Keynote Forum
November 02, 2017

Drug Discovery & Biochemistry Conference 2017

Joint Event

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DRUG DISCOVERY, DESIGNING AND DEVELOPMENT &

International Conference and Exhibition on
BIOCHEMISTRY, MOLECULAR BIOLOGY: R&D

November 02-03, 2017 Chicago, USA

Marvin W Makinen

The University of Chicago, USA

Inhibition of protein tyrosine phosphatase 1B *in vitro* and *in vivo*

A large number of studies of protein tyrosine phosphatases (PTPases) have been directed towards drug design for therapeutic intervention because of their critical roles in homeostasis and disorders of metabolism. In contrast to protein tyrosine kinases, virtually all inhibitors tested against PTPases exhibit only competitive behavior because of their consensus, active site sequence H/V-C-X5-R-S/T, a condition leading to low specificity. Having identified protein tyrosine phosphatase-1B (PTP1B) as the target enzyme of the vanadyl (VO2+) chelate bis(acetylacetonato)oxidovanadium(IV) [VO(acac)2] in cultured 3T3-L1 adipocytes [Ou et al. (2005) J. Biol. Inorg. Chem. 10, 874-886], we have investigated the basis of inhibition by the VO2+-chelate through steady-state kinetic investigations of the recombinant human enzyme (residues 1– 321). Our results differ from investigations by others because we compared the influence of the chelate in the presence of the synthetic substrate p-nitrophenylphosphate (pNPP) and the phosphotyrosine-containing undecapeptide DADEpYLIPQQG mimicking residues 988 – 998 of the epidermal growth factor receptor, a physiologically relevant substrate. We also compared the inhibitory behavior of VO(acac)2 to that of two other VO2+-chelates similarly known for their capacity to enhance cellular uptake of glucose as insulin mimetics. The results indicate that VO(acac)2 acts as a classical uncompetitive inhibitor in the presence of DADEpYLIPQQG but exhibits only apparent competitive inhibition with pNPP as substrate. Because uncompetitive inhibitors are more potent pharmacologically than competitive inhibitors, structural characterization of the site of uncompetitive binding of VO(acac)2 toPTP1B may provide a new approach to design of inhibitors of high specificity for therapeutic purposes.

Speaker Biography

Over the past 40 years at the University of Chicago, research in the Makinen lab has been directed towards the structural basis of enzyme action. Earlier research was focused on metalloenzymes and the application of magnetic resonance methods to characterize active site structure and stereochemical relationships of substrate atoms to catalytic residues in the active site in true reaction intermediates. More recent studies have been carried out to identify the target enzymes of metal-chelates that enhance the cellular uptake of glucose. Because some metal-chelates are associated with the capacity to enhance preferential uptake of glucose into xenograft tumors in small laboratory animal models, present research has been directed towards testing their potential as pharmacologic reagents to increase sensitivity of detection of malignant lesions by PET imaging.

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Luke S Fisher

Collaborative Drug Discovery, USA

Drug discovery informatics for collaborative teams: Innovations available today and planned for tomorrow

Collaborative Drug Discovery (CDD) provides trailing innovation for today's chemical and biological data needs, differentiated by ease-of-use and superior collaborative data sharing workflows. Within the CDD vault software, activity and registration, visualization, inventory, and ELN capabilities all address today's markets. Secure, web-based collaborative technologies are especially applicable to the informatics needs of (and broadly used by) public-private-partnerships (PPPs). Web-based platforms are a natural fit for collaboration due to the economic, architectural, and design benefits of a single platform that transcends any one organization's solo requirements. In contrast to the CDD vault for today's collaborations, CDD's Research Informatics Group invents bleeding edge technologies for tomorrow's needs. For example, open source descriptors and model sharing capabilities allow for platform-independent collaborations, even for sensitive data and IP, with groups reticent to share. CDD and Pfizer have demonstrated that these open source descriptors and models were statistically like commercial models. The main idea is to democratize model building to engage experimentalists to want to use models. As a second example, the recently developed BioAssay Express (BAE) technology streamlines the conversion of human-readable assay descriptions to computer-readable information Tanimoto (Jaccard) chemical and biological sequence similarity searches. BAE uses. Here the main idea is to allow researchers to easily search and combine similar bioassay protocols, even though those similarity searches are much more difficult than semantic standards to markup bioprotocols, which unleashes the full power of informatics technology on data that could previously only be organized by crude text searching (https://peerj.com/articles/cs-61/). These two newer web-technologies may be used not only with the CDD Vault, but also with other commercial, academic, or government built software tools. All open source components are in GitHub.

Speaker Biography

Luke's background brings twenty years of experience in scientific informatics solutions. Managing Pre-Sales, Post-Sales and working in Account Management has expanded his domain knowledge of scientific informatics and provided him the ability to maintain a successful track record. Luke serves leading pharmaceutical, biotech, agricultural, chemicals, academic and government labs. Luke has experience in scientific software solutions from the smaller scale deployment of point solutions like molecular modeling packages to the larger enterprise scale of ELNs, scientific workflow technologies, data content, analysis and visualization. His background also includes managing the support complexity of software integration strategies based on numerous mergers and acquisitions.

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Michael Crider

Southern Illinois University Edwardsville, USA

Development of Somatostatin Subtype 4 (SST4) agonists for potential use in Alzheimer's disease

Somatostatin (SST) occurs in two biologically active forms SST-14 and a N-terminally-extended form SST-28. SST exerts its effects by binding to a family of G protein-coupled receptors designated sst1-sst5. Structure-activity studies have shown that the tetrapeptide fragment, Phe7-Trp8-Lys9-Thr10, comprises the critical β-turn of SST. Although Phe7 and Thr10 can be modified, Trp8 and Lys9 are essential for biological activity. Since nonpeptide SST ligands offer therapeutic advantages over peptides, a screening program was initiated to identify a nonpeptide SST ligand with affinity for sst1-sst5. The search focused on the following: An aromatic moiety to mimic Phe7; a heteroaromatic nucleus to mimic Trp8, and a primary amine or other basic group to mimic Lys9. Using these search criteria, NNC 26-9100 was identified as the first sst4 agonist having high affinity (Ki=6 nM) and 100-fold sst4/sst2 selectivity at cloned human sst4 receptors. In a forskolin-induced cAMP assay, NNC 26-9100 potently inhibited cAMP accumulation and was shown to be a full agonist. NNC 26-9100 increased the expression of the enzyme neprilysin in the SAMP8 mouse model of Alzheimer's disease. Neprilysin is the major Aβ-42 peptide degrading enzyme in the brain. Our studies demonstrate that NNC 26-9100 reduces Aβ-42 peptide levels in mouse cortex and that this reduction is associated with increased expression of neprilysin. Acute and chronic administration of NNC 26-9100 also increased learning and memory in SAMP8 mice using the T-maze test. These results suggest that NNC 26-9100 is a disease-modifying agent with potential use in the treatment of Alzheimer's disease. Current studies in our laboratory are focused on the discovery on novel heterocyclic scaffolds with high affinity and selectivity at sst4 receptors.

Speaker Biography

Michael Crider is Professor and Chair of the Department of Pharmaceutical Sciences at the School of Pharmacy at Southern Illinois University Edwardsville. Prior to assuming his present position, he held faculty positions at the University of Toledo and the University of Louisiana at Monroe. He has directed the research of 19 MS and PhD students. The focus of his research is in the design and synthesis of anticonvulsants, dopaminergics, and nonpeptide somatostatin agonists.

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Gail Adinamis

GlobalCare Clinical Trials, USA

Innovative patient-centric service model helps speed patient recruitment and increase retention in virtual and traditional study designs

Patient recruitment and retention are key factors, and generally the most challenging, in meeting the objectives and success of clinical trials. Clinical trial costs, complexity and development timelines have continued to increase over the past several years as well as the burden to participating patients and caregivers. We are approaching a critical juncture where traditional trial designs can no longer be justified or sustained. More patient-centric trial models and novel trial designs incorporating mobile technologies are available to make studies more patient-friendly as well as more cost efficient. A patient-centric service model has evolved over the past two decades allowing study visits to be conducted at the patient's home where it is more convenient and comfortable than at the investigator site. By conducting selected protocol visits at home, the workplace or other alternate location, ambulant healthcare providers offer a way for patients to participate in trials regardless of typical barriers of study duration, visit frequency, disease state, distance to site, site office hours, or family, school or work obligations. By making trials more convenient for patients, this service model has demonstrated that more patients are willing and able to participate and remain in studies. Virtual study (central-site) designs have been introduced to also address real world challenges to gain access to hard to reach patients residing in rural areas and those who may have mobility issues and to utilize available technologies to remotely consent and monitor patients. There remains the need for local clinical support to obtain safety labs or train patients on utilizing the mobile devices. The use of ambulant healthcare providers to conduct at-home study visits can result in significantly more cost-effective, efficient and patient-friendly clinical trial programs conducted globally than traditional studies. This session will explore the use of an innovative, patient-centric approach to conducting selected study visits via an ambulant healthcare network to reduce patient burden and other barriers to study participation; Show, how conducting selected protocol visits at the patient's home or alternate location rather than at the investigator site can make study participation more convenient and comfortable for patients resulting in faster recruitment and better compliance and retention; Present case studies using ambulant care services and demonstrate win-win benefits for all stakeholders.

Speaker Biography

Gail Adinamis is Founder and CEO of GlobalCare Clinical Trials, LLC, a global niche patient-centric service organization that takes study visits to the patient's home or alternate setting via a global network of ambulant healthcare providers in over 60 countries. She has over 35 years of comprehensive global clinical trials experience including over 12 years of global trials management at Abbott Laboratories and Astellas. She has founded the in-home business model for study visits in 1992 and established and headed clinical trials divisions for three national home infusion companies and was a Founder, President and CEO of the first independent ambulant care service company for clinical trials. She is a Member of the Women Presidents' Organization, National Association of Professional Women, and DIA and has been an Invited Speaker at several industry conferences and recipient of numerous awards/recognitions including twice being among INC 5000's fastest growing private companies, and Game Changer and CEO of the Year.

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Robert M Stroud

University of California at San Francisco, USA

Unlocking the membrane proteome: New opportunities for diagnostics and therapeutics

Integral membrane proteins provide the interface between cells and their environment. As doors and windows of the cell, some inside the cell also, they control essential processes with abject precision. Therefore they offer many drug targets for control of disease. In humans, the serotonin transporter, the glucose transporter, and many drug resistance drug exporters are prime examples. In pathogenic organism's essential transporters and membrane viral restriction factors play essential roles that if blocked or otherwise modulated provide new avenues to therapeutics. Using several examples, I outline the new horizons available with integral membrane proteins as new technologies have opened the way. Targeting by organic compounds as drug leads and by antibody therapeutics are possible. Ways of presenting purified membrane proteins for antibody selection and maturation are presented. As new technologies are developed the molecular structures of membrane proteins can be obtained by X-ray and cryo electron microscopy methods. I will present inroads into these processes.

Speaker Biography

Robert M Stroud is Professor of Biochemistry and Biophysics, University of California in San Francisco. He focuses on the molecular basis for function of transmembrane transporters and channels, and on structure-assisted drug discovery. He has contributed to fundamental mechanisms of receptor proteins, lipid-protein interactions, enzymes and protein-RNA recognition. He has obtained his BA and MA in Natural Sciences from the University of Cambridge (UK), his PhD is from University of London (JD Bernal). From a Postdoctoral and Professorship in Biological Chemistry at the California Institute of Technology, he came to UCSF. His research involves structural determination engineering and function of molecules and cells using X-ray crystallography, electron-cryo microscopy, computational simulations, spectroscopy, super-resolution optical microscopy. He is a Member of the National Academy of Sciences, a Fellow of the American Academy of Arts and Sciences, a Fellow of the Royal Society of Medicine (UK), Fellow and Former President of the US Biophysical Society.

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Elizabeth Kwong

Kwong Eureka Solutions, Canada

Just right: Process from drug discovery to development

The discovery and development of new drugs is a very complex machine. Despite increasing investments and process improvements in research and development, the survival rates of drugs in late phases of development has languished during the past decade. Recent analysis of such decline in late phase drug development was attributed to non-drug like compounds synthesized by Medicinal Chemists which exhibit low aqueous solubility with highly potent ligands which will bind to a target. With the current challenges facing "big Pharma", small biotech start-up (BSU's) with limited internal research and development resources in addition to true virtual pharmaceutical companies (VPC's) with only an experienced team of managers without any R&D capabilities are quickly emerging which adds another layer of complexity in arriving to a "just right" approach from drug discovery to development. To recover from such failed approaches, a gate-keeper approach is now the norm, where preclinical and discovery collaborations result in a structure and property-based design. This design now used in lead optimization combines biological activity/potency focus with optimizing structural features of the candidate to optimize absorption and pharmacokinetics. This approach is then effectively progressed to the understanding and defining of solid state phase and formulation of the drug candidate when more material is available. Early engagement of the pharmaceutical development scientists on the identification of an optimal phase and formulation during drug discovery can add significant benefits in drug discovery efforts and downstream development. These benefits include the demonstration of dose limiting toxicity to establish acceptable and reproducible safety margins. Another benefit is the early identification of an optimal phase that minimize multiple changes in phase that can contribute to irreproducible plasma levels in various PK studies as candidate are being considered in toxicity studies. Furthermore, formulation development in preclinical studies will also provide some risk mitigation in the development of clinical trial materials. The current presentation will focus on the "must do" list to successfully help progress drug discovery candidates from any pharma organization to development with low risk that provide a balance of speed and quality.

Speaker Biography

Elizabeth Kwong retired from Merck after 23 years of service. She currently established her own company (Kwong Eureka Solutions) as a consultant for small start-up companies and specialty drug products. Before she retired she was Senior Scientific Director at Merck & Co. Basic Pharmaceutical Sciences. She was also adjunct professor in the Dept of Pharmaceutics at the University of Montreal and Dept of Chemistry at Concordia University. She received her B.S. Pharmacy (1980) and PhD degree (Pharmaceutical Chemistry -1984) from University of British Columbia, Canada. She completed a postdoctoral fellowship in Pharmaceutics at the School of Pharmacy, University of Washington in Seattle (1984-1986).

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Makoto Ubukata

Hokkaido University, Japan

New strategy for discovering biologically active small molecules

The term antibiotic was coined by Selman Waksman to describe any compound produced by a microorganism that is antagonistic to the growth of other microorganisms in high dilution. Forty-three years after the structure determination of penicillin, the structure of liposidomycin B, an inhibitor of bacterial peptidoglycan synthesis, was uncovered in 1988. The structure explains the function of the antibiotic and was used as a motif for a science fiction film, Godzilla vs. Biollante in 1989. A derivative having liposidomycin core-structure, CAPZEN-45 has been recognized as a drug candidate for extremely drug resistant (XRD) *Mycobacterium tuberculosis*. In Japan, antibiotics and other microbial products has been explored as enzyme inhibitors, antiviral and anticancer agents. The *Journal of Antibiotics*, a flag journal for biologically active small molecules from microorganisms, has many articles on such microbial products as well as antibiotics. In addition, we have clarified the structures and functions of many biologically active small molecules such as tautomycin, tautomycetin, reveromycin, ascamycin, epiderstatin, epogymnolactam, and so on. Recently, we have uncovered a growth mechanism of previously uncultured *Leucobacter* sp. by novel growth factors released by *Sphingopyxis* sp. strain ASN212. In this seminar, I will discuss the discovery of growth factors for Actinobacteria for the understanding the complex microbial communities as a network system, and for a general strategy for discovering biologically active small molecules using coproporphyrin in lieu of siderophore.

Speaker Biography

Makoto Ubukata has earned his PhD from Hokkaido University, the first modern educational institution in Japan and started his career as a Synthetic Chemist in 1980. After Postdoctoral fellowships at Indiana University and RIKEN, he became a Scientist at RIKEN in 1984. In RIKEN, he had spread his wings into the biological area probing for deeper understanding in Chemistry and Biology using biologically active small molecules. After 11 years working as a Scientist and Senior Scientist, he was appointed as a Full Professor of Biotechnology Research Center, Toyama Prefectural University. In 2003, he has moved his laboratory to Research Faculty of Agriculture, Hokkaido University. He is the recipient of JSBBA Award for Young Scientist (1989), Sumiki-Umezawa Memorial Award (1995), Japan Prize of Agricultural Science (2017), and Yomiuri Award of Agricultural Science (2017). He has been Professor Emeritus since 2015 and JSBBA Fellow since 2016. His current research interest includes the study on the structure and function of biologically active small molecule, which might help people.

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Susan Ciotti

NanoBio Corporation, USA

Nanoemulsion-Based therapies: Antimicrobial, anti-inflammatory and drug delivery properties

Nanoemulsions (NE) are oil-in-water emulsions containing high energy nanometer-sized droplets stabilized by surfactants, and specifically designed for topical and mucosal targeted delivery. Due to their size (less than 500nm) and surface-active properties they to traverse the skin via pores, hair follicles, and mucosal membranes, but are excluded from entering the tight junctions of the epithelium. As a result, they can be highly bioavailable in the tissues, without causing disruption of the normal epithelial matrix. Nanoemulsions can delivery agents across the nasal mucosa for the desired clinical (therapeutic) effect. We have testing these formulation in high-throughput screens and found NE induced immunogenicity and antigen delivery are facilitated through initial contact interactions between the NE droplet and mucosal surfaces, which promote prolonged residence of the vaccine at the site of application, and thus cellular uptake. We have incorporated small molecule, peptides/proteins and large macromolecules in optimized nanoemulsion formulation for transmucosal delivery. Nanoemulsions can delivery agents across the nasal mucosa for therapeutic effects. Nanoemulsions delivered topically are inherently antimicrobial and lyse pathogens upon contact, thereby overcoming existing resistance mechanisms. Other anti-microbial, anti-fungal and anti-viral agents can be entrapped inside the nanoemulsion and enhanced drug delivery of these agents. Studies of a novel nanoemulsion formulated with other agents demonstrates significantly higher levels are achieved as compared to commercially available products. Recently discovered, a topical nanoemulsion therapy acting as a topical antimicrobial was found to halt burn wound progression in a swine burn wound model. The nanoemulsion reduced the bacterial growth in the burn wound to minimal levels compared to saline and silver sulfadiazine and significantly reduced levels of dermal inflammatory cytokines. By reducing excess influx of neutrophils into the burn wound and modulating the pro-inflammatory response, the nanoemulsion formulations attenuated burn wound progression in the early post-injury phase and prevented conversion of burn wounds from partial thickness to full thickness. This discovery, if demonstrated in man, would lessen the need for skin grafting, speed recovery, result in fewer infectious complications, and improve the outcomes by preventing the conversion to full thickness wounds. Among its many uses nanoemulsion therapy is a potential new breakthrough treatment for preventing burn wound progression.

Speaker Biography

Susan Ciotti, PhD is the Director of Formulations at NanoBio Corporation, where she directs the nanoemulsion adjuvant formulation efforts. She is responsible for developing novel nanoemulsion formulations, nanoemulsion manufacturing (process optimization/scale-up) and clinical trial materials for the vaccine clinical trials. Her career has focused on principally on developing nanotechnology formulations. During her tenure at Johnson and Johnson, she spearheaded several projects related to developing formulations for the treatment of topical and nasal preparation, as well as sterile parental formulation. She has served as the lead for several projects at various stages of dermatological, parenteral and biological drug product development. She is currently leading NanoBio's formulation efforts on a NIAID contract entitled "Next Generation Anthrax Vaccine". She was the co-investigator on Nanoemulsion-based antimicrobials for the protection against burn and wound infection funded by the U.S. Army Medical Research and Material Command (USAMRC, Award Number: W81XWH-11-2-005). Dr Ciotti received her graduate degrees in Pharmaceutical Sciences from the University of Michigan, Ann Arbor, MI. She is a Professor of Pharmaceutical Sciences at the College of Pharmacy where she teaches novel drug delivery and nanotechnology to graduate students.

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