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901st Conference

Joint Event on
15th World Congress on
BIOTECHNOLOGY AND BIOTECH INDUSTRIES MEET
&
2nd International Conference on
ENZYMOLOGY AND MOLECULAR BIOLOGY
March 20-21, 2017 Rome, Italy

Keynote Forum

Day 1

Gregg B Fields

Florida Atlantic University, USA
The Scripps Research Institute, USA

Structure-guided design of selective matrix metalloproteinase (MMP) inhibitors and their application in animal models of multiple sclerosis, sepsis, and osteoarthritis

Analysis of matrix metalloproteinase (MMP) expression profiles in various pathologies correlated their presence in promoting disease progression. Drugs were designed to inhibit MMPs by chelating the active site zinc ion. This approach did not distinguish between the MMP family members and had devastating consequences during clinical trials. Subsequent knockout mouse studies showed that some MMPs were beneficial in regulating tumor growth and metastasis and stimulating indirectly the immune system. The broad-spectrum inhibitor approach was rethought in order to increase the specificity, taking into account the non-conserved secondary binding sites (exosites) within MMPs. Structural evaluation of the collagenolytic mechanisms of MMP-1 and MT1-MMP revealed differences in exosites, facilitating the development of triple-helical peptide inhibitors (THPIs). THPIs achieved selectivity within the MMP family and showed efficacy in *in vivo* models of multiple sclerosis and sepsis, where MMP-9 and MMP-8, respectively, were targeted. MMP-13 has been identified to be mainly responsible for the cleavage of type II collagen in osteoarthritis, which leads to the destruction of articular cartilage. The development of an allosteric MMP-13 inhibitor began with a lead compound identified as part of a high throughput screening campaign. Subsequent biochemical experiments and X-ray crystallographic structure determination revealed that our hit bound to the S1' subsite, which is surrounded by a long loop that differs significantly among MMPs. Comparative structural analysis and molecular modeling enabled the design and synthesis of small molecules three orders of magnitude more potent (IC50≤5 nM) than the original hit. Further optimization has led to highly potent and selective inhibitors of MMP-13 with favorable PK properties. The recent technological advances that allow us to better understand the function and structure of MMPs are aiding in the development of selective inhibitors.

Biography

Gregg B Fields is the Director at the Center for Molecular Biology & Biotechnology in Florida Atlantic University, USA. He did his PhD in the year 1988 from Florida State University. He has been an elected President of American Peptide Society and Full Member at University of Minnesota Comprehensive Cancer Research Center. He also received BIT Life Sciences Lifetime Membership Award and Texas Higher Education Science and Technology Acquisition and Retention (STAR) Plus Award. He performs research focusing on collagen-mediated diseases. Cancer, arthritis and neurodegenerative diseases (such as multiple sclerosis) which are commonly treated as distinct maladies. However, each of these diseases has overlapping factors that contribute to disease progression. Amongst these factors are proteases that enhance the breakdown of collagen. The progression of cancer, arthritis and neurodegenerative diseases involve similar or even identical proteases. His current researches are to evaluate the link between inflammation and cancer, arthritis and neurodegenerative diseases and developing new drugs that block the action of proteases common to all of these disease states.

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Lene Lange, J Biotechnol Biomater 2017, 7:1(Suppl)
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Lene Lange

Technical University of Denmark, Denmark

Developing the bio-economy: Fast track discovery of new enzymes for efficient and value added biomass conversion

A new fast track enzyme discovery technology platform has been developed. It differentiates from existing approaches as it is non-alignment based and facilitates prediction of function of the enzyme directly from the (genome) sequence. New enzymes and enzyme-based processes are being developed for producing biomass-based food ingredients, feed additives, health-promoting products, components for skincare and wound healing as well as fertilizer, fibers and building blocks for chemicals. Enzyme discoveries of relevance for the following types of biomass feed stock have recently been made: The green biorefinery, making value added products from green grass, clover, etc. Seaweed biomass, from species of brown algae, growing meters high in temperate/colder waters, have already now been documented to hold several components with potentials for being developed into new value chains. Feather is composed of the proteinaceous, highly recalcitrant keratin. It has been shown that a blend composed of three specific types of fungal enzymes can be used for decomposing the keratin into peptides and amino acids. Interestingly, the keratin-degrading fungi in these studies showed four different *LPMO* genes, (Lytic Polysaccharide Monooxygenases) which may be directly involved in breaking down the keratin. Enzymes of relevance for improved processing of fish skin collagen are being studied in the project Collagen Hydrolysate funded as a Nordic Innovation program.

Biography

Lene Lange is a Professor at the Center for Bioprocess Engineering, DTU Chemical Engineering, Denmark. She has held Research Director Positions in both industry and academia. Currently, she holds advisory positions at: The Danish National Bio-economy Panel, the Nordic Bio-economy Panel, Scientific Committee for the BBI JU and IAB BIOTEC Thailand. Her fields of research are discovery of novel enzymes for improved biomass conversion and biorefinery processes, with specific focus on generating value from agro-industrial side streams and waste products; development of the new enzyme discovery platform, PPR, a non-alignment based sequence analysis method, predicting function directly from sequence and using PPR analysis, combined with MS, phylogenetic analysis.

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Marvin W Makinen

The University of Chicago, USA

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

A large number of studies on 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-X 5-R-S/T, a condition leading to low specificity. Having identified protein tyrosine phosphatase-1B (PTP1B) as the target enzyme of the vanadyl (VO^{2+}) chelate bis(acetylacetonato)oxidovanadium(IV) [$VO(acac)^2$] in cultured 3T3-L1 adipocytes, we have investigated the basis of inhibition by the VO^{2+}-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 VO^{2+}-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 $VO(acac)_2$ to PTP1B may provide a new approach to design of inhibitors of high specificity for therapeutic purposes.

Biography

Marvin W. Makinen is Professor in the Department of Biochemistry and Molecular Biology in The University of Chicago, USA and has served as chairman of the department from 1988 to 1993. He is also a founding member of the Human Rights Board at the university. He did his D.Phil., in the year 1976 in Molecular Biophysics at Oxford University, U.K. Over the past 40 years at The University of Chicago, research in the Makinen lab has been directed towards the structural basis of action of metalloenzymes and the application of magnetic resonance methods to characterize active site structure and stereochemical relationships of substrates to active site residues 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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Paul A Calvo, J Biotechnol Biomater 2017, 7:1(Suppl)
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Paul A Calvo

Sterne Kessler Goldstein & Fox, USA

Choosing between patents and trade secrets for protecting biotech products or bio-production processes

The choice of trade secrets versus patent protection has taken on renewed importance in the biotechnology sector with the advent of biosimilar biologics. From an originator perspective, increasing importance is being placed on secondary patent protection, i.e., patents that cover manufacturing processes, formulations, etc. The goal of these filings is to extend protection of the original composition and method, and use of patents by covering production methods or the commercial formulation. However, there are many originator companies which can bypass filing for patent protection, and the disclosure of their bioprocess that comes with it, in favor of keeping some of their critical processes secret. Factors that weigh in favor of patent or trade secret protection will be outlined in the context of products versus processes.

Biography

Paul A Calvo is the Director of the Biotechnology/Chemical Group at the Washington, DC-based law firm Sterne Kessler Goldstein & Fox which represents a diverse group of US and international companies innovating in the field of Biotechnology and Pharmaceuticals Industries. He provides counsel with regard to global patent portfolio strategy, licensing, patent validity, infringement, and design around strategies. He also has extensive expertise in prosecuting and investigating patents related to bio-production methods and therapeutic formulations. He has extensive technical expertise in the areas of vaccines, therapeutic antibodies, cellular immunology, and bio-therapeutics during his graduate studies and Post-doctoral fellowships at the University of Pennsylvania and National Institutes of Health.

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Rita De Santis, J Biotechnol Biomater 2017, 7:1(Suppl)
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Rita De Santis

Sigma Tau SpA, Italy

AvidinOX-targeted delivery: A new way to improve efficacy of well-known monoclonal antibodies for cancer therapy

We recently discovered that the oxidized version of hen egg white avidin, named AvidinOX, can chemically link to tissue proteins when injected or nebulized, thus becoming an artificial receptor for biotinylated therapeutics. This product is currently under investigation in phase I clinical trials for targeting intravenously administered ^{177}Lutetium-biotinDOTA to inoperable tumor lesions and liver metastases, pre-injected with AvidinOX (ClinicalTrials.gov NCT02053324). Several published and some non-published data from our group indicate that AvidinOX-targeted delivery of the biotinylated version of some marketed monoclonal antibodies turns non-effective doses of such antibodies effective for cancer treatment. Among the antibodies tested, AvidinOX-targeted delivery of biotinylated anti-EGFR cetuximab and panitumumab, and anti-*ErbB2/neu* trastuzumab and pertuzumab were particularly effective. Molecular mechanisms explaining the improved anti-tumor activity of AvidinOX-anchored biotinylated antibodies have been also described by our group. Overall, our data provide a scientific rational for further pre-clinical and clinical investigation of therapeutic approaches based on the local delivery of AvidinOX (i.e., intra-tumor, aerosol or intra-peritoneal delivery) followed by local or systemic delivery of low dose biotinylated antibodies. The expectation of our AvidinOX-targeted delivery platform is to reduce the cost of cancer treatments and improve tolerability by reaching anti-tumor efficacy with significantly less amount of expensive antibodies.

Biography

Rita De Santis has a degree in Biological Sciences and PhD in Experimental Medicine from Rome University and National Institutes of Health, USA, respectively. Since 1999, she directs the group of Biotech Products at Sigma Tau SpA, leading innovative products from bench to clinical trials. She is the author of 70 papers and 20 patents. Her work focuses on the development of the AvidinOX-based therapeutic platform for cancer therapy and looking for collaborations to fully exploit the potential of AvidinOX for targeted delivery of biotinylated drugs in additional therapeutic fields.

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Day 2

Jan Szopa, J Biotechnol Biomater 2017, 7:1(Suppl)
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Jan Szopa

University of Wroclaw, Poland

Optimizing flax fibers for tomorrow's therapeutics

Flax fiber served as a major source to manufacture textiles, whereas seeds were pressed to extract edible oil. In the last decades devaluation of flax fiber in the world has been observed. Recently, the renewed interest in flax products has been noticed due to better understanding of the genes involved in flax productivity and fiber quality. All these provide targets for fiber improvement by the novel genetic/epigenetic methods leading to more diverse products based on flax fibers. For example manipulation of gene expression significantly increases antioxidant potential, affected lignin and pectin synthesis and cell wall arrangement. Up-regulation of β-*glucanase* gene protects plant against pathogenic infection, and thus increases fiber productivity and quality. Unique flax fiber was obtained, by genetic engineering, with novel constituent that strongly affects fiber properties and application, for example the production of a polyhydroxybutyrate (PHB) which was accomplished by simultaneous expression of three bacterial genes under vascular bundles specific promoter. The unique application of PHB-fibers has been shown in chronic wound healing. Pre-clinical study revealed healing improvement of chronic ulcers upon treatment with wound dressing based on new fibers. The healing effect was potentiated by supplementation of PHB-fibers with two activators derived from seeds and seedcake of flax accumulating antioxidant compounds. Up-regulation of antioxidants was achieved by simultaneous expression of three genes from flavonoid pathway. The PHB-fiber embedded in polylactide may serve as a scaffold for tissue engineering and has been shown to be useful as biodegradable implant. Micronization process can introduce structural changes in fibers constituents to exhibit more functional groups, and thus might potentiate fiber functionality. Indeed, highly reactive micronized flax fibers might serve as a carrier for biologically active compounds.

Biography

Jan Szopa is currently working as a Professor in the Department of Biochemistry and Genetics at the University of Wrocław, Poland. His international experience includes various programs, contributions and participation in different countries for diverse fields of study. His research interests reflect wide range of publications in various national and international journals.

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Shree Kumar Apte

Homi Bhabha National Institute, India

Uranium bio-precipitation and recovery from high radiation environments: New approaches

Removal of traces of uranium from nuclear waste poses a big challenge for its disposal. Our laboratory has genetically engineered the extremely radio-resistant bacterium *Deinococcus radiodurans* to over-express either an acid phosphatase PhoN, or an alkaline phosphatase *PhoK*, to achieve impressive uranium bio-precipitation (up to 7-10g U/g dry biomass) over a wide pH (5-9) and uranium concentration (0.2-10 mM) range. Successful preservation of bioprecipitation-active dry biomass for up to 2 years at ambient temperature has been achieved. Conditions have been optimized to accomplish easy and complete recovery of precipitated uranium. Further augmentation of uranium bioremediation has been accomplished by: pyramiding *phoN* and *phoK* genes in a single strain, employing radiation-responsive *Deinococcus* gene promoters, and by surface display of bioremediation-active enzymes.

Biography

Shree Kumar Apte is the Former Director, Bio-Science Group, BARC and currently serves as a Professor at the Homi Bhabha National Institute. He is a JC Bose National and Raja Ramanna Fellow at BARC, Mumbai, India. His laboratory has unraveled stress and adaptive responses of several bacteria and developed many biotechnologies for metal bioremediation from high radiation environments. He is a fellow of all National Science Academies and Agriculture Academy in India.

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Claudio Santi, J Biotechnol Biomater 2017, 7:1(Suppl)
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Claudio Santi

University of Perugia, Italy

New drugs and catalysts inspired by glutathione peroxidase

Glutathione peroxidase (GPx) among the currently known selenoenzymes is the best characterized in terms of chemical structure and reaction mechanism. The catalytic center of this enzyme is a selenocysteine and more specifically, a selenium atom that is stabilized by a catalytic triad in the form of nucleophilic selenate. In this form, the selenium is reactive toward peroxides determining their reduction into the non-harmful alcohol or water. The selenol by reaction with the peroxide is transformed into the corresponding selenenic acid which is rapidly reduced by two molecules of glutathione affording a molecule of oxidized glutathione and the native selenate which is ready to start a second cycle. Glutathione peroxidase have a crucial role in the control and prevents the damage produced by the reactive oxygen species (ROS) in living system and from one side it is important to maintain a healthy status from the other it is necessary to reinforce it during a number of pathologic situation. During the last decades, several small molecules containing selenium as well as some artificial selenoenzymes were developed and tested as antioxidants but also as pro-oxidants as enzyme inhibitors, hormetic agents, antiviral, anticancer, antimicrobial agents. In this talk, the author will report the state of art of the research on this field focusing some new prospective that is currently ongoing in our laboratory: Discovery of new biologically active organoselenium compounds and determination of their reaction mechanism in living systems. Besides that the bio inspiration is an excellent strategy for the development of new efficient and eco sustainable catalyst for application in Green Chemistry, some recent examples of these results will be presented and discussed.

Biography

Claudio Santi received his PhD in Chemical Sciences from the University of Perugia under the supervision of Professor Marcello Tiecco. Currently, he is a Professor of Organic Chemistry and leads the Group of Catalysis and Organic Green Chemistry in the Department of Pharmaceutical Sciences. His research interests range from the application of selenium reagents in green chemistry to the development of new organoselenium containing drugs. He is author of more than 130 publications including review articles and book chapters.

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Toshiyuki Moriuchi, J Biotechnol Biomater 2017, 7:1(Suppl)
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Toshiyuki Moriuchi

Osaka University, Japan

Bromoperoxidase mimicking bromination catalysts

Haloperoxidases are enzymes that are able to catalyze the oxidation of halide ions by using hydrogen peroxide. Catalytic activities of haloperoxidases have received great attention because of their capability to halogenate a variety of organic compounds. Vanadium bromoperoxidase (V-BrPO), which is a naturally occurring enzyme in marine algae, is a kind of haloperoxidase. V-BrPO catalyzes two-electron oxidation of the bromide ion in the presence of hydrogen peroxide, leaving a bromonium cation-like species. V-BrPO has been demonstrated to perform the catalytic bromination of organic compounds. Bromination reaction is one of the most fundamental reactions in organic synthesis, providing important precursors and substrates in various coupling reactions. Conventional bromination reaction is performed by using hazardous and toxic elemental bromine. Considerable efforts have been focused on developing a versatile bromination method with a bromide ion as a bromide source instead of bromine. So, the V-BrPO mimicking bromination reaction systems induced by a vanadium catalyst and hydrogen peroxide have attracted much attention. These catalytic systems, however, require a stoichiometric amount of a strong oxidant to generate the bromonium-like species. A more practical catalytic bromination reaction system without the use of hazardous reagents needs to be developed. From the view point of green chemistry perspective, molecular oxygen is regarded as the best candidate for oxidants. We embarked upon the development of an environmentally-favorable catalytic method for selective bromination of a wide range of substrates. In this presentation, bromoperoxidase mimicking versatile and practical bromination catalytic systems by the combination of a commercially available inexpensive ligand-free vanadium catalyst and a Brønsted acid or a Lewis acid under molecular oxygen will be described.

Biography

Toshiyuki Moriuchi received his Bachelor's degree in 1991 and Doctoral degree in 1995 under the supervision of Professor Toshikazu Hirao, from Osaka University. He became an Assistant Professor at Osaka University and was a Post-doctoral Fellow at California Institute of Technology with Professor Jacqueline K Barton (1996-1997). He was promoted to the position of Associate Professor in 2004. His current research interests focuses on the development of novel artificial bio-conjugated systems based on self-organization of biomolecules and redox-active π-conjugated systems for functionalized catalysts and materials. He received the Inoue Research Award for Young Scientists in 1997 and HGCS Japan Award of Excellence 2011 in the year 2012.

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