Keynote Forum
October 18, 2017

Applied Microbiology & Microbial Tech 2017

Joint Conference

GLOBAL APPLIED MICROBIOLOGY CONFERENCE

&

International Congress on

MICROBIAL & BIOCHEMICAL RESEARCH AND TECHNOLOGIES

October 18-19, 2017 | Toronto, Canada

Marc Beauregard

UQTR, Canada

A biochemist's odyssey in microbial research and techniques

Microbes are the workhorses of most biochemistry laboratories, especially those focusing on proteins and enzymes. While everyone recognises their value as production machines (providing large quantities of pure proteins in a few hours), some other aspects deserve consideration. Protein evolution, new enzyme identification and genetic modification are some examples of extremely useful abilities afforded by our microscopic friends. In this talk the author will quickly browse through several and very different achievements that were made possible by microbes in this laboratory. The author will then focus on methodologies that they developed, especially regarding microbial lipases characterisation. At the end this presentation, the author will present our most recent findings on a microbial cocktail found on an oil recycling plant. Using used lubricant as a carbon source, this unique microbial consortium produces a bioplastic whose structure resembles that of a polyvinyl.

Speaker Biography

Marc Beauregard got his PhD in Biophysics from UQTR in 1989 and then moved to pursue his Post-doc positions with Max-Planck-Institute (Germany), University of Liège (Belgium) and Agriculture Canada. After being tenured at UPEI (1997) and Université de Moncton (1998), he became full Professor of Biochemistry at UQTR (Québec, Canada) and is a member of the Research Center on Lignocellulosic Materials since 2011. His teaching duties include Protein Spectrocsopy and Bioinformatics. He has his expertise in protein biotechnology, and his contributions rely on a wealth of various techniques spanning from plant heterologous expression, accelerated evolution, and development of industrial applications. With his group he has published 70+ papers, some in high impact journals (Nature Biotechnology, Green Chemistry, PNAS) and has contributed to preparing four patents. He founded a Biotechnology company in 2000, has served as Director of Graduate Studies (Biophysics) and has been invited on major research committees in Canada.

e: marc.beauregard@uqtr.ca

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Steven J Projan

MedImmune, UK

Novel monoclonal antibodies for the prevention and treatment of bacterial infections

The second decade of the twenty-first century marks a perfect storm of patent expirations, contracting western economies, and increasing demands from "payers" that pharmaceuticals demonstrate cost effectiveness of their drugs. The result is the shrinking of "big pharma" right before our eyes and nowhere has the impact been felt more than in infectious disease research at large pharmaceutical companies. All the while bacterial resistance to antibiotics is increasing even as the number of new drugs being developed to treat bacterial infections is at its lowest point, since the dawn of the antibiotic era. This surfeit of new agents implies that the traditional approaches to drug discovery and development have run their course and novel (entrepreneurial, opportunistic) approaches for the treatment and prevention of microbial infections (and forestalling the emergence of resistance) are required. Against that background, we have seen an increasingly convoluted regulatory regime with indications being parsed finer and finer yet with larger numbers of patients required to reach arbitrary (but often clinically meaningless) statistical endpoints. To date, there has been some modest biologics drug discovery efforts to discover novel antibacterial agents for the prevention and/or treatment of *Staphylococcal, Pseudomonal* and *Clostridium difficile* infections but these efforts now appear to be picking up speed and are progressing in the clinic. Is there hope?

Speaker Biography

Steve J Projan is the head of Infectious Diseases and Vaccines Innovative Medicines unit (iMED) at MedImmune, leading a cross-functional team dedicated to the therapeutic area strategy, prioritization and advancement of the company's infectious disease and vaccine portfolio. He has joined MedImmune in 2010 as Senior Vice President of Research and Development and head of the Infectious Diseases and Vaccines iMED. Prior to joining MedImmune, he served as Vice President and Global Head of Infectious Diseases at Novartis. He has previously spent 15 years at Wyeth in roles of increasing responsibility, with his last post as Vice President and Head of Biological Technologies. During his time at Wyeth, he has started the Biologics Discovery Group (covering all therapeutic areas) and initiated multiple collaborations and partnerships, most notably with Cambridge Antibody Technology (now a part of MedImmune/AZ). Prior to his work in the industry, he spent 14 years at the Public Health Research Institute and presently has over 110 publications to his credit. He has received a Bachelor of Science from MIT, and, from Columbia University, a Master of Arts and Philosophy in Biological Sciences and a Doctorate in Molecular Genetics.

e: projansj@medimmune.com

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Clifford Lingwood

University of Toronto, Canada

Prokaryote remedy to genetic misfolding diseases: Inactivated bacterial subunit toxoids block ER associated degradation of misfolded proteins to rescue the phenotype

Statement of the Problem: Many (>30) genetic diseases result from a single amino acid or small mutation which leaves considerable residual activity but induces a degree of misfolding of the mutant protein which targets it for endoplasmic reticulum associated degradation (ERAD), resulting in the complete loss of mutant protein activity. ERAD, rather than the mutation per se, precipitates disease symptoms.

Methodology & Theoretical Orientation: Several pathogenic bacterial protein subunit toxins have evolved to hijack ERAD as a means for A subunit access to the cytosol where the pathological effect becomes manifested. These toxins e.g. cholera toxin, shiga toxin, use the same ER translocon as is used in ERAD. Indeed the A subunit contains a C terminal sequence which mimics an unfolded protein. Such toxins provide a basis for the direct control of the ERAD translocon and hence temporarily block ERAD to rescue the mutant protein and ameliorate disease symptoms. We have inactivated the catalytic A subunit activity and added a hydrophobic C terminal addition to generate toxoids which reverse disease symptoms in cell and animal models

Findings: Cholera toxin and shiga toxin with a 0, 9 or 18 polyleucine tail, were able to partially block ERAD of F508del CFTR cystic fibrosis cells and G370S GCC Gaucher disease cells and increase CFTR mediated chloride transport and GCC glucocerobrosidase activity in these cells and their mouse models without significant induction of ER stress.

Conclusion & Significance: These benign prokaryotic toxoids represent a new means to treat a large number of inherited diseases

Speaker Biography

Clifford Lingwood completed his PhD at the University of London in 1974, and Post-doctoral studies at the Universities of Washington and Toronto. He has been a Full Professor at the University of Toronto since 1997 and is a Senior Scientist within the Molecular Medicine Program of the Research Institute at the Hospital for Sick Children, Toronto. His research program is concerned with the biochemistry, chemistry, metabolism and function of glycosphingolipids with a view to the therapy of diseases in which they are involved. He has published more than 200 papers in reputed journals.

cling@sickkids.ca

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Akira Kaji

University of Pennsylvania, USA

In vivo and *in vitro* studies of RRF (ribosome recycling factor) revealed that its major function is to release mRNA from the post-termination complex and not splitting of the ribosomal subunits

In prokaryotes two adjacent ORF are often linked with an overlapping combination of termination and initiation codons with a total of 4 or 5 nucleotides, for example UAAUG or AUGA. In these junctions, ribosomes at the stop codon are released by RRF and some of them re-bind to the nearby AUG and start translating the downstream ORF. In the absence of RRF, the ribosome at the stop codon remains on the mRNA and would read it in frame with the termination triplet. We studied the role of RRF in these junctions *in vitro* and *in vivo*. For *in vivo* studies, we used an *E. coli* strain with a temperature sensitive mutation of RRF, so that we could inactivate the function of RRF at the non-permissive temperature (39°C). We show that for correct reading of the downstream ORF, AUG is essential. The shorter the upstream ORF the lower will be the downstream reading. Introduction of a complementary sequence to the 3'-terminal regions of 16S rRNA into the mRNA increased downstream reading from AUGA. Shortening of the upstream ORF to 4 codons completely abolished the downstream reading of UAAUG. This suggests that if Shine-Dalgarno (SD) sequence is near the termination codon, the RRF-released ribosome is attracted by the SD sequence to the extent that it loses the downstream movement after it is released. For *in vitro* studies, we used the PURE system, so that we could omit RRF in the reaction mixture. We have confirmed, *in vitro*, the essence of the *in vivo* observation described above using a mRNA having the following sequence: "GGGAAUUCAAAAAUUUAAACAGGUAUACAUACU AUG UUU ACG AUU ACU ACG AUC UUC UUU ACG AUC UUC UUU ACG AUU ACU ACG AUC UUC UUU ACG AUU ACU ACG AUC UUC UUU ACG AUU ACU ACG AUC UUC UUU ACG UAAUG CGU CUG CAG GCA UGC AAG CUA A24A" (Bold character is the junction sequence broken underline is the Shine-Dalgarno sequence). In the presence of RRF, the downstream reading starts from AUG causing the incorporation of [14C]-Leucine (CUG and CUA). On the other hand in the absence of RRF, the first triplet read was UGC of UAAUG CGUC and [14C]-Valine was incorporated due to the codon GUC. Upstream reading was detected by [3H]-phenylalanine incorporation (due to UUUs and UUCs). With this assay, we also showed that Fusidic Acid could inhibit RRF at lower concentration than that necessary to inhibit translocation (monitored by the incorporation of [3H]-phenylalanine), causing the inhibition of the incorporation of [14C]-Leucine. Moreover, using ribosome with tethered subunits (1), we were able to show that the splitting of the ribosomal subunits was not necessary in the recycling reaction, demonstrating that recycling of the ribosome take place also in the absence of the splitting of the ribosomal subunits.

Speaker Biography

Akira Kaji is a Professor of Microbiology, School of Medicine, University of Pennsylvania. He has contributed to the deciphering of genetic code by his discovery of the fact that the complex of poly-U with ribosome binds specifically to tRNA specific for phenylalanine. He also discovered RRF.

e: kaji@pennmedicine.upenn.edu

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Khaled Barakat

University of Alberta, Canada

Rational design of small molecule immune checkpoints' inhibitors: The PD-1 challenge

Blocking the PD-1/PD-L1 pathway recently emerged as a 'game changer' in cancer immunotherapy, leading to the selection of monoclonal-antibodies (MABs) targeting PD-1 as 'drug of the year' for 2013. Although these antibodies restored exhausted T cells' function to recognize and kill tumor cells, these MABs have numerous disadvantages. These include their very high cost and very severe side effects. Our team has been focused on designing small molecule inhibitors for this pathway. Compared to available MAB therapies, our small molecules may offer a more affordable; more easily administered and better controlled treatment for a variety of cancers. Here, we demonstrate our efforts toward this goal and summarize preliminary data on one of our promising compounds, a small molecule inhibitor for the PD-1/PD-L1 pathway that binds to PD-1 and restores the polyfunctionality of exhausted T cells..

Speaker Biography

Khaled Barakat is the Leader of a multidisciplinary world-class research team to develop novel immunotherapy drugs targeting the immune checkpoints' proteins. He received his PhD in Biophysics from the University of Alberta in 2012 followed by a Post-doctoral fellowship in Professor Michael Houghton's Lab for two years. During his career, he received numerous awards including the CIHR and AIHS Post-doctoral fellowships, the prestigious UofA dissertation award, the ACRI Studentship and many distinction awards throughout his undergraduate and graduate studies. He also served as an editor for a number of journals. His lab is supported by different funding agencies including the Alberta Cancer Foundation, Li Ka Shing Applied Virology Institute, Natural Sciences and Engineering Research Council (NSERC), Li Ka Shing Institute of Virology and IC-IMPACTS Centres of Excellence.

e: kbarakat@ualberta.ca

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