
2005 Society Award Designates

Dr. R. Christopher Bleackley from the Department of Biochemistry, University of Alberta, has been chosen to receive the 2005 Roche Diagnostics Award which recognizes outstanding achievement in research in one or more of the fields of biochemistry, molecular or cellular biology undertaken in Canada by a Canadian scientist. This year, in a rare decision, the Society has decided to award the Merck Frosst Prize for meritorious research by a young Canadian scientist with ten years or less of independent research in the areas of biochemistry, molecular or cellular biology to two equally accomplished individuals, Dr. Mark Glover from the Department of Biochemistry, University of Alberta, and Dr. Eric Brown from the Department of Biochemistry, McMaster University. These awardees will be presenting Plenary Lectures at the 48th Annual General Meeting of the Canadian Society of Biochemistry, Molecular and Cellular Biology to be held March 16-20, 2005 at the Banff Center (Banff, Alberta).

The 2005 CSBMCB Roche Diagnostics Prize for Biomolecular & Cellular Research **Dr. R. Christopher Bleackley**



Dr. Chris Bleackley received his Ph.D. from the University of Birmingham (U.K.) in 1975. He then moved to Canada where he joined the Department of Biochemistry at the University of Alberta to undertake a postdoctoral fellowship. Upon completing his training, he was hired as a faculty member in that Department and rose progressively through the ranks to the level of Professor.

Dr. Bleackley is best known for his pioneering work on the function of cytotoxic lymphocytes, and continues to provide important and original ideas in the field. In the mid-1980s he used cutting edge molecular techniques to identify some of the proteases of the cytotoxic granules, including the protease now known as granzyme B. This was followed by studies demonstrating that granzyme B can act by directly processing and activating caspases in the target cell, leading to apoptosis. More recently, his laboratory has shown that granzyme B can also target the Bcl-2 family protein Bid to activate its proapoptotic function, and that this can dominate the apoptotic pathway. The identification of granzyme B and elucidation of its function in apoptosis are landmark achievements in the field.

More recently, Dr. Bleackley has made another remarkable discovery of major importance. A longstanding paradigm in the field of cytotoxic lymphocyte function was that a protein called perforin formed holes in the target cell membrane, through which the granzyme B passes. Based on observations made in his laboratory, Dr. Bleackley questioned this view and discovered that cells actually have a granzyme B receptor on their surface - which as it turns out is a mannose-6-phosphate receptor - and that this receptor permits entry of the protein via receptor-mediated endocytosis. This seminal observation, which was published in the prestigious journal *Cell*, alters our fundamental understanding of mechanisms of viral and tumor evasion of cytotoxic lymphocytes, and provides new strategies for improving immune therapy against infection and cancer, and consequently has considerable potential for improving human health.

Dr. Bleackley has established an international reputation for his research on the cellular immune system, and is clearly among the most recognizable names over the past ten years in the field of cytotoxic lymphocyte function. He has been well recognized for this research as an Alberta Heritage

Foundation Medical Research Scholar and Scientist, a Howard Hughes Medical Institute International Research Scholar, Fellow of the Royal Society of Canada, a CIHR (MRC) Distinguished Scientist, and a Canada Research Chair in Molecular Biology. This year Dr. Bleackley received the most significant research award at the University of Alberta, the 2004 J. Kaplan Award for Excellence in Research. In this past year, he was awarded Canada's most prestigious cancer research award, the Robert L. Noble Prize of the National Cancer Institute of Canada. In the citation, NCIC Executive Director, Dr. Bob Phillips, indicates "Dr. Bleackley has done a great deal to advance our knowledge of how the immune system can be used in the fight against cancer". Chris has been tremendously productive, and his opinion is widely sought both locally and internationally.

Dr. Bleackley's accomplishments mark him as among the best molecular biologists/ immunologists currently working in Canada. He represents international scientific excellence, leadership in the field, superior achievements, intellectual strength, innovation and commitment, and is highly deserving of the Roche Diagnostics Prize.

Co-Recipient of the 2005 CSBMCB Merck Frosst Prize Dr. Eric Brown

Dr. Brown earned his B.Sc. in physical sciences at the University of Guelph in 1987 and followed this up with M.Sc. studies in the Department of Food Sciences at Guelph under the supervision of Dr. Rickey Yada. This research in fungal proteases laid the foundation for Dr. Brown's interest in microbial enzymes which he went on to pursue under Dr. Janet Wood's supervision, earning his Ph.D. in the Department of Chemistry and Biochemistry at Guelph in 1992 on elegant studies on the redox enzyme PutA from *E. coli*. He then followed this up with postdoctoral studies at Harvard Medical School under the supervision of Prof. Christopher Walsh. His research at Harvard focused on a key enzyme in bacterial cell wall synthesis, MurA, which is the target for the antibiotic

fosfomycin. He was continuously supported in this research with postdoctoral fellowships from both NSERC and MRC.

Dr. Brown's postdoctoral research on the molecular target of the antibiotic fosfomycin inspired him to continue work in the drug discovery vein and he elected to pass up an opportunity to start his own lab in academia to explore opportunities in the private sector - then just in the early stages of the 'Boston Biotech Boom' of the late 1990s. He spent time in both an early stage biotech start up, Myco Pharmaceuticals, and an established pharma research lab, Astra Research Center. His work in the latter milieu was focused on mining the newly sequenced whole genome of the gastrointestinal pathogen *Helicobacter pylori* for new antimicrobial targets. This work both built on his considerable experience in protein chemistry and enzymology and now added genome scale science including genome sequencing and annotation (published in both *Nature* and *Microbiol. Mol. Biol. Rev.*), and high throughput screening. At this point Dr. Brown was enticed to return to Canada, specifically to the Department of Biochemistry at McMaster University, to establish an independent research lab in the areas of antimicrobial physiology and drug discovery.

Since establishing his lab in 1998, Dr. Brown has focused on three major lines of research: 1) the examination of the biochemistry and molecular microbiology of wall teichoic acid biosynthesis in Gram-positive bacteria as novel targets for antibiotics, 2) the investigation of so-called "unknown" essential bacterial proteins, and 3) the application of small molecule screening and chemical genetics to infectious disease targets. Teichoic acids are polyol polymers that are components of the cell walls of all Gram-positive bacteria. Dr. Brown re-



soned that these may therefore be essential to cell viability and that therefore their biosynthesis, like that of peptidoglycan, would be a target for new antibiotics, which are especially needed for Gram-positive pathogens. To study these polymers, Eric and his team established a novel xylose-dependent conditional expression system for the model Gram-positive bacterium *Bacillus subtilis*. Both academic and private sector labs all over the world have since used this elegant approach. Dr. Brown's group has gone on to use this approach, together with some impressive protein chemistry, to single-handedly show that cell wall teichoic acids are bona fide new targets for antibiotics.

Dr. Brown's research on essential proteins of unknown function has been equally visionary. Over one-third of sequenced microbial genomes contain genes encoding proteins whose functions are completely unknown, and a subset of these are essential to cell growth. Using a combination of state-of-the-art bioinformatics, structural biology, steady and pre-steady state kinetics, molecular microbiology and a keen biochemical insight, Dr. Brown has begun to unravel some of these important biochemical mysteries, and as a result has published some of the first descriptions of biochemical functions for these proteins. This line of novel research will continue to bear fruit over the next few years and, combined with his interests in small molecule screening, could form the basis for new antibiotic development.

The third area Dr. Brown has pioneered in Canada is small molecule screening and chemical genetics and their application to antibiotic research. Dr. Brown's experience in the private sector in the mid-1990s convinced him that small molecule screening is a mechanism that provides tremendous opportunities in biochemical research. In particular, application of screening in the emerging area of chemical genetics or genomics, where high throughput screening is combined with newly emerging genome scale platforms to answer questions of biological interest, is especially profitable. As a result of these scientific opportunities, Eric co-founded the McMaster High Throughput Screening Laboratory. He did this not only with a

view to serving his own interests in screening and chemical genetics, but also with a sincere desire to build a scientific platform that could serve the large research community in Ontario and Canada as a whole. As a result, he has been a tireless advocate for Chemical Biology approaches to research in Canada and has collaborated with researchers across the country. A good example of this is his contribution to the SARS outbreak through speedy mobilization of the McMaster High Throughput Screening Laboratory resources to work with colleagues at the University of British Columbia to rapidly screen the SARS protease for small molecule inhibitors published in *Chemistry & Biology* in 2004. At the same time, his own research on screening has resulted in a number of publications and patents. In this area Eric has again ploughed new ground and, like his work on teichoic acids and proteins of unknown function, he is innovating and driving the agenda, not merely incrementally adding to existing fields.

In addition to his remarkable contribution to the Canadian research landscape through his management and founding of the McMaster High Throughput Screening Laboratory, he has also served on a number of important committees including membership on CIHR and NIH review panels, and the scientific advisory boards of several biotechnology companies and other organizations.

In short, Dr. Brown has established an outstanding research program using innovative and original approaches and has contributed very positively to the research community in Canada. He is therefore highly deserving of the recognition of the prestigious Merck Frosst Prize.

Co-Recipient of the 2005 CSMCB Merck Frosst Prize Dr. J. N. Mark Glover

Dr. Mark Glover received an Honours B.Sc. Science degree in Biochemistry and Chemistry, with a minor in Mathematics, from Dalhousie University in 1985. These early choices foreshadowed his ultimate interest in structural biology. From 1985-1991, he carried out graduate studies with Dr. David Pulleyblank in the Department of

Biochemistry at the University of Toronto. As a graduate student, he made clever use of existing techniques to draw astute conclusions on alternate structures of DNA and received the David A. Scott Award for the most outstanding graduate student at the University of Toronto. As a postdoctoral fellow in the laboratory of Dr. Stephen Harrison, one of the world's leading X-ray crystallographers, he immersed himself in a new set of sophisticated techniques in structural biology. In this transformative part of his career, he determined the crystal structures for the c-Fos-c-Jun transcription factor bound to DNA. This seminal paper - among the first structures for a DNA/protein complex - was published in *Nature* and provided details on the interaction of one of the most important cellular transcription factors with DNA.

Since 1996, Dr. Glover has been a faculty member in the Department of Biochemistry, University of Alberta, and has established his laboratory as a world leader in the structural biology of oligonucleotides bound to proteins. In particular, Dr. Glover is one of the few investigators to tackle RNA/protein interactions, a particularly challenging area given the labile nature of RNA. Undeterred, he has recently determined the crystal structure for the FinO bacterial conjugation repressor protein in a complex with RNA and further showed that FinO functions as an RNA chaperone that facilitates sense-antisense RNA interactions. These studies were published in *Nature Structural Biology* and *The EMBO Journal* and highlight a feature of Dr. Glover's research - combining structural information with insights into the biochemistry and biology of the system.

Perhaps Dr. Glover's greatest biomedical impact has been in the area of breast cancer research. He recently determined the crystal structure for a portion of the BRCA1 protein which is by far the major gene mutated in hereditary breast cancer. The crystal structure showed for the first time the way that the C-terminal repeats of BRCA1 interact with other DNA binding proteins involved in DNA repair or transcriptional control. Most importantly, the structure provided a basis for understanding the pathobiology of many BRCA1 mutations.

Dr. Glover has received many prestigious awards throughout his career, including a Medical Research Council (MRC) of Canada Studentship Award, an MRC Postdoctoral Fellowship, a Howard Hughes Postdoctoral Fellowship and Scholar, and Senior Scholar awards from Alberta Heritage Foundation for Medical Research. Most significantly, Mark received an Investigator Award from CIHR in 2002 and was awarded a Tier 2 Canada Research Chair in Structural Molecular Biology.

In addition to his prominence as a researcher, Dr. Glover has engaged himself in other scientific activities that further attest to his scientific standing and contributions to Canadian science. He served as a member of the CIHR New Investigator Grant Panel and is currently a member of the CIHR Biochemistry A Grant Panel. Dr. Glover has also taken a leading role in Canada's protein X-ray crystallographic community by heading the organizing committee for the third annual "Frontiers in Structural Biology" meeting recently held at the Banff Centre.

Dr. Glover has clearly established himself as a leading authority on the structural biology of oligonucleotide/protein interactions and is a most deserving recipient of the Merck Frosst Prize.

