# Bulletin

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

**2002**

www.csbmcb.ca

COVER PHOTO:
A schematic diagram of the Smad signalling system. (Illustration by Etienne Labbé.)

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# CSBMCB President's Report

## Dr. David Andrews

Do all presidents reports start off by saying it has been a busy, productive year? It has certainly been a year of change at CSBMCB! The Society continues to promote biological sciences in Canada by providing exciting annual meetings and by supporting advocacy and policy activities. The executive have been very active in a number of areas and I think that we are making progress towards an even more energetic and vital society.

The past year has seen another excellent meeting at the Banff site that has become one of our regular venues. Once again the meeting featured a mix of top international and national researchers. It is always gratifying to see Canadians sharing the podium with the best from around the world. For me high-points included presentations of new, controversial data that later appeared in Cell, Nat. Cell Biol., JCB and JBC in excellent talks by Drs. Bergeron, Grinstein, Wickner and others. The award lectures by Drs. Wrana and Nemer were also very impressive. I am very pleased to say that we were able to sponsor a record number of students to attend this fabulous meeting. We all thank Joe Casey and his team for the work they did organizing it.

Although not possible to organize, the weather and the scenery were fantastic, as always. If you have not yet attended one of our meetings I strongly urge you to do so. To get a feel for it imagine the best attributes of a Keystone meeting and a Gorden Conference combined. The facilities in Banff are so well suited to our meetings that we plan to meet there again in 2005! However, our 2003 meeting will be somewhat different as it will be held jointly with the International Union of Biochemistry July 20-24,2003. If you have not already marked this meeting on your calendars - do it now! The meeting features symposia organized around 9 thematic areas that cover virtually all of Biochemistry, Cellular and Molecular Biology (more information can be found at: http://www.nrc.ca/confserv/iubmb2003/). It will be an event that you will not want to miss. The organizing committee headed by Joel Weiner have done a fantastic job on this meeting.

Frances Sharom has put a lot of work into our web site this year. New features including an employment opportunities page and electronic membership pages. We plan to keep improving this site to make it more useful and integrate it with both our major activities. In progress is a program to manage memberships that will permit us to accept membership payments over the internet and it will include our own system for managing meeting registrations in the future.

Thanks to the efforts of David Litchfield, we funded more student activities this year than in any previous year. They included:

University of Saskatchewan - Research Day
Dalhousie - Research Symposium
Cross Cancer Centre (Univ. of Alberta) - Research Symposium
York University - Research Symposium
York University - Career Day
UWO - Open House/Poster Day
University of Calgary - Research Retreat

The backbone of the society is the work done by the Treasurer and the Secretary. Fred Palmer has done an excellent job as treasurer for many years. As a result the society is financially healthy, able to maintain non-profit status and continues to use the resources available in the most effective manner to support science in Canada. Our society functions smoothly and things get done on time thanks to the tremendous efforts of Gene

Tustanoff. He also provides much needed corporate memory for those of us that are 'transients' within the executive.

Advocacy or Lobbying - depending on your point of view - was a major activity this year. I have listed many of our efforts in this regard below:

1) We put out a position paper on overhead, many of the details of this position paper were incorporated into a report prepared and distributed to decision makers in Ottawa on our behalf by CFBS.
2) Together with CFBS we prepared a report that was used in personal visits and distributed to decision makers in Ottawa. A copy of the report can be viewed at: http:/ /www .cfbs.org/CapacityforInnovation.html.
3) We participated in the direct lobbying of MPs and other decision makers in Ottawa. This lobby effort was conducted together with CFBS and made use of the report described above. For the first time we met with members of the opposition party as well as with the governing Liberals. In our meetings with members of Parliament and senior bureaucrats in Ottawa we stressed: A) The need for more and greater versatility in training programs for graduate and postgraduate students. B) The need for further investments to attract and retain the best and brightest scientists in order to further improve productivity in both basic and health research. C) The importance of the government living up to its commitment to future increases in the budget of CIHR. D) The importance of funding indirect costs in a manner that is accountable, transparent and efficient.
4) Through our association with CFBS we joined the newly formed Health Research Advocacy Network. Joe Casey participated in the 'day on the hill' organized by HRAN to promote health research directly to politicians and senior bureaucrats.
5) Joe Casey also represented us in the lobby effort mounted by the Canadian Consortium for Research (CCR) in Ottawa.
6) I addressed MPs and other decision makers in a well attended presentation organized by the Partnership Group for Science and Engineering (PAGSE) as part of their annual gala event on Parliament Hill. The topic this year was the importance of cancer research.
7) Bruce Sells and I met with both Alan Bernstein and the president of CFI to promote our views on the payment of indirect costs to universities.
8) Several of our board members (Leon Browder, Joe Casey, Claude Lazure, Bruce Waygood and myself) have been working with a group brought together by CIHR with the intention of establishing a new grassroots organization to advocate on behalf of health research to the general public and politicians. It is currently called the Canadian Society of Health Researchers, but this working name will likely evolve along with the organization.
9) We have been working on the development of more sophisticated printed materials that we hope will be useful for lobbying the federal government.

Our most important goal for next year will be to increase our membership base. That is the only way to significantly increase our effectiveness in advocacy, increase participation in our meetings and assure continued enthusiasm for our society. I urge you to talk to your colleagues, inform them of what we are doing, encourage them to attend the IUBMB meeting next summer and helps us become an even more effective voice in Ottawa by joining CSBMCB.

We also want to hear from you! Any ideas that you have for improving the effectiveness of the society are always welcome.

# Incoming Members of CSBMCB Executive Board 2002-2003

### Dr. John ORLOWSKI, Vice-President

John Orlowski was born in London, England in 1956, but shortly thereafter emigrated with his family to Montreal, Quebec, where he received his formative education. As a high school student, his academic strengths lay in the physical sciences - mathematics, physics and chemistry. However, he found himself more captivated by the complexities of biological systems, and what better place to pursue this interest than right next door at McGill University, well respected for its strengths in the biological/biomedical sciences. John undertook his undergraduate studies in the Department of Biology, majoring in the Molecular, Cellular, and Developmental Biology program. It was during this time that he became intrigued by exciting developments in the field of endocrinology, particularly following a series of biochemistry lectures by Samuel Solomon on the molecular diversity of steroid hormones and their mechanisms of action. These lectures were seminal in the sense that they seeded his aspiration to become a biomedical scientist, quelling any earlier thoughts of pursuing a career in family medicine.

Following completion of his baccalaureate, John pursued his interests in steroid hormone action at Queen's University in Kingston, Ontario, where he obtained his M.Sc. and Ph.D. degrees in Biochemistry under the supervision of Albert Clark. By coincidence, Albert Clark had completed his doctoral studies with Samuel Solomon about a decade earlier, and had formed a strong research group investigating mechanisms of androgen action, utilizing the prostate gland as a model system. Up to this point, most of the research in this area had been performed using whole animals or tissue explants, yet there were indications from developmental studies that molecular communication between the epithelial and stromal cells of the prostate was critical for organ development. John's project was to investigate whether these two cell types metabolized androgens (as well as estrogens) differently and, if so, how this might influence prostate growth and differentiation. This was particularly challengingly as few studies to that point had been successful in separating and maintaining these distinct cell types in primary culture for sufficient periods of time to permit detailed characterization. Moreover, techniques to resolve and quantify the myriad of newly discovered steroid metabolites in an efficient manner were still in their infancy. Through considerable trial and error, John developed a number of innovative methodologies that accomplished just that and uncovered significant differences in each cell type's ability to form and clear biologically active androgens as well as to express androgen-dependent proteins, providing new insights into androgen-mediated differentiation of the prostate. Being persistent is perhaps one of his traits and he is forever grateful for the strong support, encouragement and patience of his mentor. In later years, he also had the opportunity to finally thank Samuel Solomon for those early motivational lectures; and Samuel now affectionately refers to John as his academic grandson!

John also found life at Queen's to be enriching in areas outside his academic pursuits. Initially acting as the Biochemistry representative on the Graduate Student Society Council, he subsequently went on to serve terms as Vice-President, President and Past President of the Society where he contributed significantly to the development

and implementation of a university-wide policy regarding working conditions for graduate teaching assistants. He also served in various other capacities, including President and Past-President, on the Board of Directors of Queen's Grad Club, a semi-autonomous organization that catered to the other, some might say more important, needs of graduate students - i.e., providing the best assortment of fine brews and weekend entertainment on Campus! In 1984, he was the recipient of the Queen's Tricolour A ward, bestowed by the student body "For Outstanding Contribution to the University Community". While honoured by the recognition, John best describes the award as a reflection of the collective contributions of several individuals who tried to make a small improvement in graduate student life at Queen's.

After completing his Doctorate towards the end of 1985, John decided that to better understand the molecular mechanisms underlying hormonal control of tissue differentiation, it was essential to acquire skills in molecular biology, particularly in the field of gene transcription where considerable advances had been made. As good fortunate would have it, an opportunity arose in the laboratory of Jerry Lingrel at the University of Cincinnati College of Medicine. Jerry's laboratory was already well known for its pioneering work on understanding transcriptional regulation of globin gene expression during development, and had just received international acclaim for cloning the genes for the catalytic alpha and beta subunits of the sheep Na+/K+-ATPase, one of the most extensively studied ion transporters in mammals because of its importance in forming the plasma membrane electrical potential. During the course of this work, they also discovered the existence of novel isoforms for the alpha subunit. These developments were tremendously exciting as they were amongst the first mammalian ion transporters to be cloned and represented a wonderful opportunity for study at the transcriptional level. Supported by an Medical Research Council of Canada Postdoctoral Fellowship, John performed some of the initial characterizations of the tissue-specific, developmental and hormonal regulation of the various Na+/K+-ATPase subunit genes. It was during the course of these studies that John became fascinated by ion transporters and their diverse contributions to cell and organ function.

At the end of his postdoctoral fellowship, John accepted a faculty position in the Department of Physiology at McGill University, where he has remained since. He has continued his research on ion transporters, but shifted his focus to the study of mammalian Na+/H+ exchangers which contribute significantly to cellular acid-base and volume homeostasis. His most significant scientific contributions include the molecular cloning of novel members of the mammalian Na+/H+ exchanger gene family that are targeted not only to the plasma membrane but also to distinct organellar compartments, supporting broader physiological roles for these transporters than previously anticipated. This research has also been greatly enriched by a productive and enjoyable collaboration with Sergio Grinstein at the Hospital for Sick Children in Toronto, who has provided not only a strong intellectual stimulus, but also a cell biological component, to these studies. Since his appointment at McGill University, John has been the recipient of Scholarships from the "Fonds de la Recherche en Sante du Quebec" and is presently supported by an Investigator Award from the Canadian Institutes of Health Research. His research is currently funded by grants from the Canadian Institutes of Health Research and the Kidney Foundation of Canada. Over the last several years, John has been actively involved in the peer-review process, serving on Scientific Review Committees for the "Fonds de la Recherche en Sante du Quebec", the Heart and Stroke Foundation of Canada and the Canadian Institutes of Health Research. He is also currently a member of the Editorial Board for the Journal of Biological Chemistry.

John has been quite impressed by the high quality of the Winternational and Summer Symposium series sponsored by the CSBMCB, and welcomes the opportunity to contribute to its mission of promoting science in Canada.

## Dr. Caren HELBING, Councillor

I was the kind of kid that needed to know how things worked. For my third birthday, I received a toolbox, complete with real hammer and saw (I think this is banned now for safety reasons)! I'd spend many hours examining insects in the backyard or building something or other. My undergraduate years studying Biological Sciences at the University of Windsor were spent learning many details about living organisms in a broad sweep from the molecular to the population. My father, a physicist, was amazed at the sheer volume of memorization that needed to be done compared to learning the fundamental physical equations and then working with those. My first introduction to research was a memorable one in the laboratory of Paul Hebert (now at U. of Guelph). Up until that point in my life, I had never imagined that Daphnia could be so diverse and fascinating! Paul's enthusiasm for science (embodied in his frequent leaps over lab furniture) had a lasting impression on me. I spent two summers working in his lab and witnessed pioneering work into characterizing crustacean populations living in different environmental conditions. This included trips up to Churchill, Manitoba and Igloolik, Nunavut, where hoards of mosquitoes were battled daily in the name of science! The following summer was spent studying genotoxicity in the lab of Michael Petras. Again a fascinating world opened up that was bringing me into the organism and studying the effects of chemical exposures on DNA damage. In those years, I was fortunate to have received two NSERC summer studentships. Seeing how scientific knowledge is generated first-hand and being involved in discovery is invaluable training. A subsequent honors thesis project with Alden Warner on cysteine protease inhibitors in dystrophic mice made it clear to me that research was what I wanted to do. I interviewed for graduate positions in several places. I made a point of visiting each place that I was interested in to get a feel for the people and the environments. I found this to be extremely informative, going beyond the glossy brochures!

Dr. Warner recommended that I go chat with Burr Atkinson in the Zoology Department at the University of Western Ontario. My interest was piqued when he mentioned that Burr was interested in frog metamorphosis as a model developmental system. I learned the amazing fact that only a single hormone (thyroid hormone) was required to trigger the complete remodelling of the tadpole into a frog. I wanted to learn more, so I joined Burr's lab in 1988 armed with a NSERC 1967 scholarship. I spent many, long hours mastering molecular techniques and two-dimensional gels in my quest for understanding how the tadpole liver managed to produce the entire urea cycle during metamorphosis in anticipation of the need for these enzymes to deal with nitrogenous waste on land as a frog. Not many gene sequences were known at that time and I cloned several of the urea cycle enzymes from the bullfrog. I also cloned the first bullfrog thyroid hormone receptor and demonstrated the sequential up-regulation of the receptor and urea cycle enzymes during natural and precociously-induced metamorphosis. Since Burr's lab was also actively involved in understanding the mechanisms controlling the stress response, particularly heat shock, I cloned a hsp30 gene and showed that it was thyroid hormone-responsive. In order to elucidate the mechanisms involved in thyroid hormone responsiveness in different tissues with different metamorphic fates, I showed that thyroid hormone-responsive gene transcripts are differentially affected by heat shock and that their responses are tissue context-dependent. As I was busy developing my scientific skills, my mother (a multi-talented lecturer in German with degrees in social work, languages and education), would always remind me that it was important to have balance and encouraged me to develop other skills. Heeding her advice, I was actively involved in grad student government,

organized a university-wide grad student research symposium and became involved with the "Let's Talk Science" program that was just getting off the ground. I was responsible for training several undergraduate students in the lab keeping in mind how valuable the experience was for me when I was an undergrad. I completed my doctorate in 1993 and was given the Detweiler Award for the best Ph.D. in Zoology; an award that was shared that year with my husband, Dennis Churchill, who was working in Stan Caveney's lab on gap junctions.

Dennis and I decided to go to Calgary for postdoctoral work. The move was a daring one for me in that I decided to do my postdoctoral work in cancer research focussing on the role of the c-myc oncogene in regulating cell proliferation and apoptosis. This oncogene is often found to be upregulated in cancer cells and the degree of overexpression correlates with prognosis of the tumour. I was intrigued by the creative science that was being done at the University of Calgary in Randy Johnston's lab and was convinced that this would greatly benefit my development as a scientist. As anyone who has worked on c-myc can attest to, it is particularly difficult to work on. Thousands of papers have been published, yet we still understand relatively little about how Myc really works in cells. I decided to follow the lead from another postdoc in Randy's lab at the time, Cheryl Wellington, who was developing a tetracycline-regulated gene expression system for studying RNA stability. Gossen and Bujard had just published their novel eukaryotic gene expression system that seemed perfect to study the early cellular effects of c-myc overexpression in native cells. With a great deal of effort, the tet-myc cells were made and used to show surprising relationships between cyclin-dependent kinase activities and the induction of apoptosis and quiescence. At the same time, Igor Garkavtsev, a postdoc in Karl Riabowol's lab next door had discovered the ING tumour suppressor. In collaboration with them, I showed that ING could regulate c-myc-induced apoptosis. Later studies from several labs supported ING's role in apoptosis and some have linked p53 with this regulation.

Discussions with fellow postdocs and the inability to answer the seemingly simple question of "How many postdocs are there at the University of Calgary and who are they?" gave birth to a joint venture with Cheryl Wellington in an ambitious survey of Canadian postdocs. Through the unwavering support of Randy, Hans van de Sande and Matt Spence, NSERC and SSHRC, we garnered the expertise of Marja Verhoef and ended up with the questionnaire responses of over 1300 postdocs covering all disciplines. The work helped raise awareness about postdoctoral issues and contributed to positive steps taken by research councils and universities to improve the postdoctoral experience. The birth of another venture also occurred with the arrival of my son in 1997.

A chance to lecture in part of Leon Browder's Developmental Biology course helped consolidate my love for teaching and encouraged me to pursue an academic career. In 1999, I joined the Department of Biochemistry and Microbiology at the University of Victoria as a NSERC university faculty award recipient. Over my postdoctoral years, I was exposed to several examples where multiple cellular outcomes could be produced by the same stimulus. If one could understand how a cell decides when it will proliferate or apoptose, perhaps one could harness that information to design ways to induce cancer cells to selectively kill themselves. In designing my own research program, I decided to go back to the tadpole metamorphic system to address how a single extracellular signal is capable of eliciting multiple, sometimes paradoxical, cellular outcomes. Through the hard work of a talented team, my laboratory has made novel contributions in three areas. First, we have developed a unique frog cDNA array for the analysis of gene expression in multiple species. We have used this to analyse gene expression in the regressing tadpole tail during natural and precocious metamorphosis and have uncovered novel gene targets. In collaboration with Environment Canada and the US Environmental Protection Agency, we are using this technology to identify disruptors of thyroid hormone action. Second,

we have cloned frog ING genes and have shown that their expression is controlled by thyroid hormone. ING proteins appear to be involved in regulating cell fate. Third, we have shown that cyclin dependent kinases are essential for thyroid hormone-dependent apoptosis. We are currently developing the lab's proteomic capabilities to be able to assess the relationship between the transcriptome and proteome in thyroid hormone-dependent pathways.

It's been an exciting four years as an assistant professor: teaching new classes, setting up a new lab, and giving birth to my daughter in 2001. During my entire training in Canada, I am grateful for the wonderful interactions that I have had with the many talented scientists that make up our community. I am very excited about representing the CSBMCB community as an executive board member and hope to contribute to our success in the bright future ahead!

## Dr. Linda PENN, Councillor

The journey of how and why I became a research scientist is credited to two influential groups of people that made an enormous impact during my early years. The first were my parents. As first generation Canadians of Ukrainian extraction they were in the small hotel business in northern Ontario town and worked hard and long hours to ensure their children had all the opportunities a life in Canada could offer. I think my earliest experiment was to perfect the Shirley Temple. My folks taught me the value of a strong work ethic and provided me the opportunity to appreciate the payback of trying your best at whatever you tackle.

The second major influence in the early years came from two extraordinary high school teachers. Now living just outside of Toronto, I was fortunate to have a female math teacher — Mrs. Howatson — who encouraged a handful of girls to pursue their love of math. Importantly she also taught us to simply 'go for it' and do what we like to do even though the rest of the world expected us to focus and excel in 'Home Ec' , a course that prepared you to be the perfect homemaker. The other educator that deserves special mention is a chemistry teacher, who came alive when working with those who participated in science fair projects. His enthusiasm for science was infectious. To my pleasant surprise, in Grade 11 he arranged for me to spend a full week with the electron microscope at the Ontario Science Centre. That week really changed everything. There was no turning back. I was hooked. Science was cool. I only hope my own children are similarly encouraged by such caring and extraordinary teachers in whichever field they thoroughly enjoy and wish to further pursue.

What about later in life and the more formal scientific training? My stint with the EM at the Science Centre taught me there was a microscopic world out there that was fascinating. This led me to a B.Sc. in Microbiology at the University of Guelph where I was inspired by virology as taught by Peter Dobos. I liked the logical and ordered gene regulation required for productive viral replication. That various viruses had adapted to their host with specialized genomes, coat proteins and mechanisms to release progeny was astounding. I then acquired a job in industry, bought my first car and married my husband Richard Penn. After a few months, the boredom of working as a quality control technician made us realize it was time for me to go back to school. With Richard's encouragement I then conducted my Ph.D. with Bryan Williams at The Hospital for Sick Children/University of Toronto studying the cellular genes involved in the antiviral effects of interferon. Bryan was a wonderful mentor who really let me carve my own path in research, learning from both my successes and failures. It was an exciting time in research as recombinant DNA technology (molecular biology) was just taking off. Journal club at Sick Kids was always

one of the highlights of the week and involved PI's such as Ron Worton, Roy Gravel and Manuel Buchwald as well as post-doctoral fellows who have since become top Canadian research scientists, such as Lap-Chee Tsui, Peter Ray, Irene Andrulis, Bob Korneluk and Martin Breitman. Journal club often included a debate over the implications of the latest discoveries that continued well past the hour. This enthusiasm for science and knowledge only fueled my own passion for research.

During my Ph.D., it became clear that interferon could block cell division as well as viral replication but how this magic bullet worked as an antiproliferative agent remained unclear. Indeed, the molecular mechanism of tumorigenesis was largely a black box. To dive into this field and learn about cancer I conducted my post-doctoral studies in London, UK at the Imperial Cancer Research Fund. My direct supervisor was Hartmut (Hucky) Land who would insist we discuss the long-term implications of the latest results, not just tomorrow's gel. The focus was the product of the myc oncogene and the discovery of a negative feedback loop that enabled autoregulation at the level of gene transcription. The strength of working in a strong and focussed Research Institute enabled me to also enjoy the teachings and participate in the discoveries of other scientists at the ICRF, such as Gerard Evan. Understanding how Myc can drive the development of such a wide-range and large number of human cancers became my Holy Grail and the primary topic with which I would establish my own research lab.

Returning to Canada I held a complex position at The Hospital for Sick Children in Toronto. On the clinical side, I developed novel molecular assays to identify the presence of pathogenic viral genomes in patient samples and ran a molecular diagnostic lab. On the research side, we began to tackle the Myc question thanks to generous funding from the NCIC. Moreover, on the home front, we initiated our own studies of growth and development and were blessed with two children (Jessica and Adam). Needless to say this was a crazy and fragmented period of time. In addition to research I learned about administration, turn-around-times, budgets, fighting for equipment, and how to metastasize space. Science is a funny business. We just become proficient at research and suddenly we are swamped with all the issues of running a small business. With my clinical duties taking precedent, conducting research became a treat and would not have been possible without the support of colleagues like Sean Egan and John Dick, mentors - such as Bob Phillips and Brenda Gallie, as well as the stellar folks in their labs, including Paul Hamel, Eldad Zackzenhaus, Lina Dagnino and Rod Bremner, who have each established their own independent research program here in Canada. After becoming Senior Scientist at Sick Kids I elected to focus exclusively on research. However, the Ontario Cancer Institute was moving to its new location in the heart of the research belt in Toronto and an opportunity to join the OCI team could not be ignored. Indeed, moving to the OCI enabled me to focus all efforts exclusively on research with a powerful force of Research Scientists all similarly tackling the cancer problem.

Briefly, the lab now focuses on two major areas of research. We continue to work on understanding the regulation and function of Myc oncoprotein with emphasis on identifying the molecular program triggered by Myc as a regulator of gene transcription, delineating the key interactors required for Myc-induced transformation and understanding how Myc potentiates apoptosis. In addition, we are developing novel anti-cancer agents that target the Myc pathway. Indeed, we also aim to exploit the unique apoptotic potential of cells of malignant transformation in an effort to uncover novel agents that target tumour cell destruction without causing collateral damage to neighbouring normal cells. To this end, we have agents in both early and late stage development. We have enjoyed continuous funding from both NCIC and CIHR and more recently from venture capital funds as well as American granting agencies. Of course, all of this was only possible with the dedicated trainees and staff that have participat-

ed and contributed to the research along the way. Moreover, it has been particularly rewarding to be able to collaborate with stellar Canadian scientists from coast to coast on these projects. In recent years these include Ivan Sadowski (UBC), Mark Minden (OCVPMH), Cheryl Arrowsmith (OCI/PMH), David Andrews and Brian Leber (McMaster), Jim Dimitroulakos (Ottawa) and Rick Langler (Mnt. Allison).

Why get involved in the CSBMCB? I have tried to highlight some of the many bright and dedicated Canadians who have held a major role in helping to shape my scientific career. Hearing the stories of many of my Canadian colleagues over the years, it is not unusual to find researchers like myself who did not grow up in an environment full of test tubes and museums. Yet through exposure at school, soon learned that our curiosity gene(s) could be satisfied through a career in research. We must ensure the next generation of Canadian Scientists has the same or better support that we enjoyed. Despite this conviction, I found I was a member of several American societies and actively participated in their conferences and committees yet was not similarly involved in the Canadian equivalent. My goal as councilor is to increase membership and awareness of the CSBMCB. Beware, if your name was mentioned in this piece, I will be looking for your membership and participation in this important Canadian Society!

In addition to direct research, I am on the Board of Directors and Vice-President of the Canadian Cancer Society/Ontario Division, Graduate Admissions Coordinator for the Dept of Medical Biophysics/University of Toronto and sit on many grant panels both here and abroad. Thanks to Richard for encouraging me to pursue this unique career. Spouses of scientists deserve special mention for all the ups/downs of this business, the absenteeism particularly during grant season, acceptance that the work is never done, and that research is an addiction to which we have (happily) fallen victim.

CSBMCB Executive Board – Front row: Claude Lazure, Leon Browder, Linda Penn, John Orlowksi, Fred Palmer. Back row: David Litchfield, Joseph Casey, David Andrews, Caren Helbing, Eugene Tustanoff, Bruce Waygood.

# Minutes of the 45th Canadian Society of Biochemistry, Molecular and Cellular Biology Annual General Meeting

Max Bell Auditorium, Banff Centre, Banff, Alberta, Saturday, March 23, 2002, 4.00 p.m.

Chair: Dr. Leon Browder, President CSBMCB

## 726. Approval of Agenda,

The agenda was approved as circulated on a motion from Dr. R. Baker which was seconded by Dr. Frances Sharom. CARRIED

## 727. Approval of Minutes of the 44th AGM (Published in the 2001 BULLETIN)

The minutes of the 44th AGM were approved upon the Chair receiving a motion from Dr. J. Davie which in turn was seconded by Dr. Palmer. CARRIED

## 728. Business Arising from the Minutes.

Dr. Browder opted to meld any outstanding matters into the Reports which were to follow.

## 729. Presidents Report.

a) State of the Society

**1). 2001 Alliston Meeting**

Dr. Browder reported that the Society's first independent meeting was both a scientific and financial success. The meeting was oversubscribed with 235 registrants and a net profit of approximately $28,000 was realized. Dr. Peter Davies is to be commended for his fund-raising efforts with more than $60,000 being collected from various agencies and corporations. The concept of a theme programme proved to be very successful and this pattern will be followed in subsequent Society Meetings. A number of important lessons were garnered from organizing our first scientific meeting. It is imperative to put together a very high level scientific programme. The Society should not be involved in dealing with hotel registrations and payment, this should be done directly by the registrants or should be handled through a professional agency hired by the Society. Lastly, there should be enough lead time to ensure proper organization with adequate staff in place.

**2). Banff Meeting**

The attendance at this year's meeting "Membrane Proteins in Health and Disease" will finalize out at 190 registrants, attracting speakers and attendees from England, Germany, Israel, Japan, Kuwait, Spain, Switzerland, United States and Canada. The two satellite meetings, "Bicarbonate Transporter" and "Nucleoside Transporters" which were held Wednesday evening and Thursday morning, were well attended and scientifically stimulating, drawing on the leaders in both fields. The meeting should net the Society a small profit. Dr. Joe Casey and his Organizing Committee have done an excellent job in putting this meeting together with every thing running effectively without problems.

**3). Membership recruitment**

Dr. Palmer presented a graph outlining membership enrolment trends since 1994. A high point of was achieved in 1996 with approximately 450 Regular paid-up members however, these numbers since then have declined by approximately 25%. It is hoped with the new image and programmes that are being put in place, the Society will increase its numbers. A number of different recruitment projects are being formulated to encourage new membership especially from the ranks of junior university appointments.

**4). Contract with CFBS**

Dr. Browder stated that the Society is now in the second year of a contract that was signed with CFBS to financially support a national lobbying effort in Ottawa. This support amounts to $40 per member. CFBS mounts a strategic lobbying programme which is difficult to gage regarding the impact it has had on increasing funding of basic research in Canada. The Society contributes one tenth of the Federation's operating budget and the question raised is whether the Society is getting its moneys worth in relation to its own specific lobbying agenda. Dr. Andrews has been charged to restate the Society's specific interests in participating in CFBS's lobbying programme. Pending the establishment of new relationship with CFBS, which will satisfies the science policy aims of the Society, it has been decided to put on hold the renewal of our contract with CFBS for 2003.

**5). Electronic Membership Data Base**

Dr. Sharom reported that Dr. Uwe Oehler, University of Guelph, has been contracted to set up an electronic data base for the Society. A beta version has been put in place and after a shakedown period, a final form should be up and running by the first of July. It will be possible for members to access the data base for Directory information, update their personal files, and pay their membership fees. This data base will make life much easier for the Society's Treasurer.

**6). Society's Web Page and new Server site**

Dr. Sharom has updated the Society's Web Page and will be responsible for its maintenance. As the computer server used by the Society is resident in his Department at Dalhousie University, Dr. Palmer indicated that he cannot guarantee its use after he steps down from the Chair. As a result, Dr Andrews is investigating the possibility of purchasing a dedicated server in partnership with a second party from McMaster University at a cost to the Society of approximately $3,000 with a maintenance cost of $1,500 per year.

## b) Future Direction of CSBMCB

**1). 2003 IUBMB Toronto Congress**

The Society will host the 19th International congress of Biochemistry and Molecular Biology in Toronto, July 20-24, 2003. The Society's appointed members of the 2003 Congress Planning Committee have been meeting on a regular scheduled basis for the past three years and are now well advanced in developing the Congress programme and arrangements. Eleven Plenary Lectures, 64 Symposia, large poster sessions and several workshops have been planned. In addition 13 Satellite meetings have been arranged at different Canadian venues along with a pre-Congress 3 day Young Scientist Programme which will bring 120 young investigators to Toronto from all parts of the world. It is the Society's intent to have a student poster competition, capped off with a reception for Canadian registrants, the afternoon prior to the opening Session of the Congress similar to the programme the Society organized at the joint ASBMB/PABMB/CSBMCB meeting held in San Francisco in 1999. Regular paid up members of the Society who will register for the Congress will receive a $75 rebate, however, the mechanism for this has not as yet been finalized. The Society plans to offer 25 student and postdoctoral travel awards to our members to encourage Congress attendance.

**2). 2004 and 2005 Society Meetings**

The 2004 AGM meeting is planned to be held in February or March at the same venue used for the 2001 Winternational meeting, Château Mont Saint-Anne near Quebec City. The theme of this meeting will be "Signalling from the Membrane to the Nucleus". According to our meeting schedule, the 2005 meeting is slated to be held in Banff and a tentative booking has been made for March 15-18, however a proposal was received from Dr. Sean Brosnan, Memorial University of Newfoundland, to hold a joint meeting with the British Biochemical Society in St. John's Newfoundland on the topic of Metabolism in the Genomic's Era. Dr. Browder stated that the Society needs more infor-

mation and further discussions with Dr. Brosnan will commence shortly to explore this possibility.

3). **Joint meeting with the Genetics Society of Canada and the Canadian Physiological Society.** Dr. Browder reported that he has been contacted by Dr. Shiva Singh, President of the GSC to investigate the possibility of holding joint scientific meetings and this could be considered for 2004 if a suitable topic amenable to both Organizations could be found. Dr. Browder and Dr. Andrews will explore this possibility and failing this, they will propose a joint meeting with CPS for 2004. In another vain, it has been suggested by the Secretary of GSC that our two Societies should consider combining some of our administrative operations to save money, e.g., dues collections, database maintenance, publishing a combined newsletter journal, etc. Dr. Browder indicated that further discussions on this matter will take place.

### c) Support of Student Activities

Dr. Browder commented that Dr. Litchfield has received a number of requests for financial aid from several university student groups. It is the policy of the Society to encourage student research days and colloquia and have set up a yearly budget to support these activities with individual $500 grants. He asked Society members to make this policy known to their student bodies so they can compete for these funds.

## 730. Past President's Report.

Dr. Sharom reported that she is in the process of putting a slate together for this year's Board election which will be held in May.

## 731. Vice-President's Report.

### a) Society Server to host CSBMCB Web Page

Dr. Andrews suggested that the Society either buy a server or enter into a lease agreement to procure one. He presented details of a specific server and proposed that the Society share it with a central facility at McMaster University. An equitable arrangement is currently being worked out. He is also currently exploring additional services and methods for making secure payments on our CSBMCB web site.

### b) Society Newsletter

Dr. Andrews described a plan for a newsletter that the Society could use to recruit members and for lobbying efforts. This idea using a template that could also be used by other societies in partnership to promote an effective Lobby. The Executive agreed to an expenditure of approximately $2,000 to initiate this project and then to come back in stages with further proposals for consideration. The first step is to be a layout of a four page single sheet newsletter. The Executive strongly proposes that CFBS should help with this lobby effort by funnelling back some of our money that the Society contributes to support lobbying in order to help underwrite this programme. Most importantly, we want access to their contact lists.

### c) Research Grant Overhead

Dr. Andrews reported that he prepared with the help of the Executive, a statement paper "Research Grant Overhead - A Strategy for Implementation" outlining the Society's position on the Federal Government's proposed financial support of overhead cost for research. This paper was sent to key members of the Cabinet and Members of Parliament over Dr. Browders signature (Appendix A).

## 732. Treasurer's Report.

### a) 2001 and 2002 Budgets

Dr. Palmer circulated the Financial statement for 2001 (Appendix B). The total receipts for 2001 amounted to $269,460.56 with expenditures of $214,198.08 netting a balance for fiscal 2001 of $55,262.48, however, there was a $20,426.91 obligation carried forward for 2002. He also circulated a separate financial statement for the Alliston Meeting. The total income for this meeting was $211,739.02 which included $78,979.02 in sponsor donations with expenses amounting to $183,760.09. Dr. Palmer moved that his 2001 statement be accepted and this was seconded by Dr. Sharom. CARRIED

### b) Special Fund

Dr. Palmer reported that the Special Fund as of March 22 stood at $377,423.71 and for the first time in nine years there was no need to withdraw money from this fund for Society needs.

### c) Membership Dues

Membership dues for 2002 and 2003 will remain at $100 of which $40 will be transferred to CFBS in 2002 for the science policy programme. Dr. Palmer stated that the credit card payment option has proven to be very popular, 55% of the membership have elected to pay their fees by this means.

## 733. Secretary's Report.

### a) BULLETIN

Dr. Tustanoff commented that Dr. Tinker, Editor of the BULLETIN, has done a superb job in putting out the latest issue of the journal. During his tenure as Editor, this publication has been turned into a very professional looking publication and has vastly been improved in contents and layout. Dr. Tinker recently contacted Dr. Browder and suggested that since the Society was contemplating joining forces with GSC to issue a combined joint society publication, it was time the Society thought about replacing him. He felt he did not have the scientific background to adequately serve both disciplines. After much discussion the Executive decided reluctantly to accept Dr. Tinker's resignation and praised him for this work as Editor for the past three years. Dr. Sharom and Dr. Reithmeier volunteered to take over the Editorship on a temporary basis for the next year.

### b) Update IUBMB Congress

As the two Society award Lectureships for 2003, the CSBMCB's Merck Frosst Prize and the Roche Diagnostics Award for Biomolecular and Cellular Research, will be presented as part of the IUBMB Congress plenary lecture programme, the Society has been asked by the IUBMB Planning Committee to submit the names of our designated award lecturers by June 1st, 2002 in order to comply with advertizing and publication deadlines that face the Congress. Even though nominations for the 2002 awards were closed only on January 1st , 2002, it will be necessary to have all submissions for the 2003 competition in by May 1st , 2002. The 2002 nominations for the Merck Frosst Prize will be considered as submitted for the 2003 competition and no further documentation will be required.

### c) Society Awards

1) 2002 CSBMCB's Merck Frosst Prize and The Jeanne Manery Fisher Memorial Lectureship. There were nine nomination received for the 2002 MF Prize and five for the JMF Lectureship. The winner of the 2002 MF Prize is Dr. Jeffery Wrana, Samuel Lunenfeld Research Institute, Mount Sinai Hospital, Toronto and Dr. Mona Nemer, Institut de recherches de Montréal, is the recipient of th JMF Memorial Lectureship. Dr. Wrana presented his lecture, "The Smad signal transduction pathway" Friday morning and Dr, Nemer her lecture "Transcriptional regulation of cardiac growth" this morning.
2) Graduate student and PDF Travel Awards. There were 22 travel awards granted to assist graduate and PD Fellows to attend the Banff Meeting: 10 - $750 Merck Frosst Graduate Student Travel Grants, 3 - $750 Perkin Elmer Travel Awards for PDFs, 5 CSBMCB Trainee Travel Awards (2 x $750, 1 x $500 and 2 x $250), 2 -$250 BD Biosciences Travel Awards and 2 - $250 PENCE Alberta Travel Awards.

### d) Dr. Peter Dolphin Memorial Programme

Dr. Peter Dolphin who served the Society as Treasurer and President, passed away unexpectedly a year ago. Peter was largely responsible for the Society obtaining the 2003 IUBMB meeting for Canada. He was appointed the Secretary General of The Pan American Association for Biochemistry and Molecular Biology and Treasurer of the IUBMB. To commemorate his contributions to our Society and Biochemistry in general, the Society contributed $1,000 to the Dr. Peter Dolphin Memorial Fund set up at Dalhousie University in his memory. In addition the Society has organized two memorial symposia in his honour and memory, the Peter Dolphin Symposium: Structural Biology, at this year's Banff Meeting and the Peter Dolphin Memorial Lipoprotein Symposium at the 2003 IUBMB Congress in Toronto.

### e) Digital Camera

The Executive authorized Dr. Tustanoff to purchase a digital camera for Society use. A4 mega Canon PowerShot G2 was purchased with a 256 flash card.

### f) 2001 Winternational Meeting Mont Sainte-Anne Quebec

The 2001 Winternational Meeting organized by Dr. J. Bergeron, Dr. D. Williams and Dr. J. Aitchison was a very successful meeting both from its superb science, organization and financial success. Dr. Palmer has received a cheque for approximately $19,000 from the profits of this meeting.

### g) Directory of Canadian Chairs of Biochemistry

Dr. Tustanoff stated that he has received numerous requests for listing and addresses of the university Department of Biochemistry Chairs. As there was no updated listing, he made a concerted effort to compile such a list which he subsequently circulated to all Department heads. The Executive endorsed this undertaking and suggested that it should be expanded to included departments of molecular and cellular biology.

## 734. Other Reports.

### Biochemistry and Cell Biology.

Dr. J. Davie Editor of Biochemistry and Cell Biology reported that the journal now has attained the highest impact rating of all the NRC publications. Great efforts have been made to speed up publication times. Accepted papers are now being made available on the Web within four to six weeks, but the publication of the printed journal versions is still too slow.

## 735. New Business.

There was no new business.

## 736. Approval of Signing Officers for 2002-2003.

It was moved by Dr. J. Casey and seconded by Dr. R. Baker that Dr. Andrews, Dr. Palmer and Dr. Tustanoff should be the Society's signing officers for 2002-2003. CARRIED

## 737. Adjournment.

The meeting was adjourned at 5:20 pm on a motion from Dr. Palmer which was seconded by Dr. Sharom. CARRIED

## APPENDIX A

On behalf of the Canadian Society of Biochemistry, Molecular & Cellular Biology, I wish to commend the Government of Canada for recognizing the needs of Canadian universities for support of the infrastructure required to conduct federally-funded research activity at universities and research hospitals. The $200,000,000 announced by the Minister of Finance in December was a good start and has enabled universities to begin the process of restoring overburdened physical plants and modernizing outmoded facilities. However, this is a first step in what must be an ongoing process if Canada is to realize the Government's stated goal of joining the first tier of developed countries in investment in research and development.

In response to the pledge of the Government of Canada to work with the research community on ways to provide ongoing support for indirect research costs that is predictable, affordable and incremental to existing support, our Society has developed a proposal that meets the goals of provincial and federal governments and the needs of the research community. I have attached our proposal as Appendix B, which we have sent to Alberta MPs and relevant ministers of the Federal Government. If you believe this proposal has merit, please circulate it more widely with the proviso that it be attributed to the Society.

Sincerely,
Leon W. Browder, President CSBMCB

# Research Grant Overhead - A Strategy for Implementation

Prepared by The Canadian Society of Biochemistry, Molecular & Cellular Biology

## APPENDIX B

Overhead payments for research are essential for universities and institutes to continue to value and support Tri-council funded research. However, it is essential that overhead payments be in addition to current and promised funding of the granting councils.

The aims of overhead payments are to contribute some of the funds required to provide and maintain the infrastructure required by grantees. The universities have argued persuasively that overhead payments are essential, and consensus is building that an appropriate level of support is approximately 25% of Tri-council funding. The government and the grantees have a shared interest in overhead funds being used in the most effective manner to support excellent peer-reviewed research.

**We suggest that the government build on the success of recent programs like the CFI in implementing overhead funding.** In this model, universities would apply every 3-5 years for overhead funding, including an Implementation Plan for utilization of requested funds and a Progress Report detailing the utilization of previously awarded overhead funds. Each institution would submit a single application for overhead funding to each of CIHR, NSERC and SSHRC with the maximum amount of funds set at 25% of the peer-reviewed funding provided from that government agency. We also strongly advise against a requirement for provincial matching funds. To include such a requirement would penalize provinces that lack the necessary resources.

This funding model would accomplish the following goals:

1) **Accountability.** Universities would be accountable to both researchers and government to demonstrate that overhead funds are being used to support government funded research. Overhead funds would be awarded based on peer-reviewed evaluation of both the excellence of the current research program (the overhead cap is set by current funding levels) and planned improvements to infrastructure that would benefit researchers with Tri-council funding.

2) **Autonomy**. Because overhead could only be obtained through a successful grant application and because the extent of funding (to the 25% maximum) would be determined every 3-5 years, overhead payments would not become part of the university or institute base-budget. It is essential to prevent overhead payments from becoming part of base-budgets so as to discourage provincial governments from reducing their contributions to university funding by all or some fraction of the overhead payments.

3) **Transparency.** The planned and actual use of overhead dollars would become part of the public record. Grant applications subsequent to the initial round should incorporate the past records of universities use of overhead dollars as part of future funding decisions.

By providing overhead grants that are subject to peer-review, government has the opportunity to provide a more appropriate level of support for its grantees .and also create an environment within universities in which an excellent research program is valued, rather than perceived as a drain on university resources. It will also reverse the current trend to over-value contract research that is revenue neutral or revenue generating for universities. However, to be successful, overhead grants must support excellent research. **Therefore it is essential that funds provided as overhead must not reduce the government's commitment to increased funding for CIHR or prevent expansion of the CIHR model to NSERC and SSHRC.**

# CSBMCB/SCBBMC Financial Statement for 2001

| | | |
|---|---|---|
| **BALANCE BROUGHT FORWARD** (Jan.1, 2001) | | |
| Secretary's Account | 5,561.03 | |
| Treasurer's Account | 1,814.74 | |
| | | 7,375.77 |
| **RECEIPTS** | | |
| Award Sponsors | | |
| Merck Frosst | 3,500.00 | |
| Roche Diag. | 1,500.00 | |
| Total Award Sponsors | 5,000.00 | |
| Corp. Sponsors | 2,500.00 | |
| CSBMCB Dues (GST incl) | 31,410.50 | |
| Exchange | 82.74 | |
| Interest Earned | 1,055.58 | |
| Membership list sale | 1,521.95 | |
| Miscellaneous income | 136.00 | |
| Subscriptions: | | |
| Annual Reviews | 668.00 | |
| Elsevier | 2,431.00 | |
| NRC | 540.00 | |
| Total Subscriptions | 3,639.00 | |
| Summer Allison Meeting Income | | |
| Hotel Accommodations | 91,800.00 | |
| Registration | 40,960.00 | |
| Sponsors | 67,729.02 | |
| Travel Grants | 11,250.00 | |
| Total Meeting Income | | 211,739.02 |
| Winternational 2001 reimbursement | | 5,000.00 |
| **TOTAL RECEIPTS** | | **269,460.56** |
| **EXPENDITURES** | | |
| Awards; | | |
| J. Manery-Fisher, 00 | 1,000.00 | |
| J. Manery-Fisher, 01 | 1,000.00 | |
| Merck Frosst, 01 | 1,000.00 | |
| Total Awards | | 3,000.00 |
| Board Meeting-Feb 01 | | 3,338.74 |
| Board Meeting-Nov 01 | | 6,395.38 |
| CFBS Lobby levy | | 14,081.20 |
| Industry Canada | | 30.00 |
| Intern. Fed. Cell Biol dues | | 473.31 |
| Na/Ca Meeting | | 2,000.00 |
| Peter Dolphin Fund (Dal.Univ.) | | 1,000.00 |
| PABMB dues | | 884.13 |
| President's Expenses | | 564.48 |
| Secretary Expenses | | |
| Miscellaneous | 239.81 | |
| Offices supplies | 232.73 | |
| Plaques/certificates | 1,025.37 | |
| Postage/phone/FAX | 776.58 | |
| Total Secretary's Expenses | 2,274.49 | |
| Subscription Payment | | |
| Annual Reviews | 685.99 | |
| Elsevier | 2,455.42 | |
| NRC | 545.70 | |
| Total Subscription Payment | | 3,687.11 |
| Student Symposia | | 1,500.00 |
| Allison Meeting Expenses | | |
| Bank Card Charge | 5,604.34 | |
| Bank transfer Fees | 30.00 | |
| Career Workshop | 1,157.05 | |
| Nottawasaaga Hotel | 101,890.97 | |
| Advance payment | -10,000.00 | |
| AV Equipment rental | 345.00 | |
| Bar Service | 3,462.40 | |
| Coffee breaks | 3,231.03 | |
| Food charges | 12,436.03 | |
| Meeting Rooms | 5,911.75 | |
| Total Hotel charges | | 117,277.84 |
| Management | | |
| MMS (Meeting services) | 8,025.00 | |
| Miscellaneous | 287.62 | |
| Poster Boards rental | 1,035.00 | |
| Secretarial | 6,500.00 | |
| Shipping (Poster Boards) | 963.00 | |
| Travel | 810.02 | |
| Web Site Management | 750.00 | |
| Total Management | | 18,370.64 |
| Poster Prizes | | 500.00 |
| Programmes (printing) | | 3,139.60 |
| Speakers Travel | | 12,279.38 |
| Student Travel Awards | | 11,250.00 |
| Total Meeting Expenses | | 169,608.75 |
| Treasurer's Office Supplies | | 271.13 |
| Vice-President's Expenses | | 362.24 |
| Web Site maintenance | | 250.00 |
| Winternational Travel Student Awards | | 3,750.00 |
| GST/HST (2000) | | 1,226.12 |
| **TOTAL EXPENSES** | | **214,198.08** |
| 2001 YEAR END BALANCE | | 55,262.48 |
| SPECIAL FUND (market value) | | 336,463.75 |
| Capital asset (Editors computer) | | 595.00 |
| **TOTAL ASSETS** | | **392,321.23** |
| **OBLIGATIONS CARRIED FORWARD** | | |
| Roche Prize 01 | | 1,500.00 |
| PENCE Proteomics Conference | | 5,000.00 |
| Canadian Developmental Biology | | 2,500.00 |
| GST/HST (2001) | | 3,387.89 |
| Summer 01 invited speaker travel | | 1,471.71 |
| Credit card setup fee | | 250.00 |
| 2001 BULLETIN (editing + printing) | | 4,439.04 |
| Treasurer's Postage (2000+2001) | | 1,878.27 |
| **TOTAL COMMITMENTS** | | **20,426.91** |

# 45th Annual Meeting of the CSBMCB, Banff, Alberta. "Membrane Proteins in Health and Disease"

The Banff Centre in Banff, Alberta was the site of a very successful symposium on "Membrane Proteins in Health and Disease". This meeting was organized by members of the Canadian Society of Biochemistry and Molecular & Cellular Biology, led by Joseph Casey (University of Alberta). Other members of the Organizing Committee from Alberta included Carol Cass, Chris Cheeseman, Xing-Zhen Chen, Larry Fliegel, Bernard Lemire, Marek Michalak and James Young, with expert administrative support from Barbara Thom. Society Past-President Frances Sharom (University of Guelph) and Councillor Reinhart Reithmeier (University of Toronto) rounded out the Organizing Committee.

This meeting was a combination of the CSBMCB 45$^{th}$ Annual Meeting and the 12$^{th}$ Winternational Symposium, and provided a very rich menu of presentations by an international array of speakers. The meeting began with Satellite Meetings on Bicarbonate Transporters and Nucleoside Transporters. Participants in the Satellite Meetings were greeted by clear blue Alberta skies and an invigorating –26°C, prompting interesting comments by registrants from Australia and Kuwait. The satellite meetings attracted a dedicated group of researchers who then stayed on for the main meeting.

The meeting comprised six sessions. Session 1 was held in honour of Peter Dolphin (Dalhousie U.) who passed away suddenly. Fred Palmer introduced the audience to the many accomplishments of Dr. Dolphin, his science, his passion for teaching, his role as mentor and as a loyal member of the Society. Peter will be missed. A graduate student prize in Peter's name has been created in the Biochemistry Department at Dalhousie University.

The sessions covered a range of topics including the structural biology of membrane proteins, pH regulation and cell health, organellar membrane proteins and function, transporter function and dysfunction, and finished off with a session on the implications of membrane proteins for therapeutics, sponsored by the CIHR Institute of Genetics. The talks were excellent, and presented by a stellar cast of Canadian and International scientists. Although there were many opportunities for recreational activities, the lecture hall held a full complement of participants for all sessions. The poster sessions were packed as well, with many lively discussions.

## Travel Awards and Poster Prizes

Participation in the meeting by graduate students and post-doctoral fellows was facilitated by numerous travel grants. Merck-Frosst travel awards were presented to the following graduate students: Mona Abu-Abed (U. Toronto), Victoria Ahn (U. Toronto), Denise Bay (U. Manitoba), Anne Bergeron (U. Laval), Joanne Cheung (U. Toronto), Anathea Flaman ( Dalhousie U.), Steve Huntley (U. Toronto), Daniel Krofchick (U. Toronto), Qin Qu (U. Guelph), Felicia Vulcu (McMaster U.). Perkin-Elmer supported travel grants to the following post-doctoral fellows: Emmanuelle Cordat (U. Toronto), Michelle Furtado (U. Toronto), and Rongmin Zhao (U. Toronto). Additional travel grants provided by BD Biosciences were presented to Fred Loiselle and Frank Visser, and PENCE Alberta gave travel grants to Xiuju Li and Les Grad (all from U. Alberta). The CSBMCB presented a slate of trainee travel awards to: Vitaly Khutorsky (U. Toronto), Robert Sasata (NRC, Saskatoon), Laila Singh (Simon Fraser U.), Marcela Aliste (U. Calgary) and Stephen Brokx (U. Alberta).

Many of the invited speakers were assigned the additional duty of judging the posters displayed

by graduate students and post-doctoral fellows. The poster judges are thanked for reviewing posters.

Roche Diagnostics Canada generously sponsored three awards for the best poster presentations given by graduate students. The winners of awards for the two best posters in biochemistry were Isabelle Carrier (McGill U.) and Patrick Lusk (U. Alberta), while the winner of the Jake Duerksen Memorial poster award for the best poster in the cellular biology area was Quansheng Zhu (U. Alberta). Special mention went to graduate students Oleh Petriv (U. Alberta) and Curtis Oleschuk (Queen's U.). The CSBMCB Post-doctoral Poster Prize was awarded to Roger Bascom (U. Alberta), with special mention to Anass Haimeur (Queen's U.) and Nicolas Touret (U. Toronto and Sick Children's Hospital).

## Merck Frosst Award and Jeanne Manery Fisher Memorial Lecture

The Annual Meeting features presentations by winners of the Merck Frosst Award and the Jeanne Manery Fisher Memorial Lectureship. This year's winner of the Merck Frosst Award was Jeff Wrana from the University of Toronto and the Lunenfeld Research Institute, Mount Sinai Hospital. This award is given for meritorious research by an investigator in Canada within the first ten years of their independent research career. Dr. Wrana gave an impressive presentation on the molecular analysis of the complexities of "The Smad signal transduction pathway". This pathway is involved in morphogenesis and involves a series of fine-tuned regulatory and inhibitory interactions that modulate information flow from the cell surface to the nucleus.

Mona Nemer from the Université de Montréal and the Clinical Research Institute of Montreal was the winner of the Jeanne Manery Fisher Memorial Lectureship. The award is given in honor of the late Jeanne Manery Fisher, who was an outstanding biochemist and outspoken advocate for women in science. This lectureship is presented to a woman scientist working in Canada who has a distinguished career in biochemistry, molecular and cellular biology. Dr.

Christian Riel of Merck Frosst Canada (right) presents the **2002 CSBMCB Merck Frosst prize** to Dr. Jeff Wrana (left).

Nemer spoke on her studies of "Transcriptional regulation of cardiac growth". This lecture also had a signalling theme and featured the role of GATA transcription factors in heart development and disease.

Dr. Mona Nemer (left) receives the **2002 CSBMCB Jean Manery Fisher Award** from Dr. Leon Browder, CSBMCB President (right).

A meeting of this calibre could not be held without the generous support of our many sponsors (Agilent Technologies Canada, Inc., Alberta Heritage Foundation for Medical Research, AMGEN, AstraZeneca, BD Biosciences, Beckman-Coulter Bioresearch, Caprion Pharmaceuticals, Cedarlane Laboratories, Canadian Institutes of Health Research, Institute of Genetics (CIHR), Interscience, Invitrogen, Merck-Frosst, PENCE (Alberta), Perkin-Elmer, Roche Diagnostics, the University of Alberta and the Department of Biochemistry, University of Toronto. We thank them for their continued support of our Annual and Winternational Meeting. Frances Sharom is congratulated on her success in securing corporate sponsorship for this meeting.

## CSBMCB Executive

Frances Sharom (University of Guelph) completed her term as Past-President. Frances played a major role in the organization and success of this meeting and the previous 44$^{th}$ Annual Meeting held at Alliston, Ontario in 2001. She has also moved the Society into the electronic age with on-line registration for meetings and membership dues collections (coming soon). Leon Browder (University of Calgary) now assumes the position of Past-President. Leon has worked hard to improve the effectiveness of the Society and to promote its activities. David Andrews (McMaster University) moves to the President's office after a year as Vice-President. David has been very involved in the lobbying efforts our Society has initiated in partnership with CFBS. Reinhart Reithmeier (University Toronto) has completed his 3-year term as Councillor. Reinhart has been very active in the organization and promotion of our Annual Meetings. Gene Tustanoff (emeritus member, University of Western Ontario) and Fred Palmer (Dalhousie University) are tireless in their duties as CSBMCB Secretary and Treasurer, respectively.

## International Congress of Biochemistry and Molecular Biology

The 46th CSBMCB Annual Meeting will be held in conjunction with the XIX International Union of Biochemistry & Molecular Biology Congress, at the Metro Toronto Convention Centre, Toronto, Canada, July 20-24, 2003. For information, connect to the Congress web-site: (www.nrc.ca/confserv/iubmb2003). We encourage all our members to attend this exciting meeting, which will showcase the work of researchers from Canada and abroad. See you in Toronto!

Winners of the **Roche Diagnostics Graduate Student Poster Prizes:** (left to right) Isabelle Carrier, Patrick Lusk and Quansheng Zhu (Jake Duerkson Cell Biology Poster Prize), with Anita Erasmus of Roche Diagnostics.

Winner of the **CSBMCB Post-doctoral Fellow Poster Prize**, Dr. Roger Bascon, is congratulated by CSBMCB President Dr. Leon Browder.

**Merck Frosst Travel Awards for graduate students**; (front row from left to right), Mona Abu Abed, Victoria Ahn, Denise Bay, Anne Bergeron, Joanne Cheung, Christian Riel (Merck Frosst Canada), (back row from left to right) Anathea Flaman, Steven Huntley, Daniel Krofchick, Qin Qu and Felicia Vulcu.

**Perkin Elmer Travel Awards for post-doctoral fellows**: (left to right) Emmanuelle Cordat, Michelle Furtado and Rongmin Zhao, with Janice Watkin (Perkin Elmer).

**CSBMCB Trainee Travel Awards:** (left to right) Vitaly Khutorsky, Robert Sasata, Laila Singh, Marcela Aliste, Stephen Brokx and Frances Sharom (Past-President CSBMCB).

Organizing Committee Chair Joe Casey receives a gift of appreciation from Reinhart Reithmeier on behalf of the other members of the committee.

**BD Biosciences Travel Awards:** (left to right) Fred Loiselle, Frank Visser and Ivy Cook (BD Biosciences).

**PENCE Alberta travel awards:** (left to right) Les Grad, Xujiu Li and Frances Sharom (Past-President CSBMCB).

**The Organizing Committee for the Banff conference:** (left to right) Committee Chair Joe Casey, Larry Fleigel, Xing-Zhen Chen, Chris Cheeseman, Carol Cass, Bernard Lemire, Frances Sharom, Reinhart Reithmeier, and James Young (not present, Marek Michalak).

# 2002 Society Graduate Student/PDF Travel and Poster Awards

The following travel stipends were awarded to Society graduate student and post-doctoral fellow members to encourage their participation in the Society's Annual Meeting and Symposium "Membrane Proteins in Health and Disease" held in Banff, Alberta March 21-24, 2002, by assisting in their travel and meeting expenses. These competitive stipends are awarded based on the merit of their submitted poster abstracts. The Society is indebted to Merck Frosst Canada, Perkin Elmer Canada, BD Biosciences and Roche Diagnostics PENCE Alberta, for the financial sponsorship of this programme.

### $750 awards - Merck-Frosst Travel Awards for graduate students

Mona Abu Abed. Banting and Best Department of Medical Research, University of Toronto. Supervisor: Dr. David MacLennan " Zooming in on the ATP-binding Domain of the Sarco/Endoplasmic Reticulum $Ca^{2}$+ATPase: Examining Ligand-Induced Effects by Multidimensional NMR".

Victoria E. Ahn, Department of Medical Biophysics, University of Toronto. Supervisor: Dr. Gil Prive. "A Structure of a Small Sphingolipid Binding Protein".

Denise Bay, Department of Microbiology, University of Manitoba. Supervisor: Dr. Deborah Court. Structural and Functional Studies of Neurospora crassa Mitochondrial Porin Mutants Using Black Lipid Bilayers and Circular Dichroism Spectrapolarimetry".

Anne Bergeron, Laboratory of Cell and Developmental Genetics, Department of Medicine, Univerité Laval. Supervisor: Dr. Robert Tanguay. "Fumarylacetoacetate causes disruption of ER function and apoptosis through a CHOP/GADD153 independent pathway".

Joanne C. Cheung, Department of Biochemistry, University of Toronto. Supervisor: Dr. Reinhart Reithmeier. "Human anion exchanger 1 (band 3) is not palmitoylated in transfected cells."

Anathea S. Flama, Department of Biochemistry and Molecular Biology, Dalhousie University. Supervisor: Dr. Melanie Dobson. "Molecular genetic analysis of the yeast Niemann-Pick C-related gene, NCR1".

Steven Huntley, CIHR Group in Membrane Biology, Department of Medicine, University of Toronto, Supervisor: Dr. Mel Silverman. "Functional characterization of the Q170CrSGLT1 mutant of Xenopus oocytes: modification of polarity and charge regulates empty carrier kinetics and charge transfer."

Daniel Krofchick, Department of Electrical and Computer Engineering, University of Toronto, Supervisor: Dr. Mel Silverman. "Novel Decay Components of the Rabbit $Na^{+}$ /Glucose Co-transporter (rSGLT1) are Exposed, Indicating a Minimum of Two Transitions at the Extracellular Surface Prior to Glucose Binding".

Qin Qu, Department of Chemistry and Biochemistry, University of Guelph. Supervisor: Dr. Frances Sharom. "Proximity of bound Hoechst 33342 to the ATPase catalytic sites places the drug binding site of the P-glycoprotein multi-drug transporter within the cytoplasmic membrane leaflet".

Felicia Vulcu, Department of Biochemistry, McMaster University. Supervisor: Dr. David Andrews. "FtsY interacts with phosphatidylethanolamine and a proteinaceous component on the inner membrane of Escherichia coli."

### $750 awards - Perkin Elmer Travel Awards for post-doctoral fellows

Dr. Emmanuelle Cordat, Department of Biochemistry, University of Toronto. Supervisor: Reinhart Reithmeier. "Carboxyl-terminal truncations of human AE1 impair its normal trafficking to the plasma membrane".

Dr. Michelle Furtado, Division of Cell Biology, Research Institute, Hospital for Sick Children. Supervisor: Dr. Amira Klip "Insulin-dependent interaction between p38 MAPK and GLUT4".

Dr. Rongmin Zhao, CIHR Research Group in Membrane Biology, Department of Medicine, University of Toronto. Supervisor: Dr. Reinhart Reithmeier "Hydrodynamic stability of the yeast anion exchanger homologue in detergent solutions".

### CSBMCB Trainee Travel Awards - $750, $500 and $250 awards

Dr. Vitaly Khutorksy, $750. CIHR Membrane Biology Group, Department of Medicine, University of Toronto. Supervisor: Dr. Mel Silverman. "Molecular modelling of the putative TM helices IV and V of the rabbits sodium glucose co-transporter SGLT1".

Robert J. Sasata, $750. Plant Biotechnology Institute, University of Saskatchewan, Supervisor: Dr. Patrick Covello. "Using mutagenesis to investigate structure/function relationships in fatty acid desaturates".

Laila M. R. Singh, $500. Department of Molecular Biology and Biochemistry, Simon Fraser University, Supervisor: Dr. Jennifer Thewalt. "Transmembrane Peptides in Cubic Lipid Phases: NMR investigations".

Dr. Marcela P. Aliste, $250. Department of Biological Sciences, University of Calgary. Supervisor: Dr. Peter Tieleman. Molecular Dynamics of Pentapeptides at Interfaces".

Stephen Brokx, $250. Department of Biochemistry, University of Calgary. Supervisor: Dr. Joel H. Weiner. "Investigation of yedYZ, a novel oxidorductase from Escherichia coli"

### BD Biosciences Travel Awards

Frederick B. Loiselle, $250. Department of Physiology, University of Alberta. Supervisor: Dr. Joseph R. Casey. "Potentiation of Bicarbonate Transport Activity by Direct Interaction of NBC3 Sodium Bicarbonate Co-Transporter with Carbonic Anhydrase II".

Frank Visser, $250. Department of Oncology, University of Alberta. Supervisor: Dr. Carol E. Cass. "Asn 338 of human equilibrative nucleoside transporter 1 (hENT1) is critical for interaction with high-affinity inhibitors".

### PENCE Alberta Travel Awards

Dr. Xuiju Li, $250. Department of Biochemistry, University of Calgary. Supervisor: Dr. Larry Fliegel. "Carbonic Anhydrase II Binds to and Enhances Activity of the Na+ /H+ Exchanger".

Leslie I. Grad, $250. Department of Biochemistry, University of Alberta. Supervisor: Bernard D. Lemire. "Modelling of human mitochondrial disease in the nematode Caenorhabditis elegans."

### Roche Diagnostics Graduate Student Poster Awards

Isabelle Carrier, Department of Biochemistry, McGill University, Supervisor: Dr. Philippe Gros. "Disssecting the catalytic mechanism of P-glycoprotein."

C. Patrick Lusk, Department of Cell Biology, University of Alberta, Supervisor: Dr. Richard W. Wozniak. "The efficient assembly of Nup53p into the nuclear pore complex is a karyopherin-mediated process".

Quansheng Zhu (Jake Duerksen Cell Biology Prize), Department of Physiology, University of Alberta. Supervisor: Dr. Joseph R. Casey. "Topology of the C-terminal region of the human plasma membrane $Cl^-/HCO_3^-$ anion exchanger, AE1".

### CSBMCB Post-Doctoral Poster Award

Dr. Roger A. Bascon, Department of Cell Biology, University of Alberta, Supervisor: Dr. Richard Rachubinski. "Yarrowia lipolytica Pex3p Initiates Peroxisome Assembly by Sequestering Components of Peroxisome Biogenesis".

The presenters for the various awards were Christian Riel (Merck Frosst), Janice Watkin (Perkin Elmer) Ivy Cook (BD Biosciences), and Anita Erasmus (Roche Poster awards)

# 19th International Congress of Biochemistry & Molecular Biology

Toronto, Canada - July 20-24, 2003
www.iubmb2003.org
Dr. Joel H. Weiner, Congress President

Canada hosted the 11th International Congress of Biochemistry in Toronto in 1979. All who attended remember this as a highlight of their scientific careers. The financial success of the Congress has left a legacy for Canadian biochemistry for the past 23 years.

In 1996 the late Peter Dolphin and Sean Brosnan prepared a bid, on behalf of CSBMCB, to the IUBMB executive committee to host the 19th International Congress of Biochemistry and Molecular Biology in Canada. The bid was successful and now some six years later the Congress is nearly here. In the intervening years a large number of biochemists have volunteered their time to serve on the Executive Committee, Program Committee and local Arrangements Committee. All these committees have done an enormous amount of work to insure that the Toronto Congress will be a scientific and social success. An outstanding scientific program has been consisting of 11 plenary lectures, 64 symposia and 11 satellite meetings. Registration is now open and it is time to plan your trip to Toronto. This is also a good time to invite your colleagues from the United States and abroad to come to Canada for the Congress. We need the help of every one of you to make the Congress a success. We have worked hard to keep the registration fees as low as possible. Students will be offered reduced registration fees and early registration reductions are now in effect.

The Congress is held every three years and has become the principal international conference for Biochemistry and Molecular Biology with a long-standing reputation for excellence. The CSBMCB will host the Congress, which is jointly sponsored by the National Research Council of Canada, the International Union of Biochemistry and Molecular Biology, and the Pan-American Association for Biochemistry and Molecular Biology.

## Scientific Program

The incredibly rapid pace of genomics, proteomics, metabolomics and structural biology has been accompanied by an explosion of the application of biochemistry and molecular biology to a diversity of fundamental biological and medical problems, and to the development of new technologies. The scientific program will emphasize current exciting developments and emerging areas of biochemistry and molecular biology, reflecting the level of sophistication that has been achieved in this field and the promise that it holds for the future. The most obvious challenge posed by our knowledge of the human genome sequence is to determine the functions, regulation and interactions of the proteins encoded by the genome. The ways in which this challenge is being met, and the success stories to date, will be a common thread throughout the program. The following major thematic areas will be covered in the Symposia which offer something for everyone:

*Proteomics and Functional Genomics;*
*Signal Transduction;*
*Gene Structure, Function and Regulation;*
*Specialized Subcellular Systems;*
*Molecular Basis of Developmental Biology;*
*Metabolic Regulation and Metabolic Engineering in Health and Disease;*
*Molecular Medicine;*
*Molecular Structure, Simulation and Evolution;*
*Biochemical and Molecular Biological Education.*

In addition to the symposium program there will be open poster sessions and several workshops.

## Plenary Lectures

Through the financial support of IUBMB, PABMB and CSBMCB we have invited 11 outstanding scientists to present plenary lectures at the Congress.

The plenary lectureships and the speakers are individuals are:

*Osamu Hayaishi Lecture: Tony Pawson (Canada);*
*E. C. Slater Lecture: Suzanne Pfeffer (USA);*
*IUBMB/PABMB Lecture: Alberto Kornblihtt (Argentina);*
*Kunio Yagi Lecture: Dr. Shuh Narumiya (Japan);*
*Severo Ochoa Lecture: Jean Marc Egly, (France);*
*Chester Beatty Lecture: Tim Hunt (UK);*
*PABMB Lecture: Ramon Latorre (Chile);*
*FEBS Lecture: Aaron Ciechanover (Israel);*
*EMBO Lecture: Ari Helenius (Switzerland);*
*CSBMCB Roche Diagnostics Award Lecture; Victor Ling (Canada);*
*CSBMCB Merck-Frosst Award Lecture: Charles Boone (Canada)*

## A Very Special Event

2003 marks the 50th anniversary of the publication of the DNA double helical structure. A special evening session will be organized by the Biochemical Society (UK) to celebrate the 50th anniversary of discovery of DNA. This event will be open to the public as well as Congress participants. Speakers will include Dr. Sydney Brenner, 2002 Nobel Prize winner, Dr. Lap-Chee Tsui and Dr. Tim Caulfield.

## Young Scientists Program

A pre-Congress, 3-day Young Scientists' Program, for up to 120 young scientists, will be held at the University of Toronto Scarborough Campus. This has been a popular event at the IUBMB Congresses for two decades. Many international friendships and scientific collaborations have begun at these meetings. Young scientists at the late post-graduate and post-doctoral phase of their careers will be chosen from all parts of the world based on the quality of submitted abstracts describing their most recent research. A call for abstracts from interested young scientists was made in the Fall of 2002. The IUBMB will provide a travel grant to the successful applicants. Accommodation, including meals, will also be provided at the pre-congress meeting. All participants will present their work as posters and some will also be invited to make oral presentations. The program will include some invited speakers. There will be free time and some social events to allow the young scientists to make friends from around the world. Participating young scientists will be transported to the downtown University of Toronto residences for the main congress in the Toronto Convention Centre. Their accommodation and registration for the main congress will also be provided by the IUBMB. All participants will have the opportunity to present their posters as part of the main congress poster sessions.

## Satellite Meetings

Several Satellite Meetings are being organized immediately prior to and following the Congress. These will complement the themes of the Congress and be attractive to a large number of Congress participants. Please contact the individuals indicated if you are interested in attending a satellite meeting.

*Recent Advances in the Study of Protein-Ligand Interactions.* Montreal. July 26-28, 2003; Dr Francois Denis, Email: francois.denis@inrs-iaf.uquebec.ca

*Liposomes: Drug Delivery Vehicles and Models of Biological Membranes*. Toronto, July 19-20, 2003; Dr Pieter Cullis, Email: pieterc@interchange.ubc.ca

*Delivery of Macromolecules into Cells Using Non-viral Vectors.* Toronto, July l8-l9, 2003; Dr Jean Gariepy, Email: gariepy@uhnres.utoronto.ca

*Stress Signalling in Cancer.* Quebec City, July 25-27,2003; Dr Jacques Huot, Email: jacques.huot@phc.ulaval.ca

*Pushing the Limits of Pathogenomics: Array Technologies to Study Virus-Host Cell Interactions*, Vancouver, July 17-19,2003; Dr François Jean, Email: fjean@interchange.ubc.ca

*4th International Conference on Protein Kinase CK2: From Structure to Regulation and Function,* London, Ontario, July 25-27, 2003; Dr David Litchfield, Email: litchfi@uwo.ca

*Proteases in Health and Disease*. Montreal, July 18-25,2003; Dr Nabil Seidah, Email: seidahn@ircm.gc.ca

*3rd International GATA Transcription Factors in Health and Disease*. Montreal, July 16-18,2003; Dr Mona Nemer, Email: Mona.nemer@ircm.gc.ca

*Education in the Molecular Life Sciences: The Central Role of Biochemistry and Molecular Biology* (sponsored by IUBMB, ASBMB and Project Kaleidoscope). Toronto, July 18-20,2003; Dr Ellis Bell, Email: jbell2@richmond.edu and Kelly Gull, Email: kgull@asbmb.faseb.org

*Biomolecular Structure and Drug Discovery;* Toronto, July 25-26,2003; Dr Emil Pai, Email:pai@hera.med.utoronto.ca and Dr Lakshmi Kotra, Email: pkotra@phm.utoronto.ca

*International Society for Enzymology.* Niagara Falls, New York, July 18-19,2003; Dr David Goldberg, Email: david.goldberg@utoronto.ca

## Social Program

In addition to the strong scientific program we have planned a number of social events to allow you to meet with colleagues. This includes the Opening Reception on Sunday evening after the Opening Ceremony and the Soiree Dansante, Music of the 21st Century to be held on Tuesday evening. We have also organized a number of Tours to allow congress attendees to appreciate the museums, history and scenic attractions of Toronto as well as the McMichael Art Gallery and the Niagara region.

## Accommodation

We have booked blocks of rooms in a number of hotels as well as dormitories at Ryerson Polytechnic University and the University of Toronto.

## Commercial Exhibition

An extensive Commercial Exhibition, located in a spacious hall adjacent to the poster area, will provide the opportunity for first-hand examination of the latest instrumentation and techniques in diverse fields.

I sincerely hope to see you in Toronto in July. We want to make this Congress as memorable for all participants as the extremely successful 1979 Congress. You can do your part by attending and bringing your trainees and inviting your colleagues.

# 2003 IUBMB Toronto Congress

## Background

At the conclusion of the IUBMB Congress in New Delphi in 1994, the venue for the 2003 IUBMB Congress was open for bids. As the Society's Executive expressed an interest in holding this Congress, Dr. Walsh, the Society's President, contacted Dr. Kleinkauf, the Secretary General of IUBMB in 1995 to explore the possibility of staging the 2003 IUBMB Congress in Canada. After receiving a positive response, Dr. Walsh was charged by the Executive to communicate with university biochemistry chairs in Montreal, Toronto and Vancouver to gauge their interest in holding this meeting in their city. As the Toronto group was the only one to show a keen interest in organizing this meeting, the Society's Board at its Meeting of June 15, 1995 endorsed Toronto and this proposal then was ratified at the Society's Annual General Meeting on June 16, 1995. Dr. Walsh contacted Dr. Andrée Bichon, NRC International Affairs, and informed her of the Society's proposal. Since the Society is not able to negotiate directly with IUBMB, this matter was channelled through the NRC, Canada's affiliate with the International Council of Scientific Unions. Since the invitation to hold the meeting in Toronto had to be submitted to the General Secretary of the IUBMB by March 1, 1996, two organizational meetings were held in Toronto to prepare Canada's bid for the Congress. The IUBMB Executive Committee was scheduled to draw up a short list from the submitted competitors at their meeting in Edinburgh on 14 July, 1996 and those approved contenders were to make their presentations at the San Francisco 1997 IUBMB Congress. At the Edinburgh Meeting four applications had been received, Toronto, Budapest, Cape Town and Athens

The first organizational meeting of the Canadian bid committee was held on August 18, 1995 in the Department of Biochemistry, University of Toronto. Dr. Brosnan, the then President of CSBMCB, chaired the meeting and along with Dr. Tustanoff, represented the Society. Dr. Bichon and Mr. Laurier Forget represented NRC and Dr. Peter Lewis and Dr. Harry Schachter represented Toronto's interests. The second meeting was held on the 3rd of November with Dr. Bibuhendra Sarkar replacing Dr. Schachter and Ms. Elizabeth Leyva (Metropolitan Toronto Convention Centre and Visitor's Association) in attendance. Dr. Brosnan reviewed the criteria on which the Congresses are awarded. These were (1) time since last Congress was held in the nation, (2) contribution to international biochemistry, (3) infrastructure and facilities, (4) estimated attendance, (5) least cost and greatest ease of travel, (6) recent Congresses in the same geographical area, (7) probability of political problems, (8) probability of financial success and (9) attractiveness of the venue. He further developed the role of the players in the proposed bid. The Toronto organizers are to be responsible for packaging the scientific aspects of the meeting and here Dr. Brosnan underscored the philosophy of the Toronto group. Dr. Lewis and his group emphatically wanted this meeting to be organized as a Canadian meeting with input from the four corners of Canada and not ruled by the Torontonions. The nuts and bolts of managing the meeting are to be undertaken by the NRC Conference Services. This is an all-encompassing service, assisting in preparation and presentation of the invitation, mailing of congress announcements, registration, housing, meeting facilities, secretarial assistance, printing abstracts etc. Since the NRC will cover any financial deficiency resulting from the Congress, they basically will control the meeting, with the exception of the scientific programme. In contrast to the 1979 IUB Toronto Congress, NRC Conference Services now operates on a total recovery basis and share in any profits which may accrue.

In preparing the invitation brochure, letters of support from all corners of Canada, industry, academia and government were solicited by Dr. Brosnan, Dr. Tustanoff and Dr. Lewis. The responses were extremely positive and supportive from all contacted parties.

The Metropolitan Toronto Convention Centre and Visitor's Association put together an excellent package in which they compared the cost of housing and hotels in Toronto as opposed to other international venues as well as outlining other proposed features. The use of the University's housing facilities and the planned expansion of the Toronto Convention Centre facility added to the strength of the Society's submission. As there was no choice available during the whole summer other than the week of July 17-25, the Toronto Convention Centre was booked for that period. A preliminary budget was presented by the NRC Conference Board based on their experiences with organizing the 12th International Congress of Pharmacology in Toronto in 1995. Initially, expenditures were forecasted to be $1,802,000 and revenue $1,885,00 based on 3,000 attendees. The NRC management fee of $350,000 was questioned by the Board and Dr. Brosnan countered that there was still room for further negotiations with the Conference Board on this matter. The Society's Board approved donating $25,000 to the Congress budget if the Toronto venue was approved by the IUBMB. A preliminary Congress organizational structure was presented by Dr. Bichon and it was approved in principal.

With the concerted efforts of the Society's President, Dr. Brosnan, Vice-President, Dr. Dolphin and the NRC Conference Services a superb proposal with expansive documentation was put together and sent off by Dr. Carty, President NRC, to the IUBMB Secretariat in Vienna at the end of February 1996, supporting the Toronto bid. Dr. Peter Dolphin attending the 8th PAMBM Congress in Puçon Chile, November 16-21, 1996 had occasion on behalf of the Society to effectively lobby a number of the attending IUBMB Executives on the merits of the Toronto bid.

On receipt of the Society's application for hosting the 19th IUBMB Congress, the Society was invited to make a formal presentation to the IUBMB Executive in Gifu, Japan on March 29, 1997 instead of appearing in San Francisco as originally scheduled. As Dr. Dolphin had already established rapport with members of the IUBMB Executive, he was delegated as President of the Society to present the Canadian bid in Gifu in the company of Mr. Laurier Forget, NRC Conference Services. Dr. Dolphin put together a very slick dossier summarizing our bid document along with a number of pertinent graphs which were used as background for the Gifu presentation. With his persuasive manner, Dr. Dolphin was able to privately sway a number of the IUBMB Executives to support the Toronto bid and consequently Canada was chosen by a margin of one vote to hold the 2003 IUBMB Congress.

After formal notification was received from IUBMB that Toronto was to be the site for their 2003 Congress, a meeting of the Bid Committee was convened on April 23, 1997 in Toronto to finalize the structure and organization of the Steering and Executive Committees for the Congress as well as outline the responsibilities of the membership of these committees. After discussion, a time table, 1997 -2003, was drawn up outlining a schedule of Congress matters that had to be attended to. In addition, an organization flow chart was presented by Dr. Bichon. At that time, the Society was asked to consider signing an Agreement (i.e., contract) with the National Research Council of Canada which laid out the obligations (financial and organizational) of both parties in staging the 2003 IUBMB Congress.

The Committee met again in Toronto on Sunday, November 16, 1997 to finalize the structure and organization of the Steering and Executive Committees for the 2003 IUBMB Toronto Congress. The Agreement between the National Research Council of Canada and the Canadian Society of Biochemistry, Molecular and Cellular Biology Society was discussed and modified to the agreement of both parties. The following changes were made to this agreement: the Society was to contribute $25,000 to the Congress

budget, $5000 in April of 2001, $10,000 in April of 2002 and $10,000 in April of 2003. If a profit is to accrue as a result of the Congress, the Society will be the first to draw back its $25,000 contribution and the rest of the profits are to be shared on a 50 -50 basis between the Society and NRC. This amended document was subsequently signed on behalf of the Society by Dr. Weiner, President CSBMCB and by Dr. S. Vohra, Director General, Administrative Services, NRC. The Society nominated Dr. P. Dolphin and Dr. W. Bridger, Vice-President Research, University of Western Ontario, to be the Society's representatives on the Congress Steering Committee. with Dr. Bichon and Mr. Forget acting on behalf of NRC. After a thorough assessment of potential candidates, the Executive Board of the Society selected Dr. Joel Weiner to represent the Society as the Chair of the Executive Committee of the Planning Committee and to be President of the 2003 Toronto IUBMB Congress, Dr. Michael Walsh to Chair the Programme Committee and Dr. Peter Lewis to head up the Local Organizing Committee. The appointments of members to other committees were left to the discretion of the Executive Planning Committee. A reception for the IUBMB Executive at the 2000 IUBMB Birmingham Congress was planned with Tourism Toronto taking on this responsibility, and a web site for the 2003 Congress approved. Informal talks were held with Dr. Zimmerman, President of the International Federation of Cell Biology on the possibility of holding a joint Congress with IUBMB and IFCB, however, this was untenable and the idea was not pursued further. Dr. Hickey, University of Ottawa, had contacted Dr. Dolphin with the suggestion that Canada would be seeking the venue for the 2003 International Genetics Congress and he thought it would be possible to explore holding a joint congress. Dr. Tustanoff contacted Dr. Whelan, President of IUBMB, to seek out his feeling on this matter. This idea was then discussed with the Executive Board and it was unanimously decided that this was impractical and therefore unacceptable and Dr. Hickey was so informed. Dr. Dolphin was seconded to the Toronto IUBMB Planning Committee as an ex officio non voting member and is to remain on the Society's Executive Board until 2003, acting as liaison between the Society and the 2003 Organizational Committee.

On June 17, 1998, a meeting attended by newly appointed Executive of the Toronto IUBMB Congress and representatives of Society's Board was held in Edmonton concurrent with that year's CFBS Meeting. Dr. Weiner laid out a nine-page draft of a critical path he prepared for the organization and implementation of the Congress. The document outlined each task with a time frame associated with the various aspects of the Congress. Dr. Walsh reported that he was in the process of forming a general plan for the scope of the meeting and was seeking input form all quarters. Dr. Lewis presented the new Congress logo and letterhead which were designed in Toronto and chosen over those submitted for the contest held by the Society. The subject of satellite meetings and possible conveners was discussed. Dr. Weiner concluded that NRC will set up a home page for the Congress on the World Wide Web.

Subsequent Congress planning meetings were held on October 16, 1998, May 28, 1999 November 6, 1999, November 18, 2000, April 27, 2001, October 12, 2001, January 12, 2002, April 13, 2002 and August 17, 2002. Liaison between the Society's Executive Board and the Congress Planning Committee was put in place at the November 16, 1997 meeting in the person of Dr. Dolphin, however, this relationship was never sustained. At the Society's Alliston Meeting the Board appointed Dr. David Andrews to stand in for the late Dr. Dolphin and attend Planning Committee meetings as a non -voting member in order to keep the Society's Executive apprised on Congress developments.

E. R.Tustanoff.
Secretary, CSBMCB.

# Retrospective Reflections of the 11th IUB Toronto Congress

(Reprinted from the BULLETIN, XVI , November 1979.)

**Dr. J. G. KAPLAN (1922 -1988)**
President of the 11th IUB Congress and President of the Canadian Biochemical Society 1978-79,
Vice-President (Research) University of Alberta.

I was named to the Executive Committee of the Congress in June, 1977 when I took office as Vice-President and President-elect of the Canadian Biochemical Society. By this time, the structure of the Congress had already taken shape. In particular, George Connell had organized the Executive and other Committees on a firm basis and had placed the financial and organizational details in the hands of the Conference Services division of the National Research Council (at that time directed by Ray Dolan and soon thereafter by Ken Charbonneau). John Colter's Programme Committee had designated the subject areas and subcommittees were picking speakers; Bob Painter's Planning Committee had the local arrangements well in hand. I viewed my role as being, together with Cyril Kay, my predecessor, the designated representative of the Society; we were to look out for those special interests of the Society that were in some measure distinct from those of the Congress.

Several of us on the Executive Committee were of the opinion that the post of President of the Congress, a largely symbolic office, should be filled by one of our distinguished elder statesmen of biochemistry. This solution proved to be impractical for several reasons and, at a meeting in London, Ontario in June 1978, I found myself elected to that position. My own view of my functions in this perhaps prestigious but not very busy post was that I should keep quiet and make myself as useful as possible to Connell, Colter and Painter and my other colleagues and do whatever they told me to do. And so I did. We were very pleased that Drs. Hanes and Quastel agreed to serve as Honorary Co-presidents and participate so actively in the proceedings.

In September of 1978, George Connell met with the Executive of the International Union of Biochemistry in Caracas. It was put to him that there was advantage in increasing the number of plenary session speakers from the two originally scheduled. During a hastily convened telephone conference call involving 3 Edmontonians, 3 Ottawans, 2 Torontoians and 1 Londonian, it was agreed that I be empowered to plan such an expanded plenary programme. In view of the fact that the second Congress mailing containing the final programme was to go to the printer by the beginning of October, I had all of 10 days in which to complete the arrangements. Bob Painter and I ultimately decided to reject a variety of alternatives in favour of a second plenary session on Tuesday evening, July 10th. By this time, I had been turned down by Fred Sanger, despite considerable pressure applied by John Spencer and myself, I had tracked down Feodor Lynen to a meeting in Soviet Georgia and had been turned down by him as well and had made unsuccessful efforts to hunt down Francois Gros who was in

Senegal somewhere; I was getting somewhat uneasy. I rang up Bill Whelan, Secretary-General of I.U.B. to discuss my idea of getting an outstanding biochemist from the U.S.S.R. for the programme; Whelan was then in Athens with other I.U.B. officers, including Academician Bayev. At my request, Whelan established that an invitation to a scientist of our choice would be conveyed by Bayev and that chances of acceptance were excellent. My first idea was to invite the well known bioorganic and protein chemist Ovchinnikov. Ron Williams persuaded me to consider his younger colleague V. Skulatchev; I looked up some of the latter's papers on the varied uses of protomotive force- or proticity, to use the felicitous phrase of Peter Mitchell -and invited him on the spot via Bayev. He telephoned me one day at noon (Moscow time) to accept; I would have been happier had this not corresponded to 4:00 a.m. Ottawa time. (He gave me his title over the phone and I was too sleepy to take it down correctly; the incorrect title appeared in the second Bulletin but was corrected in the Congress programme. I forgave him my lost sleep during his talk when he showed us the moving pictures of the algal chloroplasts rotating madly under the control of H+).

I then conceived of a three person symposium going from the physical-organic 'lower' limit of biochemistry, through membrane physical chemistry up to the biological organization of electron transport and oxygen fixing components. David Shugar, then visiting Ottawa from Warsaw, suggested Ephraim Katchalski whom Cyril Kay agreed to contact; Katchalski promised to consider it. A few days later he rang me up at 4:00 a.m. (Israel time thank God!) and after some hesitation, he accepted. The choice of this speaker, whose function was to hold an impatient audience to the end of a long programme, was obvious - Gottfried Schatz. He accepted and delivered the goods: there were almost two thousand people in the Hilton auditorium when he finished at 10:30 p.m. and I do believe he could have gone on another 30 minutes without losing his audience so gripping was his talk. In sum, I was well pleased with this session.

Prior to the Congress, I took part in several initiatives involving relations with biochemical colleagues in other countries. One of the most interesting and fruitful of these followed a call from Bill Whalen in October 1978, pointing out that mainland Chinese biochemists had pulled out of the I.U.B. twenty years before owing to recognition of the Taiwanese biochemists by the international body. He asked me whether I knew anyone at the Chinese embassy and urged me to issue a cordial invitation to our Chinese colleagues and to assure them that we would take any reasonable steps to make it possible for them to participate in the Toronto Congress. In fact, I did know the Counsellor of the Embassy, Mr. Wang Chu-Liang who also serves as scientific attache, and I wrote him about the matter. The question of Chinese attendance at the Congress was thereafter raised with Bill Slater, Treasurer of the I.U.B. during a visit to Peking. While Slater was in China I was contacted about several conditions for attendance that our Chinese colleagues regarded as essential, one of which involved how they and the Taiwanese were to be styled on the congress badges. A satisfactory solution to these problems was worked out with Ken Charbonneau and this assurance was conveyed to Slater before he left China. Soon thereafter we learned that a Chinese delegation would attend the meeting and that an application from Peking for membership in the I.U.B. Assembly had been received. A formula permitting the Chinese biochemists to adhere to the I.U.B without eliminating the Taiwanese was quickly worked out and this should set a precedent for the other international scientific unions. It was my pleasure to welcome the official Chinese delegates to Canada and the Congress on behalf of the Society and to express the hope that with normalization of relations would come increasingly close contact and scientific exchange between Chinese and Canadian biochemists.

Another agreeable duty that I performed on behalf of the Society took place immediately before the Congress when I visited with Mrs. Charles Best in her home and presented her with copies of the special C.H. Best memorial issue of the Canadian Journal of Biochemistry. She was

most interested in the reminiscences of old times in Best's lab, contained in the paper by Tom Jukes, as well as in the biographical sketch by David MacLennan and the historical article by Rachmiel Levine. I was very moved by my few hours with this gallant and charming lady.

The special 540 page issue, consisting of 64 articles invited by an ad hoc committee chaired by Cyril Kay, was distributed to all of those who registered at the Congress. The costs of the extra press run were divided among the National Research Council of Canada, the J.R. Kroc Foundation of Santa Ynes, California and by the Society. Reaction from many quarters indicated that it was quite successful promotional venture, not only on behalf of the Journal, but also on behalf of Canadian biochemistry itself. Morris Kates and I also invited a number of distinguished Congress lecturers from other countries to prepare their papers for publication in the Canadian Journal of Biochemistry; these will appear during the months to come, starting with the November issue. Among the plenary lecturers, papers were received from Kornberg, Handler and Skulatchev and others were received from speakers at various of the symposia; the first three to appear will be those of Wittman, Racker and Koshland.

Another pleasant duty that I undertook on behalf of the Society was to preside at the unveiling of the historical plaque commemorating the life and work of Maud Menten on Wednesday, July 11th; the plaque is located at Queen's Park, just in front of the Medical Sciences Building of the University of Toronto. Despite a most violent thunder storm that threatened to drown more than voices of the speakers, this little ceremony, that included a review of Maud Menten's science by Jean Manery-Fisher as well as some moving and extemporaneous remarks by Stanford Moore, came off without a hitch. The storm indeed relented just in time for the party to venture forth to witness the unveiling presentation in the presence of a group of invited guests which included David Smith, Harold Stewart and Jean Manery-Fisher who were responsible for initiating and organizing this seminal event honouring a pioneering Canadian woman biochemist.

The Editors of the Bulletin have asked me fearlessly to point out the negative aspects of the Congress and I shall try to oblige. These are not numerous and, indeed, some were not apparent until it was too late to take corrective action. With the wisdom of hindsight, it is evident that there was severe under representation of women among the symposium and plenary session speakers and Chairmen. This has been drawn to our attention not only by several women biochemists but also by Dr. Edward W. Westhead, Chairman of the Committee on Equal Opportunities for Women of the American Society of Biological Chemistry. I raise this question not to throw stones at others or to flagellate myself for that matter. I do so to emphasize that in planning future scientific programmes, our Society must fact squarely me phenomenon of the relative invisibility of excellent scientists of the feminine persuasion. The invisibility is, of course, self-perpetuating, those at the Congress who will be planning the next one will naturally think of inviting those whom they heard present outstanding papers at this one and so on ad infinitum. Unless we break with tradition and confront this problem, outstanding women scientists will continue to remain invisible and inaudible.

Only at one point during the Congress did I fear that disaster might overtake us. This was during the so-called Canada night; had a rainstorm - such as that of the day before- occurred as indeed seemed likely, it would have converted Black Creek Pioneer Village into a mud swamp and I hesitate to think of what the hungry and thirsty would then have said or done about their $16.00 investment in what was billed as a subsidized affair. As it was, only the heroism of Ken Charbonneau saved the day; he borrowed as much cash as he could and went off into the gloaming to fetch the foaming and this prevented a riot. However, everyone survived and those addicted neither to drink nor to food may even have enjoyed it.

The other negative comment heard during and after the Congress was that one was simply overwhelmed by the simultaneous symposia and poster sessions scattered among the five down-

town hotels. I had already dealt with this argument in an article in Trends in Biochemical Research (TIBS, January , 1979) pointing out the frustration of excess choice on the menu was a necessary consequence of the determination of the Programme Committee to cover all the major frontier areas of biochemistry in a five-day meeting. Agonizing choices among competing attractions are a necessary, if disagreeable, feature of large and comprehensive triennial congresses of this sort. I did not hear the complaint that important subject areas had been omitted entirely; that would have been a more serious matter.

The key question to be asked and answered is this: what did we want from the Toronto Congress and did we get it? I was never in any doubt as to the reason for which the Society wished to persuade the International Union of Biochemistry to hold the eleventh Congress in Canada. Our main motive was to improve the image of Canadian bio chemistry, and of Canada itself, in the world scientific community; in other words, the vast amount of effort that went into the organization of the Congress was an exercise in public relations, a way of telling the world that Canadian biochemistry had come of age. Was this effort a success, was the goal realized? The answer is plainly yes; not only did our foreign colleagues see that Canadian science was world-class, but more important, Canadian scientists themselves were able to see this for themselves. This is surely one of the major and long-lasting benefits of the exercise; by itself it justifies the massive effort that went into the Congress.

Let me conclude this retrospective article by a few reflections about the image that Canada presents to the work and to itself. Everyone knows that we are basically a nice, clean, respectable and well-meaning people with a high standard of living and with some of the technological expertise of the Yanks without being pushy or too aggressive. Alas, the image includes quite a few entries on the negative side of the ledger as well: the Canadian, it is said, is grim in his pursuit of mediocrity, he lacks humour, warmth, culture, generosity of spirit, savoir faire and savoir vivre, and so on. There is probably a measure of truth in this unflattering image ; indeed, the hysterical adulation of our new Prime Minister in 1968 seemed to suggest that he (He) was supposed single-handedly to relieve us of it. Whatever the truth of the matter, I believe that there was a clear, if subliminal, determination on the part of many Executive and General Planning Committee members that these unhappy criticisms would not occur to anyone, foreign or Canadian, who attended the 11th Congress. In this I believe we were successful; I do no more than repeat what many biochemists from all over the world have told me and written me: delegates and their spouses were charmed and delighted by the way in which the Congress was organized and by the Congress people with whom they came in contact.

To come now to the (quite literal) bottom line of the Congress, it is now evident that there will be a substantial surplus of revenues over expenditures. At our annual meeting in Toronto the argument was put that any substantial surplus should be parcelled out to those who paid the full registration fee, in the form of a rebate. I expressed my strong opposition to this view at our meeting and I repeat it now; had we not received gratis the services of Ken Charbonneau and his team, we would have required at least $100,000 in order to buy the equivalent, a point which I have made in a previous issue of this Bulletin (15, No.2, November, 1978, 1-4). In other words, no NRC Conference Services, no surplus. Hence, the excess revenue should remain in Canada; the altruistic might justify returning it to the N.R.C. but I wish it to go to support the educational and scientific programmes of the Society where it will produce maximum benefit for Canada. The Council of the Society has already declared at its meeting of June 8th, 1979 that it recognizes its obligation to the international community of biochemists, and in particular to replenish the travel funds of the I.U.B.; the Society also recognizes its responsibilities vis-a-vis our Latin American colleagues and will look favourably on educational exchange schemes to increase the number of Latin American scientists trained in Canadian biochemical laboratories. The Council also agreed with my view that mon-

eys which we inherit from the Congress should be regarded as a precious patrimony, a fund to be carefully husbanded and to be used for the benefit of future generations of Canadian biochemists. Judicious use of our patrimony will give the Canadian Biochemical Society the opportunity and the challenge of becoming a dynamic force in world biochemistry and a centre of excellence and excitement in Canadian science. Let us rise to this opportunity! Here is the challenge to future leaders of our Society!

I wish to express my pleasure at working with people like Connell, Colter, Painter, Charbonneau and the other members of the Executive and General Planning Committees and my gratitude to the members of the Canadian Biochemical Society who, by confiding in me the leader ship of the Society during the year of the Congress, gave me the opportunity to participate in its organization and to make a small contribution to its success. It was one of the most moving and satisfying experiences of my professional life.

## DR. A.L. LEHNINGER

Symposium Speaker and Poster Presenter
Chairman, Department of Physiological Chemistry, The Johns Hopkins University, Baltimore, Maryland

The reactions of participants to the XI International Congress of Biochemistry in Toronto, 1979 will inevitably be conditioned by their personal scientific histories and by their expectations of scientific meetings. Because it was my ninth successive IUB Congress the invitation to comment on the Toronto Congress evoked a retrospective view. The first Congresses I attended came in a more impressionable period of my career. They were characterized by the great excitement of presenting my work to an international audience, the privilege of meeting famous elders, and the pleasure of making friends of my own scientific generation. As I attended subsequent Congresses some of the novelty wore off, but I have always found them interesting and the triennial change of scenery enjoyable.

Some years ago I began to feel skeptical, as did many others, about the future viability of traditional international congresses. The increased opportunities for younger biochemists to attend meetings and to communicate their work, the greatly increasing number of specialized international symposia and conferences, the increasing depth of biochemical knowledge, and the ever-widening scope of biochemical inquiry into biology, medicine, agriculture, and technology, all seemed to militate against the traditional broad-spectrum international congress. But the Congresses of Biochemistry have weathered a period of skepticism and, if anything, seem to have gained a healthy "second wind".

Now, what about the Toronto Congress? In short, I found it to be excellent, the best I have ever attended, given my personal set of Congress experiences, perceptions, and prejudices. And in saying this I mean no slight to our former hosts in Germany, Sweden, Japan and other countries; each Congress was to me memorable.

In the first place the Toronto Congress was certainly one of the easiest to enjoy, in the sense that everything ran smoothly, meeting rooms were appropriate in size and facilities, travel between hotels and meeting places was rapid and well-organized, restaurants were excellent and the hotels were comfortable. Remarkably, those among the Canadian organizing group whom I know seemed relaxed and worry- free, the sign of a well-organized effort.

Scientifically, and here I can speak only of the fields that interested me in particular, I found the Symposium programs well chosen, the papers extremely well prepared and presented, and the audiences interested and enthusiastic. The number of poster papers that I found of interest was very large and of high quality , with much informal discussion. I believe them to be infinitely superior to the drone of ten minute platform papers in darkened halls. It was my perception that there was more intense scientific participation and involvement than in most Congresses I have attended.

Third I had an impression that, on the average, the Symposium speakers selected by our hosts seemed to represent a very fair distribution of

prime movers in their respective fields, regardless of age and country of origin. I believe the Congress speakers presented some of the best work of the times, although I know that many others not invited deserved star billing as well.

Fourth the choice of Schatz, Skulachev, and Katchalsky as evening plenary speakers, was absolutely brilliant and provided an interesting mix of science, personalities, and history, something for everyone.

The few shortcomings in the XI Congress I noted were technical in nature, and general to all large meetings of this sort. The most important, scientifically speaking, was really caused by an embarrassment of riches. Quite simply, there were so many excellent poster papers in the sessions of interest to me that there simply was not enough scheduled time for me to visit more than a small fraction. From my abstract book I have reconstructed the situation. The Tuesday morning poster sessions on electron transport contained altogether 60 papers. As it happened, two papers from my own laboratory were also scheduled then. It was all I could do to handle the discussion of one of our papers, leaving little opportunity to examine and discuss the great many interesting posters from other laboratories scheduled that morning. Possibly this problem was not typical of all the poster sessions, but in this special case it was remarked upon by many individuals in my hearing. Poster sessions have proven their great value, not only in our Congresses, but also in FASEB and FEBS meetings. Perhaps there is no easy solution to this scheduling problem, which also probably has space constraints.

A second problem concerns the many "satellite" meetings before and after the Congress, which seemed to me to have reached an apogee in 1979, which I realize are beyond the control of the Congress hosts. Such extracurricular meetings represent a magnificent (and economical) opportunity for much more detailed discussion and communication in special fields of biochemistry than can ever be accommodated by the Congress program itself. Moreover, such satellite meetings have often aided significantly in the birth of important new fields or sub fields of biochemistry. This year I was invited to a grand total of five such meetings, which together with the Congress, were held within a period of 27 days. All I attended were excellent, taken singly. But there was over lap and duplication; more than one jaded biochemist may have wished to be back in the lab. Satellite meetings have become a standard and important add-on to our Congresses. While it is unlikely that they will often be quite as numerous, one might wish for some improved coordination of these events in the future.

It is cavalier for me to say I heard mixed comments on the Canada Night outing. I personally enjoyed the occasion very much, but it is clear that such a large social party presents almost insuperable problems for Congress organizers anywhere. Our Canadian hosts were very generously endowed with a very large and attractive outdoor setting for the occasion, which for all was a welcome change from the hotel and city ambiance. But I suppose there is almost no way in which hordes of very thirsty and hungry biochemists can be accommodated without long lines. Nor can one expect Cordon Bleu fare. Canada Night had its very bright moments and lively music, but let us all hope that the advance party of Australian observers was making copious notes on the beer supply. Who knows, we may look forward to an "Out-back Outing" in 1982!

To my Canadian hosts I say again that it was the finest Congress I have attended and offer my thanks and congratulations on such a superb effort.

# China and the IUB(MB)*

## Invited Essay

**Dr. William J. Whelan**
Editor-in-Chief, IUBMB Life,
University of Miami School of Medicine.
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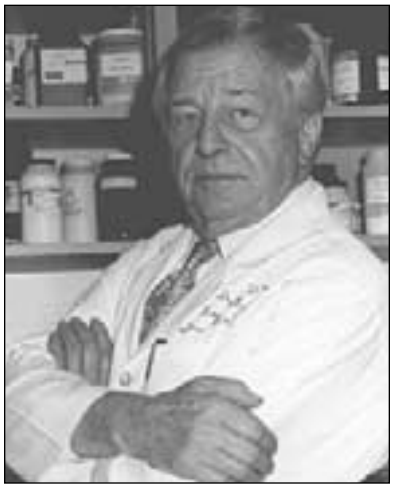
This is an account of science politics that centred on the International Congress of Biochemistry in Toronto in July 1979 that has previously been told only in part. I shall use the opportunity afforded by the invitation to write something about that Congress to put this in the public domain.

It concerns the successful negotiations to readmit a representative body of biochemists from the People's Republic of China (PRC) as an Adhering Body of the International Union of Biochemistry (IUB, now IUBMB). Adhering Bodies are most commonly the National Academies or Biochemical Societies of a particular region, which constitute the General Assembly, the governing body of the Union. In 2002, there are approaching 70 representations, although a number of them are Associate Adhering Bodies, smaller communities that do not pay an annual fee or exercise a vote.

An account of these negotiations has already been published by the author and E.C. (Bill) Slater (Slater, E.C., and Whelan, W.J. III-V. (1980) China to rejoin the IUB.( TIBS, 5, 1). This explained how the problem began and how it was solved, but lacked the details of what were sometimes hectic negotiations. The initial events parallelled a decision in the United Nations, where the PRC (mainland China) was successful in bringing about the expulsion of the Republic of China (Taiwan), and its replacement by the PRC, which has always claimed that its authority extends over Taiwan.

Similarly in the scientific community, where governance is exercised by Unions such as the IUB, collected together in the International Council of Scientific Unions (ICSU), the PRC demanded the expulsion of Taiwan where Taiwan was in separate membership. The IUB admitted Taiwan as a separate member in 1963, resulting in the withdrawal of the Academia Sinica, representing the PRC, in 1965.

In 1967 the IUB moved to try to make it possible for Taiwan and the PRC both to be represented, by redefining its Adhering Bodies, which were now not to be countries, but scientific communities of a country or a defined geographical area that has an independent budget for scientific purposes.



No more was heard on the question for about 10 years. Mainland China was undergoing the Cultural Revolution which greatly restricted the contacts of mainland Chinese scientists with their colleagues abroad. Towards the end of the 1970's, representations from the PRC began again and in two ICSU Unions Taiwan was replaced by the PRC. ICSU proposed a formula for representation of scientific communities similar to what had been done in the IUB and recommended that members be listed under a name that will avoid any "misunderstanding about the territory represented". In the spring of 1979 I, as the General Secretary of the IUB, received a request from the PRC for re-admission to the IUB in the guise of a new body, the Chinese Biochemical Society, that was about to be formed. The proposal was coupled with the condition that separate membership from Taiwan should cease.

While welcoming the approach, the IUB Executive Committee took the line that the Statutes, as modified in 1967, did not justify this latter request. It was at this point that the detailed negotiations began. We needed to act rapidly, if possible, because it was in Toronto, in July, that the General Assembly would meet, and the situation could be discussed. The Assembly ordinarily

meets only each three years, during the Congress.

Slater and I accepted an invitation to Taiwan and travelled to Taipei in June 1979 to discuss the matter with representatives of their Academia Sinica. After several days of discussion it became clear that no-one in Taiwan saw any prospect of reaching an accommodation. I recall a feeling of despair while sitting in the Grand Hotel, Taipei, waiting for our hosts to take me to the airport for the journey home. But, as I waited, two thoughts came to mind, One was having seen the letterhead being used by one of the Taiwanese biochemists in which his address was given as Taipei, China, not the almost universal Taiwan, Republic of China. It occurred to me that "China" could be used as a description without any political connotation.

I took out a yellow pad, which I still have, on which I wrote:

"For the time being there will be two Adhering Bodies from China".

If all parties could agree to this, then the Society being formed on the mainland could be admitted to the IUB while, following the suggestion made by ICSU, a body representing biochemistry in Taiwan could be formed and have a non-political name.

The IUB Executive Committee agreed to this proposal, though I recall that in the days immediately before the Toronto Congress I was still missing the vote of the President of the IUB, Alexander Bayev. Coming from Moscow, would he go along with a proposal which involved our disagreeing with mainland China about the expulsion of Taiwan? He did.

The next step was to learn the opinions of the representatives of mainland China and Taiwan. To our delight, mainland China dropped its insistence that Taiwan be expelled. It was now all up to the Taiwanese.

Negotiations began in earnest once we had all assembled in Toronto for the Congress and continued through the early hours of the day when the General Assembly was to be held in the afternoon. I woke up my wife at 4:30 a.m. to tell her that we had reached agreement, only to learn after little sleep that the Academia Sinica in Taipei did not agree with what we had negotiated with its delegates.

It became clear that everything hinged on the name to be given to the Body ( a Society, replacing their Academia Sinica) that would in future represent Taiwan. Slater and I got in touch by phone with the Foreign Secretary of the Academia Sinica, Taipei and after about an hour of sometimes heated discussion, with the General Assembly about to begin, finally agreed on a form of wording that could be put to the delegates to the Assembly. They agreed with the proposal and immediately after the Assembly ended they remained, so that Wang Yin-lai, one of the two delegates from the PRC, could address the Assembly at that historic moment. The final resolution did not, however, end there on 11 July. The precise name of the Body from Taipei was still a sticking point. About seven weeks later, in August, after a visit by me to Beijing and two visits to Taipei, I was joined by Slater in Taipei and a nomenclature was finally agreed. Then the Society from the PRC was admitted to membership of the IUB, following a mail ballot of the Adhering Bodies on the final terms of the agreement.

As a footnote, during these travels, that took me around the world twice in 3 weeks, I picked up an amoeba, which laid me low for the whole of September.

The 1979 IUB agreement was immediately adopted by two other ICSU Unions, while ICSU itself adopted a similar formula in 1982. In 2002 mainland China and Taiwan are separately represented in ICSU and in all but one of the 26 ICSU Unions.

"For the time being" has now lasted for 23 years.

**This article has been solicited by the Editors. Dr. Whelan has had a distinguished career as a researcher, Editor In Chief of a number of Scientific Journals (TIBS, 1975-78, BioEssays, 1983-88, FASEB J. 1986-), IUBMB Life, 2000 -) and Member of the IUBMB Executive: Secretary General, 1973-83, President, 1997-2000*).

# The History of Biochemistry at the University of Toronto


## Dr. Marian Packham

Department of Biochemistry, University of Toronto


Over the years University Professor Emeritus Marian Packham has assumed the mantle of "Official Historian" of the Department of Biochemistry. Recently, she has taken on the task of writing a Departmental History and, on the occasion of the XIX International Union of Biochemistry & Molecular Congress which will take place in Toronto July, 2003, she has kindly provided an abridged version for inclusion in the Bulletin.

University Professor Emeritus Marian Packham

The Department of Biochemistry at the University of Toronto was founded in 1907-08, with Prof. Archibald Byron Macallum, who was head of the Physiology Department, as its first chairman. It was the first biochemistry department in Canada and one of the first in the world. Prof. Macallum is credited with the organization and extension of the Medical School at Toronto in the early 1900's and he was a strong advocate for the construction (1902-1904) of the original Medical Building, on the third floor of which the Department of Biochemistry was housed for 60 years.

Macallum's research was influential in its time. He contributed to the knowledge of the localization of calcium, potassium and iron in plant and animal tissues by microchemical tests, and his comparisons of absolute and relative concentrations of the inorganic elements in sea-water and in the body fluids of many animals supported the concept of the origin of land animals from the sea. He received the unusual honour, for a Canadian, of election to Fellowship in the Royal Society of London. He was part of a small group who organized the American Society of Biological Chemists, was active on the executive of the Society and served as its president from 1911 to 1913 at the time when the Federation of American Societies of Experimental Biology was created.

Between 1919 and 1951, the Department had only two chairmen, Andrew Hunter (1919-1929) and Hardolph Wasteneys who had joined the Department in 1917. A Department of Zymology, formed in 1919 under Prof. Horace Speakman, merged with the Biochemistry Department in 1929.

In Andrew Hunter's time, biochemistry was mainly the servant of clinical medicine, with emphasis on chemical analysis of tissues, urine and blood in health and disease. His monograph on creatine and creatinine was a definitive work before the discovery of phosphocreatine.

Wasteneys (1929-1951) was interested in the synthesis of protein, before the days of tRNA, mRNA or ribosomes. His main collaborator in the field was Henry Borsook who worked with him during the 1920's. They investigated conditions that would reverse the proteolytic action of pepsin.

During the 1930's, Wasteneys brought a succession of professors from the U.K. for short terms. Among these was Guy Marrian whose work with his graduate students on the isolation and structure of estrogenic hormones received world-wide recognition. During World War II, many members of the Department were engaged in secret projects for the Department of National Defence, including work on BAL (British Anti-Lewisite), an antidote to mustard gas. In connection with the war effort, radioactive sulphur was used in the Department in 1941; these experiments were one of the earliest applications of the radioisotope technique that became a major tool in biochemical research.

Because of the depression of the 1930's and the war years, the Department grew very slowly and in 1950 there were only 5 professors on the staff. Nevertheless, by this time 75 Masters degrees and 59 Ph.D. degrees had been awarded and many of the graduates went on to professorial positions in the biochemistry departments and life science departments that were being established throughout Canada, the United States, and other countries. One of the earliest Ph.D. students in the Department of Zymology was Arthur Wynne who became a professor in Biochemistry upon the merger of Zymology with Biochemistry in 1929 and remained in the Department until his retirement in 1960, serving as Chair from 1951 to 1960. In 1958 he was elected as the first president of the Canadian Biochemical Society, which had been formed as a result of the deliberations of an unofficial committee chaired by Gordon Butler, at that time a professor of Biochemistry at Toronto.

Jeanne Manery Fisher was the first woman to achieve professorial status in the Department. In 1932 she graduated from the Biological and Medical Sciences course given by the Department of Biochemistry at the University of Toronto and after obtaining her Ph.D. in Physiology, and post graduate studies in the United States, she returned to the Department in Toronto in 1940. Although she carried heavy teaching responsibilities and established an active research program, prejudices against women academics prevailed and she was not appointed to the professorial staff until 1948. She maintained her research program until her death in 1986, and achieved world wide recognition for her studies on electrolytes, during the development of this field from doubts about the reality of a true plasma membrane to the isolation from the membrane of the key molecule involved in transporting Na+ and K+ across cell walls. Very aware of the need to increase the visibility and participation of women in the Canadian Biochemical Society, she was instrumental in establishing its Equal Opportunities Committee in 1981. Following her death, the Society established the Jeanne Manery Fisher Lecturer Award to honour her memory.

Gordon Butler was a professor in the Department for 12 years (1947-1959) and with his 19 graduate students initiated and carried out a ground-breaking research program on what was then known as thymus nucleic acid. According to TIBS (4, June, N124) their contributions included introduction of the light-scattering method for measuring the molecular weights of DNA molecules; introduction of the 'SDS method' as a general procedure for preparing DNA; introduction of a method for effecting a quantitative conversion of DNA to its constituent 5'-deoxyribonucleotides; discovery that there are enzymes that can degrade DNA by an 'exo' action at the termini of polynucleotide chains; definitive characterization of 2-deoxy-D-ribose as the sole sugar component of DNA; and introduction of the gel-electrophoresis approach for separating nucleate-associated proteins.

Charles Hanes joined the Department in 1951 and chaired it from 1960 to 1965. During his term, money became available to add 9 new professors to the core staff and to appoint 3 part-time tutors for the laboratory classes. He was responsible for introducing the procedure of appointing the Departmental chairman for a 5 year term (renewable once) instead of the chairmanship being a "life sentence".

Before coming to the Department, Hanes had become well known for his discovery and initial characterization of plant phosphorylases and had been involved in the development of paper chromatography for the separation of phosphoric esters. In Toronto, he refined this technique and

applied it to the separation of amino acids and peptides. In his laboratory, diverse products of transpeptidation were characterized and quantitated, kinetic studies were carried out of sucrose phosphorylase and alcohol dehydrogenase, and elastase was used to investigate the structure of elastin. Hanes' first two graduate students in Toronto were George Connell and Gordon Dixon, both of whom produced Ph.D. theses on transpeptidation reactions, later joined the professorial staff of the Department, and then went on to more and more illustrious achievements. When they were in the Department, their research on the chemistry of haptoglobulins and immunoglobulins led to the development (with Oliver Smithies) of the technique of starch gel electrophoresis which was widely used for many years.

In addition to his research program on the structure and function of antibodies and enzymes, George Connell chaired the Department from 1965 to 1970, held major administrative positions at the University of Toronto, was president of the University of Western Ontario from 1977 to 1983, and president of the University of Toronto from 1984 to 1990. Upon his retirement, generous donations were made to establish a lectureship in his name to support a visiting lecturer each month.

The 1960's were good years, with funding for a new Medical Sciences Building, completed in 1968, new equipment, and new staff. As the members of the Department moved into the fifth floor of the new building, there were few regrets to leaving behind the cockroaches, mice, mercury in the cracks between the floor boards from the van Slyke equipment, inadequate cold rooms, and lack of air conditioning. Space was also available for the members of the core Department who had had laboratories in a building on Spadina Avenue. The professorial staff was expanded by introducing the practices of giving cross-appointments to members of other departments such as the Banting and Best Department of Medical Research, and of making honorary appointments of some members of the research institutes, particularly at the Hospital for Sick Children. As a result, the graduate student population increased enormously, to 70 students in 1970. Fearing that there would not be positions for the anticipated large numbers of new biochemists since the graduate student population at other Canadian universities was also expanding, the graduate students persuaded the department to limit each professor to no more than 2 graduate students at any one time (previously, 5 or 6 had been the norm). However, this restriction lasted for only a few years.

In the early 1970's, undergraduate instruction in biochemistry for Arts and Science students was greatly increased to include students in disciplines other than biochemistry, as well as larger numbers of biochemistry specialist students. The Department continued its teaching responsibilities for medical students, and took major roles in a new 'systems' curriculum introduced at this time.

G. Ronald Williams chaired the Department from 1970 to 1977 and later continued the involvement of Toronto biochemists in major administrative roles as Principal of Scarborough College. During his chairmanship, research blossomed and on 3 occasions, members of the Department received Canadian Biochemical Society Ayerst (Merck-Frosst) awards. In response to the student unrest of the 1960's, a Departmental Constitution was written, a Departmental Council with broad representation was established, and a graduate student organization was set up to co-ordinate graduate student activities in the Department. This Biochemistry Graduate Students Union (BGSU) is very active to-day, coordinating the student seminars and organizing social events.

In the 1970's, there were 27 appointments to the professorial staff, 8 of these to the core Department, but during Keith Dorrington's chairmanship (1977-1982) repeated cuts of the Departmental budget almost eliminated new appointments to the core. Dorrington's work after joining the Department in 1970 focussed on the structure and function of immunoglobulins and resulted in an Ayerst award in 1977. He was another biochemist with administrative talents and served as Vice Provost, Health Sciences and Associate Dean, Basic Sciences, in the Faculty of Medicine.

In July of 1979, the XIth International Congress of Biochemistry was held in Toronto with 7500 scientists in attendance. The 75th anniversary of the founding of the Department was held in 1983 during Marian Packham's term as Acting Chair. The activities included a symposium, an Open House, and a banquet in Hart House at which Dr. Thomas Jukes (Ph.D. 1933) was the keynote speaker. The 320 registrants, many of them former students, came from across Canada and the United States.

Harry Schachter became chair in 1984 for a 5-year term. He had been Gordon Dixon's first graduate student in Toronto and had been immediately appointed to the core professorial staff upon completion of his Ph.D. in 1964. Well before becoming chair he had gained international recognition for his studies of the complex structures of the oligosaccharides of glycoproteins. As an emeritus professor of Biochemistry, he continues his active research program at the Hospital for Sick Children where he moved in 1976 and, for a number of years, chaired the Division of Biochemical Research.

A recurring theme in the Department's history is the choice of members from our core for major administrative roles elsewhere in the University; some of these have been mentioned earlier. In 1989, for example, George Connell was President of the University, G. Ronald Williams was Principal of Scarborough College, Robert Painter was Provost and Vice Chancellor of Trinity College, and Anders Bennick was Chairman of the Graduate Department of Dentistry.

From 1989 to 1991, search committees were repeatedly unsuccessful in attracting a chair from outside the University of Toronto while William Thompson served capably as Acting Chair. During this time, the Protein Engineering Network of Centres of Excellence (PENCE) was set up and Toronto became one of the four academic centres participating in it. Professors Emil Pai and Harry Schachter became co-leaders with 9 professors in Biochemistry participating. A protein crystallography centre was established in the Department, also under the direction of Emil Pai.

In 1991, Peter Lewis, who had joined the Department in 1974, was chosen as Chair. He served two terms, during which major changes were made in staff and in the focus of the research being carried out. The hiring frenzy of the 1960's inevitably resulted in a large number of retirements in the 1990's – 9 professors from the core department and 5 status-only and cross-appointed professors. Despite base budget cuts, the department was able to recruit 8 core department primary appointees and 9 status only or cross-appointed members, bringing the present total to 55, with 20 of these based on the campus. Credit for this renewal into a vigorous and youthful department belongs to Peter Lewis who was exceptionally active in finding opportunities for growth and arranging joint appointments with sister departments. In 1993, the installation of a 600MHZ NMR instrument in the Medical Sciences Building facilitated the research of newly recruited Julie Forman-Kay and Lewis Kay. Faculty "Retreats" in 1993 and 1998 ensured that all members of the Department participated in planning. Decisions made during this time resulted in at least half of the departmental members focusing their research activities on proteins, including structure determination, dynamics, in vitro and in vivo folding, proteomics, and structure-function studies. A highly-rated Collaborative Program in Biomolecular Structure has been set up involving 25 investigators from four departments. This program is designed to provide a stimulating training environment for Ph.D. students and serve as a forum to foster interactions among the participating research groups. The three focus groups are Protein Crystallography, NMR, and Protein Folding.

In 1998, a new multi-departmental program in Proteomics and Bioinformatics (P&B), with Peter Lewis as director, was initiated. Some of the new members of the Department of Biochemistry were hired through this program.

The present Chair, Reinhart Reithmeier, began his term in July of 2002, taking over a Department filled with enthusiastic, award-winning researchers and teachers. Instruction is provided for the education of students in the Faculties of Medicine, Arts and Science and the School of Graduate Studies.

The annual enrolment in all these courses exceeds 1800 students. Biochemistry courses for undergraduate students in the Life Sciences are offered during the second, third and fourth years; courses on special topics are available to graduate students.

The Department is geographically diverse with faculty based in the Medical Sciences Building, the Research Institute at the Hospital for Sick Children, the Banting and Best Department of Medical Research, and several other sites, including the University of Toronto at Mississauga and at Scarborough.

Many members of the Department have received prestigious awards for their research. Fifteen of them were or are Fellows of the Royal Society of Canada. Among them is David MacLennan of the Banting and Best Department of Medical Research who has been an active cross-appointed member of the Department since 1980; his long list of prizes includes appointment in 2002 as an Officer of the Order of Canada for the investigations in his laboratory of how normal sarcoplasmic reticulum proteins carry out their functions of calcium transport, sequestration and release and how mutant forms cause abnormalities or disease.

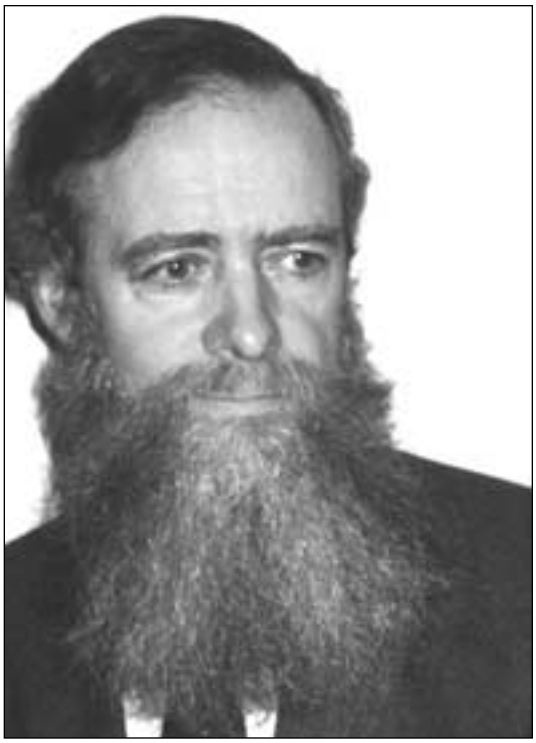
It remains for later historians to document the impressive achievements that our younger members are in the midst of accomplishing. As we approach our 100th anniversary, we look forward to an even greater future for the Department of Biochemistry in the Faculty of Medicine at the University of Toronto.

# DNA 50 Years After: A Personal Perspective


## Dr. David Pulleyblank

Department of Biochemistry, University of Toronto


50 years ago a trio of brief papers in Nature exposed the mechanism underlying Darwin and Wallace's theory of evolution and offered explanation for the experimental results of Mendel. Society has never looked back. These papers changed our understanding of our biology and of our relationship to the natural world. Although it is often said that these papers presented the discovery of the structure of our genetic material: DNA they in fact simply presented a culminating flash of insight that followed almost a century of investigation. I recently asked a third year undergraduate audience to the name the discoverer of DNA. I was surprised when several among them assured me that (he) had in fact been Watson and Crick. Only one ventured the correct name of Meischer. Their embarrassment deepened when I asked them to name those involved in elucidating the structure of DNA. Several, who once again assured me that Watson and Crick had been alone, reddened when when I rephrased the question and asked who had been awarded the Nobel prize for the discovery. They added the name Wilkins - of course they knew it - and some were even aware of the controversy surrounding the treatment given Rosalind Franklin – but only from the less than objective account given in Watson's "Double Helix". None were aware of the essential groundwork done by Nobel laureates Fischer, Kossel or the Braggs. Nor were any aware of the work of Levene, Astbury, Gulland or of others upon whose contributions Watson and Crick directly built their own - and who might with luck and added longevity have won that prize for themselves. Even Erwin Chargaff and Linus Pauling, the quasi and actual Nobel laureates whose contributions were fundamental and who were fixtures on the international stage until the very recent past did not achieve a mention. The current generation has all but forgotten that Levene had worked out the structure of the DNA polynucleotide strand more than a decade before the Nature papers. Although he correctly established covalent linkage of base, sugar and phosphate he was trapped by his technology. With dogmatic determination he asserted the structure to be a simple tetranucleotide. Two generations before Levene's work Meischer had understood DNA to be very large and had even discussed the complexity that could be generated by combinatorial assortment of a limited number of monomer units. Although insightful, without the benefit of knowing Mendel's work or the results of the painstaking analysis by the organic



chemists Meischer could not have made the next great leap. Griffiths and later Avery with McLoed established the ability of high molecular weight DNA to transfer a genetic trait and incidentally performed the first cloning experiments.

It was only one vitally important detail that was presented in the Nature papers – the helical paired antiparallel arrangement of the DNA stands. Even that was more a matter of conjecture than proven fact. The specific pairing of the bases and the antiparallel arrangement of strands were fortunate guesses but they provided a mechanism for both the replication of genetic information and the occasional variation that provides a basis for natural selection. The thin evidence of helicity and base stacking provided by the initial fibre diffraction patterns required almost two decades of refinement before the models could be considered finished. Almost as soon as this had been done Donohue, piqued by the failure of the community to grant adequate recognition to his role in informing Watson of the correct tautomeric forms of the bases, challenged the legitimacy of the interpretation and offered an alternative model. By that time the weight of accumulated evidence did strongly favour the revised Watson-Crick models – but the evidence of 1953 could as easily have been interpreted in terms of the straw man offered by Donohue.

I grew up in Cambridge, the son of a Canadian Don whose unlikely field of study - Chinese history and linguistics -brought our family into even more unlikely contact with the eminent sinologists: JD Bernal and Joseph Needham who had converted from biochemical science. The excitement surrounding the newly proposed model for DNA was inescapable. While still a high school student I attended the 1966 meeting of the British Association for the Advancement of Science where Watson and Crick each made an appearance for the benefit of interested members of the public. Crick and Brenner's work defining the triplet basis of the genetic code was still fresh and the code itself was still being worked on. From the audience an elderly professor of Zoology scolded the heroes of the moment for their mistaken belief that a molecule with the simplicity of DNA could possibly encode life – only proteins had the needed complexity! Of course he was right. Sadly, it is unlikely that the gentleman lived to see the developing revolution in the byway of epigenetic inheritance. So easily do we forget, that while DNA may serve as library for genetic information, a library is not a society of learned readers. That same meeting provided opportunities to visit the Cavendish laboratory where I squinted at a homebuilt X-ray camera and a sensual 8A balsa model of myoglobin. Physically far more impressive was the Mullard Cambridge Observatory where the brightly coloured ink was still fresh on the skymaps of Quasars 3C48 and 3C273 and where the meaning of their redshifts were being actively debated. At that meeting Fred Hoyle was still confidently defending his steady state model of the Universe. The announcement of the first pulsar was only months away. To a high school student with the hope that science was a place where one might mark the world this was heady stuff. A visiting family friend later provided an opportunity to visit the nuclear accelerator at Harwell and even peek into the room where the Atlas computer – then one of the largest (and least reliable) in the world was – once again being given an overhaul. Its hand built core memory, knitted together from tiny ferrite rings, each capable of holding one bit of information, was out and being worked on.

I remember trying rather unsuccessfully to present the ongoing work on the genetic code to the members of my all boys high school science club. For them the Chemistry of Genetics was a matter of testosterone enforced practical concern rather than a subject for academic study. The subsequent year that I spent teaching at a village high school in India under the auspices of the British Voluntary Service Overseas organization brought home the international nature of the Scientific endeavour and of the pride that came with having a shared cultural background with a famous contributor. The name of Har Gobind Khorana was known to all the students and teachers at that unsophisticated village school, although none had any idea of the nature of his contribution. Little did I then know of the indirect but profound influence that H.-G. Khorana would soon play

upon my own life. Upon completing my year I joined my family who had in the meantime returned to Canada, and enrolled in the Biochemistry program at the University of British Columbia. I chose the program because of the high excitement that surrounded the recent elucidation of 'the code". Two members of that Department, Michael Smith and Gordon Tener had trained directly under Khorana while he worked at the BC Fisheries Research Board. It was in my final year as 4'th year project student that Khorana spent a sabbatical year at UBC and had the pleasure of being almost knocked over by myself, wine glass in hand, while celebrating some now forgotten success of one of the Dixon lab's graduate students. Soon after, beginning graduate work in Edmonton I fell under the supervision of Richard Morgan who had been directly involved in the elucidation of "the code" while in Khorana's lab in Wisconsin.

By 1970, despite the enormous progress that had been made in the analysis of nucleic acids there were still many unresolved issues concerning the finer points of DNA structure, replication and transcription. DNA Polymerase I had only just been knocked off its pedestal as THE putative replicative enzyme. Okazaki fragments were about to be announced and DNA polymerases II and III were about to be discovered. The problem of establishing the sequence of a particular high molecular weight DNA molecule seemed insurnountable. It was not until 1971 that the 12 residue sequences of the cohesive ends of lambda bacteriophage were reported: a result of three years work using methods derived from the earlier sequencing of t-RNA. Gel electrophoresis was still used only for the analysis of proteins. The methods of restriction analysis, blot hybridization and cloning that underpin modern methods of Molecular Biology were yet to be invented. My graduate years were spent performing enzyme preparations – DNA polymerase I and T4 ligase, were not yet commercially available – and manning the Department's only analytical ultracentrifuge during graveyard hours whenever time became available. Closed circular DNA was not readily obtainable and the class of enzymes now called topoisomerases were still to be described. Preparation of the closed circular replicative form of phiX174 DNA was an iffy month long affair involving first phage preparations and then repeated preparative cesium chloride ultracentrifuge runs. Often at the end of the prep residual viscous cell wall polysaccharide would prevent the supercoiled DNA band from being unloaded from the gradient

My thesis topic: arose out of a controversy that developed over the handedness and magnitude of natural DNA supercoiling. Ethidium, an antitrypanosomal drug with a large planar phenathridinium ring was introduced to the study of DNA by Paoletti and Lepecq. Unlike the previously studied acridine dyes it bound DNA almost exclusively by an intercalative mode. One of the most spectacular effects upon binding was its dramatically enhanced and very pretty red fluorescence when excited by ultraviolet light. The supercoiling of circular viral DNA was first reported in 1965. Ethidium was used soon after to titrate those natural supercoils, but 1971 measurements of the fluorescence depolarization due to resonance transfer between Ethidium molecules when bound to DNA suggested that the earlier proposal that Ethidium unwound the helix had been incorrect and that overwinding actually occurred. The result was that both the magnitude and sense of the supercoiling of natural DNA circles remained controversial. By 1974 we had solved the issue by directly synthesizing negatively supercoiled DNA and in the process made the unexpected discovery that previous estimates of the numbers of superhelical turns present in all naturally occurring closed circular DNA had been too low by a factor of at least 2. As a bonus I was able to confirm the assignment of handedness of the supercoiling on the basis of the unexpected treble clef appearance of our DNA in some electron micrographs. There had also been one of those moments of private exhilaration. I had read that the ribosomal RNA's had been successfully resolved by electrophoresis in an agarose gel and detected by staining with methylene blue. Agarose at that time was a rare and precious commodity used in bead form for gel exclusion chromatography but not yet as a

support medium for electrophoresis of DNA. I scrounged an obsolete vertical mode starch gel electrophoresis apparatus and poured a 0.2% agarose gel – it was too expensive to make the gel stronger and I knew the supercoiled circles I was working with were far larger than the ribosomal RNA's that had been tested previously. The gel was too fragile to be run in the normal vertical position used for starch gels so I arranged paper wick electrodes and set the gel horizontally over the buffer chambers on the metal bench top of our cold room. Knowing the fluorescent property of ethidium when bound to DNA, I added a little to the buffer. Because of the risk that someone in authority might terminate my experiment for safety reasons – or worse, electrocute themselves - the run was started late one evening before the weekly graduate student trip to an evening of beer consumption at the Faculty club. In the wee small hours, half soused and with a hand held UV lamp I stared over the many brilliantly fluorescing bands that my supposedly pure DNA samples presented. It was both a thrilling and an apalling prospect. There was no way to record the result – the Department did not then have the kind of photographic facilities that later became standard. Without further study it was not possible to eliminate the possibility that the multiplicity of bands was some peculiar artefact. Had my supervisor been made aware of the many bands in my supposedly homogeneous samples there would certainly have been a delay before I could present my thesis. I switched the current back on and went home thinking that the morrow would resolve the matter. In a way it did. The gel had done what agarose gels always do if not adequately buffered. It had proceeded to migrate through itself to leave only a pile of compressed gel. With no more agarose and fearing the complications that had presented themselves I let the matter drop.

The following year, after starting my Post Doc at Cal Tech I took the matter up again. By then others had reported extraordinary resolving powers of agarose gels and of the sensitive detection of DNA afforded by ethidium. A whole new domain of DNA fine structure opened itself as we became able to separate isomers that differed by a single topological linking number. We initially used tube gels with the slippery agarose gel held in place by a fragment of dialysis tubing and a rubber ring. To get a flat surface upon which to layer our samples it was necessary to slide the newly formed gels out past the end of their supporting glass tubes and slice off the concave end formed by capillary action as the gel set. During runs the gels would frequently collapse or disintegrate. Sometimes a retaining ring would fall off, dumping gel and upper buffer chamber. Despite the limitations the tube gel system did lend itself to rapid experimentation with different gel consistencies and buffers. The antimalarial drug: Chloroquine, was found to allow fine manipulation of the superhelical state of plasmids and to give superior electrophoretic resolution of the topological isomers. Eventually we acquired one of the new flat plate vertical apparatuses developed by the Cold Spring Harbour Laboratory. When the glass plates were roughened by sandblasting agarose gels would sometimes remain in place long enough to allow exquisite resolution. The flat arrangement of bands also facilitated the quantitation needed to establish relationships among the various species. Upon presenting our results at a Gordon Conference we ran headlong into unanticipated controversy. Workers at Cold Spring Harbour suspected that a student from our laboratory had spied on them while taking one of their courses. It took the personal intervention of the respective resident Nobel Laureates, James Watson and Max Delbruck to restore a semblance of peace.

At that same 1975 Gordon conference the earliest versions of the modern DNA sequencing methods were announced. Chemistry dating from the 1940's had been applied to the creation of the base specific cleavage method of Maxam and Gilbert while the Sanger lab developed chain termination methods, using properties of DNA polymerase, discovered in the 1950's by Kornberg's lab. Both labs resolved their fragments using a denaturing electrophoretic technique that had been developed by Hans van de Sande and Tom Maniatis for the separation of oligonu-

cleotides. The effect of these presentations was stunning. So was the report of the first relatively rapid method for oligonucleotide synthesis developed by Narang in Ottawa. Against this background, a spectacular row over who had the correctly calibrated fragment lengths that enveloped the discussion of newly discovered ladder of nucleosomal chromosome fragments now seems a sideshow.

Although DNA cloning methods had been reported almost two years earlier, a moratorium was in force that prevented newcomers from flooding into the field. Type II restriction enzymes were just beginning to be discovered and made commercially available. Southern Blot Hybridization was also about to appear. As confidence grew the moratorium on cloning was lifted. With almost no warning we launched headlong into the breathtaking new era of genomics. Apart from the sudden flood of new gene sequences the structure of DNA presented new phenomena. Anomalies in the migration rates of DNA fragments became apparent. Voltage dependence of the migration of high molecular weight DNA was eventually recognized to be a consequence of the DNA molecules aligning themselves with the electrical field as they progressed through the gel. In the laboratory of Charles Cantor these observations became the basis of the pulse field electrophoretic separation of whole chromosomes. Other anomalies in the migration of small fragments through acrylamide gels were eventually recognized to be a result of intrinsic bending of the DNA fragments. In turn these bends were recognized as contributing to the interaction of proteins that control the expression of many genes.

Despite the sudden and dramatic progress brought about by the introduction of gel electrophoresis and cloning the other key element of the new technology: oligonucleotide synthesis was still far from routine. It was not until 1979 that an unambiguous structural assignment based on analysis of diffraction by a single crystal of DNA oligonucleotide appeared. This structure was one that left the field breathless. The strange left handed "Z" structure with its alternating syn- and anti- bases and crooked backbone was revealed. This novelty was so totally unlike the familiar A and B families that many wondered whether we did indeed know the structure of DNA. DNA was clearly far more versatile than had initially been assumed. Even the true "B" single crystal structure that quickly followed proved to contain a wealth of detail not anticipated from the earlier work using fibre diffaction. We now recognize the contributions that end effects and crystal packing forces play in distorting the structures of short oligonucleotides that form single crystals. The new reality: that naked DNA is not the simple object described in fibres under tension opened a new era in the study of the 3 dimensional structure of natural DNA sequences. In a brief period of new exploration it was found that torsion built into closed circular molecules could cause some DNA to form Z-structures and hairpins as well as other "excited" state structures that were quite distinct from the familiar A and B-DNA families. DNA triplexes and the G tetraplex had previously been described in simple DNA polymers, but it was only with their appearance as a result of strand disproportionation under environmental influence in ordinary DNA that serious attention was given to their possible roles in Biology. The G tetraplex is almost certainly involved in stabilizing the single stranded ends of eukaryotic telomeres while triplexes and Z-DNA may have transient roles accomodating superhelical torsion during replication and transcription. Even in such an apparently simple molecule as DNA, the complexities created by the competing effects of bending and twisting moments in the context of varying base sequence defy straightforward analysis. Crystal structures necessarily represents a ground state, but living systems are dynamic. Once proteins are added new deformations are imposed on DNA that wildly exceed those thus far observed in naked DNA.

Single stranded nucleic acids are far more conformationally mobile than their double stranded counterparts. We now have a growing family of well characterized RNA structures, many with special binding properties and in some cases catalytic activities. Thus far similar attributes have not been detected in naturally occurring DNA

molecules but it is likely to be a simple matter of time before this happens. Although we still have few dramatic examples of how local DNA structure is biologically important there is a widely held suspicion that evolution cannot have failed to assign function to subtle conformational effects which would reveal themselves were we able to perform experiments on the time scale of generations. With the nearly complete sequencing of human and mouse genomes a new class of conserved sequences have been discovered which appear not to be transcribed and which certainly do not encode proteins in the usual way. At the present time there are no clues to the possible reasons for the conservation of these sequences. Apart from the knockout experiments there is not even an obvious experimental route to assigning them a function. A new generation of graduate students have an adventure before them.

Often we forget that key elements in the developing story of the nucleic acids were contributed by scientists working with very few resources. Among many important Canadian contributions Gordon Tener at UBC developed a key method for purifying single species of t-RNA that played an essential role in determination of their structure. Mike Smith participated in the development of the Sanger Sequencing technique and later earned his own Nobel prize by setting forth the first site directed mutagenesis method. Hans van DeSande, in collaboration with Tom Maniatis developed the denaturing gel technique that later became a basis for both Sanger and Maxam and Gilbert sequencing methods. Narang in Ottawa developed the first rapid method for DNA synthesis that pointed the way to the later development of the phosphoramidite method. Richard Morgan in Edmonton did important work on multistranded DNA structures. Large laboratories with million dollar budgets easily overwhelm the product of isolated small laboratories once a key technique has been developed but that key initial phase of scientific invention is almost always carried out by individuals. It is tragic that in our anxiety to emulate the big science being done elsewhere, that small Canadian science has largely disappeared. Small scale science, most particularly that which is at the bleeding edge is always vulnerable to being eliminated in a bad year. Small science has given very good value for money and frequently has produced great insight.

This last 50 years coincided with the brief period in history that may mark the high point of human civilization. We careen towards an uncertain future of runaway population growth, resource depletion and global overheating. Despite the human catastrophes of the 20'th century and early 21'st, the wealth of knowledge handed us by past generations has for this brief period created a world society with the leisure to inquire into the full range of life's complexity and even approach the probable limits to knowledge of our Universe. In the flood of new information and in our rush to acquaint students with the latest results we frequently forget to tell the story of how it all came about. In the modern western world few children learn a trade or even wisdom at the feet of parents. They are instead left to pick up what they can at the hands of the overtaxed schools. Few of them have the patience or time needed to search the older literature buried in the deeper stacks of our libraries. The oral tradition, which our forbears used to educate their young is now largely displaced by the twin cacophonies of consumer advertising and popular mass culture. We rely upon storytelling by others, either through the medium of television or through the University lecture hall to provide the younger generation with basic elements of culture. It is the duty of those still working in the field to retell this story so that some of the coming generation of scientists can continue this tradition when their time comes. Without conscientious effort, collective amnesia otherwise assigns the results of creative endeavors of the preceding many to the singular heroes of the moment.

# The 2002 CSBMCB's Merck Frosst Prize Lecture

## Dr. Jeffrey L. Wrana

Dr. Wrana obtained his Ph.D. in 1991 from the Department of Biochemistry, University of Toronto under the supervision of Dr. Jaro Sodek, head of the MRC Group in Periodontal Physiology. His graduate work which focussed on understanding how the secreted factor, Transforming Growth Factor-beta, (TGFß) altered cell function produced 15 papers, 5 as first author. He embarked on a post-doctoral fellowship programme with Dr. J. Massague at Memorial Sloan Kettering Cancer Center in New York City. While there, he made major contributions to the identification and characterization of a family of transmembrane serine/threonine kinases as receptors for TGFß superfamily members. During this time he published extensively in top-tier journals (Cell and Nature). This work culminated in his elucidation of the mechanism of Ser/Thr kinase receptor activation (Wrana et al., 1994; Nature, **370**, 341-347). This paper, in which he is first author, has been and continues to be extensively cited (around 1,000 citations to date) and is considered a "classic" in the field of signal transduction.

Dr. Wrana started his independent research program in 1995 at the Hospital for Sick Children in Toronto and is currently a Senior Scientist at the Samuel Lunenfeld Research Institute. He has continued to make significant and lasting contributions to the TGFß signalling field in particular and signal transduction pathways in general. When Dr. Wrana started his laboratory, the intracellular mediators of the TGFß pathway were completely unknown and he has made critical contributions to the identification of the Smad signal transduction pathway and towards its functional analysis. To this end, Dr. Wrana identified the first R-Smad (called MADR1 at the time) and went on to show that R-Smads are direct substrates of Ser/Thr kinase receptors. This was the first demonstration of a physiologically relevant substrate of the Ser/Thr kinase class of receptors. He also identified the inhibitory class of Smads

and identified a novel FYVE domain protein that controls Smad subcellular localization. In addition, Dr. Wrana has demonstrated the contribution of Smads in human diseases such as cancer. In his more recent work, Dr. Wrana was instrumental in the identification of the Smurf family of E3 ubiquitin ligases and he has shown that, in additional to transcriptional mediators, Smads also function to control protein turnover.

During his independent career, Dr. Wrana has received several prestigious awards. He is a 'first round' PREA award recipient and has won Scholarship and Investigator awards from the MRC/CIHR. In addition, Dr. Wrana was the first non-American ever to receive the Gertrude B. Elion Award ward in 1997, which is given to one outstanding young investigator each year by the American Association for Cancer Research (AACR). In 1998, he was also awarded the William E. Rawls prize from the National Cancer Institute of Canada and just last year won the Allan Bruce Robertson young investigator award from the Clinical Research Society of Toronto. Recently Dr. Wrana has been named a Howard Hughes International Research Scholar.

# TGFß and the Smad Signal Transduction Pathway

Dr. Jeffrey L. Wrana

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## Abstract

Transforming Growth Factor-beta (TGFß) superfamily members are important regulators of many diverse developmental and homeostatic processes and disruption of their activity has been implicated in a variety of human diseases ranging from cancer to chondrodysplasias and pulmonary hypertension. TGFß family members signal through transmembrane ser/thr kinase receptors that directly regulate the intracellular Smad pathway. Smads are a unique family of signal transduction molecules that can transmit signals directly from the cell surface receptors to the nucleus, where they regulate transcription by interacting with DNA binding partners as well as transcriptional coactivators and corepressors. In addition, more recent evidence indicates that Smads can also function both as substrates and adaptors for ubiquitin protein ligases, which mediated the targeted destruction of intracellular proteins. Smads have thus emerged as multifunctional transmitters of TGFß family signals that play critical roles in the development and homeostasis of metazoans.

## Introduction

Transforming Growth Factor ß (TGFß) is the canonical member of a large family of polypeptide growth factors. Currently there are well over 50 evolutionarily conserved superfamily members that are found in all metazoan organisms studied. Based on similarity of sequence and function, superfamily members have historically been grouped into families which include: TGFßs; activins and inhibins; Bone Morphogenetic Proteins (BMPs) and Growth and Differentiation Factors (GDFs); and more distantly related molecules such as Mállerian Inhibitory Substance (MIS) and Glial cell line-Derived Neurotropic Factor (GDNF) (Kingsley, 1994). However as a number of TGFß superfamily members have properties that span these ancestral classifications, it is likely that superfamily ligands actually belong to a continuous spectrum of related factors rather than specific families.

TGFß superfamily signals are utilized at different times and are required in specific tissues throughout development and adulthood. The label Transforming Growth Factor (TGF) was first applied to peptides that, when present in growth medium, conferred a malignant or transformed phenotype on untransformed rat kidney fibroblasts in vitro (Assoian et al., 1984; Roberts and Spom, 1985). Despite these early observations, TGF is somewhat of a misnomer as subsequent work showed it to be a multifunctional factor that regulates an array of biological processes. For example, TGFß can be mitogenic for fibroblasts, whereas it inhibits in vitro proliferation of epithelial and endothelial cells (Moses et al., 1987). During tumorigenesis and wound repair, TGFß chemoattracts and modulates the activity of blood cells (Postlethwaite et al., 1987; Tsunawaki et al., 1988). In addition, TGFß is involved in the initiation of a cascade of events that lead to neovascularization and matrix synthesis. TGFß also exerts control over proliferation and differentiation of a variety of cell types. Targeted disruption of the mouse TGFß1 gene has profound effects on the development of the immune system and the heart (Letterio et at, 1994; Shull et al., 1992). The broad range of TGFß effects thus make it a central protein during embryogenesis and development (Roberts et at, 1990; Roberts and Spom, 1987).

Other members of the TGFß superfamily are also involved in numerous biological processes. Activins and inhibins are gonad-secreted factors (Lee et al., 1989) that were first described as crucial

**Abbreviations:** (R) R-Smad, (C) C-Smad, (I) I-Smad, (P) phosphorylation, (S) Smurf, (ubiq/deg) ubiquitination and degradation.

regulators of certain endocrine functions including secretion of pituitary hormone (Ling et al., 1986). Bone Morphogenetic Proteins (BMPs), as their name suggests, were originally identified as a group of proteins that cause de novo bone formation in muscle tissue. In addition to these functions, TGFß superfamily ligands control a host of early developmental decisions and mouse knockouts of these factors have provide fundamental insights into ligand functions revealing that TGFß superfamily signalling plays important roles in almost all homeostatic and developmental processes examined (reviewed in Kluppel et al., 1999).

## Structural Properties of Mature TGFß Superfamily Ligands

TGFß superfamily members are dimeric molecules that share a conserved structure. Crystallographic analysis reveals that TGFß2 is comprised of two monomers and each monomer consists of two antiparallel pairs of ß-strands that form a flat surface and a separate α-helix (Schlunegger and Grutter, 1992). The α-helix of one subunit interacts with the flat surface of the other subunit to form active dimer. Each monomer contains four intrachain disulfide bonds and one interchain disulfide bond. Based on amino acid sequence conservation, this structure is predicted to be conserved in TGFß1 through TGFß5 (Daopin et al., 1992). Two intrachain disulfide bonds form a ring that is threaded by a third intrachain disulfide bond and this arrangement is known as the cystine-knot. Other TGFß superfamily members, including activin, inhibin and BMP7, also possess a conserved arrangement of six cysteines that likely form this cystine-knot conformation (Griffith et al, 1996). Thus, while amino acid sequences between TGFß superfamily ligands vary, dimerization and the cystine-knot are common features of these factors.

Strikingly, the cystine-knot is found in the peptide sequences of a number of growth factors. These factors, that include Platelet-Derived Growth factor (PDGF) and glycoprotein hormone, share no other sequence homology to TGFß and together they define the cystine-knot growth-factor superfamily (Sun and Davies, 1995). Interestingly, phylogenetic analysis reveals an evolutionary link between these factors and extracellular matrix proteins that also form cystine-knots (Vitt et al., 2001). Cystine-knot containing structures are not found in unicellular yeasts and this observation suggests that the cystine-knot may have evolved with the advent of multicellularity and the need for intracellular communication.

While most TGFß superfamily ligands consist of homodimers, examples of functional heterodimers also exist. For instance TGFß1.2, a heterodimer of TGFß 1 and TGFß2, has been identified in vivo and appears to display activity and receptor binding properties intermediate to those of TGFß1 and TGFß2 (Cheifetz et al., 1988b). Furthermore BMP4/BMP7 heteromers act as mesoderm inducers in frog embryos and do so at increased potency relative to either homomer (Suzuki et al., 1997). Consistent with BMP4/BMP7 action in vivo, synthetic BMP2/BMP7 heterodimers possess 20-fold the activity of either homodimer in Xenopus mesoderm induction assays (Israel et al., 1996). In contrast to enhancing activity, BMP7 can form heterodimers with Nodal and this Nodal/BMP7 heteromeric complex is inhibitory for both Nodal and BMP7 signalling (Yeo and Whitman, 2001). Such a strategy of mixing ligand monomers to achieve novel activity or varying efficacy may help to explain the wide range of TGFß superfamily effects.

## Regulation of TGFß Superfamily Ligands

Members of the TGFß superfamily are synthesized as large precursors that are subsequently cleaved to generate mature ligands. TGFß superfamily ligands are initially synthesized as 100 kDa pro-proteins that consist of an amino-terminal pro-region and a carboxy-terminal mature region (Gentry et al., 1988). The pro-region facilitates proper dimerization of these pro-proteins and these dimers are subsequently cleaved by endoproteases at a conserved RXXR amino acid sequence located just upstream of mature TGFß superfamily peptide sequence. Cleavage is thought to be mediated by furins which are proprotein convertases that process latent precursor proteins into their biologically active forms (Matthews et al., 1994). For TGFß1, the cleaved

pro-region, known as the Latency-Associated Peptide (LAP), has been shown to remain non-covalently associated with the mature peptide to form a latent TGFß1 complex also known as the Small Latent Complex (SLC). In this state, the SLC is secreted and undergoes further processing in the extracellular matrix. While SLC-Iike complexes have not been observed for other superfamily ligands, there are likely analogs as pro-regions can be swapped between ligands and can direct cleavage of heterologous mature regions (Thomsen and Melton, 1993).

## The Receptors

TGFß superfamily ligands bind a variety of transmembrane receptors. Receptors for TGFß were first characterized by studies in which radioactively labelled TGFß was chemically cross-linked to cell-surface proteins (Massague and Like, 1985). These analyses revealed that TGFß binds to three types of receptors. These cross-linked receptors segregated according to mobility on SDS-PAGE gels (Cheifetz et al., 1986) and were named type I, type II or type III receptors (Cheifetz et a1., 1988b).

## Type I and Type II Receptors

Type II receptors comprise a family of related transmembrane serine/threonine receptor kinases. Expression cloning approaches identified the first type II receptors and these preferentially bound activin (ActRII, ActRIIB) (Mathews and Vale, 1991; Mathews et al., 1992) and TGFß1 (TßRII) (Lin et al., 1992) respectively. Cloning and characterization of additional type II receptors, including those which selectively bind BMPs (BMPRII) (Liu et al., 1995) and MIS (Baarends et al., 1994), reveals that together they comprise a family of highly related serine/threonine kinases. Type II receptors are glycoproteins of approximately 70 kDa. Type II receptors consist of a cysteine-rich extracellular domain, a single-membrane spanning domain and an intracellular serine/threonine kinase domain that is followed by a serine/threonine rich C-terminal extension. In most type II receptors, the kinase domain is capable of autophosphorylation on serine and threonine residues in vitro and is constitutively active.

Similarly, type I receptors comprise a family of related transmembrane ser/thr kinases. Use of degenerate primers directed against ActRII identified a number of type I receptors that were called activin receptor-like kinases 1:.4 or ALK1-ALK4 (ten Dijke et al., 1993). These, and other type I receptors, were also cloned independently and were named according to specificity of ligand binding. These type I receptors include: the TGFß receptor (ALK5, TßRI) (Franzen et al., 1993; Yamashita et al., 1994b); an activin receptor (ALK4, ActRIB) (Carcamo et al., 1994; ten Dijke et al., 1993); the BMP receptors (ALK3, BMPRIA and ALK6, BMPRIB and ALK2, ActRI) (Attisano et al., 1993; Ebner et al., 1993; Koenig et al., 1994; Yamashita et al., 1995); as well as other receptors not yet fully characterized (ALK7 and ALK1, TSR1 or Tsk 7L) (Attisano et a1., 1993; Ryden et al., 1996; ten Dijke et al., 1994; Tsuchida et al., 1996). Comparison of amino acid sequences reveals that type I receptors are a highly related group of single-membrane spanning kinases. Type I receptors are glycoproteins of approximately 55 kDa and are composed of four regions: an extracellular portion; a cytoplasmic juxtamembrane region; a serine-glycine repeat region (SGSGSG and flanking sequences) known as the 'GS domain'; and a C-terminal serine/threonine kinase domain. Type II and type I receptors are highly related, however amino acid sequences of their extracellular domains vary dramatically. Nonetheless there are characteristic cysteines in the extracellular portions that presumably confer structural relatedness (Ebner et al., 1993) and divergence in extracellular sequences likely confers specificity on ligand-receptor interactions.

## Mechanism of Receptor Activation

To initiate signalling, TGFß superfamily ligands bind receptor and these ligand-bound receptors oligomerize. For TGFß and activin, ligand binds to the appropriate type II receptor and this results in a stepwise recruitment of the cognate type I receptor into the complex (Moustakas et al., 1993; Wrana et al., 1992). Some BMP-type ligands bind to type II and type I receptors together in a cooperative, rather than a stepwise, manner (Gilboa et

al., 2000). Cooperative binding of BMPs is suggested by the observation that BMP ligands have low affinity for either receptor type alone, however when ALK2, 3 or 6 and BMPRII receptors are co-expressed, BMP ligands bind with higher affinity (Liu et al., 1995). Upon ligand binding, a heteromeric complex of ligand, a dimer of type II and a dimer of type I is formed (Yamashita et al., 1994b), although the precise mechanism of ligand-dependent receptor recruitment and oligomerization remains unknown.

Once constitutively active type II receptors are brought in proximity to type I receptors, a transphosphorylation event occurs. For TGFß receptors, TßRII transphosphorylates TßRI (Wrana et al., 1994) on conserved residues in the GS domain (Wieser et al., 1995). Multiple serines in this region must be phosphorylated to allow for signal propagation. Transphosphorylation is likely a direct event as the kinase cascade can be recapitulated with baculovirally-expressed receptor complexes (Ventura et al., 1994). Moreover, if only the cytoplasmic domains of type II and type I are fused as a chimeric type I/II receptor, the result is constitutive signalling (Feng and Derynck, 1996). While most work on the mechanism of receptor action has focussed on TGß3 receptors, in cases that have been examined, other TGFß superfamily receptor systems follow a similar pattern. Thus upon ligand binding, constitutively active type II receptors transphosphorylate type I receptors.

When type I receptors are phosphorylated, they become activated and thereby specify downstream signalling events. Significantly, mutation of a threonine to aspartate (or glutamate) in the GS domain of TßRI creates a constitutively active receptor (Wieser et al., 1995). This constitutively active receptor can recapitulate known signalling responses of type II/type I heteromeric complexes (Massague and Weis-Garcia, 1996). Analogous activating mutations in BMP type I receptors are also constitutively active and can mediate BMP-type signalling. This class of hypermorphic receptors convincingly demonstrate that type I receptors are sufficient to specify responses downstream of ligand binding.

A controversial report proposes that different regions on type I receptors specify distinct types of signals (Saitoh et al., 1996). TßRI lacking a region of the cytoplasmic juxtamembrane domain can support immediate transcriptional responses, but cannot support growth inhibitory responses to TGFß. TßRI in which either serine 172 or serine 176 is replaced with alanine mimics loss of this juxtamembrane region. In another study, mutations of Ser165 cause an increase in growth inhibition and extracellular matrix formation, but in contrast, a decrease in apoptosis (Souchelnytskyi et al., 1996). In both studies, transcriptional activation signals from mutant receptors were not affected. A third study, however, disputes these results (Dore et al., 1998) and currently the ability of the cytoplasmic juxtamembrane domain to specify growth inhibitory versus immediate transcriptional signals remains an open question.

### Type III Receptors

In contrast to type I and type II receptors, type III receptors may play more of an ancillary role as they modulate activity primarily by regulating ligand access to type I and type II receptors. Type III receptors contain two distinct members, a proteoglycan and a glycoprotein known as betaglycan and endoglin, respectively (Cheifetz et al., 1988a). Type III receptors have been identified only for TGFß and it is not known whether correlates of type III receptors exist for other TGFß superfamily ligands.

### Betaglycan

Betaglycan exists in two forms, a membrane-bound and a soluble version each of which has opposing effects on TGFß signalling (Andres et al., 1989). The membrane-bound form has a short intracellular tail and can be cleaved by plasmin on its extracenurar surface to produce the soluble form (Lopez-Casillas et al., 1991). The usual role of membrane-bound betaglycan is to present ligand to type II receptor (Lopez-Casillas et al., 1993; Wang et al., 1991). In contrast, the soluble form of betaglycan can act as an inhibitor of TGFß action (Lamarre et al., 1994; Lopez-Casillas et al., 1994).

*In vivo*, the membrane-bound betaglycan seems to be required for TGFß-mediated inhibition of lung vessel branching as antisense betaglycan oligonucleotides cause insensitivity to TGFß in ex vivo lung cultures (Zhao et al., 1998). In addition to this TGFß-promoting role, membrane-bound betaglycan can inhibit activin signalling by forming a complex with inhibin and ActRIIB (Lewis et al., 2000). Thus multiple forms of betaglycan can control TGFß/activin signalling by modifying ligand access to the type II receptor.

## Endoglin

Endoglin, which is also implicated in TGFß signalling, is highly related to betaglycan in its transmembrane and intracellular sequences (Cheifetz et al., 1992). Endoglin forms a complex with signalling receptors (Barbara et al., 1999; Yamashita et al., 1994a) and seems to modulate cellular responses to TGFß in a complex manner. Overexpression of endoglin in transfected cells can mitigate TGFß responses (Guerrero-Esteo et al., 1999; Lastres et al., 1996), however defining the precise role of endoglin from overexpression experiments can be problematic. On the other hand, endoglin lack-of-function phenotypes are definitive. Mutations in endoglin result in a human pathology known as hereditary haemorrhagic telangiectasia (HHT) type I (McAllister et al., 1994) a disease characterized by vascular defects. Moreover defects in endoglin lead to defective angiogenesis (Li et al., 1999) and HHT (Bourdeau et al., 1999) in mice. Interestingly, knockout of ALKl recapitulates HHT in a mouse model (Urness et al., 2000) and, moreover, TGFßs are required for both vasculogenesis and angiogenesis. Though a precise mechanism of endoglin action remains unclear, this relationship between endoglin mutant phenotypes and TGFß action suggests that endoglin may play a role in facilitating, and not inhibiting, TGFß signalling.

## Signalling Receptor-Associated Molecules

As part of the complex regulation of TGFß superfamily signalling, TGFß superfamily receptors are negatively regulated by a number of receptor-associating molecules. These include FK506-binding protein 12 (FKBP 12), BMP and activin membrane hound inhibitor (BAMBI) and BMP receptor associated molecule 1 (BRAMl). FKBP12 associates with TßRI and prevents its phosphorylation by TßRII (Chen et al., 1997c). Consistent with this observation, a crystal structure of TßRI in complex with FKBP 12 reveals that TßRI is kept in an inactive conformation and that sites for TßRII transphosphorylation are capped in the presence of FKBP12 (Huse et al., 1999). In spite of these data, FKBP 12 knockout mice do not exhibit increased TGFß activity (Bassing et al., 1998) and this undisturbed phenotype might reflect redundancy in FKBP12 function at the biological level. Next, BAMBI resembles a type I receptor that is truncated on its intracellular surface; its short intracellular domain has weak homology to regions of type I receptors thought to be important for homodimerization (Huse et al., 1999). While the so-called pseudoreceptor BAMBI retains the ability to heterodimerize, it does not transmit signal. It likely works in a dominant negative manner and prevents formation of activated receptor complexes and acts as a general inhibitor of TGFß superfamily signalling (Onichtchouk et al., 1999). Finally, a yeast two-hybrid screen identified the cytoplasmic BRAM1 protein which associates with BMPRI receptor (Kurozumi et al., 1998). The C. elegans BRAM1 homolog, bra-l, is thought to inhibit BMP-type signalling in amphid neurons (Morita et al., 2001). Thus, FKBP12, BAMBI and BRAMl are unrelated receptor-binding factors that negatively regulate receptor action by unique mechanisms. Tissue- or time-specific expression of these factors is likely a method of inhibiting TGFß superfamily signalling.

Another set of molecules that can associate with receptor complexes include the TGFß-receptor interacting protein-l (TRIP-1), protein phosphatase 2A Bα–subunit (PP2ABα), and serine-threonine kinase receptor associated protein (STRAP), all of which contain a WD40 repeat. WD40 repeats provide a pliable interaction surface utilized in protein-protein interactions (Neer et al., 1994) and thus diverse WD40-repeat containing. proteins can either positively or negatively modify TGFß superfamily effects. TRIP-1 contains five

WD-40 repeats and interacts with TßRII that has heteromerised with type I receptor (Chen et al., 1995). In vitro, TRIP-1 is phosphorylated by TGFß receptor complexes and since TRIP-1 and Tl3RII are co-expressed throughout development, perhaps similar phosphorylation events also occur in vivo. In signalling assays, overexpression of TRIP-1 acts to inhibit TGFß transcriptional responses by receptor-dependent and receptor-independent mechanisms (Choy and Derynck, 1998). Another WD40-repeat containing protein, PP2ABα, associates with the cytoplasmic domain of activated TßRI (Griswold-Prenner et al., 1998). PP2ABα is a cytoplasmic protein that regulates the catalytic activity of protein phosphatase 2A and this regulation is implicated in cell cycle control (Mayer-Jaekel et al., 1993). Given that TGFß can regulate cell division, the interaction between PP2ABα and TGFß receptor complexes may be of some significance. Importantly, PP2ABα has a growth inhibitory effect on cells in culture and this inhibition appears to enhance and is dependent on TGFß receptors (Griswold-Prenner et al., 1998) possibly through regulating S6-kinase activity (Petritsch et al., 2000). Finally, STRAP is a WD40 repeat containing protein that is also phosphorylated by TßRI and acts to inhibit TGFß receptor activity (Datta et al., 1998). In addition to binding receptors, STRAP associates with a known negative regulator of receptors, called Smad7 and may act to bridge Smad7 with receptor complexes (Datta and Moses, 2000). Thus, a number of proteins containing WD40-repeats play distinct and important roles in modifying receptor action. The structural basis underlying TGFß receptor interactions with WD40-repeat proteins is unknown, although this could be an interesting area for developments.

The cytoplasmic domain of Tß3RI has also been shown to interact with the α-subunit of farnesyl-protein.transferase-alpha (FT-α) (Kawabata et al., 1995). FT-α associates preferentially with activated TßRI and may be a direct target of phosphorylation. FT-α adds isopreny1 or geranylgeranyl moieties to various targets including G-proteins and cytoskeletal components. Currently a functional consequence for TGFß signalling due to FT-α association has not been established as FT-α is dispensable for studied aspects of TGFß signalling (Ventura et al., 1996). Nonetheless the presence of this (and likely other) receptor-interacting proteins in specific cellular environments might allow for the fine-tuning of TGFß superfamily ligand effects. In addition these interacting proteins might allow for signal integration from a variety of inputs. This growing group of receptor-interacting proteins present experimental opportunities to further study the extensive range of TGFß superfamily receptor action and regulation.

## Receptor Trafficking

Mounting evidence suggests that TGFß superfamily receptors are involved in complex receptor trafficking events. In signalling cascades, receptors are typically internalized after ligand binding and upon internalization, receptors can be recycled to the plasma membrane or they can be downregulated through endocytosis (Mellman, 1996). For TGFß receptors, ligand-receptor complexes rapidly internalize in fibroblast cells (Massague and Kelly, 1986). It is unclear what role ligand plays in receptor internalization, since type II receptors have been suggested to be constitutively internalized and possibly recycled in the absence of ligand (Ehrlich et al., 2001; Dore et al., 2001). Furthermore, the half-live of TßRII in mink lung epithelial cells (Mv1Lu) and 293T cells is quite short and is only modestly affected by TGFß signalling (Wells et al., 1997; Kavsak et al., 2000), contrasting TßRI, which is considerably more stable. However, activation of type I receptors, specifically by type II transphosphorylation, leads to rapid down-regulation of occupied receptors that can be mediated by complexes of inhibitory Smads bound to Smurf ubiquitin ligases (Anders et al., 1997; Anders et al., 1998; Ebisawa et al., 2001; Kavsak et al., 2000). Hence internalization may indeed be followed by down-regulation of the occupied receptor and in cells that have a limiting pool of cell surface receptors, this could service to limit TGF signalling. In further support of a role for receptor trafficking and downregulation, proteins of the sorting nexin (SNX) family can also interact with TGFß receptors (Parks et al., 2001). SNX proteins play a role in receptor trafficking for

a variety of tyrosine kinases. Overexpression of SNX proteins inhibit TGFß signalling and this inhibition is consistent with the possibility that SNX proteins may shuttle TGFß receptors to degradative compartments. One important area of future research will be to define how the trafficking routes of the individual TGFß receptors versus the occupied receptor complex function to control cellular responses to TGFß.

In addition to down-regulation, ligand-bound receptor internalization may be a mode for transporting ligand from one cell to another. Interestingly, trafficking of DPP receptors appears to be necessary for long-range movement of this ligand (Entchev et al., 2000). Moreover this mode of DPP transport might require dynamin, a protein necessary for clathrin-coated pit internalization (Mellmant 1996). This observation may signify a novel paradigm for the role of trafficking ligand-bound receptors. While these results provide tantalizing hints as to the role of receptor trafficking in TGFß superfamily signalling, a critical advance will be to determine precisely in which subcellular compartment(s) signalling occurs.

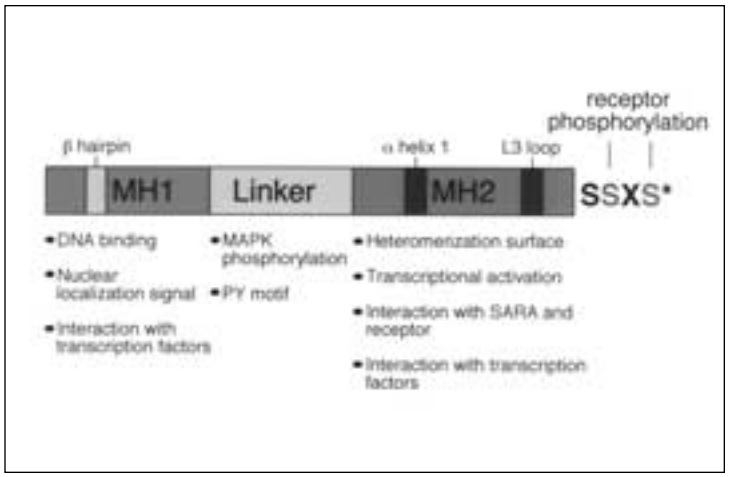


**Figure 1.** R-Smad Schematic

A schematic representation of R-Smads depicting the location of key structures and functions associated with various regions of the R-Smads is shown. R-Smads are comprised of three regions, two highly conserved Mad homology regions (MH1 and MH2) at the N and C-termini respectively and a non-conserved, intervening linker region. In various R-Smads, the MhI domain contacts DNA and contains a nuclear localization signal. The MH2 domain is a multifunctional region that is responsible for intra- and intermolecular interactions as well as transcriptional transactivation. Smads are phosphorylated in response to TGFß superfamily signalling on critical serines at the C-terminus. The asterisk indicates the terminus of the protein.

## Signal Transducers: Smads

*Identification of Smads, Downstream Signal Transducers in the TGFß Pathway*

After type I receptor activation, TGFß superfamily signalling is mediated by intracellular substrates known as Smads. Genetic approaches in *Drosophila* and *C. elegans* first identified downstream pathway components and one of the best genetically characterized TGFß superfamily pathways is that of the *dpp* gene (Padgett et al., 1987). Maternal effect enhancer screens of dpp hypomorphs first revealed components in the black-box downstream of receptors (Raftery et al., 1995). These screens identified novel components in the DPP pathway and the first such molecule cloned was *Mothers-against-4ecapentaplegic (Mad)* (Sekelsky et al., 1995). Mad encodes an intracellular protein that acts genetically downstream of *dpp* and is essential for *dpp* activity (Newfeld et al., 1996). Importantly, a hypomorphic allele of *Mad* is epistatic to an activated *dpp* receptor allele and thus *Mad* activity is downstream of receptor action (Hoodless et al., 1996). At the time of its cloning, predicted MAD lacked known motifs however, homologs existed in *C. elegans* and in mammalian sequence databases. Three *C. elegans* loci *(sma-2, sma-3 and sma-4)* display loss-of-function phenotypes that also places them downstream of the worm TGFß-like receptor *dauer-forming-.4 (daf-4)* (Savage et al., 1996). Together these molecules foreshadowed a growing family of intracellular signal transducers downstream of receptors.

A large number of MAD-related proteins were subsequently identified from a variety of vertebrates. These proteins are now called Smads in recognition of the founding *sma* and *Mad* genes (Derynck et al., 1996). Characterization of the many Smad proteins reveals 8 members to date that sort into three functional categories of Smads: the receptor-regulated Smads (R-Smads), the Common Smads (C-Smads), and the inhibitory-Smads (I-Smads). R-Smads and C-Smads are intracellular proteins that are each comprised of three parts: the Mad Homology 1 and 2 (MH1 and MH2) regions that are highly conserved sequences

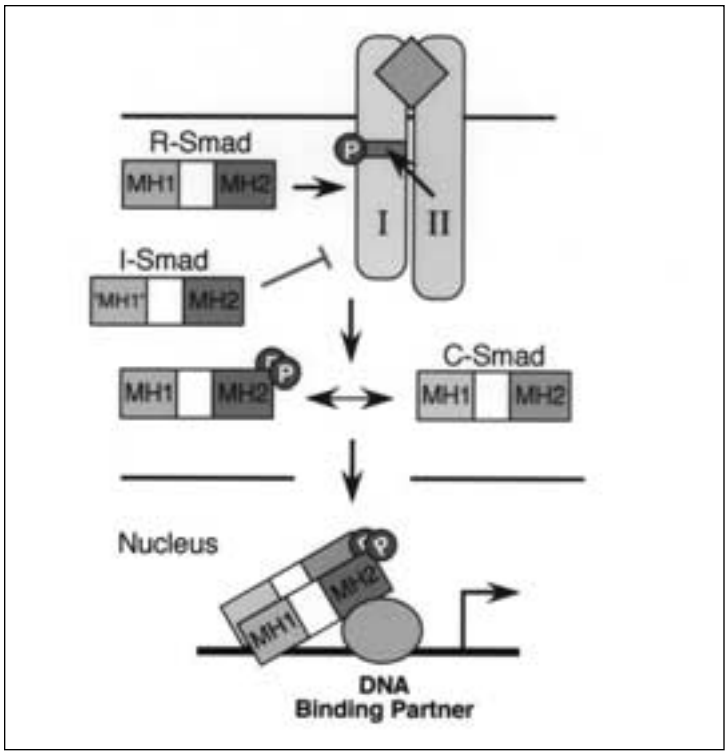


**Figure 2.** The Canonical Smad Pathway

TGFß/activin and BMPs bind to heteromeric complexes of transmembrane type II and type I receptors. The type I receptor directly phosphorylates R-Smads, which then dissociate from the receptor and bind the common Smad, Smad4. The complex then accumulates in the nucleus where R-Smads associate with different DNA-binding proteins (DBP-BPs) and MH1 domains bind directly to DNA. Thus regulation of distinct target genes is achieved to generate diverse biological responses.

at the N- and C-termini respectively, and an intervening, non-conserved linker section (Fig. 1). I-Smads are similar to R-Smads except that they have a poorly conserved MH1 domain. These three groups of Smads represent a major intracellular pathway for TGFß superfamily signalling that transmits signals directly from the receptor into the nucleus to regulate transcriptional responses (summarized in Fig. 2). Moreover, genetic analysis in the mouse has revealed that all of the Smads analyzed thus far play critical functions at various aspects of development (Table 1).

## Mechanism of Signalling via Smads

*Type I Receptors Phosphorylate R-Smads.* Type I receptors directly phosphorylate R-Smads in response to TGFß superfamily signalling. Smad 1 is phosphorylated in response to BMP addition and this phosphorylation is achieved by type I BMP receptor kinases (Hoodless et al., 1996; Kretzschmar et al., 1997b). Moreover endogenous *Drosophila* MAD is phosphorylated *in vivo* within 15 m of ligand addition (Newfeld et al., 1997). Similarly, Smad2 is phosphorylated by TGFß and activin receptors (Eppert et al., 1996; Nakao et al., 1997b; Yingling et a1., 1996) on two terminal serines in an SSXS motif and these phosphorylations are required for activity (Abdollah et al., 1997; Macias-Silva et al., 1996; Souchelnytskyi et al., 1997) Mutant Smad2 bearing alanines substituted for these terminal serines cannot be phosphorylated and instead associates constitutively with activated TßRI. Together these observations support the model that activated type I receptors can directly phosphorylate Smads.

While type I receptors are thought to phosphorylate R-Smads directly, other essential factors may be present in the signalling complex. Disabled-2 (Dab2) is an adaptor molecule that is required for signalling in the context of some tyrosine signalling pathways. Interestingly, Dab2 associates with TGFß receptors, Smad2 and Smad3 and Dab2 may be required for the phosphorylation of these R-Smads (Hocevar et al., 2001). Accordingly Dab2 may be an essential component of the TGFß signalling pathway that helps to transmit TGFß signals from receptors to Smads as part of a multiprotein complex.

## Subgroups of R-Smads Specify BMP or TGFß Signals.

Upon phosphorylation by type I receptors, R-Smads specify downstream biological responses and subgroups of R-Smads transduce subsets of TGFß superfamily signals. For instance in *Xenopus,* overexpression of Smad1 yields ventral mesoderm-a typical BMP response, whereas Smad2 overexpression results in dorsal mesoderm-a TGFß/activin response (Graff et al., 1996; Thomsent 1996). These and related studies have led to the conclusion that Smads 1, 5 and 8 comprise the BMP-responsive group of Smads while Smads 2 and 3 constitute the TGFß/activin responsive group. In general Smads in these two groups mediate ligand-dependent effects and thus

two subgroups of R-Smads are primary effectors of either BMP or TGFß/activin signalling. Consequently, this dichotomy of R-Smads suggests a similar convenient categorization of ligands as BMP-type or TGFß-type.

Specificity of R-Smad receptor interactions is ensured by determinants on R-Smads and receptors. On R-Smads, a solvent-exposed region of the MH2 known as loop ß (L3) (Chen et al., 1998; Lo et al., 1998) and α-helix-l (aH1) (Chen and Massague, 1999) determine the specificity of R-Smad/receptor interactions (Figure 1). Exchanging amino acids in these regions between R-Smads in the subgroups causes a switch in signalling specificity. R-Smads also contain a highly positively charged surface groove adjacent to L3 and this basic surface can bind phosphoserines and is postulated to bind the phosphorylated GS domain (Wu et al., 2001; Huse et al., 2001; Wu et al., 2000). Additionally, a region on TßRI known as loop-4-5 (L45) lies adjacent to the GS domain and specifies interactions with Smad2 (Feng and Derynck, 1997; Huse et al., 1999). One model proposes that L45/L3 interactions provide specificity while GS domain/basic groove interactions increase the overall strength of binding (Shi, 2001).

**Table 1. Smads and the Knockout Phenotypes in Mice**

| Type<br>Member | Loss-of-function phenotype(s) (L) or<br>Other (e.g. hypermorph) characterization (O) | Reference(s) |
|---|---|---|
| **R-Smads - TGFβ/activin** | | |
| Smad2 | (L) embryonic lethal, defects in proximal/distal axis, extraembryonic ectoderm and epiblast | (Nomura and Li, 1998; Waldrip et al., 1998; Weinstein et al., 1998) |
| Smad3 | (L) metastatic colon cancer, diminished T-cell response to TGFβ, accelerated wound healing | (Ashcroft et al., 1999; Datto et al., 1999; Yang et al., 1999b; Zhu et al., 1998) |
| **R-Smads - BMP** | | |
| Smad1 | (O) mediates BMP signalling. (L) Defects in extraembryonic tissues and germ cell formation | (Hoodless et al., 1996; Kretzschmar et al., 1997b; Tremblay et al., 2001) |
| Smad5 | (L) die between E9.5 and E11.5, multiple defects in amnion, gut, heart, face, neural tube, heart looping, embryonic turning, angiogenesis defects, mesenchymal apoptosis | (Chang et al., 1999; Chang et al., 2000; Yang et al., 1999a) |
| Smad8 | (O) mediates BMP signalling | (Chen et al., 1997b) |
| **C-Smads** | | |
| Smad4 | (L) embryonic lethal, heterozygotes have intestinal tumours, variable requirement in murine cells | (Sirard et al., 1998; Sirard et al., 2000; Takaku et al., 1999; Takaku et al., 1998) |
| **I-Smads** | | |
| Smad6 | (L) viable, multiple cardiovascular abnormalities, aortic ossification, elevated blood pressure | (Galvin et al., 2000) |
| Smad7 | (O) antagonist of TGFβ superfamily signalling | (Hayashi et al., 1997; Nakao et al., 1997a) |

Table 1

## R-Smad Access to Receptor

Since type I receptors directly phosphorylate R-Smads, it is a reasonable expectation that appropriate machinery is required to help cytoplasmic R-Smads localize to their membrane-bound target receptors (Fig. 3). Two proteins, Smad anchor for receptor activation (SARA) (Tsukazaki et al., 1998) and Hgs (Miura et al., 2000), each contain a FYVE-domain for membrane localization and also bind Smad2 and Smad3. The FYVE-domain is a double zinc-finger that binds phosphotidyl inositol-3-phosphate (PI-3P) in the plasma membrane (Wurmser et al., 1999). By binding the membrane and the target R-Smad, SARA and Hgs may act to recruit Smad2 to TßRI. SARA binds TGFß/activin responsive Smads but not BMP responsive Smads. These associations depend on a critical arginine residue that is present in TGFß/activin responsive R-Smads, but is not present in Smad1 (Wu et al., 2000). Interestingly, SARA and Hgs are enriched in the early endosome and recent studies have suggested that endocytosis through the clathrin pathway is important for TGFß signal transduction (Itoh et al., 2002; Panopoulou et al., 2002; Penheiter et al.t 2002). Also, a BMP-type SARA has not yet been identified. Smads can also associate with microtubules and thereby possibly preventing spurious activation of the pathway; this regulatory step precedes the interaction of R-Smads and SARA (Dong et al., 2000). While key players that are likely required for membrane localization have been identified, further work is needed elucidate precise mechanisms of Smad delivery to, and association witht membrane-bound receptors.

## Heteromerization with C-Smad and Nuclear Entry

Once phosphorylated, R-Smads heteromerise with the C-Smad, Smad4. Smad4 independently identified as DPC4 (Hahn et al., 1996), lacks the SSXS sequence and is phylogenetically more dis-

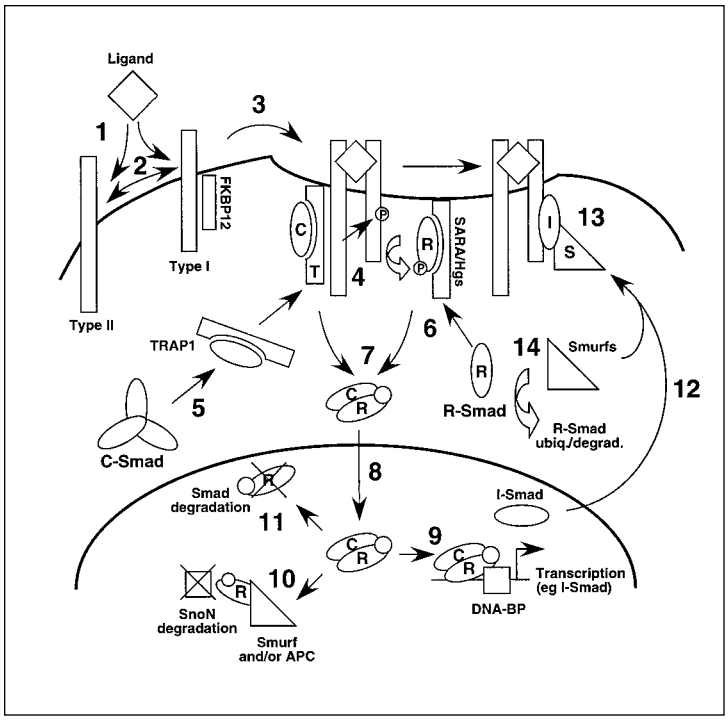


**Figure 3.** Model of Intracellular TGFß Signalling Events

This schematic depicts the complex molecular activities that underlie TGFß signalling. Arrows depict movement or enzyme activity and events are not necessarily sequential. 1) Dimeric mature ligand binds receptors in sequential (TGFß) or cooperative (BMP) mode. 2) Type II and type I receptors form heteromeric complexes. 3) Heteromeric complex appears to colocalize in an endosomal compartment shared by SARA. 4) Type II receptor transphosphorylates type I thereby activating the type I. 5) Trimeric C-Smad changes multimerisation state and is brought to receptor complex by TRAP1. 6) Trimeric R-Smad associates with SARA, is brought to receptor complex and is phosphorylated on terminal serines by type I receptor. 7) Phosphorylated R-Smad associates with C-Smad and this complex trans locates to the nucleus. 8) Smads accumulate in the nucleus. 9) Smads bind DNA-binding proteins, to regulate transcriptional responses. 10) Smads can also recruit the ubiquitin ligases Smurf and APC to target the corepressor SnoN for degradation. 11) R-Smad will be degraded by Smurf-independent mechanisms. 12) In addition to being transcriptionally induced, Smad7 is exported from the nucleus and binds the receptor to inhibit signalling. 13) The I-Smads bound to receptor also act as adapters for Smurf ubiquitin ligases which can degrade receptor complexes. 14) Smurfs can also directly target R-Smads for degradation.

tantly related to R-Smads than R-Smads are to each other. Smad4 is not a direct substrate of receptors, instead Smad4 interacts with both TGFß- and BMP-activated R-Smads (Lagna et al., 1996; Zhang et al., 1997). The Drosophila homolog of Smad4, MEDEA, functions in a similar manner as it associates with activated MAD (Das et al., 1998; Hudson et al., 1998; Wisotzkey et al., 1998).

As described above for R-Smad/SARA interactions, C-Smads also appear to be shuttled to the membrane, in this case by TßRI associated protein-l (TRAP1). TRAP1 is a protein that preferentially interacts with activated TßRI receptor in the yeast two-hybrid assay (Charng et al., 1998). In cells, TRAP1 associates strongly with activin and TGFß receptors in their basal state and TRAP1 is released upon receptor activation. Importantly, TRAP1 also interacts with Smad4 and is thought to act as a carrier of Smad4 (Wurthner et al., 2001; Fig. 3). Perhaps increasing the local concentration of Smad4 in membrane-proximal domains permits efficient heteromeric complex formation.

Upon heteromeric complex formation, Smad complexes enter the nucleus (Baker and Harland, 1996; Hoodless et al., 1996). While R-Smads can accumulate independently of C-Smads, the latter are brought along into the nucleus upon their association with R-Smads (Wisotzkey et al., 1998). In the case of Smad3, nuclear import occurs in an importin ß-dependent manner (Kurisaki et al., 2001; Xiao et al., 2000b). Consistent with this phenomenon, a distinct nuclear localization signal (KKLKK) resides in the N-terminus of Smad3 (Xiao et al., 2000a). Smad2 however, bears an insert which prevents its interaction with importin ß and thus other distinct sequences in the MH2 domain are thought to allow for nuclear localization. In addition to regulated nuclear import, Smad4 contains a nuclear export sequence (NES) in its linker region (Watanabe et al., 2000). Heteromeric complex formation inactivates this NES and this inactivation further contributes to nuclear accumulation of the complex. Thus a number of mutually compatible sequence-dependent mechanisms regulate proper Smad subcellular localization.

While R-Smad and C-Smad heteromeric complexes are necessary for most TGFß superfamily signalling, heteromerisation of R- and C-Smad may not be required for all signalling responses. In *Drosophila* some R-Smad responses are supported in C-Smad deficient cells (Wisotzkey et al., 1998) and in murine cells some non-essential

roles for Smad4 have been observed (Sirard et al., 2000). Such a variable requirement for Smad4 may allow for some of the pleiotropic effects of TGFß superfamily action.

Although it is known that Smads exist as homomers and heteromers, the precise stoichiometries of R-Smads, C-Smads and R/C-Smad complexes remain unclear. X-ray crystallographic analysis of Smad4 MH2 (Shi et al., 1997) and a slightly larger transcriptionally active fragment of Smad4 (Qin et al., 1999) reveals that this protein exists in a trimeric arrangement. Interestingly, three amino acids that are thought to participate in hydrogen bonding in Smad4 trimers are conserved across Smads and this conservation hints at the possibility that all Smads may exist as trimers. However, gel filtration, sedimentation and structural studies suggest the Smads are monomers in their basal state and oligomerize into trimers upon signalling (Kawabata et al., 1998). This observation of Smads as monomers in their basal state is consistent with monomeric Smad observed in the Smad2 MH2/SARA SBD crystal structure (Wu et al., 2000). Furthermore, recent structural studies indicate that phosphorylation may drive R-Smad trimer assembly by stabilizing phosphorylation-independent MH2 domain interactions (Wu et al., 2001; Qin et al., 2001). However there is considerable controversy regarding the stoichiometry of R-Smad/C-Smad heteromeric complexes. Some argue that a trimer is formed (Kawabata et al., 1998) whereas others conclude that heterodimers form (Jayaraman and Massaguet 2000; Wu et al. 2001). Furthermore, a recent study on Smad1 and Smad3 bearing pseudoactivating mutations reveals trimers of these R-Smads and heteromers containing two Smad3 and one Smad4 (Chacko et al., 2001; Qin et al., 2001). The apparent observation of Smads in both heterodimeric and heterotrimeric states suggests that the multimeric states suggests that the multimeric state of Smads may vary in a context-dependent manner. Further such observed heterogeneity in the stoichiometry of complexes might reflect differing *in vivo* spatiotemporal states and varying functions and signalling efficacies of these complexes. This should be an exciting and challenging area of investigation in the future as very little is understood of how the stoichiometry of signalling complexes in general affect biological responses.

## DNA binding and Smad-mediated Activation and Repression of Transcription.

Upon entering the nucleus, Smads can directly bind target DNA sequences via their MH1 domains. An amino-terminal fragment of *Drosophila* MAD binds directly to an enhancer of the vestigial (vg) gene and this binding is required for vg transcription (Kim et al., 1997). Smad3 and Smad4 can directly bind to regions in the plasminogen activator inhibitor 1 (P AI -1) promoter (Dennler et al., 1998) and Smad4 can bind DNA in response to TGFß (Yingling et al., 1997). A co-crystal of the Smad1 MH1 and DNA demonstrates that sequence-specific DNA binding depends on a ß-hairpin found in the MH 1 and three amino acids in this hairpin make hydrogen bonds with nucleotides in Smad target DNA (Shi et al., 1998).

Smads bind weakly to GC-rich sequences. Smad1 binds DNA with an affinity of approximately $5 \times 10^{-7}$ M (Shi et al., 1998) and this relatively low affinity likely requires assistance from other DNA-binding factors. Various studies with differing results have claimed to define different consensus Smad binding sites (Dennler et al., 1998; Johnson et al., 1999; Shi et al., 1988, Zawel et al., 1998). However it is unlikely that there is a single consensus Smad binding site and Smads bind DNA with relatively low specificity and numerous G/C rich sequences are also bound by Smad MH1 domains (Labbe et al., 1998). A preponderance of Smad binding sites throughout promoters is not incompatible with a broad biological role for Smads.

DNA elements that can bind Smads occur frequently in the genome, thus partner DNA-binding is essential for defining specificity of gene targets. Indeed, Smads can associate with DNA-binding partners. The first such protein identi-

fied was the *Xenopus* winged-helix/forkhead factor, the forkhead activin signal transducer 1 (FAST1) (Chen et al., 1996), now known as FoxH1. Factors such as FoxH1 are critical for recruitment of Smads to appropriate DNA targets. The *Xenopus* FoxH1 or its mammalian counterpart bind in a complex with Smad2 and Smad4 to the promoters of the activin-response gene *Mix. 2 (*Chen et al., 1998) and *goosecoid* (gsc) genes respectively (Labbe et al., 1998). In the mouse, FoxH1 plays a key role in mediating specific activities of Smad2 and Smad3 during gastrulation (Hoodless et al., 2001; Yamamoto et al., 2001).

One of the striking aspects to emerge from investigation of Smads has been that these factors associate with a wide range of DNA binding partners as well as transcriptional coactivators and corepressors (reviewed in Attisano and Wrana, 2000). For instance Smads bind to partners that include Jun, Atf2, TFE3, vitamin D receptor, OAZ and many others as well as to transcriptional coactivators such as CBP/p300, MSG and SMIF. Additionally Smads can bind the corepressor TGIF, which recruits the transcription-silencing histone deacetylases (HDACs) and thereby represses transcription of Smad-bound promoters/enhancers as well as HDAC itself. Another pair of related Smad-interacting proteins, the nuclear oncoproteins Ski (Luo et al., 1999) and SnoN, associate with R-Smads and recruit nuclear ß-Iepressor (N-CoR) to repress transcription (Stroschein et al., 1999). Thus Smads, in conjunction with sequence-specific DNA binding partners and transcriptional coactivators or corepressors can direct a vast array of transcriptional responses.

Variable transcriptional responses are directed by peptide sequences in MH2 and MH1 domains and these sequences regulate binding of associated factors or binding to DNA. For instance, the C-terminus of Smad1 acts as a transcriptional trans activator (Liu et al., 1996). Similarly, Smad4 requires its MH2 and a proline-rich stretch just upstream, known as the Smad4 activation domain (SAD), to direct transcriptional responses (Liu et al., 1997a; Qin et al., 1999). Mutations in these regions can abrogate transcriptional responses, likely by disrupting association with transcriptional activators. In addition, differences in the MH1 domains of highly related Smads can confer dramatic changes in their ability to activate transcription. Smad2 and Smad3 have nearly identical MH1 domains but have opposing activities on the *gsc* promoter; while Smad2 activates, Smad3 represses (Labbe et al., 1998). Smad3 binds *gsc* DNA while Smad2 does not and this difference may account for the observed opposing activities. Interestingly, using a different CAGA containing promoter another study shows a related but opposite result, Smad3 activates while Smad2 represses transcription (Dennler et al., 1999). In this case, as in the previous study, Smad3 binds DNA but Smad2 does not. The latter study further argues that a short insert in the MH1 of Smad2 is responsible for preventing Smad2 from binding DNA. While it is not entirely clear why Smad2/3 have opposing activities on different promoters, their opposite activities seem to depend on their DNA binding statuses on each promoter.

## Antagonistic Smads: I-Smad.

In contrast to R-Smads that propagate TGFß superfamily signals, I-Smads inhibit TGFß superfamily signalling. Smad6 and Smad7 were first identified in endothelial cells exposed to conditions of non-laminar shear stress (Topper et al., 1997). TGFß superfamily ligands induce the expression of Smad6 and 7 messages and Smad6 or 7 proteins prevent TGFß signalling by interacting constitutively with activated TßRI and preventing access of R-Smads (Hayashi et al., 1997; Imamura et al., 1997; Nakao et al., 1997a). I-Smads have a poorly conserved MH1 domain but possess an MH2 that lacks a C-terminal SSXS and in a manner opposite to R-Smads, Smad7 trans locates from nucleus to cytoplasm in response to signalling (ltoh et al., 1998). In addition, I-Smads also recruit Smurf ubiquitin ligases to catalyze degradation of the receptor complex. I-Smads thus provide a tight layer of control on

Smad activation by closing a negative feedback loop (Fig. 3). Such a feedback loop might allow a tight readout of ligand activity and I-Smads might thus delimit Smad activation to provide appropriate spatiotemporal control of ser/thr kinase receptor activity during development.

### Ubiquitin-Mediated Degradation of Smads and Receptors

Many cellular processes are controlled by degradation of proteins and a number of TGFß superfamily components are subject to degradation. Specific degradation of proteins is accomplished by diverse mechanisms including lysosomal degradation and the ubiquitin-proteasome system. In the latter mechanism, ubiquitin protein moieties are covalently linked to proteins which are targeted for degradation. Enzymes ensuring that only appropriate proteins are destroyed include ubiquitin-Iigase enzyme 1 (E3) and ubiquitin-conjugating enzyme 2 (E2). C2-WW-HECT domain containing E3 ligases recognize the sequence PPXY (PY-motif) in their targets and mediate ubiquitination of those targets by facilitating the conjugation of ubiquitin side-chains (Huibregtse et al., 1995). Ubiquitinated proteins targeted for degradation are ultimately destroyed by a multiprotein complex known as the proteasome.

R-Smads are regulated by ubiquitin-mediated degradation. The Smad ubiquitination regulatory factors 1 and 2: (Smurf1 and Smurf2) are both E3 ligases that facilitate Smad destruction. Consistent with a requirement for E3 ligase targets, R-Smads contain PY-motifs. Interestingly, Smurfl triggers the degradation only of Smad1 (Zhu et al., 1999) and inhibits BMP signalling in *Xenopus* embryos. Smurf2 has a more controversial role. One study argues that Smurf2 preferentially targets Smad 1 (Zhang et al., 2001), a second study reports that Smurf2 preferentially mediates the destruction of Smad2 (Lin et al., 2000), while a two other reports show that Smurf2 does not mediate R-Smad destruction (Kavsak et al., 2000; Bonni et al., 2001); these conflicting data await clarification.

In addition to being degraded through Smurfs, Smads can also serve as adapters for Smurf-mediated degradation of Smad-associated proteins (Fig. 3). For instance, Smurfs in concert with Smad7 mediate the destruction of activated receptors. Both Smurfl and Smurf2 translocate to activated TßRI and bind to the receptor complex using Smad7 as an adapter (Ebisawa et al., 2001; Kavsak et al., 2000). Once bound to the receptor these proteins initiate the destruction of activated receptor complexes. Also, Smad2 can act as an adapter for Smurf2 and recruit SnoN for ubiquitin-dependent degradation (Bonni et al., 2001). R-Smads can also facilitate APC-dependent degradation of SnoN (Stroschein et al., 2001; Wan et al., 2001), suggesting that they may playa more general role in the ubiquitin-proteasome system as adaptors that regulate steady-state levels of proteins in reponse to TGFß family signals.

Finally, phosphorylated R-Smads can also be degraded by Smurf-independent pathways. For instance, Smad2 lacking its PY-motif is still ubiquitinated (Lo and Massague, 1999) and this degradation requires Smad2 to be localized to the nucleus. Such nuclear localization-dependent ubiquitination may serve to limit spurious DNA binding in the nucleus by destroying Smad2 that is not tightly bound to target DNA. Additionally, this mode of degradation may simply down-regulate Smad2 signals. In a related manner, Smad3 bound to transcription factors is recognized by a protein called ROC 1 and in turn this complex becomes part of a larger E3 ubiquitin ligase complex (Fukuchi et al., 2001). This assembly is exported from the nucleus and is subject to degradation (Wan et al., 2002). Smad4 can similarly be targeted for destruction by the Jab 1 ubiquitin ligase. These modes of destruction of nuclear R-Smads provide yet more ways of restricting TGFß superfamily ligand effects.

## Cross-talk with Other Signalling Pathways

Cells *in vivo* are subject to inputs from multiple signalling pathways. As more signalling pathways are elucidated, it becomes increasingly clear that signalling pathways do not work in isolation of each other (Jordan et al., 2000). Signalling cas-

cades may intersect or their activities may depend on the output of other simultaneous signals. TGFß superfamily signalling can be influenced by and can modulate other distinct signalling pathways. Understanding how and when Smads cross-talk therefore represents an important arm of TGFß signalling research.

## Mitogen Activated Protein Kinases (MAPKs) Involved in TGFß Signalling

MAPK signalling intersects with TGFß superfamily pathways. MAPKs are a family of serine/threonine kinases that comprise signalling cascades and MAPK signalling is required for many facets of cellular regulation (Chang and Karin, 2001). MAPK cascades are initiated downstream of signals that activate certain receptor tyrosine kinases (RTKs) and the multifunctional GTPase effectors related to the oncoprotein Ras (Boguski and McCormick, 1993). TGFß family members can also activate these MAPK cascades and in various systems TGFß has been reported to activate Erk, JNK and p38 (reviewed in Moustakas et al., 2001).

Multiple interactions between MAPK pathways and TGFß superfamily pathways have been described and a number of these result in inhibition of TGFß superfamily signalling. For example, Smad1 is phosphorylated in its linker region by MAPKs and this phosphorylation appears inhibitory (Kretzschmar et al., 1997a). Furthermore Smad2 and Smad3 phosphorylation downstream of activated Ras also leads to inhibition of TGFß signalling (Kretzschmar et al., 1999). Some controversy exists for this role of MAPK. Others have reported minimal effects of MAPK activation on Smad2 function (Lehman et al., 2000) and studies in *Drosophila* support a role for MAPK-mediated inhibition of TGFß signalling that does not require phosphorylation of R-Smad (Kubota et al., 2000). Furthermore, in certain systems MAPK activity may be required to activate TGFß superfamily signalling and under some conditions TGFß and BMP signalling appears to require co-activation by Ras (Yue et al., 1999; Yue and Mulder, 2000). Complementary genetic evidence exists for this positive role of MAPK in the example of *Drosophilia* endoderm development (Szuts and Bienz, 2000; Szuts et al., 1998). Given the diversity of RTK signalling, opposite effects on TGFß superfamily signalling (inhibitory versus activating) are not necessarily mutually incompatible, and the precise *in vivo* mechanisms whereby MARK and TGFß signals intersect both positively and negatively awaits further research.

## TGFß3 Associated Kinase 1 (TAK1)

TAK1 signalling also interconnects with TGFß superfamily signalling. TAK1 is a MAPK kinase kinase (MAPKKK) and its activity is upregulated by TGFß and BMP. In addition, TAK1 modifies TGFß transcriptional responses (Yamaguchi et al., 1995). In *Xenopus* activated TAK 1 can mimic overexpression of BMP signalling in the early *Xenopus* embryo (Shibuya et al., 1998) and this role is linked to the BMP receptors by the *Xenopus* inhibitor of apoptosis protein (XIAP) (Yamaguchi et al., 1999). While the precise role of TAK1 awaits a knockout, these initial results indicate a potentially important, positive role for TAK1 in TGFß superfamily signalling.

## Wingless/WNTPathways

Along with TGFß superfamily pathways, the *Drosophila wingless (wg)* pathway and its mammalian correlate, the wingless/int or Wnt pathway play crucial roles in embryonic development and tumor progression (Akiyama, 2000). Together these pathways positively or negatively interact to regulate a range of biological effects. For instance, genetic Control of *Drosophila optomotor-blind (omb)* (Grimm and Pflugfelder, 1996), a gene involved in wing formation, and activation of the extradenticle homeodomain protein in the embryonic midgut (Mann and Abu-Shaar, 1996) are dependent on *dpp* and *wg*. In *Xenopus,* TGFß and Wnt pathways are required for formation of anterior endomesoderm (Zorn et al., 1999) and certain target genes are synergistically activated by both pathways which cooperatively pattern mesodenn using TGFß/activin (Crease et al., 1998) or BMPs (Hoppler and Moon, 1998). In addition, simultaneous repression of Wnt and BMP sig-

nalling is required for head induction in amphibians (Glinka et al., 1996). Together these observations are good circumstantial evidence in favour of wg/TGFß cross-talk.

Consistent with these biological data, TGFß and Wnt pathway effectors interact directly. First, a protein-protein interaction complex may exist between ß-catenin, lymphoid enhancer binding factor-l/T cell-specific factor (LefI/Tct) and Smad4 (Nishita et al., 2000). Furthernore, a TGFß-dependent interaction between Smad3 and LefI has also been demonstrated and shown to regulate synergistic induction of WNT target genes (Labbe et al., 2000). In another interesting example, the inhibitory Wnt pathway protein, axin, associates with Smad3 and facilitates its phosphorylation by TGFß receptors (Furuhashi et al., 2001). Mutants of axin which fail to bind SmadJ, inhibit Smad3 phosphorylation which suggests that axin association with Smad3 is required for signalling. Together these results suggest a certain interdependence between TGFß and WNT pathways. It is unknown how extensive this interplay will turn out to be, but it may be a critical factor in governing the precise execution of complex developmental programs and may be important in the initiation or progression of human cancer

## Conclusions.

Elucidation of the molecular components of the TGFß superfamily signal transduction pathways has provided important insights into the fundamental molecular events that underlie developmental processes and human disease. Indeed, many human syndromes and illnesses, both hereditary and spontaneous, have been attributed to mutations in components of TGFß family signalling pathway. For instance mutations in receptors are associated with Hereditary Hemmorhagic Telangiactasia, Primary Pulmonary Hypertension, Persistant Mullerian Duct Syndrome, Juvenile Polyposis Syndrome and colorectal and gastric carcinomas. Mutations in Smads have also been associated with cancers, particularly those of the colon and gastrointestinal tract. Undoubtedly, further elucidation of the molecular mechanisms in this signalling pathway promises to provide new insights into cellular regulation and physiology in health and disease.

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# The 2002 Jeanne Manery Fisher Memorial Lectureship Award

## Dr. Mona Nemer

Dr. Mona Nemer is the Director of the Cardiac Growth and Differentiation Laboratory at the Institute recherches cliniques de Montréal (IRCM) and Professor, Department of Pharmacology, Université de Montréal. A chemist and molecular biologist, Dr. Nemer is recognized for her work in the field of transcriptional regulation of cardiac growth and differentiation. One of the three top scientists working in this field, Dr. Nemer is credited as being the first to isolate transcription factor GATA-4 in cardiac myocyte differentiation and to propose common molecular pathways for cardiac and hematopoietic cell differentiation. Her analysis of cardiac transcription in normal and diseased hearts may lead to a better understanding of, and treatment for, congenital or acquired cardiac disease.

Dr. Nemer received her Ph.D. in 1982, studying the chemistry of nucleotides and nucleosides with Professor Kelvin Ogilvie at McGill University. As a graduate student, Dr. Nemer developed chemistry responsible for automating DNA synthesis. She was also the first to synthesize several modified nucleotides including nucleotide amidites and thiophosphates as replacements for the phosphodiester chain. Such modified oligonucleotides are now used routinely in antisense based mRNA targeting. She completed her postdoctoral research training in molecular biology with Dr. Jacques Drouin at the Institut de recherches cliniques de Montréal (IRCM). During her fellowship, she made important contributions to the mechanisms of action of steroid receptors (glucocorticoid) and was the first to isolate the gene encoding for a novel cardiac hormone called ANF (atrial natriuretic factor). In 1985, Dr. Nemer was appointed to the position of Senior Researcher in the Laboratory of Molecular Genetics at IRCM. In 1991 she was appointed Director of a newly established Research Unit in Cardiac Growth and Differentiation at IRCM.

Early in her career, Dr. Nemer developed an interest in the regulation of the ANF gene. ANF (atrial natriuretic factor), the major secretory product of the heart, is a potent hypotensive peptide hormone. ANF was initially assumed to be an exclusively atrial product, but she showed that this gene was also expressed in ventricles where its presence correlates with cardiac cell growth and ventricular stress. This finding, which was later confirmed by several groups, prompted multicenter clinical studies aimed at correlating plasma ANF levels with the initiation of cardiac stress preceding cardiac dysfunction. These studies confirmed that increased ANF levels constitute an exquisite marker for cardiac dysfunction and subsequently led to the commercialization of diagnostic tests presently in use in Japan, the United States and Europe. In addition to analyzing ANF gene regulation, Dr. Nemer cloned the related BNP gene and used both cardiac natriuretic genes as markers for studying transcriptional regulation in the heart and for isolating the transcription factors that control cardiac cell fate.

Dr. Nemer was the first to tackle the area of cardiac transcription and to establish cellular models and methodologies that allowed analysis of cardiac promoters in vitro. This led to identification of novel regulatory pathways including the isolation of several cardiac transcription factors. For example, Dr. Nemer was the first to show the importance of the transcription factor GATA-4 in transcriptional regulation and in cell differentiation in cardiac myocytes. She was the first to clone GATA-4 and to suggest its importance in cardiac development, a suggestion that was proven by others, via generation of knockout animals, to be valid.

Dr. Nemer was also the first to propose a new paradigm for the mechanism underlying cardiac differentiation. Given that the heart is a muscle, paradigms common to both cardiac and skeletal muscle formations had long been sought. Dr. Nemer was the first to note similarities between the mechanisms underlying both the formation of the heart and the generation of different cells in the blood system (the hematopoietic system). She further showed both biochemically, and at the cellular level, that GATA-4 is a key regulator of the heart, both independently and through its interaction with other transcription factors such as the homeodomain factor known as NKX2.5. Dr. Nemer contributed significantly to understanding the role of this factor in the heart by identifying the first target genes of NKX2.5 and natural binding sites, for which she coined the term NKE (the current terminology). GATA-4 and NKX2.5 are the earliest markers of cardiac differentiation and are presently the most studied transcription factors in the field of cardiology. Dr. Nemer has also gone on to identify other collaborators of GATA-4 that modulate cardiac response to various stimuli.

She was the first to identify transcriptional regulatory mechanisms for catecholamine action on cardiac genes. Her group successfully cloned the transcription factor required to mediate $\alpha$1-adrenergic stimulation of cardiac genes and several other novel transcription factors that are important regulators of the cardiac genetic program. Her current work focuses on areas of prime importance for cardiac homeostasis, including the nuclear signalling mechanisms of angiotensin II and endothelin I, as well as the functions of the latter in cardiac development and pathogenesis. In these studies, she combines molecular dissection of transcription complexes with large-scale gene expression profiling and in vivo analysis of relevant gene products.

An internationally renowned scientist and a dedicated mentor, Dr. Nemer has contributed significantly to the advancement of biomedical research in Canada. Dr. Nemer is a member of Royal Society of Canada's Academy of Science and holds a Canada Research Chair in Molecular Biology that was granted to her. She was an invited professor at the College de France in 1999 and nominated as vice-chair (2002) and chair (2003) of a Gordon Conference entitled Molecular Mechanism of Hormone Action. Dr. Nemer was a council member of the Medical Research Council of Canada and is presently a member of the Research Policy and Planning Advisory Committee of the Heart and Stroke Foundation of Canada.

Dr. Nemer is regarded as a role model not only by the young female scientists at the IRCM but also by the numerous graduate students, postdoctoral fellows and colleagues that she has supervised or has simply interacted with.

# GATA-4: An Integrator of Hormonal and Growth Factor Signaling in the Heart

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## ABSTRACT

Congenital heart defects in children and cardiac disease in adults are the leading cause of mortality in industrialized countries. In recent years, identification of a number of transcription factors involved in cardiogenesis has greatly enhanced our understanding of the mechanisms underlying heart formation and function. The present review will focus on the zinc finger transcription factor GATA-4 that has emerged as a key regulator of cardiac gene expression, and an important survival factor for cardiomyocytes. GATA-4 is also a nuclear effector of several signalling pathways, which modulate its function through post-translational modification of the GATA-4 protein, or regulation of its co-factors.

## RÉSUMÉ

Les maladies cardiaques sont les principales causes de mortalité dans les pays industrialisés. Au cours des dernières années, l'identification de plusieurs facteurs de transcription impliqués dans la cardiogenèse, ont contribué à améliorer notre compréhension des mécanismes moléculaires qui régissent la formation et le fonctionnement du coeur. Cette synthèse portera plus particulièrement sur le facteur de transcription GATA-4, un régulateur-clé de l'expression genique et de la survie des cardiomyocytes. De plus, GATA-4 s'avère être un indispensable effecteur nucléaire de plusieurs voies de signalisation qui convergent sur GATA-4 et modulent sa fonction soit en affectant la protéine GATA-4 directement ou par le biais de leurs effets sur ses co-facteurs.

## INTRODUCTION

Cardiomyocytes respond to growth stimulation via two distinct pathways depending on their developmental stage (Fig. 1). During embryonic life, heart growth involves cell proliferation but the post-natal heart grows essentially by increasing the size but not the number of its cardiomyocytes, a phenomenon known as hypertrophic growth. In the ventricles, post-natal growth (i.e. physiologic hypertrophy) is accompanied by a genetic switch that involves down-regulation of embryonic genes -like the atrial natriuretic peptide (ANP) - and upregulation of the adult pattern of gene expression. Another type of hypertrophic growth often referred to as compensatory or pathologic hypertrophy, occurs in response to work-overload of the post-natal heart; work-overload

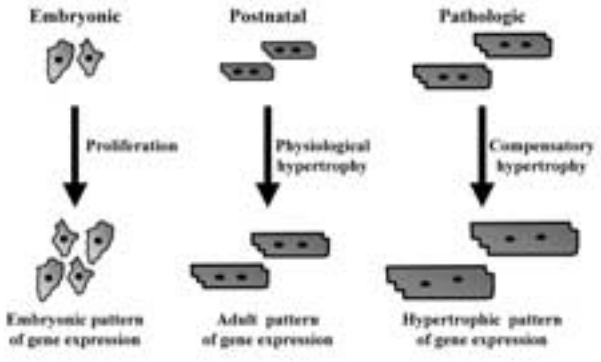


Figure 1. Developmental dependent patterns of myocyte growth

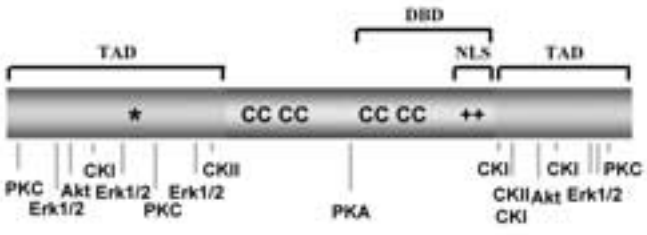


**FIGURE 2. Schematic representation of the GATA-4 protein showing the functional domains and putative phosphorylation sites. TAD = transactivation domain; DBD = DNA binding domain; NLS = nuclear localization signal. The * denotes a confirmed MAPK phosphorylation site**

may be due to a variety of physical or hormonal stimuli such as increased pressure, mechanical stretch, vasoactive hormones and myocardial infarction. Although in these cases, myocyte hypertrophy is initially a compensatory response, it often leads to decompensatory, cardiac dysfunction and ultimately, heart failure. Understanding the molecular mechanisms required for proper myocyte function is therefore of great scientific, medical and economic relevance. Because each stage of heart development is characterized by a distinct pattern of gene expression, defining the mechanisms that regulate gene transcription constitutes an important step towards understanding the molecular basis of myocyte function. Interestingly, many embryonic genes are reexpressed during pathologic hypertrophy, a finding that has lead to the hypothesis that the mechanisms of gene transcription in embryonic and hypertrophic (pathologic) growth are similar.

## The ANP gene, an exquisite marker of cardiac growth

In order to define transcriptional control of cardiac growth, we have used as marker the gene encoding atrial natriuretic peptide (ANP), the major secretory product of the heart. ANP is a hypotensive hormone with natriuretic and diuretic properties that acts on target organs via membrane receptors that have guanylate cyclase activities. The physiologic importance of the ANP system was evidenced by the phenotype of mice in which the ANP receptor or the ANP genes were inactivated leading in both cases to hypertension [reviewed in (13)]. The ANP gene is expressed predominantly in the heart, where its transcription is dynamically regulated in a spatial and temporal manner. In particular, ventricular expression of ANP characterizes the embryonic but not postnatal heart as ANP transcription is rapidly downregulated after birth but is again upregulated in conditions of pathologic hypertrophy, be it in animal models or human subjects [reviewed in (16)]. In fact, increased ventricular ANP level is a widely accepted hallmark of the genetic switch that accompanies pathologic hypertrophy, and measurement of the resulting increased plasma ANP is routinely used in clinical settings for the diagnosis of cardiac dysfunction (13). A genomic fragment containing the first 700 bp of ANP upstream sequences is sufficient to recapitulate the cardiac and temporal expression of the ANP gene. Work carried out in our laboratory over the past 10 years identified, within this region, numerous cis-regulatory elements required for proper cardiac transcription. The transcription factors that bind these DNA sequences were also characterized, including GATA-4 (Fig. 2), a cardiac-enriched member of the GATA family of zinc finger proteins, which were shown to play crucial roles in hematopoiesis (6).

## GATA-4 and cardiac transcription factor

Members of the GATA family of transcription factors are zinc finger proteins that bind specifically to (AfT)GATA(A/G) DNA sequences (1). The founding member of this family, GATA-1, as well as GATA-2 and GATA-3, is largely restricted to the hematopoietic lineage, and targeted disruption of their genes have revealed an essential non-redundant function for each of these factors in hematopoiesis. Analysis of cardiac-specific promoters led to the cloning of an additional member of the GATA family, GATA-4, whose expression is mainly restricted to the heart and gonads

(6). GATA-4 can be detected in the bilateral cardiac primordia and, together with Nkx2-5, constitutes the earliest markers of heart field induction. Later, GATA-4 transcripts and proteins are detected throughout the myocardium and endocardium and persist at all stages of heart development. Transfection studies in noncardiac cells established that GATA-4 is a potent transactivator of numerous cardiac promoters.

As shown in Figure 3, GATA-4 binds the proximal ANP promoter where it physically and functionally interacts with several other transcription factors to regulate compartment-specific gene expression as well as hormonal response (4,19,20). Thus, a multimeric protein complex coordinated by GATA-4 is targeted by various extracellular stimuli and controls transcriptional changes of ANP and other cardiac genes. How cell signalling modulates this multimeric complex has not been fully elucidated. Bioinformatic analysis mapped several putative phosphorylation sites on GATA-4 (Fig. 2) and work in our laboratory and elsewhere confirmed that GATA-4 can be regulated by several kinases, including the ERK and p38 MAP kinases (3,14). In fact, GATA-4 appears to be an essential nuclear mediator of the Rho family of small GTPases that coordinate Rho effects on gene expression and cytoskeletal remodeling (3). Although recent work in our lab indicates that other kinases also directly regulate GATA-4 (Wang et al, unpublished data), it is important to note that GATA-4 activity may be indirectly regulated by numerous intracellular pathways that target GATA-4 collaborators (Fig. 4). These include the calcium-calcinurin pathway which targets transcription factor NFAT which was shown to playa role in cardiac hypertrophy (18) as well as the protein kinase C and JNK pathways which target the AP1 proteins jun/fos, and the CAM kinase and p38 MAPK which target the Mef2 proteins (11,21). In the next years, it will be interesting to determine, through proteomics and mass spectroscopy, the exact composition of the GATA complex in cardiomyocytes at different developmental stages and in response to various agonists, and how different post-translational modifications influence the ability of GATA-4 to assemble distinct,transcriptionaly active complexes.

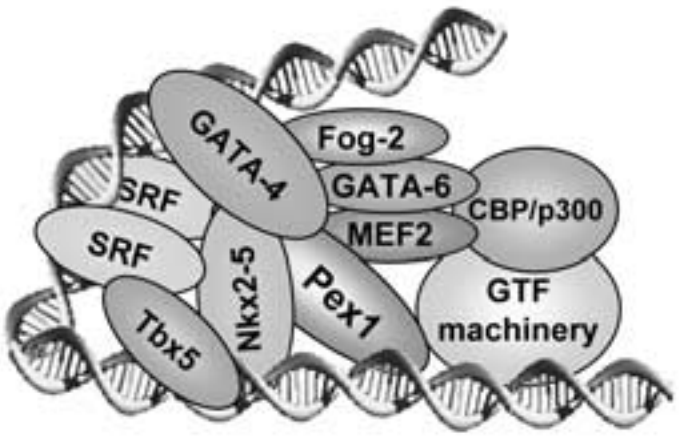


**Figure 3. The Proximal ANP Enhanceosome**

## GATA-4, a survival factor for cardiomyocytes

In addition to its function as a potent activator of cardiac genes, gain- and loss-of-function studies in various experimental models indicated that GATA-4 is essential for cardiomyocyte survival, proliferation and differentiation. For example, in *drosophila*, the GATA-4 ortholog pannier, is required for proliferation of cardioblasts (5), a result consistent with our finding that embryonic stem cells in which GATA-4 protein was downregulated undergo apoptosis at a cardioblast stage (7). Mice lacking both GATA-4 alleles die *in utero* due to a migration defect of precardiac cells which fail to form a primitive heart tube (17). In human, GATA-4 haplo-insufficiency is associated with congenital heart defects (22). These results indicate that GATA-4 is an essential component of cardiogenesis and suggest that GATA-4 may be required for the action of one or more growth factors required for cardiomyocyte survival/ proliferation/differentiation. Indeed, GATA-4 is one of the earliest targets of the TGF/BMP family of cardiac inducers (23). GATA-4 is also a target of retinoic acid and may mediate its effects during cardiac development (12). In support of the hypothesis that

GATA-4 is a target of cardioregulators, we found that overexpression of GATA-4 enhances in vitro cardiogenesis of embryonic stem cells (7).

The essential role of GATA-4 during development prompted us to analyze its role in the terminally differentiated postnatal heart. For this, we engineered adenoviral vectors that express sense or antisense GATA-4 transcripts and used them to infect post-natal cardiomyocytes in primary cultures. Decreased GATA-4 protein levels led to decreased expression of several cardiac genes including ANP, BNP, and amyosin heavy chain (2). Remarkably, the cellular response of myocytes to hypertrophic stimuli like endothelin-1 (ET1) and α1-adrenergic agonists was also blunted as evidenced by the inability of cells to reorganize their cytoskeletal or increase their size (3). Ectopic expression of GATA-4 mimicked the hypertrophic changes elicited by ET-1 and α1 adrenergic agonists suggesting that GATA-4 is essential, and its activation, sufficient for the adaptive response of post-natal cardiomyocytes. This conclusion is supported by several studies showing that GATA elements are required for activation of cardiac genes in response to in vivo pressure or volume overload (8,10,15), and that GATA-4 levels and/or activity are upregulated in in vivo models of cardiac hypertrophy (9) and our unpublished data.

## Conclusions and perspectives

The discovery and characterization of GATA-4 represent a major advance in our understanding of the mechanisms underlying cardiac function. GATA-4 is central to embryonic cardiomyocyte growth, to maintenance of the differentiated state of postnatal cardiomyocytes and their adaptive response to work overload. That a single transcription factor can exert such pleitropic effects highlights the efficiency of the cell but also raises important questions as to how a given protein can mediate distinct function. Obviously, protein-protein interactions as well as post-translational modifications must play essential roles in this process. In coming years, the identification of GATA-4 target genes as well as GATA-4 collaborators at different stages of cardiomyocyte growth will further enhance our understanding of the role of GATA-4 in the heart and also of the molecular basis of myocyte growth and function. Finally, knowledge of GATA-4 upstream regulators might offer new avenues for pharmacologic regulation of GATA-4 for purposes of cardioprotection.

## ACKNOWLEDGMENTS

I wish to acknowledge the invaluable contributions of all past and present members of the lab and the expert secretarial help of Use Laroche. Special thanks to Dr Pierre Paradis for discussions and assistance with the illustrations. Work carried in our lab is supported by grants from the Canadian Institutes of Health Research, the Heart and Stroke Foundation of Canada and the Société de recherche sur le cancer. MN holds a Canada Research Chair in Molecular Biology.

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# 2003 Society Award Designates

Dr. Victor Ling, BC Cancer Research Centre, Vancouver, B.C. has been chosen to receive the 2003 Roche Diagnostics Prize for Biomolecular and Cellular Research and the 2003 CSBMCB's Merck Frosst Award has been granted to Dr. Charles M. Boone, Banting and Best Department of Medical Research, University of Toronto. The 46th Annual General Meeting of the Canadian Society of Biochemistry, Molecular and Cellular Biology will be held July 20 -24, 2003 at the Toronto Convention Centre conjointly with the 19th Congress of International Union of Biochemistry and Molecular Biology. Both of our Society's Award Lecturers have been honoured by being designated as Plenary Speakers at the 2003 IUBMB Congress.

## Dr. Victor Ling

Dr. Ling's primary research accomplishments stem from his discovery in 1972 of multi-drug resistance (MDR). This was truly a pioneering effort, since it was rare at that time to induce and study mutants in mammalian cells. Subsequent investigation by Dr. Ling showed that P-glycoprotein is associated with MDR. He then cloned the gene for P-glycoprotein and transfected it into mammalian cells to show that it is responsible for MDR. Cloning also facilitated the characterization of P-glycoprotein, its relationship to hemolysin B, its identification as a member of the ABC-transporter superfamily and characterization of related genes of medical relevance.

Cancer cells acquire the metastatic phenotype during disease progression. Dr. Ling showed in 1982 that metastatic variants are stochastically generated at a high rate in tumour cell lines and that this can account for the correlation between cancer progression and genome instability. He subsequently showed that poor clinical outcome in a number of cancers is the consequence of P-glycoprotein expression. This provided a potential approach to cancer therapy, which Dr. Ling applied successfully in 1995 when he demonstrated that cyclosporine A inhibition of P-glycoprotein greatly improves long-term response to chemotherapy of children with retinoblastoma.

Dr. Ling plays a major leadership role in the cancer community in Canada. He developed the Division of Structural Biology at the Ontario Cancer Institute and recruited a number of Canada's premier structural biologists into the Division. This greatly increased Canada's profile in structural biology and had a major impact on cancer research in this country. He currently serves as Vice President (Research) at the BC Cancer Agency and as Vice-Dean (Cancer Research) at the University of British Columbia. He also developed and leads a cancer genomics program in BC, funded by Genome Canada. Dr. Ling established the BC Genome Sequencing Centre as an integral component of the BC Cancer Agency. This was the first sequencing centre in Canada to be directly linked to a cancer treatment organization. He recruited Michael Smith to be the first Director of the Centre. This initiative ultimately led to the establishment of the Centre for Integrated Genomics and a new Cancer Research Centre. In addition to his efforts in British Columbia, Dr. Ling serves on the Board of the National Cancer Institute of Canada and the Governing Council of CIHR.

Vic Ling is a distinguished scientist and a true academic leader. He is a credit to the Canadian biochemistry community and a worthy recipient of the Roche Diagnostic Award.

## Dr. Charles Boone

Dr. Boone is one of Canada's foremost young biochemists - his work in proteomics has been internationally recognized because it has provided important concepts concerning the way that multiple signalling pathways are connected in a single cell, to control state changes in response to extracellular signals.

Dr. Boone demonstrated outstanding research abilities as a graduate student in Biology with Dr. Howard Bussey at McGill University. He demonstrated that the unprocessed precursor of a secreted protein could have a unique biological function and he defined the series of genes which encode proteins in the pathway of α-glucan biosynthesis; some of these genes are essential for viability and represent antifungal drug targets. These findings formed the basis for a patent on glucan genes which provided intellectual property for the founding of an antifungal drug discovery company, Mycota Biosciences. In his postdoctoral studies, Charlie became interested in signal transduction. He determined that the third intracellular loop of the yeast a-factor receptor, Ste3, functions as a negative regulatory domain. In this work, he was the first to characterize a constitutive G protein-coupled receptor.

In independent studies, Dr. Boone became interested in cell polarity and the role of signalling to actin and myosin assemblies. In 1997, he was able to demonstrate that formins, which are involved in the establishment of cell polarity in Drosophila oocytes and embryos, link Rho-type GTPase signalling molecules to actin assembly proteins. He followed this work up in 2000, with a study showing that SH3 domains in myosin-1 bind the yeast homologues of human WASP and WIP. Since these proteins link actin assembly and signalling molecules, Dr. Boone was beginning to put together a very important signalling complex involved in cell polarity and motility. His studies provided the first evidence that myosin-1 motors participate in motility through a role in actin assembly. In his most recent work in this area, he showed that yeast formins assemble actin cables. This observation provided a very simple model for the control of polarized cell growth in yeast cells: signalling molecules activate formin proteins, which assemble actin cables at a growth site

to guide myosin motor-directed secretion.

In later studies, Dr. Boone's interest in signalling through protein-protein interactions led him to a collaboration with Rosetta Inpharmatics to use microarrays to look at changes in transcription that could be related to activation of parallel MAP kinase pathways in a single cell. His studies in this field provide the very best illustration of how DNA microarrays can be used to trace signalling networks. They also illustrate Dr. Boone's early interest in using the most elegant emerging technologies to advance his ideas.

Most recently Dr. Boone has been involved in large scale proteomics efforts. One of these is the investigation of protein-protein interactions on a genome scale in yeast. In one study, he collaborated with 10 other laboratories to map 191 protein-protein interactions that control cell polarity development in yeast. In a second study, initiated in his laboratory, but ultimately involving 4 laboratories, two different protein-protein interactions networks for yeast SH3 domain proteins were generated: one was derived from phage display ligand consensus sequences and another from two-hybrid interaction assays. This prototype study will be expanded as a rapid and general method that can be implemented readily for analysis of protein complexes formed through other peptide recognition modules. It will be equally useful for other organisms with a sequenced genome.

# News from Biochemistry Departments

## University of Alberta

### Department of Biochemistry

*Correspondent: Brian Sykes*

(From left to right) David Stuart, Carlos Fernandez-Patron, Andrew MacMillan, Kevin Wilson, Luis Schang, Leo Spyracopoulos, Mark Glover and Howard Young.

Andrew MacMillan

Carlos Fernandez-Patron

New Look Biochemistry at the University of Alberta!

The Department of Biochemistry at the University of Alberta has undergone tremendous change over the last decade. On the down side we have seen the retirement, promotion elsewhere, and/or departure of a number of stalwarts of the department - people like **Cyril Kay** and **Larry Smillie**, **Neil Madsen** and **Bill Bridger** (Head of Alberta Ingenuity), **Vern Paetkau** (Dean of Science at Victoria), **Doug Scraba** and **Dick Morgan**, **Carol Cass** (Acting Head of the Cross Cancer Institute) and **Bob Hodges** (Director of Structural Biology at the UCHSC in Denver). These people were, and are, icons on the Canadian biochemistry scene, and leave a legacy of excellence behind. On the other hand it has been a time of renewal in the department, and we have hired 8 active young investigators whose presence has added new vitality and breadth to our program. A recent picture of this group includes (from left to right) **David Stuart**, **Carlos Fernandez-Patron**, **Andrew MacMillan**, **Kevin Wilson**, **Luis Schang**, **Leo Spyracopoulos**, **Mark Glover** and **Howard Young**. Their research is highlighted below.

**Andrew MacMillan** (Ph.D., Harvard, 1992; PDF, MIT, 1993-1996)

We use the techniques of organic synthesis as well as other biophysical approaches to investigate the mechanisms of gene regulation at the RNA level. Research in our laboratory is focused on the chemistry and biochemistry of nucleic acids with an emphasis on biologically important reactions involving RNA. Large RNAs and complex ribonucleoprotein machines such as the spliceosome and ribosome play a key role in constitutive and regulated cellular processes and in the life cycle of viral pathogens.

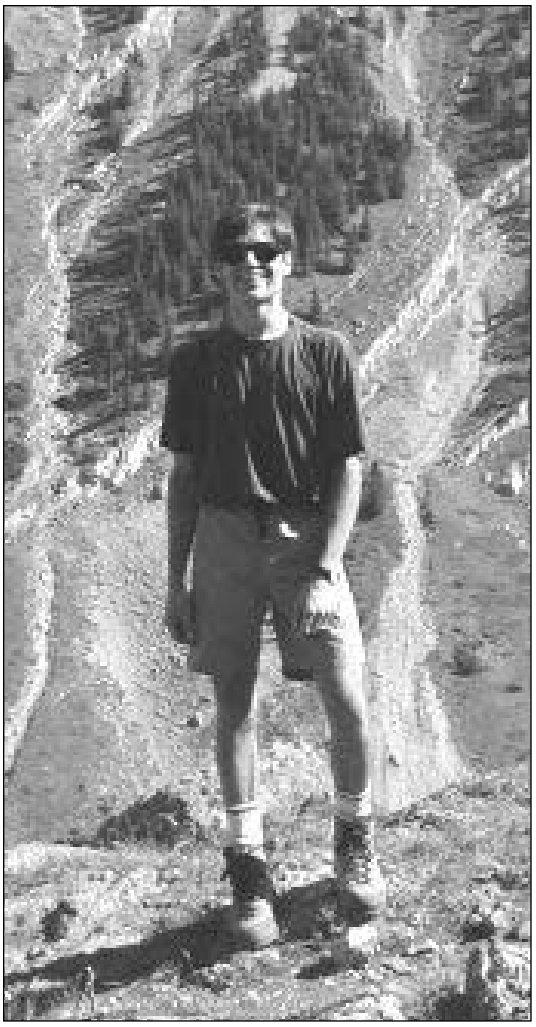
**Carlos Fernandez-Patron**

(B.Sc.,/M.Sc., Dresden, 1988; Ph.D., University of Havana, 1995; PDF, University of Alberta, 1997-2001)

My laboratory is characterizing novel roles played by matrix metalloproteinases in the regulation of vascular tone, cardiovascular remodeling and blood pressure. We are applying interaction proteomics to substantiate our pharmacological observations. In addition, we plan to map the cardiovascular proteome and characterize its dynamics in hypertension, as opposed to normotension.

**David T. Stuart**

(M.Sc., University of Waterloo, 1986; Ph.D., University of Alberta, 1991; PDF, Scripps Research Institute, 1992-1998)



Mark Glover

My lab studies the mechanisms that regulate DNA replication and chromosome division during meiotic differentiation. We focus on the budding yeast *Saccharomyces cerevisiae* as sporulation in this organism is an excellent model for mammalian spermatogenesis. We also study the function and activity of meiosis-specific kinase Ime2. We are using contemporary proteomic and microarray analysis in our program to gain further insight into the mechanisms that regulate meiotic differentiation.

**Howard Young** (Ph.D., University of Connecticut, 1994; PDF & Instructor, New York University School of Medicine, 1995-2002)

Calcium is an important signalling molecule, particularly in heart muscle where abnormal calcium signalling contributes to hypertension and end-stage heart failure. ATP-dependent calcium transporters play a primary role in the regulation of cytosolic calcium. Regulation of these transport processes provide a dynamic calcium metabolism that is coupled to precise physiological responses. My research utilizes the tools of structural biology to reveal fundamental aspects of calcium transport regulation implicated in heart disease.

**Kevin Wilson** (Ph.D., University of Oregon, 1995; PDF, University of California (Santa Cruz), 1995 - 2000)
My lab is studying fundamental mechanisms of translation, involving the ribosome and universally conserved translation factors. Our research focus is on the mechanism of translation initiation. We have recently developed a novel method for watching the assembly of translation initiation complexes, involving the 30S and 50S ribosomal subunits, fMet-tRNA, a model mRNA, and bacterial initiation factors IF1, IF2, and IF3. We are currently investigating the roles of the three initiation factors in the assembly of the initiation complex, making use of recently determined x-ray structures of the ribosome.

Howard Young

Kevin Wilson (right)

Leo Spyracopoulos

Luis Schang (center)

Chris Bleackley

Michael James

Ronald McElhaney

Marek Michalak

**Leo Spyracopoulos** (Ph.D., Manitoba, 1996; PDF, University of Alberta, 1996-2000)
The research focus of my laboratory is to gain an understanding of biological functions carried out by proteins and their complexes, and the kinetics, dynamics, and thermodynamics of proteins and protein-ligand interactions using nuclear magnetic resonance spectroscopic techniques. Our current objective is to elucidate the mechanism of protein ubiquitination at the molecular level by studying the structure, interactions, and dynamics of the human UEV–Ubc13 protein heterodimers.

**Luis Schang** (DVM, University of Buenos Aires, 1987; Ph.D., University of Nebraska-Lincoln, 1996; PDF, University of Pennsylvania, 1997-2000)
We study the roles that cellular proteins play in viral replication and pathogenesis, especially the roles of cyclin-dependent kinases in the replication cycle of herpes simplex viruses. The three areas of current research interest of the lab are: the mechanisms whereby cellular cyclin-dependent kinases regulate expression of viral genes, the effects of neuronal expression of proteins involved in cell-cycle progression, and the possibility that pharmacological cdk inhibitors may be useful as antiviral drugs against HSV, HIV and other viruses.

**Mark Glover** (Ph.D., University of Toronto, 1991)
My lab investigates fundamental molecular mechanisms that regulate the expression of genetic information. We have determined the 3D structure of the BRCT domain of the breast cancer-associated protein, BRCA1. This domain is a critical transcriptional activation domain that is essential to the tumour suppressor function of BRCA1. We are probing the structure and function of a novel RNA-based mechanism that controls the conjugative transfer of genes involved in antibiotic resistance and virulence between bacteria. We have determined the structure of a key regulator of meiosis in yeast, Ndt80.

The 'old guard' have also been active and successful, and carry on the tradition of excellence of our department. Our faculty have continued to garner many honours and awards in recent years. **Chris Bleackley** was awarded the 2001 Robert L. Noble Prize of the National Cancer Institute and was reappointed as a Howard Hughes International Scholar. **Marek Michalak** won the Astra/Zeneca Award in Molecular Biology. **Ronald McElhaney** received the 2001 Avanti Award in Lipids from the Biophysical Society. **Brian Sykes** won the Gerhard Herzberg Award of the Spectroscopy Society of Canada, and **Michael James** and **Joel Weiner** have both won the G. Malcolm Brown Award of the Canadian Federation of Biological Societies. In addition, **Chris Bleackley** and **Carol Cass** join nine other members of the Department as Fellows of the Royal Society of Canada and **Brian Sykes** joins **Michael James** as a Fellow of the Royal Society of London. **Chris Bleackley, Carol Cass, Michael James, Brian Sykes, Dennis Vance** and **Joel Weiner** have been appointed Tier 1 Canada Research Chairs and **Mark Glover** has been recently appointed a Tier 2 Canada Research Chair.

# University of Calgary

## Department of Biochemistry and Molecular Biology

*Correspondent: Leon Browder*

The Department of Biochemistry & Molecular Biology in the Faculty of Medicine at the University of Calgary is very diverse, with members belonging to ten different interdepartmental Research Groups. At the present time, 46 faculty members hold primary or secondary appointments in the department. Two new members will join the department in January. There are three Emeritus Professors and 13 adjunct appointees. Our research activities are supported by a number of excellent core facilities, including UCDNA Services, the Peptide Synthesis Facility, the Southern Alberta Mass Spectrometry Facility (SAMS), the Southern Alberta Microarray Facility (SAMF), the Embryonic Stem Cell/Targeted Mutagenesis Facility (ESTM), the SACRC Hybridoma Facility & Cell Bank and the Bio-NMR Centre and most recently the Sun Center of Excellence for Visual Genomics. The department offers graduate training leading to Ph.D. and M.Sc. degrees in Biochemistry and Molecular Biology.

### Faculty Transitions

**Dr. Phyllis Luvalle** has relocated to the University of Florida in Gainesville. She remains associated with us as an Adjunct Associate Professor.

**Dr. Randy Johnston** is President and Chief Executive Officer of Genome Prairie. Randy remains a member of our department and has an active research laboratory.

**Dr. Jonathan Lytton and Dr. Joe Goren** have assumed the roles of Co-coordinators of the graduate program in Biochemistry & Molecular Biology.

**Dr. Frank Jirik** was awarded a Tier 1 Canada Research Chair. Frank has a diverse functional genomics research program involving using cell biology, biochemistry, and transgenic approaches.

**Dr. Jim McGhee** was awarded a Tier 1 Canada Research Chair. Jim studies gut development in *C. elegans* (the Nobel Prize-winning worm).

### New Members of our Department

**Dr. George Chaconas** has recently returned to Calgary as a Professor and Alberta Heritage Foundation Medical Scientist. George obtained his Ph.D. in Calgary with Bob Church and Hans van de Sande before embarking on a very successful academic career at the University of Western Ontario. George studies telomere resolution, DNA replication and mechanisms of pathogenesis in *Borrelia burgdorferi*, the Lyme disease spirochete.

**Dr. Yang Yang** joined the department as an Assistant Professor in July. Yang holds a prestigious Career Development Award from the Juvenile Diabetes Foundation International. His research focuses on T cell immunology and autoimmune diabetes.

**Dr. Justin MacDonald** joins us in January, 2003 as an Assistant Professor and as recipient of the first PENCE Chair in Protein Sciences Research. Justin has been a Postdoctoral Fellow in Tim Haystead's lab at Duke University. Justin conducts proteomic investigations on smooth muscle function.

**Dr. Shirin Bonni** also joins the department in January, 2003 as an Assistant Professor. She has been a Postdoctoral Fellow in Jeff Wrana's lab at Sick Kids Hospital and the Samuel Lunenfeld Research Institute of Mount Sinai Hospital in Toronto. Shirin studies signalling and the regulatory mechanisms downstream of the TGFß receptor.

**Dr. Jens Coorsen** has his primary appointment in the Department of Physiology & Biophysics. Jens recently moved to Calgary from the NIH and has established a functional proteomics research program.

**Dr. Peter Vize** has become an Adjunct Associate Professor in our department. His primary appoint-

ment is in the Department of Biological Sciences. Peter came to Calgary from the University of Texas at Austin. He studies kidney development in *Xenopus laevis* and has a major interest in bioinformatics, particularly in correlating gene expression with development, both chronologically and spatially.

**Dr. Chris Brown** has his primary appointment in the Department of Medicine. His research involves physiological and pathological analyses of hematopoietic development and function.

**Dr. Mike Surette** has his primary appointment in the Department of Microbiology & Infectious Diseases. Mike studies bacterial signal transduction and physiology within the context of the individual cells and in interacting populations of cells. Mike has been awarded a Canada Research Chair (Tier II).

### Training Opportunities

Members of the Department of Biochemistry & 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.**


# University of Calgary

## Division of Biochemistry, Department of Biological Sciences, Faculty of Science

*Correspondent: Raymond J. Turner*

The past couple of years have seen some significant personnel changes in our division. Dr. **Peter Tieleman**, a computational biologist, has joined our division in 2001 whereas Drs. **Barry Phipps** and **Leslie Tari** have now both left to pursue careers in industry. Furthermore, Dr. **Susan Lees-Miller** has reduced her role in the Division to be able to contribute more actively to proteomics developments with the Department of Biochemistry and Molecular Biology in the Faculty of Medicine. The summer of 2002 saw the addition of two new protein crystallographers, Drs. **Marie Fraser** and **Kenneth Ng**, and the membrane biochemist Dr. **Elmar Prenner**. The stability of the faculty positions in our division has been significantly improved by the promotion of our two senior instructors Drs. **Robert Edwards** and **Elke Lohmeier-Vogel** to tenure-track positions. Moreover, tenure and promotion to associate professor was granted to Drs. **Raymond Turner** and **Greg Moorhead** as well. This results in the following makeup of our division: six AHFMR scholars/scientists, two tenured instructors, two tenured associate professors and one tenured full professor (Dr. **Gene Huber**). The division is currently being captained by an AHFMR scientist, Dr. **Hans Vogel**.

The addition of the new faculty members was possible through their success in obtaining Alberta Heritage Foundation for Medical Research Scholar positions and establishment awards. Research in our division is well funded by NSERC and CIHR operating grants as well as support from the Heart & Stroke Foundation and the Alberta and Canadian Cancer boards. Members of our division have also been very successful in obtaining infrastructure support from CFI and the Alberta Network for Proteomics Innovation. Additionally, some of our faculty members are

actively involved with the Alberta Synchrotron Institute, which contributes to the development of the Canadian Light Source in Saskatoon.

Research in the division is largely focused on structural biology and membrane biochemistry, with some activities in the area of control of metabolism. Our research interests range from purely theoretical molecular dynamics calculations, protein structure determination by NMR spectroscopy and x-ray crystallography, proteomics and bioinformatics, to the characterization of enzymatic catalysis and membrane function and architecture. Additionally, emphasis is being placed on various biophysical approaches such as protein-chip technology, microcalorimetry, fluorescence and infrared spectroscopy and stop-flow kinetic studies. The Division's Bio-NMR center has recently been enhanced by the incorporation of Canada's first NMR cryoprobe and the installation of a new 700 MHz NMR.

Our faculty is responsible for the undergraduate degree program in Biochemistry at the University of Calgary graduating an average of 35 Biochemistry majors, with ~40% being honours students. In addition to the training of biochemistry majors, our members also contribute significantly to the teaching of more general undergraduate programs in BioScience and Natural Science. A high level of research activity is maintained by undergraduate project students (averaging 20/year), summer students (16-20/year), graduate students (21 presently), and postdoctoral fellows (14 presently).

A more detailed description of the Division of Biochemistry and the research programs of its members can be found at **www.ucalgary.ca/UofC/faculties/SC/BI/biochem**.

# University of Guelph

## Biochemistry Group, Department of Chemistry and Biochemistry

*Correspondent: Frances Sharom*

Preparations are well advanced in support of the construction to start on Phase 1 of the Science Complex, the second part in the SuperBuild Growth Fund enhancements to the University of Guelph campus. The Classroom and Science Complex total over 400,000 square feet of new facilities and is one of the biggest construction projects in the University's history. The new science complex will accommodate many of the biological science units, including Molecular Biology, Biochemistry, Microbiology, Botany and Zoology, under one (large) roof. Partial demolition of one wing of an existing building took place in Fall 2002, and construction on the first phase of the project is slated for early 2003. Although the project will be disruptive for several years, everyone is looking forward to moving into well-planned modern research lab space 2-3 years down the road. The complex will also include completely new teaching lab facilities for biochemistry, molecular biology, and microbiology undergraduate students.

This has been another successful year for the group:

**Alan Mellors** is taking early retirement after 34 years in the Department of Chemistry and Biochemistry. He joined the Department in 1968. Previously he had obtained his degrees from the University of Liverpool, followed by a Fulbright Scholarship at the University of California, Davis, and a research appointment with Canada Agriculture, Ottawa. In 1975-76 he was a Nuffield Scholar on sabbatical leave at the Institute for Animal Physiology, Babraham, U.K. Subsequent sabbaticals were spent at the Hospital for Sick Children, and at the Toronto Hospital. Alan's research encompassed a broad range of topics, all connected with the interface between membrane components and enzymes. His interests in lipid

biochemistry included antioxidants, cannabinoids, and phosphoinositides. He studied phospholipases from sources as diverse as mammalian lysosomes, lymphocytes, and African trypanosomes. He and his students described an enzyme from *Mannheimia haemolytica* which is still the only known glycoprotease, that is, a proteolytic enzyme specific for a narrow range of O-sialoglycoproteins or O-sulfoglycoproteins. Alan hopes to be fit enough to fritter away his retirement years hiking, ski-ing and canoeing.

**John Dawson** joined the biochemistry group as of July 2002. John obtained his B.Sc. at Laurier (Honours Biology & Chemistry) and moved out west to Edmonton in 1992 to do a Ph.D. in the Department of Biochemistry at the University of Alberta. There, he was the first graduate student of a new professor, Dr. Charles Holmes. John studied protein phosphatases and a handful of natural toxins that specifically inhibit them. As part of this work, he used *S. pombe* and *E. coli* expression systems and also learned how to culture marine dinoflagellates. John met his wife Amanda in Edmonton and one month after they were married, they moved to California. His protein biochemistry background was put to good use in the laboratory of Dr. Jim Spudich in the Biochemistry Department at Stanford University, where he began postdoctoral work in 1998. There, he was exposed to a multidisciplinary group that studied molecular motors using a variety of innovative and powerful techniques. John began to study actin, because its ability to self-assemble into long filaments is the core problem hindering the production of atomic resolution pictures of the actomyosin complex. In Jim's lab, John set up a very productive collaboration with Drs. Sablin and Fletterick at UCSF, and together they determined the crystal structure of an actin trimer; the first crystal structure of an F-actin derived fragment ever produced. As with many research projects, this work has led to unexpected and exciting avenues of study which John is pursuing here at Guelph, including the cell biology of yeast strains that harbour significant actin mutations, and the effect of nucleotide hydrolysis on the structure and regulation of F-actin. John has already obtained an NSERC Discovery Grant, and is working on CFI New Opportunities and CIHR applications.

**Marc Coppolino**, who arrived in the department in May 2001, was awarded a CIHR New Investigator Award, a CIHR Operating Grant, and an NSERC Discovery Grant. He has also been awarded CFI New Opportunities funding for a confocal microscope. Marc's group is currently studying the molecular mechanisms of cell motility. Specifically, they are analyzing the proteins that control the membrane remodelling (SNAREs), the actin reorganization (paxillin), and the adhesion (integrin-linked kinase) that are required for cells to spread upon or migrate over extracellular matrices.

**Frances Sharom**

The Sharom group is continuing their studies of membrane proteins, including the P-glycoprotein multidrug transporter. Fluorescence spectroscopy now plays a central role in the life of the lab in general, and has led to some exciting insights into the interaction of the protein with its substrates, and its mechanism of action. Another project looks at the structure, function and membrane interactions of various GPI-anchored enzymes and adhesion proteins. Collaborations with research groups in Granada (Spain) and Lyon (France) led to the visit in Fall 2002 of two Ph.D. students, Paco Muñoz and Olivier Dalmas, both supported by European exchange scholarships. Together with Miguel Lugo, a visiting professor from the University of Caracas, Venezuela, on a 2-year fellowship, they greatly added to the multinational nature of the laboratory. Both returned to warmer climes before Christmas, but have promised to return when it warns up next summer. Frances is looking forward to a reciprocal visit to both European locations.

**David Josephy**

The focus of the Josephy laboratory is on chemical mutagens and carcinogens, especially the aromatic amines. These chemical are used industrially and they also occur as natural products in the environment. Potently mutagenic heterocyclic

amines are formed by the grilling of protein-rich foods, especially meat and fish. Analytical chemistry approaches are used to investigate the kinds and amounts of these substances present in the environment and in human biofluids, where they may be biomarkers of human health risk. Another area of interest is in the metabolism and bioactivation of carcinogens, especially the development of animal-free experimental systems. Recombinant human enzymes, such as P450 1A2, which metabolize carcinogens and other xenobiotics, are being expressed in bacteria. This work has led us to a detailed study of the structure and function of P450 and other enzyme proteins. Another system which we are investigating is the BigBlue transgenic rodent mutagenicity assay, which allows us to study the genotoxicity of carcinogens in cultured mammalian cells.

**Rod Merrill**

The Merrill lab is involved in several project related to protein structure-function and protein folding, especially as it relates to membrane-targeted toxins, such as the colicins. They are also seeking to elucidate the mechanism of mono-ADP-ribosyltransferases using a combination of molecular biological, biochemical, and biophysical techniques, especially fluorescence spectroscopy. They are currently investigating the mechanism of an enzyme produced by the human pathogen, Pseudomonas aeruginosa, known as Exotoxin A (ETA). An NSERC Major Equipment Grant was awarded to Rod this past spring for a Fluorescence Lifetime Fluorimeter, which Rod's research group is now putting to good use. One of Rod's graduate students, Susan Yates, received a Canadian Cystic Fibrosis Ph.D. Studentship in April 2002 to work on a CCFF project to characterize competitive inhibitors of Pseudomonas aeruginosa exotoxin A.

**Dev Mangroo's** research projects include identification and characterization of novel proteins involved in nucleocytoplasmic export of RNA in Saccharomyces cerevisiae, as well as translational control of gene expression in eukaryotes and bacterial protein initiation. Dev is currently on sabbatical leave, and has been spending time in the labs of various collaborators in the US and Canada. **Bob Keates** is continuing his very productive collaboration with Dev, involving prediction of the protein domain organization, structure and folding from amino acid sequences. His insights are allowing members of the Mangroo lab to test various hypotheses by site-directed mutagenesis.

**Fred Brauer's** group is using nuclear magnetic resonance (NMR) imaging and spectroscopy to elucidate the mechanisms of altered energy metabolism in the livers of intact, living animals non-invasively. NMR imaging can provide information, in spectacular detail, about the anatomy of an organ within the body. Localized in vivo NMR spectroscopy can, at the same time, provide valuable biochemical information from any defined region determined from the NMR image. These techniques are used to study the effects of classical hepatotoxicants such as bromobenzene, the halocarbons, and chronic ethanol administration on rat liver. They are also investigating how these toxic compounds alter hepatic water, lipid and electrolyte distribution, bioenergetic status, and the liver's ability to metabolize test compounds. High resolution multinuclear one- and two-dimensional NMR spectroscopy of in vitro tissue extracts are used to complement the in vivo studies, and as an independent analytical technique.

# University of Guelph

## Department of Molecular Biology and Genetics

*Correspondent: David Evans*

The last eighteen months have been busy in the Department of Molecular Biology and Genetics.

Four new faculty have joined us: **Joe Colasanti** (plant molecular biology), **Dick Mosser** (heat shock), **Andrew Bendall** (developmental biolo-

gy) and **Ray Lu** (herpes virus) and all have succeeded in attracting funding from the Federal granting councils. Dick, Andrew, and Ray are also to be congratulated for their recent success with a CFI application. The new microscopes they will be purchasing will significantly improve the advanced imaging capabilities in the department. MBG also welcomed **Steven Rothstein** back to the department. Steven left the University in 1998 to take up a posting at Pioneer-Hybred in Iowa. Upon his return to Guelph he was appointed a University Research Chair in plant molecular biology.

In the last year we also noted the retirement of **Dr. Stan Blecher**. A long-time member of our Faculty and co-founder of the biotechnology company Gensel, Stan is a medical geneticist and one-time Director of Guelph's Human Biology program.

On the teaching front the Department was recently awarded funding from Agilent under their Colleges and Universities Grant program. The first award of its kind in Canada, the funds have permitted the purchase of several advanced pieces of instrumentation including a capillary electrophoresis system and LC-Mass spectrometer. This equipment will dramatically improve the quality of our advanced undergraduate instruction as well as meet many of the separation and analytical needs of our researchers.

The department has also been working to bring into full operation DNA chip fabrication facilities and a MALDI-TOF mass spectrometer funded with the assistance of the CFI and the Ontario Research and Development Challenge Fund. Two new research technicians have been hired to operate these facilities, Ms. M. Howes and Dr. D. Brewer, and as a result of their capable management both operations are now fully functional. Readers interested in accessing these services are invited to contact this correspondent at dhevans@uoguelph.ca.

# University of Lethbridge

## Departments of Biological Sciences, and Chemistry and Biochemistry

*Correspondent: Marc R. Roussel*

At the University of Lethbridge, research in biochemistry and cell and molecular biology is spread over two departments, namely Biological Sciences and Chemistry and Biochemistry. The two departments have a close working relationship. Among other things, this benefits our graduate students who often have substantial interactions with faculty members in both Departments.

Good things happening in one department are often cause for rejoicing in both. We were thus doubly pleased to celebrate the appointments of our colleagues **Stewart Rood** (Biological Sciences) and **Randall Weselake** (Chemistry and Biochemistry) to University of Lethbridge Board of Governors Research Chairs last year. These Chairs provide Randall and Stewart with reduced teaching loads to enable them to focus more of their attention on their highly successful research programs.

Stewart's work on gibberellins is probably known to many readers of the Bulletin. Stewart's recent work in this area has focused on the involvement of gibberellins in the control of shoot dormancy. Stewart also has an active research program on the ecophysiology of river valley cottonwoods, with particular emphasis on the effect of the water table both on individual trees and on cottonwood populations. The multidisciplinary approach which Stewart takes to these complementary research areas creates a vibrant training environment in his lab to which students are strongly drawn, with good reason.

Randall's research, which is again probably not unknown to many readers of the Bulletin, focuses on triacylglycerol biosynthesis in oilseeds and in cattle. On the plant science side of his operation, Randall has been focusing on oil formation in canola and flax seeds. He is interested in increasing seed oil content and in modifying the fatty acid composition of oil by altering the expression and properties of key enzymes in the oil formation pathway. He is also investigating the effect of environmental stresses, such as low temperatures and drought, on oil formation in developing seeds. In his research with cattle, Randall has spent a number of years investigating intramuscular fat deposition in an effort to develop predictors of the marbling trait which is an important determinant of flavor. In recently initiated research, he has also been studying aspects of milk fat production. This extraordinarily active research program has attracted more than ß300 000 in funding in the current year alone from the Alberta Agricultural Research Institute, the Alberta Crop Industry Development Fund, the Dairy Farmers of Canada, the Flax Council of Canada, Genome Prairie and NSERC. Randall believes in a multidisciplinary approach and has a number of collaborations both locally, notably at the Agriculture and Agri-Food Canada Lethbridge Research Centre, and within the broader research community across Canada and around the world. These collaborations create opportunities for students to travel and to experience first-hand the research culture of other regions of the world.

We have hired a number of talented scientists in both Departments in recent years. All have received operating grants from NSERC, and there have been a number of successful equipment grant applications as well. In addition, **Igor Kovalchuk** received an Alberta Ingenuity Establishment Grant of $230 000 in April for his research on pathogen-induced plant genome instability. Igor used some of this money to purchase a plant growth chamber and a gel imaging system. The rest will pay for a postdoc and for some students. Igor joined the Department of Biological Sciences in 2001.

**Steven Mosimann**'s macromolecular X-ray diffraction system became operational this year. This is a $500,000 Bruker-Nonius instrument which was funded by the Alberta Heritage Foundation for Medical Research and by the Canada Foundation for Innovation New Opportunities Fund. The installed system includes a 6 kW rotating anode X-ray generator with confocal Osmic optics, an Oxford Cryostream cooler, a 4-circle goniostat, and a CCD detector built around a 135 mm actively cooled chip. Steven's group is using this equipment to investigate the structure and function of RNA processing enzymes. Steven has been with the Department of Chemistry and Biochemistry since the Fall of 2000.

Stewart Rood

Randall Weselake

Igor Kovalchuk

Steven Mosimann

# University of Manitoba

## Department of Biochemistry and Medical Genetics

*Correspondent: Spencer Gibson*

**Dr. Jane Evans**, Head, has accepted the Chair of the Manitoba Health Research Council.

**Patrick Frosk**, graduate student of **Dr. Klaus Wrogemann** (Professor) discovered the gene for limb girdle muscular dystrophy type 2H (LGMD2H). This muscular dystrophy is common in the Hutterite population. The gene, TRIM32, has the structure of an E3-ubiquitin ligase. Patrick also discovered a second gene for LGMD in Hutterites, the FKRP gene, causative for LGMD2I. Klaus was invited to speak of these findings at the ENMC workshop on limb girdle muscular dystrophies in Naarden Holland, at the Xth International Congress on Neuromuscular Disease in Vancouver and at the 7th International Congress of the World Muscle Society. Patrick also was selected to give a platform presentation at the Congress in Vancouver in July of this year.

**Dr. Jim Davie**, Professor and Director of the Manitoba Institute of Cell Biology, has received funding from CFI to establish the Manitoba Breast Cancer Research Centre to be housed on the 6$^{th}$ floor of the CancerCare Manitoba building. The mandate of the Centre is to identify biomarkers in the early detection of breast cancer. State of the art platforms in advanced cytogenetics, gene profiling, proteomics and functional genomics will be featured in the Centre. Pivotal to this endeavor is the Manitoba Breast tumor bank, established and operated by **Dr. Peter Watson**, which will be housed in the Centre. Dr. Davie received invitations at NIH and at the DFG sponsored meeting called "Growth Factors, Tissue Repair, and Cancer", Cadenabbia, Lake Como, Italy to present his research on the role of signal transduction pathways in modifying the structure and function of chromatin.

**Dr. Davie**, as Editor of Biochemistry and Cell Biology, continues to support the Society's Winternational Symposia. The journal now has electronic submission and review processes in place. The journal welcomes manuscripts and minireviews. The journal would be particularly pleased if members of the Society would cite the timely reviews in members' research areas.

**Dr. Dakshinamurti**, Professor Emeritus, gave a keynote address entitled "Hypertension and Micronutrients" at the 4th Food Data conference of the Food and Agricultural Organization (FAO) at Bratislava, Slovak Republic, August 24, 2001. He was a member of the International Scientific Advisory Board of the triennial 5th International Symposium on Vitamin B6, Carbonyl Catalysis and Quinoproteins organized under the aegis of the International Union of Biochemistry and Molecular Biology at University of Southampton, U.K.(April 14-19, 2002). He gave an invited talk entitled "Neuroprotection by pyridoxine" and also chaired a Session at this Conference. He was invited by the Russian Academy of Sciences to give a Commemorative Address celebrating the 100th Birth Anniversary of the noted Russian Biochemist Akademician Alexander Braunstein at the Special Session of the Academy (May 28-31, 2002). His address given on May 30th was entitled "The Pharmacology of Vitamin B6 and Beyond". He has been invited by the Editors of the "Encyclopedia of Molecular Cell Biology and Molecular Medicine" (with an Editorial Board of eight Nobel Laureates) to contribute a review chapter on "Vitamin Receptors" to the 2nd Edition. He was a contributor to the 1st edition of this encyclopedia as well.

**Dr. Spencer Gibson**, Assistant Professor received a grant from the Cancer Research Society to study the role of growth factors in prevention of apoptosis. He presented his work at the 44$^{th}$ Annual Meeting of the American Society of Hematology and at the Annual Meeting of the American Society of Cell Biology. Dr. Gibson was also selected to represent Manitoba Medical Researchers in the newly organized Health Researcher Society of Canada that will advocate medical research in Canada.

**Dr. Sabine Mai**, Associate Professor in collaboration with Drs. B. Betty and J. Squire edited and co-authored the first textbook on FISH and molecular imaging (Oxford University Press, 2002). The C.I.H.R. Strategic Training Program Grant entitled "Innovative Technologies in Multidisciplinary Health Research Training" was awarded to Dr. Mai as the principle applicant. The first workshop was held on "Principles of Microcopy and Imaging". Participants came from France, Germany, Thailand, and Canada and enjoyed the multidisciplinary training atmosphere. Dr. Mai also spent a three month research study leave at the German Cancer Research Centre in Heidelberg, Germany to study proteins that interact with telomeres. Dr. Mai presented her research on c-Myc and genomic instability ("Les nouveaux aspects de l'instabilite genomique induite par c-myc) at the Congress de la societe francaise d'hematologie, Paris. She presented new imaging tools at the Euroconference on Quantitative Molecular Cytogenetics in Stockholm and a presented a workshop on TLS and genomic stability in Vancouver. Finally, she was invited to speak about "Novel aspects of c-Myc dependent genomic instability" at the OCI in Toronto.

**Dr. Geoff Hicks**, Associate Professor received renewed funding for his Functional Genomics Centre at Manitoba Institute of Cell Biology from C.I.H.R. He was also Chair for the CIHR Institute of Genetics New Principle Investigators Priority and Planning Committee. This committee successfully organized the first New Principle Investigator Meeting held at The Briars Resort and Conference Centre at Jackson's Point, Ontario. By all accounts it was a successful meeting and will hopefully be repeated in the future. Dr. Hicks has presented his research on TLS regulation of transcriptional activation at the Ewing's Sarcoma 2nd International Symposium in Dartmouth College, USA and conducted a workshop on large scale sequence-based screens in mouse embryonic stem cells at the 2nd International Gene Trap Workshop, Frankfurt, Germany.

# McGill University

## Department of Biochemistry

*Correspondent: David Y. Thomas*

The past year has been a very productive and exciting one for the Biochemistry Department. There have been new recruits, major successes in funding, and an expansion in the number of graduate students.

The Department of Biochemistry of McGill University has 20 faculty members and 21 associate members from other McGill departments and from hospital research institutes. There are major links with McGill Cancer Centre (director **Michel Tremblay**) and the Molecular Oncology group (director **Vincent Giguere**) and most of the members of these groups are also members of the Biochemistry Department. There are also 13 adjunct members of the Department who are located mainly in the biopharmaceutical research industry and research institutes. There are close scientific ties with new Montréal Genomics (director **Tom Hudson**) and Proteomics (director **John Bergeron**) building and with the McGill Centre for Bioinformatics (director **Michael Hallett**). There are presently 35 post-doctoral fellows and 142 graduate students in the Department, and operating grant funding is approximately $7.5M dollars per year. The Department has 350 undergraduate students who may enroll in the faculty, major or honors programmes.

Research in the Biochemistry Department covers a wide variety of areas in which specialized training for graduate degrees may be obtained. The Department is well equipped, and with the planned expansion. Major areas are Molecular and Cell Biology, Proteomics and Genomics, Chemical Biology, Cancer, Regulation of Gene Expression and Translation, Neurobiology, Lipid Biology, Enzymology, the Function of Membrane Proteins, and Structural Biology. Montréal has a dynamic and highly interactive

life sciences research community and a large number of biopharmaceutical companies. Montréal is a unique city combining North America with European cultures to generate an unmatchable lifestyle and with its 5 universities has a large student community.

The Biochemistry Department plans to expand its capabilities in Structural Biology, Chemical Biology and Genetics.
Prospective recruits, post-doctoral fellows and graduate students should see our website for details http://www.medicine.mcgill.ca/biochem/

## Kudos

We wish to share some of the achievements of our colleagues.
**Dr. Rose Johnstone**, a former Chair of the Biochemistry Department and now Professor Emerita, has prepared a fascinating history of the early years of the Biochemistry Department, with many interesting facts and insights into the development of Biochemistry at McGill University in Canada. She was recently persuaded to present a lecture to the James McGill Society and will publish this history soon.

The Biochemistry Department held its very successful research day in May organized, by the Department Associate Chair **Peter Braun** and the graduate students. The keynote lecturer was Lee Hood from the Institute for Systems Biology in Seattle. Pictures of the event are on our website.

**Philip Branton** a former Chair of the department who is the Director of the Cancer Institute of the **Canadian Institutes of Health Research,** has been elected Fellow of the Royal Society of Canada.

**Morag Park, Nicole Beauchemin,** and **Michel Tremblay** were all made full professors.

**Albert Berghuis, Imed Gallouzi, William Muller, and David Thomas** were all awarded Canada Research Chairs, together with the associated Canadian Foundation for Innovation awards.

**Philippe Gros** was appointed as a Distinguished Investigator of the CIHR.

**Jerry Pelletier** and **Morag Park** were appointed as Senior Investigators of the CIHR.

**Anne-Claude Gingras,** a graduate student from the Sonenberg laboratory, recently graduated, and was awarded the Governor General's Gold Medal and the award of les Grandes Montrealaises. She is now in the laboratory of Ruedi Aebersold at the Institute for Systems Biology in Seattle.

**Nahum Sonenberg** was made a James McGill professor, a Distinguished Investigator of the CIHR, a Howard Hughes International Fellow, and has also been awarded the Robert L. Noble prize of the National Cancer Institute of Canada for his achievements in determining the mechanism of the initiation of protein translation and its control.

## Recent Developments

New colleagues in the Department are
**William Muller** joined the Molecular Oncology Group at the MUHC and is a full member of the Department. Bill is a former McGill graduate student welcomed back to Montréal by old friends and new. William and his mice come to us from McMaster University.

**Arnim Pause,** a former graduate student from many years ago, joined the Cancer Centre and Biochemistry Department after a post-doc with Rick Klausner, a post at the Max-Planck at Martinsreid Munchen, and a stint as the group leader at Boehringer Ingelheim.

**Imed Gallouzi** joined us from the laboratory of Joan Steitz at Yale. He has a CRC chair and was also awarded a FRSQ chercheur-boursier.

**Karine Auclair** is a new associate member of the Biochemistry Department with a primary appointment in Chemistry. She joins us from post-doctoral training at Stanford and has research interests in chemical biology.

**Michael Hallett** is a new associate member of the Biochemistry Department with a primary appointment in Computer Science. He was trained at the University of Waterloo and at the ETH Zurich. He has research interests in Bioinformatics and is acting director of the McGill Bioinformatics Centre.

New adjunct professors are **Enrico Purisima** of the National Research Council of Canada, who has interests in macromolecular structure modeling, and **Prabhat Arya,** also of the NRC, who is a leading chemist who is interested in combinatorial methods and is collaborating with several members of the Department.

In addition to the continued success in operating grants and salary awards competitions, there were also successes in renewing our infrastructure and research capabilities.

**Dr. Kalle Gehring** led two successful applications to the Fonds de la recherche en santé du Québec (FRSQ) and the Canadian Foundation for Innovation (CFI); the first application together with colleagues at the Université de Montréal for a 600 MHz and 700 MHz NMR machines, and the second together with colleagues at the University of Ottawa, Université de Montréal, Sherbrooke, Laval and Dalhousie Universities for an 800 MHz NMR installation to serve Eastern Canada. This latter instrument will be installed in the old Paprican building on the McGill campus, which is presently undergoing extensive renovations.

A successful application to the FRSQ and CFI for establishing the McGill University Life Sciences Complex was led by **David Y. Thomas**. This was a joint application with the Faculty of Medicine, the Faculty of Science and the McGill University Health Sciences Complex, and together with a generous gift from Dr. Francesco Bellini, the new Bellini Life Sciences Building (BLSB) will join the venerable McIntyre Medical Sciences and Stewart Biology buildings to form the McGill University Life Sciences Complex. The new BLSB will house about 50 principal investigators and over 500 staff. There will be thematic research pursued by researchers from the participating departments in the areas of chemical genetics, cancer, the genetics of complex traits, and cell information transfer systems. The BLSB will also house an extensive mouse transgenic facility, chip fabrication facilities, and high throughput screening laboratories. The BLSB planning is overseen by the steering committee of **Michel Tremblay** (Cancer Centre & Biochemistry), **Paul Lasko** (Biology), **Alvin Shrier** (Physiology), **Hans Zingg** (MUHC) and **David Thomas**, and completion is planned for 2004.

The Biochemistry Department collaborated with the Département de Chimie and Département de Biochimie at the Université de Montréal in an application led by William Lubell to the Valorisation-Recherche Québec (VRQ) for the Québec Combinatorial Chemistry Consortium. This has enabled the director **Jerry Pelletier** to expand our chemical libraries and set up our screening facility which is now in cramped operational quarters.

The Biochemistry Department led an application to the CIHR for a Strategic Training Programme in Chemical Biology. The objective of this programme is to produce graduate students who pursue focussed research projects in chemical biology while receiving training in the broader set of disciplines needed to study the interaction of small molecules with proteins. Mentors for this programme are in the Departments of Biochemistry, Chemistry, and Pharmacolgy and the Director of the programme is **John Silvius**.

Finally, last but not least, **Albert Berghuis** is directing the approval of the McGill Structural Biology Centre through its initial development and approval.

We hope that during the **2003 International Congress of Biochemistry and Molecular Biology (IUBMB)** to be held July 20-24, 2003 in Toronto, Ontario, that many former colleagues will take the opportunity to visit Montréal and the Department.

# Memorial University of Newfoundland

## Biochemistry, Molecular and Cellular Biology

*Correspondent: Dr. Sean Brosnan*

The past year has been one of new hirings and some departures.

The Biochemistry Department saw the arrival of three new faculty members. Two of these (**Rob Bertolo and Janet Brunton**), who came from the University of Alberta, work in the area of Nutritional Biochemistry, which has long been a strength of the department. Rob joins us as a Canada Research Chair in Human Nutrition. Both Rob and Janet use the piglet as a model for the human neonate for their work on amino acid metabolism. **Kaushik Nag** has joined us from the University of Western Ontario, as a CIHR New Investigator. Kaushik works on the physical biochemistry of membrane lipids and lung surfactant. A fourth faculty member (**Ross McGowan**) will arrive this July from the University of Manitoba. Ross is a developmental biologist who uses zebra fish to study DNA methylation and gene imprinting. **Bill Driedzic**, formerly director of Memorial's Ocean Sciences Centre and head of the NCE in Aquaculture, has been awarded a Canada Research Chair in Marine Biochemistry, which he will hold, jointly, in the Ocean Sciences Centre and in the Department of Biochemistry.

In addition to these new arrivals, some of the old hands have also been busy. **Sean Brosnan** was appointed Chair of the Advisory Board for CIHR's Institute for Nutrition, Metabolism and Diabetes as well as a CIHR Senior Investigator. **Sukhinder Kaur** (hardly an old hand) was appointed a CIHR New Investigator. **Margaret Brosnan, Gene Herzberg** and **David Heeley** serve on CIHR grants committees. **James Friel** left us to become the Chair of the Department of Nutrition at the University of Manitoba. **Garth Fletcher** (who, together with **Choy Hew**, discovered arctic antifreeze proteins at Memorial) retired. Happily, he continues his activity via AFP, the Biotech company that exploits this protein.

The Division of Basic Medical Sciences has also attracted new faculty. **Bob Gendron** and **Helene Paradis**, who work on angiogenesis and developmental biology, have been recruited from the University of Cincinnati. **Jules Dore** has arrived from the Mayo Clinic to work on TGF-beta signalling. **Mishuru Hirosawa** and **Ken Hirosawa** will soon arrive from the University of Calgary to work, respectively, on neurobiology and rhea viruses.

On the Biotech front, Newfound Genomics opened its new laboratories. Newfound's scientific director, **Proton Rahman**, will exploit the genetic resource provided by the Newfoundland founder population to search for genes and polymorphisms associated with complex diseases such as obesity, Type 2 diabetes and arthritis.

# Université de Montréal

## Département de Biochimie

*Correspondent: Jurgen Sygusch*

In 2001, our department introduced the first undergraduate program in Bioinformatics, which was followed up by a M.Sc./Ph.D. program commencing in September 2002. By Fall of 2003, we also hope to have in place a professional Masters' program in Biochemistry. This program is intended to respond to the high demand for M.Sc. graduates by the biotechnology and pharmaceutical sector in Montreal. In addition to the theoretical courses, special emphasis will be placed on developing instrumentation and entrepreneurial skills.

Over the course of the last three years, the department has seen an infusion of young researchers with the arrivals of **Pascal Chartrand**, **Mounib Elchebly**, **Gerardo Ferbeyre**, **Nikolaus Heveker**

and **Alain Moreau**. **Hervac Philippe**, who obtained a Canada Research Chair in Bioinformatics and Genomic Evolution, was our latest addition as associate professor. **Sylvie Mader**, also associate professor, was recently awarded a CIBC Research Chair in Breast Cancer. Another Canada Research Chair in Integrative Genomics went to associate professor **Stephen Michnick** while **Michel Bouvier**, our chair, obtained a Canada Research Chair in Molecular and Cellular Pharmacology.

Faculty size in the department increased during this period with only two retirements: **Margaret Mamet** leaving in 2000 and **Rejean Morais** in 2001. The continuing pressure on additional laboratory space by our department is starting to bear fruit, and the department has been able to expand by 25% in recent years. However we still covet broom closets as potential lab space. The department is particularly pleased with its high performance in the university survey of per capita research funds obtained.

# Queen's University

## Department of Biochemistry

*Correspondent: Albert Clark*

**Dr. Glenville Jones** became Head of the Department of Biochemistry on July 1st, 2002, replacing **Albert Clark**, who had been in the position for 7 years (2 years as Acting Head plus a 5 year term). Dr. Jones has been a member of the Department since 1984. He has been a major world player in the field of vitamin D metabolism research. He is a member of the CIHR Institute of Nutrition, Metabolism and Diabetes Advisory Board. Dr. Clark remains in the Department as an active teacher and Coordinator of Graduate Studies.

Recent faculty changes include the appointments in 2001 of **Dr. Stephen Smith**, and in 2002 of **Dr. Andrew Craig** as Assistant Professors. Dr. Smith is a graduate of the University of Western Ontario, Department of Biochemistry following which he undertook post-doctoral studies at Oxford University in England. He brings protein NMR spectroscopy expertise to the Department. Dr. Craig is a graduate of the McGill University Department of Biochemistry. He then pursued post-doctoral work with Dr. Peter Greer in the Cancer Research Laboratories at Queen's University. He brings cell biology expertise to the department.

Two new Adjunct Assistant Professors have been appointed - **Dr. David Hyndman**, who supervises the Protein Function Discovery equipment facility and **Dr. Sonoko Masuda**, who is a Research Associate with Dr. Jones.

**Dr. Geoff Flynn**, a former Head of the Department, retired in June 2002 after 33 years in the Department, but is still seen regularly. He is CEO of Cardiomics, a venture capitol supported company developing therapeutic and diagnostic products for cardiovascular disease. **Dr. Eileen Walters**, an Associate Adjunct Professor, also retired after 33 years in the Department. Dr. Walters had coordinated and supervised the teaching laboratories, coordinated the Coop stream and taught the Biochemistry course for nursing students.

**Dr. Alan Mak** is Director of the recently formed Protein Function Discovery Group, a multi-disciplinary group crossing departmental and faculty boundaries, formed in relationship to installation of new equipment funded through the Canadian Foundation of Innovation and Ontario Innovation Technology funds in the amount of $9 million. The new equipment includes a 600 MHz NMR spectrometer, a mass spectrometer, and various other items which will be used for protein function discovery research. The departmental shared equipment was also updated significantly as the result of a successful CIHR multi-user equipment application.

Two successful CIHR training program applications will have an impact on the

Biochemistry Department graduate program - training programs are being initiated in Protein Function Discovery and in Cancer. A new stream has been initiated in the Honours undergraduate program - a major program which has less emphasis on laboratory work in fourth year and is primarily designed for those who don't plan to undertake graduate work. This adds to the Subject of Specialization stream which emphasizes laboratory based research and the Coop stream.

# University of Saskatchewan

## Department of Biochemistry

*Correspondent: Suzanne Laferté*

The Department of Biochemistry extends a warm welcome to five new faculty members.

**Dr. Kathy Hamilton**, a biochemist and nuclear magnetic resonance spectroscopist, is currently undertaking studies aimed at understanding the mechanistic details of protein ubiquitination, an important post-translational modification implicated in the regulation of many cellular processes, including cell cycle control and tumorigenesis.

**Dr. Hong Wang's** research focuses on the molecular and biochemical mechanisms of cell cycle regulation in plants, with a current focus on a family of plant cyclin-dependent kinase inhibitors. He is also interested in elucidating the differences in cell cycle regulation between plants and animals as well as understanding the relationship between the cell cycle and other plant developmental processes.

**Dr. Ron Geyer** will focus his research efforts on developing novel approaches and tools for analyzing signal transduction pathways. More specifically, he will use peptide-based reagents (peptide aptamers) to analyze the activities and interactions of proteins.

**Dr. Yu Luo's** research program is aimed at studying signal transduction in the bacterial SOS response to DNA damage. Using molecular and structural approaches, including x-ray crystallography, Dr. Luo hopes to shed light on the molecular mechanisms underlying the bacterial SOS pathway and provide rational targets for designing antimicrobial compounds.

**Dr. Stan Moore's** research program will map out interactions between components of the flagellar export pathway of the bacterium *Helicobacter pylori* by X-ray crystallography. In light of the importance of *Helicobacter pylori* in gastric disease, this research will provide pioneering insights about the function of the multicomponent protein export machine in bacteria as well as provide crucial information for the development of novel anti-bacterial agents.

The Department congratulates all of our new members for their success in the recent HSURC (Health Services Utilization Research Commission) grant competition. Each faculty received a two-year grant of $40,000 per annum with an additional $30,000 for equipment. In addition, Drs. Geyer and Wang have received $465,000 and $150,000, respectively, from the Canadian Foundation for Innovation.

# Université de Sherbrooke

## Département de Biochimie

*Correspondent : Marcel Bastin*

Récemment, le Département de biochimie a recruté deux nouveaux professeurs. Le docteur **Simon Labbé** s'intéresse à l'identification et à la caractérisation moléculaire de composantes qui contrôlent l'entrée d'ions métalliques comme le cuivre et le fer. Le docteur **Martin Bisaillon** étudie le mécanisme moléculaire des protéines impliquées dans la synthèse de la coiffe des ARN messagers.

# University of Toronto

## Department of Biochemistry

*Correspondent: David Williams*

### Faculty News

We are very pleased to announce that **Reinhart Reithmeier** commenced a 5 year term as Chair of the Department beginning July 1, 2002. Reinhart previously held his primary appointment in the Department of Medicine and is a member of the CIHR Group in Membrane Biology. He takes over from **Peter Lewis**, who led the Department since 1991, and **David Isenman**, who served as Acting Chair from January - June 2002.

Reinhart Reithmeier

**Peter Lewis** continues to assume a leadership role within the University as Vice Dean of Research in the Faculty of Medicine, a position he assumed July 1, 2002.

**Bibudhendra (Amu) Sarkar**, who led the Division of Structural Biology and Biochemistry at the Research Institute of the Hospital for Sick Children for the past 12 years, has announced that he is stepping down as Head as of December 31, 2002. **Lynne Howell** has been appointed as

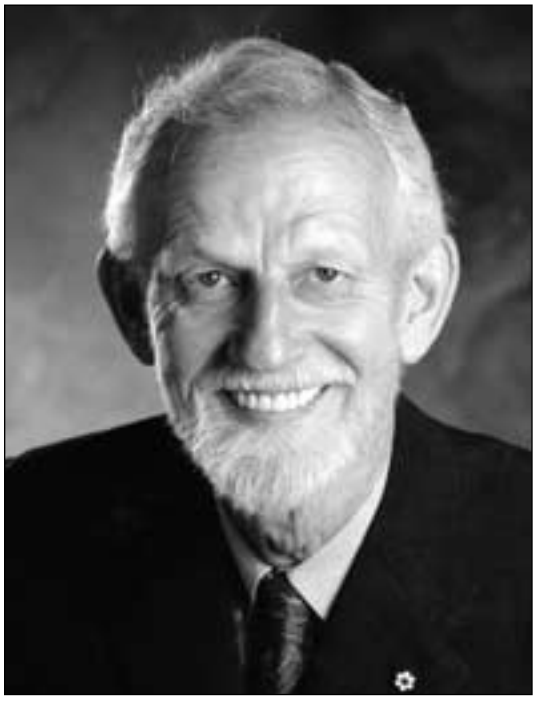
Peter Lewis

Interim Head. **Hugh Lawford** retired from the Department this year and we all wish Hugh the best for the future. **Theo Hofmann** continues to enjoy an active retirement, dividing his time between his two passions: in the lab studying aspartyl proteinases, and in the field, birding. He is currently Regional Coordinator in the collection and processing of data for an Atlas of the Breeding Birds of Ontario.

**David Williams** became Graduate Coordinator for a three year term beginning Nov. 1, 2001. He succeeds Jacqueline Segall, who did a terrific job in this position from 1999-2001.

On November 5$^{th}$, 2001, the Department lost a longtime colleague and friend in Dr. Dorothy (Dorrie) Johnson. Dorrie was a Lecturer from 1972-1976, during which time she was very active in running our advanced laboratory course for biochemistry specialists. She was subsequently a Research Associate at the Hospital for Sick Children, and maintained her interests in science well beyond retirement. She was an enthusiastic participant at the CSMBCB Winternational meeting at Mont Ste. Anne in 2001 at the age of 79! We all fondly remember Dorrie's warm nature and good humour.

Several faculty were honoured with awards in the 2001-2002 academic year. The Royal Society of Canada recognized the scientific accomplishments of two of our colleagues. **Lewis Kay** received the Flavelle Medal, which is awarded every two years to a Society Fellow for "an outstanding contribution to biological science during the preceding ten years, or for significant additions to a previous outstanding contribution to biological science". **Sergio Grinstein** was awarded the McLaughlin Medal, which is bestowed annually to recognize "distinguished achievement in medical science in Canada". We were also pleased to learn that **Emil Pai** and **David Clarke** were named as Tier 1 Canada Research Chairs this year. **Amira Klip** was honoured with the University of Toronto Dales Award, which is awarded to "a U. of T. investigator of outstanding calibre whose research has had a substantive impact in the areas of basic or clinical sciences or community health". A Premier's Research Excellence award went to **Gil Privé**, and **Emil Pai** was a joint awardee of a CFI-International Joint Venture grant.



David MacLennan

Our congratulations also go to **Chris Hogue**, who was named by the Globe and Mail as one of this year's "Top 40 Under 40". Selection is based on the criteria of "vision and leadership, innovation and achievement, community involvement, impact, and strategy for growth".

## Events

A symposium organized by Reinhart Reithmeier was held to honour **David MacLennan's** lifelong scientific contributions, as well as his role as mentor to many young scientists who continue his tradition of excellence in research. Attendees, including MacLennan alumni from around the world, gathered on October 3-4, 2002 to pay tribute to David's many accomplishments. David also was honoured this year by being named an Officer of the Order of Canada. Our congratulations go to David on this exceptional achievement.

## Appointments

We are pleased to welcome **Avi Chakrabartty**, a Scientist at the Ontario Cancer Institute and Assistant Professor in the Department of Medical Biophysics, who was cross-appointed to the Department of Biochemistry. Avi's research is in the area of protein folding and design, with particular emphasis on amyloid fibril formation and the design of polypeptide mimics of helical cytokines.

We are also happy to announce that **Gil Privé**, also a Scientist at the Ontario Cancer Institute and Associate Professor in Medical Biophysics, has accepted a cross-appointment in the Department of Biochemistry. As a crystallographer interested in protein-lipid interactions, Gil is pursuing the structures of membrane proteins and exploring the use of lipopeptides as detergents.

**Professors Lilianna Attisano, Annelise Jorgensen** and **Vitauts (Vic) Kalnins**, formerly of the Department of Anatomy and Cell Biology, have accepted primary appointments within the Department of Biochemistry. Lilianna's lab studies molecular mechanisms underlying TGFß superfamily signalling using biochemical and molecular genetic approaches. Annelise is inter-

ested in the structure, function, and biogenesis of calcium-storage-release sites of the sarcoplasmic reticulum in adult and developing cardiac and skeletal muscle cells. Vic's interests lie in the organization and function of different components of the cytoskeleton and the centrosome. We are delighted to welcome them all to the Department.

Our congratulations to **Hue Sun Chan,** who received tenure, and to **Lynne Howell** and **Julie Forman-Kay,** who were promoted to the rank of Full Professor.

### Graduate Studies

The Department held its annual graduate student poster day on May 31, 2002. The poster day took place in conjunction with the annual Theo Hofmann Lecture which was presented this year by **Dr. Nahum Sonenberg** of the Department of Biochemistry, McGill University. Dr. Sonenberg's lecture was entitled: "Signalling to the Translational Machinery".

As usual the judging was difficult but with Dr. Sonenberg's help the following winners (who receive cash awards) were chosen:

Winners in the Ph.D. category were: FIRST, **Arianna Rath** (Davidson lab): "*In vitro* analysis of Abp1p SH3 domain substitutions that alter peptide binding specificity"; SECOND, **Tony Mittermaier** (Kay and Forman-Kay labs): "Studying excited states of proteins by NMR spectroscopy"; THIRD, **Roberto Botelho** (Grinstein lab): "Diacylglycerol-dependent Ras stimulation during Fcγ receptor-mediated phagocytosis".

Winners in the M.Sc. category were: FIRST, **Urszula Wojtyra** (Houry lab): "One piece of the puzzle: Role of the zinc binding domain of chaperone ClpX"; SECOND, **Jennifer Marles** (Davidson lab): "Significance of ligand binding specificity of the SH3 domain for HOG pathway function"; THIRD, **Linh Van** (Siu lab): "Exploring the mechanism of neurite outgrowth from L1-v3 interaction".

### Additional Graduate Awards:

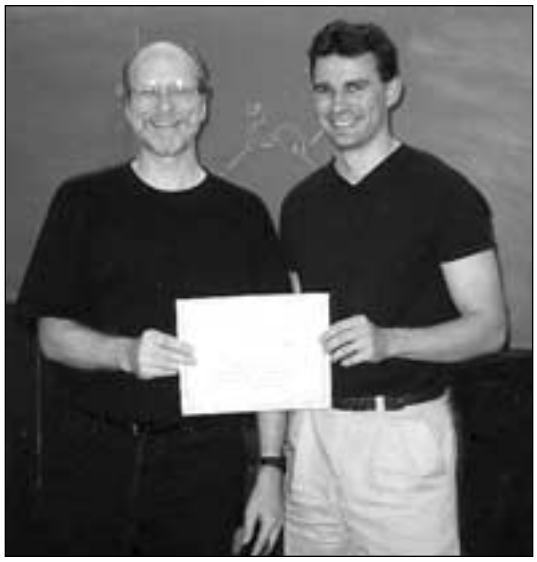
The winner of the Beckman Paper of the Year Award for 2001 was **Christopher Lemke** (Howell lab) for his paper entitled "The 1.6 A crystal structure of *E. coli* argininosuccinate synthetase suggests a conformational change during catalysis" published in Structure (2001) 9(12):1153.

John Wang with judges Grant Brown and Nahum Sonenberg

The annual David Scott prize for outstanding all-round graduate student was shared this year by **Paul Yip** and **Tony Harris** (both members of the Siu lab).

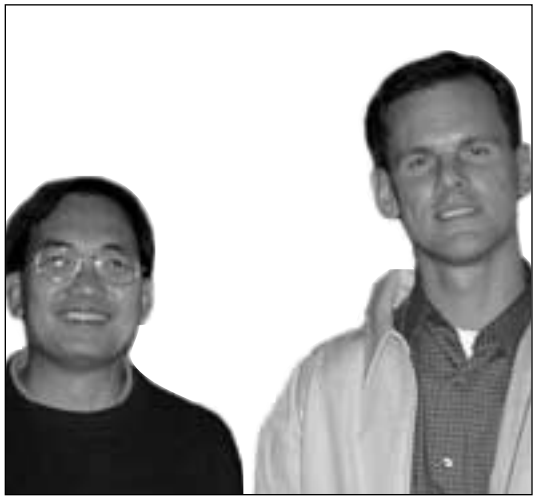
Congratulations to all winners for their achievements.

Happy winners from left: Urszula Wojtyra, Tony Mittermaier, Jennifer Marles, Chris Lemke, Arianna Rath, (David Isenman), Linh Van & Roberto Botelho



Beckman Paper of the Year winner Chris Lemke with Grad. Coordinator David Williams

Paul Yip with supervisor Chi-Hung Siu



Tony Harris with supervisor Chi-Hung

# University of Waterloo

## Department of Chemistry

*Correspondent: John Honek*

**Gary Dmitrienko's** research group is involved in the design, synthesis and enzymology of inhibitors of bacterial zinc-dependent beta-lactamases as well as the development of new structural classes of HIV-1 reverse transcriptase inhibitors. A new NSERC Strategic grant involving collaborations with A.M. Berghuis at McGill and Crompton Chemical Ltd. in Guelph has been awarded to Gary for discovery of highly specific antifungal agents for plant pathogenic fungi, targeting lysine biosynthesis in fungi. A new NSERC CHRP grant involving collaborations with A.J. Clarke at U. of Guelph and **T. Viswanatha** at UW and MethylGene Inc. has also been awarded to Gary for strategies to combat bacterial resistance to beta-lactam antibiotics.

**Guy Guillemette's** research group investigates the structure-function and mechanism of metalloproteins including nitric oxide synthases, calmodulin and aldolases. **John Honek's** group is involved in the area of mechanistic enzymology of metalloenzymes as well as the structure-function of enzymes involved in methionine biochemistry. He has been appointed to the editorial board of Letters in Drug Design and Discovery (Bentham Press) this year and is currently an associate editor of Biochemistry and Cell Biology (NRC). **Elizabeth Meiering's** group is conducting research on the folding, structure, function and dynamics of medically and biologically important proteins. **Susan Mikkelsen** is interested in biosensors and bioassays. Her group invented the world's first voltammetric sensor for DNA sequence detection, and is now actively developing a new electrochemical antibiotic susceptibility assay for microorganisms; technology available includes screen-printing for disposable sensor design and atomic force microscopy for surface characterization. **Michael Palmer**'s research is focused on the study of novel pore-forming toxins from pathogenic bacteria, and on protein-cholesterol interactions. Biochemical research in **Scott Taylor**'s group involves the design, synthesis and evaluation of enzyme inhibitors, enzyme mechanisms and the generation of catalytic antibodies (abzymes). The inhibitors are being examined as potential leads for the treatment of diabetes, breast cancer as well as other forms of cancer. Collaborators on enzyme inhibitor projects include Dr. Debasish Ghosh, a crystallographer at the Hauptmann-Woodward Medical Research Institute in Buffalo, Dr. Stephen Bearne at Dalhousie Medical School and Merck-Frosst Canada. His CHIR-funded research on catalytic antibodies involves using abzymes to activate anticancer prodrugs. The Chemistry department has completed setting up a new 600 MHZ NMR spectrometer and a MicroMass Q-TOF Global ESMS/MALDI mass spectrometer. Radek Laufer completed his Ph.D. degree and is now a senior research scientist with OSI Pharmaceuticals in Long Island NY. Jennifer Steere completed her M.Sc. degree and is now a research scientist at Xerox (Canada). Hanna Wong completed her M.Sc. thesis and is now at the University of Toronto. Justin Wu completed his M.Sc. thesis and is now a research scientist with Brantford Chemicals.

An OGS scholarship was awarded to Heather Montgomery. Pei Hang and Paula Walasek have joined John Honek's lab this year and are involved in studying an rRNA methyltransferase and a metzincin protease respectively. Miriam Heynen (M.Sc. in Biology at UW) has joined the Dmitrienko group as a research associate.

# University of Western Ontario

## Department of Biochemistry

*Correspondent: Eric Ball*

Biochemistry at the University of Western Ontario consists of some 60 members and associate members located at the main campus and several research institutes in the city of London,

Ontario. The Department was established in 1924, initially focusing on carbohydrate metabolism. Later it became noted for strength in lipids and membranes before a molecular biology section was added. Most recently a focus on physical methods and structural biology has been developed and expansion in the area of human genetics is planned. The Medical Sciences Building on campus, where a major part of the Department is housed, has finally begun renovations forcing many labs to move. A modern, well organized facility is eagerly anticipated, albeit five years down the road.

The Department wished a fond farewell and best of luck to two of our members, **Drs. Marie Fraser** and **George Chaconas**, who have moved west to take up positions at the University of Calgary. We will certainly miss their expertise and fellowship. We were very pleased to welcome **Dr. Fred Dick** as an Assistant professor in connection with our human genetics initiative. Dr. Dick did his graduate work at Dartmouth medical school, followed by a postdoctoral stint with Dr. N. Dyson working on mutations in pRB

Several faculty have taken sabbatical opportunities. **Dr. Ilona Skerjanc** returned from a short sabbatical spent learning about transgenic approaches to muscle differentiation at the University of Ottawa. **Dr. Chris Grant** is currently on sabbatical pursuing a new interest in medical imaging. **Dr. Gary Shaw** is on a sabbatical sojourn to Australia until the new year.

In the past year both **Drs. Shawn Li** and **Ilona Skerjanc** received a Premier's Research Excellence Award (PREA), the latter in combination with the Foundation for Gene and Cell Therapy. **Dr. Ken Yeung** received a CFI award for New Investigators. **Dr. Gary Shaw** was awarded a Canada Research Chair.

A number of new research initiatives have recently begun in the Department. Thus **Dr. Stan Dunn** has a lead role in setting up the London Regional Proteomics Centre that will coordinate facilities for both individual analyses and proteomics approaches. **Dr. Rob Hegele** is Director of the London Regional Genomics Centre (www.lrgc.ca) that specializes in high throughput genome analysis. The Dr. Don Rix Protein Identification Facility is led by **Dr. Gilles Lajoie** and uses mass spectrometry as a major tool (www.biochem.uwo.ca/wits/bmsl/bmslhome.html; supported by grants from ORDCF, CFI and Genome Canada). Dr. Lajoie is also group leader of the Ontario-wide protein identification facility that has recently received funding from the ORDCF: **Dr. Ken Yeung** is also part of this initiative. **Drs. Gary Shaw and Shawn Li** are part of the NMR Structural Proteomics team, while **Drs. Shilton and Fraser** are part of the Protein Crystallography for Structural Proteomics application. **Dr. David Litchfield** led a local group of researchers that recently received CFI funding to establish facilities for molecular imaging and dynamics of cell signalling networks.

In undergraduate education, the Department of Biochemistry has played a major role in establishing the new Bachelor of Medical Sciences Program. This program is offered jointly by the Faculty of Medicine and Dentistry and the Faculty of Science. We are offering a 4 year BMSc General degree and BMSc Honors degrees with specialization in six areas, including Biochemistry. A concurrent 5 year honors program in Medical Sciences and Business Administration was just approved by the University Senate. This is a joint program between the Faculty of Medicine and Dentistry and the Ivey School of Business. Departmental chair Dr. **Ted Lo** is the Program Director and J. Ball is the Program Counsellor.

# York University

## Biology and Chemistry Moving Forward Together

*Correspondent: Logan Donaldson*

I am one of seven new faculty members recruited by the Departments of Biology and Chemistry at York University since January 2000. In this article, I will begin by introducing some of the new faculty members at York University and highlight aspects of our interdisciplinary research and funding activities. Finally, I will summarize some of the very notable achievements of our faculty in the last two years.

In November 2001, I presented a poster on behalf of the York Biotechnology Network at the Ottawa Life Sciences Council BioNorth conference. The York Biotechnology Network is represented by a group of three senior (**Drs. Ronald Pearlman, Michael Organ** and **Michael Siu**) and six junior researchers (**Drs. Logan Donaldson, Kathi Hudak, Philip Johnson, Sergey Krylov, Sylvie Morin** and **Gary Sweeney**) from the Biology and Chemistry departments. As our interests share a common foundation of molecular biological and biochemical techniques, we have sought to amalgamate our strengths in microscopy, spectroscopy (NMR / MS), high throughput DNA sequencing and combinatorial chemistry into a package that is readily available to on- and off-campus researchers.

The first wave of new recruits began in Summer 2000 with the appointments of **Drs. Sergey Krylov** and **Philip Johnson** to the Department of Chemistry. Dr. Krylov uses a combination of microscopy and capillary electrophoresis called chemical cytometry to interpret biochemical events at a single cell level. Dr. Krylov's research is supported by an NSERC operating grant, a CFI/OIT New Opportunities Award and an Ontario Premier's Research Excellence (PREA) award. Dr. Philip Johnson uses NMR spectroscopy to study the structural biology of RNA and RNA-protein interactions. His research is funded by an NSERC operating grant. I joined the Department of Biology in Fall 2000. My NSERC funded research explores the biochemistry and structural biology protein-protein interactions involved in signal transduction and gene expression. At the 2002 Canadian Chemical Society meeting, Dr. Johnson and I had the opportunity to describe our research along with a number of junior NMR spectroscopists from Canada at a mini-symposium organized by Dr. Lawrence McIntosh (UBC).

In 2001, **Dr. Kathi Hudak** and **Dr. Gary Sweeney** joined by the Biology Department to support a new Biotechnology initiative. Dr. Hudak is interested in the antiviral properties of a ribonuclease produced by the Pokeweed plant. She is a 2002 NSERC and CFI/OIT recipient. Dr. Sweeney is interested in the molecular and cell biology of insulin resistance and glucose update. In addition to a CFI/OIT New Opportunities award, he holds a Canadian Diabetes Foundation Junior Research Fellowship. Following the appointments of Drs. Hudak and Sweeney, **Dr. Patricia Lakin-Thomas** joined to the Biology Department. Dr. Lakin-Thomas is a cell and molecular biologist who studies circadian rhythms in yeast. Her research is currently supported by an NSERC operating and equipment grant.

Since Fall 2002, students enrolled in the third and fourth years of the Honours Biology Program have had the option of selecting a Biotechnology stream of studies. The jewel of this stream is a laboratory course organized by **Drs. Kathi Hudak** and **Gary Sweeney** where students gain hands on experience with yeast two hybrid systems, confocal microscopy, western blot analysis, protein purification, and *in vitro* transcription / translation. Lecture periods concentrate on timely issues related to medical, pharmaceutical and agricultural applications of biotechnology.

Given the growing overlap in the research and academic offerings by the Departments of Biology and Chemistry, we are considering imple-

menting a degree program in Biochemistry. As our course offerings continue to evolve, we anticipate the inclusion of bioinformatics, advanced metabolism and structural biology to our combined curriculum.

**Dr. Michael Siu**, the MDS-Sciex Chair in Mass Spectrometry and **Dr. Diethard Bohme**, the Chairman of Chemistry and a recent Tier-1 Canada Research Chair recipient welcome **Dr. Robert Hudgins**, a fellow mass spectrometrist to the Chemistry Department. Dr. Hudgins is a specialist in FT-ICR mass spectroscopy. This technique couples mass spectrometry with a high field magnet to provide unrivaled sensitivity and accuracy. This year, Dr. Siu was a recipient of a 2002 Ontario Cancer Institute Research Grant. As well, Funds from ORDCF and Ontario Genomics Institute support some of his collaborative efforts. Together, the Siu, Bohme and Hudgins laboratories are exploring means to integrate mass spectrometry with structural and biophysical programs at a facility-wide scale.

Many research laboratories on campus benefit from instrumentation housed in the Biomolecular Core Facility. Drawing on support from NSERC, CIHR and the CFI, the Core Facility supports a nucleic acid sequencing service, gel documentation, phosphoimaging, and real time PCR. This facility exists largely through the efforts of **Dr. Ronald Pearlman**. Working in conjunction with the Core Facility is the CFI/OIT funded Biomolecular Expression and Characterization Facility. Hosted by the Donaldson laboratory, this new facility supports fermentation, chromatography, distributed computing and fluorescence spectroscopy. Many research laboratories in the Departments of Biology and Chemistry appreciate the addition of protein-ligand interaction instrumentation (isothermal titration calorimetry and BiaCore) from **Dr. Philip Johnson** and **Dr. Kathi Hudak** in partial fulfillment of their recent CFI/OIT New Opportunities Awards. The cell biologists in the Department of Biology welcome a new confocal microscope obtained through CFI/OIT funding awarded to Dr. Gary Sweeney.

The Department of Biology congratulates **Dr. K. Andrew White**, a molecular virologist, as a 2002 recipient of a Tier-II Canada Research Chair. In addition, Dr. Tara Haas became a CIHR Young Investigator. Five year CIHR operating grants were awarded to **Dr. Ronald Pearlman** and **Dr. Gillian Wu**, our new Dean in the Faculty of Pure and Applied Sciences. National Cancer Institute of Canada operating grants were awarded this year to **Dr. John Heddle** and **Dr. Michael Siu**.

Over the last two years, several researchers in the Department of Biology have received Premier's Research Excellence Awards. Funds from this award ($100 000 from PREA and a $50 000 contribution from York University) are designated to support the training of graduate students and postdoctoral fellows. We congratulate **Dr. Imogen Coe, Dr. Chun Peng, Dr. K. Andrew White, Dr. Bridget Stutchbury** and our newest recipient **Dr. John McDermott**. Dr. McDermott's research is an excellent example of the strong relationship between the Departments of Biology and Chemistry. Working with **Dr. Michael Siu** (Chemistry) and **Dr. David Cox** (Biology), he has discovered new phosphorylation sites in the myogenic transcription factor Mef-2 using a combination of tandem affinity tag purification and mass spectrometry.

**Dr. Ronald Pearlman** is the Department's strongest advocate for research in genomics. Currently, his research group is sequencing ESTs from a variety of protists in collaboration with a number of laboratories funded by Genome Atlantic. Dr. Pearlman also lead a proposal with Drs. Donaldson, Siu and Morin which secured a $1 million gift from the R. Samuel McLaughlin Foundation to establish a Functional Genomics program and recruit a senior level Chair.

The Departments of Biology and Chemistry are moving forward together to further establish York University in molecular biological and biochemical research. We anticipate that this interdepartmental effort will continue to grow in the upcoming years.