Bulletin

The Canadian Society of Biochemistry, Molecular & Cellular Biology /
La Société canadienne de biochemie, de biologie moléculaire et cellulaire

2004

www.csbmcb.ca

FRONT COVER IMAGE: Supplied by Dr. Richard Wozniak, University of Alberta

Contents

CSBMCB Board for 2004-2005

PRESIDENT
Dr. Joseph R. Casey
Department of Physiology
University of Alberta
Edmonton, Alberta, T6G 2H7
Tel: (780) 492-7203
FAX: (780) 492-8915
E-mail: joe.casey@ualberta.ca

PAST-PRESIDENT
Dr. John Orlowski
Department of Physiology
McGill University
3655 Promenade Sir-William-Osler,
Room 1112
Montreal, Quebec H3G 1Y6
Tel: (514) 398-8335
FAX: (514) 398-7452
E-mail: john.orlowski@mcgill.ca

VICE-PRESIDENT
Dr. David Y. Thomas
Department of Biochemistry
McGill University
3655 Promenade Sir-William-Osler
Montreal, Quebec, H3G 1Y6
Tel: (514) 398-2973
FAX: (514) 398-7384
E-mail: david.thomas@mcgill.ca

TREASURER
Dr. Vincent Duronio
Department of Medicine, UBC
Jack Bell Research Centre
2660 Oak St
Vancouver, British Columbia
Tel: (604) 875-4707
FAX: (604) 875-4497
E-mail: vduronio@interchange.ubc.ca

SECRETARY
Dr. Albert F. Clark
Department of Biochemistry
Queen's University
Kingston, Ontario K7L 3N6
Tel: (613) 533-2975
FAX: (613) 533-2022
E-mail: clarkaf@post.queensu.ca

COUNCILLOR
Dr. Caren Helbing
Department of Biochemistry
and Microbiology
University of Victoria
Victoria, British Columbia V8W 3P6
Tel: Office (250) 721-6146
Tel: Lab: (250) 721-7086
FAX: (250) 721-8855
E-mail: chelbing@uvic.ca

COUNCILLOR
Dr. Linda Penn
Ontario Cancer Institute
610 University Avenue
Toronto, Ontario M5G 2M9
Tel: (416) 946-2276
FAX: (416) 946-2840
E-mail: lpenn@uhnres.utoronto.ca

COUNCILLOR
Dr. George Chaconas
Biochemistry and
Molecular Biology
The University of Calgary
3330 University Drive, NW
Calgary, Alberta T2N 4N1
Tel: (403) 210-9692
FAX: (403) 270-2772
E-mail: chaconas@ucalgary.ca

COUNCILLOR
Dr. Guy Poirier
Health and Environment Unit
CHUL Research Centre
2705 Boul. Laurier
Ste-Foy, Quebec G1V 4G2
Tel: (418) 654-2267
FAX: (418) 654-2159
E-mail guy.poirier@crchul.ulaval.ca

COUNCILLOR
Dr. Frances Sharom
Department of Microbiology
University of Guelph
Guelph, Ontario N1G 2W1
Tel: (519) 824-4120 Ext. 52247
FAX: (519) 837-1802
E-mail: fsharom@uoguelph.ca

COUNCILLOR
Dr. Dev Mangroo
Department of Microbiology
University of Guelph
Guelph, Ontario N1G 2W1
Tel: (519) 824-4120 x53432
FAX: (519) 837-1802
E-mail: dmangroo@uoguelph.ca

COUNCILLOR
Dr. Eric Brown
Department of Biochemistry
McMaster University
Health Sciences Centre,
Room 4h2
1200 Main St. W.
Hamilton, Ontario L8N 3Z5
Tel: (905) 525-9140 ext: 22392
FAX: (905) 522-9033
E-mail: ebrown@mcmaster.ca

CHAIR, NOMINATING COMMITTEE
Dr. John Orlowski

BULLETIN EDITOR
Dr. Frances Sharom

CFBS HEAD OFFICE
Mrs. Wafaa Antonius
Office Manager, CFBS
305- 1750 Courtwood Crescent
Ottawa, Ontario K2C 2B5
Tel: (613) 225-8889
FAX: (613) 225-9621
E-mail:wantonious@CFBS.org

CSBMCB President's Report

Dr. Joe Casey

Foreword

Why do we need CSBMCB? At our meeting I posed this question to the CSBMCB board. As a group we were highly biased to think positively about CSBMCB, but our answers to this simple question were still informative. We need CSBMCB to: 1. Act as the professional society for a large group of Canada's researchers, 2. Provide a strong voice, advocating the needs of these scientists to the government, 3. Organize scientific meetings, placing Canadian researchers on stage with the world's best, 4. Recognize excellence in Canadian biochemists, molecular biologists and cell biologists through significant achievement awards. From this discussion it was clear that we are doing a good job on some of these areas, and need to improve in others. We have ideas and enthusiasm to further improve CSBMCB in the coming year. We hope that you agree that there is a real need for CSBMCB. Please tell your colleagues about CSBMCB and encourage them to join!

Upcoming CSBMCB Meetings

2005- Meeting organizers Rick Wozniak (University of Alberta) and Rick Rachubinski (University of Alberta) have put together an amazing group of speakers for the upcoming 48th Annual CSBMCB Meeting, "Cellular Dynamics" (March 16-20). The meeting opens with Nobel Prize winner, Dr. Günter Blobel and continues with world leaders speaking on the topics of Organelles of the secretory pathway, Imaging Technologies, Organelle Inheritance, Protein Folding, Nuclear structure, mRNA localization and Systems approaches to Cell Biology. More information, including registration, is available at: http://www.csbmcb.ca/. Did we mention that the meeting is at the Banff Centre (Banff Alberta, one hour from Calgary), in the middle of one of the world's most beautiful areas, during spring ski season (afternoons are scheduled open during the meeting)?

2006- Planning for the 49th Annual meeting is well under way. A committee headed by Reinhart Reithmeier (University of Toronto) is organizing the meeting "Membrane Proteins in Health and Disease" at Niagara-on-the-Lake, Ontario, from May 31- June 4, 2006.

2007- The 50th Anniversary meeting for CSBMCB will be something special! David Thomas (McGill) and Eric Brown (McMaster) head the organizing committee for this meeting on "Systems Biology," which will be held in summer 2007 in Québec.

CSBMCB Awards

One of the most important roles of CSBMCB is to recognize excellence in Canada's biochemists, molecular biologists and cell biologists. In 2004 we awarded the Merck-Frosst Award for meritorious research by a scientist in the first 10 years as an independent scientist to Rick Wozniak of the Department of Cell Biology, University of Alberta. Rick's work on nuclear pores has been published in the top journals and has made a major impact on the field. Morag Park of the Department of Biochemistry, McGill University received the Jeanne Manery Fisher Memorial Award for scientific achievements by an eminent woman scientist. Both award recipients presented fascinating talks at the 2004 CSBMCB Meeting at Mt. Tremblant. You can read more about the research of Drs Wozniak and Park later in this issue of the Bulletin.

Advocacy Survey

This year we decided to find out what your opinion was about science policy, and you told us!

CSBMCB Vice-President, David Thomas (McGill) has summarized the results in an article in this issue of the Bulletin. The results show that many of you are passionate about science policy and support the CSBMCB in an invigorated approach to advocacy for our member's research interests. The message to us was clear: continue to push the interests of CSBMCB with members of the federal government, but also have a greater dialogue with the granting councils. Please continue to give us your opinions so that we can truly act as the voice for CSBMCB members!

Science Policy and Advocacy

One of the key roles of CSBMCB is to keep government officials aware of the needs of biochemists, molecular biologists and cell biologists. Our ongoing efforts in this direction include our support of the Canadian Federation of Biological Societies (CFBS). Part of your CSBMCB membership supports the advocacy efforts of CFBS. Bruce Sells, executive director of the Canadian Federation of Biological Societies, has developed excellent contacts with Parliamentarians. Through working with Bruce we have affected CFBS policy and gained access to Parliamentarians for discussions. Clearly the major issue confronting CSBMCB members is sustained, or increased operating budgets and we continue to press this point in all of our meetings with the government. The good news is that advocacy efforts work. Parliamentarians and senior government officials know about the importance of our research, but still need continued polite pressure.

Over the last year we have taken on two new initiatives in our advocacy efforts. First, we helped to sponsor the "Leader's Forum for Health Research in Canada" (see report at http://www.cfbs.org/newsletterLeadersFrm.html). The goal of the event was to bring together a wide range of Canadians working in health research, to try to drive a common view and thereby increase research support. We are hopeful that from the Leader's Forum will come more effective advocacy for our research activities. Second, we have begun to develop interactions with the Council for Health Research in Canada (CHRC). CHRC has emerged as an effective group advocating on behalf of health researchers. Since their interests are very much aligned with ours we have begun to work with them, with the hope of affecting their policy to the benefit of CSBMCB members. Working with CHRC we hope to amplify our advocacy efforts.

Each CSBMCB member can help in our advocacy work. Like everyone else, our Parliamentarians need encouragement when they do the right thing! If you receive a new operating grant from a Government agency, write a letter of thanks to your MP, the minister responsible and the Prime Minister. Letters to Parliament can be sent without postage. You can find the address for your Member of Parliament at http://www.parl.gc.ca/. It is also very effective to invite your MP to visit your laboratory. Many know little about our research and showing them what we do can be a real eye-opener for them. One last piece of advice when contacting MPs is to stay positive. We all know that there are frustrating aspects to science funding in Canada, but the most effective strategy is to stay positive, to encourage our government to do the right thing: stabilize and increase research support.

Membership

CSBMCB needs a strong membership base in order to thrive. Annual membership fees provide the operating budget for the society. Of equal importance is to have a large numerical base of support. When we lobby politicians on policy they want to know how many scientists we represent. How valid is our voice? With a strong membership base we can advocate strongly for Canadian biochemists, molecular biologists and cell biologists. CSBMCB councillor Linda Penn (Toronto) has done a terrific job to build our membership through several initiatives. Among these, Linda has found CSBMCB representatives at departments at Universities across the country. Thank you to each of you who have agreed to take on this task! Thanks go also to each CSBMCB member for the continued support of CSBMCB and its activities.

Communications

You hold in your hands the Bulletin, one of our most important tools to communicate with the

CSBMCB membership. We thank CSBMCB Councillor, Frances Sharom (Guelph), for putting the Bulletin together. We also thank CSBMCB Departmental representatives for supplying the departmental news reports!

The CSBMCB Link is now one year old. The link is published three times per year and serves as a more regular way to communicate with the CSBMCB. The link contains articles about the science successes of CSBMCB members and reports on science advocacy efforts of the CSBMCB. We thank founding Editor, Caren Helbing (Victoria), for her great work on The Link. John Orlowski (McGill) will take over as Editor. You can send John articles at john.orlowski@mcgill.ca.

Thank you(s)

CSBMCB is an active organization with a surprising amount going on behind the scenes. Keeping CSBMCB running requires the efforts of many people, some of whom I would like to thank here. CSBMCB has contracted CFBS to take care of some of our administrative needs. Wafaa Antonious, CFBS Manager, Administration and Planning, has been tireless in her efforts to keep us on track from our emailings, to our website and financial affairs. Laila Riad, CFBS Administrative Assistant, has also worked with Wafaa on our behalf. Kim Bournat of the Department of Physiology, University of Alberta, has been very helpful with secretarial assistance, in particular with the advocacy policy survey.

The annual meetings of CSBMCB occur because of the hard work of many people. The 2004 CSBMCB meeting was organized by Terry Hebert (Université de Montréal). Terry put together an outstanding program on "Cell Signaling" From the Membrane to the Nucleus", which was held at Mt. Tremblant Québec.

In most organizations, and CSBMCB is no exception, it is actually the Secretary and Treasurer who do most of the work. This has been particularly true over the last year for our Secretary Albert Clark (Queen's) and Treasurer, Vince Duronio (UBC). Vince and Albert have done a terrific job, working with dedication as we all have scrambled to figure out how to function after our long-time Treasurer (Fred Palmer) and Secretary (Gene Tustanoff) retired earlier this year.

Each of the members of the CSBMCB board (see who they are on the previous page) is an active researcher, who has given up their time to attend our board meetings, to help to run CSBMCB so that the Society can function. This year Eric Brown (McMaster), Frances Sharom (Guelph) and Dev Mangroo (Guelph) have infused the board with enthusiasm as new CSBMCB Councillors. David Thomas, Chair of Biochemistry at McGill, has stepped up to act as CSBMCB Vice-President and will be President next year. Caren Helbing (Victoria) and Bruce Waygood (Saskatchewan) have completed their terms as Society Councillors, with thanks for their contributions! David Andrews has completed his three years as Vice-President, President and Past-President of CSBMCB. David put tremendous energy and creativity into his time on the CSBMCB executive and set a great example for those of us following him.

Future Outlook

The future looks bright. The current CSBMCB board is energized and full of ideas. The challenge is to convince the government to continue to increase research funding. However, lobbying efforts are paying off. From discussions with the government it is clear they have heard our message. Increasing CSBMCB membership gives us more clout when we lobby. The recent advocacy survey was a shot in the arm; many CSBMCB members feel strongly about policy issues, and thankfully, for the most part our views seem to represent the survey responses. Please keep us relevant by giving us your opinions on science policy issues! CSBMCB annual meetings continue to be a source of pride. These meetings have attracted considerable positive feedback for their combination of cutting-edge science in enjoyable places. We are certain that the upcoming scheduled meetings will continue to be outstanding. It has been a pleasure to be involved in honouring Canada's amazing scientists with CSBMCB awards.

Finally, thank you to CSBMCB members, whose financial and moral support make the Society viable!

Incoming Members of the CSBMCB Executive Board 2004-2005

Dr. David Y. Thomas, Vice-President

I was born and grew up in Llandaff, a small town outside Cardiff in Wales. While at high school I had vague notions of becoming a lawyer or a nuclear physicist. But it was not until I encountered a course on genetics and molecular biology that I became hooked on science and research. I did my Ph.D. in genetics with David Wilkie at University College London, still a leading institution in biological sciences research. My first week as a Ph.D. student at UCL is memorable. My supervisor David Wilkie left for a year's sabbatical and I attended a series of lectures on the derivation of the triplet code by Francis Crick during which he announced the "swan song of molecular genetics". This was truly being thrown into research at the deep end. Thanks to the fantastic research environment of UCL and the help of David Wilkie's supervisor, the eminent Guido Pontecorvo, who had moved to ICRF at Lincoln's Inn Fields, and a lot of naivety on my part, I managed to find an interesting and productive research topic. There had been reports of antibacterial antibiotics such as chloramphenicol, erythromycin and some aminoglycoside antibiotics inhibiting various yeast strains. I was able to show that the target of these drugs was in fact mitochondria, and also to show the targets were encoded by mitochondrial DNA. Then I was able to demonstrate recombination between mitochondrial DNA molecules and then follow the inheritance of mitochondria. Mitochondrial genetics has now become a subject in its own right. I also had the opportunity whilst a graduate student, thanks to the kindness of David Wilkie, to work in Nigeria at the University of Ile-Ife, for many reasons a very interesting experience in life. In fact the manuscript that described the recombination of mitochondrial DNA was typed on an IBM Selectric in a hotel room in Lagos and submitted to BBRC, as this was the only journal for which I could find an address in those days before the Internet.

I was offered a number of post-doctoral opportunities to work in Europe and the US but I received an offer from Peter Medawar to work in the Microbiology Division at the National Institute for Medical Research at Mill Hill. Sir Peter Medawar was one of the intellectual giants of biology research and ran an institute of 600 people, but still found time to do bench work and to discuss other people's research, and also to read and make constructive criticism on every manuscript that left Mill Hill. There was a lot of interest in mitochondria at Mill Hill. Margaret Ashwell, Terry Rabbits and Tommy Work were struggling to isolate mitochondrial ribosomes and finally accomplished this difficult feat. I continued to work on mitochondrial protein synthesis, and showed for the first time with Don Williamson that the products of mitochondrial were components of the cytochrome oxidase and ATPase complexes. During this time Ben Hall visited Mill Hill from the renowned Department of Genetics, University of Washington, and invited me to spend some time in his lab. He and Mike Smith at UBC had an application to NIH (eventually not funded as being "too ambitious") to clone the gene for isocytochrome c1. So I spent 1972-73 on leave from the MRC isolating mRNA, making antibodies and doing in vitro protein synthesis, while Jerry McDonnell produced polyA polymerase and Maxine Linial made AMV reverse transcriptase and EcoRI restriction enzyme that Herb Boyer personally delivered. We waited for Cor Hollenberg in Mike's lab at UBC to synthesize a 9-mer oligonucleotide. I made many visits to the UBC lab and spent many wet weekends distilling reagents and

running incredibly slow cellulose columns. Unfortunately we were unable to synthesize the required oligonucleotide, and the cloning of the iso-cytochrome I gene was accomplished a few years later by Donna Montgomery in Ben's lab, by Jack Szostak in Ray Wu's lab, and in Fred Sherman's lab (the latter with an oligonucleotide synthesized by a Canadian company, ENS Biologicals of Ottawa). I learnt a lot from my experience in the superb Genetics Department in Seattle and it made me ambitious to try new directions in research.

I returned to Mill Hill, which now had a new director Arnold Burgen, who just had arrived from McGill. I was full of enthusiasm to do recombinant DNA work, but the Asilomar inspired moratorium was in effect and the Rothschild Report was causing the MRC severe problems. I received an attractive offer from the Institut fur Genetik at the University of Munich, which was a centre of mitochondrial research, and spend two very enjoyable years finishing some work on mitochondria. Then I was offered a job at the NRC in Ottawa in the Biological Sciences Division, which I had visited a couple of years before. So, I joined several of my relatives in the Welsh diaspora and moved to Canada. NRC was an interesting new experience, since there was access to oligonucleotide synthesis in Saran Narang's laboratory and I was able to start some new research directions. In one of these I collaborated with David Baulcombe in Desh Verma's lab at McGill to clone the first plant gene, in this case for leghaemaglobin. At the NRC I became involved in a series of applied projects with companies, but I developed a basic research interest in protein folding and processing. We found Ottawa a very pleasant town to bring up a family, and three of our children were born at the Riverside Hospital. But I was thinking about moving from the NRC and Ottawa when Lou Visentin persuaded me to stay at the NRC "for a couple of years" and to move to the, as yet unconstructed NRC Biotechnology Research Institute in Montreal. My wife is from Montreal and so we moved in with four young children in the summer of 1984 and I spent the first couple of years in laboratories at the Royal Victoria Hospital, and then moved to the new institute at Avenue Royalmount when it was completed.

The concept of biotechnology was new, and in those days the ideas of where it would have the greatest impact in Canada were, in retrospect, misplaced. But I was fortunate to be able to build a group of productive and superb colleagues, and we were able to make significant contributions in the areas of G protein coupled receptors, MAP kinase signaling, innate immunity, protein processing and glycoprotein folding. Thus I stayed at the NRC rather longer than I had intended, but eventually in 2001 I moved as a Canada Research Chair and Chair of the Biochemistry Department to McGill. Before I made this move, McGill had agreed to the construction of a new multidisciplinary, multifacility, research building (now known as the Bellini Life Sciences Building, it joins the Stewart Biology Building and McIntyre Medical Sciences Buildings). We were able to obtain significant CFI and FRSQ and private support for this new building, which is scheduled for completion in July 2007. The Biochemistry Department and McGill are proving to be a stimulating and challenging environment that I am enjoying immensely.

Science is an exciting enterprise, and while I look forward to new ideas and new experiments, I think my most important contribution has been the 150 plus students, post-docs and technicians that have been in my various laboratories. It is a continuing pleasure to see their careers develop. Of course, superb mentors and collaborators have also been the key to my success and I should mention David Wilkie, Don Williamson, Sir Peter Medawar, Ben Hall, Mike Smith, Allen James, Rudolf Schweyen, as past mentors and Howard Bussey, Malcolm Whiteway, Thierry Vernet, John Bergeron and Ekkehard Leberer as ongoing collaborators. I am now interested in promoting the interface between chemistry and biology, and the impact that academia can make in research on orphan and neglected diseases, and I look forward to new experiments and new collaborators.

Science in Canada is at present enjoying good levels of support from all levels of government. However, the CSBMCB and all of us must commu-

nicate with decision makers at all levels about the successes and benefits of our research. The biopharmaceutical industry (I am on the SAB of several pharmaceutical and venture capital companies) is going through a bad patch right now, and I believe that we must sustain our research enterprise and excellence through new models of funding. The arguments for basic research that underpin our future prosperity need to be stated and restated in an understandable fashion to as wide an audience as possible.

Dr. Eric Brown, Councillor

I grew up in rural southern Ontario and attended high school in Dundas, a little town West of Hamilton that lays claim to an international 'cactus festival.' Guelph became my second home after high school – I spent 10 years there completing my undergraduate and graduate degrees. The latter began with a Masters in the Food Science department with Dr. Rickey Yada where I discovered my passion for protein biochemistry studying the stability fungal aspartic proteases on the pretext that they were key ingredients in cheese-making. It was, nevertheless, as a Ph.D. candidate in Biochemistry at Guelph that my future was cemented in molecular approaches to understanding the puzzles of bacterial physiology in the laboratory of Dr. Janet Wood. There I studied the PutA protein, a fascinating flavoprotein that binds to and represses its own operon in addition to interacting with the cell membrane where it catalyzes the oxidation of proline.

After receiving my Ph.D. in 1992, I accepted a postdoctoral fellowship to train with Dr. Christopher Walsh in the department of Biochemistry and Molecular Pharmacology at Harvard Medical School where I worked to describe the mechanisms of enzymes in bacterial cell wall biosynthesis. There I learned a great deal about pre-steady state kinetics, characterizing enzyme intermediates and enzyme inhibitor complexes. During the same period I embarked on studies of the dispensability of cell wall biosynthesis genes in E. coli, a collaboration that placed me in the laboratory of Dr. Roberto Kolter in the Department of Microbiology and Molecular Genetics at Harvard Medical School. After postdoctoral studies, I decided to stay in the Boston area and work in the biotechnology sector where I spent more than three years, principally at Astra Research Center Boston, using enzymology and molecular genetic approaches to develop drugs against the gastric pathogen Helicobacter pylori. While in Boston I became a huge admirer of the city and was an enthusiastic sampler of New England attractions, especially its pro sports venues, golfing and Irish pubs.

After six years in Boston, I elected to return to Canada to develop an independent research program and took up a position in Department of Biochemistry at McMaster in July of 1998, first as a CIHR Scholar and now as a Canada Research Chair. Perhaps indelibly marked by my time in pharma, my group has adopted the motto 'the only good bacterium is a dead bacterium.' We have concentrated to date on addressing the inadequacies of conventional antibiotics with research into new approaches to the discovery of antibacterial drugs. Those directions have included careful analyses of the phenotype associated with loss of novel and essential functions to help us understand their importance to bacterial physiology. We have likewise occupied ourselves with rigorous biochemical studies of key proteins in an effort to learn more about their roles in physiology and to facilitate their exploitation in antibacterial drug discovery. Most recently, we have been developing chemical genomic approaches where, with the benefit of state of the art small molecule screening, we are working toward building a chemical-genetic interaction network for the essential physiology in bacteria. Since returning to the Hamilton area, it's been a great to spend time again with family and old friends. I attribute any perspective I have to my wife Zuhal and seven year old Jacob, not to mention my very average skills in golf and ice hockey.

Dr. George Chaonas, Councillor

George Chaconas was born in 1952. He began his career as a biochemist in 1953 by conducting experimental taste tests on a box of Borax discovered under the kitchen sink. Thereafter, smitten by the thrill of research, curious George set his sights on a career as a scientist. He completed his undergraduate training in Biological Sciences at Queens College of the City University of New York in 1973. His last year of undergraduate study was spent at the University of Southern California in Los Angeles where he took several courses and worked in the laboratory of Dr. Caleb Finch on the biochemistry of ageing. It was during this time that his fascination with nucleic acids and gene expression was kindled. George went on to pursue graduate studies in this area in the Division of Medical Biochemistry at the University of Calgary under the supervision of Drs. R.B. Church and J.H. van de Sande. During his tenure as a graduate student his interests grew in the area of nucleic acid structure and protein-DNA interactions. George's thesis work involved studies on T4 polynucleotide kinase and the interaction between restriction endonuclease HhaI and its recognition site.

During his graduate training in Calgary, George became interested in the process of DNA transposition and moveable genetic elements. Thereafter he spent more than 25 years studying Mu DNA transposition, which began with a postdoc at Cold Spring Harbor Laboratory from 1978-1981with the late Dr. Ahmad Bukhari. In 1981 George returned to Canada to take up a position as an Assistant Professor at the University of Western Ontario where he remained for 21 years.

In 1999-2000, with the help of a Guggenheim Fellowship, George spent a sabbatical year in the lab of Dr. Patricia Rosa at the NIH Rocky Mountain Labs in Hamilton Montana. He became fascinated with the exotic pathogen, Borrelia burgdorferi, which causes Lyme disease and has a segmented genome with many linear replicons carrying covalently closed hairpin ends. The mechanism by which these molecules replicate was unknown and has become the focus of George's recent research. In 2002 George moved his lab to the University of Calgary where the mountains, ski hills and trout streams are within easy reach. He is currently appointed as a Canada Research Chair in the Molecular Biology of Lyme Disease and as a Scientist of the Alberta Heritage Foundation for Medical Research.

When time permits George likes to pretend that he is working in the lab. His precocious entry into the field of biochemistry in 1953 surprisingly didn't leave a bad taste in his mouth; whenever possible he designs his experiments using borate buffers (which for some strange reason he insists on mouth pipetting).

On a more personal note, George enjoys family life with his wife Genevieve and their two grown daughters, Christina (and husband Simon) and Aletheia. He is an active church member and plays renaissance lute with the Early Music Ensemble at the University of Calgary.

Dr. Dev Mangroo, Councillor

Dev Mangroo was born in Guyana, South America, and was raised in Toronto, Canada. He did both his B.Sc. and Ph.D. in the Department of Biochemistry at McMaster University. Dr. Mangroo's Ph.D. supervisor was Dr. G. E. Gerber, and his research was on the mechanism of long chain fatty acid permeation of the cell membrane of Escherichia coli. After his Ph.D. he was awarded an NSERC postdoctoral fellowship to work with Dr. U.L. RajBhandary at the Massachusetts Institute of Technology, Cambridge,

Massachusetts, on bacterial protein initiation. Dr. Mangroo is presently in the Department of Molecular and Cellular Biology at the University of Guelph, and the primary focus of his research is on identification and characterization of components of the nuclear tRNA export machinery of *Saccharomyces cerevisiae*.

Minutes of the 47th Canadian Society of Biochemistry, Molecular and Cellular Biology Annual General Meeting

Fairmont Hotel, Mont Tremblant, Quebec
Saturday, May 29, 2004, 5:30 pm

Chair: Dr. John Orlowski, President, CSBMCB

751. Approval of Agenda

The agenda was approved as circulated on a motion from Dr. Andrews which was seconded by Dr. Tustanoff.

752. Approval of Minutes of the 45th AGM

Three corrections were noted. The word "only" was removed from line 2, paragraph 3 on page 3; "notice" was added after "short" on line 2, paragraph 4, page 3; "She" was replaced by "Dr. Andrews" on line 2, paragraph 3 on page 4 (paragraph on Membership Recruitment Strategies).

753. Business Arising from the Minutes

It was noted that any business arising from the minutes of the last AGM would be discussed under other agenda items.

754. President's Report

1.CSBMCB/HUPO/IUBMB 2003 Congress Update

One of the outstanding issues following last year's CSBMCB Annual General Meeting held jointly with the HUPO/IUBMB Congress in Montreal (Oct. 8-11, 2003) was the Society's obligation to repay the National Research Council (NRC) Conference Services the $25,000 that they lent the Society in 2000 to cover the Society's contribution to the Toronto Congress. It was hoped initially that the Society would recoup this seed money from the profits generated from the Toronto IUBMB Congress. However, following the cancellation of the Toronto congress because of the SARS outbreak and the large financial losses incurred by NRC, the NRC initially refused to transfer the $25,000 that the Society originally subscripted to the IUBMB Toronto Congress to the HUPO/IUBMB organization in Montreal. In essence, the NRC wanted CSBMCB to repay the $25,000 loan as a way of recovering some of their losses, while at the same time the HUPO/IUBMB organization was still expecting CSBMCB to contribute $25,000 to the resuscitated Montreal Congress. This saddled the Society with an inequitable financial liability of $50,000. However, after extensive negotiations between NRC and the Society (thanks to the considerable efforts of Past-President David Andrews), this matter has been satisfactorily resolved in favour of the Society. NRC has agreed to transfer the $25,000 commitment to HUPO. While the exact profits generated from the HUPO/IUBMB Congress have yet to be resolved, initial estimates project a recovery of ~80% of our original contribution (i.e., a $5000 loss).

2. 47th AGM 2004 (Mont Tremblant, QC)

The enrolment for the 47th AGM has been very positive, with approximately 120 registrants. Several commercial booths were also sold. The scientific program consists of 27 speakers from across Canada, the United States and Europe, and 47 poster presentations.

Dr. Terry Hébert did an excellent job in organizing the program and in raising approximately $65,000 from corporate and government sponsors; $18,000

of which was available for student and postdoctoral travel awards. There were 23 students/postdocs who were eligible to receive an award, allowing the Society to raise the stipend for "local" individuals from $375 to $600, and for "distant" individuals from $750 to $1200. In addition, awards for best posters by graduate students were presented: 3 were sponsored by Roche Diagnostics and 2 were sponsored by CSBMCB ($250 each).

Copies of the LINK Issue 2 were handed out as well as registration forms for new memberships. It is important to promote the Society, especially during the times of the poster sessions, and to this end members of the Society's Executive encouraged and cajoled students/postdocs and independent investigators to become members and get involved.

Dr. Orlowski also reminded everyone that Dr. Andrews was able to convince MBI Fermentas to underwrite the cost of a T-shirt Society promotion campaign. MBI Fermentas supplied 300 T shirts which have a Society design emblazed on the front side of the shirt with Fermentas' logo on the back. Half of these were given to registered members present at the 2003 CSBMCB/HUPO/IUBMB Meeting, with the remainder distributed at the 2004 Mount Tremblant meeting.

During the final Banquet, presentations were made to Dr. Terry Hebert for his exceptional efforts in organizing the Mont Tremblant meeting. A gift and a plaque were presented to Dr. Tustanoff who retired as Secretary after 12 years of diligent service to the Society, and Dr. David Andrews who served as Vice-President, President and Past-President. Finally, a plaque was presented to Bruce Waygood who retired after serving 3 years as a councillor.

3. 48th AGM (2005 Banff)

Dr. Richard Wozniak (Department of Cell Biology, University of Alberta) will be serving as Chair of the organizing committee for the Society's 2005 annual scientific meeting in Banff, Alberta and has prepared a preliminary program. The meeting is entitled "Cellular Dynamics" and will be held at the Banff Conference Centre (Alberta) between March 16-20th. The scientific programme is completed with gender balanced speakers from Europe, United States and Canada. Efforts have been made to have representative speakers from the biotechnology industry on the programme to discuss the latest in scientific hardware and applications. The meeting will open Wednesday evening with a keynote address given by Nobel Laureate Dr. Gunter Blobel.

There will be seven sessions on: (1) Nuclear Structure; (2) Organelle Inheritance; (3) Imaging Technologies; (4) Protein Folding; (5) mRNA localization; (6) Organelles of the Secretory Pathway; (7) Systems Approaches to Cell Biology. To date, approximately 30 speakers have confirmed their attendance, with 5 pending.

The cost for single occupancy plus meals for 3 full days is $608 plus registration charges: $420 for members, $500 for non-members and $350 for students and postdoctoral fellows.

The maximum number of attendees will be limited to 225.

Dr. Wozniak has presented a preliminary budget with the Society contributing $5,000 in seed money. To date, $5000 has been collected from the University of Alberta Faculty of Medicine and Dentistry. Some letters have already been sent to potential corporate sponsors, with more to be sent shortly.

There will also be space for commercial booths at the meeting for which Dr. Wozniak suggested there would be a $2,000 charge.

Posters will be prepared both in English and in French to advertise the meeting and these will be sent to all university and institutional departments of biochemistry, molecular biology, genetics and cell biology in Canada. In addition, registration forms, the preliminary scientific programme and meeting information will be prepared and sent to Mrs. Antonious at the CFBS office for posting on the Society's web page.

Negotiations were underway with the Canadian Genetic Society to "piggy back" our meeting with theirs so that there will be one day overlap between both meetings. For that day, a common

session will be planned to the mutual interest of both Societies.

Dr. Orlowski reported that the CFBS initiative to act as sponsors and meeting coordinators for various scientific organizations such as CSBMCB under the umbrella called "Northern Lights Conferences" seems to have drifted from its original intent. It now seems that the CFBS will simply be running their Annual Meeting under the title of "Northern Lights".

4. 49th AGM (2006)

To be held in Ontario. Topics are being solicited.

5. Joint Meetings with other Societies

On behalf of the Society, Dr. Mike Walsh (U. Calgary) is spearheading an effort to explore the possibility of having joint meetings with the British Biochemical Society.

6. Communication

Web Site: A significant effort has gone into increasing our visibility with our membership and the broader scientific community in Canada. At the forefront of this change was a major overhaul in the maintenance and management of the CSBMCB Web site. In the past, the Web site was managed largely in-house; however the upkeep of the site suffered due to the annual turnover of Board members responsible for this task. To create some stability, we have now taken advantage of new contractual services offered by CFBS (Ms. Wafaa Antonious) to maintain our Web site and perform book keeping services for the Society. The services include an Email List Server so that we can rapidly communicate with our membership, and the invoicing and processing of membership applications over the internet using a secure server. This new arrangement will also facilitate the management of registrations for our Annual Meetings. Our Web site contains notices of upcoming meetings and special events, as well as a poster board for employment opportunities! Ms. Antonious has also been extremely helpful in assisting our Treasurer Dr. Duronio in arranging a thorough audit of our finances with a registered chartered accountant. So far the service provided has been very satisfactory and the Board has agreed to continue with this arrangement. It was also decided to extend the lobbying contract with CFBS for another year.

The Link: Another initiative was the first publication of our Society's bilingual newsletter The Link which appeared in October (Issue1) and the second issue being released in time for this meeting. In order to keep the impetus rolling behind "the Link", Dr. Orlowski asked the Board and Society members to pitch in behind Caren and either submit or encourage articles for publication. Articles for the next Link should be submitted by June 30th. This is intended as a community newsletter, so your valued input regarding the content is most welcome! I encourage you to send in short news & views articles regarding research accomplishments of your colleagues, upcoming conferences of interest, or opinion pieces on science advocacy and policy in Canada. The plan is to publish on a quarterly basis. Accolades go to Dr. David Andrews who spearheaded this project from concept to design, and Dr. Caren Helbing who did a marvelous job of editing and producing the first issue (send articles to Caren at: chelbing@uvic.ca).

7. Membership Recruitment Strategies:

Dr. Penn has been very active in setting up and implementing new strategies in membership recruitment. The plan is to setup a series of regional CSBMCB volunteers from across the country to serve as representatives of the Society in terms of recruiting new members and distributing hard-copy materials sent out by the Society.

8. The CSBMCB Board

It was with some sadness and trepidation that we bid farewell to a long-standing Board member Dr. Eugene Tustanoff who has served diligently as Secretary for the past 12 years. Dr. Tustanoff has been an adept manager and an invaluable source of information about Society's affairs, and will be a hard act to follow. Also stepping down after 3 years of valued contributions is Dr. David Andrews, who served as Vice-President/President/Past-President, and Councillor Dr. Bruce Waygood. Thankfully, we have been able to recruit enthusiastic individuals to fill the void. Dr. Albert

Clark (Queen's U.) is joining us as Secretary and Dr. David Thomas (U. Alberta) was elected as Vice-President. Joe Casey will be assuming the position of President commencing July 1st. Also joining us as councillors are Dev Mangroo (U. Guelph) and Eric Brown (McMaster U.)

9. Advocacy and Lobbying

Lobbying the federal government for increased and stable funding is an ongoing priority of CSBMCB. While in past years we have been successful in accessing the decision makers in Ottawa, our efforts this year were stymied by the upheaval on the Hill as few politicians were in a listening mood while the Liberal leadership game was afoot followed by federal elections. After these events are resolved, we intend to pick up where we left off. The upcoming election will certainly be a good time to bring our issues to the forefront of the political debate. We are continuing to voice our concerns in a unified manner through our association with CFBS and through a new CFBS initiative called the **Leaders' Forum.**

During the past 4 months, Dr. Bruce Sells, CFBS Executive Director, has been part of the steering committee and the smaller working group charged with the responsibility of organizing the Forum. The purpose of the Leaders' Forum is to initiate dialogue that will lead to development of a comprehensive and integrated vision for health research in Canada. This vision will assist leaders in the health research community to identify a common direction for advocacy efforts and at the same time demonstrate whether or not we have the capacities, (e.g. Infrastructure, human capital), to achieve our vision. The Forum will also provide an opportunity to develop messages and advocacy strategies that are consistent with the evolving strategy and can be used immediately with the new federal government. It will also assist health research leaders in identifying common messages and strategies.

The Leaders' forum will also provide to the Government advice about the importance that the health community places on working collaboratively to develop solutions to the most pressing issues affecting the advancement of the national health research effort.

At the moment efforts are being made to (1) Establish the list of invitees from across Canada (2) identify a consultant to write a brief summarizing where we are currently and possible partnerships that are missing and (3) establishing a Program Framework. The forum is scheduled to take place in Ottawa for late September. It is expected that there will be a 100 invited participant from the research community."

To facilitate the formation of this initiative, the Society has contributed $2000 dollars. Other Societies (CPS) have also contributed monetarily to create the Leaders Forum. An issue of utmost concern is the dire financial situation of the CIHR. We will continue to emphasize the necessity of more funding and greater flexibility in training programs for graduate students and postdoctoral fellows.

In closing, CSBMCB remains a vibrant organization that speaks on behalf of the biochemistry, molecular and cellular biological communities in Canada. We warmly welcome all ideas to make this organization a more effective voice for your interests!

It was moved by Dr. Tustanoff and seconded by Dr. Andrews that the President's Report be received.

CARRIED

755. Past President's Report

Dr. Andrew's report on HUPO was covered in discussion during the President's Report (Item 754). He reported briefly on the upcoming CFBS Northern Lights Conference in Vancouver.

756. Vice-President's Report

Dr. Casey began his report by thanking Dr. Orlowski for his term as President of CSBMCB.

Dr. Casey reported on his activities related to advocacy for the CSBMCB community. He sees it important that our voices be amplified and that we're "at the table" with other groups.

Dr. Casey requested that CSBMCB donate $150 to Canadians for Health Research.

He discussed renewal of the relationship of CSBMCB with CFBS.

Receipt of Dr. Casey's report was moved by Dr. Duronio and seconded by Dr. Penn.

CARRIED

757. Treasurer's Report

Dr. Duronio began his report by asking that the work of the retiring Treasurer Dr. Fred Palmer be recognized in the minutes and that he be thanked for his contributions to CSBMCB.

A detailed written Financial Report was circulated by Dr. Duronio. This report included statements to December 31, 2003 and an Auditor's Report (a copy of this report will be filed with the minutes of this meeting).

758. Secretary's Report

Dr. Tustanoff noted Dr. Palmer's dedication to CSBMCB adding to the Societies' appreciation of Dr. Palmer's contributions to CSBMCB. Note: Dr. Tustanoff's contributions to the Society were recognized at the Conference Dinner.

759. Councillors' Reports

Dr. Penn led discussion on activities to recruit new members for the Society. These included getting representatives at each of the institutions. Communications should be both via email and paper copy. There is a need to update the "Join Us" pamphlet. We must all work to make people constantly aware of the Society.

There will be drives to recruit faculty during June and students and post-doctoral fellows during September.

Receipt of Dr. Penn's report was moved by Dr. Penn and seconded by Dr. Casey.

CARRIED

760. New Business

I. Number of signatures required for nomination to the Board of Directors. It was moved by Dr. Casey, seconded by Dr. Andrews that the Constitution be amended to reduce to one the number of member's signatures required to nominate a person to the Board of Directors. Carried.

II. Bulletin 2003 and onwards.
No report available.

III. Web Site renovations. There was a brief discussion on the Web Site (also covered in President's report). The estimate for Steve Law to further develop it was $3000. This would include a pass-word system.

IV. AGM for 2006
(See President's report)

V. PABMB – There had been no response from CSBMCB member Dr. Duckworth who had been asked at the last AGM to contact PABMB to ascertain the vitality of their organization. However, in the interim, a letter was received from Juan José Cazzulo, Chairman, PABMB (included with the Agenda) describing various steps being implemented by their Society to improve the management and effectiveness of their organization. After some discussion, it was felt that PABMB had made sufficient strides in the last several months to improve the operation of their Society. It was moved by Dr. Andrews and seconded by Dr. Casey that CSBMCB continue to maintain its relationship and membership with PABMB

CARRIED

761. Adjournment.

The meeting was adjourned at 19:00 p.m. on a motion from Dr. Andrews which was seconded by Dr. Casey.

CARRIED

CSBMCB/SCBBMC Financial Statement for 2004

Treasurer's note: With the change of the treasurer's office from Dr. Fred Palmer to Dr. Vincent Duronio, a complete audit was undertaken for the 2003 fiscal year (Jan. 1-Dec. 31, 2003) by Ms. Tammy Bastarache (Ottawa, ON) which had not been done for several years. The application of strict accounting rules resulted in some adjustments being made to previous financial statements, but these were primarily due to deferred expenses and revenues. A decision was made by the executive to retain Ms. Bastarache as the society's accountant, and do a yearly audit. In this year's bulletin, numbers are included from the official audit for 2003, as well as an unofficial financial statement for 2004.

Statement of Financial Position - December 31, 2003

Assets	
Current assets	
Bank	$11,130
GST receivable	305
Accounts receivable and accrued membership fees	1,282
Prepaid expenses	6,000
	18,717
Investments – at market value	354,503
	373,220
Liabilities and surplus	
Current liabilities	
Accounts payable and accrued liabilities	5,036
Deferred revenue	10,019
	15,055
Net assets	358,165

Statement of Changes in Net Assets

Net assets, beginning of year	344,232
Excess of revenues over expenses for the year	13,933
Net assets, end of year	358,165

Statement of Revenue and Expenses - 2003

Revenue from operations	
Memberships	15,998
Corporate contributions	33,000
NRC loan forgiveness	25,000
Other	1,554
	75,552
Investment revenue	
Interest, dividends and other investment income	13,689
Realized and unrealized capital gains	11,450
Proceeds on sales of investments	49,300
Purchases of investments	(15,628)
	58,811
Expenses	
Annual meeting	82,580
Bank and credit card fees	655
Board meetings	7,874
Bulletin	7,761
Management fees	4,473
Dues and subscriptions	464
Computer support	5,708
Lobby expenses	78
Newsletter	2,880
Publicity	1,955
Office	1,218
Postage and courier	333
Travel	2,251
Audit	2,200
	120,430
Excess of revenues over expenses for the year	13,933

Statement of Cash Flows

Cash flows from operating activities	
Cash received from members and events	66,136
Cash paid to suppliers	(126,257)
Cash flows from operating activities	(60,121)
Cash flows from investing activities	
Investment income	24,025
Proceeds from sale of investments	49,300
Purchase of investments	(15,628)
	57,697
Net change in cash and cash equivalents	(2,424)
Cash and cash equivalents, beginning of year	13,554
Cash and cash equivalents, end of year	11,130

Income Statement - 1/1/2004 to12/31/2004

REVENUE	
Membership Revenue	
Total Membership Revenue	28,279.31
Annual Meeting Revenue	
Meeting Sponsors	66,812.14
Annual Meeting Registration	4,887.06
Meeting Revenue Total	71,699.20
Other Revenue	
Member List Sales	953.25
Website	200.00
Interest Revenue	0.05
Bulletin Sales	18.69
Total Other Revenue	1,171.99
TOTAL REVENUE	101,150.50
EXPENSE	
Bulletin Expenses	
Bulletin Printing	5,209.87
Bulletin Mail out	869.28
Total Bulletin Expenses	6,079.15
Annual Meeting Expenses	
Speakers Travel & Expenses	40,724.53
Merck Frosst Award and Trainee Travel Awards	19,400.00

Roche Poster Awards	500.00
Meeting Supplies	531.05
Board Travel to AGM	531.42
Other Meeting Expenses	2,698.10
Total Annual Meeting Expenses	64,385.10
Other Expenses	
CFBS Fees	12,360.00
The Link Expenses	1,765.45
Science Policy Funding	2,000.00
Student Event Sponsorship	2,500.00
Other Org. Mmb. Fees (IFCB & PABMB)	1,317.1
Board meetings & Travel Expenses	8,138.69
CFBS Admin Contract	8,160.00
Total Other Expenses	36,241.29
General & Administrative Expenses	
Accounting & Legal	2,875.00
Courier & Postage	162.86
Credit Card Sales Discount Fees	846.21
Credit Card Interest & Fees	12.00
Interest & Bank Charges	214.98
Office Supplies	100.16
Miscellaneous	1,700.00
Telephone	12.50
Total General & Admin. Expenses	5,923.71
TOTAL EXPENSE	112,629.25
NET INCOME	(11,478.75)
SPECIAL FUND	
MARKET VALUE, 12/31/03	354,503.00
WITHDRAWALS FROM FUND	5,000.00
MARKET VALUE, 12/31/04	385,721.48

47th Annual Meeting of the CSBMCMB: Musings on Mont Tremblant 2004

John Orloswki, Past-President CSBMCB

Our 47th Annual Scientific Meeting at Mont Tremblant (Québec) - entitled "Cellular Signalling: from the Membrane to the Nucleus" - has come and gone and, without reservation, was a resounding scientific and social success. The venue was beautiful and the hotel accommodations, facilities and food were top-notch, albeit pricey. André Lou and Associates did a great job handling the logistics of arranging the meeting (registrations, hotel accommodations, airport bus shuttles, etc...). Needless to say, but said anyway, you get what you pay for. The Scientific Organizing Committee, headed by Dr. Terry Hébert, did a superb job of recruiting a stellar slate of 27 speakers from across Canada, the United States and Europe, and assembling 47 poster presentations. Attendance reached a respectable — 120 registrants, mainly from Québec and Ontario, but there is still room for improvement. The Society needs to do a better job of getting the message out to Canadian scientists — neophytes and seasoned individuals alike — that these are great meetings that should not be missed. A committee of the CSBMCB Executive Board, headed by Councillor Dr. Linda Penn, is currently developing a broad strategy to address this very issue, which hopefully will bear fruit in the near future. That said, the Executive has received many positive comments from the meeting participants — some of which have translated into new memberships for the society.

Terry Hébert also deserves our highest praise and thanks for doing an outstanding job of raising funds from corporate and government sponsors. Because of his efforts, we were able to provide generous travel awards to every graduate student and post-doctoral fellow who presented a poster of their work at the meeting, and whose supervisor was a member of the Society. Indeed, the awards were double our initial budgeted amounts (stipends for "local" and "distant" individuals were $600 and $1200 respectively). A few were also selected and awarded prizes for the quality of their posters. If these aren't sufficient incentives for investigators to join the Society and to send their trainees to the annual meetings, then what is? Well, we had that covered too. Fancy oversized CSBMCB T-shirts — leftovers from the 2003 HUPO/IUBMB/CSBMCB joint meeting — were freely dispensed to those in need to new pajamas.

As for the Annual General Meeting itself, it was perhaps the most efficiently run session we have had in many a year — done in record time (less than 30 minutes). I attribute this to the administrative dexterity of the Executive, although perhaps the rather low attendance of the membership (is anyone out there?) might have been a contributing factor. If anyone has any advice one how to attract members to such events, let the Executive Board know, and you will receive a free T-shirt!

The final Banquet, as always, was a feast fit for royalty. Presentations were made to Dr. Terry Hébert for his exceptional efforts in organizing the Mont Tremblant meeting. A gift and a plaque of commendation were presented to Dr. Gene Tustanoff, who retired as Secretary of the CSBMCB after 12 years of diligent service to the Society, and to Dr. David Andrews, who served as Vice-President, President and Past-President. Other announced changes to the Board included the ascendance of Dr. Joe Casey to the position of President, and the recruitment of Dr. David Thomas, McGill University, as Vice-President, and Dr. Albert

Clark, Queen's University, as Secretary of the Society.

In closing, we have had another successful meeting as a vibrant and dynamic Society. As a member of the Executive for the past two years, I have personally benefitted from my involvement in the Society through my interactions with dedicated and hardworking individuals who are committed to fostering science in Canada. Through their efforts, the Society continues to thrive and prosper. So, check the CSBMCB web site (http://www.csbmcb.ca) regularly, and keep your Palm Pilots, Blackberrys or good old-fashioned calendars on hand, as there are a number of great meetings being planned for the upcoming years.

Travel Award Recipients for the 2004 CSBMCB Annual Scientific Meeting

Mont Tremblant, Quebec

AWARDEE	UNIVERSITY	SUPERVISOR
Amgen Inc. 3 x $1200 Stipends		
Kewei Ma	University of British Columbia	Dr. V. Duronio
Mary Ellen K. Olsten	University of Western Ontario	Dr. D. Litchfield
Dharini van der Hoeven	Dalhousie University	Dr. M. Dobson
Amgen Inc. 6 x $600 awards		
Mohamed Abu-Farha	Carleton University	Dr. W. Willmore
Alessandra Baragli	Université de Montréal	Dr. T. Hébert
Marie-Josée Benoit	Université de Montréal	Dr. B. Allen
A. Bibeau-Poirier	Université de Montréal	Dr. M. Servant
André Boivin	Université Laval	Dr. J. St.-Amand
Benoit Boivin	Université de Montréal	Dr. B. Allen
Merck Frosst 3 x $1200 awards		
Dmitri Satsoura	McMaster University	Dr. D. Andrews
Katrina Teske	University of Western Ontario	Dr. F. Possmayer
Lieven Billen	McMaster University	Dr. D. Andrews
Merck Frosst 7 x $600 awards		
Julie Brind'Amour	Université Laval	Dr. G. M. Shah
Mathieu Cotton	Université de Montréal	Dr. A. Claing
Denis Dupré	Université de Montréal	Dr. T. Hébert
Medini M. Ghodgaonkar	Université Laval	Dr. G. M. Shah
Viktoria Lukashova	McGill University	Dr. J. Orlowski
Marie-Eve Poupart	Université de Montréal	Dr. A. Claing
Hans-Christian Zaun	McGill University	Dr. J. Orlowski
BioRad Laboratories $600 award		
Maxime Richer	Université de Montréal	Dr. T. Hébert
Faculty of 1000 $600 award		
Rashmi G. Shah	Université Laval	Dr. G. M. Shah
New England Biolabs $600 award		
Nishida, Yuichiro	Université Laval	Dr. J. St-Amand
Upstate Technologies $600 award		
Mélanie Robitaille	Université de Montréal	Dr. T. Hébert

Scenes from the 2004 CSBMCB Annual Meeting

Terry Hébert, Chair of the CSBMCB Scientific Organizing Committee for the 2005 Mont Tremblant Conference

John Orlowski, President of CSBMCB

Intense scientific discussion at the poster session

The 2004 winners of the Merck Frosst Prize, Richard Wozniak (left), and the Jeanne Manery Fisher Memorial Award, Morag Park (right), with John Orlowski, President of the CSBMCB

More discussion at the poster session

Richard Wozniak, winner of the 2004 Merck Frosst Prize, receives his award plaque from John Orlowski, President of the CSBMCB

Morag Park, winner of the Jeanne Manery Fisher Memorial Award, receives her award plaque from John Orlowski, President of the CSBMCB

Sergio Grinstein and Amira Klip at the conference banquet

Incoming CSBMCB President, Joe Casey, playing I spy with my little eye

Presentation by John Orlowski, President of the CSBMCB, of the "Certificate of Commendation" to Dr. Terry Hébert in recognition of his meritorious service as Chair of the Organizing Committee for the 47th Annual General Meeting of the Society held at Mont Tremblant, Québec

Presentation by John Orlowski, President of the CSBMCB, of the "Certificate of Commendation" to Dr. David Andrews in recognition of his meritorious service as Vice-President, President and Past-President of the Society (2001-2004)

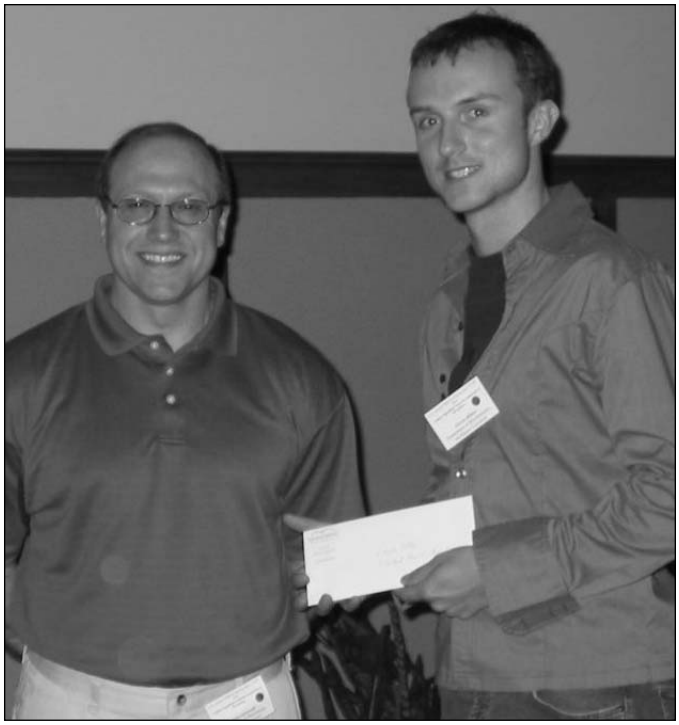
Presentation by John Orlowski, President of the CSBMCB, of the "Certificate of Commendation" to Dr. Eugene Tustanoff in recognition of his longstanding meritorious service as Secretary of the Society (1992-2004).

Presentation of the Roche Diagnostics Award for the Best Poster Presentation to Annie Bibeau-Poirier by the Representative of Roche Diagnostics and John Orlowski, President of the CSBMCB

Presentation of the Roche Diagnostics Award for Best Poster Presentation to Dharini Van Der Hoeven by the Representative of Roche Diagnostics and John Orlowski, President of the CSBMCB

Presentation of the Roche Diagnostics Award for Best Poster Presentation by the Representative of Roche Diagnostics and John Orlowski, President of the CSBMCB

Presentation of the CSBMCB Award for Best Poster Presentation to Medini M. Ghodgaonkar by John Orlowski, President of the CSBMCB



Presentation of the CSBMCB Award for Best Poster Presentation to Lieven Billen by John Orlowski, President of the CSBMCB

Conference attendees relax at the banquet

Winners of the CSBMCB Travel Awards

CSBMCB 48th Annual Meeting

Meeting Organizers: Rick Wozniak, Rick Rachubinski (University of Alberta)

Cellular Dynamics

March 16-20, 2005

Banff Centre for the Arts, Banff, Alberta

WEDNESDAY MARCH 16, 2005

PM SESSION

CSBMCB Awards Lectures

Keynote Speaker:
Günther Blobel (New York)

THURSDAY MARCH 17, 2005

AM SESSION

Organelles of the Secretory Pathway

Scott Emr (San Diego)
Juan Bonifacino (Washington D.C.)
Charles Barlowe(Hanover, NH)
Paul Melancon (Edmonton)
Sergio Grinstein (Toronto)
Gerrit van Meer (Netherlands)

PM SESSION

Imaging Technologies

David Bazett-Jones (Toronto)
Tom Kirchhausen (Boston)
Jennifer Lippincott-Schwartz (Bethesda MD)
Robert Campbell (Edmonton)

FRIDAY MARCH 18, 2005

AM SESSION

Organelle Inheritance

Lois Weisman (Iowa City)
Michael Yaffe (San Diego)
Susan Ferro-Novick (New Haven, Conn.)
Benjamin Glick (Chicago)
Graham Warren (New Haven)

PM SESSION

Protein Folding

Art Horwitz (New Haven)
David Thomas (Montreal)
Peter Walter (San Francisco)
Reed Wickner (San Francisco)

SATURDAY MARCH 19, 2005

AM SESSION

Nuclear Structure

Mike Rout (New York)
Ulf Nehbass (Paris)
John Aitchison (Seattle)
Richard Wozniak (Edmonton)
Tom Mistelli, (Washington D.C.)
Susan Gasser (Geneva)

PM SESSION

mRNA Localization

Paul Lasko (Montreal)
Thomas Okita (Seattle)
Rob Singer (New York)
Kerry Bloom (Chapel Hill)

SUNDAY MARCH 20, 2005

AM SESSION

Systems Approaches to Cell Biology

John Bergeron (Montreal)
David Sabatini (Boston)
Trey Ideker (Boston)
Charlie Boone (Toronto)
Mike Tyers (Toronto)

John Alexander McCarter - Obituary

1918-2005

Eugene Reno Tustantoff, Professor Emeritus of Biochemistry, University of Western Ontario

The Society is grieved to report that Dr. John Alexander McCarter passed away on February 14, in Victoria British Columbia. Alec, as he was known to his colleagues, was one of the founding members of our Society, having served as President of our organization from 1965 to 1967 during its fledgeling years. A renowned Canadian scientist, Dr. McCarter made his mark as a biochemical virologist. Born in England on the 25th of January 1918, Dr. McCarter immigrated with his family to Canada and spent his early youth in the gold rush town of Dawson City, in the Yukon Territories. While attending Dawson Public School he became a life-long friend of Pierre Berton. He completed his secondary school education at the King Edward High School in Vancouver when his family relocated to Vancouver. He matriculated at the University of British Columbia where he received both his baccalaureate degree in Chemistry in 1939, and his Master's degree in Biochemistry in 1941. During the period of the second World War he was invited to join a chemical research programme for National Defence at the University of Toronto, working under the supervision of Dr. Leslie Young. In 1945 he submitted his thesis entitled "The Biological Aspects of Mustard Gas Poisoning" , for which he was awarded his Ph.D. degree from the U of T in 1945. Upon graduation he served from 1945 to 1948 as an Assistant Research Officer with the National Research Council Atomic Energy Project at both McGill University and Chalk River. In 1948 he was appointed an Associate Professor in the Department of Biochemistry, Dalhousie University. In 1950 he became Professor and Head of that Department. During his tenure at Dalhousie, Dr. McCarter was instrumental in establishing the Division of Medical Research, as a part of the National Research Council of Canada, and saw its subsequent transition into the Medical Research Council of Canada. In 1965, Dr. McCarter was appointed Director of the National Cancer Institute of Canada's Cancer Research Laboratory and Professor in the Department of Biochemistry at the University of Western Ontario. From 1980 to 1983, he held the position of Research Professor, National Cancer Institute of Canada along with his professorship in the Department of Biochemistry at Western. In 1983 he was appointed a Visiting Professor in the Department of Biochemistry and Microbiology, University of Victoria, and from 1985 to 1990 he served as an Adjunct Professor in the same Department. He authored over 50 scientific papers and received a number of accolades for his research. Amongst these were the Exchange Fellowship of the British Empire Cancer Campaign in 1959, the Queen's Silver Jubilee Medal in 1977, and a Fellowship in the Royal Society of Canada. Dr. McCarter is survived by his wife Peggy, four children and nine grandchildren.

J.A. McCARTER: Recollections

Christopher Helleiner, Professor Emeritus, Dalhousie University

J.A. McCarter (Alec to everyone), one of Canada's most distinguished senior biochemists died in

Victoria on February 14, 2005. Alec was born in 1918 and spent his early life in the Yukon gold rush town of Dawson City. He sometimes reminisced about playing street hockey there with Pierre Berton, and showed us a large gold nugget he had inherited from his grandfather. His undergraduate degree in Chemistry and Biochemistry was from the University of British Columbia. His enduring interest in carcinogenesis probably had its beginning when he worked on secret defence research projects during World War II at the University of Toronto, where he obtained his Ph.D. He then went on to continue similar work at Chalk River. His first academic appointment came in 1948, at the then tiny Department of Biochemistry at Dalhousie University. He succeeded Gordon Young as Department Head in 1950, only the second person to hold that position. Department Heads served for many years in those days — no rotating chairmanships.

Alec's influence on the development of the Department, the Faculty of Medicine and the University as a whole was profound. Dalhousie was a very small university in those days "The Little College by the Sea" , as it was described in the Calendar. Alec played an important part in bringing it into the twentieth century both academically and socially. He introduced graduate programmes and modern research in a very modest physical plant. A number of senior people in the Faculty of Medicine, including Alec, formed the Izaak Walton Fishing Club. It was said that many important decisions taken by the Faculty had their beginnings during their annual trip each May to their 'camp' in remote Guysborough County. Alec's was the voice of basic science; he laid the foundation for the explosive increase in the preclinical departments at Dalhousie just after he left. Among his other avocations, he became a keen birder. (That was how I first got to know him, watching the Caspian Terns on Georgian Bay at Honey Harbour during a National Cancer Institute conference there).

Alec's continuing work on skin carcinogenesis, using a colony of inbred mice which he skillfully maintained under rather difficult conditions, resulted in his election to the Royal Society of Canada. At the same time he served a term as President of the Canadian Biochemical Society and was a member of the group of medical researchers who pioneered the transition of the Division of Medical Research of the National Research Council into the Medical Research Council.

Alec left Dalhousie in 1965 to become the Director of the National Cancer Institute Cancer Research Laboratory at the University of Western Ontario. His interests broadened to include the burgeoning field of RNA tumour virus research. In 1980 he moved again, to the University of Victoria. There he was able to combine his biochemical research with his enthusiasm for fishing. Trout he caught in streams on Vancouver Island were analyzed for their metallothionein as an indicator of heavy metal pollution of the water in which they lived. He retired in 1983.

Alec had contracted polio as a child; he always walked with a pronounced limp, and several times suffered fractures after falling. His condition worsened as he developed post-polio syndrome, and in his last years he was able to navigate only with a walker; he refused to resort to a wheel chair. He took up painting, and became a skilled amateur artist. He and his wife, Peggy developed an exceptionally fine flower garden at their house in Victoria, the uniquely favourable climate playing on their side. Alec contributed many thoughtful and evocative pieces to the Newsletter of the Victoria Rhododendron Society and the Finnerty Gardens Letter.

Alec's long career spanned the period during which biochemists put the finishing touches on our understanding of metabolic pathways, and moved on to the study of genetic mechanisms and control networks. He kept up to date in his field, moving with the times both as a scientist and as an administrator. His gentle persuasiveness concealed a stubborn determination to keep Canadian science moving forward, taking its rightful place on the world stage.

New Ways to Skin a Kap: Mechanisms for Controlling Nuclear Transport

C. Patrick Lusk, Taras Makhnevych and Richard W. Wozniak*

Department of Cell Biology, University of Alberta, Edmonton, Alberta, Canada, T6G 2H7
*Corresponding author (e-mail: rick.wozniak@ualberta.ca)

Abstract

Transport between the nucleus and the cytoplasm occurs through large macromolecular assemblies called nuclear pore complexes (NPCs). The NPC is traditionally viewed as a passive structure whose primary role is to provide an interface for the soluble transport machinery, the karyopherins and their cargos, to move molecules between these compartments. Recent work has challenged this view of the NPC and provides support for a dynamic structure that can modify its architecture to actively regulate nuclear transport.

Introduction

In eukaryotic cells, the contents of the nucleus are physically separated from the cytoplasm by an impermeable double membrane called the nuclear envelope (NE). This separation of the contents of the nucleus, including the cell's chromatin and transcriptional machinery, from the cytoplasm, containing the cell's translational machinery, demands that cells regulate a vast array of macromolecular traffic between these compartments. All this traffic occurs through nuclear pore complexes (NPCs), which extend across the NE and act as gatekeepers for all transport. The NPCs function in concert with a family of soluble factors, termed karyopherins or kaps (also termed importins or exportins) that recognize cargos by binding a nuclear localization signal (NLS) or a nuclear export signal (NES) in either the cytoplasm or nucleus, respectively, and docks them to the NPC for subsequent translocation (Macara, 2001; Fried and Kutay, 2003). Individual karyopherins have the ability to bind specific classes of cargos, thus providing the cell with a means to independently regulate the transport of different classes of molecules including most proteins and ribonucleoprotein particles between the cytoplasm and the nucleoplasm (reviewed in Fried and Kutay, 2003). Understanding the mechanisms that underlie these pathways is paramount to understanding normal cellular function, including how cells regulate gene expression, progress through the cell cycle, transduce both intra- and extra-cellular signals, and how viruses gain access to the nucleus for productive infection.

Current models of nuclear transport come from studying both the NPC itself and kaps that recognize molecules to be transported through the NPC. The NPC is a huge, extraordinarily complex octagonally symmetric structure. In vertebrates, its mass has been estimated at ~60 million Daltons (Cronshaw et al., 2002). By comparison, the mass of the yeast NPC is estimated at ~44 million Daltons (Rout et al., 2000). Morphologically, this difference appears to be due to the more complex cytoplasmic and nucleoplasmic rings in vertebrate NPCs. However, the majority of the structure is extremely well conserved (Yang et al., 1998). This conservation is such that many proteins involved in nuclear transport are conserved and some NPC proteins (termed nucleoporins or nups) can function across phyla from yeast to mammals (Aitchison et al., 1995b)

In recent years, biochemical and genetic approaches have led to the identification of most, if not all, nups (reviewed in Suntharalingam and Wente, 2003). These studies have culminated with mass spectrometry (MS) analyses performed on enriched fractions of yeast and rat NPCs that suggest NPCs are composed of ~30 nups (Rout et al., 2000; Cronshaw et al., 2002) many of which are conserved between species. Nups can be divided into three subgroups. One group is composed of integral membrane proteins that are believed to play a role in NPC assembly and anchoring the NPC to the membrane. The two remaining groups are divided based on the presence or absence of repeated peptide motifs of the type GLFG, FXFG, PSFG or FG. The 'FG-nups', consisting of ~12 members, play a direct role in transport and several members have been shown to physically interact with karyopherins (reviewed in Ryan and Wente, 2000). The FG-nups have been detected throughout the NPC thus creating a series of kap binding sites along the ~200 nm pathway that extends from the tips of the cytoplasmic filaments to intranuclear fibres that form a structure called the nuclear basket (Suntharalingam and Wente, 2003). It has been estimated that there are ~160 FG-nucleoporins per NPC, many of which contain multiple FG-repeats (Rout et al., 2000, Strawn et al., 2004). Thus, the NPC is literally lined with kap binding sites.

Functions for non-repeat nucleoporins are less clear. These proteins, which are the most evolutionarily conserved of the nups, are considered to be integral to NPC assembly and are thought to provide the scaffold on which the FG-nups are organized. Consistent with this idea, a vertebrate NPC subcomplex consisting largely of non-repeat nups, including Nup107 and Nup160, has been shown to play a central role in the initial steps of NPC formation (Walther et al., 2003; Harel et al., 2003). The yeast counterpart of this complex has also been proposed to function in NPC assembly (Aitchison et al., 1995a; Doye and Hurt, 1997). Similarly, Nic96p and its vertebrate orthologue Nup93, are required for proper NPC formation and distribution along the surface of the NE (Zabel et al., 1996; Grandi et al., 1997; Galy et al., 2003). Nup170p is another non-repeat nup that appears to be a central player in organizing the FG-nups. In its absence there are changes in the localization and stoichiometry of several FG-nups including Nup1p, Nup53p and Nup2p (Kenna et al., 1996; Lusk et al., 2002). In fact, there appears to be a significant destabilization of NPC's lacking Nup170p, as many FG and non-FG nups alike are dissociated from nup170D NPCs in the presence of aliphatic alcohols or energy poisons (Shulga and Goldfarb, 2003). These effects also seem to manifest themselves by increasing the size of the diffusion channel through the NPC, an effect mimicked in nup188D strains (Shulga et al., 2000). Importantly, there are physical and genetic interactions between the non-FG and FG-nups, reinforcing the idea that while the non-repeat nups may not directly interact with kaps, they are nonetheless vital for nuclear transport.

The soluble transport machinery

The NPC controls constitutive transport by two basic mechanisms: (1) it acts as a passive diffusion barrier to molecules <9 nm in diameter and (2), through a more widely studied pathway, it mediates macromolecular traffic using kaps and other soluble factors including the small GTPase Ran (for reviews see Macara, 2001; Weis, 2003; Fried and Kutay, 2003). The advances in our understanding of macromolecular transport are the result of biochemical and genetic studies in metazoan cells and yeast. While certain nuances exist, the fundamental processes are conserved throughout all eukaryotes.

A broad spectrum of macromolecules cross the NE, including mRNAs, tRNAs, ribosomal proteins, ribosomal subunits, snRNPs and many soluble proteins. These various classes of molecules contain different NLSs or NESs. In most cases, they are recognized by different members of a family of structurally related kaps collectively referred to as ß-karyopherins (or ß-kaps), of which there are 14 in yeast that function primarily as either importers or exporters (Wozniak et al., 1998; Strom and Weis, 2001; Fried and Kutay, 2003). While the overall structure of the ß-kaps is believed to be

similar, their sequence similarity is low, except for a region near the N-terminus that contains a binding site for the GTPase Ran. The differences in their sequences likely reflect their ability to recognize different cargos. However, it is important to note that an individual signal can be recognized by more than one ß-kap suggesting some level of overlap between their functions. Examples are the ability of the ß-kaps Kap121p and Kap123p to both import the ribosomal protein rpl25 (Rout et al., 1997), and the need for Kap114p, Kap121p and Kap123p to import histones (Mosammaparast et al., 2001). Such examples may explain the observation in yeast, that deletions of some ß-kap genes are lethal while others are not.

In addition to the ß-kaps, nucleo-cytoplasmic exchange requires the activity of the GTPase Ran (Macara, 2001; Weis, 2003; Fried and Kutay, 2003). Ran is the only known energy source required for maintaining the transport cycle and the energy for transport likely comes from a potential energy gradient across the NPC established by the maintenance of distinct pools of Ran. In the nucleus, Ran is maintained in its GTP-bound state by the nuclear-restricted GTP exchange factor, Ran-GEF. In contrast, the Ran GTPase activating protein (Ran-GAP) is primarily cytoplasmic, ensuring that this pool of Ran is in its GDP-bound form. This distribution contributes to the directionality of transport by triggering the assembly and disassembly of transport complexes in the correct compartments. That is, the formation of import complexes between ß-kaps and their cargo is stable in the presence of cytoplasmic Ran-GDP. However, once the ß-kap/cargo complexes traverse the NPC and enter the nucleoplasm, Ran-GTP binds to the ß-kaps and displaces their cargo, terminating import. On the other hand, the formation of export complexes is stabilized in the nucleus by Ran-GTP and as these complexes reach the cytoplasm, the GTP is hydrolyzed and the complex disassembles. Moreover, the Ran-GTP gradient provides energy for recycling kaps back to the cytoplasm and continued rounds of transport.

Transport models

While the individual components of nuclear transport are well defined, the way in which they functionally interact to drive nuclear transport is not well understood. This is particularly true with respect to the role that kap-nup interactions play in moving the kap-cargo complex through the central channel of the NPC. In general, the binding of FG-nups to kaps is believed to facilitate the movement of the kap-cargo complex through the NPC. This idea has been incorporated into several nuclear transport models. One current model argues that, due to the hydrophobic nature of the FG-repeats and their abundance within the pore, FG-nups form a hydrophobic meshwork or "selective phase" that is impermeable to most molecules. Kaps together with their cargos, however, are able to partition into this matrix to facilitate their movement through the NPC (Ribbeck and Gorlich, 2001; Ribbeck and Gorlich, 2002). Another model envisions that the vast majority of molecules are excluded from the NPC channel due to their inherent entropy. The FG-nups are considered to be flexible disorganized proteins that occlude the central channel, and actively brush away molecules that cannot interact with them. In this fashion they further increase the entropic barrier of the NPC. By selectively interacting with kaps, the tentacle-like FG-nups also act as a "virtual gate" that allows the concentration of kap/cargo complexes within the NPC, lowering their entropy and allowing them to move through the pore (Rout et al., 2000; Rout et al., 2003).

In order to achieve rates of import sufficient to accommodate the huge flow of molecules across the NE, both of these models rely on the idea that the kap/nup interaction is weak (Ribbeck and Gorlich, 2001). Differences in affinity between kaps and FG-nups have been measured, however, and there is a tendency for the affinity of kaps for certain FG-nups to increase from the cytoplasmic filaments to the nuclear basket (Ben-Efraim and Gerace, 2001; Pyhtila and Rexach, 2003). These observations have been incorporated into an 'affinity gradient' model of nuclear transport, whereby kaps are pulled through the pore by an ever increasing affinity for nups along their route.

While these models provide a basic framework for

understanding transport, they represent broad strokes in what is likely a finely detailed landscape. For example, the models discussed above do not adequately incorporate a growing body of evidence that suggests that kaps do not all travel similar routes through the NPC. There are clearly specific binding sites, some of which are of high affinity, that have been proposed to play roles in regulating specific transport pathways. Furthermore, these models place tremendous emphasis on the FG-repeats as the main effectors of nuclear transport, which may, in fact, be an overstatement. As a case in point, a recent study evaluates the importance of individual FG-repeats in nuclear transport by systematically deleting FG regions of nups (Strawn et al., 2004). Amazingly, half of the total mass of FG's could be simultaneously deleted without dramatically affecting cell viability. Furthermore, while transport defects were observed, they were linked to specific transport pathways and did not represent a general inhibition of import and export processes. These data are therefore consistent with a model of nuclear transport that is more elaborate than those described above, supporting the idea that there are distinct transport routes through the NPC that are followed by specific karyopherins. They also underscore the involvement of non-FG binding sites in key transport roles (see below).

Regulation of nuclear transport

As a blueprint has emerged for the basic mechanisms of nuclear transport, so has the idea that specific transport pathways can be regulated to orchestrate changes in nuclear physiology including gene transcription, DNA replication, and chromosome segregation. The mechanisms governing this regulation can be broadly grouped into two categories: mechanisms that directly affect kap binding to cargo and those that encompass regulation of the kap-nup interaction. In this review, we will only highlight some of the mechanisms governing the kap-cargo interaction as they have been extensively reviewed elsewhere (Kaffman and O'Shea, 1999) and will focus on the regulation of transport by the NPC.

Regulating the kap-cargo interaction

Certainly the most well studied form of transport regulation relies on the modification or masking of an NLS or NES from its cognate kap, to prevent its import or export. Modifications such as phosphorylation and acetylation have been shown to either enhance or inhibit the binding of cargos to karyopherins (Kaffman and O'Shea, 1999; Madison et al., 2002). There is also recent evidence that implicates methylation as a key regulator of the import of certain NLSs (Smith et al., 2004). As an example, the distribution of the yeast transcription factor Pho4p is determined by binding to either the import ß-kap Kap121p or the export ß-kap Kap142p/Msn5p (Kaffman et al., 1998a; Kaffman et al., 1998b). Under phosphate-rich conditions Pho4p is phosphorylated, which results in the simultaneous inhibition of its interaction with Kap121p (import inhibition) and stimulation of its interaction with Kap142p/Msn5p (increased export), the end result being the exclusion of Pho4p from the nucleoplasm. Under conditions of phosphate-starvation, Pho4p becomes dephosphorylated which allows it to interact with Kap121p and breaks its interaction with Kap142p/Msn5p, driving the accumulation of Pho4p in the nucleus and subsequent transcriptional activation (Fig. 1). A reciprocal effect is observed with cyclin B1, which accumulates in the nucleus at the beginning of mitosis due to a block in export caused by its phosphorylation (Yang et al., 1998).

Several examples also exist where protein-protein associations between members of a complex can be altered to expose or hide a transport signal from a kap. p53, a well studied transcription factor linked to tumor suppression, dynamically shuttles between the nucleus and cytoplasm. When cells are stressed, p53 is tetramerized which enhances its ability to bind DNA and activate transcription. Interestingly, the tetramerization domain overlaps a leucine-rich NES that is recognized by the export kap Crm1p. Tetramerization of p53 thus hides the NES from Crm1p and effectively traps p53 in the nucleus, allowing it to continually promote transcription (Stommel et al., 1999)(Fig. 2).

Regulation of transport by the NPC

In addition to mechanisms that modulate interactions between kaps and their cargos, there is accumulated evidence supporting a role for the NPC in changing levels of nuclear transport. One can envision mechanisms that both globally alter the permeability of the NPC as well as those that affect the transport of specific karyopherins and their cargos. This concept requires one to reconsider the role of the NPC in regulating transport from a more traditional view of the NPC, as a passive constitutively active channel, to one that is more dynamic, capable of altering transport through changes in its structure. For example, permeability changes driven by molecular rearrangements of the NPC could occur in response to changes in cellular physiology. In support of this idea, evidence in BALB/c 3T3 cells suggests that the size of the NPC channel can be significantly altered. When comparing nuclear transport between proliferating and quiescent cells, Feldherr and Akin (1993) observed that the size of the NPC translocation channel was larger in cells that were actively growing. They also detected changes in NPC permeability throughout the cell cycle, reinforcing the idea that the NPC can gear its transport capability to elicit cellular functions (Feldherr and Akin, 1994). The molecular mechanisms causing these changes, however, are not yet known.

Along similar lines, it is hypothesized that cells may regulate transport by altering the complement of nucleoporins in NPCs. This has been observed at both the level of individual NPCs as well as in the tissue-specific expression of certain nup genes. Mlp1p, for example, is absent from NPCs surrounding the nucleolus in yeast. The functionality of this unique distribution is not yet clear, but is proposed to link transcription with mRNA export by promoting the nuclear retention of unspliced mRNAs in regions associated with chromatin (Galy et al., 2004). Importantly, these data raise the exciting possibility that cells can regulate the function of individual pores and, therefore, their ability to transport specific cargos. This idea may also be relevant to the unique tissue-expression

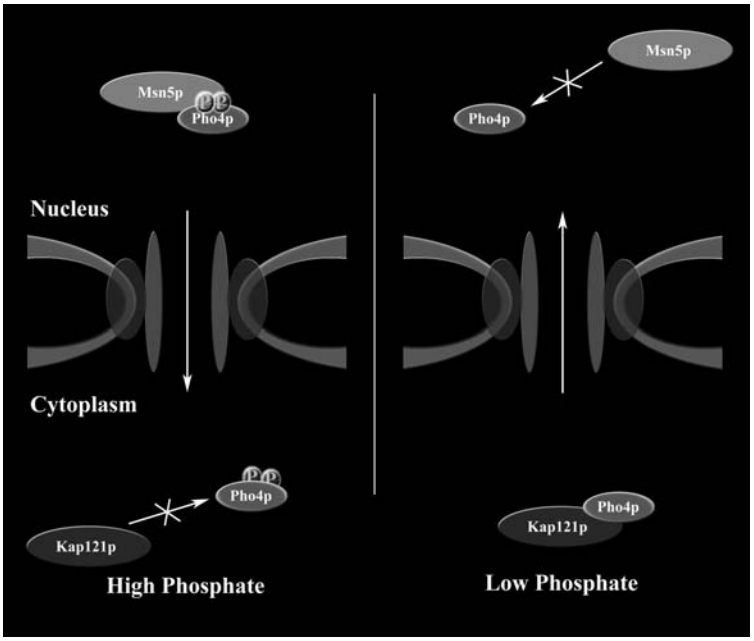


Figure 1. The regulation of Pho4p transport. Under growth conditions in which the concentration of phosphate ions is high, Pho4p is phosphorylated (P). The phosphorylation of Pho4p inhibits its interaction with the import karyopherin Kap121p, while enhancing its interaction with the export karyopherin Msn5p, resulting in a steady state accumulation of Pho4p in the cytoplasm. The reciprocal occurs when the concentration of phosphate ions are lowered, which results in the dephosphorylation of Pho4p and its accumulation in the nucleus.

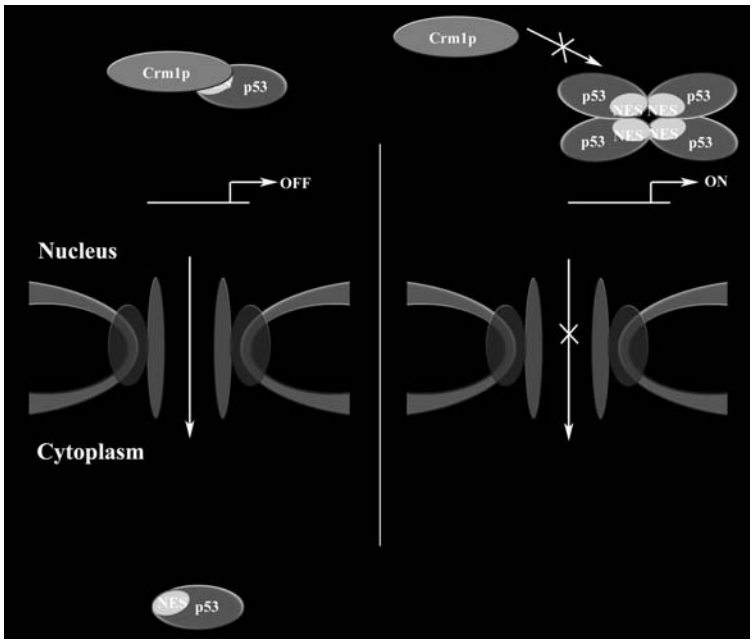


Figure 2. The regulation of p53 localization. The export karyopherin Crm1p recognizes a nuclear export signal (NES) on p53 and actively maintains p53 in the cytoplasm. When cells are stressed, p53 tetramerizes which enhances its ability to activate transcription (represented by the "ON" state of the diagrammed promoter). The tetramerization of p53 masks its NES, blocking its interaction with Crm1p and its export from the nucleus.

patterns of certain nup genes and their possible ability to gear nuclear transport to a specific tissues needs. Recent work has detailed differences in the expression of gp210 and Nup50 in different tissues (Olsson et al., 2004; Smitherman et al., 2000). In addition, the Drosophila homolog of Nup88, members only (mbo), is differentially expressed during larval development in specific cell types (Uv et al., 2000). Interestingly, mbo mutants exhibited developmental defects that were linked to tissue-specific import defects. These data suggest that tissues that lack mbo expression have NPCs that are structurally and functionally distinct and that they play key roles in larval development. Importantly, mbo mutants were also shown to have nuclear import defects for only certain NLS-bearing proteins, suggesting that mbo plays a role in controlling specific transport pathways (Uv et al., 2000).

The idea that individual nups can influence specific transport pathways has been developed in both yeast and vertebrates. During poliovirus infection, for example, distinct nuclear import pathways are inhibited. This effect is thought to be mediated by the selective degradation of two nups, Nup153 and p62, during viral infection (Gustin and Sarnow, 2001). Similarly, during vesicular stomatitis virus infection, specific nuclear transport pathways are also inhibited (Her et al., 1997; Peterson et al., 2000). In this case, transport inhibition is thought to be a direct consequence of the inhibitory effects of the viral M-protein and its interaction with Nup98 (von Kobbe et al., 2000). Importantly, these effects are supported by a number of studies evaluating the role that Nup98 and Nup153 play in regulating distinct nuclear transport pathways. The inhibition of Nup98 in Xenopus oocytes by injection of anti-Nup98 antibodies results in the specific inhibition of snRNA, mRNA and rRNA export but does not affect the export of tRNA (Powers et al., 1997). Similar experiments using antibodies against Nup153 also have no effect on tRNA export, but clearly inhibit the export of snRNA, mRNA and 5sRNA (Ullman et al., 1999). Perturbations of nuclear import pathways have also been observed. The depletion of Nup153 from Xenopus extracts results in the specific disruption of Kap-ß1/Kap-a mediated import, but the Kap-ß2 transport pathway is unaffected (Walther et al., 2001). Furthermore, the overexpression of dominant negative truncations of Nup153 can have specific effects on both the Kap-ß1 and Kap-ß2 import pathways (Shah and Forbes, 1998).

One logical assumption to explain these results is that there are unique pathways traveled by karyopherins as they move through the NPC that involve their binding to specific nups. The first of these binding sites was initially revealed between the yeast proteins Nup53p and Kap121p (Marelli et al., 1998), but has since been shown to include other kap/nup pairs. For example, in yeast, Kap95p has a specific binding site on Nup1p (Pyhtila and Rexach, 2003; Gilchrist and Rexach, 2003), and Nup2p has a specific binding site for Kap60p (Booth et al., 1999; Hood et al., 2000; Solsbacher et al., 2000; Matsuura et al., 2003; Gilchrist and Rexach, 2003). In vertebrates, specific binding sites have been mapped on Nup153 and Nup98 (Nakielny et al., 1999; Fontoura et al., 2000; Shah et al., 1998).

A common feature of these binding sites is that they are devoid of FGs and, in cases where it has been measured, they have affinities for kaps that are much stronger than the Kap-FG-repeat interaction (Pyhtila and Rexach, 2003; Matsuura et al., 2003; Ribbeck and Gorlich, 2001). Importantly, there is evidence linking these sites to the regulation of distinct nuclear import pathways (Gilchrist and Rexach, 2003; Pyhtila and Rexach, 2003; Matsuura et al., 2003; Makhnevych et al., 2003). The deletion of the specific binding site in Nup1p, for example, lowers the binding affinity for Kap95p 450-fold and has specific effects on Kap95p/Kap60p mediated import (Pyhtila and Rexach, 2003). Similarly, the mutation of the Kap60p binding site on Nup2p affects the efficiency of NLS import (Gilchrist and Rexach, 2003; Matsuura et al., 2003).

Another common feature of these binding sites is that, with the exception of Nup53p, they appear to cluster on the nuclear basket (Marelli et al., 1998; Rout et al., 2000; Cronshaw et al., 2002). The significance of this distribution may reflect a role for

these sites in promoting the dissociation of cargo from karyopherins and thus an aid in the termination step of specific import reactions (Fontoura et al., 2000; Gilchrist and Rexach, 2003; Matsuura et al., 2003). This idea has been developed in detail with respect to the Kap60p/Nup2p interaction, and has culminated with the elucidation of the crystal structure of Kap60p in complex with the high affinity Nup2p binding site (Matsuura et al., 2003). The structure revealed that the Nup2p peptide bound to a region of Kap60p that partially overlapped the NLS-binding groove. Since Kap60p binds Nup2p with a higher affinity than NLSs, this interaction is thought to displace the NLS. This observation has been independently confirmed biochemically by other groups (Solsbacher et al., 2000; Gilchrist and Rexach, 2003).

Perhaps another reason that these binding sites cluster on the nuclear side of the NPC, is that based on the transport models described earlier, high affinity kap binding sites within the NPC could function to inhibit nuclear import. Therefore, the symmetrical distribution of Nup53p on both the nuclear and cytoplasmic sides of the NPC would, superficially, be incompatible with current transport models. Yeast, however, have devised an elegant mechanism for sequestering and exposing Nup53p at specific stages of the cell cycle as a means of regulating Kap121p-mediated transport (Makhnevych et al., 2003). Kap121p interacts directly with Nup53p through an NLS-like site referred to as the KBD (Kap-Binding Domain)(Lusk et al., 2002). During interphase, Nup53p is bound to a neighbor nup, Nup170p, which interacts with a region of Nup53p that overlaps the KBD, thereby masking it from Kap121p. Upon entry into M-phase Nup53p is phosphorylated and there are discrete molecular rearrangements within the NPC that break the interaction between Nup53p and Nup170p, exposing the KBD to Kap121p. The binding of Kap121p to Nup53p inhibits its import into the nucleus and likely causes the premature release of its cargo. The result is a striking inhibition of the nuclear accumulation of Kap121p cargos during mitosis (Fig. 3). While it has yet to be determined which Kap121p cargos are affected by this pathway, constitutive activation of this inhibitory pathway by overexpression of NUP53 leads to a delay in mitotic progression. Importantly, this work is the first to describe a transport inhibitory function for a nup and further establishes a more elaborate role for the NPC in mediating nucleocytoplasmic transport than previously appreciated (Makhnevych et al., 2003).

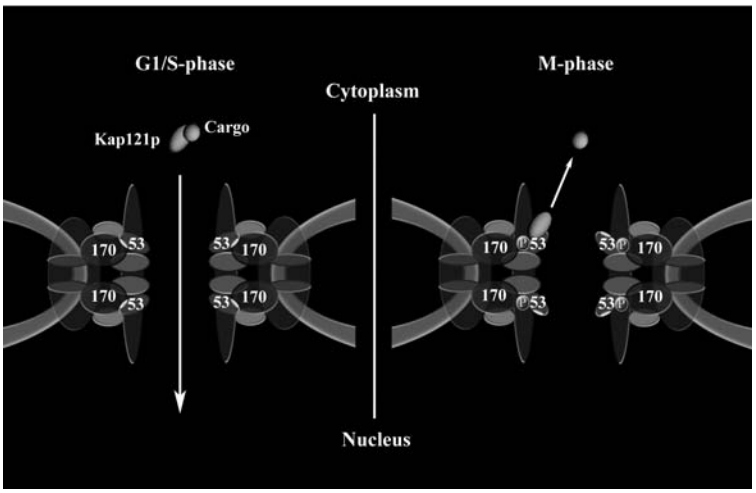


Figure 3. Regulating the Kap121p-mediated transport pathway. The interaction of Nup53p (53) with a neighbor nucleoporin, Nup170p (170), is altered between G1/S and M-phase of the cell cycle. The binding of Nup53p to Nup170p during G1/S masks a high affinity Kap121p binding domain (diagrammed as a yellow oval on Nup53p) and allows Kap121p import to procede unimpeded. In M-phase, Nup53p is phosphorylated (P) and the interaction between Nup53p and Nup170p is broken, exposing the Kap121p binding domain. The interaction between Kap121p and Nup53p inhibits Kap121p import and may induce the premature release of its cargo in the cytoplasm.

It is unlikely that this mechanism is unique to yeast. Recent functional links have been established between the phosphorylation of nups in Aspergillus nidulans and progression through the cell cycle (De Souza et al., 2003). The phosphorylation of Nup98 and Gle2 by NIMA kinase is necessary for the nuclear accumulation of both the mitotic kinase cdc2/cyclin B complex and tubulin in the nucleus. These events are essential for the timely progression into mitosis and the formation of the mitotic spindle (De Souza et al., 2003; Ovechkina et al., 2003). Furthermore, similar mechanisms likely function in organisms with an open mitosis at points prior to NE disassembly or shortly after its reformation, as well as at other points in the cell cycle. This intriguing idea is stimulated by previous observations in mammalian cells showing that a subset of nups, including

Nup153, Nup214, and Nup358, are phosphorylated during S-phase when the NE is intact (Favreau et al., 1996), as well as data showing that phosphorylation, most likely of nups, can inhibit nuclear transport (Kehlenbach and Gerace, 2000).

Conclusions

While it is clear that our current inventory of the components that make-up the transport machinery is nearly complete, our understanding of how they functionally interact to control transport continues to evolve. As this review details, this is particularly true with respect to the role of the NPC in modulating its molecular architecture to regulate its association with the soluble transport machinery. The capacity of the NPC to regulate nuclear transport of specific karyopherins and their cargos, or to globally alter levels of transport is indicative of both the fidelity and range of this transport system. The challenge ahead is to define the nuances of interactions that define these regulatory mechanisms, and how they impinge on cellular function.

References

Aitchison, J. D., G. Blobel and M. P. Rout 1995a. Nup120p: a yeast nucleoporin required for NPC distribution and mRNA transport. J. Cell Biol. 131: 1659-75.

Aitchison, J. D., M. P. Rout, M. Marelli, G. Blobel and R. W. Wozniak 1995b. Two novel related yeast nucleoporins Nup170p and Nup157p: complementation with the vertebrate homologue Nup155p and functional interactions with the yeast nuclear pore-membrane protein Pom152p. J. Cell Biol. 131: 1133-48.

Ben-Efraim, I. and L. Gerace 2001. Gradient of increasing affinity of importin beta for nucleoporins along the pathway of nuclear import. J. Cell Biol. 152: 411-7.

Booth, J. W., K. D. Belanger, M. I. Sannella and L. I. Davis 1999. The yeast nucleoporin Nup2p is involved in nuclear export of importin alpha/Srp1p. J. Biol. Chem. 274: 32360-7.

Cronshaw, J. M., A. N. Krutchinsky, W. Zhang, B. T. Chait and M. J. Matunis 2002. Proteomic analysis of the mammalian nuclear pore complex. J. Cell Biol. 158: 915-27.

De Souza, C. P., K. P. Horn, K. Masker and S. A. Osmani 2003. The SONB(NUP98) nucleoporin interacts with the NIMA kinase in Aspergillus nidulans. Genetics 165: 1071-81.

Doye, V. and E. Hurt 1997. From nucleoporins to nuclear pore complexes. Curr. Opin. Cell Biol. 9: 401-11.

Favreau, C., H. J. Worman, R. W. Wozniak, T. Frappier and J. C. Courvalin 1996. Cell cycle-dependent phosphorylation of nucleoporins and nuclear pore membrane protein Gp210. Biochemistry 35: 8035-44.

Feldherr, C. M. and D. Akin 1993. Regulation of nuclear transport in proliferating and quiescent cells. Exp. Cell Res. 205: 179-86.

Feldherr, C. M. and D. Akin 1994. Variations in signal-mediated nuclear transport during the cell cycle in BALB/c 3T3 cells. Exp. Cell Res. 215: 206-10.

Fontoura, B. M., G. Blobel and N. R. Yaseen 2000. The nucleoporin Nup98 is a site for GDP/GTP exchange on ran and termination of karyopherin beta 2-mediated nuclear import. J. Biol. Chem. 275: 31289-96.

Fried, H. and U. Kutay 2003. Nucleocytoplasmic transport: taking an inventory. Cell Mol. Life Sci. 60: 1659-88.

Galy, V., O. Gadal, M. Fromont-Racine, A. Romano, A. Jacquier and U. Nehrbass 2004. Nuclear retention of unspliced mRNAs in yeast is mediated by perinuclear Mlp1. Cell 116: 63-73.

Galy, V., I. W. Mattaj and P. Askjaer 2003. Caenorhabditis elegans nucleoporins Nup93 and Nup205 determine the limit of nuclear pore complex size exclusion in vivo. Mol. Biol. Cell 14: 5104-15.

Gilchrist, D. and M. Rexach 2003. Molecular basis for the rapid dissociation of nuclear localization signals from karyopherin alpha in the nucleoplasm. J. Biol. Chem. 278: 51937-49.

Grandi, P., T. Dang, N. Pane, A. Shevchenko, M. Mann, D. Forbes and E. Hurt 1997. Nup93, a vertebrate homologue of yeast Nic96p, forms a complex with a novel 205-kDa protein and is required for correct nuclear pore assembly. Mol. Biol. Cell 8: 2017-38.

Gustin, K. E. and P. Sarnow 2001. Effects of poliovirus infection on nucleo-cytoplasmic trafficking and nuclear pore complex composition. Embo J. 20: 240-9.

Harel, A., A. V. Orjalo, T. Vincent, A. Lachish-Zalait, S. Vasu, S. Shah, E. Zimmerman, M. Elbaum and D. J. Forbes 2003. Removal of a single pore subcomplex results in vertebrate nuclei devoid of nuclear pores. Mol. Cell 11: 853-64.

Her, L. S., E. Lund and J. E. Dahlberg 1997. Inhibition of Ran guanosine triphosphatase-dependent nuclear transport by the matrix protein of vesicular stomatitis virus. Science 276: 1845-8.

Hood, J. K., J. M. Casolari and P. A. Silver 2000. Nup2p is located on the nuclear side of the nuclear pore complex and coordinates Srp1p/importin-alpha export. J. Cell Sci. 113: 1471-80.

Kaffman, A. and E. K. O'Shea 1999. Regulation of nuclear localization: a key to a door. Annu. Rev. Cell Dev. Biol. 15: 291-339.

Kaffman, A., N. M. Rank, E. M. O'Neill, L. S. Huang and E. K. O'Shea 1998. The receptor Msn5 exports the phosphorylated transcription factor Pho4 out of the nucleus. Nature 396: 482-6.

Kaffman, A., N. M. Rank and E. K. O'Shea 1998. Phosphorylation regulates association of the transcription factor Pho4 with its import receptor Pse1/Kap121. Genes Dev. 12: 2673-83.

Kehlenbach, R. H. and L. Gerace 2000. Phosphorylation of the nuclear transport machinery down-regulates nuclear protein import in vitro. J. Biol. Chem. 275: 17848-56.

Kenna, M. A., J. G. Petranka, J. L. Reilly and L. I. Davis 1996. Yeast N1e3p/Nup170p is required for normal stoichiometry of FG nucleoporins within the nuclear pore complex. Mol. Cell Biol. 16: 2025-36.

Lusk, C. P., T. Makhnevych, M. Marelli, J. D. Aitchison and R. W. Wozniak 2002. Karyopherins in nuclear pore biogenesis: a role for Kap121p in the assembly of Nup53p into nuclear pore complexes. J. Cell Biol. 159: 267-78.

Macara, I. G. 2001. Transport into and out of the nucleus. Microbiol. Mol. Biol. Rev. 65: 570-94.

Madison, D. L., P. Yaciuk, R. P. Kwok and J. R. Lundblad 2002. Acetylation of the adenovirus-transforming protein E1A determines nuclear localization by disrupting association with importin-alpha. J. Biol. Chem. 277: 38755-63.

Makhnevych, T., C. P. Lusk, A. M. Anderson, J. D. Aitchison and R. W. Wozniak 2003. Cell cycle regulated transport controlled by alterations in the nuclear pore complex. Cell 115: 813-23.

Marelli, M., J. D. Aitchison and R. W. Wozniak 1998. Specific binding of the karyopherin Kap121p to a subunit of the nuclear pore complex containing Nup53p, Nup59p, and Nup170p. J. Cell Biol. 143: 1813-30.

Matsuura, Y., A. Lange, M. T. Harreman, A. H. Corbett and M. Stewart 2003. Structural basis for Nup2p function in cargo release and karyopherin recycling in nuclear import. Embo J. 22: 5358-69.

Mosammaparast, N., K. R. Jackson, Y. Guo, C. J. Brame, J. Shabanowitz, D. F. Hunt and L. F. Pemberton 2001. Nuclear import of histone H2A and H2B is mediated by a network of karyopherins. J. Cell Biol. 153: 251-62.

Nakielny, S., S. Shaikh, B. Burke and G. Dreyfuss 1999. Nup153 is an M9-containing mobile nucleoporin with a novel Ran-binding domain. Embo J. 18: 1982-95.

Olsson, M., S. Scheele and P. Ekblom 2004. Limited expression of nuclear pore membrane glycoprotein 210 in cell lines and tissues suggests cell-type specific nuclear pores in metazoans. Exp. Cell Res. 292: 359-70.

Ovechkina, Y., P. Maddox, C. E. Oakley, X. Xiang, S. A. Osmani, E. D. Salmon and B. R. Oakley 2003. Spindle formation in Aspergillus is coupled to tubulin movement into the nucleus. Mol. Biol. Cell 14: 2192-200.

Petersen, J. M., L. S. Her, V. Varvel, E. Lund and J. E. Dahlberg 2000. The matrix protein of vesicular stomatitis virus inhibits nucleocytoplasmic transport when it is in the nucleus and associated with nuclear pore complexes. Mol. Cell Biol. 20: 8590-601.

Powers, M. A., D. J. Forbes, J. E. Dahlberg and E. Lund 1997. The vertebrate GLFG nucleoporin, Nup98, is an essential component of multiple RNA export pathways. J. Cell Biol. 136: 241-50.

Pyhtila, B. and M. Rexach 2003. A gradient of affinity for the karyopherin Kap95p along the yeast nuclear pore complex. J. Biol. Chem. 278: 42699-709.

Ribbeck, K. and D. Gorlich 2001. Kinetic analysis of translocation through nuclear pore complexes. Embo J. 20: 1320-30.

Ribbeck, K. and D. Gorlich 2002. The permeability barrier of nuclear pore complexes appears to operate via hydrophobic exclusion. Embo J. 21: 2664-71.

Rout, M. P., J. D. Aitchison, M. O. Magnasco and B. T. Chait 2003. Virtual gating and nuclear transport: the hole picture. Trends Cell Biol. 13: 622-8.

Rout, M. P., J. D. Aitchison, A. Suprapto, K. Hjertaas, Y. Zhao and B. T. Chait 2000. The yeast nuclear pore complex: composition, architecture, and transport mechanism. J. Cell Biol. 148: 635-51.

Rout, M. P., G. Blobel and J. D. Aitchison 1997. A distinct nuclear import pathway used by ribosomal proteins. Cell 89: 715-25.

Ryan, K. J. and S. R. Wente 2000. The nuclear pore complex: a protein machine bridging the nucleus and cytoplasm. Curr. Opin. Cell Biol. 12: 361-71.

Shah, S. and D. J. Forbes 1998. Separate nuclear import pathways converge on the nucleoporin Nup153 and can be dissected with dominant-negative inhibitors. Curr. Biol. 8: 1376-86.

Shah, S., S. Tugendreich and D. Forbes 1998. Major binding sites for the nuclear import receptor are the internal nucleoporin Nup153 and the adjacent nuclear filament protein Tpr. J. Cell Biol. 141: 31-49.

Shulga, N. and D. S. Goldfarb 2003. Binding dynamics of structural nucleoporins govern nuclear pore complex permeability and may mediate channel gating. Mol. Cell Biol. 23: 534-42.

Shulga, N., N. Mosammaparast, R. Wozniak and D. S. Goldfarb 2000. Yeast nucleoporins involved in passive nuclear envelope permeability. J. Cell Biol. 149: 1027-38.

Smith, W. A., B. T. Schurter, F. Wong-Staal and M. David 2004. Arginine methylation of RNA helicase a determines its subcellular localization. J. Biol. Chem. 279: 22795-8.

Smitherman, M., K. Lee, J. Swanger, R. Kapur and B. E. Clurman 2000. Characterization and targeted disruption of murine Nup50, a p27(Kip1)-interacting component of the nuclear pore complex. Mol. Cell Biol. 20: 5631-42.

Solsbacher, J., P. Maurer, F. Vogel and G. Schlenstedt 2000. Nup2p, a yeast nucleoporin, functions in bidirectional transport of importin alpha. Mol. Cell Biol. 20: 8468-79.

Stommel, J. M., N. D. Marchenko, G. S. Jimenez, U. M. Moll, T. J. Hope and G. M. Wahl 1999. A leucine-rich nuclear export signal in the p53 tetramerization domain: regulation of subcellular localization and p53 activity by NES masking. Embo J. 18: 1660-72.

Strawn, L. A., T. Shen, N. Shulga, D. S. Goldfarb and S. R. Wente 2004. Minimal nuclear pore complexes define FG repeat domains essential for transport. Nat. Cell Biol. 6: 197-206.

Strom, A. C. and K. Weis 2001. Importin-beta-like nuclear transport receptors. Genome Biol 2: REVIEWS3008.

Suntharalingam, M. and S. R. Wente 2003. Peering through the pore: nuclear pore complex structure, assembly, and function. Dev. Cell 4: 775-89.

Ullman, K. S., S. Shah, M. A. Powers and D. J. Forbes 1999. The nucleoporin nup153 plays a critical role in multiple types of nuclear export. Mol. Biol. Cell 10: 649-64.

Uv, A. E., P. Roth, N. Xylourgidis, A. Wickberg, R. Cantera and C. Samakovlis 2000. members only encodes a Drosophila nucleoporin required for rel protein import and immune response activation. Genes Dev. 14: 1945-57.

von Kobbe, C., J. M. van Deursen, J. P. Rodrigues, D. Sitterlin, A. Bachi, X. Wu, M. Wilm, M. Carmo-Fonseca and E. Izaurralde 2000. Vesicular stomatitis virus matrix protein inhibits host cell gene expression by targeting the nucleoporin Nup98. Mol. Cell 6: 1243-52.

Walther, T. C., A. Alves, H. Pickersgill, I. Loiodice, M. Hetzer, V. Galy, B. B. Hulsmann, T. Kocher, M. Wilm, T. Allen, I. W. Mattaj and V. Doye 2003. The conserved Nup107-160 complex is critical for nuclear pore complex assembly. Cell 113: 195-206.

Walther, T. C., M. Fornerod, H. Pickersgill, M. Goldberg, T. D. Allen and I. W. Mattaj 2001. The nucleoporin Nup153 is required for nuclear pore basket formation, nuclear pore complex anchoring and import of a subset of nuclear proteins. Embo J. 20: 5703-14.

Weis, K. 2003. Regulating access to the genome: nucleocytoplasmic transport throughout the cell cycle. Cell 112: 441-51.

Wozniak, R. W., M. P. Rout and J. D. Aitchison 1998. Karyopherins and kissing cousins. Trends Cell Biol. 8: 184-8.

Yang, J., E. S. Bardes, J. D. Moore, J. Brennan, M. A. Powers and S. Kornbluth 1998. Control of cyclin B1 localization through regulated binding of the nuclear export factor CRM1. Genes Dev. 12: 2131-43.

Yang, Q., M. P. Rout and C. W. Akey 1998. Three-dimensional architecture of the isolated yeast nuclear pore complex: functional and evolutionary implications. Mol. Cell 1: 223-34.

Zabel, U., V. Doye, H. Tekotte, R. Wepf, P. Grandi and E. C. Hurt 1996. Nic96p is required for nuclear pore formation and functionally interacts with a novel nucleoporin, Nup188p. J. Cell Biol. 133: 1141-52.

The Jeanne Manery Fisher Memorial Scholarship

Mariam Packham,

University Professor Emeritus,
Department of Biochemistry, University of Toronto

It is now 18 years since the establishment in 1987 of the Jeanne Manery Fisher Memorial Lectureship of the Canadian Biochemical Society (now the Canadian Society of Biochemistry, Molecular and Cellular Biology). On alternate years, this lecture is to be given by an eminent Canadian woman scientist who has been singled out for her outstanding career in either research, teaching, or social accomplishments associated with the fields of biochemistry, molecular or cellular biology.

Jeanne Manery Fisher

Why is Jeanne Manery Fisher's memory honoured in this way? Those of us who were inspired by her as their teacher, mentor, colleague and friend know why, but we are reaching, or have reached, retirement age. Younger members of the Society who did not have the privilege of knowing Jeanne may not realize the size of the debt they owe her for blazing a trail for them. She was certainly a feminist, but often in a subtle way so that some of those she influenced were probably unaware of the effect she was having on their attitudes. At a time when very few women were in the professorial ranks in the sciences at the University of Toronto, she showed the way to those who were to follow her, setting standards of excellence, yet warmth and tolerance, that deeply influenced all who knew her. Above all, she was a dedicated scientist and teacher who stimulated and encouraged both undergraduate and graduate students.

Jeanne died in 1986 after 46 years in the Department of Biochemistry at the University of Toronto, but the dry recital of her CV offers few hints about the effect that this remarkable woman had on several generations of scientists, both women and men, in Canada. Born in 1908, she grew up near the small town of Chesley, Ontario where her imagination was caught by a young teacher of biology who introduced her to the fascinating study of how living things work. After a year at Normal School (i.e. Teachers' College) and two years of teaching public school, she had saved enough money, supplemented by help from her family and an impressive list of scholarships, to earn her B.A. in Biological and Medical Sciences in 1932 at the University of Toronto. Supported by demonstratorships, she obtained her M.A. in 1933 and her Ph.D. in 1935 with Prof. Laurence Irving in the Department of Physiology at Toronto, and thus began her life-long interest in biomembranes. They saw "active transport" of electrolytes into fish embryos before the term was coined, and observed the protective hardening by calcium of the soft, external capsule of unfertilized fish eggs. Summers with Prof. Irving's group at the Marine Biological Laboratory at Woods Hole exposed her to bright young scientists who later became leaders in their fields. Jeanne's post-doctoral studies were with Dr. Wallace O. Fenn in the Physiology Department at the University of Rochester in New

York and with Dr. A. Baird Hastings at Harvard University in Boston, where she honed her skill with the van Slyke blood gas analyser and pursued her interest in pH control and electrolytes in living systems. During these post-doctoral studies, she was a Fellow of the U.S.A. National Research Council in the Biological Sciences, a position that she later noted "was not usually held by either foreigners or females".

Jeanne then returned as a staff member to Rochester which at that time was one of only three places in the world with a cyclotron producing short-lived radio-isotopes of inorganic ions which she used in studies demonstrating their transport across the plasma membrane. Later, she wrote that "the years in Rochester were among the happiest of my life. They were most productive in terms of research, of developing self confidence, of acquiring a love of teaching and of making lifelong friends."

Jeanne's marriage to Kenneth Fisher in 1938 brought her back to Toronto (although she commuted to Rochester for another year). Dr. Kenneth Fisher had been appointed as a staff member in the Zoology Department at the University of Toronto, but Jeanne's way was blocked because of the university's policy that there were to be no married women on staff. However, Prof. Wasteneys, the chairman of the Biochemistry Department, was able to appoint her as a junior demonstrator because "the position was so unimportant". She remained at this rank until 1948, while trying to adjust to the prevailing attitude that "women in science were indeed second rate citizens". The list of her accomplishments during these 8 years is astonishing. She carried a full undergraduate teaching load in the Biochemistry Department, including teaching double classes of medical students destined for war service; took over her husband's lecture and laboratory teaching in the Department of Zoology when he was in the Operational Research Unit of Canada during World War II; carried out research on shock in collaboration with Prof. Donald Solandt; established her own research laboratory focused on electrolytes where, with the connivance of Prof. Wasteneys, she was allowed to supervise graduate students; and gave birth to two children (in 1942 and 1945). But not until 1948 was she finally appointed as an Assistant Professor in the Department. She later wrote that at that time she began to sense that discrimination against women "in her immediate environment" was starting to lessen, but this was a slow process and she was not promoted to a full professorship until 1965, despite her active research program and heavy teaching loads.

In 1950 and 1951 she served as a Senior Scientist in the Defence Research Northern Laboratory at Fort Churchill, Manitoba, working on military problems as they were affected by life in the arctic. In 1965, she spent a short sabbatical leave in Cambridge, England.

With her graduate students and research assistants, Jeanne carried out investigations of the plasma membrane, beginning at a time when it was generally considered to be an inert wrapping to be discarded before studying the reactions of the inner contents of cells. Her research projects included the control of Na+ and K+ concentrations in cells, the effect of insulin on electrolytes in muscle, and the role of Ca2+ in the structure and function of membranes; her group was one of the first to recognize cation-dependent, nucleotide-converting ectoenzymes. In addition, she was given numerous departmental, faculty and university administrative responsibilities, including serving on the committee that organized a new medical curriculum that was introduced in 1970, serving on and chairing the Admissions Committee of the Faculty of Medicine, and chairing the Senate Committee on 'The Role of the Faculty of Food Sciences in the University and in the Province". Recognizing the need to "disseminate information in understandable terms to those around us", Jeanne took an active role in the Royal Canadian Institute as a Councillor, Treasurer, Vice-President, and Honorary Secretary in the late 1970's.

Although she became Professor Emeritus in 1976, she continued research and publishing until her death, 10 years later. She was honoured in 1977 by the award of the Queen's Jubilee medal for her

contributions to science, and the University of Toronto Sesquicentennial Celebration Long Service Honour Award. In 1982, Memorial University of Newfoundland conferred on her the degree of Doctor of Science, honoris causa.

A charter member of the Canadian Biochemical Society, she was acutely aware of the lack of involvement of women scientists in its affairs. This problem came to a head as a result of the International Congress of Biochemistry which Canada hosted in Toronto in 1979 on behalf of the International Union of Biochemistry. The relative lack of women participants prompted the Chairman of the Equal Opportunities Committee of the American Biochemical Society to write a letter saying that he was "dismayed that the symposium speakers and chairpersons were so overwhelmingly male." Thus chastised, the Canadian Biochemical Society established an Equal Opportunities Committee in 1980 with Jeanne Manery Fisher as its first chairperson. Since that time, the participation and visibility of women in the Society has increased. Her achievements as a trail-blazer were recognized by the Canadian Association for Women in Science and the Equal Opportunities Committee of the Canadian Biochemical Society by sponsorship of a dinner in her honour in Montreal in1981.

The Jeanne Manery Fisher Memorial Lectureship honours her for her scientific achievements, her dedication to teaching, her warm and encouraging relationships with students and colleagues, and her leadership toward the acceptance of women as equal partners in the field of science.

Jeanne Manery Fisher Memorial Lectureship Award Winners*

1988 Dorothy Crowfoot Hodgkin, Laboratory of Molecular Biophysics, Department of Zoology, University of Oxford, Oxford, U.K.
The X-ray analysis of the structure of insulin 1935-1972 to the present

1991 Rose M. Johnstone, Department of Biochemistry, McGill University
Reticulocyte maturation: circulating transferrin receptors and the development of assays for anemias

1994 Shirley Gillam, Department of Pathology, University of British Columbia
Molecular biology of rubella virus structural proteins

1996 Nicole Bégin-Heick, Department of Biochemistry, University of Ottawa
Mice and women: leptin, and the b3-adrenergic receptor and obesity

1998 Rhoda Blostein, Departments of Biochemistry and Medicine, McGill University
Structure-function studies of the sodium pump

2000 Amira Klip, Division of Cell Biology, Hospital for Sick Children, and Department of Biochemistry, University of Toronto
Insulin-regulated glut4 traffic in muscle cells: a concerted action of the cytoskeleton, selective fusion proteins and endosomal sorting mechanisms

2001 Carol E. Cass, Department of Oncology, Cross Cancer Institute and the University of Alberta, Edmonton
Nucleoside transporter proteins. From membrane biology to therapeutic applications

2002 Mona Nemer, Laboratory of Cardiac Growth and Differentiation, Institut de Recherches Cliniques de Montréal
GATA-4: An integrator of hormonal and growth factor signalling in the heart

2004 Morag Park, Departments of Medicine, Oncology and Biochemistry, McGill University, and the McGill University Health Centre
The Met receptor tyrosine kinase: from tubes to tumorigenesis

*In 1987, Rose Sheinin presented a lecture in memory of Jeanne Manery Fisher at the CBS Equal Opportunities Committee Luncheon during the CFBS Annual Meeting in Winnipeg. The title was ***Jeanne Manery Fisher: Scientist, feminist, a model of excellence***.

The Jeanne Manery Fisher Award Revisited

Rose M. Johnstone
Department of Biochemistry, McGill University

The Jeanne Manery Fisher award has now been on the roster of recognition offered by the Canadian Society for Biochemistry and Molecular Biology for nearly 20 years. Its first recipient was one of the giants of modern biology/chemistry, Dorothy Crowfoot Hodgkin. The honoree was an outstanding crystallographer and a social activist. As the guest of the Society, she gave the keynote address at the annual meeting in St. Foy (Quebec City) in 1988, after being named the Jeanne Manery Fisher Lecturer.

To date, Dr. Hodgkin has been the only non-Canadian woman to be given this award and she regarded it as an honour to keep alive the memory of a female Canadian Scientist. The fact that the scientist whose name was attached to the award had striven to push aside the barriers to recognition of women and their achievements in the Canadian Society of Biochemistry and Molecular Biology seemed to add to Dr. Hogkin's pleasure in accepting the award.

For those of you who are too young or perhaps have forgotten the history of this award, Jeanne convinced the Canadian Biochemical Society to set up an Equal Opportunities Committee (EOC), to examine ways and means to enhance the opportunities for women in the Society. The Committee sought ways to improve the recognition and participation of women in the Society's activities, including opportunities to run for executive positions instead of being relegated to benign neglect. It was hoped that with a higher profile and increased awareness would come also the likelihood of being remembered and invited to lecture at the Annual Meetings sponsored by the Society, as well as internationally. Although both the size of the EOC (5 individuals) and its budget were small, important measures were implemented which changed the face of the Society and made it more representative of its membership. Two important recommendations adopted by the Society were: 1) The Chair of the Nominating Committee went to the individual who won the largest number of votes in elections for the Nominating Committee. 2) At least two members of the nominating Committee had to be women. If two were not elected, they would be co-opted.

These simple measures proved highly effective in bringing women into the Executive. In fact, in many of the next elections, there was no need to enforce the regulation of two women on the Nominating Committee by co-option, since at least two were elected from the slate of men and women, even when the majority of the slate were men. There were other new committees set up to help and advise graduate students — male and female alike — on fostering their careers and overcoming obstacles and just plain encouragement at time of need. Many of these are still ongoing.

The changes which have come about in society at large have had an impact on our Society as well. Turn back the clock to 1979, when two women were invited speakers out of 200 at the IUBMB Congress. Many of us recall the days when all correspondence from the then MRC was addressed only to the male gender! Without action, the women in the Society might still be in the camp of the forgotten and neglected. There is no doubt that the establishment of the EOC had a major impact on the status of women in our Society. Until the mid-seventies, after twenty years in existence, there had been but a single woman elected President of the Society, Rose Sheinin, who was President from 1975-76. After 1980, the following women served in that capacity: Rose Johnstone, 1985-1986; Catherine Lazier, 1986-1987; Yvonne

Lefevre, 1991-1992; Frances Sharom, 2000-2001.) Without conscious effort to keep a high profile in the Society, it won't take a decade before the female scientists find themselves returned to the back benches of the Society's activities at all levels.

Prior to 1980, the number of woman invited from within or outside the Society to present major papers at our meetings was negligible. Subsequent to 1980, in the last twenty years, women have more frequently been selected as major speakers, as anyone interested in the Society's record can check. The Jeanne Manery Fisher Award made certain that at least a single woman would be visible to the many young, aspiring female scientists in our discipline. We owe a debt to Jeanne for helping to make our Society more democratic, representing all its participants, not only half of the human race.

In the years since the inaugural lecture, a strange malaise has befallen a significant number of practicing female scientists in the biological/medical arena, when they are proposed as recipients to honour Jeanne Manery Fisher. They excuse themselves because they do not want to be considered for an award exclusive to women! Presumably, the argument would run that if women only are eligible, the scientific merit of the award is demeaned because the competition is reduced. Such an argument would and could logically apply to any restricted award, whatever the basis of the restriction; ethnic origin, mother tongue or even age. Indeed, one could argue that in a democratic, multiracial society, any attempt to discriminate between citizens on any basis except merit is inconsistent with the democratic values of the society. Taken to its extreme, there should be no prize that is limited to a select group in the general community. In Canada, the Giller Prize for literature would include all writers and not just those published in English. I have heard no outcry that in a country like Canada, there should be no provincial awards, or even civic awards — except those run on a national basis. The absurdity of such regulations is immediately apparent, and it has never been shown that a potential honoree in Quebec turned down the honour because the basis for making the award was restricted to Quebeckers!

In the particular case under discussion, the main objective is to honour the memory of Jeanne Manery Fisher. Dismayed by the evidence that women were overlooked in our scientific community, she used her determination and influence to bring about change and create a more even playing field. The second objective is to raise the profile of outstanding female scientists and recognize their achievements by the members of our discipline in Canada, thereby helping to attain a higher visibility for practising female scientists. The third objective in seeking a candidate for this award is to choose an individual who has taken a lead from Jeanne's footsteps and tries to improve, foster and elevate the participation of woman in our discipline. The up and coming — or the "arrived" — female scientists who are nominated and named as awardees of the Jeanne Manery Fisher Prize, should recognize that they bring honour to Jeanne's name and acknowledge her important contributions. The high quality of the recipients' scientific work bears witness to Jeanne's belief in fostering scientific achievement by women and to have it recognized publicly inside and outside our community. In addition, we have a commitment to her memory to foster equal opportunities for all.

The Jeanne Manery Fisher Memorial Award Lecture

The Met RTK: from Tubes to Tumorigenesis

Morag Park,

Molecular Oncology Group, McGill University Hospital Centre, Montreal

Abstract

The receptor for hepatocyte growth factor/scatter factor (HGF/SF), Met, controls a program of invasive epithelial growth through the co-ordination of cell proliferation and survival, cell migration and epithelial morphogenesis. This process is important during embryogenesis and for organ regeneration in the adult. However, when deregulated the HGF/SF-Met signalling axis contributes to tumorigenesis and metastasis.

Discovery of Met and HGF/SF

Hepatocyte growth factor, the ligand for the Met receptor tyrosine kinase, was originally identified as a mitogen for hepatocytes in culture (Nakamura et al., 1989; Zarnegar and Michalopoulos, 1989). HGF is identical to scatter factor, a fibroblast-derived factor that promotes dispersal of sheets of epithelial cells (Stoker et al., 1987) as well as branching tubulogenesis of epithelia grown in three dimensional cultures (Montesano et al., 1991a). HGF/SF is thus a unique growth factor that elicits multiple cellular responses including mitogenesis, cell motility and morphogenesis (reviewed by Comoglio and Boccaccio, 2001; Birchmeier et al., 2003). HGF/SF is produced primarily by mesenchymal cells and is secreted as an inactive precursor (pro-HGF/SF) which is activated by proteolytic cleavage into disulfide-linked a and b chains (Nakamura, 1991).

The high affinity receptor for HGF/SF is the Met receptor tyrosine kinase (Bottaro et al., 1991). Met was first identified as the product of a human oncogene, generated following a chromosomal rearrangement, where a protein dimerization motif (Tpr) is fused to the cytoplasmic kinase domain of Met (Cooper et al., 1984; Park et al., 1986) (Fig. 1). Cloning of the Met gene identified it as a transmembrane receptor tyrosine kinase (Park et al., 1987). The Tpr-Met fusion protein is oncogenic, and is constitutively dimerized and activated in the absence of HGF/SF (Rodrigues and Park, 1993). Tpr-Met now acts as a prototype for a large family of receptor tyrosine kinase (RTK) oncogenes that are activated following chromosomal rearrangements in human tumors (Rodrigues and Park, 1994b; Lamorte and Park, 2001).

Structure of Met and HGF/SF

Met is synthesized as a single chain precursor of 170 kDa that is glycosylated, then cleaved at a furin site, as it matures on the cell surface, to generate a disulfide-linked heterodimer of 190 kDa

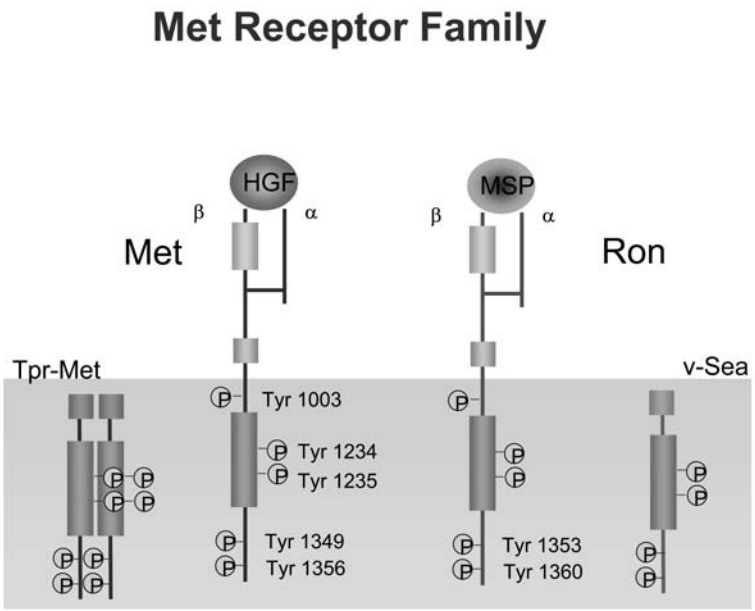


Figure 1. The Met receptor tyrosine kinase family contains the Met and Ron RTKs. Met was first identified as an activated oncogene, Tpr-Met. V-Sea is the avian oncogenic homologue of Ron

(Giordano et al., 1989; Komada et al., 1993). This consists of a 50 kDa extracellular α-chain and 140 kDa membrane spanning ß-chain (Fig. 1). The latter contains the juxtamembrane and kinase domains as well as the C-terminal tail, which is essential for downstream signalling. Based on shared structural homology, Met is classified as the prototype member of a RTK subfamily that also contains the Ron RTK (Ronsin et al., 1993) (Fig. 1). In addition, the ligand for Ron, macrophage stimulating protein (MSP), is highly homologous to HGF (Gaudino et al., 1994). HGF and MSP contain a domain structure typical of the proteinases of the plasminogen family, and constitute a family with related biological activities, termed plasminogen-related growth factors (Donate et al., 1994). The extracellular portions of Met and Ron, contain a region of homology to the SEMA domain of the semaphorin axon guidance proteins (Maestrini et al., 1996; Artigiani et al., 1999). This region contains the α-chain, and 212 residues of the ß-chain, that together are predicted to fold into a ß-propellor structure (Gherardi et al., 2003). ß-propellor structures are found in other proteins and are thought to be involved in protein-protein interaction (Xiong et al., 2002). In Met, the integrity of this domain is required for HGF/SF binding, as well as receptor dimerization (Gherardi et al., 2003; Kong-Beltran et al., 2004).

Functions of HGF/SF and Met

HGF/SF and Met are expressed in many tissues in the adult. In these tissues, HGF/SF is produced by mesenchymal cells and activates its receptor Met, expressed in epithelial and endothelial cells through a paracrine mode of action. HGF/SF is a potent mitogen for primary hepatocytes and renal tubule cells (Zarnegar and Michalopoulos, 1989), stimulates epithelial cell dissociation and invasion (Stoker et al., 1987), and acts as an initiating signal for an intrinsic cellular morphogenic program of kidney, breast and lung epithelium grown in matrix culture (Montesano et al., 1991b; Weidner et al., 1993; Sachs et al., 1996). In the adult, HGF/SF and Met are thought to be involved in a general repair of tissue damage. Elevated levels of HGF/SF and Met are observed in both injured tissues following kidney, liver or heart injury, as well as in the circulating plasma (Michalopoulos and DeFrances, 1997; Nakamura et al., 2000; Matsumoto and Nakamura, 2001). HGF/SF has cytoprotective activity *in vivo* and protects against various types of tissue injury (Roos et al., 1995; Jin et al., 2003). HGF/SF is also a potent angiogenic factor (Grant et al., 1993) through induction of VEGF, a positive regulator of angiogenesis, as well inhibition of thrombospondin, a negative regulator of angiogenesis (Zhang et al., 2003; Saucier et al., 2004).

HGF/SF and Met are essential during embryogenesis and mice null for either gene die in utero, with reduced proliferation and survival of placental trophoblasts as well as hepatocytes (Schmidt et al., 1995; Uehara et al., 1995). This is consistent with HGF/SF acting as a potent mitogen for hepatocytes and the important role of Met in liver regeneration (Borowiak et al., 2004; Huh et al., 2004). In addition, these studies have demonstrated a role for Met and HGF/SF in the development and innervation of skeletal muscle, and directing the growth of axonal cones (Schmidt et al., 1995; Uehara et al., 1995; Yang and Park, 1995; Ebens et al., 1996; Maina et al., 1997). The phenotypes of the Met and HGF/SF null mice are identical, indicating that during embryogenesis Met is the only receptor for HGF/SF and vice versa (Schmidt et al., 1995; Uehara et al., 1995; Birchmeier and Gherardi, 1998).

Met signal transduction

While signaling pathways downstream from RTKs involved in a mitogenic response had been characterized in detail, until recently, little was known about the signalling pathways involved in the complex program of invasive growth regulated by the Met receptor. Epithelial cells, and in particular, the Madin-Darby canine kidney (MDCK) cell line, respond to HGF/SF and Met signals by scattering in two dimensional cultures, and in the formation of branching tubules in three dimensional cultures (Fig. 2), and have been a cell line of choice to dissect the signals involved in these processes. HGF/SF-induced dispersal of epithelial colonies occurs in a stepwise transition, where HGF/SF first promotes the breakdown of cell-cell junctions, and

induces changes in epithelial morphology to cells of a more fibroblastic cell shape, with increased motility and invasiveness (Royal and Park, 1995)(Fig. 2). When seeded in a collagen matrix, MDCK cells form hollow cysts of polarized epithelial cells (Fournier et al., 1996). Treatment of MDCK cells with HGF/SF induces the formation of branching tubules (Weidner et al., 1993). Tubular branching is a complex morphogenic process that requires tight co-ordination of cell growth, cell polarity, movement and invasion (reviewed in Pollack et al., 1998).

The use of receptor chimeras demonstrated that the Met cytoplasmic domain is sufficient to mediate all of the pleiotropic biological responses attributed to HGF in epithelial cells, and that these events require Met protein tyrosine kinase activity (Zhu et al., 1994b). Phosphorylated tyrosine residues in the non-catalytic cytoplasmic domains of RTKs act as specific binding sites for Src homology 2 (SH2) and phosphotyrosine binding (PTB) domain-containing proteins, and these in turn transduce intracellular signals (reviewed in Pawson and Scott, 1997).

Upon stimulation with HGF/SF, the Met receptor cytoplasmic domain becomes highly phosphorylated on tyrosine residues (Zhu et al., 1994b). The phosphorylation of two tyrosine residues within the activation loop of the kinase domain is required for the intrinsic kinase activity of Met (Rodrigues and Park, 1994a). Two tyrosine residues within the carboxyl terminus (Y1349 and Y1356) are crucial for cell scatter and branching morphogenesis in Madin-Darby canine kidney (MDCK) epithelial cells (Ponzetto et al., 1994; Zhu et al., 1994a; Fixman et al., 1995). Phosphorylation of these tyrosine residues generates a multisubstrate docking site that is highly conserved between other members of the Met RTK gene family, v-Sea and Ron.

When phosphorylated, Y1356 provides a direct binding site for the Grb2 and Shc adapter proteins, as well as the p85 subunit of PI3kinase (Fig. 3). Shc and Grb2 can couple Met to the Ras-MAPK pathway. In addition, Grb2 acts as an adapter to indirectly recruit multiple proteins to Met. These

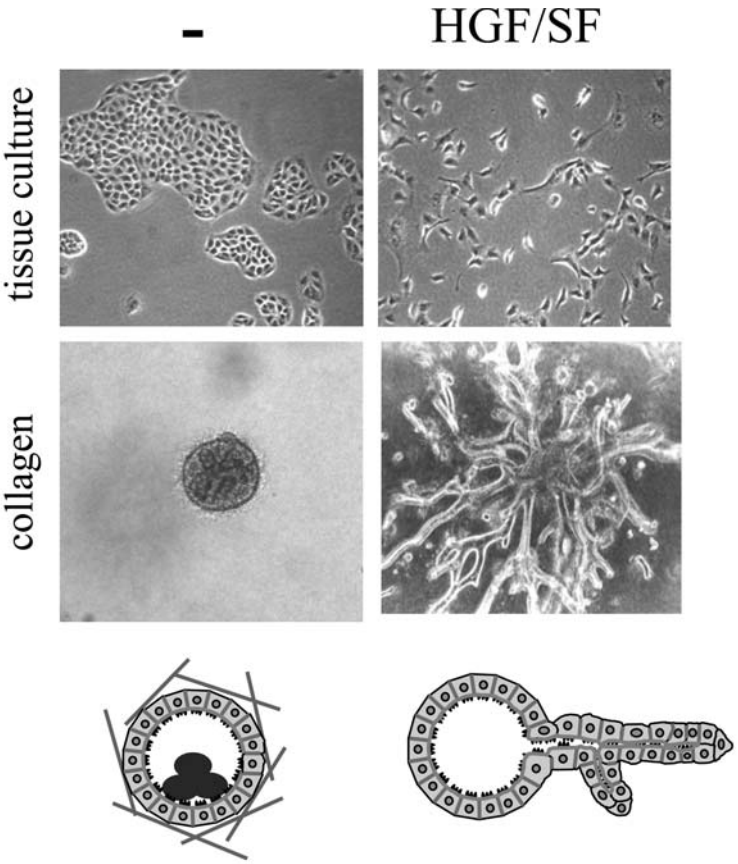


Figure 2. Hepatocyte growth factor scatter factor (HGF/SF) stimulates cellular scattering and branching morphogenesis. HGF/SF stimulates the scattering of colonies of MDCK cells grown on plastic dishes, but stimulates the reorganization of these cells from a hollow cyst into branching tubules when grown in three-dimensional collagen gels.

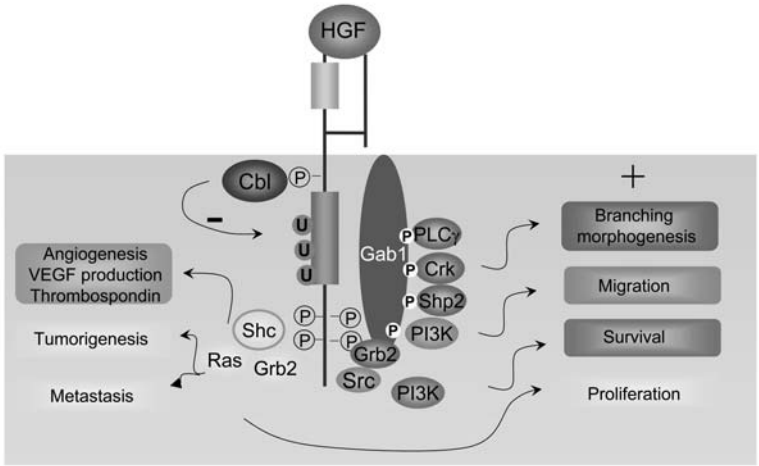


Figure 3. Substrate binding sites and recruitment of proteins to the Met receptor. Twin tyrosines in the carboxyterminal tail of Met (Y1349 and 1356) act as a multisubstrate binding site conserved in Met family members. Y1356 serves to recruit the adaptor proteins Grb2 and Shc. Grb2 in turn indirectly recruits Gab1 and Cbl to Met. Once phosphorylated, Gab1 recruits the SHP-2 tyrosine phosphatase, Crk adaptor protein, phosphatidylinositol-3'-kinase (PI3'kinase) and phospholipase Cg.

include the Gab1 docking protein as well as the cCbl ubiquitin ligase. Gab1 was initially identified in a library screen as a Grb2 binding protein (Holgado-Madruga et al., 1996) and belongs to a family of docking proteins, including closely related proteins Gab2 and Daughter of Sevenless (DOS), and the more remotely related, Insulin Receptor Substrate-1 (IRS-1), IRS-2, IRS-3, Downstream of Kinases (Dok), and FGF receptor substrate 2 (FRS2) (reviewed in Liu and Rohrschneider, 2002). These proteins lack enzymatic activities. Following activation of tyrosine kinase, and cytokine receptors, they become phosphorylated on tyrosine residues, providing binding sites for multiple proteins involved in signal transduction. In this manner they act to potentiate and diversify the signals downstream from receptors by virtue of their ability to assemble multiprotein complexes.

Gab1 and tubulogenesis

In epithelial cells, Gab1 is the major substrate for the Met receptor tyrosine kinase (Nguyen et al., 1997), and from genetic (Sachs et al., 2000) and cell biological studies (Maroun et al., 1999a; Maroun et al., 1999b; Maroun et al., 2000; Maroun et al., 2003), Gab1 is crucial for many of the biological responses downstream from Met. Although Gab 1 is recruited to many RTKs indirectly through Grb2, its interaction with the Met receptor is unique and involves both indirect as well as direct recruitment of Gab1 (Lock et al., 2000; Lock et al., 2002). The direct interaction of Gab1 with Met requires 13 amino acids within the Gab1 Met binding domain that interact directly with Y1349 of the multisubstrate binding site on the Met C-terminus (Schaeper et al., 2000). This sequence does not resemble classical SH2 or PTB domains and is not conserved in other members of the Gab family. Instead it associates with the Met receptor as a peptide motif that requires structural integrity and amino acids within the Met kinase domain for binding to pY1349 (Lock et al., 2003). This defines a unique interaction between a RTK and its substrate. It allows a direct and robust association between Gab1 and Met that results in prolonged phosphorylation of Gab1 in response to HGF. Prolonged signalling downstream from Gab1 is required for the morphogenic response, whereas other receptors, such as the epidermal growth factor receptor (EGFR), that recruit Gab1 indirectly through Grb2, are unable to induce a morphogenic response in MDCK cells (Maroun et al., 1999a).

Upon tyrosine phosphorylation, Gab1 interacts with multiple proteins involved in signal transduction through their SH2 domains. These include the tyrosine phosphatase, SHP-2, the p85 subunit of PI3'K, PLCg, as well as the Crk adaptor protein (Holgado-Madruga et al., 1996; Garcia-Guzman et al., 1999; Maroun et al., 1999a; Gual et al., 2000; Maroun et al., 2000; Schaeper et al., 2000; Ma et al., 2003; Maeda et al., 2004). The association of Gab1 with the SHP-2 phosphatase or the Crk adapter protein, as well as an intact Gab1 PH domain, is required for the ability of Gab1 to promote the morphogenic program of MDCK epithelial cells downstream from the Met receptor (Fig. 3)(Maroun et al., 1999a; Maroun et al., 2000; Lamorte et al., 2002b). The PH domain of Gab1 binds to phosphatidylinositol-3,4,5-trisphosphate (PIP3), which is essential for subcellular localization of Gab1 and efficient branching tubulogenesis downstream from the Met receptor (Maroun et al., 1999a; Maroun et al., 1999b). SHP-2 contains two tandem SH2 domains followed by a phosphatase domain. Both tyrosine phosphorylation of SHP-2, and binding of its SH2 domains to tyrosine-phosphorylated peptides, enhance its catalytic activity (Neel et al., 2003), possibly through the release of negative regulatory constraints on the phosphatase domain mediated by the SH2 domains of SHP-2 (Barford and Neel, 1998). SHP-2 enhances MAPK activation downstream from Met, indicating a positive function in Met signalling (Fig. 3) (Maroun et al., 2000; Schaeper et al., 2000). The importance for Gab1 downstream from Met signalling has been supported from knock-out studies. Embryos nullizygous for Gab1 display all of the defects observed in Met or HGF/SF null embryos (Itoh et al., 2000; Sachs et al., 2000).

The formation of tubules from polarized epithelia grown in three dimensional organ cultures is a complex cellular response that requires all known Met signals (reviewed in Rosario and Birchmeier,

2003; Zegers et al., 2003). From the use of inhibitors, PI3K and ERK/MAPK and Src pathways are required for the disassembly of adherens junctions cell spreading and cell motility (Royal and Park, 1995; Potempa and Ridley, 1998; Rahimi et al., 1998). The sustained ERK kinase cascade, mediated by Gab1-SHP-2 interactions, is required for the remodelling of adherens junctions and cell proliferation during the morphogenic response (Maroun et al., 2000; Schaeper et al., 2000). Met also activates pathways that modulate the actin cytoskeleton, Src as well as Rho, Rac and PAK that control cytoskeleton rearrangement, cell adhesion and migration (Rahimi et al., 1998; Royal et al., 2000). Some of these are mediated through Gab1-Crk interactions, whereby Crk can couple Gab1 to Rap1 and Rac (Lamorte et al., 2002a). A functional Crk protein is also required for breakdown of cell-cell junctions and cell dispersal, as well as branching morphogenesis in response to HGF/SF (Lamorte et al., 2002b). Cell survival is primarily controlled through PI3K dependent activation of Akt and downstream pathways (reviewed in Birchmeier et al., 2003).

Crosstalk with other signalling pathways

In addition to HGF/SF, Met is the major host receptor for the InlB protein of L monocytogenes (Shen et al., 2000). Entry of L. monocytogenes into epithelial cells, endothelial cells and hepatocytes is considered to play an important role in its pathogenesis. InlB/Met interactions promote entry of L. monocytogenes in cells that are normally non-phagocytic. This occurs through the activation of Met-dependent signalling pathways. These promote remodelling of the actin cytoskeleton required for phagocytic entry of the bacterium and involves Gab1 and recruited PI3'K and Crk (Sun et al., 2005).

Met can also interact with several cell surface proteins that influence its activity and cooperate with Met to elicit a biological response. These include ß4 integrin (Trusolino et al., 2001), the hyaluronan receptor CD44 (Orian-Rousseau et al., 2002), the Fas receptor (Wang et al., 2002), semaphorin (Giordano et al., 2002) and ezrin (Crepaldi et al., 1997). These complexes may act to localize Met signals to specific membrane microenvironments, as well as establishing complexes whose signals act in a synergistic manner. For example, in a variety of carcinoma cells, HGF/SF-induced cell invasion is coupled with association between Met and α6ß4 integrin, where activation of Met induces tyrosine phosphorylation of ß4 integrin and enhanced integrin signalling (Trusolino et al., 2001). Similar complexes between Met and semaphorin, or Met and CD44, have been associated with invasive growth (Orian-Rousseau et al., 2002). In addition, Met signals co-operate with the HER-2 RTK to promote loss of epithelial polarity and organization, and enhanced cell invasion, in three dimensional epithelial cell cultures, although in this case no physical interaction between Met and HER-2 was observed (Khoury et al., 2005).

HGF/SF and Met in tumorigenesis

The expression pattern of Met and HGF/SF, promotes crosstalk between the epithelial and stromal compartments required for normal physiological processes (Thiery, 2003). Under normal conditions HGF/SF and Met crosstalk is tightly regulated (Taub, 2004). Deregulation of the Met and HGF/SF signalling axis occurs in many human tumors, through co-expression of HGF/SF and Met, through receptor amplification and through point mutations in the juxtamembrane domain as well as the kinase domain of Met (reviewed in Birchmeier et al., 2003 and www.vai.org/HgfSf-METandcancer). Overexpression of HGF/SF alone in mammary stroma of mice is sufficient to promote loss of organization of mammary epithelium corresponding to hyperplasia (Kuperwasser et al., 2004). Mutations within the tyrosine kinase domain of Met have been found in both sporadic and hereditary forms of human papillary renal cancer (Schmidt et al., 1997), whereas mutations in the juxtamembrane domain of Met are found predominantly in human gastric and lung cancers (Lee et al., 2000; Ma et al., 2003). Under experimental conditions, Met receptors with these mutations are transforming in fibroblasts (Jeffers et al., 1997a; Jeffers et al., 1998; Lee et al., 2000; Ma et al., 2003). Some are tumorigenic in transgenic ani-

mals, (Jeffers et al., 1998) and when substituted in the germline, induce multiple tumor types (Graveel et al., 2004).

The ability of Met to drive cells to invade and form metastases has been validated in model systems, involving transfected cells as well as transgenic animals (Rong et al., 1994; Jeffers et al., 1996; Saucier et al., 2002). Pathways driving metastatic spread are considered to represent the deregulated activation of those corresponding to the invasive growth regulated by Met during embryogenesis and under physiological conditions. Structure-function studies have identified the requirement of Grb2 and Shc dependent pathways for cell transformation, tumorigenesis and metastatic spread (Fixman et al., 1996; Saucier et al., 2002). Grb2 recruitment not only activates the Ras-MAPK pathway, but also recruits the docking protein Gab1. These studies have revealed a role for the Shc signalling pathway, independent of Grb2, for tumorigenesis through the induction of VEGF. This is required for an angiogenic response downstream from Met as well as the HER2 RTK, a step essential for tumor growth (Saucier et al., 2004).

Cbl and Met receptor endocytosis and degradation.

In addition to the enhanced Met signaling observed with oncogenic Met receptor mutants, recent studies have demonstrated that loss of negative regulation also contributes to oncogenic activation of Met (Peschard et al., 2001a), and may represent a common mechanism that contributes to oncogenic activation of other RTKs in human cancer (Peschard and Park, 2003). The rapid removal of growth factor receptors from the cell surface, and subsequent targeting to lysosomal degradative compartments, provides a downregulation mechanism important for preventing sustained stimulation, which could potentially lead to cellular transformation (Fig. 5) (reviewed in Marmor and Yarden, 2004). Many of these interactions are dependent on RTK activation and ubiquitination (Katzmann et al., 2001; Buchberger, 2002; Davies et al., 2004) which involve the Cbl family of ubiquitin ligases (Joazeiro et al., 1999; Keane et al., 1999; Yokouchi et al., 1999; Thien and Langdon, 2001).

The recruitment of the Cbl family of ubiquitin-protein ligases is required for ligand-induced degradation of many RTKs, among them the EGFR, the platelet-derived growth factor receptor (PDGFR), the colony-stimulating factor-1 receptor (CSF-1R) (reviewed by Thien and Langdon, 2001) and the Met receptor (Peschard et al., 2001b; Peschard et al., 2004). Growing evidence indicates that ubiquitination of RTKs is critical for their lysosomal degradation through their ubiquitin-dependent protein sorting, which retains RTKs in late endosomes and subsequently targets these receptors to intralumenal vesicles of MVBs and lysosomal degradation (Urbe et al., 2000; Raiborg et al., 2002; Duan et al., 2003; Jiang et al., 2003; Yamasaki et al., 2003). RTKs including Met are multi-monoubiquitinated rather than being poly-ubiquitinated (Haglund et al., 2003; Mosesson et al., 2003; Carter et al., 2004). The multi-mono-ubiquitinated RTKs may be selectively recognized by proteins of the endocytic pathway that contain a ubiquitin-interacting motif (UIM), such as Epsin, Eps15 and Hrs (Hepatocyte Growth Factor regulated tyrosine kinase substrate) (Hofmann and Falquet, 2001) among others.

Stimulation of the Met receptor with HGF/SF induces tyrosine phosphorylation of the receptor, and stimulation with high levels of HGF/SF leads to detectable Met receptor ubiquitination and enhanced degradation (Jeffers et al., 1997b; Kamei et al., 1999; Shen et al., 2000). The juxtamembrane region of Met contains an additional docking site at Y1003, which acts as a negative regulator of Met biological activity, and is absent in the Tpr-Met oncogene (Fig. 1). Although c-Cbl can be recruited to Met indirectly through the Grb2 adapter protein (Fig. 2) , phosphorylation of Y1003 provides a direct docking site for the SH2-like TKB domain of the c-Cbl ubiquitin ligase, and is required for ubiquitination and ligand-dependent degradation of the Met receptor (Peschard et al., 2001b). Met receptor mutants uncoupled from Cbl dependent ubiquitination are transforming and tumorigenic, through enhanced stability of Met

and sustained signalling of downstream pathways (Peschard et al., 2001b).

Although a consensus for c-Cbl TKB domain binding has been established (D/NxpYxxD/EF), this motif is not present in Met, and instead, a DpYR motif, including Y1003, is required for the direct recruitment of the c-Cbl TKB domain and for ubiquitination of the Met receptor (Peschard et al., 2004). The DpYR motif is conserved within Met family members, Met, Ron and Sea, as well as in Met orthologues in puffer fish, suggesting a conserved function for this motif in Cbl recruitment and negative regulation of the Met receptor family (Penengo et al., 2003).

Loss of Cbl ubiquitylation in oncogenic RTKs

The observation that the specific uncoupling of the Met receptor from ubiquitination is associated

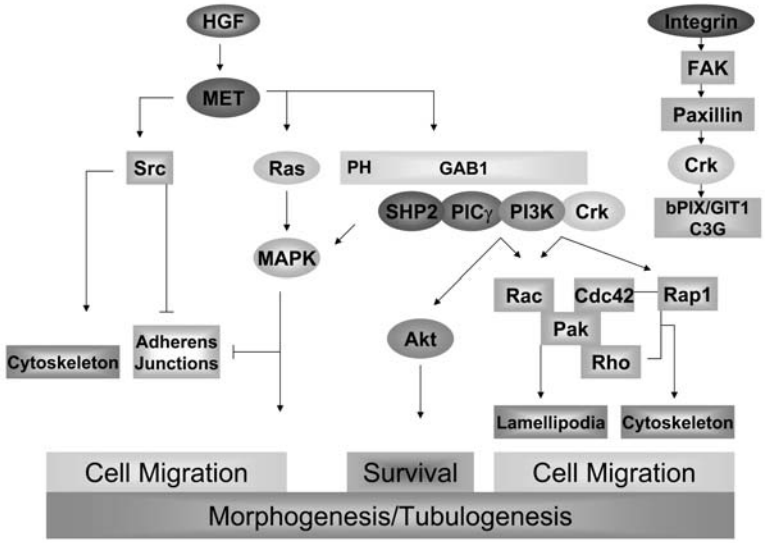


Figure 4. Signalling by the Met receptor tyrosine kinase during tubulogenesis. Activation of the Met receptor results in the recruitment of numerous signalling proteins to the receptor. Regulation of cellular proliferation, adhesion, cytoskeletal reorganization and cell survival are required to co-ordinate the reorganization of cysts of polarized epithelial cells into polarized tubular structures.

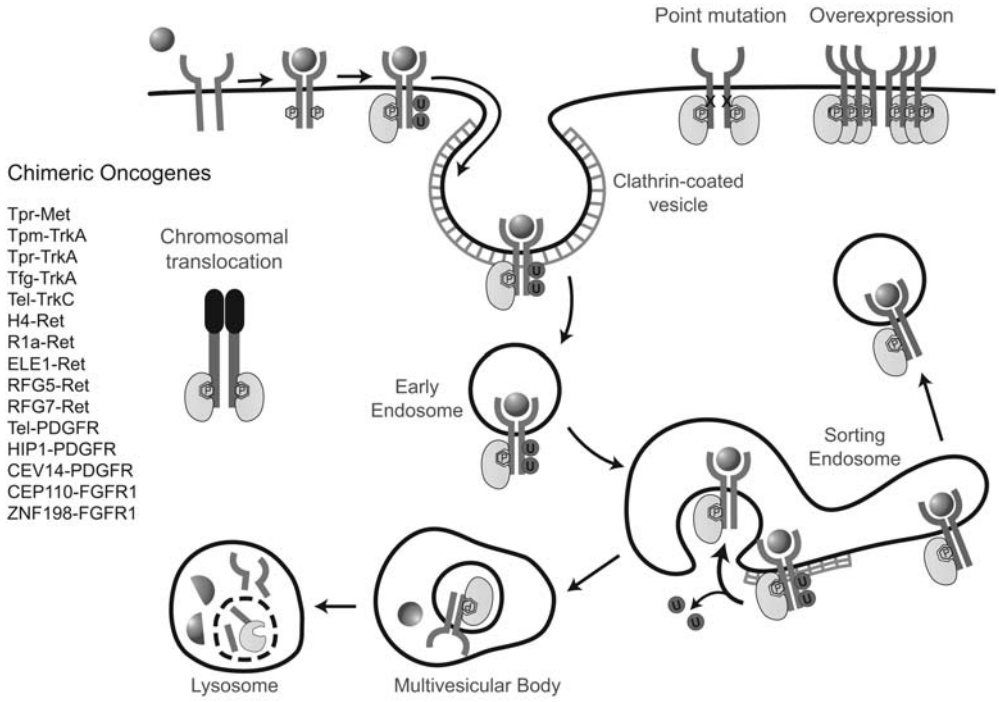


Figure 5. RTK ubiquitination and downregulation. Subsequent to the activation of several RTK's, Cbl is recruited to the receptor and induces receptor ubiquitination. Following internalization, ubiquitinated RTKs are enriched in an endosomal microdomain characterized by a bilayered clathrin coat. Receptors are subsequently internalized in inner vesicles. The process of receptor enrichment and subsequent internalization involves multiple proteins that contain ubiquitin interacting motifs (Hrs, STAM and proteins of the ESCRT complexes) as well as deubiquitinating enzymes (DUBs) that remove ubiquitin moieties from receptors. Fusion of multivesicular bodies with lysosomes leads to the degradation of inner vesicles and their contents by lysosomal proteases. RTKs that are not ubiquitinated can be recycled back to the plasma membrane. RTKs can be dysregulated in human tumors through several mechanisms. This includes amplification and point mutation. Many like Tpr-Met are activated following chromosomal translocation, where in each case a protein dimerization motif is fused to the cytosolic kinase domain of the receptor. These proteins would not be expected to enter the endosomal pathway, and escape lysosomal degradation.

with cell transformation, identified the importance for negative regulation of RTKs to suppress their transforming activity (Peschard et al., 2001a; Peschard and Park, 2003). Multiple mechanisms that reduce Cbl-mediated ubiquitination of RTKs, such as enhanced Cbl degradation, or sequestration, have been identified (Wong et al., 2002; Bao et al., 2003; Wu et al., 2003; Lee et al., 2004). In addition, mutations in RTKs or Cbl proteins that impair Cbl-mediated RTK ubiquitination have been observed in tumours (Peschard and Park, 2003). These observations suggest that loss of a Cbl TKB binding site may be a common mechanism that contributes to full oncogenic activation of RTKs. Moreover RTKs are frequently activated in human tumours following chromosomal translocation (Fig. 5). In general, this fuses a protein dimerization domain with the cytosolic kinase domain of the receptor, resulting in constitutive receptor dimerization and activation (Lamorte and Park, 2001). Over 25 RTK-derived fusion proteins have been identified in human tumours. In most cases, the N-terminal signal peptide, necessary for protein targeting to the membrane, is deleted in the rearranged kinase and where studied, these proteins are cytosolic (Lamorte and Park, 2001). Localization to the cytosol would preclude their entry in the endocytic pathway and hence, their lysosomal targeting and degradation (Fig. 5). However, it remains to be determined whether these oncoproteins are ubiquitinated and targeted for degradation by the proteosomal pathway. Hence, the loss of negative control exerted through Cbl proteins, through chromosomal rearrangements, or mutations that delete Cbl binding sites, may be an important contribution to the deregulation of Met and other RTKs observed in cancers.

Met and cancer therapy

Met was initially identified as an oncogene, and since many studies have now established that Met and/or HGF/SF are inappropriately expressed or activated in many human cancers, it is considered that Met and HGF/SF are important therapeutic targets. In the past few years multiple strategies have been developed to target Met activity and attenuate Met signalling. These include decoy receptors, and a recombinant Sema domain that competes with HGF binding (Kong-Beltran et al., 2004; Michieli et al., 2004), anti-Met or anti-HGF/SF antibodies, siRNA or ribozymes that target Met or HGF/SF (Date et al., 1997; Cao et al., 2001; Abounader et al., 2002), geldanamycin and derivatives that inhibit molecular chaperone function (Webb et al., 2000), inhibitors that compete for recruitment of key signalling proteins, as well as small molecule inhibitors that target Met catalytic activity (Atabey et al., 2001; Christensen et al., 2003). The widespread expression of HGF/SF and Met in cancers may provide an attractive and possibly general therapeutic target for many human cancers.

References

Abounader, R., Lal, B., Luddy, C., Koe, G., Davidson, B., Rosen, E.M., and Laterra, J. (2002). In vivo targeting of SF/HGF and c-met expression via U1snRNA/ribozymes inhibits glioma growth and angiogenesis and promotes apoptosis. Faseb J 16, 108-110.

Artigiani, S., Comoglio, P.M., and Tamagnone, L. (1999). Plexins, semaphorins, and scatter factor receptors: a common root for cell guidance signals? IUBMB Life 48, 477-482.

Atabey, N., Gao, Y., Yao, Z.J., Breckenridge, D., Soon, L., Soriano, J.V., Burke, T.R., Jr., and Bottaro, D.P. (2001). Potent blockade of hepatocyte growth factor-stimulated cell motility, matrix invasion and branching morphogenesis by antagonists of Grb2 Src homology 2 domain interactions. J Biol Chem 276, 14308-14314.

Bao, J., Gur, G., and Yarden, Y. (2003). Src promotes destruction of c-Cbl: implications for oncogenic synergy between Src and growth factor receptors. Proc Natl Acad Sci USA 100, 2438-2443.

Barford, D., and Neel, B.G. (1998). Revealing mechanisms for SH2 domain mediated regulation of the protein tyrosine phosphatase SHP-2. Structure 6, 249-254.

Birchmeier, C., Birchmeier, W., Gherardi, E., and Vande Woude, G.F. (2003). Met, metastasis, motility and more. Nat Rev Mol Cell Biol 4, 915-925.

Birchmeier, C., and Gherardi, E. (1998). Developmental roles of HGF/SF and its receptor, the c-Met tyrosine kinase. Trends Cell Biol 8, 404-410.

Borowiak, M., Garratt, A.N., Wustefeld, T., Strehle, M., Trautwein, C., and Birchmeier, C. (2004). Met provides essential signals for liver regeneration. Proc Natl Acad Sci USA 101, 10608-10613.

Bottaro, D.P., Rubin, J.S., Faletto, D.L., Chan, A.M., Kmiecik, T.E., Vande Woude, G.F., and Aaronson, S.A. (1991). Identification of the hepatocyte growth factor receptor as the c-met proto-oncogene product. Science 251, 802-804.

Buchberger, A. (2002). From UBA to UBX: new words in the ubiquitin vocabulary. Trends Cell Biol 12, 216-221.

Cao, B., Su, Y., Oskarsson, M., Zhao, P., Kort, E.J., Fisher, R.J., Wang, L.M., and Vande Woude, G.F. (2001). Neutralizing monoclonal antibodies to hepatocyte growth factor/scatter factor (HGF/SF) display antitumor activity in animal models. Proc Natl Acad Sci USA 98, 7443-7448.

Carter, S., Urbe, S., and Clague, M.J. (2004). The met receptor degradation pathway: requirement for Lys48-linked polyubiquitin independent of proteasome activity. J Biol Chem 279, 52835-52839.

Christensen, J.G., Schreck, R., Burrows, J., Kuruganti, P., Chan, E., Le, P., Chen, J., Wang, X., Ruslim, L., Blake, R., Lipson, K.E., Ramphal, J., Do, S., Cui, J.J., Cherrington, J.M., and Mendel, D.B. (2003). A selective small molecule inhibitor of c-Met kinase inhibits c-Met-dependent phenotypes in vitro and exhibits cytoreductive antitumor activity in vivo. Cancer Res 63, 7345-7355.

Comoglio, P.M., and Boccaccio, C. (2001). Scatter factors and invasive growth. Semin Cancer Biol 11, 153-165.

Cooper, C.S., Park, M., Blair, D.G., Tainsky, M.A., Huebner, K., Croce, C.M., and Vande Woude, G.F. (1984). Molecular cloning of a new transforming gene from a chemically transformed human cell line. Nature 311, 29-33.

Crepaldi, T., Gautreau, A., Comoglio, P.M., Louvard, D., and Arpin, M. (1997). Ezrin is an effector of hepatocyte growth factor-mediated migration and morphogenesis in epithelial cells. J Cell Biol 138, 423-434.

Date, K., Matsumoto, K., Shimura, H., Tanaka, M., and Nakamura, T. (1997). HGF/NK4 is a specific antagonist for pleiotrophic actions of hepatocyte growth factor. FEBS Lett 420, 1-6.

Davies, G.C., Ettenberg, S.A., Coats, A.O., Mussante, M., Ravichandran, S., Collins, J., Nau, M.M., and Lipkowitz, S. (2004). Cbl-b interacts with ubiquitinated proteins; differential functions of the UBA domains of c-Cbl and Cbl-b. Oncogene 23, 7104-7115.

Donate, L.E., Gherardi, E., Srinivasan, N., Sowdhamini, R., Aparicio, S., and Blundell, T.L. (1994). Molecular evolution and domain structure of plasminogen-related growth factors (HGF/SF and HGF1/MSP). Protein Sci 3, 2378-2394.

Duan, L., Miura, Y., Dimri, M., Majumder, B., Dodge, I.L., Reddi, A.L., Ghosh, A., Fernandes, N., Zhou, P., Mullane-Robinson, K., Rao, N., Donoghue, S., Rogers, R.A., Bowtell, D., Naramura, M., Gu, H., Band, V., and Band, H. (2003). Cbl-mediated ubiquitinylation is required for lysosomal sorting of epidermal growth factor receptor but is dispensable for endocytosis. J Biol Chem 278, 28950-28960.

Ebens, A., Brose, K., Leonardo, E.D., Hanson, M.G., Bladt, F., Birchmeier, C., Barres, B.A., and Tessier-Lavigne, M. (1996). Hepatocyte growth factor/scatter factor is an axonal chemoattractant and a neurotrophic factor for spinal motor neurons. Neuron 17, 1157-1172.

Fixman, E.D., Fournier, T.M., Kamikura, D.M., Naujokas, M.A., and Park, M. (1996). Pathways downstream of Shc and Grb2 are required for cell transformation by the tpr-Met oncoprotein. J Biol Chem 271, 13116-13122.

Fixman, E.D., Naujokas, M.A., Rodrigues, G.A., Moran, M.F., and Park, M. (1995). Efficient cell transformation by the Tpr-Met oncoprotein is

dependent upon tyrosine 489 in the carboxy-terminus. Oncogene 10, 237-249.

Fournier, T.M., Kamikura, D., Teng, K., and Park, M. (1996). Branching tubulogenesis but not scatter of Madin-Darby canine kidney cells requires a functional Grb2 binding site in the Met receptor tyrosine kinase. J Biol Chem 271, 22211-22217.

Garcia-Guzman, M., Dolfi, F., Zeh, K., and Vuori, K. (1999). Met-induced JNK activation is mediated by the adapter protein Crk and correlates with the Gab1 - Crk signaling complex formation. Oncogene 18, 7775-7786.

Gaudino, G., Follenzi, A., Naldini, L., Collesi, C., Santoro, M., Gallo, K.A., Godowski, P.J., and Comoglio, P.M. (1994). RON is a heterodimeric tyrosine kinase receptor activated by the HGF homologue MSP. Embo J 13, 3524-3532.

Gherardi, E., Youles, M.E., Miguel, R.N., Blundell, T.L., Iamele, L., Gough, J., Bandyopadhyay, A., Hartmann, G., and Butler, P.J. (2003). Functional map and domain structure of MET, the product of the c-met protooncogene and receptor for hepatocyte growth factor/scatter factor. Proc Natl Acad Sci USA 100, 12039-12044.

Giordano, S., Corso, S., Conrotto, P., Artigiani, S., Gilestro, G., Barberis, D., Tamagnone, L., and Comoglio, P.M. (2002). The semaphorin 4D receptor controls invasive growth by coupling with Met. Nat Cell Biol 4, 720-724.

Giordano, S., Di Renzo, M.F., Narsimhan, R.P., Cooper, C.S., Rosa, C., and Comoglio, P.M. (1989). Biosynthesis of the protein encoded by the c-met proto-oncogene. Oncogene 4, 1383-1388.

Grant, D.S., Kleinman, H.K., Goldberg, I.D., Bhargava, M.M., Nickoloff, B.J., Kinsella, J.L., Polverini, P., and Rosen, E.M. (1993). Scatter factor induces blood vessel formation in vivo. Proc Natl Acad Sci USA 90, 1937-1941.

Graveel, C., Su, Y., Koeman, J., Wang, L.M., Tessarollo, L., Fiscella, M., Birchmeier, C., Swiatek, P., Bronson, R., and Vande Woude, G. (2004). Activating Met mutations produce unique tumor profiles in mice with selective duplication of the mutant allele. Proc Natl Acad Sci USA 101, 17198-17203.

Gual, P., Giordano, S., Williams, T.A., Rocchi, S., Van Obberghen, E., and Comoglio, P.M. (2000). Sustained recruitment of phospholipase C-gamma to Gab1 is required for HGF-induced branching tubulogenesis. Oncogene 19, 1509-1518.

Haglund, K., Sigismund, S., Polo, S., Szymkiewicz, I., Di Fiore, P.P., and Dikic, I. (2003). Multiple monoubiquitination of RTKs is sufficient for their endocytosis and degradation. Nat Cell Biol 5, 461-466.

Hofmann, K., and Falquet, L. (2001). A ubiquitin-interacting motif conserved in components of the proteasomal and lysosomal protein degradation systems. Trends Biochem Sci 26, 347-350.

Holgado-Madruga, M., Emlet, D.R., Moscatello, D.K., Godwin, A.K., and Wong, A.J. (1996). A Grb2-associated docking protein in EGF- and insulin-receptor signalling. Nature 379, 560-564.

Huh, C.G., Factor, V.M., Sanchez, A., Uchida, K., Conner, E.A., and Thorgeirsson, S.S. (2004). Hepatocyte growth factor/c-met signaling pathway is required for efficient liver regeneration and repair. Proc Natl Acad Sci USA 101, 4477-4482.

Itoh, M., Yoshida, Y., Nishida, K., Narimatsu, M., Hibi, M., and Hirano, T. (2000). Role of Gab1 in heart, placenta, and skin development and growth factor- and cytokine-induced extracellular signal-regulated kinase mitogen-activated protein kinase activation. Mol Cell Biol 20, 3695-3704.

Jeffers, M., Fiscella, M., Webb, C.P., Anver, M., Koochekpour, S., and Vande Woude, G.F. (1998). The mutationally activated Met receptor mediates motility and metastasis. Proc Natl Acad Sci USA 95, 14417-14422.

Jeffers, M., Rong, S., and Vande Woude, G.F. (1996). Enhanced tumorigenicity and invasion-metastasis by hepatocyte growth factor/scatter factor-met signalling in human cells concomi-

tant with induction of the urokinase proteolysis network. Mol Cell Biol 16, 1115-1125.

Jeffers, M., Schmidt, L., Nakaigawa, N., Webb, C.P., Weirich, G., Kishida, T., Zbar, B., and Vande Woude, G.F. (1997a). Activating mutations for the met tyrosine kinase receptor in human cancer. Proc Natl Acad Sci USA 94, 11445-11450.

Jeffers, M., Taylor, G.A., Weidner, K.M., Omura, S., and Vande Woude, G.F. (1997b). Degradation of the Met tyrosine kinase receptor by the ubiquitin- proteasome pathway. Mol Cell Biol 17, 799-808.

Jiang, X., Huang, F., Marusyk, A., and Sorkin, A. (2003). Grb2 regulates internalization of EGF receptors through clathrin-coated pits. Mol Biol Cell 14, 858-870.

Jin, H., Yang, R., Li, W., Ogasawara, A.K., Schwall, R., Eberhard, D.A., Zheng, Z., Kahn, D., and Paoni, N.F. (2003). Early treatment with hepatocyte growth factor improves cardiac function in experimental heart failure induced by myocardial infarction. J Pharmacol Exp Ther 304, 654-660.

Joazeiro, C.A., Wing, S.S., Huang, H., Leverson, J.D., Hunter, T., and Liu, Y.C. (1999). The tyrosine kinase negative regulator c-Cbl as a RING-type, E2- dependent ubiquitin-protein ligase [see comments]. Science 286, 309-312.

Kamei, T., Matozaki, T., Sakisaka, T., Kodama, A., Yokoyama, S., Peng, Y.F., Nakano, K., Takaishi, K., and Takai, Y. (1999). Coendocytosis of cadherin and c-Met coupled to disruption of cell-cell adhesion in MDCK cells--regulation by Rho, Rac and Rab small G proteins. Oncogene 18, 6776-6784.

Katzmann, D.J., Babst, M., and Emr, S.D. (2001). Ubiquitin-dependent sorting into the multivesicular body pathway requires the function of a conserved endosomal protein sorting complex, ESCRT-I. Cell 106, 145-155.

Keane, M.M., Ettenberg, S.A., Nau, M.M., Banerjee, P., Cuello, M., Penninger, J., and Lipkowitz, S. (1999). cbl-3: a new mammalian cbl family protein. Oncogene 18, 3365-3375.

Khoury, H., Naujokas, M.A., Zuo, D., Sangwan, V., Frigault, M.M., Petkiewicz, S., Dankort, D.L., Muller, W.J., and Park, M. (2005). HGF converts ErbB2/Neu epithelial morphogenesis to cell invasion. Mol Biol Cell 16, 550-561.

Komada, M., Hatsuzawa, K., Shibamoto, S., Ito, F., Nakayama, K., and Kitamura, N. (1993). Proteolytic processing of the hepatocyte growth factor/scatter factor receptor by furin. FEBS Lett 328, 25-29.

Kong-Beltran, M., Stamos, J., and Wickramasinghe, D. (2004). The Sema domain of Met is necessary for receptor dimerization and activation. Cancer Cell 6, 75-84.

Kuperwasser, C., Chavarria, T., Wu, M., Magrane, G., Gray, J.W., Carey, L., Richardson, A., and Weinberg, R.A. (2004). Reconstruction of functionally normal and malignant human breast tissues in mice. Proc Natl Acad Sci USA 101, 4966-4971.

Lamorte, L., and Park, M. (2001). The receptor tyrosine kinases: role in cancer progression. Surg Oncol Clin N Am 10, 271-288, viii.

Lamorte, L., Rodrigues, S., Naujokas, M., and Park, M. (2002a). Crk synergizes with epidermal growth factor for epithelial invasion and morphogenesis and is required for the met morphogenic program. J Biol Chem 277, 37904-37911.

Lamorte, L., Royal, I., Naujokas, M., and Park, M. (2002b). Crk adapter proteins promote an epithelial-mesenchymal-like transition and are required for HGF-mediated cell spreading and breakdown of epithelial adherens junctions. Mol Biol Cell 13, 1449-1461.

Lee, C.C., Putnam, A.J., Miranti, C.K., Gustafson, M., Wang, L.M., Vande Woude, G.F., and Gao, C.F. (2004). Overexpression of sprouty 2 inhibits HGF/SF-mediated cell growth, invasion, migration, and cytokinesis. Oncogene 23, 5193-5202.

Lee, J.H., Han, S.U., Cho, H., Jennings, B., Gerrard, B., Dean, M., Schmidt, L., Zbar, B., and Vande Woude, G.F. (2000). A novel germ line juxtamembrane Met mutation in human

gastric cancer. Oncogene 19, 4947-4953.

Liu, Y., and Rohrschneider, L.R. (2002). The gift of Gab. FEBS Lett 515, 1-7.

Lock, L.S., Frigault, M.M., Saucier, C., and Park, M. (2003). Grb2-independent recruitment of Gab1 requires the C-terminal lobe and structural integrity of the Met receptor kinase domain. J Biol Chem 278, 30083-30090.

Lock, L.S., Maroun, C.R., Naujokas, M.A., and Park, M. (2002). Distinct recruitment and function of Gab1 and Gab2 in Met receptor-mediated epithelial morphogenesis. Mol Biol Cell 13, 2132-2146.

Lock, L.S., Royal, I., Naujokas, M.A., and Park, M. (2000). Identification of an atypical Grb2 carboxyl-terminal SH3 domain binding site in Gab docking proteins reveals Grb2-dependent and -independent recruitment of Gab1 to receptor tyrosine kinases. J Biol Chem 275, 31536-31545.

Ma, P.C., Kijima, T., Maulik, G., Fox, E.A., Sattler, M., Griffin, J.D., Johnson, B.E., and Salgia, R. (2003). c-MET mutational analysis in small cell lung cancer: novel juxtamembrane domain mutations regulating cytoskeletal functions. Cancer Res 63, 6272-6281.

Maeda, K., Murakami, H., Yoshida, R., Ichihara, M., Abe, A., Hirai, M., Murohara, T., and Takahashi, M. (2004). Biochemical and biological responses induced by coupling of Gab1 to phosphatidylinositol 3-kinase in RET-expressing cells. Biochem Biophys Res Commun 323, 345-354.

Maestrini, E., Tamagnone, L., Longati, P., Cremona, O., Gulisano, M., Bione, S., Tamanini, F., Neel, B.G., Toniolo, D., and Comoglio, P.M. (1996). A family of transmembrane proteins with homology to the MET-hepatocyte growth factor receptor. Proc Natl Acad Sci USA 93, 674-678.

Maina, F., Hilton, M.C., Ponzetto, C., Davies, A.M., and Klein, R. (1997). Met receptor signaling is required for sensory nerve development and HGF promotes axonal growth and survival of sensory neurons. Genes Dev 11, 3341-3350.

Marmor, M.D., and Yarden, Y. (2004). Role of protein ubiquitylation in regulating endocytosis of receptor tyrosine kinases. Oncogene 23, 2057-2070.

Maroun, C.R., Holgado-Madruga, M., Royal, I., Naujokas, M.A., Fournier, T.M., Wong, A.J., and Park, M. (1999a). The Gab1 PH domain is required for localization of Gab1 at sites of cell-cell contact and epithelial morphogenesis downstream from the met receptor tyrosine kinase. Mol Cell Biol 19, 1784-1799.

Maroun, C.R., Moscatello, D.K., Naujokas, M.A., Holgado-Madruga, M., Wong, A.J., and Park, M. (1999b). A conserved inositol phospholipid binding site within the pleckstrin homology domain of the Gab1 docking protein is required for epithelial morphogenesis. J Biol Chem 274, 31719-31726.

Maroun, C.R., Naujokas, M.A., Holgado-Madruga, M., Wong, A.J., and Park, M. (2000). The tyrosine phosphatase SHP-2 is required for sustained activation of extracellular signal-regulated kinase and epithelial morphogenesis downstream from the met receptor tyrosine kinase. Mol Cell Biol 20, 8513-8525.

Maroun, C.R., Naujokas, M.A., and Park, M. (2003). Membrane targeting of Grb2-associated binder-1 (Gab1) scaffolding protein through Src myristoylation sequence substitutes for Gab1 pleckstrin homology domain and switches an epidermal growth factor response to an invasive morphogenic program. Mol Biol Cell 14, 1691-1708.

Matsumoto, K., and Nakamura, T. (2001). Hepatocyte growth factor: renotropic role and potential therapeutics for renal diseases. Kidney Int 59, 2023-2038.

Michalopoulos, G.K., and DeFrances, M.C. (1997). Liver regeneration. Science 276, 60-66.

Michieli, P., Mazzone, M., Basilico, C., Cavassa, S., Sottile, A., Naldini, L., and Comoglio, P.M. (2004). Targeting the tumor and its microenvironment by a dual-function decoy Met receptor. Cancer Cell 6, 61-73.

Montesano, R., Matsumoto, K., Nakamura, T., and

Orci, L. (1991a). Identification of a fibroblast-derived epithelial morphogen as hepatocyte growth factor. Cell 67, 901-908.

Montesano, R., Schaller, G., and Orci, L. (1991b). Induction of epithelial tubular morphogenesis in vitro by fibroblast-derived soluble factors. Cell 66, 697-711.

Mosesson, Y., Shtiegman, K., Katz, M., Zwang, Y., Vereb, G., Szollosi, J., and Yarden, Y. (2003). Endocytosis of receptor tyrosine kinases is driven by monoubiquitylation, not polyubiquitylation. J Biol Chem 278, 21323-21326.

Nakamura, T. (1991). Structure and function of hepatocyte growth factor. Prog Growth Factor Res 3, 67-85.

Nakamura, T., Mizuno, S., Matsumoto, K., Sawa, Y., and Matsuda, H. (2000). Myocardial protection from ischemia/reperfusion injury by endogenous and exogenous HGF. J Clin Invest 106, 1511-1519.

Nakamura, T., Nishizawa, T., Hagiya, M., Seki, T., Shimonishi, M., Sugimura, A., Tashiro, K., and Shimizu, S. (1989). Molecular cloning and expression of human hepatocyte growth factor. Nature 342, 440-443.

Neel, B.G., Gu, H., and Pao, L. (2003). The 'Shp'ing news: SH2 domain-containing tyrosine phosphatases in cell signaling. Trends Biochem Sci 28, 284-293.

Nguyen, L., Holgado-Madruga, M., Maroun, C., Fixman, E.D., Kamikura, D., Fournier, T., Charest, A., Tremblay, M.L., Wong, A.J., and Park, M. (1997). Association of the multisubstrate docking protein Gab1 with the hepatocyte growth factor receptor requires a functional Grb2 binding site involving tyrosine 1356. J Biol Chem 272, 20811-20819.

Orian-Rousseau, V., Chen, L., Sleeman, J.P., Herrlich, P., and Ponta, H. (2002). CD44 is required for two consecutive steps in HGF/c-Met signaling. Genes Dev 16, 3074-3086.

Park, M., Dean, M., Cooper, C.S., Schmidt, M., O'Brien, S.J., Blair, D.G., and Vande Woude, G.F. (1986). Mechanism of met oncogene activation. Cell 45, 895-904.

Park, M., Dean, M., Kaul, K., Braun, M.J., Gonda, M.A., and Vande Woude, G. (1987). Sequence of MET protooncogene cDNA has features characteristic of the tyrosine kinase family of growth-factor receptors. Proc Natl Acad Sci USA 84, 6379-6383.

Pawson, T., and Scott, J.D. (1997). Signaling through scaffold, anchoring, and adaptor proteins. Science 278, 2075-2080.

Penengo, L., Rubin, C., Yarden, Y., and Gaudino, G. (2003). c-Cbl is a critical modulator of the Ron tyrosine kinase receptor. Oncogene 22, 3669-3679.

Peschard, P., Fournier, T.M., Lamorte, L., Naujokas, M.A., Band, H., Langdon, W.Y., and Park, M. (2001). Mutation of the c-Cbl TKB domain binding site on the Met receptor tyrosine kinase converts it into a transforming protein. Mol Cell 8, 995-1004.

Peschard, P., Ishiyama, N., Lin, T., Lipkowitz, S., and Park, M. (2004). A conserved DpYR motif in the juxtamembrane domain of the Met receptor family forms an atypical c-Cbl/Cbl-b tyrosine kinase binding domain binding site required for suppression of oncogenic activation. J Biol Chem 279, 29565-29571.

Peschard, P., and Park, M. (2003). Escape from Cbl-mediated downregulation: a recurrent theme for oncogenic deregulation of receptor tyrosine kinases. Cancer Cell 3, 519-523.

Pollack, A.L., Runyan, R.B., and Mostov, K.E. (1998). Morphogenetic mechanisms of epithelial tubulogenesis: MDCK cell polarity is transiently rearranged without loss of cell-cell contact during scatter factor/hepatocyte growth factor-induced tubulogenesis. Dev Biol 204, 64-79.

Ponzetto, C., Bardelli, A., Zhen, Z., Maina, F., dalla Zonca, P., Giordano, S., Graziani, A., Panayotou, G., and Comoglio, P.M. (1994). A multifunctional docking site mediates signaling and transformation by the hepatocyte growth factor/scatter factor receptor family. Cell 77, 261-271.

Potempa, S., and Ridley, A.J. (1998). Activation of both MAP kinase and phosphatidylinositide

3-kinase by Ras is required for hepatocyte growth factor/scatter factor-induced adherens junction disassembly. Mol Biol Cell 9, 2185-2200.

Rahimi, N., Hung, W., Tremblay, E., Saulnier, R., and Elliott, B. (1998). c-Src kinase activity is required for hepatocyte growth factor-induced motility and anchorage-independent growth of mammary carcinoma cells. J Biol Chem 273, 33714-33721.

Raiborg, C., Bache, K.G., Gillooly, D.J., Madshus, I.H., Stang, E., and Stenmark, H. (2002). Hrs sorts ubiquitinated proteins into clathrin-coated microdomains of early endosomes. Nat Cell Biol 4, 394-398.

Rodrigues, G.A., and Park, M. (1993). Dimerization mediated through a leucine zipper activates the oncogenic potential of the met receptor tyrosine kinase. Mol Cell Biol 13, 6711-6722.

Rodrigues, G.A., and Park, M. (1994a). Autophosphorylation modulates the kinase activity and oncogenic potential of the Met receptor tyrosine kinase. Oncogene 9, 2019-2027.

Rodrigues, G.A., and Park, M. (1994b). Oncogenic activation of tyrosine kinases. Curr Opin Genet Dev 4, 15-24.

Rong, S., Segal, S., Anver, M., Resau, J.H., and Vande Woude, G.F. (1994). Invasiveness and metastasis of NIH 3T3 cells induced by Met-hepatocyte growth factor/scatter factor autocrine stimulation. Proc Natl Acad Sci USA 91, 4731-4735.

Ronsin, C., Muscatelli, F., Mattei, M.G., and Breathnach, R. (1993). A novel putative receptor protein tyrosine kinase of the met family. Oncogene 8, 1195-1202.

Roos, F., Ryan, A.M., Chamow, S.M., Bennett, G.L., and Schwall, R.H. (1995). Induction of liver growth in normal mice by infusion of hepatocyte growth factor/scatter factor. Am J Physiol 268, G380-386.

Rosario, M., and Birchmeier, W. (2003). How to make tubes: signaling by the Met receptor tyrosine kinase. Trends Cell Biol 13, 328-335.

Royal, I., Lamarche-Vane, N., Lamorte, L., Kaibuchi, K., and Park, M. (2000). Activation of cdc42, rac, PAK, and rho-kinase in response to hepatocyte growth factor differentially regulates epithelial cell colony spreading and dissociation. Mol Biol Cell 11, 1709-1725.

Royal, I., and Park, M. (1995). Hepatocyte growth factor-induced scatter of Madin-Darby canine kidney cells requires phosphatidylinositol 3-kinase. J Biol Chem 270, 27780-27787.

Sachs, M., Brohmann, H., Zechner, D., Muller, T., Hulsken, J., Walther, I., Schaeper, U., Birchmeier, C., and Birchmeier, W. (2000). Essential role of Gab1 for signaling by the c-Met receptor in vivo. J Cell Biol 150, 1375-1384.

Sachs, M., Weidner, K.M., Brinkmann, V., Walther, I., Obermeier, A., Ullrich, A., and Birchmeier, W. (1996). Mitogenic and morphogenic activity of epithelial receptor tyrosine kinases. J Cell Biol 133, 1095-1107.

Saucier, C., Khoury, H., Lai, K.M., Peschard, P., Dankort, D., Naujokas, M.A., Holash, J., Yancopoulos, G.D., Muller, W.J., Pawson, T., and Park, M. (2004). The Shc adaptor protein is critical for VEGF induction by Met/HGF and ErbB2 receptors and for early onset of tumor angiogenesis. Proc Natl Acad Sci USA 101, 2345-2350.

Saucier, C., Papavasiliou, V., Palazzo, A., Naujokas, M.A., Kremer, R., and Park, M. (2002). Use of signal specific receptor tyrosine kinase oncoproteins reveals that pathways downstream from Grb2 or Shc are sufficient for cell transformation and metastasis. Oncogene 21, 1800-1811.

Schaeper, U., Gehring, N.H., Fuchs, K.P., Sachs, M., Kempkes, B., and Birchmeier, W. (2000). Coupling of Gab1 to c-Met, Grb2, and Shp2 mediates biological responses. J Cell Biol 149, 1419-1432.

Schmidt, C., Bladt, F., Goedecke, S., Brinkmann, V., Zschiesche, W., Sharpe, M., Gherardi, E., and Birchmeier, C. (1995). Scatter factor/hepatocyte growth factor is essential for liver development. Nature 373, 699-702.

Schmidt, L., Duh, F.M., Chen, F., Kishida, T., Glenn, G., Choyke, P., Scherer, S.W., Zhuang, Z., Lubensky, I., Dean, M., Allikmets, R., Chidambaram, A., Bergerheim, U.R., Feltis, J.T., Casadevall, C., Zamarron, A., Bernues, M., Richard, S., Lips, C.J., Walther, M.M., Tsui, L.C., Geil, L., Orcutt, M.L., Stackhouse, T., Zbar, B., and et al. (1997). Germline and somatic mutations in the tyrosine kinase domain of the MET proto-oncogene in papillary renal carcinomas. Nat Genet 16, 68-73.

Shen, Y., Naujokas, M., Park, M., and Ireton, K. (2000). InIB-dependent internalization of Listeria is mediated by the Met receptor tyrosine kinase. Cell 103, 501-510.

Stoker, M., Gherardi, E., Perryman, M., and Gray, J. (1987). Scatter factor is a fibroblast-derived modulator of epithelial cell mobility. Nature 327, 239-242.

Sun, H., Shen, Y., Dokainish, H., Holgado-Madruga, M., Wong, A., and Ireton, K. (2005). Host adaptor proteins Gab1 and CrkII promote InlB-dependent entry of Listeria monocytogenes. Cell Microbiol 7, 443-457.

Taub, R. (2004). Liver regeneration: from myth to mechanism. Nat Rev Mol Cell Biol 5, 836-847.

Thien, C.B., and Langdon, W.Y. (2001). Cbl: many adaptations to regulate protein tyrosine kinases. Nat Rev Mol Cell Biol 2, 294-307.

Thiery, J.P. (2003). Epithelial-mesenchymal transitions in development and pathologies. Curr Opin Cell Biol 15, 740-746.

Trusolino, L., Bertotti, A., and Comoglio, P.M. (2001). A signaling adapter function for alpha6beta4 integrin in the control of HGF-dependent invasive growth. Cell 107, 643-654.

Uehara, Y., Minowa, O., Mori, C., Shiota, K., Kuno, J., Noda, T., and Kitamura, N. (1995). Placental defect and embryonic lethality in mice lacking hepatocyte growth factor/scatter factor. Nature 373, 702-705.

Urbe, S., Mills, I.G., Stenmark, H., Kitamura, N., and Clague, M.J. (2000). Endosomal localization and receptor dynamics determine tyrosine phosphorylation of hepatocyte growth factor-regulated tyrosine kinase substrate. Mol Cell Biol 20, 7685-7692.

Wang, X., DeFrances, M.C., Dai, Y., Pediaditakis, P., Johnson, C., Bell, A., Michalopoulos, G.K., and Zarnegar, R. (2002). A mechanism of cell survival: sequestration of Fas by the HGF receptor Met. Mol Cell 9, 411-421.

Webb, C.P., Hose, C.D., Koochekpour, S., Jeffers, M., Oskarsson, M., Sausville, E., Monks, A., and Vande Woude, G.F. (2000). The geldanamycins are potent inhibitors of the hepatocyte growth factor/scatter factor-met-urokinase plasminogen activator-plasmin proteolytic network. Cancer Res 60, 342-349.

Weidner, K.M., Sachs, M., and Birchmeier, W. (1993). The Met receptor tyrosine kinase transduces motility, proliferation, and morphogenic signals of scatter factor/hepatocyte growth factor in epithelial cells. J Cell Biol 121, 145-154.

Wong, E.S., Fong, C.W., Lim, J., Yusoff, P., Low, B.C., Langdon, W.Y., and Guy, G.R. (2002). Sprouty2 attenuates epidermal growth factor receptor ubiquitylation and endocytosis, and consequently enhances Ras/ERK signalling. Embo J 21, 4796-4808.

Wu, W.J., Tu, S., and Cerione, R.A. (2003). Activated Cdc42 sequesters c-Cbl and prevents EGF receptor degradation. Cell 114, 715-725.

Xiong, J.P., Stehle, T., Zhang, R., Joachimiak, A., Frech, M., Goodman, S.L., and Arnaout, M.A. (2002). Crystal structure of the extracellular segment of integrin alpha Vbeta3 in complex with an Arg-Gly-Asp ligand. Science 296, 151-155.

Yamasaki, S., Nishida, K., Yoshida, Y., Itoh, M., Hibi, M., and Hirano, T. (2003). Gab1 is required for EGF receptor signaling and the transformation by activated ErbB2. Oncogene 22, 1546-1556.

Yang, X.M., and Park, M. (1995). Expression of the hepatocyte growth factor/scatter factor receptor tyrosine kinase is localized to epithelia in the adult mouse. Laboratory Investigations 73, 483-491.

Yokouchi, M., Kondo, T., Houghton, A., Bartkiewicz, M., Horne, W.C., Zhang, H., Yoshimura, A., and Baron, R. (1999). Ligand-induced ubiquitination of the epidermal growth factor receptor involves the interaction of the c-Cbl RING finger and UbcH7. J Biol Chem 274, 31707-31712.

Zarnegar, R., and Michalopoulos, G. (1989). Purification and biological characterization of human hepatopoietin A, a polypeptide growth factor for hepatocytes. Cancer Res 49, 3314-3320.

Zegers, M.M., O'Brien, L.E., Yu, W., Datta, A., and Mostov, K.E. (2003). Epithelial polarity and tubulogenesis in vitro. Trends Cell Biol 13, 169-176.

Zhang, Y.W., Su, Y., Volpert, O.V., and Vande Woude, G.F. (2003). Hepatocyte growth factor/scatter factor mediates angiogenesis through positive VEGF and negative thrombospondin 1 regulation. Proc Natl Acad Sci USA 100, 12718-12723.

Zhu, H., Naujokas, M.A., Fixman, E.D., Torossian, K., and Park, M. (1994a). Tyrosine 1356 in the carboxyl-terminal tail of the HGF/SF receptor is essential for the transduction of signals for cell motility and morphogenesis. Journal of Biological Chemistry 269, 29943-29948.

Zhu, H., Naujokas, M.A., and Park, M. (1994b). Receptor chimeras indicate that the Met tyrosine kinase mediates the motility and morphogenic responses of hepatocyte growth/scatter factor. Cell Growth & Differentiation 5, 359-366.

The 2004 CSBMCB Science Policy Questionnaire

An important function of your Society is to accurately represent your interests and concerns to government and decision makers. The usual mechanism for this advocacy is through our support of the lobbying efforts of the Canadian Federation of Biological Sciences (CFBS) http://www.cfbs.org/policy.html.

The goal of the 2004 CSBMCB Science Policy Questionnaire was to give you an opportunity to express your concerns and make suggestions that we will then transmit to the CFBS.

Although the response to the survey was not overwhelming, the data obtained and the perceptive comments of the respondents are an eloquent expression of the concerns of us all. Thus the responses were to some extent predictable and similar -

• Yes there is considerable concern about the level of funding and much anecdotal evidence that operating grant funding has not increased in the past 5 years, and has for many decreased when the inflation cost of scientific supplies and increased personnel support is taken into account.

• Question 2 about the increased size of the scientific work force generated some interesting responses. The recent results of the CIHR operating grants competition with 1687 applications and a success rate of 24% is an unfortunate illustration of the problems that we are all facing. The federal government has made remarkable investments in science in foundations such as the Canada Research Chairs and the Canadian Foundation for Innovation but has not matched this with investments in operating grants that support the investigators and the new infrastructure. This lack of synchrony is having an effect on our ability to make maximum use of these opportunities.

• Question 3 about the stability of research funding and your views on longer term funding generated many suggestions, including the ability of the granting councils to carry funds from one fiscal year to another. Continuity of research and keeping highly trained research personnel is a major concern and the falling success rate of grant renewals will make this more acute.

• Questions 4 and 5 on the availability of equipment generated the observation that although equipment is easier to obtain, operating funding for its functional upkeep is hard to find.

• Question 6 on graduate student stipends brought some interesting responses. Although the level of funding has been gradually increasing and Canada Graduate Scholarships are certainly well funded, opinion is that we need funding for more students. The linkage between better funding levels for investigators generating greater student enthusiasm was commented upon by several of you.

• Question 7 on the salary levels of post-doctoral fellows generated the comments that the salary levels are too low in Canada.

• Question 8 asked whether the CSBMCB should also represent your concerns to the granting councils. From your comments in response to the other questions it is obvious that many of you are questioning the need for some of the 13 CIHR Institutes and the targeted programs. In contrast there were a few suggestions to create a CIHR Institute of Molecular Biology or Basic Medical Sciences (but none for a CIHR Institute for Biochemistry, Molecular and Cell Biology).

• Question 9 on the allocation at various institutions of the 20% overhead given by the federal government generated some fiery comments. Some were unaware of these funds, but the majority of us are unaware of how our institutions spend them in support of the research that generated them. There was a call for greater transparency and I guess this is a "could try harder" message for some institutions

What happens next?

• We will continue to represent (now, thanks to the survey, more accurately) your concerns to the federal government through the advocacy group of the CFBS.

• We will also meet with the CIHR and with NSERC to transmit your views.

• We will continue to keep you informed of our progress (or lack of it).

The importance of our research for the health of Canadians and the continued development of the knowledge economy are best communicated by us, the researchers. The best recipients of this passion are our elected representatives. Tell your local MP of your successes and frustrations, and perhaps arrange to visit your local MP on "the hill" when you are in Ottawa.

David Thomas, Vice-President CSBMCB

News from the Essex Marches - or does British biochemistry have a future?

Peter Nicholls

Visiting Professor of Biological Sciences, University of Essex, Colchester, U.K.
Emeritus Professor, Biological Sciences, Brock University, St. Catharines

In optics, Alhazen's problem is: "Given a light source and a curved mirror, find the point on the mirror where light will be reflected into the eye." Alhazen (Arabic al-Haytham), the author of a 7-volume work on optics 700 years before Newton, was probably the first to understand — in the year 1000 — that vision does involve reflection of light from object into eye (1). This non-intuitive idea had taken long to be established. Known as al-Basri from the city of his birth, Alhazen had begun a career as minister for Basra, but became disenchanted with religion and politics, and took up science and mathematics. Narrowly escaping execution for displeasing the Caliph, he spent a large part of his later life under house arrest like Galileo. The next serious advances in optics had to wait about half a millennium. Cultures can enter stasis, or decline, for reasons both internal and external. Could we be entering a twilight era of Western science?

Biochemistry in the 21st century will inevitably be different from that in the last century. Internal reasons already include changes in emphasis away from the metabolism of small molecules and towards the complexities of proteomics. When we step out of a time machine to meet students in 2100, if there are any, we shall amaze them with our knowledge of the minutiae of carbon chain metabolism (aka the Krebs cycle) while their computers may baffle us with a technical grasp of cell biology. A look at the complex descriptions of carbohydrate metabolism in the late 1930s made one appreciate the simplification created by Krebs' deep insights. But when I learned the cycle it was only 15 years old. 50 years have passed since then. Similar simplifications may be hidden within the complexities of protein-protein interactions during the cell cycle. But I doubt it, though I hope to be proven wrong.

Biochemistry in the 21st century will also be affected by external causes. The well-documented retreat of undergraduate academic science, both in numbers of students opting for university courses and in types of course available, is accompanied by a governmentally-supported commercialisation of research. Funds are also increasingly targeted at an elite. We in the UK all compete for research funds departmentally, less individually than in Canada, and departments are graded in five or six categories from 1 to 5*. To be a 1, 2 or even 3 is to be unfunded and almost certain of closure; to be well-funded the RAE grade (2) must be 5 or preferably 5*; Essex is a 4.

The RAE for research is matched by a TQA for teaching (3). Both involve immense input of administrative time and effort. Imaginative (or ordinary) teaching is also threatened by a mountain of bureaucracy and paperwork. Decisions about student marking, procedures and extensions, which in Canada used to take a few moments, require official forms, records, meetings and decisions in committee. Outside social change means that biomedical and sports sciences are chosen

options rather than classical biochemistry. The trend to professional organizing and administration, seen most dramatically in government with most decisions and plans made by highly paid appointed technocrats rather than unpaid elected politicians, now extends to academia. The UK Biochemical Society abandoned its tradition of multiple meetings throughout the year, based in universities and free to all members, and replaced it with a single annual event (in Glasgow for the next 5 years) at a conference centre with professional organizers and a substantial registration fee. We hosted the last old style biochemical meeting in Essex in mid-2003.

Enrolment and funding declines have seen many university science departments closed. Essex has lost chemistry and physics, replacing the former with a multiplicity of biomedical courses and the latter by Electronic Systems Engineering. Biological Sciences seem safe because of our links to medicine, both theoretically and politically, with links to projects within the National Health Service and the prospect of becoming part of a new medical school.

In January 2005 the UK Biophysics Society and the Inorganic Biochemistry Discussion Group organised a meeting on protein mechanisms in Leicester. Leicester has Newtonian connections — his home at Woolsthorpe is not far — and a sundial Newton bust has just been placed in the university garden designed from his famous picture holding a prism. The work on light, following Alhazen's, was both physics and biophysics — his most dramatic experiment on his own eye involved pushing a bodkin behind the retina to show that it gave a sensation of colour. Newton died a long time ago and the Newtonian "research programme" (4) was abandoned for biology in the 19th century. This now is the year of Einstein, centenary of his three most revolutionary papers. But Einstein's method is about to join Newton's as a past way of thinking. *Nature*, in its Einstein commemorative issue (Jan 20th 2005), calls for his death to be accepted and for physics to "become" engineering (5), as has already happened here at Essex.

Steven Rose, biochemist at the Open University (appointed many years ago in a competition for which the writer was unsuccessful), is the establishment's gadfly. In a Guardian article (Dec 8th 2004) he linked the technocratic business orientation towards universities with the disappearance of socialism (6): "Building socialism may be a past dream but we could at least hope that New Labour could aspire to the broader vision of a science more accountable to the needs and concerns of civil society."

Together with Ian Gibson (previously Dean of Biology at the University of East Anglia, now Labour MP for Norwich, government critic and chair of the House standing committee on science and technology), Rose keynoted a meeting in the House of Commons on January 19th. The occasion was the launch of a report by Scientists for Global Responsibility (7) on military involvement in science, which is not just a matter of nuclear weapons. It includes all hi-tech areas, including much electronics, and the US is now engaged in a massively funded research effort in 'Biodefence' — a grey area bridging defensive and possibly illegal offensive study of lethal bacteria, viruses and proteins. Rose himself was recently invited by the US military to collaborate (8). He declined. But one colleague here is cooperating with the Homeland Security-sponsored computer modelling of smallpox enzyme inhibitors, a project offered to the entire microcomputer-using world as a disseminated screen saver alternative to SETI under the unsubtle name of "patriotgrid" (9). It would be interesting to compare military and civilian R & D expenditure in the US and Canada with that in the UK.

The biochemical growth area of substantial pharmaceutical if not military interest in which our group is involved is the hormonal and cellular activity of nitric oxide. NO targets several heme proteins including both guanylate cyclase and cytochrome oxidase (10). NO generators, and direct and indirect (cGMP) target inhibitors, the most notorious being ViagraJ, are money spinners. And fortunately NO ligation is still a key to basic heme enzyme function and mechanism. But my

own most recent contribution combined traditional spectrophotometry and electron paramagnetic resonance (EPR) with the low temperature X-ray crystallography of formate-peroxidase (11). It is hard to make formate clinically or commercially relevant although it is responsible for binding liver catalase in one striking EPR-detectable symptom of death. The crystal structures were personally satisfying because they helped solve a problem I had as a graduate student (12). But in the drive to improve our RAE from a 4 to a 5 we are told that it is papers in *Nature* or *Science* that are essential. My own recent effort (13) sadly will not count.

1. Alhazen is at http://www-gap.dcs.st-and.ac.uk/~history/Mathematicians/Al-Haytham.html
2. The last RAE is at http://www.hero.ac.uk/rae/ the next at http://www.rae.ac.uk/default.htm
3. The last TQA is at http://www.qaa.ac.uk/revreps/reviewreports.htm
4. Popper, K.R. & Eccles, J.C. (1977) The Self and its Brain (Springer International).
5. Editorial (2005) Einstein is dead. Nature 433, 179.
6. Rose at http://www.guardian.co.uk/life/last-word/story/0,13228,1368972,00.html
7. The report "Soldiers in the Laboratory: Military involvement in science and technology - and some alternatives" is a 560kb pdf file available at http://www.sgr.org.uk
8. Rose at http://www.guardian.co.uk/life/last-word/story/0,13228,1393730,00.html
9. Patriotgrid is at http://www.3nw.com/pda/patri-otgrid.htm
10. Cooper, C.E. (2003) Competitive, reversible, physiological? Inhibition of mitochondrial cytochrome oxidase by nitric oxide. IUBMB Life, 55: 591-7.
11. Carlsson, G.H., Nicholls, P., Svistunenko, D., Berglund, G., & Hajdu, J. (2005) Complexes of horseradish peroxidase with formate, acetate and carbon monoxide. Biochemistry, 44: 635-642.
12. Nicholls, P. (1961). The action of anions on catalase peroxide compounds. Biochem. J., 81: 365-374.
13. Lalanne, D., Nicholls, P. & Rotblat, J. (2005) Letter on nuclear weapons proliferation. *Nature*, 433: 571.

Recollections: How I Became A Biochemist

Rose M. Johnstone

Department of Biochemistry, McGill University

Bound to be in Biochemistry

Circumstance and happenstance are probably major factors in the choice of a career. In many parts of the world one may be born into a family of bankers and become a banker, or into a baker's family and bake bread for the rest of one's life. The children of immigrants to North America often find themselves following inclinations beyond any of the family's horizons.

During the period when I was growing up, the idea of becoming a biochemist would have been akin to planning a flight to the moon at the turn of the nineteenth century. Even the thought of a University education was outside any realistic dream. When my teenage older brother spurned my father's plans to become an apprentice glove-maker and chose instead to go to high school and beyond to follow his dream of becoming a mathematician, he became the first member of the known generations of my family to attend university. Most had not been to secondary school. Any formal schooling had been to learn a trade. Education was highly valued, but the cost was outside the reach of their skimpy bank accounts and the bottom line of their mere survival incomes. When I arrived in Montreal from Poland in 1936 at the age of eight, even high school attendance required tuition fees. There was no certainty that when I reached adolescence, I would find a way to attend secondary school as a full-time student. A number of my classmates in the early forties, still on the edge of the Great Depression, had to take whatever work was available to help their families survive. I had the luck to be with the chosen ranks and was given the opportunity and a scholarship to continue in high school until graduation, without being required to contribute to the family's meagre income. My community was one of working class parents or families of self-employed modest shopkeepers. None of us came from families with professional parents.

By today's student parlance, I would have been considered a swot. My modest demands meant that I did not have to take on after-school jobs to earn money for clothes and cosmetics. I was hopeless at all sports. I was convinced that I had poor hand-to-eye coordination until I learned to play tennis after age 55. I did my homework assiduously and actually loved school. Vacation time was the time to work for extra cash — vista-broadening trips or summer camps were not part of our lives. I was not a 'hit' with my fellow male students, so distraction by teenage male songs did not interfere with my primary focus of doing well in school. Had I been a sought-after 'high school sweetheart' my career path might have taken a different turn. In my high school class of some 35 female teenagers, only one other followed a professional career requiring extended post B.A./B.Sc. university training. Less than a dozen of us continued on to university. For the young males in this school, the picture was quite different — a large percentage went to university and followed professional careers. Indeed, our high school has been immortalized by one of Canada's best known novelists, Mordechai Richler, as Fletcher's High. Some of Canada's outstanding artists, mathematicians, physicians and scientists are (or were) graduates of Baron Byng High School in Montreal.

Reading was a passion from my earliest years, and the trials and successes of the medical men (and the few women) of the century hit a responsive chord from the very first. I savoured the idea of being amongst the group of individuals whose lives were recounted by Paul de Kruif. However, medicine as an ultimate profession was beyond the pale for a mountain of reasons; expense, lack of adequate government subsidies, length of training before beginning to earn a stipend and, perhaps the two most persuasive arguments, the cap to the number of Jews accepted into the local medical school (living away from home was totally unrealistic), and the even fewer number of women admitted into the Faculty, (less than 10% of the annual admission).

During my last two summer vacations in high school, I found work as a nurse's aid in our local (and famous) Montreal Neurological Institute. One of the assigned duties was to bring patients down to the basement of the building where the EEG was conducted. I thought a technical assistant in this area would be my "dream career" and at the end of high school, applied for a posted position in this area as a trainee. An answer from the hospital was slow in coming. I had made no other plans for the post-high school era, except that I knew I did not favour my father's choice of career (a bookkeeper in some small or large shmate factory). He was deadly opposed to a college education for two reasons — the extra financial burden with no additional income and the fact that I would be outside my natural group of potential husbands. I don't know which one concerned him more.

As the deadline for admission to University drew closer and no word from the hospital about the training program, I decided to apply for admission to the University to follow a program in science. Since my brother had already become a 'college boy', my feminist mother could not see why I should be denied the same opportunity. So despite my father's objections, I registered, was accepted but promised to find my own source of money — loans, grants, scholarships and summer jobs, to pay my own fees and out of pocket expenses. The hospital never acknowledged my application and in 1946, I became a science student at McGill University. A new world was opened for me. I loved it — new classes new encounters and anonymity. Just one body amongst many!

I decided that a specialization in Microbiology would, at the end of four years and a B.Sc. degree, provide the greatest opportunities for employment. Every hospital and laboratory needed technical microbiologists. Besides, Paul de Kruif's 'Microbe Hunters' was still a part of my vivid memory. Along the way, organic chemistry gave me newfound pleasure. Botany and zoology left me out in the cold — largely because I couldn't draw what I saw — no doubt part of the same problem which led me to fail art in my high school matriculation.

In my sophomore year, the first undergraduate course in biochemistry — taken along with the first year medical students — was part of the curriculum. The instructor, the Chairman of the Department as well as the Dean of Graduate Studies, D. L. Thomson, was charismatic. No one who has ever studied biochemistry at McGill University from the mid- thirties to the late fifties, will ever forget Thomson's spellbinding expositions. For me the combination of organic chemistry, biology and the dynamic events of living cells was like drinking a fine wine, even though at that time I had never had a sip of fine wine! That people could deduce experimentally how a cell carried out its daily business of converting energy, making more of its components, converting all manner of seemingly, stable compounds into the vast variety of the cell's constituents, gave me a tremendous sense of satisfaction. To this day, seeing a beautiful experiment, to establish even the most esoteric fact, fills me with pleasure. I see it as a true work of art and imagination-almost like seeing a beautiful painting. I was hooked! After the first two weeks of the sophomore year, I switched programs and studied Biochemistry as my major. I now knew where I belonged. I also knew that upon graduation I would pursue graduate work to become a member of my favourite club — the Biochemists.

The most distinguished biochemist at the time at McGill University was J. H. Quastel. D. L. Thomson was very supportive and encouraged me

to apply to work with Quastel, who headed the McGill-Montreal General Hospital Research Institute. Curiously, the only problem that concerned Quastel during the interview was not my academic ability or my reasons for choosing to work under his supervision, but rather my marital status. Was I married, was I engaged, did I intend to marry and have children? I wasn't married, I wasn't engaged, I didn't have children, and I managed to assure him that I would solve those problems when confronted with them. (I did in due time.) He accepted me into his lab without ever inquiring why I wanted to be a biochemist or whether I had the academic wherewithal to succeed in the graduate program.

Despite the normal disappointments and tribulations of graduate work, the occasional successes convinced me that I had chosen work which appealed to me at all levels. After obtaining my Ph.D. degree, I was awarded a modest fellowship from the National Cancer Institute of Canada, which permitted me to work for a year at the National Institutes of Medical Research at Mill Hill in England. During my post- doctoral period in England, I acquired a son in addition to training in enzyme induction in Martin Pollock's laboratory studying penicillinase formation. My stay at Mill Hill was abruptly terminated because the Director, Sir Charles Harrington, refused to sign my application for a Fellowship from the National Research Council of Canada to extend my stay. In his opinion, no woman with a young baby could apply herself adequately to the demands of a research program. His major argument was that his own daughter had not been able to do so! Undiplomatically, I responded by telling him I was grateful not to have been born his daughter! I managed to get a small fellowship to work elsewhere for a few months and left the NIMR. At Mill Hill I had the opportunity to meet some of England's most distinguished scientists, which gave me a perspective on science and research I had sorely lacked till then.

My late husband and I had toyed with the idea of taking up residence in England because North America was in the throes of McCarthyism. However, the openings were few and poorly paid. Eventually we concluded that the opportunities to pursue our respective careers in science and business were better in North America. When Quastel offered me a junior staff position at my old place of work, I was happy to return to Montreal and heated living quarters! Later I joined the staff of the Department of Biochemistry at McGill University, where I have remained in different capacities, including Chair of the Department (between 1980-1990).

Work begun upon returning to Canada on Na+-coupled amino acid transport led to the discovery of Na+-dependent ascorbate transport in the adrenal and the pituitary glands, and the reason why these glands maintain much higher levels of ascorbate than the blood stream. Isolated plasma membranes of mammalian cells were shown to carry out Na+-gradient driven transport, both in the native state and after reconstitution of detergent-solubilized membranes. Later, the studies on the loss of Na+-dependent amino acid transport in maturing reticulocytes led to the discovery of a novel method for removing obsolete, but intact, proteins (such as the transferrin receptor) from the reticulocyte plasma membrane. This novel route for the formation and release of small vesicles (exosomes) rich in membrane proteins into the extracellular milieu is now being studied by immunologists in exploring the routes for antigen presentation.

After a lifetime in the field, I realize that the die to enter biochemistry was cast when I switched programs in my sophomore year and never found other venues either more appealing or worth trying to swim up another stream.

*This article is reprinted from IUBMB LIFE, vol. 56, 109-111, 2004 with permission of the publishers Taylor & Francis Healthsciences.

Addendum

In addition to revisiting the events which drew me into biochemistry, this is an opportunity to reflect on events which shaped my views on biochemistry at McGill, including my views on the participation of women in the discipline over the course of forty years.

From the earliest days, women have been present in visible numbers in biochemistry at McGill. A woman, Evelyn Anderson, was amongst the first three or four to be granted a Ph.D. degree in biochemistry in the mid thirties. During Collip's thirteen-year tenure between 1928 and 1941, twelve men and two women received graduate degrees. During my ten-year tenure as Chair (1980-1990) of the Department, nearly 50% of the graduate student population was female. In the twenty-first century, the number has risen to over 50%. At present in 2005, there are 75 woman and 56 men registered in the graduate program at McGill. This rise in women's participation follows the pattern also seen in the number of women acquiring degrees in medicine and law in the last 25 years.

However, the impact of the increase of women in medicine and law is much more evident than the rise of women in the professorial ranks of University Departments of Biochemistry. It is true that it is no longer novel to have a female as Chair of Biochemistry in universities in North America but it is still relatively rare. Nor do I believe that all problems for women will melt away when more are offered a Chair! There are female Deans and even Principals, but the swelling in the academic ranks in Canada has not reflected the growth of the number of women in the graduate student body. No one would expect a linear relationship, given the long lag time between qualification and being a candidate for a position. However, the gender gap in hiring for tenure track positions seems to be closing at a snail's pace. At a recent meeting of the Chairs of Biochemistry Departments of North America (which includes Canadians) over sixty Chairs participated, four of whom were women. Twenty years ago, when I participated, we were 3-4. The numbers speak for themselves.

During my term as the Chair, I followed closely the number of applications for positions which crossed my desk. Far fewer were from women than would be expected from their number in the trained pool. The feeling arose that even if eligible, they were reluctant to apply without some specific encouragement from an individual who was interested in that particular woman's career. But mentors are not a common commodity. Furthermore, women's professional lives get heavily entwined with their personal lives. They are in the forefront in supporting the needs of spouses and children, even with helpful partners. Does an academic career in our highly competitive system, requiring both external, competitively acquired research money and the challenge of tenure considerations, become an unacceptable burden for many? Has the growth of the commercial biotechnology industry in Canada (and elsewhere) opened up other professional opportunities for women, which make fewer personal demands in all facets while probably being more lucrative? Perhaps to some the latter positions may lack the "cachet" of university professorships, but they do provide an opportunity to follow a career and have economic independence. This view is consistent with, but hardly proof of, the view that while the majority of female Ph.D. graduates do maintain professional lives, there are relatively few knocking on the doors and being admitted through the doors of traditional Biochemistry Departments.

There is another factor which may influence women's careers at universities. Overall, women fare better in academic careers when they remain at the institution in which they obtained their original training (or had postdoctoral experience). Too frequently, when they move away, it is more likely that they follow a partner's career than an invitation to fill a position. Then they must find their way around a new environment, where they know few people who have developed faith in their abilities over many years of contact. This may play a role in many men's careers as well, but more frequently a man's move is based on an invitation to relocate, where it is important for the recruiters to help the "new man" to succeed. These opinions are based on observations through a narrow window, seen from a career of over forty years in the Biochemistry Department at McGill. The issue has been discussed with similar conclusions in a book published by Rutgers University Press (1996) called *Creative Couples in the Sciences*. Perhaps the time has come to undertake a thorough statistical study of the career choices of

woman with Ph.D. degrees in Biochemistry countrywide. Are women selecting themselves out of academic careers or they being selected out as in the past? If there is interest in changing the present status, we need up-to-date information. From a personal perspective, with the rapid expansion in the number of participants in the field, the relative position of the female "professoriate" is ebbing away despite their keen interest in basic biochemical research as viewed by their large numbers in the graduate student body.

Leaving the gender issue and considering the growth of our discipline in Canada, one cannot but applaud the growth in stature and the scientific quality of the work currently carried out by Canada's biochemists. Few Canadian biochemists had a high profile in the international community when the Canadian Biochemical Society was launched in 1957. The majority of western countries have not witnessed growth of the discipline comparable to that seen in Canada. Most universities across the country can name members in their departments who are recognized in the forefront of their respective specialities. We still suffer from the fact that our country is huge, and interaction between individuals with common interests is north to south rather than east to west. That, too may change with better communications, but will not overcome the high density of scientists in common areas to the south of us, right across the continent.

The issue of adequate financial backing is always with us. It is unlikely that our researchers will ever find all the funding to fulfill their aspirations. I suspect, even without having the data, that the number of practitioners keeps increasing faster than the money put into the kitty. I believe it is unrealistic to think that the growth in funding will ever meet the demands. But certain aspects of the funding to university-based researchers needs re-examination. Only two, which are close to my heart, will be addressed.

The first issue is funding for ideas, which are not on the mainstream and where little preliminary data are available. A university should be and, in the past has been, the place to examine entirely new ideas and concepts without reference to their immediate commercial or medical value. In recent years, the interest and pressure has been to commercialize, often putting to use information and concepts discovered in a previous era. Universities and governments have encouraged commercialization. Universities have set up expensive offices to help commercialize the research findings of the staff in all fields. By and large, these commercializations are based on work originally driven by the individual's curiosity which created an unexploited pipeline of information. Now with the emphasis on "putting out a product" the pipeline is being emptied. Less attention and funding is given to examine "off the wall" ideas which may be fruitful in years to come — or fall with a thud. I consider such undertakings to be a fundamental aspect of university-based research. No commercial enterprise will do it. Would today's research councils support Faraday's original tinkering on electricity before he had practical evidence for his ideas? Peter Mitchell was fortunate to have private funds to follow his insight on the chemiosmotic hypothesis in the era when the majority of biochemists recoiled from the notion of being "electricians" and his work was not considered realistic. A special fund is needed to support imaginative ideas which are too "young" even for seed money. The university is the natural home for this type of exploration. In the normal processing of grants to research councils, both private and public, such applications would not be considered. Another venue is needed to foster the development of the earliest stages of ideas which may — or realistically may not — expand the frontiers of knowledge without the criterion of the birth of a commercial product.

The second issue is the active reclamation of productive scientists who lose their footing and research grants in the middle of their careers. These not infrequent occasions create problems both for the individual and the department. The problem in my view is particularly acute for the well-established individuals who, after a number of productive years, suddenly find themselves without funding in an active research community. Young investigators also face serious problems if they can-

not get external funding in research-oriented environments. However, these are not the subjects of my concern in this commentary. In my experience loss of funding in mid-career affects university teaching departments and the core staff more than in affiliated research institutes. Research institutes frequently have funding in their endowments or from public money raised during financial campaigns to support their research. Such funds can be and are used to help their members over the rough spots. University departments have basic budgets which fail to meet even operating costs. It's not uncommon for a department to restrict the availability of free pencils to stay within budget, let alone find financial support to keep a research project going.

Lack of participation in the research life of a Department, especially where the latter forms a major time commitment of its staff, leads to demoralization of the individual and the department. Reinstatement is important for the individual himself/herself and for the research life of the Department as a whole to maintain the natural cohesiveness of being an "equal amongst equals". The support required to ameliorate this problem need not be extensive and must be time-limited, but should provide more than the six months or so to return to an external funding agency with a new application. The amount of "security" funding might reflect a small fraction of the total research budget that the departmental members bring into the university. Often short-term interest is accrued on research grants which are not available to the departments. Some of the money should be made available to the department to save a research career of a heretofore successful and productive researcher. Most of us, who are involved in research and are faced with the challenges of a changing technology, are anxious about stumbling and tripping. Few escape a long research career without a few "downs". As someone now "out the door" who no longer has worries about finding funds for students or expensive reagents and supplies, a vivid memory remains of the occasions when an able colleague lost funding and was faced with fading into the woodwork. Such individuals, I believe, need inside support to provide an opportunity to retool and revise the research approach and even get a preliminary set of data. How much time would be necessary? This judgement is going to reflect the confidence of the department in the individual's progress and ability, as well as the available money. The bottom line is money is required for this purpose. We all chose experimental work when we joined this profession. One fumble should not close the chapter on a productive career.

In closing this addendum on my entry into biochemistry with my views after I have gone out the door, I never regretted my choice of career. There have been frustrations, disappointments and the occasional truly exciting moments. What I do regret is the sparseness of same gender colleagues with whom to "gossip" about science in daily interactions. This is an aspect of a career in biochemistry that few men face.

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 proteinases 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. BioI 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 rea-

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 molecular 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 CSBMCB Merck Frosst Prize Dr. J. N. Mark Glover

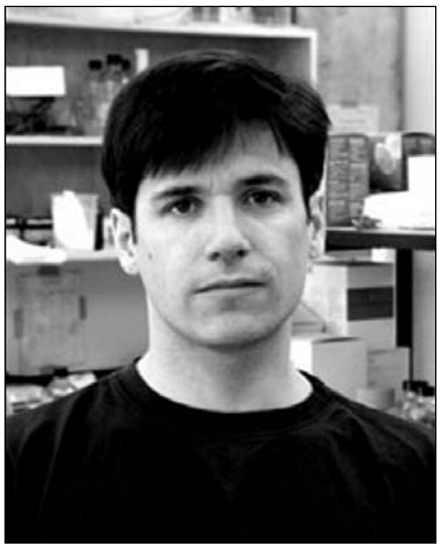
Dr. Mark Glover received an Honours B.Sc. Science degree in Biochemistry and Chemistry, with a minor in Mathematics, from Dalhousie University in 1985. These early choices foreshadowed his ultimate interest in structural biology. From 1985-1991, he carried out graduate studies with Dr. David Pulleyblank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

"OneLinerImages" by Ed Munn

(see back cover of the Bulletin)

Introduction

As a senior research scientist at Babraham Institute, Cambridge U.K., Dr. Ed Munn's work ranged from membrane characterization to molecular immunology. Early work with David Green's group in Wisconsin and collaborations with Guy Greville formed the impetus for his classic monograph, "The Structure of Mitochondria", E.A. Munn (1974). Studying mitochondrial development in insects, he discovered with the electron microscope a protein which he characterized and called calliphorin. This proved to be the archetype for the hexamerin (arylphorin) family of proteins. He had a long and productive collaboration with Arnold Feinstein on the structure of immunoglobulins, pentraxins and other blood proteins. In addition, working with Colin Orpin, he was much involved in the structural characterization of anaerobic fungi. Finally he developed a highly effective molecular vaccine against the parasitic nematode *Haemonchus contortus*. On my last sabbatical year I worked with Ed on aspects of this program. Ed now concentrates on drawing, writing and lecturing. On a recent visit to Ontario he first showed me his artistic vision of the common birthright of all living things in the original and beautiful representations he calls "OneLinerImages". The maple leaf illustration on the back cover of this edition of the CSBMCB Bulletin, inspired by our autumn emblem, was his gift to my wife and me. It gives me great pleasure to introduce these unique structures to Canada.

Dr. W.C. McMurray, Professor Emeritus,
University of Western Ontario

"OneLinerImages"

In every day life, the intricate internal beauty of living cells is hidden from view. Specialist textbooks of cell biology, reproducing the details of research by light microscopists and electron microscopists, can provide clues about this hidden world, but the biologist and artist Ed Munn was looking for an effective means of representing this hidden beauty in the context of the familiar external outline and thus making it accessible to the non-specialist. To this end he has developed a form he calls "OneLinerImages".

"OneLinerImages" ("OneLiners", OLIs) are representations of living things (plants and animals in particular) intended to show first, the paradoxical situation in which in order to exist, individuals must be separated from their environment, but yet are interactive with and wholly dependent on it; and secondly, the interactions between individuals essential for the survival of populations. In "OneLiner" images, the outline is a **continuous, single line** defining the surface separating the individual or group from their surroundings. The line is regularly indented to represent the internal and usually invisible complexity within living cells, many of which contain arrays of folded membranes (mitochondria, chloroplasts, endoplasmic reticulum and Golgi apparatus). The space enclosed by the line consists of continuous colour, sometimes constant but usually varying. On one level this can be taken as an expression of the differentiation of the parts of the organism into tissues and cell types and the cells into their component parts. On another level, in combination with the shapes given to the indentations it provides a means to impart texture and, obviously, external colour. The resultant images are at once easily recognisable representations of external form (oak leaf, cat, frog, heron and so on) with the striking patterns generated by the form-filling arrays of indented lines giving sense of depth and movement.

The current range of OLIs extends from the abstract, for example *Rock Pool*, to plant leaves such as *Monstera II*, fruits as in *Autumn Sumac* and *Sea Grape II* and animals (insects, e.g. *Red Admiral*; fish, e.g. *Yellow-Finned Tuna*; reptiles, e.g. *Snake I*; birds, e.g. *Green Heron*; and mammals). In one of the latter (*Dolphin II*) the inner space is shown to be continuous with part of the external space (the ocean) to show their flowing interdependence.

OLIs created by Dr. Munn are patent protected.

News From Member Departments

McMaster University

Department of Biochemistry

Correspondent: Eric Brown

The Department of Biochemistry underwent a name change this year to the Department of Biochemistry and Biomedical Sciences. The new name is in line with the research interests of a growing department and emerging strengths in research in the health sciences. The department has grown considerably in recent years and we are now 27 core faculty with nine associate members. The new name thus more accurately reflects the constituents and ambitions of a department on the increase.

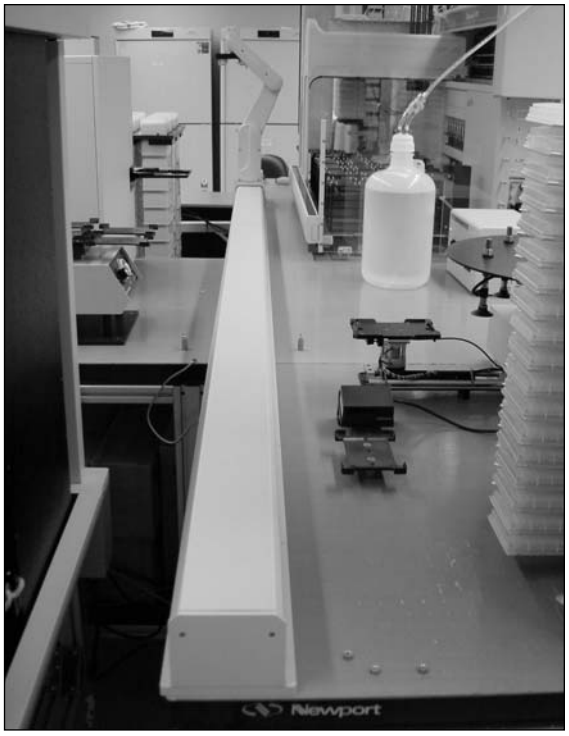
Undergraduate program. In the spring of this year, we graduated 71 undergraduate students in Biochemistry, 25 of them with Distinction! This past year new undergraduate offerings have included a new inquiry-based third-year course, reworked labs and a new course in computational biology. At the same time, core faculty have been working hard this year on a complete reinvention of the undergraduate curriculum. The goal is a redesigned, innovative and more effective new program that will give students more flexibility and emphasize problem-based learning.

Graduate program. We have also been implementing progressive change in the graduate program. Those changes have included improvements to the M.Sc.-Ph.D. transfer process and the institution of an optional laboratory rotation program for incoming graduate students. These and other changes have met with enthusiastic approval from the graduate students and in September of this year we had a new record enrollment of 23 new graduate students in the department.

New infrastructure. 2004 has been a bumper year in the department for infrastructure development. This summer, several of our members moved into the newly completed Michael G. DeGroote Centre for Learning and Discovery, a fabulous new building with state-of-the-art laboratory space, meeting rooms and lecture theatres. In another exciting development, David Andrews and John Hassell led a successful infrastructure application to the Canadian Foundation for Innovation (and Ontario Innovation Trust) for new laboratories and cutting edge high-content imaging and genetic profiling instrumentation. The total value of the project is $11 million.

Faculty highlights. In June of this year **V.S. Ananthanarayanan** officially retired but will not be leaving us, as he will continue his research with the renewal of his Heart and Stroke Foundation of Ontario grant. This amounts to 27 years of continuous support from the HSFO for Ananth! **David Andrews** was responsible for the apoptosis session at the CSBMCB meeting on Cellular Signaling in Mont Tremblant, and finished his third year on the Executive as Past-President. At the same time, David is moving from President of CFBS to Past-President. This year David joined the editorial board of the journal BMC Cell Biology. Felicia Vulcu, a graduate student in David's lab, was awarded an NSERC scholarship. **Jonathan Bramson, Karen Mossman, Mark Loeb** and **Jim Mahony** were awarded a large research contract from NIH to study the population genetics of West Nile virus infection. The budget will be approximately $13 million, and they will be looking for single nucleotide polymorphisms that are associated with susceptibility to neuroinvasive West Nile virus infection. This program will be carried out in collaboration with the McGill Genome Center, the University Health Network, and a number of partners across the U.S. **Eric Brown** continued as Director of the McMaster High Throughput Screening Lab. He gave seminars at the Canadian Society for Microbiology Annual Meeting, the 6th Annual Conference in Signaling in Normal and Cancer Cells in Banff, the Second International *E. coli* Alliance Conference on Systems Biology in Banff, and the Harvard Conference on Academic and Industrial Approaches to HTS and Drug Development.

Eric's students Tracey Campbell and Jeffrey Schertzer were awarded CIHR Doctoral Awards, and he took on two new graduate students this year, Chand Mangat and Kathryn Millar. **Alba Guarné** was awarded a new three-year CIHR Operating and Equipment grant and a new five-year NSERC discovery grant. She gave an invited talk at the American Crystallographic Association in July and has accepted two new M.Sc. students into her lab, Shirley Ng and Lisa Naylor. **Yingfu Li's** NSERC grant was renewed for five years, and Yingfu has a key role in a successful $4.2 million Genome Canada grant (led by John Dick at the University Health Network) entitled "Mass spectrometer-based flow cytometer, methods and applications." **Graham McGibbon** was awarded an NSERC Operating and Equipment grant. **Giuseppe Melacini** was awarded two operating grants, one from NSERC and the other from CIHR. He was also appointed to serve on the scientific review committee of the Heart and Stroke Foundation of Canada. **Evert Nieboer** and his colleagues at the University of Tromso in Norway had a letter published in the July 23rd issue of Science on "Cancer Risk and Salmon Intake". It reports never before published epidemiologic data on cancer risk in relation to salmon consumption in Norway. He was also a contributor to the successful McMaster University "AllerGen" Network Centre of Excellence application by Judah Denburg. **Dino Trigatti's** Heart and Stroke Foundation of Ontario operating grant was renewed for three years, and he and co-applicant Suleiman Igdoura were awarded a new HSFO operating grant. Dino was awarded an Alumni Arch Award from the McMaster Alumni Association for exceptional work as a young scientist and teacher, and he gave invited talks at the University of Alberta, the Robarts Research Institute and St. Michael's Hospital in Toronto. **Jeffrey Weitz's** HSFO grant was renewed for four years. He presented seminars at VBWG National Update Conference in Orlando, the American Heart Association Meeting in Orlando, the American Society for Hematology Annual Meeting in San Diego, and the American College of Cardiology in New Orleans. David Boehr (Ph.D.) and Gloria Yang (M.Sc.) graduated from **Gerry Wright's** lab.



View of the High Throughput Screening (HTS) Laboratory at McMaster University

This was Gerry's third year as Chair of the Department. He gave invited seminars at Queens University and the University of Waterloo, and members of his group gave presentations at a variety of conferences, including the Annual General Meeting of the American Society of Microbiology. Graduate students Tariq Muktar and Ishac Nazi were awarded Ontario Graduate Scholarships. New graduate students Tushar Shakya, Laura Thompson and Jen Baysarowich joined Gerry's lab in September.

McMaster HTS Laboratory. The compound collection of the High Throughput Screening Laboratory reached 160,000 small molecules this year. The HTS Lab hosted an international competition in computational screening with more than 70 registrants worldwide. Screening Lab researchers gave presentations at a variety of conferences this year including Screening Europe, London, UK, and MipTec, Basel, Switzerland, Society for Biomolecular Screening, Harvard Meeting, and the International Conference on SARS, Lubeck, Germany.

Queen's University

Department of Biochemistry

Correspondent: Albert Clark and Glen Jones

The Queen's Department of Biochemistry continued to cope with an ever increasing number of undergraduate students, both in its own Honours program with its regular subject of specialization, major and coop streams, and in the Life Science program. The latter became the largest undergraduate program at the university years ago, and continues to grow.

During the past year **Dr. Zongchao Jia** took up his NSERC Steacie Fellowship. **Dr. Steven Smith** who joined the Department in 2001 was reappointed for his second 3-year term. **Drs. Zongchao Jia** and **Donald Forsdyke** were promoted to Professor. **Dr. Martin Petkovich** is on sabbatical for 2004-05. **Dr. John Spencer**, Professor Emeritus and former Department Head (1978-1990) has relinquished his Department office, but is a regular visitor. Dr. Forsdyke retired as Professor Emeritus in August 2004, but continues to be active in his bioinformatics research.

Dr. Colin Funk joined Queen's University faculty in July 2004, as a joint appointment as Professor in the Departments of Biochemistry and Physiology. He was awarded a Tier 1 Research Chair. Dr. Funk obtained his undergraduate education in the Department of Biochemistry at Queen's and his Ph.D. in Experimental Medicine from McGill University in 1985. Following a postdoctoral stint with Dr. B. Samuelson at the Karolinska Institute in Stockholm, he joined the faculty of the Department of Pharmacology at Vanderbilt University in Nashville, TN. In 1995, he joined the Department of Pharmacology, Center for Experimental Therapeutics, at the University of Pennsylvania School of Medicine in Philadelphia. He has over 100 peer reviewed publications in his field of eicosanoid research in health and disease. He has obtained research funding from CIHR, the Heart and Stroke Foundation, the National Heart, Lung and Blood Institute in the USA, the European Union 6th Framework Program, and Merck and Co.

Dr. Michael Boffa, previously an Adjunct Assistant Professor, was appointed as Assistant Professor in 2004 for a five-year term. Dr. Boffa obtained his education at Queen's in the Biochemistry Department; he completed his Ph.D. in 2000 working in Dr. Michael Nesheim's laboratory. He had remained in the Department as a post-doctoral fellow with Drs. Nesheim and Koschinsky working primarily on Thrombosis-Activable Fibrinolysis Inhibitor (TAFI). He has been contributing significantly to departmental teaching activities as co-coordinator of the third-year undergraduate teaching laboratory program and by giving some lectures in fourth year courses. He continues to be extremely active in his research on the regulation of TAFI gene expression using animal models.

University of Alberta

Department of Biochemistry

Correspondent: Bernard Lemire

Dr. Marek Michalak, our new Chair as of September 1, 2004, is shaking up the Department of Biochemistry at the University of Alberta with a mission of innovation and recruitment. He will lead the recruitment of up to six new faculty members within the next five years, ensuring the department maintains a reputation for dynamic and innovative research. Along with this, he has initiated plans to increase graduate student enrollment and to reform the undergraduate curriculum.

Bitten by the calcium bug during his Ph.D. thesis work (Structure and Function of Skeletal Muscle Sarcoplasmic Reticulum, 1978, Department of Biochemistry, Nencki Institute of Experimental Biology, Warsaw, Poland), Marek has ever pursued this passion. He first joined the laboratory of Dr. David McLennan at the Banting and Best Institute of the University of Toronto as a postdoctoral fellow. Later, he worked as Research Associate with Dr. Ernesto Carafoli at the Swiss Federal Institute of Technology (ETH) in Zürich, Switzerland. In 1984, he became an MRC Scholar and an

Assistant Professor in the Departments of Biochemistry and Pediatrics at the Hospital for Sick Children, University of Toronto. He was awarded the Young Investigator Award from the Canadian Cardiovascular Society in 1986. He moved to the University of Alberta in 1987, with appointments in Biochemistry and Pediatrics, and became a Full Professor in 1994. The Alberta Heritage Foundation for Medical Research immediately recognized his achievements and promise with a Scholar Award. This was followed by Senior Scholar and Medical Scientist awards from the AHFMR, and Scientist and Senior Scientist awards from the MRC. In 1999, he was the recipient of the AstraZeneca & CFBS Award in Molecular Biology. He has been Director of the CIHR Membrane Protein Research Group since 1997.

Mareck Michalak

Chris Bleackley

Brian Sykes

Marek's research is centered on the proteins of the endoplasmic reticulum and their functions in intracellular signaling, inter-organellar communication, regulation of protein synthesis and folding, modulation of gene expression, and calcium homeostasis. Recent murine transgenic and gene knockout studies have revealed an unexpected role for ER membrane-associated proteins in cardiac muscle development during embryogenesis. In addition to his passion for calcium, Marek has developed a high affinity for full-bodied wines. He has mingled these interests with sabbatical research visits to Geneva, Switzerland (1995-96) and to Montpellier, France (2002). He generously shares the results of these research trips by hosting post-seminar gatherings that feature samplings of his enological discoveries during discussions of scientific breakthroughs.

After six years as Chair of the Department of Biochemistry at the University of Alberta, **Dr. Brian Sykes** has accepted a position as Visiting Research Scientist in the Department of Chemistry and Biochemistry at the University of California San Diego. During his administrative leave, Brian will be working with Dr. Stanley Opella and exploring how new developments in solid state NMR can be applied to understanding muscle structure and muscle contraction.

Dr. Chris Bleackley was the recipient of the 2004 J. Gordin Kaplan Prize for Excellence in Research at the University of Alberta. The prize is the most prestigious research award at the University. Dr. Bleackley was also a finalist for the 2004 Outstanding Leadership in Science Award, which recognizes leadership in scientific innovation. This award is presented by The Alberta Science and Technology (ASTech) Leadership Foundation.

Dr. Bleackley's research has focused on understanding how cytotoxic T cells destroy tumour or virus-infected target cells. The cytotoxic T cells also attack transplants and can elicit autoimmune disorders. The precise mechanism by which cytotoxic T cells kill target cells has been an area of intense investigation. In 1986, Dr. Bleackley discovered a family of genes encoding proteolytic enzymes, now known as granzymes. Granzyme B initiates a proteolytic cascade mechanism essential for the induction of DNA fragmentation and apoptosis in target cells. In 2000, Dr. Bleackley showed that granzyme B could bind to the cation-independent mannose 6-phosphate receptor and use it to enter target cells. This work provides insight into how tumours may evade the immune system.

Dr. Bleackley has been supported by the Alberta Heritage Foundation for Medical Research (AHFMR), first as a Scholar and subsequently as an AHFMR Medical Scientist. He currently holds a Tier I Canada Research Chair in Molecular Biology and is a Canadian Institutes of Health Research (CIHR) Distinguished Scientist.

The Department of Biochemistry was honored this year by a visit from **Professor John E. Walker** of the Medical Research Council Dunn Human Nutrition Unit in Cambridge, UK. On October 27th, Dr. Walker presented the 17th John S. Colter Lecture in Biochemistry entitled "The Swings and Roundabouts of F- and V-ATPases". Dr. Walker was elected a Fellow of the Royal Society of London in 1995. He received the Peter Mitchell Medal of the European Bioenergetics Congress in 1996, and was awarded the Nobel Prize in Chemistry in 1997 for his outstanding studies on ATP synthesis.

The Lectureship was created by the colleagues, friends, and associates of John S. Colter to recognize his vision and achievements. Dr. Colter joined the Department of Biochemistry at the University of Alberta in 1961, and served as chairman for twenty-six years. During this time, he built an outstanding department recognized for its strength in biomedical research

University of British Columbia

Correspondents: Vince Duronio and Vanessa Auld

This year's correspondents' report comes from two members of the CSBMCB community not in the Biochemistry department. Your treasurer is based at the Vancouver Hospital site, where one of the significant developments has been to incorporate the hospital's research efforts under the umbrella of the Vancouver Coastal Health Research Institute. Much like the UBC campus, there are plans for substantial additions to the research space that were finalized in the past year. With major CFI and RHF awards to the Prostate Cancer Research Centre and the Centre for Hip Health, plans are underway to more than double the size of the Jack Bell Research Centre, and ground will be broken on the new iCORD facility – for research in spinal cord injury.

The most significant event in the Biochemistry and Molecular Biology Department this past year was the appointment of **Christopher Proud** as the new Chair. He will be joining the Department on March 1, 2005, while **Roger Brownsey** has been doing a fine job as the Acting Head. The department's leader for the past 10 years has been **George Mackie**, who decided not to take too much of a break from administration, moving to the President's office in the position of Associate VP, Academic Planning. We're sure that George will take on these responsibilities with his usual determined and insightful manner.

The following is a short bio of the incoming head, Dr. Proud. He obtained his B.Sc. (Biochemistry) at Bristol (UK) in 1974 and his Ph.D. (Biochemistry) at Dundee in 1978. His graduate studies with Professor Sir Philip Cohen gave him a strong interest in the mechanisms by which hormones and growth factors control mammalian cells, which has formed the theme of his subsequent research career.

Dr. Proud worked at the University of Göttingen (Germany) as a junior lecturer and then pursued additional postdoctoral training at the University of Sussex (UK) which introduced him to the field of protein synthesis and its control. After holding lectureships and then a readership at the University of Bristol, he transferred in 1995 to the University of Kent at Canterbury as a Chair, and then to Dundee in 1998 as Professor of Biochemical Physiology. In 2001, he became Head of the Division of Molecular Physiology in the School of Life Sciences in Dundee.

Dr. Proud's research has largely focused on understanding how signaling pathways are activated by nutrients, hormones and mitogens regulate the translational machinery in mammalian cells. Dr. Proud's research now encompasses a range of studies into how defects in protein synthesis or its control lead to human diseases. Examples of these include inflammatory diseases, overgrowth (hypertrophy) of the heart, certain kinds of cancer, and inherited conditions that cause neurodegeneration. He utilizes a range of approaches to address these issues, from biochemical and structural studies to work using transgenic models. Dr. Proud's research

group collaborates with academic institutions and drug companies to understand how these defects arise and, ultimately, to try to develop strategies for their effective therapy.

In taking over the department, Dr. Proud will join many of the other basic sciences departments on campus in a major move into the new Life Sciences Centre. In the case of the cell biologists at UBC, this event has resulted in the realization of a long term plan to get as many cell biologists from across campus as possible under one roof. The Life Sciences Centre is a 565,000 sq. ft. facility, with 150,000 sq. ft of educational space and 280,000 sq. ft of research space. The administrative entity governing the research space is called the Life Sciences Institute, in which research space is allocated based on themes, regardless of the individual PI's department. For example, many members of the Cell Biology Group will be located on the same floor regardless of their "home" department. The building was also greatly enhanced by the successful CFI application for the Centre of Disease Modeling spearheaded by **Francois Jean** and **Hung-Sia The** of the Department of Microbiology and Immunology (which incidentally has also recruited a new head, **Dr. Charles Thompson**).

The first annual Cell Biology retreat was held at Loon Lake in May 2004. Researchers from UBC, SFU and the University of Victoria came to hear the latest research from cell biologists from all three universities as well as the plenary speaker **Jim Woodgett** (University of Toronto). The weather cooperated and so everyone could enjoy the canoeing and smores around the camp fire. This year's retreat will be held at Loon Lake on April 15-17 and is being sponsored by SFU; (http://www.sfu.ca/mbb/cellbio_retreat/index.htm).

The cell biology community at UBC has expanded this year due to a number of hirings. **Geoff Wasteneys** moved to the Department of Botany, and **Hakima Mouhkles**, **Robert Nabi**, and **T. Michael Underhill** have all recently joined the Department of Cellular and Physiological Sciences (which arose from the merger of the Departments of Anatomy and Cell Biology, and Physiology). In the Biochemistry and Molecular Biology Department, the newest addition is **Leonard Foster**, who has returned to his home province to take the first of five new positions in the area of proteomics. Leonard recently completed his PDF in the laboratory of Matthias Mann, and will be utilizing quantitative proteomic approaches to study organelles.

University of Calgary

Biochemistry, Department of Biological Sciences, Faculty of Science

Correspondent: Raymond J. Turner

Biochemists at the University of Calgary are divided into those in the Faculty of Medicine and our group in the Department of Biological Sciences in the Faculty of Science. As members of the Faculty of Science our mandates are split between undergraduate teaching and research endeavors. Despite the continuing budget cuts to the Faculty of Science I am happy to report that our group has demonstrated another year of excellence in research and teaching. Presently our group consists of two senior instructors (**Elke Lohmeier-Vogel** and **Rob Edwards**), three regular faculty members (**Gene Huber**, **Greg Moorhead**, and **Ray Turner**), and five AHFMR scholars/scientists (**Marie Fraser**, **Ken Ng**, **Elmar Prenner**, **Peter Tieleman**, and **Hans Vogel**). Senior instructors have a larger portion of their time dedicated to teaching, while AHFMR-supported faculty have a larger portion of their time protected for research. Although we are under budget constraints, a miracle has occurred and we have been given permission to recruit a new faculty member to our biochemistry group. At the time of writing this, the search committee is reviewing CVs and we are hopeful to have a new faculty member join us before the end of summer 2005.

The most significant news that continues to haunt the University of Calgary is that of continuing budget cuts. For the past seven years our department has had to withstand between 2-4 % cuts per

year. We now are looking at further cuts of 5% for the next four years. The frustration on campus is emphasized by the observation that Alberta is a rich province. We can only hope and wait that the new regime will start to send funds our way rather than on ridiculous new initiatives.

Teaching News:

Our Department of Biological Sciences is presently undergoing administrative revision. For anyone that has gone through faculty or department rearrangements, fusions or breakoffs will appreciate the unique pleasures of this endeavor. At any rate, we envision a strong Biochemistry undergraduate program teaching group to exist after the dust settles. Furthermore, continuing budget cuts here at the University of Calgary have lead to increasing challenges in offering our program, however, through extra effort from our group we continue to provide an excellent education in biochemistry. We continue to offer undergraduate laboratory exercises at all levels of our curriculum with a full year of advanced laboratory experience for our third year biochemistry majors.

We have spent considerable effort rethinking our undergraduate biochemistry program. The past year has been a year of preparation for the installation of our redeveloped program. **Rob Edwards** has been instrumental as our new program director/division head in coordinating this changeover. The change is being implemented starting this academic year and will not be complete until the end of the 2005/2006 academic year. The new program will separate our service courses from our mainstream biochemistry program, after the first introductory biochemistry course. Furthermore it will allow more flexibility for the students in choices of double majors and senior courses. It will also provide an excellent undergraduate laboratory experience. Of course the challenges of implementing this program under the present university budget cuts will make for an interesting ride.

Elke Lohmeier-Vogel, one of our two senior instructors, was away on Sabbatical for half the year at the Department of Applied Microbiology, University of Lund in Sweden doing metabolic engineering of *Lactococcus lactis*. Such an opportunity gives her the ability to communicate to students this important area of research in the biotechnology course she participates in.

Research news:

The research programs of the biochemists in the Faculty of Science focus mainly on Structural Biology problems. As a reflection of this, we have received funds from CFI and other sources to generate a biophysical chemistry equipment laboratory as part of the Alberta-wide CyberCell initiative. Our groups already have strong resources in this area for X-ray crystallography, NMR, Fluorescence and FTIR spectroscopy. The space is expected to be completed, with new equipment in place, by Spring 2005. This new facility is being designed to allow for the production of protein through fermentors, cell harvesting and protein purification (FPLCs) to the protein analysis by calorimetry, fluorescence, FTIR, CD, NMR, and computational methods. Its establishment is the outcome from significant effort by **Hans Vogel**, complemented by assistance from Peter Tieleman and the rest of the group.

Although all of us have had a great year, there are some high fliers in the group worth mentioning:

Peter Tieleman, although still considered a junior person, has evolved into one of the University's most recognized scientists. This year he received a Sloan Foundation Fellowship for computational and evolutionary molecular biology and now is part of the Faculty of 1000. He has also been appointed to the editorial boards of the *Biophysical Journal* and *BMC Biochemistry*.

Ken Ng is involved in a multidisciplinary project as one of the six labs in the Alberta Ingenuity Centre for Carbohydrate Sciences exploring the recent hot topic of *Clostridium difficile*. The research of this Centre is using carbohydrate-based approaches to develop better treatments for diseases such as *C. difficile* associated enterocolitis.

Greg Moorhead's and **Raymond Turner's** research was recognized in the past year as leaders in their respective areas through contributions of key reviews in their fields of plant phosphatases and redox enzyme chaperones, respectively. In **Elmar**

Prenner's lab an imaging ellipsometer has been finally set-up after the serious problems with building vibrations have been alleviated enough to allow experiments in lateral lipid organization, membrane protein aggregation and lipid-protein interactions.

Hans Vogel over the past few years has played a key role as a member of the board of directors of the Canadian Light Source. We have a number of groups (**Marie Frasier**, **Ken Ng**, **Gene Huber**, and **Hans Vogel**) that rely on synchrotron radiation for their work, and they are all eager to access the CLS and to participate in its development.

The research of **Peter Tieleman**, **Hans Vogel**, and **Ken Ng** was highlighted in a variety of newspapers over the year including the *Globe and Mail*, *National Post*, *Edmonton Journal*, and *Calgary Herald*, to name a few.

Graduate student and undergraduate news:

Presently there are 12 postdoctoral fellows/research associates and 26 graduate students spread through our laboratories. These students have been very successful in obtaining national (NSERC & CIHR) and provincial (AHFMR & AIF) scholarship and fellowship support. Additionally, there are 27 undergraduate students doing their senior independent research projects in our laboratories this year.

Members of **Peter Tieleman's** group worked on CISS3, the Canadian Internetworked Scientific Supercomputer project, which was one of two projects in Canada that got to use most of Canada's academic computers allowing for months of computational work to be done in two days.

On a closing note there was great rejoicing in the Computational group when university accounting allowed for the use of a professor's professional expense account for the purchase of a high end coffee machine. Now the group is wired!

For more information about our biochemistry group visit: http://www.bio.ucalgary.ca/divisions/biochem/index.html.

Annual retreat of University of Calgary Structural Biologists in November 2004. Individual research groups have expanded, giving this year the largest turnout to date. Location: Kananaskis Country just west of Calgary.

University of Calgary

Department of Biochemistry and Molecular Biology, Faculty of Medicine

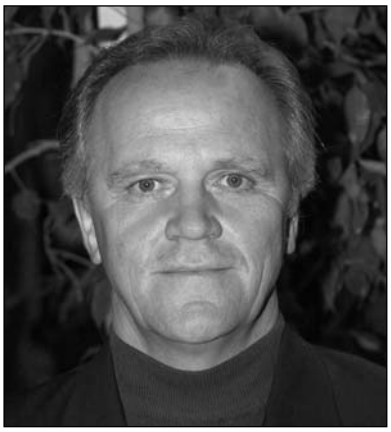
Correspondent: Leon W. Browder

The Department of Biochemistry & Molecular Biology in the Faculty of Medicine, the University of Calgary, is a diverse department with a highly productive research program. We also administer the genomics, proteomics and bioinformatics infrastructure that facilitates the research activities of biochemists and molecular biologists in Calgary and beyond. The department consists of 49 faculty members plus 20 adjunct appointees. The department offers graduate training leading to Ph.D. and M.Sc. degrees in Biochemistry and Molecular Biology. Members of the department supervise 169 graduate students.

We are pleased to acknowledge these recent accomplishments of members of our department.

Christoph Sensen, who is a Professor in this department, has been awarded an iCORE/Sun Microsystems Industrial Chair. iCORE is an Alberta-based organization that fosters informatics research. Christoph has carved out a unique niche in the informatics community by focusing on the development of tools to visualize data. This gives investigators unprecedented opportunities to determine spatial patterns of gene expression, which improves measurably our understanding of gene function.

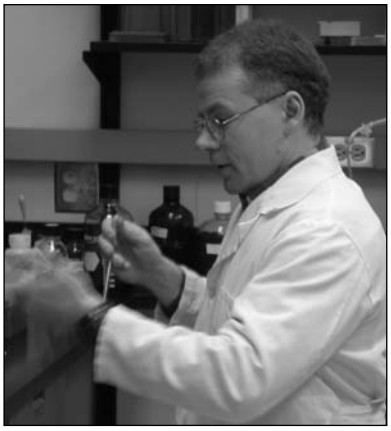
Marvin Fritzler, who holds the holds The Arthritis Research Chair in the Faculty of Medicine, has been appointed Chair of the Alberta Science and Research Authority (ASRA). ASRA's mission is to enhance the contribution of science and research to the sustainable prosperity and quality of life of Albertans. ASRA functions as the senior science and research body of the Government of Alberta and works collaboratively with government departments and agencies and other stakeholders to maximize the effectiveness of science and research as an integral component to the success of the province in the global economy.



Marvin Fritzler

We are pleased to welcome the following new members to our department.

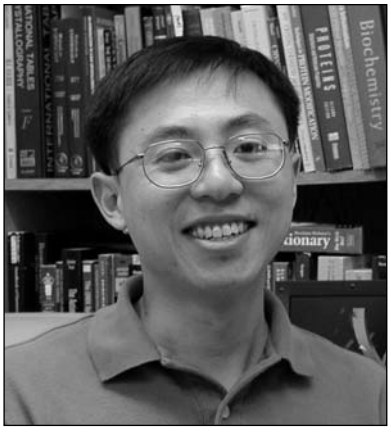
Peter Forsyth, who also holds appointments in the Departments of Clinical Neuroscience, Oncology and Paediatrics, has joined the department through a joint appointment. Peter's research focuses on inhibition of brain cancer invasion and metastasis. He conducts neuro-oncology clinical trials aimed at arresting brain cancer metastasis.



David Wilson

New Adjunct members:

Kenneth Ng is an Alberta Heritage Foundation for Medical Research Medical



Ken Ng

Jane Shearer

Peter Forsyth

Scholar and a CIHR New Investigator. His primary appointment is in the Department of Biological Sciences. He studies how the three-dimensional structures of proteins have evolved to act as highly specific and efficient chemical catalysts or binding proteins. His research focuses on RNA-dependent polymerases and carbohydrate proteins.

Jane Shearer is Director of the Centre for Mouse Genomics. Her research focuses on metabolic regulation of glucose and fatty acid utilization.

David Wilson studies smooth muscle calcium sensitization in collaboration with Mike Walsh.

Training Opportunities

Members of the Department of Biochemistry and Molecular Biology conduct exciting, leading edge research, are well funded by international, national and provincial agencies, and publish extensively in the very best journals. We invite potential graduate students and post-doctoral fellows to give Calgary careful consideration. Not only do we offer excellent training opportunities for young scientists, but the natural beauty surrounding Calgary is breathtaking, providing year-round recreational opportunities.

We invite you to visit our website at: www.ucalgary.ca/bmb.

Extraordinary Science in an Extraordinary Location!

The following photos were taken at the Departmental Retreat, which was held in Banff from October 26-27, 2004.

Why we love the Banff Centre

What was Martha Stewart doing out of jail?

The keynote Speaker at the Retreat, Dr. David Brautigan, University of Virginia

Co-winners of the Carol Braat Award for Outstanding Graduate Student Presentation: Chris Nicholls, Alexander Klimowicz, and Paul Gordon

Don Fujita takes in the posters

Mike Walsh and David Brautigan at the Beastly Macabre Bash following the posters

University of Guelph

Former Departments of Molecular Biology and Genetics, and Botany

Correspondent: George Harauz

The past year and a half has been busy with many changes. The Chair of Molecular Biology and Genetics (MB&G), **David Evans**, left Guelph in July 2003 to become Chair of Medical Microbiology and Immunology at the University of Alberta. David had spearheaded many initiatives, including CFI, during his tenure at Guelph, and his departure represents a major loss to the University. **John Phillips** has been Acting Chair of MB&G since March 2003, and has been steering us through a time of transition, including the formation of a new Department of Molecular and Cellular Biology, and planning for a move into a completed new Science Complex in 2007.

Joseph Yankulov (MB&G) is presently on a sabbatical at l'Ecole Normale Superieure de Lyon, France, in the laboratory of Prof. Eric Gilson, where he is studying the chromatin structure of telomeres in *S. cerevisiae*. The leave is well-deserved — Joseph had obtained tenure, and his wife Galina Radeva successfully completed her Ph.D. in Biochemistry at Guelph. Joseph's group has also established a DNA replication/DNA recombination club with the University of Waterloo, especially with the laboratory of Dr. Bernie Duncker.

Joe Colasanti was awarded a CFI grant ($311,000) in 2004. Congratulations, Joe! In addition, he gave a seminar at CINESTAV in Irapuato, Mexico in March 2004, and the Chailakhyan Lecture in Plant Physiology in Moscow, Russia in April 2004. Joe, Rob Mullen, and John Greenwood co-organized the Canadian Society of Plant Physiology International meeting held in Guelph in June 2004.

Derek Bewley (Botany) was on sabbatical at U.C. Davis from September until December 2003. He organized an international workshop for the International Society of Seed Science entitled 'Molecular Aspects of Seed Germination and Dormancy' in May 2004 in Wageningen, The Netherlands. He also presented a two-day seed course on 'Seed Development' to the Monsanto Company, St. Louis, in September, and research and teaching seminars at seven universities in Harbin, Shanghai, Nanjing, Guangzhou in China, and the Chinese University of Hong Kong in September/October.

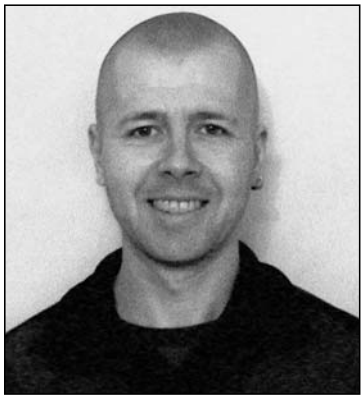
Mike Emes (MB&G and Botany, Dean of CBS) has continued to consolidate his lab since his arrival in 2002, the focus of his research being on starch metabolism in storage tissues of crops. Recent discoveries on how protein phosphorylation and protein-protein interactions contribute to the regulation of starch synthesis (Plant Cell, 16, 694-708) have attracted a lot of attention. This year has seen the arrival of a new grad student, Mark Burrell from the U.K., and a postdoc, Dr Nicole Bresolin from CSIRO, Canberra. This international flavour has been augmented by several visitors who have spent three to nine months in his lab, including Dr. Si-Myung Lee (National Institute of Agricultural Biotechnology, Korea), Ms. Gea Guerriero (Plant Physiology, University of Naples, Italy) and Ms. Kim Beisel (University of Kaiserslautern) who was awarded a Rotary Scholarship placing her in the top 2% of young scientists in Germany. Both Mike and Ian Tetlow, from the same group, have given a number of seminars around the world including Canberra, Brisbane, Tokyo, Portland Oregon, Iowa, Cornell, and Columbia Missouri. A lot of Mike's time has also been taken up with the restructuring of the College of Biological Sciences at Guelph and the building of the Science Complex, a 375,000 sq. ft. building containing state-of-the art laboratories for research and teaching, Phase I of which was completed in the summer of 2004 and is already occupied. Funding for this $144 million project has included major awards by the Canada Foundation for Innovation, the Ontario Innovation Trust and the Ontario Superbuild program.

University of Guelph

Former Department of Chemistry and Biochemistry
New Department of Molecular and Cellular Biology

Correspondent: Frances Sharom

George Van der Merwe



Andrew Preston

The past year has been one of incredible change for the biochemistry group formerly of the Department of Chemistry and Biochemistry. On May 1 2004, the eight of us (**Fred Brauer, Marc Coppolino, John Dawson, David Josephy, Bob Keates, Dev Mangroo, Rod Merrill and Frances Sharom**) were officially transferred from the Department of Chemistry and Biochemistry (in the College of Physical and Engineering Science) to the Department of Microbiology in the College of Biological Science, in preparation for our move to the new Science Complex and our integration into a newly organized Department of Molecular and Cellular Biology. The undergraduate programs in Biochemistry and Biochemistry Co-op moved with us, and our former department reverted to a Department of Chemistry. The first week of July, we all moved into the second floor of Phase 1 of the new Science Complex, the first stage of a massive 375,000 sq.ft. complex of research and teaching labs in the heart of the University of Guelph campus. The first few weeks in a construction zone were challenging, to say the least, since the other three floors of the building were neither complete nor occupied. The rest of the former Microbiology department faculty and research personnel moved into the other floors of the building in September 2004, and things settled down quite quickly after that.

On September 1 2004, the new department of Molecular and Cellular Biology came into being, made up of the former Microbiology department, the eight biochemists, the former Molecular Biology and Genetics department, and several cell biologists from the former Botany department. For now, the latter two groups remain in the Axelrod building pending completion of Phase 2 of the Science Complex in spring 2006, when they will move it to join us. The new "super-department" has over 40 faculty members, and is headed by **Chris Whitfield**, formerly of Microbiology. A faculty search is currently under way for two structural biologists at the Assistant Professor level, to round out the expertise of the new unit.

Two new faculty members joined the Department as Assistant Professors in the past year. **George Van der Merwe** received his graduate training in the Department of Microbiology at the University of Stellenbosch, South Africa, studying nitrogen-regulated transcription in *Saccharomyces cerevisiae*. He completed a term as Research Associate in the Wine Research Centre at the University of British Columbia under Dr. Hennie van Vuuren. During this time he focussed on understanding the transcriptional and metabolic responses of *Saccharomyces cerevisiae* to the changing environments presented by wine fermentations. Genome-wide transcriptional analysis revealed several meta-

Phase 1 of the new Science Complex at the University of Guelph

bolic pathways and regulatory mechanisms employed by yeast to cope with changing environmental stresses. However, the regulatory mechanisms governing the transcriptional responses, metabolic and physiological adaptations are not fully understood. These regulatory mechanisms became the focus of George's research when he accepted a faculty position in the Department of Microbiology at the University of Guelph. He has since managed to secure NSERC funding and a CFI grant in the New Opportunities program to support his research.

Andrew Preston studied Biochemistry at Oxford and then did his Ph.D. in the Institute of Molecular Medicine at Oxford in Richard Moxon's lab, studying the genetic basis for LPS biosynthesis in *Haemophilus influenzae*. The genetics of LPS biosynthesis has been a mainstay of his research ever since. Andy then did a post-doc with Mike Apicella at the University of Iowa, working on environmental response regulation in the *gonococcus*. During this time he started to develop primary urethral cell cultures to model the gonococcal-host interaction, and he took this interest in the cell biology of infection back to the U.K. to Duncan Maskell's lab at the University of Cambridge. There, Andy combined both LPS genetics and development of primary cell culture models to study Bordetella pathogenesis and these aspects are now the focus of his lab here in Guelph. The work with polysaccharides is funded by a CBDN Young Investigator Award, while the cell biology work is funded by NSERC. Andy is interested in developing novel infection models to study mixed infections, particularly mixed viral and bacterial infections of respiratory tissue.

John Dawson has had an excellent year; he successfully obtained his first CIHR grant to study mutations in actin related to heart disease, and was also awarded a New Investigator award from the Heart and Stroke Foundation of Canada. The Dawson lab personnel really enjoy being in the new facilities and the ease of access to equipment, cold room facilities, and the proximity to the other biochemists.

University of Lethbridge

Departments of Biological Sciences, Chemistry and Biochemistry, and Physics

Correspondent: James E. Thomas

The past year has brought considerable change to biochemistry at the University of Lethbridge. Biochemistry is a multidisciplinary major delivered by several departments at the U of L. While much of our focus is on agricultural systems, new areas of research also are being explored in the areas of health and theory.

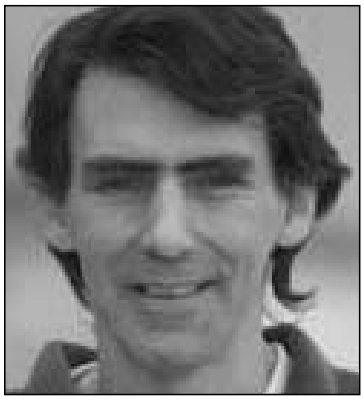
Dr. Roman Przybylski is an AVAC Chair in the Department of Chemistry and Biochemistry who comes to us from the University of Manitoba. Roman is working on development of antioxidants for edible oils and food systems; the effect of endogenous edible oil components on stability, performance and nutritional value; and assessment of food products and raw material for compounds with nutritional properties. He is interested in making contact with potential graduate students at the Masters and Ph.D. levels and prospective postdoctoral fellows.

Dr. Hans-Joachim Wieden is also a new member to the Department of Chemistry and Biochemistry. Hans comes to us from the Max-Planck-Institute for Biophysical Chemistry in Gottingen, Germany. His studies are of the functional and structural dynamics of protein biosynthesis in *E. coli*, focusing on the kinetics and functional dynamics of protein biosynthesis and its inhibition by antibiotics. A combination of techniques involving fluorescence spectroscopy, fast kinetics (quench flow/stopped flow), biochemistry, molecular biology, and molecular dynamics are being used.

Oliver Lung is a new appointment in the Department of Biological Sciences. Oliver comes to us from the Boyce Thompson Institute for Plant Research at Cornell University, Ithaca, New York. His research interests are in development of an understanding of how pathogenic viruses interact with their hosts, and how hosts respond to viral infection. His current research is focused on using the baculovirus AcMNPV as a model system for studying viral pathogenesis. AcMNPV was chosen

Roman Przybylski

because it is a highly pathogenic virus which has important practical applications in both agriculture and biotechnology. AcMNPV is widely used for production of foreign proteins in industry, can be used to safely deliver genes into mammalian cells, and is being developed as a vector for human gene therapy. Oliver is interested in contacting students interested in doing graduate studies in Molecular Virology.



Steve Mosimann

Steve Mosimann is an Associate Professor and Heritage Scholar with the Department of Chemistry and Biochemistry. Steve's research involves development of an understanding of the mechanism of mRNA turnover and the formation of long-lived mRNA species. Steve has two new Masters students in his laboratory. Paula Burke is working on ribosome biogenesis in archaeal organisms. Ribosome biogenesis in these organisms is a stepwise process that involves sequential modifications of rRNA and serves as a model for the equivalent eucaryotic process. NOP1 is an archaeal 2'-O methyltransferase that targets specific ribonucleotides and is a required component of ribosome biogenesis. Paula is utilizing biophysical techniques including X-ray crystallography, isothermal titration calorimetry and a variety of spectroscopic methods to characterize the protein-protein and protein-ligand interactions that are essential for NOP1 function. Rob Gruninger comes to Steve's lab having completed a senior undergraduate thesis in which he solved the structure of a *Selenomonas ruminantium* phytase. Rob is being co-supervised by Brent Selinger (Department of Biological Sciences) and is working on the structure and functional relationships of phytases.

James Thomas

Brent Selinger is an Associate Professor in the Department of Biological Sciences. Brent is interested in the genetics and biochemistry of microbial hydrolytic enzymes, biological control of cattle ectoparasites and microbial ecology of surface waters. Aaron Puhl, a new Master's student with Brent, is looking at the specificity of phytases related to protein tyrosine phosphatases. Jennifer Geddes, another new Masters student with Brent, is being co-supervised by Francois Eudes (Agriculture and AgriFood Canada, Lethbridge Research Centre), and is developing a proteomic analysis for Fusarium Head Blight resistance in barley.

James Thomas is an Associate Professor in the Department of Biological Sciences, and is now Coordinator of Biochemistry and Agricultural Biotechnology. Cassandra Lang, a Master's student with Jim and Brent Selinger (Department of Biological Sciences) has completed her Master's research on development of species-specific carbon-utilization profiles for use in source tracking of enteric pathogens. Cassandra used BiologTM instrumentation to develop phenotypic arrays for animal and water-borne isolates of *Salmonella* and *Enterococcus* bacteria. This work is being done in collaboration with Vic Gannon (Adjunct Professor, Department of Biological Sciences, and Research Scientist, Public Health Agency of Canada, Lethbridge) and the Canadian Water Network. In addition, Christopher Sikora, a Masters Student with Jim and John Cherwonogrodzky (Adjunct Professor, Department of Biological Sciences, and Research Scientist, Defense Research Establishment, Suffield) completed his thesis on development of a vaccine candidate in protein extracts from *Francisella tularensis*. Chris also completed his MD with the University of Manitoba in 2004, and has moved on to do a residency at the University of Alberta.

Olga Kovalchuk is an Assistant Professor with the Department of Biological Sciences. She is working on radiation carcinogenesis, the molecular mechanisms of occurrence and means of prevention. Olga's research program is devoted to uncovering

molecular and cellular effects of radiation exposure and molecular, genetic and epigenetic mechanisms of radiation carcinogenesis. The research consists of several interconnected lines of research:

- Radiation-induced oncogenic signaling upon whole body radiation exposure: sex differences and biological significance.
- Radiation epigenetics: radiation-induced DNA methylation changes and their relevance to secondary and transgenerational radiation carcinogenesis.
- Radiation-induced DNA damage, repair and recombination and their relevance to radiation-induced genome instability, bystander effect and adaptive response.

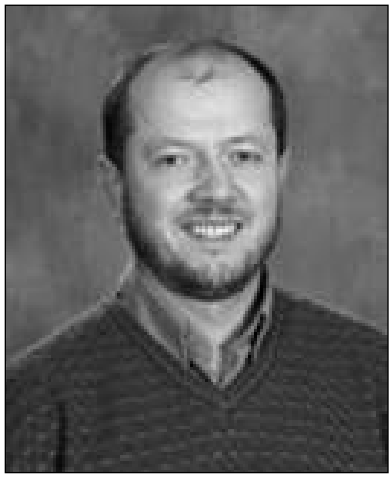
In 2004 Olga was awarded her first nationally peer reviewed CIHR operating grant in the area of cancer research to study sex differences in radiation-induced oncogenic signaling. This research is looking at:

- the role of PKB/Akt in radiation responses. Molecular mechanisms and biological significance of sex differences in radiation-induced PKB/Akt activation are being explored. **Igor Koturbash**, a new PhD Student has just begun work on this project.
- the biological significance of sex differences in radiation-induced expression of retinoblastoma binding protein 9 (RBBP9/Bog) and its role in radiation-induced changes in the RB pathway.
- sex differences in WNT pathway upon radiation exposure.

Igor Kovalchuk is an Assistant Professor with the Department of Biological Sciences. Igor is working on plant genome stability. Specifically, he is looking at:

- the influence of various abiotic (UV, draught, heavy metals, high temperatures) and biotic (pathogens, specifically viruses) factors on plant genome integrity.
- the mechanisms of protection that are developed by plants against the pathogens.
- various types of signals that plants use to warn non-targeted tissues;
- genes involved in various steps of DNA repair, specifically, double strand breaks.

This work has potential top help with improvement of transformation strategies for monocots; analysis of the safety of transgenic food; and analysis of the stability of various transgenes in transgenic organisms. Igor had three graduate students who completed their work in 2004. Jody Filkowski worked on the "Influence of pathogens on plant genome stability"; Alex Bojko worked on "Homologous recombination in Arabidopsis thaliana plants at different developmental stages and under different stress conditions"; and Yaroslav Ilnytskyy worked on "Characterization of novel DNA-repair related genes in Arabidopsis thaliana".



Igor Kovalchuk

David Siminovitch is an Associate Professor in the Department of Physics. David now is working in collaboration with the Laboratory of Physics and Helsinki Institute of Physics (Finland). Because of the hydrogen-bonding capacity of sphingomyelin phospholipids, they have been implicated in the formation of lateral domains ("lipid rafts") in eucaryotic cell membranes. David is investigating the dynamic structure of sphingomyelins using solid-state NMR techniques (Lethbridge) and molecular dynamics simulations (Helsinki). David and his colleagues hope to unravel the unique properties of these unusual lipids, and for the first time, integrate experimental NMR results from the study with theoretical molecular dynamics simulations.

André Laroche

Randall Weselake, known for his work on lipid biochemistry in plant and animal systems took a position at the University of Alberta in Fall 2004. Randy has continued to collaborate with researchers at the U of L and at Agriculture and Agri-Food Canada. Nora Foroud, a Masters student with Randy and André Laroche (Agriculture and Agri-Food Canada) completed her research on "Probing the membrane topology of a diacylglycerol acyltransferase type 1 from *Brassica napus*".

André Laroche is an Adjunct Professor in the Department of Chemistry and Biochemistry, and a Research Scientist in Plant Molecular Genetics with Agriculture and AgriFood Canada at the Lethbridge Research Centre. André currently is working in association with Genome Canada to look at stress biology in plants due to abiotic (e.g. low temperature) or biotic (e.g. fungi) factors. He is using functional genomic tools such as large scale sequencing; transcriptome profiling with DNA chips for screening large arrays of genes; real-time PCR to focus on specific genes, and transient and stable expression of candidate genes to assess their role and contribution in a plant cell; and proteomic analyses using 2D-gel electrophoresis and protein sequencing. Within his multidisciplinary research group, he is looking to use this information to improve and accelerate the selection of germplasm toward the development of commercial cultivars. These tools provide complementary information to enable André and his team, to decipher plant responses to specific forms of stress in order to better understand plant responses and better devise strategies for plant protection and adaptation to unfavorable climatic conditions.

University of Toronto

Department of Biochemistry

Correspondent: David Williams

Faculty News

Several of our faculty members were honoured for their research or administrative accomplishments during the past year. **Sergio Grinstein** was the winner of the 2004 Michael Smith Prize in Health Research. The Prize is provided annually to an outstanding Canadian researcher who has demonstrated a high degree of innovation, creativity, leadership and dedication in health research. The Prize consists of a medal, and a research grant of $100,000 per year for five years. It was presented to Sergio in a ceremony on November 24th conducted by Health Minister Ujjal Dosanjh.

The Laukien Prize for 2004 was awarded to **Lewis Kay** for his innovative contributions to nuclear magnetic resonance (NMR) of biological macromolecules, particularly for the study of side-chain motion in proteins by deuterium resonance and correlated relaxation measurements, and for gradient-and-sensitivity enhanced heteronuclear correlation spectroscopy. Established in 1999 to honor the memory of Professor Günter Laukien, a co-founder of Bruker Instruments, the Laukien award is intended to recognize cutting edge experimental NMR research with a high probability of enabling beneficial new applications. Lewis has gained a leading position in NMR of biologically relevant molecules by numerous seminal innovations relevant for the study of protein structure and dynamics.

Bibudhendra (Amu) Sarkar, Emeritus Professor of Biochemistry received a prestigious award in India, named in honour of the late Professor R.C. Mehrotra, a renowned Indian scientist, administrator and educator. Amu is the inaugural recipient of this award, presented to him by the former President of India, Dr. K.R. Narayanan, in a special ceremony held in Vigyan Bhawan in New Delhi on November 26. At the award ceremony Amu's outstanding achievements received special recognition: his interdisciplinary research and discovery of a life-saving drug treatment which is used worldwide for a fatal neurodegenerative genetic disease in children (Menkes disease), and his humanitarian work in leading a volunteer international team of scientists to alleviate the human suffering caused by arsenic contamination of drinking water in South and Southeast Asia. The award made special reference to Amu's contributions to the promotion of science and his profound sense of science's obligation to society.

At the International Endotoxin Society Meeting, which was held in Kyoto, Japan, Russell Bishop received the Nowotny Award, which is given to an independent investigator who has shown remarkable promise in endotoxin research at an early stage of his/her career.

We were also pleased to learn that **Liliana Attisano**, **Amira Klip**, and **Daniela Rotin** were awarded Tier 1 Canada Research Chairs this year. Also, **David Isenman** and **Larry Moran** were presented with Twenty-Five Year Service Awards in recognition of significant service to the University of Toronto.

A number of faculty have been busy organizing conferences and speaking on the international circuit. **Charles Deber** organized the First CIHR Strategic Training Program International Symposium on Proteins: Structure, Folding and Disease. The Symposium, held June 3-4 in Toronto, showcased the research of trainees in our two CIHR Training Programs, namely Structural Biology of Membrane Proteins Linked to Disease and Protein Folding: Principles and Diseases. The event was a great success, attracting 300 participants and featuring talks by international scientists, local training program mentors, post-docs and students. For some photos of the Symposium go to: http://biochemistry.utoronto.ca/news/CIHR_workshop_2004.html

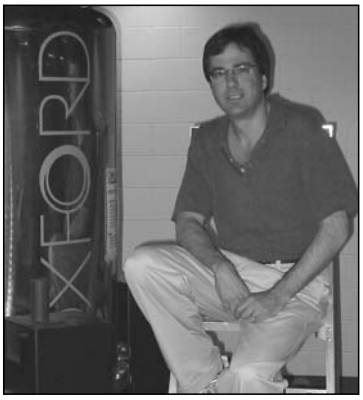
Jaro Sodek organized the 8th International Conference on the Chemistry & Biology of Mineralized Tissues, which was held in Banff in October. He was also an invited speaker at a Symposium at Nihon University, Tokyo in November and will be speaking at the first Gordon Conference on the Small Integrin-Binding Proteins. **Russell Bishop** has been popular on the speaking circuit, giving invited lectures at the Endotoxin Society Meeting in Japan, the Gordon Research Conference on Bacterial Cell Surfaces, and the upcoming Annual Meeting of the American Society for Biochemistry and Molecular Biology.

Events

The Department hosted a milestone birthday celebration for Emeritus Professor, **Theo Hofmann**, who turned 80. Theo remains very active in the Department and continues to globe trot following his passion for birding. Photos of the happy event can be seen at: http://biochemistry.utoronto.ca/news/Hofmann_80bday.html

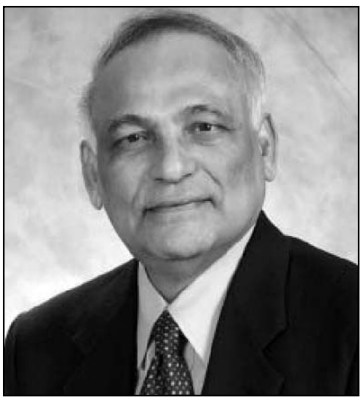
The Department has replaced its annual Graduate Student Poster Day with an off-site Research Day/Retreat which was held this year on May 18th at the Old Mill Inn. The Research Day was a resounding success featuring talks by faculty and students, poster presentations, and three sumptuous meals, all in an elegant yet relaxed setting. It was a terrific opportunity for more than 140 faculty, post-docs, and students to enjoy collegial interactions and to celebrate the accomplishments of our Department. For photos, please follow the link: http://www.biochemistry.utoronto.ca/news/research_day_04.html

Sergio Grinstein (left) with Ujjal Dosanjh



Lewis Kay

On Wednesday July 16, 2004, the Department of Biochemistry celebrated the many years of service provided by **Norman Camerman** to the University of Toronto at a retirement lunch attended by a number of close friends and colleagues. As a memento of his time in the Department as a small molecules crystallographer Norman was presented with a piece of fine Swarovski crystal. In the photo Norman and long-time Research Associate Dr. Andrew Hempel show Chair, Reinhart Reithmeier the proper procedure for mounting the crystal on a X-ray diffractometer. The Department is very proud of Norman's contributions to the



Amu Sarkar

Russell Bishop

Department and in particular his prowess as a lecturer in our introductory biochemistry courses.

As part of the celebration by the University of Toronto of the 120th anniversary of the official admission of women to our University, members of the Department met to discuss the history of women in biochemistry as well as the recent Brenda Maddox book "Rosalind Franklin: The Dark Lady of DNA". Prof. Emeritus **Marian Packham**, Departmental historian, provided some recollections about women in our Department. More information on the discussion can be found at: http://biochemistry.utoronto.ca/news/women.html

Norman Camerman flanked by Andrew Hempel (left) and Reinhart Reithmeier

Theo Hofmann lecturer Natalie Strynadka with Theo Hofmann

The Department lost a longtime friend and colleague with the passing of **William Thompson**, Professor Emeritus of the Department of Biochemistry and its Acting Chair from 1989-1991. Bill passed away peacefully April 12th. The Department celebrated Bill's life and legacy at a very touching memorial service held June 1st at Trinity College. An obituary written by Anders Bennnick and Robert Murray can be found in the 2003 Bulletin.

Appointments

We are pleased to welcome a number of new faculty members to our Department.

Shoshana Wodak, Senior Scientist and Director of the Centre for Computational Biology at the Hospital for Sick Children, was appointed to the Department of Biochemistry as a Professor. Shoshana's research is in the area of computational structural biology and bioinformatics. She was recently awarded a CIHR Institutional Establishment Grant which was designed by CIHR to recruit and repatriate excellent health researchers.

Khosrow Adeli, a Senior Scientist at the Hospital for Sick Children and Division Head of Clinical Biochemistry, was appointed as a Professor in the Department. Khosrow is well known for his work in the molecular and cellular biology of lipoprotein metabolism in insulin-resistant states and the link with cardiovascular disease.

Michael Moran has recently been appointed to the Department at the rank of Associate Professor. Michael is a Senior Scientist at the Hospital for Sick Children in the program in Structural Biology and Biochemistry and the Program in Cancer. He is also the Scientific Director of the Advanced Protein Centre at HSC and a Scientist in the McLaughlin Centre for Molecular Medicine. Michael's research is focused on molecular signal-

A great turnout for Research Day/Retreat

ing and in the application of proteomics and mass spectrometry to fundamental and medical problems in biomedical research.

Also joining the Department is **Allen Volchuk** who has been appointed at the rank of Assistant Professor. Allen is a Scientist in the Division of Cellular and Molecular Biology at the Toronto General Hospital Research Institute. He is also a member of the Diabetes Centre and works on molecular aspects of insulin signaling.

We are also actively recruiting new Faculty, with two Assistant Professor positions being advertised at this time.

Our congratulations to **Drs. Grant Brown**, **Craig Smibert**, **John Glover**, and **Boris Steipe** who were awarded tenure this year and to **Dr. Chris Hogue** who was promoted to the rank of Associate Professor.

Graduate Studies

Our M.Sc. and Ph.D. graduate programs underwent a successful review by the Ontario Council on Graduate Studies (OCGS) and received the highest possible rating. Thanks to our colleagues Patrick Chow (Manitoba), Janet Wood (Guelph) and Jonathan Lytton (Calgary) for acting as external consultants in this important review process. We are very proud of our graduate programs and now have over 100 students enrolled.

The Department held its annual graduate student poster competition on May 18, 2004 as part of our new Departmental Research Day/Retreat. The poster day took place in conjunction with the annual Theo Hofmann Lecture which was presented this year by **Dr. Natalie Strynadka** of the Department of Biochemistry, University of British Columbia. Dr. Strynadka's lecture was entitled: "Structural biology on the bacterial membrane".

As ever, the poster judging was very tough but with the help of Dr. Strynadka the following winners (who receive cash awards) were chosen:

Winners in the Ph.D. category were: **Jeff Lee** (Howell lab): "Pico- and femtomolar transition state inhibitor-complexes of a nucleosidase involved in quorum sensing"; **Ravi Ramjeesingh** (Siu lab): "CXCR1 complexes assemble in lipid rafts at the leading edge of migrating cells during chemotaxis"; and **Tania Roberts** (Brown lab): "Characterization of the novel Saccharomyces cerevisiae DNA damage response gene RTT107".

Winners in the M.Sc. category were: **Wanyi Xiang** (Siu lab): "Role of the cell adhesion molecule L1.1 in zebrafish axonal growth and guidance"; **Monika Podkawa** (Attisano lab): "Activation of LIMK1 by binding to the BMP receptor, BMPRII regulates BMP-dependent dendritogenesis"; **Ronnie Lum** (Glover lab): "Evidence for an unfolding/threading mechanism for protein disaggregation by Saccharomyces cerevisiae".

The winner in our new post-doc category was: **Shintaro Besshoh** (Gurd lab): "The effect of tran-

Beckman Paper of the Year winners Urszula Wojtyra and Guillaume Thibault with Graduate Coordinator David Williams

Ravi Ramjeesingh receives the Scott Prize from Graduate Coordinator David Williams

Michael Chang receives the Walsh Prize from Graduate Coordinator David Williams

Lia Cardarelli and Marty Dziedziura with Undergraduate Coordinator, Roy Baker

sient global ischemia on tyrosine phosphorylation of the NMDA receptor in the post synaptic densities".

Additional graduate awards: The winners of the Beckman Paper of the Year Award for 2003 were **Urszula Wojtyra** and **Guillaume Thibault** for their paper:

Urszula A. Wojtyra, Guillaume Thibault, Ashleigh Tuite, and Walid A. Houry (2003) The N-terminal Zinc Binding Domain of ClpX Is a Dimerization Domain That Modulates the Chaperone Function. J. Biol. Chem. 278: 48981–48990.

The annual David Scott prize for outstanding all-round graduate student was awarded to *Ravi Ramjeesingh* (Siu lab). Ravi was selected on the basis of research excellence, exemplary performance as a TA, and an outstanding contribution to the Department and his fellow students while president of the Biochemistry Graduate Student Union.

Michael Chang (Brown lab) was awarded the Dorothy Sterling Dow Walsh prize. It is presented each year to the highest-ranked recipient of an Ontario Government Scholarship. It provides roughly $5000 towards the total OGS award plus the recipient receives a cash prize from the Department in recognition of the achievement. Michael was selected on the basis of both academic and research excellence.

Two of our new biochemistry graduate students, **Lia Cardarelli** and **Marty Dziedziura**, have recently won awards, as they graduated from the Biochemistry Specialist undergraduate program. Lia won the newly created Advanced Biochemistry Laboratory Coordinators Award for excellence shown within the advanced fourth year biochemistry lab and Marty won the Amy Britton Award for excellence in her fourth year biochemistry courses. Both Lia and Marty are also to be commended for their many contributions as executives of the Biochemistry Undergraduate Student Society.

Congratulations to all winners for their achievements.

University of Victoria

Department of Biochemistry and Microbiology

Correspondent: Claire Cupples

Faculty Research:

Dr. J. Tom Buckley has been at work in the field of biochemistry for the last thirty years, and for much of that time he has been working with the toxin aerolysin. His interests have been focused on how a mild toxin such as this might be useful in the treatment of cancer, where harsher toxins such as ricin have failed. Within the past couple of years a breakthrough was made which has since led to the creation of the company Protox. As the company's chief scientist, Buckley has high hopes that the aerolysin treatment developed will go into human trials in the coming year.

While the potential for success looms over Protox, Buckley himself is interested in discussing the science behind the aerolysin treatment. The toxin uses a b-barrel type structure with a mushroom like head to open up holes in the membranes of cells. This allows important contents to leak out indiscriminately, and the result is cell death. This mode of killing is used by various eubacteria against eukaryotic cells. The key to aerolysin's usefulness as a cancer treatment lies in the fact that it is created as pro-aerolysin. A single polypeptide chain with two domains, it is incapable of mediating its toxic effects in this form. A sequence of amino acid residues near the C- terminus can be cut by a protease. Only once this tail comes off can the protein assume the active, barrel formation of aerolysin. In order to attack prostate cancer, the treatment of the aerolysin has been quite novel. The amino acid sequence to be cut has been altered. Taking advantage of the fact that a prostate specific antigen is a protease, the sequence has been carefully adjusted to match the antigen's specificity. The consequence is that only when the pro-aerolysin comes into contact with prostate cells will it become active aerolysin, killing the target cells.

Laboratory trials so far have shown great promise in the application of this treatment. Injecting the drug into human prostate tumour cells kills them very effectively. The one drawback to the procedure is that at this point of development, it is quite non-specific, killing all prostate cells and not just the cancerous ones. Compared to the alternatives of radiation therapy, or invasive procedures which would remove the prostate in its entirety anyway, this option is still clearly a step above the others facing those with prostate cancer.

As a developing platform technology, the potential applications of aerolysin treatment may allow even more hope in the future. As projects continue, using microarray technology and other such advanced methods, it may be possible to identify proteases that are only expressed in cancer cells. The recognition site on the pro-aerolysin could then be modified to conform to those proteases. In principle, this could allow treatment that would leave healthy prostate cells unharmed while the tumour was killed. An outgrowth of the technology has also been the application of aerolysin to the treatment of lung cancer. While it is not as far along in development, the idea has been to apply tumour-specific antibodies to the surface of the pro-aerolysin. This applies a means to control the tissue that is attacked by the toxin, giving it considerable promise for the future.

Protox Therapeutics, which is developing the aerolysin treatment, was co-founded by Buckley. Recently it has started trading on the Toronto Stock Exchange with an initial public offering of $4.5 million. This has helped the company with its ongoing move to new, purpose built laboratory facilities on the UVic campus.

The UVic - Genome BC Proteomics Centre:

Dr. Bob Olafson is very passionate about the field of proteomics and most of all the good that can come out of it. These benefits will be broad, given that all biological systems are amenable to proteomics research. As a science, proteomics has benefited greatly from the genomics era, but at the same time it is complementary to, and vitally important in the overall study of genomics. Olafson describes the genome as the dictionary of the biological world, and it is proteomics that will

perform much of the work of understanding its words. Tracing particular proteins and their functions back to specific genes gives us the definitions. The scope of proteomics though goes far beyond this general understanding. The study of the proteome is the study of the total protein content of a cell at a particular time. Unlike the genome, this is ever changing as the cell goes through its life. Some changes may be the results of age or of entering new phases of the life cycle, while others are responses to environmental stresses. The basis of all of these changes can be found within the genome, but proteomics is concerned with just what factors regulate transcription and translation of particular genes, leading to the dynamic environment found in the cell.

On the practical level, understanding these things provides the opportunity to approach issues that affect everybody. Understanding of diseases, how they mediate their functions, and how they are resisted can lead to better treatments. For example, mechanisms that allow one plant species to resist an infection, while another dies, may be applicable to the vulnerable organism. While representing just the tip of the iceberg, these medical and agricultural applications clearly demonstrate the value of the work.

With these research goals in mind, the Proteomics Centre focuses on functional proteomics and differential expression analysis. The tools at its disposal vary greatly in complexity and sensitivity. These range from two dimensional SDS-PAGE gels, and automated systems to sample isolated proteins on them, to mass spectrophotometers and the computers to support them. The genesis of the Proteomics Centre began six or seven years ago when Olafson saw that the post genomics era would demand the science. For that purpose, powerful equipment would be needed, which he was able to convince a few of the faculty to apply for. This led to the acquisition of a pair of mass spectrophotometers, but a big boost would follow from Genome Canada through Genome BC. With the additional funding, four more mass specs were purchased along with all of the necessary ancillary equipment, and ten new people were hired. This growth necessitated the move off campus to the Vancouver Island Technology Park. The choice of locations was in part to attract other user groups to the site, such as MDS Metro. While much of the work itself has been going on for the last four years under the supervision of Olafson, the lab at the Vancouver Island Technology Park has only been operating since October 2003. The equipment offered by this facility has been a considerable improvement over what had been available at the University of Victoria itself, but this may not be the biggest benefit. With accommodations for visiting scientists, and 5000 sq. ft. of space, a tremendous teaching environment has been created.

Retiring at the end of this year, Olafson leaves behind a wonderful legacy for the University of Victoria, its faculty, students, and the scientific community at large. It is unfortunate that no more classes will be able to benefit directly from his passion for proteomics, but his impact on UVic's institution will be lasting.

Graduate student research:

Graduate students in the lab of **Dr. Alisdair Boraston** has been working to identify and characterize protein molecules produced by certain disease causing bacteria. **Elizabeth Ficko-Blean** has been involved in the study of *Clostridium perfringens*, the bacterium responsible for flesh eating disease. While this is a horrible malady, and might be termed an emerging disease, it is nothing really new. In fact it is the toxins of this bacterium that are responsible for the development of gangrene in wounds, a condition which has been familiar for much longer. *C. perfringens* is a problem because it is an anaerobic spore forming bacterium. It may be found dormant just about anywhere in the environment and will only germinate once it is cut off from an oxygen rich atmosphere. When the spores work their way into wounds, the dead tissue sealed away from the environment provides the perfect habitat for resumed metabolic function. At this point the progression of disease is rapid and often fatal. The speed of onset of disease is due partially to the fact that the organism secretes exotoxins that degrade connective tissue, allowing the bacteria to spread. It is with the study of these toxins

that Elizabeth's work began. With the objective of learning the specific mechanisms by which these toxins operate, the proteins that make them up have been cloned and purified. The toxins themselves are modular, made up of a number of proteins working collectively, which can be separated and studied individually.

Breakdown of the connective tissue is mediated by the protein catalysed hydrolysis of sugars. For this to occur, all of the protein components of the exotoxin are required. While the actual catalytic component does the work, other pieces called carbohydrate binding modules are critical. Without these, there is no way for the exotoxin to attach itself to the target tissue. This is where **Alicia Lammerts Van Bueren's** work began in the lab. Alicia has been examining the biophysical and thermodynamic properties of these carbohydrate binding modules. The objective is to develop a working model of the mechanism of carbohydrate recognition. An understanding of how this function is achieved may lead, in the future, to carbohydrate based therapeutics. What's more, many of the principles learned here may be useful in combating other pathogenic bacteria which use similar strategies.

All of this represents only some of the work being done by the graduate students at the University of Victoria. Whether they are also working for Boraston, or in another lab, their resolve to achieve excellence in continuing studies is the same. The contributions of graduate students like these in the Department of Biochemistry and Microbiology may well help pave the way for the medical breakthroughs that the future demands.

Biochemistry/Microbiology 2004 Symposium:

Perhaps one of the real highlights of completing an undergraduate degree in Biochemistry or Microbiology at the University of Victoria arises from participating in the 480 seminar course. In this course, a number of topics are put forth by the instructors and the major focus of the term for each student is researching that topic. All of this studying culminates in the preparation of presentations based on the latest information on each of these topics.

Over a period of two days, all these presentations are given to the whole department, forming the basis of the Fall Symposium. All of the students involved showed a knack for, and a real dedication to the research that they had been assigned to. One topic of study was the human body's circadian clock, and how its twenty-four hour sleep/wake cycle has actually been traced back to certain control genes that originate and influence master structures in the hypothalamus. Another subject was the rapid adaptation of bacteria to the environment through a complex series of interactions between sigma factors, anti-sigma factors, and to confuse things further, anti-anti-sigma factors. While these topics were elaborated on in far more detail, they represent just the tip of the scientific iceberg that the Symposium addressed. The tension among the students presenting at the symposium varied widely, but their resolve did not. Some of the presenters were as calm as old pros during their address, while others fought a battle with their nerves that filtered down into their voices. Whatever fear they might have had speaking in public, there was truly no need for anxiety. Everyone involved had clearly researched their topic exhaustively, and when it came time for the audience to pose questions, there were answers. Some answers were straight forward, more often they were on the complex side, and then there were the cases where answers simply hadn't been found yet.

Wherever the students who participated in this year's Biochemistry/Microbiology 480 Fall Symposium wind up, they are to be saluted. Their efforts put them on the fringes of graduation and serve as an example to those who follow behind them. Good luck to each and every one of them.

University of Waterloo

Department of Biology

Correspondent: Bernard Duncker

2004 was a year of considerable change in the Biology Department. We were all saddened at the death of **Jack Carlson** last September, just a few days before he was due to take his official retirement. Jack had been with the department for 30 years, during which time he made major contributions to our understanding of the mammalian reproductive system, including mechanisms controlling the function of the ovarian corpus luteum. Jack was an incredibly generous and dedicated colleague whose consistently positive attitude set an excellent standard for us all, and his presence will be greatly missed.

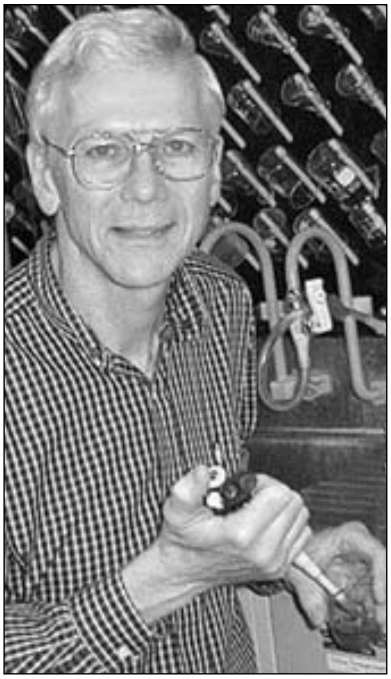
Another longtime member of the department to leave us is **Morton Globus**, who retired in October after 32 years of service. In addition to his research in the areas of animal physiology and development, Morton was a chief architect and Director of the innovative Science and Business program, and was honored in 1996 with the University of Waterloo Distinguished Teacher Award.

The past year also saw several new arrivals to the Department. **Vivian Dayeh** (Ph.D., Waterloo) joined us as a Faculty Lecturer in Cell Biology and Animal Physiology. Vivian conducted her doctoral research in Niels Bols' lab and she took up her Lecturer position in time to help cope with the double-cohort and its effect of dramatically increasing the enrollment of her former supervisors' introductory cell biology course. **Mungo Marsden** is one of two new Assistant Professors to be hired in the past year. He is a molecular developmental biologist whose research centers on the mechanisms of Xenopus cell adhesion.

Chris Jacobson is the other new Assistant Professor. Chris is a molecular neurobiologist, studying the role of neuregulin in mammalian synapse formation, and has a strong background in microarray analysis. In the coming year the influx of new faculty members will continue, with the addition of a new molecular ecologist to our ranks; the interviews for this position wrapped up in December. We will also be interviewing candidates for two animal physiologist positions shortly.

A number of faculty members were recognized with awards for their outstanding research programs in 2004, including **Marilyn Griffith** (plant antifreeze proteins) who had her Killam Research Fellowship renewed, and **Brendan McConkey** who received funding from CFI and OIT to establish a Differential In-gel Electrophoresis System for proteome analysis. **Vladimir Bantseev** of the School of Optometry was also awarded CFI/OIT funding to set up a joint Optometry-Biology Confocal Microscope Facility, which was recently inaugurated, and is housed within the Biology Department.

Brendan McConkey



Jack Carlson

Morton Globus

Marilyn Griffith

Vivian Dayeh

University of Waterloo

Department of Chemistry

Correspondent: Guy Guillemette

John Honek continues to pursue work in the area of carbon-sulfur biochemistry. He is currently on the editorial boards of: Biochemistry and Cell Biology (NRC), Letters in Drug Design and Discovery (Bentham Press), Medicinal Chemistry (Bentham Press), BioMed Central-Biochemistry, and Current Medicinal Chemistry (Bentham Press).

Guy Guillemette's group is investigating the fundamental properties of metalloproteins including mammalian and bacterial nitric oxide synthase enzymes, calmodulin as well as microbial fructose 1,6-bisphosphate aldolase enzymes.

University of Western Ontario

Department of Biochemistry

Correspondent: Eric Ball

The seemingly never-ending renovations to the Department's space in the Medical Sciences building continues, now in Phase III. Only two more years to go! We are all looking forward to the end of the process, and the modernized facilities that will result. New teaching laboratories that will allow expansion of undergraduate courses should be ready next year, as well as several more research labs.

The Department welcomed two new faculty appointments. **Dr. Wing-Yiu Choy** obtained his PhD in Chemistry from McGill University where he studied numerical methods and artificial intelligence in NMR data analysis. Most recently he has been a postdoctoral fellow in structural biology and biochemistry at the Hospital for Sick Children under the supervision of Dr. Lewis Kay. Dr. Choy's research interests are in the application of NMR to naturally disordered proteins. **Dr. Madhulika Gupta** received her PhD from the University of Lucknow, India where she studied plant hexokinases. After postdoctoral experience at Michigan State University and in the biopharmaceutical industry, she came to London and has been affiliated with the Department of Paediatrics at Western for several years. Her current research interests are in the application of proteomic methods to understanding and diagnosis of intrauterine growth restriction.

Faculty awards

Dr Robert Hegele received the 2004 Jeffrey M. Hoeg Arteriosclerosis, Thrombosis and Vascular Biology Award for Basic Science and Clinical Research from the American Heart Association. Dr. Hegele was also chosen as one of the two recipients of this year's Hellmuth Prizes for Achievement in Research by the University of Western Ontario. Dr. Hegele uses genetic approaches to identify disease-causing genes in humans.

Drs. Lars Konerman and **Bin Ma** were appointed as Tier 2 Canada Research Chairs. Dr. Konerman studies protein folding using mass spectroscopic techniques; Dr. Ma works in the area of bioinformatics and algorithm design.

A number of faculty and staff were recognized by the Faculty of Medicine and Dentistry at their annual awards ceremony. **Kathy Barber** received a Staff Award of Excellence, **Dr. Shawn Li** received a Junior Faculty Award of Excellence, and **Dr. Geoffrey Pickering** received a Faculty Award of Excellence.

Dr. Shawn Li was also selected as the recipient of the 2004 Boehringer Ingelheim Young Investigator Award in Biological Sciences. Dr. Li studies protein-protein interactions in signal transduction pathways.

Several faculty received CFI awards: **Dr. Nathalie Berube** (together with Dr. Doug Fraser of the Department of Paediatrics) to study the genetic, molecular and physiological basis of mental retardation; **Dr. Richard Rozmahel** with **Dr. Fred Dick** to research genetic applications to the study of human disease; and **Dr. Hong Ling** for her research into how cells use specialized DNA poly-

merases to continue replicating through damaged DNA.

Dr. Ling was also this year's recipient of the Peter Lougheed/CIHR New Investigator Award that recognizes outstanding researchers at the beginning of their careers. Dr. Ling will continue her research on structure and function of error-prone DNA polymerases.

Dr. Fred Dick received a CIHR New Investigators Award for his study of oncogenic determinants in the retinoblastoma tumor suppressor protein. **Dr. Hong Ling** received a CIHR New Investigator Award and also an NCIC award for new investigators.

Finally, the Department was sorry to bid **Dr. Ilona Skerjanc** farewell, but wishes her all the best at her new location at the University of Ottawa. The Department will miss her expertise in development and differentiation, but even more her wit and wisdom in everyday affairs.

York University

Department of Biology

Correspondent: Imogen Ball

Since our last update (2002), research and teaching in the areas of biochemistry, molecular and cellular biology have continued to expand at York University. Most researchers in these areas have been traditionally located within the Department of Biology but new initiatives in biochemistry and muscle physiology have brought researchers from the Departments of Chemistry and the School of Kinesiology and Health Science together into interdisciplinary research and teaching groups. A joint initiative between the Departments of Biology and Chemistry has led to a new undergraduate degree being offered in Biochemistry. Currently, approximately 70 outstanding students are enrolled and we expect this program to expand in the future.

Other interdisciplinary areas of research are increasingly using proteomic and genomic initiatives which are supported by the Core Molecular Biology Facility in the Department of Biology and the Proteomics facility which is overseen by **Dr. Michael Siu**. Dr. Siu, NSERC/MDS SCIEX Chair in Analytical Mass Spectrometry, is also the Director of the Centre for Research in Mass Spectrometry and was recently awarded the Gerhard Herzberg Award Spectroscopy Society of Canada. In addition to his established reputation as a chemist, Dr. Siu is increasingly using innovative mass spectrometry approaches to answer fundamental questions about human health and was awarded funding from the National Cancer Institute of Canada to continue his work on detection of cancer markers using proteomic approaches.

The appointment of **Dasantila Golemi-Kotra** in the Department of Chemistry, who works on mechanisms of resistance in methicillin resistant *Staphylococcus*, strengthens the biological chemistry within this department and builds on the established expertise of **Robert Hudgins, Philip Johnson** (NMR - protein-RNA complexes) and **Sergey Krylov** (CRC in Bioanalytical Chemistry, funding from OCRN) in this area. In addition, **Dr. Jorg Grigull** has recently joined the faculty with his primary appointment in the Department of Mathematics and Statistics. Dr. Grigull's expertise is in bioinformatics specializing in microarray work. He recently completed a postdoctoral period with Dr. Timothy Hughes, Banting and Best Department of Medical Research, University of Toronto. Dr. Grigull plans to do both 'wet' and 'dry' lab research and he is housed in the Farquharson Life Sciences Building in close proximity to the biochemistry, cell and molecular groups in Biology. His appointment adds to an increasing number of colleagues in the Departments of Mathematics and Statistics, as well as Computer Science, with developing research and teaching activity in bioinformatics and biostatistics. In particular, **Dr. Jianhong Wu**, Canada Research Chair in the Department of Mathematics and Statistics, heads the MITACS National Centres of Excellence high profile and very successful activity in mathematical modeling of viral diseases. This group has recently made important contributions in the areas of SARS and West Nile Virus research.

Within the Department of Biology we continue to undergo significant renewal, with almost 50% of the faculty having arrived in the last five years. This "youthful" recruitment has continued in 2004 with the arrival of **Dr. Scott Kelly**, in January 2004, from the University of Alberta. Dr. Kelly's area of expertise is the endocrine control of hydromineral balance and energy homeostasis in lower vertebrates. Dr. Kelly has secured substantial funding from CFI (for an Aquatic Facility and Center for the Integrative study of Fish Physiology and Endocrinology) and an NSERC Operating Grant and his lab is among the most relaxing in the Department as a consequence of his large and well-stocked aquaria. In the summer of 2004, **Dr. Michael Scheid** (formerly at Ontario Cancer Institute) joined the department. Dr. Scheid's area of study examines signal transduction pathways and protein kinases." Also joining in 2004 is **Dr. Stephen Wright** who did his PhD at the University of Edinburgh and more recently an NSERC post-doctoral fellowship at the University of California Irvine. Dr. Wright's area of expertise is in plant genome evolution and population genetics and he has been successful in the recent CFI competition securing funding for studies on plant genomics. Other new hirees include **Dr. Roberto Quinlan** who studies human-induced stressors on aquatic ecosystems, **Dr. Tony Amin**, molecular animal virologist specializing in HepC, and **Dr. Chris Lortie**, a plant ecologist. New recruits are busy setting up labs and writing grants.

Overall, faculty in the biochemistry, cell and molecular biology area have been very successful in obtaining operating funding from CIHR, NSERC, NCIC, HSF, etc. as well as major infrastructure funding, and a number of faculty have received awards. Among these are **Dr. Kathi Hudak**, **Dr. Gary Sweeney** and **Dr. Logan Donaldson**, who all received PREA awards. **Dr. Gillian Wu**, Dean of Science, a member of the Department of Biology, was awarded the Cinader Award by the Canadian Society of Immunology, the highest award in Immunology in Canada. **Dr. Ronald Pearlman** was installed as a University Professor at the 2004 Fall Convocation. Dr. Pearlman is also an Associate in the Evolutionary Biology Program of the Canadian Institute of Advanced Research (CIAR) and serves as York's University Delegate to CIHR.

Along with the substantial renewal of faculty, the Department of Biology will experience new leadership effective Jan 2005 with the appointment of **Dr. Imogen Coe** as Chair. The previous chair, **Dr. Arthur Hilliker**, completes a successful five year term and will now be able to focus his attentions on his other full-time administrative position as President of the Faculty Union. Dr. Coe received her undergraduate degree in the UK, obtained a Ph.D. at the University of Victoria, followed by post-doctoral fellowships at UC (San Francisco) and the University of Alberta. Dr. Coe, the first female chair of the department, is looking forward to continuing to promote the interdisciplinary nature of the research in life sciences that is one of the strengths of the Department of Biology at York University.