amino acid levels. GlyT-1 (four isoforms: Gly-T1a, Gly-T1b, Gly-T1c, Gly-T1d) is expressed in the hippocampal and cortical regions of the brain as well as in the spinal cord and brainstem. In contrast, GlyT-2 is expressed primarily in the spinal cord and cerebellum and is absent in the hippocampus and cortex. Compounds, which selectively inhibit the glycine transporter, GlyT-2 would thus be expected to alter receptor, function and therefore provide therapeutic benefit in a variety of disease states such as neuropathic pain and spasticity. This presentation describes the synthesis and biological activity of novel classes of selective GlyT-2 reuptake inhibitors highlighting the significance of double bond geometry and chirality on GlyT-2 activity.

6.

4-PIPERIDINYL-SUBSTITUTED β-ARYL BUTYRIC ACIDS: A NEW CCASS OF POTENT αVβ3/αVβ5 INTEGRIN ANTAGONISTS. ***Bart L. De Corte**, William A. Kinney, Li Liu, Shyamali Ghosh, Livia Brunner, William J. Hoekstra, Rosemary Santulli, Jef C. Proost, Bruce P. Damiano, Bruce E. Maryanoff, Dana L. Johnson, and Robert A. Galemmo, Drug Discovery, Johnson & Johnson Pharmaceutical Research & Development, Welsh & McKean Roads, P.O.Box 776, Spring House, PA 19477, Fax: 215-628-4985, bdecorte@prdus.jnj.com*

Integrins are a family of heterodimeric cell-surface glycoproteins that are involved in cell-cell interactions and communication between cells and the extracellular matrix. The integrins αIIbβ3, αvβ3, αvβ5, αvβ6, and α5β1 recognize adhesive proteins that contain the Arg-Gly-Asp (RGD) tripeptide sequence, which is critical for binding to the integrin extracellular domain. Hence, selective and bioavailable non-peptide mimics of the RGD recognition motif have been pursued in attempts to modulate integrin-mediated biological processes and treat a variety of diseases, such as cancer, osteoporosis, restenosis, and diabetic retinopathy.

indicating that NPC1L1 resides in an ezetimibe-sensitive pathway responsible for intestinal cholesterol absorption. Further characterization of this pathway may lead to discovery of new chemotypes active in blocking cholesterol absorption.

156.
DISCOVERY OF THE NOVEL ANTITHROMBOTIC AGENT BAY 59-7939, AN ORALLY ACTIVE, DIRECT FACTOR XA INHIBITOR. ***Susanne Roehrig***[1], *Alexander Straub*[1], *Jens Pohlmann*[1], *Thomas Lampe*[1], *Josef Pernerstorfer*[1], *Karl Heinz Schlemmer*[2], *and Elisabeth Perzborn*[3]. *(1) Chemical Research, Bayer HealthCare AG, Aprather Weg 18a, 42096 Wuppertal, Germany, susanne.roehrig@bayerhealthcare.com, (2) Preclinical Pharmacokinetics, Bayer HealthCare AG, (3) Cardiovascular Research, Bayer HealthCare AG*

Despite recent progress in antithrombotic therapy, there is still an unmet medical need for safe and orally available anticoagulants. The coagulation enzyme Factor Xa (FXa) is a particularly promising target, and recent efforts in this field have focused on the identification of small-molecule inhibitors with good oral bioavailability. We identified oxazolidinone derivatives as a new class of potent FXa inhibitors. Lead optimization led to the discovery of BAY 59-7939, a highly potent and selective direct FXa inhibitor with excellent in vivo antithrombotic activity and high oral bioavailability. The X-ray crystal structure of BAY 59-7939 in complex with human FXa clarified the binding mode and the stringent requirements for high affinity. BAY 59-7939 was selected for clinical development for the prevention and treatment of thromboembolic diseases.

157.
DESIGN AND SYNTHESIS OF THROMBIN RECEPTOR (PAR-1) ANTAGONISTS - AWARD ADDRESS. ***William J. Greenlee****, CNS and Cardiovascular Chemical Research, Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, william.greenlee@spcorp.com*

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 have less bleeding liability than 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 potent orally bioavailable PAR-1 receptor antagonists which block thrombin-induced activation of platelets and are active in a primate model of thrombosis. The design, synthesis and structure-activity relationships of this series of antagonists will be discussed.

158.
EXPANDING CHEMICAL DIVERSITY USING STEREOCONTROLLED SYNTHESIS. ***John A. Porco Jr.****, Department of Chemistry and Center for Chemical Methodology and Library Development (CMLD-BU), Boston University, 590 Commonwealth Avenue, Boston, MA 02215, Fax: 617-353-6466, porco@chem.bu.edu*

Complex molecules often provide opportunities for the preparation of new structures ("diversity exploration") with a goal to increase the structural diversity available from Nature and prepare molecules with novel chemical or biological properties. This presentation will outline examples from our research program illustrating our overall interest in expanding chemical diversity, including examples of projects being conducted at the Center for Chemical Methodology and Library Development at Boston University (CMLD-BU). Projects involving the synthesis of chemical libraries utilizing stereochemical and

159.
POTENTIATON OF APOPTOSIS: REMARKABLY POTENT SMALL MOLECULE SMAC REPLACEMENTS. ***Jef K. De Brabander***[1], *R. Mathew Thomas*[1], *Hidetaka Suzuki*[1], *Lin Li*[1], *Xiaodong Wang*[2], *and Patrick G. Harran*[1]. *(1) Department of Biochemistry, The University of Texas Southwestern Medical Center at Dallas, Dallas, TX 75390, Fax: 214-648-6455, jdebra@biochem.swmed.edu, (2) Department of Biochemistry and Howard Hughes Medical Institute, The University of Texas Southwestern Medical Center at Dallas*

In this presentation, I will describe a joint effort between the Harran, Wang, and De Brabander groups related to the design, synthesis and evaluation of small molecules that mimic the function of Smac (second mitochondrial activator of caspases) by neutralizing the anti-apoptotic effects of IAPs (Inhibitor of Apoptosis Proteins) and potentiate TRAIL and TNFα mediated cell death.

160.
IDENTIFICATION OF POTENT, SELECTIVE VLA-4 ANTAGONISTS AS CHEMICAL TOOLS TO ANSWER BIOLOGICAL QUESTIONS. ***Donna M. Huryn***[1], *Susan Ashwell*[1], *Reinhardt B. Baudy*[1], *Darren B. Dressen*[2], *Stephen B. Freedman*[2], *Francine S. Grant*[2], *Jeffrey Kennedy*[3], *Andrei W. Konradi*[2], *Anthony Kreft*[1], *Louis J. Lombardo*[1], *Michael A. Pleiss*[2], *Dimitri Sarantakis*[4], *and Ted Yednock*[5]. *(1) Chemical Sciences, Wyeth-Ayerst Research, CN 8000, Princeton, NJ 08543, hurynd@wyeth.com, (2) Chemistry, Elan Pharmaceuticals, (3) Neuroscience, Wyeth Research, (4) Chemical and Screening Sciences, Wyeth Research, (5) Cell Biology, Elan Pharmaceuticals*

Through a series of iterative optimizations, highly potent, selective and orally efficacious VLA-4 antagonists were developed. Optimization activities focused not only on potency, but also reduction of protein binding, enhancements in metabolic stability and improved oral absorption. The resultant compounds were used as tools to evaluate the effect of VLA-4 antagonism in a variety of disease models in which integrin-mediated adhesion has been implicated. A description of the process to develop small molecule VLA-4 antagonists, and the effects of these molecules in a number of animal models of inflammatory diseases will be described.

161.
USING SMALL MOLECULE LIBRARIES TO PROBE PHARMACOLOGICAL SPACE. ***John S. Lazo****, Department of Pharmacology, University of Pittsburgh School of Medicine, E1340 Biomedical Science Tower, University of Pittsburgh, Pittsburgh, PA 15261, Fax: 412-648-2229, lazo@pitt.edu*

The identification of novel small molecules with clinically useful pharmacological attributes requires the concerted efforts of chemists, biologists and clinicians. Time-honored processes of forward pharmacology have recently been supplanted by target-oriented reverse pharmacology strategies. In this lecture, I will outline the advantages and limitations of both approaches, using examples from both academia and industry. Moreover, I will address issues of pharmacological space and novel strategies to identify new therapeutic agents for human diseases including cancer and neurodegeneration. These will include methods to detect alterations is the spatial location of drug targets, disrupters of protein-protein interactions, inhibitors of enzyme activity, and modifiers of ion channel functionality. Preclinical hurdles for identified molecules will also be discussed.

162.
DIVERSITY-ORIENTED SYNTHESIS AND CHEMBANK. ***Stuart L. Schreiber****, Department of Chemistry & Chemical Biology, Howard Hughes Medical Institute, Harvard Institute of Chemistry & Cell Biology, Molecular Target Laboratory, Harvard University, 12 Oxford Street, Cambridge, MA 02138, Fax: 617-495-0751*

Pharmaceutical companies develop small molecule therapeutic drugs in part by drawing upon government-sponsored research performed in universities and other non-profit institutions. Academic labs have recently transitioned towards the integration of small molecule synthesis, small molecule screens, and informatics with the primary goal of illuminating principles that underlie biology and disease. My lecture aims to provide insight into the development of one such example of the latter, specifically discussing advances in diversity-oriented synthesis and the public database ChemBank.

For the academic chemistry community to succeed in such efforts, it will be important for us to use a well-considered set of small molecules. Achieving