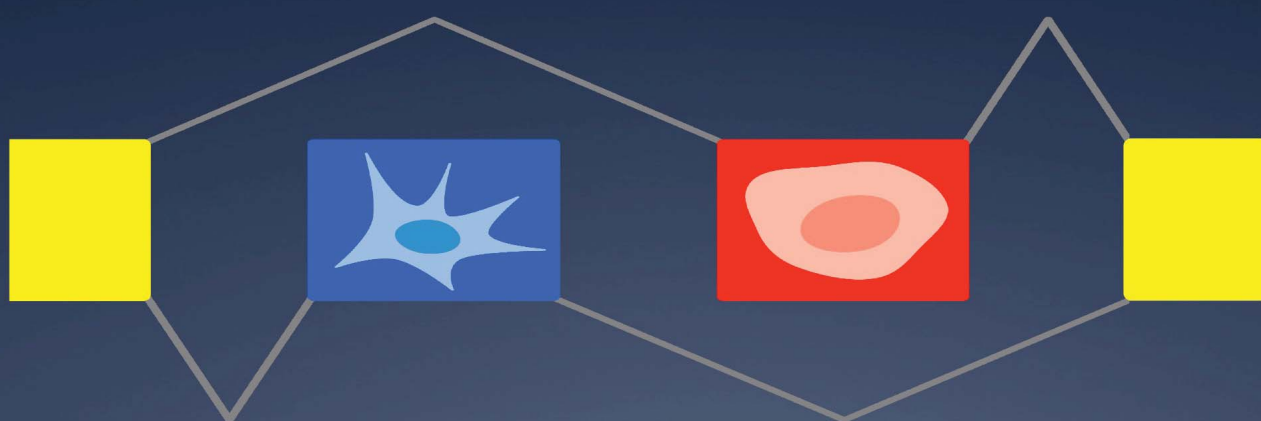


Bulletin

The Canadian Society for
Molecular Biosciences

La Société Canadienne pour
les Biosciences Moléculaires



2010 & 2011

www.csmb-scbm.ca



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Cover Image: Benjamin Blencowe

The cover image reflects the discovery of an alternative splicing switch in the forkhead family transcription factor FOXPI. Inclusion of the red exon in embryonic stem cells (ESCs) produces FOXPI-ES, a splice variant with a modified forkhead DNA binding domain that stimulates the expression of key pluripotency genes while concomitantly repressing differentiation genes. Skipping of the red exon and inclusion of the blue exon produces a splice variant that is required for ESC differentiation. Reference: Gabut et al. Cell, 147:132-46, 2011.

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CSMB Board for 2010-2011



The Board discusses implications of the merger with the Genetics Society of Canada at its meeting in Montréal, November 2010. Clockwise from front-left: Treasurer Vince Duronio (UBC), Vice President Jim Davie (Manitoba), Frances Sharom (Guelph), Secretary Randy Johnston (Calgary), Josée Lavoie (Laval), Andrew Simmonds (Alberta), Art Hilliker (York), Alba Guarné (McMaster), John Orlowski (Montréal), Linda Penn (OCI), Reinhart Reithmeier (Toronto), President Jean-Pierre Perreault (Sherbrooke), Wafaa Antonious (Secretariat) and behind the camera, Past-President David Williams (Toronto).

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Rapport du président – 2010-2011

Dr. Jean-Pierre Perreault



President's Report – 2010-2011

Dr. Jean-Pierre Perreault

Avec toutes les pressions sur le système de financement de la recherche depuis quelques années, les difficultés qui en résultent pour les chercheurs, ainsi que l'évolution des politiques scientifiques incluant la réduction de la place que les sciences de bases connaissent, le rôle des sociétés savantes dont celui de la Société Canadienne de Biochimie, Biologie Moléculaire et Cellulaire (SCBBMC), est plus que jamais essentiel. Les sociétés savantes doivent, entre autres, nous permettre de se regrouper, de supporter le développement de la connaissance, de reconnaître l'excellence, de faire la promotion de nos disciplines et de représenter nos intérêts communs auprès des décideurs gouvernementaux. C'est avec cette vision que je me suis joint au Conseil d'Administration (CA) de notre Société à l'été 2007 et que j'ai accepté d'entreprendre la rotation à titre de vice-président en 2009, président en 2010 et président sortant en 2011. Dès 2007, je me suis donné comme mandat de faire en sorte que la SCBBMC soit davantage à l'image des scientifiques canadiens. Je me disais que le CA devait davantage refléter le membership de la Société et être bien « branché » sur la base, tout en étant efficace dans ces méthodes de travail.

Au CA

Au cours des 3 dernières années, bien que le CA n'ait que peu changé en termes de nombres, la provenance de ses membres n'a cessé de s'élargir dans le but de mieux refléter le membership de la Société. En 2010-2011, le CA comptait 4 femmes et 10 hommes provenant de Halifax à Vancouver, incluant des représentants de 6 provinces. Les recrues de l'année ont été les Drs Jan Rainey (Dalhousie University) et Randall Johnston (University of Calgary), à titre de conseiller et secrétaire respectivement. Dr Rainey a été recrutée dans le but d'assurer une représentation des provinces atlantiques tandis que Dr Johnston, à titre de nouveau secrétaire. Dr David Williams (University of

The role of scientific societies such as the Canadian Society of Biochemistry, Molecular and Cellular Biology (CSBMCB) is more important than ever especially in view of the tremendous pressures on the financial support systems of scientific research, and changes in policies relating thereto including those threatening basic research. It is the duty of scientific societies to enable scientists to come together, to support the development of new knowledge, to recognize excellence, to promote our different disciplines and to represent our common interests at government decision levels. With this in mind, I joined the Board of administration of our Society in 2007 and then went on to accept the role of Vice-President in 2009, President in 2010, and Past-President in 2011. In those capacities, I always particularly strived for our Society to reflect the interests of all Canadian scientists, for the Board to be truly representative and inclusive of our Societies' broad membership, and operating procedures to work as efficiently as possible.

At the Board

From 2007 through to 2010, while the actual number of Board members did not change much, the provenance of members however widened greatly and this helped to better reflect the Society's true membership. In 2010-2011, Board members included 4 women and 10 men hailing from 6 different provinces from Halifax to Vancouver. The most recent recruits are Drs. Jan Rainey (Dalhousie University) and Randall Johnston (University of Calgary), respectively as Counsellor and Secretary. Dr. Rainey was recruited to ensure representation of the Atlantic Provinces whereas Dr. Johnston, to act as new Secretary. Dr. David Williams (University of Toronto) acted as Past-President and Chair of the Nomination Committee. Dr. James Davie (University of Manitoba) assisted me as Vice-President, and Dr. Vincent Duronio

Toronto) a agi à titre de Président sortant et responsable du Comité de nomination. Dr James Davie (University of Manitoba) me secondait, à titre de Vice-président, tandis que le Dr Vincent Duronio (University of British Columbia) assurait les fonctions de trésorier.

Le CA a tenu sa rencontre automnale à l'Université McGill et sa rencontre annuelle précédant l'Assemblée Générale Annuelle (AGA) au Mont-Orford (près de Sherbrooke). Suite à la rencontre en novembre, j'ai poussé pour développer une nouvelle méthode de travail basée sur une liste d'actions à réaliser suite à nos rencontres. Cette liste sert d'aide-mémoire, permet un suivi efficace du travail en cours de réalisation et assure une implication de l'ensemble des membres dans la multitude de tâches à effectuer. La connivence du Dr Johnston a été clé dans ce projet. Comme à son habitude, et grâce à sa remarquable éthique du travail, le Dr Duronio a fidèlement veillé au trésor de la Société. La généreuse et indéfectible implication des Drs Johnson et Duronio en font des membres clés du CA.

Les communications

Les communications avec les membres auront été nombreuses au cours de la dernière année. Vous êtes à lire le Bulletin annuel de la Société, préparé soigneusement par les Drs David Williams et Reinhart Reithmeier (tous deux de l'University of Toronto) qui agissent à titre de co-éditeurs depuis l'année dernière. Vous avez aussi reçus deux éditions du E.link qui se veut un moyen électronique de partager différentes informations avec les membres. Les E.links sont l'œuvre du Dr John Orlowski (McGill University). Le site internet de la Société (<http://www.csmb-scbm.ca/index.aspx>) a quant à lui été maintenu à jour sur une base régulière. Enfin, je vous ai fait parvenir cinq messages électroniques dont plusieurs avaient trait au changement de dénomination officielle de la Société. Chacune de ces publications a toujours pour but de demeurer en contact constant avec les membres de la Société et ainsi permettre de recueillir un maximum d'idées et d'opinions auprès de la communauté.

Le travail de rapprochement et de reconnaissance officielle

(University of British Columbia) acted as Treasurer.

The Board held its fall meeting at McGill University and its annual meeting prior to its Annual General Assembly (AGA) at Mont-Orford close to Sherbrooke in the Eastern Townships. Following the November meeting, I pushed to develop a new working method based on a list of actions and tasks to be followed through on by the Councillors before the next board meeting. This list acts as a convenient reminder enabling efficient follow-up and ensures the active implication of the entire board in the multitude of tasks at hand. Dr. Johnston acted as my willing accomplice in this project. True to his remarkable work ethic, Dr. Duronio dutifully monitored the Society's funds. The generous and unfailing efforts of Drs. Johnston and Duronio make them key Board members.

Communications

Communications with Society members have been numerous over the past year. The current Bulletin is the painstaking work of Drs. David Williams and Reinhart Reithmeier (both from University of Toronto) acting as co-editors for the past year. You have also received two editions of our E.link, an interesting electronic tool to share information amongst Society members that is the work of Dr. John Orlowski (McGill University). The Society's website (<http://www.csmb-scbm.ca/index.aspx>) has also been up-dated regularly. I have sent you five electronic messages, several of which relating to the Society's name change. Each of these publications has always aimed to keep members connected and well informed as well as to gather their input, ideas and opinions.

Promotion of the journals Biochemistry & Cell Biology and Genome has progressed nicely over the past year thanks to their respective Editors, Drs. James Davie and Arthur Hilliker (York University), who are also Society Board members. Articles published in both these journals are now available at no cost within six months. Different strategies were used to encourage members to

des revues Biochimie et Biologie Cellulaire (Biochemistry and Cell Biology) et Génome (Genome), a bien évolué au cours de la dernière année. Les éditeurs respectifs de ces revues sont les Drs James Davie et Arthur Hilliker (York University) qui sont aussi membres du CA. Les articles publiés dans ces journaux sont maintenant disponibles gratuitement en moins de six mois. Différentes stratégies seront utilisées pour stimuler nos membres à soumettre des manuscrits dont des articles de revues qui ont un intéressant facteur d'impact.

La fin de la SCBBMC et le début de la SCBM

L'année 2010-2011 est un jalon historique pour notre Société. Bien avant ma venue au CA, des discussions sur la révision de la dénomination officielle de la Société avaient déjà lieu sur une base régulière. Depuis sa fondation, en 1957, comme Société canadienne de biochimie, le membership et la représentativité de disciplines n'ont cessé de croître et de s'élargir, donnant lieu à la Société Canadienne de Biochimie, Biologie Moléculaire et Cellulaire. Le projet de fusion avec la Société de Génétique du Canada est venu ajouter à la situation sans pour autant qu'un changement de dénomination ne soit prévue à l'entente initiale, intervenue au cours de l'année 2009-2010. Désormais, l'ensemble des activités dont celles de la trésorerie, du rapport financier, des prix pour chercheurs, du représentant généticien au CA, du transfert du membership, etc., est intégré à celles de notre Société. Cette situation m'a stimulé à pousser la réflexion afin d'identifier un mécanisme pour vérifier l'existence d'une véritable volonté des membres à changer la dénomination officielle de la Société et, dans l'affirmative, de solliciter des suggestions. Une première consultation électronique, tenue en début d'été, a permis de constater que plus de 80% des membres étaient favorables à un changement de dénomination. Cette consultation a permis de générer une liste de plus de 40 suggestions de noms. Une série d'échanges courriel entre les conseillers, ainsi qu'un appel conférence a permis d'identifier les principaux critères pour fixer le choix de la dénomination la plus convenable pour notre Société. Par exemple, le nouveau nom devrait être rassembleur et intégrateur, refléter la composition présente et souhaitée en termes d'activités

submit their manuscripts including reviews which offer an interesting impact factor.

The end of CSBMCB ... the dawn of CSMB

2010-2011 is a historic marker for our Society.

Discussions over the official Society name were actively underway well before I joined the Board. Since its foundation, in 1957 as the Canadian Society of Biochemistry, the membership and representation of scientific disciplines has never ceased to widen, giving rise to the Canadian Society of Biochemistry, Molecular and Cellular Biology. While the merger with the Genetic Society of Canada compounded the situation, the name change was not part of the original merger which occurred over 2009-2010. All activities including those of the treasury, financial reports, investigator awards, geneticist on the Board, membership transfer, etc., are now fully integrated as the Society's own. This situation spurred me on to identify a mechanism enabling us to verify where the Society members' inclination rested with respect to a possible name change, and in the event that members were favorable to such a name change, to solicit suggestions. A first round of electronic consultation, early last summer, confirmed that over 80% of members were indeed favorable to a Society name change. This consultation led to an original list of over 40 name suggestions. A series of e-mails between counsellors, in addition to a conference call, enable us to establish a series of criteria to choose the most appropriate name for our Society. For instance, the new name should be inclusive, reflect the current and desired composition in terms of member activities (working in the fields of biochemistry, molecular and cellular biology, genetics, pharmacology, radiobiology, etc. ; grant holders from CIHR, NSERC, etc.), work well both in French and English, and not exist already (including an a name and address for the internet). Applying these criteria, we produced a short list of three possibilities which we asked members to vote on at the end of summer. Over two thirds of votes, the new name became the Canadian Society for Molecular Biosciences (CSMB). This name,

des membres (travaillant aussi bien en biochimie, biologie moléculaire et cellulaire, en génétique, en pharmacologie, en radiobiologie, etc. ; titulaire d'octrois des IRSC, du CRSNG, etc.), se présenter aussi bien en français qu'en anglais, et ne pas déjà exister (incluant une adresse non utilisée sur internet). L'application de ces différents critères nous a conduit à réduire la liste à trois possibilités qui ont été soumis au vote des membres en fin d'été. Avec plus des deux tiers des voix, la dénomination retenue a été la Société Canadienne pour les Biosciences Moléculaires (SCBM). Ce choix, entériné lors de l'AGA, est votre choix et une nouvelle société savante est née.

Représentations et activités de la Société

Nous avons été actifs en termes de représentation. Par exemple, nous avons poursuivi notre engagement à titre de membre de Recherche Canada en participant entre autres à l'AGA et en participant à leurs prises de positions publiques. Recherche Canada est un organisme regroupant des institutions académiques, des hôpitaux avec vocation de recherche, des sociétés savantes, des fondations, des conseils régionaux et des acteurs du secteur privé. Cette organisation est impliquée dans la promotion de la recherche en santé et l'accroissement de la prospérité de l'ensemble de la population canadienne. Aussi, nous avons participé activement à l'opération du Podium de la recherche en santé, initiée par notre collègue le Dr Reithmeier. L'objectif consistait à écrire aux représentants élus du gouvernement canadien afin de souligner notre support des IRSC et demander que le budget de cet organisme soit augmenté de 10% par année sur 7 ans afin de le doubler à l'instar du programme Podium pour Vancouver 2010. Nous avons aussi participé à la Conférence sur les politiques scientifiques canadiennes qui s'est tenue en octobre à Montréal. La Société est aussi membre de l'Union Internationale de Biochimie et Biologie Moléculaire (UIBBM), grâce à la générosité de notre partenaire, le CNR, qui défraie nos frais d'adhésion. À ce chapitre, nous avons contribué à la révision des finalités de formation attendues des étudiantes et étudiants au doctorat. Aussi, nous avons contribué au meeting de la Société panaméricaine tenu au Mexique, en défrayant une partie

ratifié at the AGA, is your choice and marks the dawn of a new scientific society.

Official Representation & Activities

We were active in terms of official representation. For instance, we pursued our commitment as a member of Research Canada and attended, amongst others, its AGA and took an active part in its public positions. Research Canada is a public organization which brings together Canadian health research stakeholders including academic institutions, research hospitals, scientific societies, foundations, regional councils and actors of the private sector. This organization promotes health research and increased prosperity for the benefit of all Canadians. We took part in the "Own the Health Research Podium Campaign", initiated by our colleague Dr. Reithmeier. The objective was to address 1000 letters to elected federal officials to stress our support of CIHR and request that its budget be increased by 7% per year, over 10 years, in order to progressively double as was done by successful "Win the the Podium Program" for the 2010 Vancouver Games. We attended the Canadian Science Policy Conference which was held in Montréal in October. The Society is also a member of the International Union of Biochemistry and Molecular Biology (IUBMB), thanks to our partner, the NRC, who has generously paid our membership fees. We contributed to the revised training objectives for PhD students. We attended the Panamerican Society Meeting in Mexico, by contributing to the travel expenses of Canadian speakers. Last but not least, we have had exchanges on the possibility of hosting the IUBMB 2016 Meeting in Vancouver.

The Society AGM was held at a joint meeting with the RiboClub in September 2011, "RNA Studies, One Molecule at a Time", in the course of which the Society's new name was adopted, its Constitution revised, current affairs presented, and the Presses of NRCC gave a presentation. We also underlined that membership has never ceased to increase over the past few years; Dr. Alba Guarne (McMaster University) is in charge

des dépenses de déplacement de conférenciers canadiens. Enfin, nous avons eu des échanges sur la possibilité d'accueillir le meeting de l'UIBBM à Vancouver en 2016.

L'AGA s'est tenue lors du meeting de la Société qui avait lieu en collaboration avec le RiboClub en septembre 2011. La saveur annuelle de ce meeting était « L'étude de l'ARN, une molécule à la fois ». En plus de l'adoption de la nouvelle dénomination de la Société et de la constitution révisée, ainsi que des affaires courantes, cette Assemblée a été marquée par une présentation de la direction des Presses du CNR. Nous avons aussi souligné l'augmentation constante du membership au cours des dernières années ; ce dossier est sous la responsabilité de la Dre Alba Guarne (McMaster University). Le RiboClub a aussi été l'occasion de remettre le Prix du scientifique chevronné au Dr Benjamin J. Blencowe de l'University of Toronto, ainsi que le Prix nouveau scientifique GE Healthcare au Dr Gerardo Ferbeyre de l'Université de Montréal. Ce dernier prix est accompagné d'une bourse de 5 000\$. Il s'agit d'une entente avec la société GE Healthcare, pour une période de 5 ans, rendue possible grâce au leadership de Mme Fiona Fitzgerald. Vous pourrez lire dans les pages qui suivent un article de revue rédigé par ces deux excellents scientifiques.

La Société a aussi supporté 5 activités organisées par des groupes d'étudiants, remis une dizaine de bourses de voyage à des étudiants qui ont participé au meeting annuel et supporté deux autres rencontres scientifiques.

Conclusion et remerciements

La présente ne constitue qu'un bref résumé du travail réalisé et coordonné par la Société et son CA, et tente de mettre en relief certaines des actions réalisées pour favoriser le bon regroupement des scientifiques des biosciences moléculaires, le support apporté au développement de la connaissance, la reconnaissance de nos collègues qui excellent, ainsi que la promotion de nos disciplines. Il s'agit des objectifs mêmes de la SCBM. Je suis satisfait « du tour de jardin réalisé » et du fait que notre Société est davantage branchée sur la base via la consultation, l'intégration et l'efficacité des méthodes de fonctionnement. Le crédit du

of that. Two important prizes were also awarded at the RiboClub Meeting: the Senior Scientist Award went to Dr. Benjamin J. Blencowe (University of Toronto), and the GE Healthcare Scientist Award went to Dr. Gerardo Ferbeyre (Université de Montréal). The GE Healthcare Award comes with a \$5,000 grant pursuant to a 5-year agreement with GE Healthcare, made possible thanks to Mrs. Fiona Fitzgerald's leadership. Both awardees have contributed an excellent scientific review to the current Bulletin.

The Society has also provided financial support for 5 scientific events held by student organizations, a dozen student travel awards to attend scientific meeting, as well as two additional scientific meetings.

Concluding Remarks and Acknowledgments

This is only brief overview of the work accomplished and coordinated on behalf of the Society and its Board, which attempts to underscore a few of the realizations to help molecular bioscientists come together, support knowledge creation, and promote the recognition of our colleagues who excel as well as our disciplines. These accomplishments are in line with the Society's goals themselves. I am proud of the work accomplished and especially of the fact that the Society is more than ever connected to its base through consultation, inclusiveness, and efficient operating procedures. The credit of these accomplishments rests with fantastic Board members, every single one of whom contributes importantly in his or her own way. I have already mentioned above the contributions of a certain number of Board members, but I also wish to underscore the contributions of Drs. Frances J. Sharom (University of Guelph), Josée Lavoie (Université Laval), Linda Penn (University of Toronto) and Andrew Simmonds (University of Alberta). Dr. Linda Penn was in charge of membership and leaves the Board with a great track record. I would also like to mention the excellent work of Ms. Wafaa Antonius who is the office administrator in charge of the Society. I truly enjoyed working with all of you first class scientists and

travail réalisé revient à un super CA où chacun des membres apportent une importante contribution, à sa manière. J'ai déjà mentionné la contribution d'un certain nombre des membres, mais je ne pourrais passer sous silence celles des Drs Frances J. Sharom (University of Guelph), Josée Lavoie (Université Laval), Linda Penn (University of Toronto) et Andrew Simmonds (University of Alberta). Dre Linda Penn a longtemps été responsable du membership pour la Société et quitte le CA avec une importante contribution réalisée. Aussi, je ne peux passer sous silence l'excellent travail réalisé par Mme Wafaa Antonius qui est la professionnelle responsable de la Société. J'ai eu beaucoup de plaisir de travailler avec ce groupe de scientifiques hors pairs et de servir la Société au cours de la dernière année. Je vous remercie de votre indéfectible soutien et implication dans les activités et consultations de la Société.

Alors que j'agis, cette année, à titre de président sortant, Dr Davie assurera le rôle de président et Dr Hilliker a été élu Vice-président. Je pense sincèrement que notre nouvelle Société, la SCBM, est en excellente santé. Je tiens à remercier de manière spéciale notre collègue Dr Reithmeier qui par un beau jour de l'été 2007 m'a téléphoné pour m'inviter à devenir conseiller au CA de la Société. L'expérience a été très enrichissante et j'espère lui avoir bien rendu.

Je ne peux passer sous silence la rencontre du Dr Michel Chrétien au meeting annuel tenue à Banff, au printemps 2010. Michel était là pour recevoir la Médaille d'Or Arthur-Wynne. Ce prix rend hommage au travail de toute une vie d'une personne dont la recherche est reconnue internationalement, dont le rôle dans le développement et la promotion de sa discipline au Canada est primordial et dont le service à la communauté universitaire reste un fait indiscutable. Michel était seulement le second à recevoir cet honneur plus que bien mérité. Lors de cette rencontre, Michel m'a mentionné combien il était important pour lui de voir un autre canadien français prendre la présidence de la Société... lui et moi l'aurions été à environ 25 ans d'intervalle. C'est en écrivant ce dernier paragraphe et en pensant à lui, que j'ai décidé de vous offrir ce rapport dans les deux langues officielles.

am grateful for the opportunity of serving the Society over the past year. Please accept my grateful thanks for your support and implication in the Society's events and consultations.

I now act as Past-President, Dr. Davie assumes the Presidency and Dr. Hilliker, the Vice-Presidency. I sincerely think that our new Society, the CSMB, is in great shape. I wish to convey my special thanks to our colleague Dr. Reithmeier who on a beautiful summer day of 2007 rang me up to invite me sit at the Board. The experience was rich and I hope to have repaid his trust in my ability.

Lastly, I would just like to mention my exchange with Dr. Michel Chrétien at the Banff Meeting in the spring 2010. Michel was receiving the Arthur-Wynne Gold Medal Award which honours the work of a lifetime of a person who is recognized worldwide and whose community service and role were exceptional in the development and promotion of his or her discipline in Canada. Michel was only the second recipient of this well-deserved distinction. When we met, Michel mentioned how important it was for him to see a fellow French Canadian take on the presidency of the Society... we will have served ~25 years apart. Remember Michel, I thought of offering you this Report in both official languages.

Minutes of the 2010 Annual General Meeting

Banff, Alberta – April 2010

Chair: David Williams; Board Members present: Linda Penn, John Orlowski, Jim Davie, Jan Rainey, Laura Frost, Jean Pierre Perrault, Randy Johnston, Vince Duronio, Wafaa Antonious (Secretariat)

Attendees: James Coulton, Moira Glerum, Joel Weiner, Hans Vogel, Janet Wood, Christian Baron, Joe Casey, Sampath Loganathan, Tushare Jinadasa, Trevor Moraes, Jonathan Lytton, Susan Cole, Joe O'Neil, Nicole Nivillac, Deborah Gordon, Nicolas Touret, Reinhart Reithmeier, Emil Pai, Chris Cheesman, Michel Chretien, David Andrews.

1. Greetings from Society President

David Williams welcomed the attendees, acknowledged the efforts of Joe Casey in organizing the 2010 CSBMCB Banff meeting which was well attended. He acknowledged the role and efforts of the outgoing members of the Executive and welcomed the incoming members of the Executive of the CSBMCB.

2. Approval of the Agenda

John Orlowski made a motion to approve the agenda of the 53rd Annual General Meeting of the CSBMCB, motion seconded by David Andrews, all in favour, agenda approved.

3. Approval of the Minutes of the 52nd Annual General Meeting

Linda Penn put a motion forward to approve the minutes of the 52nd AGM, motion seconded by Laura Frost, all in favour, motion approved.

4. Business Arising from the Minutes

David Williams stated that business arising will be discussed under later agenda items.

5. Advocacy – Deborah Gordon, President and CEO of Research Canada, addressing the membership

David Williams invited Deborah Gordon from Research Canada to present to the CSBMCB members the advocacy activities undertaken by Research Canada and its partners.

Ms. Gordon presented the mission of Research Canada (RC), philosophy and membership. She reported that membership has increased by 50 new members to over 80 Research Canada members in total. The membership is a broad based alliance which delivers a very high level of partnership and reaches out to other international health organizations. RC is acutely aware that health researchers are really challenged by the dwindling financial support for research. Granting councils have been awarded an additional \$30M, but this does not cover inflationary costs. Research Canada is having a meeting with the federal government (esp. Industry Canada) to include academia in the comprehensive review of R & D spending.

Educating members of parliament: RC created a Health Research Caucus with representatives who will be ambassadors among legislators to educate them about the importance of health research. The Health Research Caucus has a new chair, Senator Wilbert Keon, and it held 4 events.

RC also organized 15 MP visits to members' institutions in 2008 & 2009. Ms. Gordon encouraged the CSBMCB membership to communicate with their members of parliament and invite them to visit their institution. RC conducted several public opinion polls. The polls indicate that

Canadians are aware of the importance of health research. Canadians want to see more information about science and health in the media. Nearly nine out of ten Canadians report behavioural changes as a direct result of the media reports on health research. Scientists and the media need to improve their perceived utility.

The R7 Partnership consists of 7 National health organization: ACAHO, AFMC, BIOTECanda, HCCC, MEDEC, RX&D and RC. This partnership began in Fall 2008. In 2008 they submitted a “Stimulus Brief: Budget 2009”. They invested in and conducted the “Canadians Go for Gold” poll.

An Action Plan on Health Research is being reviewed and developed, and a 5 year strategic plan will be developed in partnership with stakeholders at federal and provincial levels.

The main points of the Brief to the Finance Committee 2009:

Recommendation # 1: That the federal government increase base funding to the three granting councils and that over the next five years the base funding to CIHR become equivalent to 1 percent of total health spending in Canada.

Recommendation # 2: The establishment of a national task force including representatives from the academic, private and voluntary sectors to examine the feasibility of developing a robust research strategy that would inform and direct future policy regarding health research and health innovation in Canada.

Discussion points:

In response to questions, Ms. Gordon noted that government has two lists, a “must have” list and a “nice to have” list; research is on the nice to have list and is easily cut (or not increased) during times of fiscal stress.

Ms. Gordon also noted that RC is working with AUCC and different organizations in bringing them around the table with the federal government.

Ms. Gordon encouraged the membership to meet with MPs inviting them to visit research institutions and educate them about research. A member noted a recent science policy conference and an initiative that organizes the Bacon and Eggheads meeting at parliament, which will enlist some grad students to find evidence to support return on investment in research.

Ms. Gordon also noted that RC coordinates with CIHR and other funding agencies, but of course CIHR has to be careful since they are considered civil servants and RC is an advocacy organization. Much influence is achieved through who is giving the message as well, and sometimes the personal touch is crucial. RC always engages the media and individuals with that kind of expertise. There is no harm in organizing events to show the benefits of research.

6. Merger with GSC

David Williams summarised the merger proposal. GSC will bring resources in the amount of \$60,000. Also there should be an increase in general revenue through the increase in membership and also from the attendance of former GSC members at our meetings.

David Williams moved the approval of the GSC-CSBMCB merger, seconded by John Orlowski, all in favour, no abstentions, motion approved.

7. Current and Future Meetings

Reinhart Reithmeier reported that the CSBMCB has run successful meetings with more anticipated: 2011 will be in Mont Orford, Quebec, with the topic being RNA. The meeting in 2012 will be organized in Whistler, March 14 – 18, 2012, the topic being Epigenetics and Genome Stability. The 2013 meeting will be in Ontario. The topic has not been decided,

but there was a suggestion for a Meeting on “Cellular Dynamics, Polarity and Cytoskeleton”. The 2014 meeting might be back in Banff and focused on membrane proteins. For 2015, the venue will perhaps be Halifax, NS and the topic might have a lipid focus. The current Banff meeting has been very successful.

8. Membership – Linda Penn

The Society has seen an incredible revitalization. New members are coming on board. The CSBMCB Executive have been approaching members and non members to become representatives and approach others to join the society.

9. Treasurer’s report – Vincent Duronio

The finances of the Society are in a good state. The good financial position is due to a fund that started from the IUBMB meeting about 20 years ago. The fund is managed by BMO Nesbitt Burns and we kept 25% of the fund in cash. We have been able to run the operations of the society from the cash fund that is replenished by membership fees and annual conference net profit. We did not have to withdraw from the cash portion of the investment. The PENCE fund has been accounted for separately on our books. In terms of expenses, we paid the 2nd instalment for our new website: we spent over \$32,000 in total on the new website and paid \$5,000 in support of the Canadian Science Policy Conference. We have received an additional \$18,000 from the PENCE royalty. We have lost the support of Merck Frosst and Roche Scientific for our annual awards. Despite losing their support the Society was able to support the awards on its own. The new website has had a positive impact on membership. The number of members who paid in 2008 was around 220; at the end of 2009 the membership increased to 330 paid members. In 2009, we had 34 new members, 270 renewing members and the rest are members who pay for 5 years. We have a fairly sizable membership when we count the students and post docs.

It was suggested in the board meeting that the Secretary of the Society be a signing authority on the books of the CSBMCB. Motion that the Secretary of the CSBMCB be a co-signing authority, seconded by Joe Casey, all in favour, motion approved.

10. Nominations and Election of board members for 2010 - 2011 – Laura Frost

Laura Frost thanked David Williams for being an effective President and his hard work on the CSBMCB website. She thanked Albert Clark for being the Society Secretary for 7 years. She also thanked Reinhart for all his efforts. She thanked Vincent for doing a great job with the investment. She also thanked all the members who still sit on the board. Thanks also to John Glover who became the Bulletin editor and Jim Davie for his work on the CSBMCB Journal with the NRC Research Press. She also thanked Linda Penn for her efforts to increase the membership of the society and John Orłowski for staying on the CSBMCB board and his past services to the Society.

She then made a motion to approve the nomination of Randy Johnston as Society Secretary and Jean Pierre Perrault as CSBMCB President.

Jean Pierre Perrault seconded the motion, all in favour, approved.

11. Introduction of Wafaa Antonious as new CSBMCB Administrator – David Williams

David thanked Wafaa for the work she has done in the short time she took over as the CSBMCB secretariat.

12. Other Business

No other business arose from the meeting.

13. Adjournment

David Andrews made a motion to adjourn, seconded by John Orłowski. Meeting adjourned.

CANADIAN SOCIETY OF BIOCHEMISTRY, MOLECULAR AND CELLULAR BIOLOGY

Financial Statement

STATEMENT OF FINANCIAL POSITION

AS AT DECEMBER 31, 2010
(with unaudited comparative figures as at December 31, 2009)
UNAUDITED

	<u>2010</u>	<u>2009</u>
ASSETS		
CURRENT		
Cash	\$ 20,261	\$ 14,133
Accounts receivable	3,078	40,316
	<u>32,060</u>	<u>-</u>
	55,399	54,449
INVESTMENTS (note 5)	465,076	425,509
	<u>\$ 520,475</u>	<u>\$ 479,958</u>
LIABILITIES		
CURRENT		
Accounts payable and accrued liabilities	\$ 9,304	\$ 16,468
Deferred membership fees and subscription fees	5,435	10,958
	<u>14,739</u>	<u>27,426</u>
LONG TERM		
Deferred membership fees	<u>2,391</u>	<u>5,028</u>
UNRESTRICTED NET ASSETS	503,345	447,504
	<u>\$ 520,475</u>	<u>\$ 479,958</u>

STATEMENT OF OPERATIONS AND CHANGES IN NET ASSETS

FOR THE YEAR ENDED DECEMBER 31, 2010

(with unaudited comparative figures for the year ended December 31, 2009)

UNAUDITED

	2010	2009
REVENUE		
Memberships dues	\$ 25,783	\$ 21,097
Corporate contributions	20,828	22,459
Annual meeting	57,840	39,737
PENCE transferred funds	10,682	18,415
Other	1,351	100
	<u>116,484</u>	<u>101,808</u>
Investment income	<u>7,327</u>	<u>9,247</u>
	123,811	111,055
EXPENSES		
Annual meeting (note 6)	84,822	54,650
Secretariat	21,930	13,873
Board meetings	13,021	7,344
Science advocacy	7,703	6,711
Bulletin	5,640	102
Miscellaneous	4,384	-
Website	4,255	17,530
Membership drive	2,593	-
Professional fees	2,100	2,500
Meeting sponsorship	1,500	1,250
Bank and credit card fees	1,382	2,106
Dues and subscriptions	-	500
Office	649	610
	<u>149,979</u>	<u>107,176</u>
NET REVENUE (EXPENSES) FOR THE YEAR	\$ (26,168)	\$ 3,879
Unrestricted net assets at beginning of year	\$ <u>447,504</u>	\$ <u>402,283</u>
Balance before items affecting net assets	421,336	406,162
Unrealized investment gains	30,240	41,342
Transfer of assets to the CSBMCB (note 4)	<u>51,769</u>	<u>-</u>
UNRESTRICTED NET ASSETS AT END OF YEAR	\$ <u><u>503,345</u></u>	\$ <u><u>447,504</u></u>

STATEMENT OF CASH FLOWS

FOR THE YEAR ENDED DECEMBER 31, 2010

(with unaudited comparative figures for the year ended December 31, 2009)

UNAUDITED

	2010	2009
CASH PROVIDED BY (USED FOR)		
OPERATING ACTIVITIES		
Cash from operations		
Net revenue for the year	\$ (26,168)	\$ 3,879
Non-cash portion of investment income	(9,327)	(9,247)
	<u>(35,495)</u>	<u>(5,368)</u>
 Net change in non-cash working capital balances		
Accounts receivable	37,238	(39,361)
Conference deposit	(32,060)	-
Accounts payable and accrued liabilities	(7,164)	12,621
Deferred membership and subscription fees	(8,160)	9,321
	<u>(45,641)</u>	<u>(22,787)</u>
 INVESTING ACTIVITY		
Transfer of assets from Genetics Society of Canada	<u>51,769</u>	<u>-</u>
 (DECREASE) INCREASE IN CASH	 6,128	 (22,787)
 Cash, beginning of year	 <u>14,133</u>	 <u>36,920</u>
 CASH, END OF YEAR	 \$ <u>20,261</u>	 \$ <u>14,133</u>
 CASH POSITION		
Cash	\$ <u>20,261</u>	\$ <u>14,133</u>

NOTES TO THE FINANCIAL STATEMENTS

December 31, 2010
UNAUDITED

I. PURPOSE OF THE ORGANIZATION

The Canadian Society of Biochemistry, Molecular and Cellular Biology (CSBMCB) was incorporated without share capital in 1979 under Part II of the Canada Corporations Act and is recognized as a not-for-profit organization for income tax purposes. The main objective of the Society is to foster research and education in Biochemistry, Molecular Biology and Cellular Biology in Canada.

2. SIGNIFICANT ACCOUNTING POLICIES

- (a) Capital assets
Capital assets purchased at a cost of less than \$2,000 are expensed in the year of purchase. The Society does not own capital assets at this time.
- (b) Basis of Accounting
Revenue and expenses are recorded on the accrual basis, whereby they are reflected in the period in which they have been earned and incurred respectively, whether or not such transactions have been finally settled by receipt or payment of money.
- (c) Revenue Recognition
CSBMCB follows the deferral method of accounting for contributions. Restricted contributions are recognized as revenue in the year in which the related expenditures are incurred. Unrestricted contributions are recognized as revenue when received or receivable if the amount to be received can be reasonably estimated and collection is reasonably assured.
- (d) Use of estimates
The preparation of the financial statements in conformity with generally accepted accounting principles requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities at the date of the financial statements and the reported amounts of revenues and expenses during the reported period. Actual results may differ from those estimates.
- e) Financial Instruments
CSBMCB's cash is recorded using the held-for-trading method. These financial assets are measured at fair value at the balance sheet date. Any changes in fair value, both realized and unrealized, are recorded as adjustments to revenue and expenses. CSBMCB's accounts receivable and accounts payable and accrued liabilities are accounted for at amortized cost using the effective interest rate; they include all loans and receivables and all financial liabilities. Investments are classified as available for sale and are carried at market value and any changes in market value, both realized and unrealized, are recorded as adjustments to net assets under the available for sale method.

3. FINANCIAL INSTRUMENTS

CSBMCB's financial instruments consist of cash, accounts receivable and accounts payable and accrued liabilities. The fair value of these financial instruments approximates their carrying values, unless otherwise stated. It is management's opinion that the organization is not exposed to significant interest, currency or credit risks arising from its financial instruments.

4. SUBSEQUENT EVENTS

After December 31, 2010, the Canadian Society of Biochemistry and Molecular and Cellular Biology merged with the Genetics Society of Canada (GSC). This merger had been negotiated and agreed upon by the Boards of both organizations during fiscal 2010. During fiscal 2011, the two organizations will decide on a new name, organizational structure and resolve all related administrative matters. The majority of the GSC's assets were transferred to the CSBMCB's bank account prior to December 31, 2010, all remaining GSC assets and liabilities will be merged with the CSBMCB's during fiscal 2011.

5. INVESTMENTS (at Market Value)

BMO Nesbitt Burns Canadian Account

	2010	2009
Cash and short term investments	\$ 85,400	\$ 68,920
Fixed Income	64,914	65,631
Common equity	235,797	214,327
Investment trusts	-	8,590
	<u>386,111</u>	<u>357,468</u>

BMO Nesbitt Burns US Account (in \$ Canadian)

Cash and short term investments	253	1,346
Common equity	78,712	66,695
	<u>78,965</u>	<u>68,041</u>
	<u>465,076</u>	<u>425,509</u>

6. ANNUAL MEETING EXPENSES

	2010	2009
Exhibits and facility	\$ 31,531	\$ 12,500
Travel and Expenses	18,509	15,150
Awards	16,984	9,500
Reception and Banquets	11,856	10,000
Organizing and planning	-	7,500
Supplies and other	5,942	-
	<u>84,822</u>	<u>54,650</u>

7. CAPITAL DISCLOSURES

CSBMCB defines the capital that it manages as unrestricted net assets. CSBMCB's objectives when managing capital are to generally match the structure of its capital to the underlying nature and term of the assets being financed, and to hold sufficient funds to enable that organization to withstand negative unexpected financial events, in order to maintain stability in the financial structure. CSBMCB seeks to maintain sufficient liquidity to enable it to meet its obligations as they become due.

There were no changes in CSBMCB's approach to capital management during the year ended December 31, 2010.

8. PRIOR YEAR COMPARATIVE FIGURES

Certain of the prior period's figures have been reclassified in conformity with the current period's financial statement presentation

Meeting Report:

The 53rd Annual Meeting of the CSMBCB, Banff, Alberta, 2010

Membrane Proteins in Health and Disease

Correspondents: Reinhart Reithmeier, Department of Biochemistry, University of Toronto, and Joseph R. Casey, Department of Physiology, University of Alberta

“Membrane Proteins in Health and Disease” was the topic of the 53rd Annual Meeting and Conference of the Canadian Society of Biochemistry, Molecular and Cellular Biology (CSMBCB) held at the Banff Centre April 15-18, 2010. This exciting meeting was organized by a team led by Joseph Casey at the University of Alberta. The topic proved very popular as the meeting drew over 200 participants, over half being trainees.

Membrane proteins are encoded by ~1/3 of all genomes and they serve as the most common of drug targets. Recent advances in structural biology have illuminated the structures of an increasing number of membrane proteins, most from bacterial sources. Membrane proteins have also entered the world of proteomics, as it is becoming more appreciated that membrane proteins are localized, work, and are regulated as part of integrated networks of specialized proteins. Finally, mutations that affect the functional expression of membrane proteins cause a large variety of inherited human diseases. Many of these mutations induce folding defects that impair trafficking of membrane proteins from their sites of synthesis in the endoplasmic reticulum (ER) to their final destinations, typically the plasma membrane. All of these exciting topics were covered in this meeting.

An outstanding Plenary Lecture was given by Gunnar von Heijne (Stockholm) on the insertion of membrane proteins into the endoplasmic reticulum. Dr. von Heijne described his elegant work that has defined comprehensive rules for the insertion and precise positioning of transmembrane segments into the ER membrane, using cleverly designed bacterial membrane proteins. This work is an excellent example of biophysical thinking in a cell biology context.

Session 2, chaired by Joseph Casey (Alberta), was on “Membrane Protein Trafficking and Folding”. The first speaker was David Andrews (McMaster) who described a whole genome image screen designed to detect proteins involved in ER assembly. A new investigator, Emmanuelle Cordat (Alberta), described a novel anion exchanger 1 (AE1) mutation (C479W), aptly named “Band 3 Edmonton” that in combination with another AE1 mutation (G701D) causes hereditary spherocytosis and the kidney disease, distal renal tubular acidosis (dRTA). Franck Duong (UBC) highlighted the use of “nanodiscs” as useful tools for the investigation of membrane protein oligomerization and interactions in the context of a lipid bilayer. Ron Kopito (Stanford) talked about quality control and protein degradation in the secretory pathway. He highlighted the complex interplay of the many ER components that regulate the assembly of multimeric membrane protein complexes and retain misfolded proteins for retrotranslocation and cytosolic degradation by different endoplasmic reticulum-associated protein degradation (ERAD) systems.

Session 3, chaired by Larry Fliegel (Alberta), was on the “Regulation of Membrane Proteins”. Joachim Deitmer (Kaiserslautern) spoke on functional interactions between various types of carbonic anhydrases and acid/base membrane transporters with a focus on lactate transport in various cells in the nervous system - carbonic anhydrase acting as a proton shuttle rapidly moving protons away from the surface of the membrane. Daniela Rotin (Toronto) talked about the role of the Nedd4 family of ubiquitin ligases in endocytosis, and the re-cycling defect of the ENaC epithelial sodium channel in Liddle’s Syndrome. Larry Fliegel (Alberta) followed with a presentation on mechanisms regulating the sodium/protein exchanger in the myocardium and in other tissues, pointing out the key role played by phosphorylation sites in the C-terminal domain of NHE1. Jonathan Lytton (Calgary), the final speaker in the session, discussed the role of the K⁺-dependent Na⁺/

Ca²⁺ exchangers in neuronal function, making use of knockout mouse models that exhibit unexpected dietary and behaviour deficits.

Session 4, chaired by Joel Weiner (Alberta), covered recent advances in “Membrane Protein Structure”. Joanne Lemieux (Alberta), another new investigator, described the structure of a bacterial rhomboid protease that provides new insights into its mechanism of action. These fascinating membrane proteins comprise four classes of proteases that are able to cut transmembrane segments. They are very important in the generation of peptide fragments that can aggregate and cause diseases such as Alzheimer’s. Da-Neng Wang (NYU) spoke about the structure of FocA, a pentameric organic ion channel, and how the determination of its structure revealed the basis of ion selectivity and gating. Jeff Abramson (UCLA) talked about the inverted topology structure of a bacterial sodium-dependent glucose transporter (SGLT) and the tight coupling of ion and sugar binding in an alternating sites mechanism. Crystal structures provide a static view of membrane proteins, whereas understanding function requires dynamics. The transitions that occur in membrane proteins can be followed using elegant spectroscopic techniques as illustrated by Francisco Benzanilla (Chicago) in his important studies of voltage-sensitive ion channels. The famous S4 segment is highly positively charged and its transmembrane movement evokes a transient current that can be followed using fluorescence energy transfer (FRET) in normal and mutant forms of the channel.

Session 5, chaired by Elaine Leslie (Alberta) was devoted to “Membrane Proteins in Diverse Species”. Ekkehard Neuhaus (Kaiserslautern) spoke about nucleotide transporters in plants and intracellular bacteria, emphasizing their importance in organelles such as chloroplasts, mitochondria and peroxisomes and during parasite invasion. Dean Price (Australia National University) covered his work on BicA, a bicarbonate transporter from marine cyanobacteria that serves as a model for the larger SLC26 gene family of anion transporters. BicA is part of the CO₂ concentrating mechanism that occurs through Rubisco and carbonic anhydrase, which effectively traps CO₂ as bicarbonate. In a similar vein, Etana Padan (Hebrew University) related

structural information on the bacterial NhaA Na⁺/H⁺ antiporter to human forms. She pointed out the role NhaA plays as a pH sensor and identified residues key to this function. Like many transporters, NhaA has an inverted repeat structure with disrupted or bent transmembrane helices at the heart of the transport mechanism. Janet Wood (Guelph) covered the role of the ProP symporter in osmoregulation and pointed out that water activity directly affects the transporter with water considered an inhibitor. She emphasized that many of the details of the structural mechanism of osmosensing remain to be determined.

The final session was on “Membrane Proteins and Diseases” and was chaired by Xing-Zhen Chen (Alberta). Elaine Leslie (Alberta) spoke about her studies of glutathione-dependent arsenic efflux by members of the multidrug resistance protein (MRP) family. Sven-Eric Jordt (Yale) gave a fascinating talk on the role of TRP anion channels in chemosensation and asthmatic inflammation. These membrane proteins serve as receptors that respond to heat (capsaicin), cold (menthol), odors (vanilla, allyl isothiocyanate), and irritants (acrolein). Steve Somlo (Yale) talked about the complexities of human polycystic diseases and the trafficking defects of the polycystin (PKD) membrane proteins associated with cilia formation. There are now well over 1,000 mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) that cause cystic fibrosis. Gergely Lukacs (McGill) presented his work on the turnover of CFTR mutants and quality control that occurs at the level of the plasma membrane.

The main meeting was supplemented by two satellite meetings; one on Na⁺/H⁺ exchangers organized by Larry Fliegel and Todd Alexander, and the other on bicarbonate transporters organized by Joseph Casey and Reinhart Reithmeier. Satellite meetings provide the opportunity to bring together investigators from around the world who can engage peers and trainees in detailed discussions on focused topics of mutual interest. The organizers have provided reports of these satellite meetings.

A highlight of the Annual CSBMCB Meeting is the award lectures. This year Senthil Muthuswamy from the Ontario Cancer Institute (OCI)/ University Health Network (UHN) won the CSBMCB Young Investigator Award

for his studies of cell polarity and its link to cancer. Dr. Muthuswamy highlighted his development of a unique 3-D culture system for epithelial cells and his studies of signalling cascades. Cheryl Arrowsmith, also from the OCI, won the Jeanne Manery Fisher Award. She spoke about the Structural Genomics Consortium (SGC) that has a focus on solving the structures of human proteins of vital medical interest. She highlighted SGC's recent work on chromatin biology, epigenetics and the histone code, and its move into chemical biology. Hans Vogel (Calgary), a very productive nuclear magnetic resonance (NMR) specialist, won the CSBMCB Senior Investigator Award, or the "Seniors' Award" as he called it. He gave a presentation on his work on the structure of TonB, its interactions, and its role in iron uptake in gram-negative bacteria.

Michel Chrétien (Ottawa) was recognized as the 2010 recipient of the Arthur Wynne Gold Medal given to a Canadian scientist who has an international reputation for research in biochemistry, molecular and cellular biology; has played a major role in the development and promotion of the discipline in Canada; and has a long-standing record of service to the academic community. Dr. Chrétien is well known for his work on convertases with over 500 publications to his name. He served as Director of the Clinical Research Institute of Montréal and Loeb Health Research Institute of Ottawa. Among his many awards and recognitions, Dr. Chrétien was recently elected as a fellow of the Royal Society (UK). He was President of the Canadian Biochemical Society and a recipient of the Boehringer-Mannheim Award. Michel gave a gracious after-dinner speech to the delight of the large crowd, highlighting his personal career path and the role serendipity has played in his success. Michel is often mistaken for his older brother Jean and he related some humorous encounters with everyone from car wash attendants to cabinet ministers.

The CSBMCB is very active in advocating for increased research funding and highlighting the benefits of discovery-based research. The Society supports the activities of Research Canada, which is dedicated to advancing health research in Canada. Deborah Gordon, Executive Director of Research Canada, gave a compelling presentation of the activities of this organization during the CSBMCB Annual Meeting with keen insights into "how the government decides." Research Canada coordinates its activities with

other organization such as the Partnership Group for Science and Engineering (PAGSE) and Association of Universities and Colleges of Canada (AUCC) so researchers have one strong voice in Ottawa. She emphasized the notion of telling good stories - stories about our discoveries and successes and how research can help address the problems and challenges facing Canada and the world.

Given the success of this meeting and strength of Canada in membrane proteins, the CSBMCB decided to hold the 2014 Annual Meeting and Conference in Banff on the same topic. The intervening years will see new breakthroughs as more membrane protein structures are solved, more information is obtained about membrane protein interactions and regulation, and methods to correct trafficking defects common to many membrane protein-associated diseases are developed. Exciting times lie ahead in the study of membrane protein structure and function, and their role in health and disease.

Report on the Bicarbonate Transport Satellite Meeting at the 53rd Annual Meeting of the CCBMCB

Correspondents: Reinhart Reithmeier, Department of Biochemistry, University of Toronto and Joseph R. Casey, Department of Physiology, University of Alberta

A Bicarbonate Transport Satellite Meeting organized by Joseph Casey and Reinhart Reithmeier was held at the Banff Centre April 14-15, 2010 in advance of the 53rd Annual Meeting and Conference of the Canada Society of Biochemistry, Molecular and Cellular Biology on Membrane Proteins in Health and Disease.

Session 1 on Band 3 and anion exchangers was chaired by Seth Alper (Harvard), a basic scientist and nephrologist known for his work on kidney Band 3. Dr. Alper introduced the first speaker, Ron Kopito (Stanford); Drs. Alper and Kopito were postdoctoral fellows together in Harvey Lodish's laboratory in the 1980s. The year 2010 represents the 25th anniversary of the 1985 publication in *Nature* of the cloning of the mouse Band 3 gene by Ron Kopito. Dr. Kopito gave a compelling historical and personal account of this major breakthrough. Inspired by the work of Günter Blobel (Rockefeller), Dr. Kopito

was interested in determining how polytopic membrane proteins are inserted into lipid bilayers during their biosynthesis. He joined the Harvey Lodish lab at MIT and set out to clone the cDNA for Band 3, one of the best characterized polytopic membrane proteins at the time. To do this, a good source of mRNA and a probe to screen cDNAs was needed. Anemic mouse spleen provided the RNA, but probes were more difficult due to limited protein sequence information and codon degeneracy. Using antibodies to probe a λ gt11 phage expression library, based on the work of Young and Davis, the first large 1,800-bp clone was produced in 1983. Alas, there appeared to be a long 3'UTR with only a ~80 residue predicted open reading frame starting from the C-terminus of Band 3. The Reithmeier lab at the University of Alberta had at that time a short but tentative C-terminal sequence for human Band 3 based on carboxypeptidase Y digestion experiments. A late night call to Alberta confirmed that the clone encoded mouse Band 3, and, as they say, the rest is history. Dr. Kopito has gone on to be a major player in membrane protein biosynthesis and quality control working on Band 3 and cystic fibrosis transmembrane conductance regulator (CFTR).

The next pair of talks by Yamaguchi and Hirai from the Riken in Japan dealt with the determination of the structure of human Band 3 using electron crystallography. Exciting new data was presented that provided a glimpse of the arrangement of some of the transmembrane helices. The fold represented that of the chloride channel (ClC) transporter/channel, suggesting that Band 3 has a similar inverted repeat structure and transport mechanism.

Band 3 does not work alone in the red cell membrane, but as an integral part of large protein complexes. Lesley Bruce (Bristol) spoke about the various oligomeric forms of Band 3 and their interactions with the cytoskeleton via ankyrin and junctional complexes. Other proteins also interact transiently with Band 3. Ashley Toye (Bristol) provided evidence that the tyrosine phosphatase Shp can dephosphorylate kidney Band 3, counteracting the activity of tyrosine protein kinases. The phosphorylation of kidney Band 3 may regulate its resident time at the basolateral membrane and its endocytosis, building up evidence for a role for phosphorylation in the basolateral targeting of kidney AE1.

The 2nd session chaired by Joseph Casey (Alberta) dealt with the sodium-bicarbonate carrier (NBC) members of the SLC4A family of anion transporters. It is interesting to note that anion exchangers and co-transporters are related in sequence and are members of the same gene family. This strongly suggests that they have a similar overall structure and operate by a similar transport mechanism. Mark Parker (Case) emphasized differences in the sodium dependence of electro-neutral SLC4A8 and A10 bicarbonate transporters. Jeppe Praetorius (Aarhus) presented his analysis of the properties of NBCs in the choroid plexus and duodenum and their functional coupling with sodium/proton exchangers (NHE) in mediating bicarbonate secretion. Mark Bevensee (Alabama) talked about the complexities of phosphoinositide regulation of sodium bicarbonate co-transporters. Irina Grichtchenko (Colorado) spoke about vesicular movement and the calcium dependence of exocytosis in the trafficking of NBCe1 in the kidney.

Session 3 chaired by Reinhart Reithmeier (Toronto) focused on the interaction of carbonic anhydrase and bicarbonate transporters, a discovery made John Vince, a graduate student in his lab and first published in 1998. Joachim Dietmer (Kaiserslautern) provided evidence for the functional interaction of different forms of carbonic anhydrase with electrogenic sodium bicarbonate co-transporters using various mutants and the oocyte expression system. The model proposed is that carbonic anhydrase promotes more rapid sodium/bicarbonate co-transport by maintaining an inward transmembrane gradient of bicarbonate and protons due to rapid conversion to carbon dioxide and water. Joseph Casey (Alberta) spoke on his examination of H⁺ micro-domains at the membrane surface, using anion transporters fused to pH sensitive fluorescent proteins. He emphasized that proton diffusion in the cytosol of cells such as cardiomyocytes is slow due to its titration by proteins and small molecules. It is worthwhile considering CO₂ as a "virtual" proton since it is not titrated and carbonic anhydrase catalyzes the instantaneous equilibration of carbon dioxide and water with bicarbonate and a proton.

The final session dealt with the SLC26 family of anion transporters, which includes plant and bacterial SulP members. Although not related to the SLC4A family, these membrane proteins can act as chloride/bicarbonate

exchangers like Band 3, but also as sulfate transporters and anion channels. The importance of this family is emphasized by the finding of mutations in human SLC26 members that are linked to various inherited diseases. Susan Howitt (Australian National University) summarized her work on the SHST1, a plant member of the SulP family. Using expression in yeast, residues critical for trafficking and function were identified, and evidence was obtained for the role of the C-terminal transmembrane segments and the STAS domain in dimerization. Michael Jennings (Arkansas) discussed his work on sulfate transport in yeast by the SulP family, its regulation, and the link to sulfate metabolism. Trevor Moraes (Toronto) presented the crystal structure of a complex of the C-terminal STAS domain of *E. coli* YchM with acyl carrier protein (ACP). ACP is involved in acylation reactions and is particularly important in fatty acid biosynthesis. Since bicarbonate is essential for fatty acid biosynthesis, YchM may be a bicarbonate transporter that fuels the fatty acid biosynthesis pathway at alkaline pH. Alternatively, YchM may be a sensor system for extracellular bicarbonate or pH and play a role in the regulation of cell growth that requires not only protein synthesis but also lipid synthesis.

This Satellite Meeting represented the highest concentration of workers in the bicarbonate transport field ever assembled. The close-knit and informed audience of over 50 posed challenging questions. The meeting provided the community with a picture of the current state of the field and the many questions remaining to be answered. Trainees in particular had the opportunity to meet many of the leaders in the bicarbonate transport field – investigators that had only been previously known to graduate students and post-doctoral fellows from their publications. These young scientists may be inspired to continue working on bicarbonate transport and to provide new insights into this important class of membrane proteins into the future.

Report on the Na⁺/H⁺ Exchanger Satellite Meeting at the 53rd Annual Meeting of the CCBMBCB

Correspondents: R.T. Alexander and L. Fliegel,
Department of Biochemistry, University of Alberta

The Na⁺/H⁺ exchanger Satellite Symposium was held on

Saturday April 17th from 1:00-5:00 PM in conjunction with the 53rd Annual CSBMBCB Meeting on “Membrane Proteins in Health and Disease. The session was chaired and organized by Dr. Larry Fliegel of the Department of Biochemistry of the University of Alberta.

The first speaker was Dr. John Orlowski of McGill University. His talk was titled “Organellar pH Homeostasis and Neurological Disease”. Dr. Orlowski gave a dynamic talk, first introducing the various subclasses of the Na⁺/H⁺ exchangers and then providing background on the organellar isoforms NHE6, 7 and 9. He described how these isoforms can move K⁺ and how they regulate organellar pH in concert with the vacuolar H⁺-ATPase. He described how organellar pH can be measured with fluorescent probes, which is important since NHE6 and NHE7 are in recycling vesicles. The linkage of NHE6 mutation to several human diseases, including mental retardation and epileptic seizures, was described. He also detailed studies on NHE6 localization and function and how varying NHE6 levels affect endosomes and their traffic. Overall, this was a fast paced and enjoyable talk packed with information well beyond what would normally be present in a 25-minute lecture.

The second speaker was Dr. Jan Rainey of Dalhousie University. His talk was titled “Correlating Function to Structure and Dynamics in NHE1 using the “Divide and Conquer” approach. Dr. Rainey described how nuclear magnetic resonance (NMR) can be used to examine the structure of membrane proteins. He reviewed how the structure of fragments of membrane proteins deduced by NMR have been shown to correlate very well with the structure of those regions in full length crystallized membrane proteins. He then reviewed the structure of transmembrane segments IV, VII and IX of the NHE1 isoform of the Na⁺/H⁺ exchanger. Of note, these regions are not continuous helices, but rather are interrupted by non-helical extended or bent regions. TM IV of NHE1 shows structural homology to TM IV of NhaA. TM IX shows a bent structure with amino acids Ser351 and Glu346, which are important functionally, on opposite faces of the peptide. This might indicate an alternating access region of the protein. Overall, the talk gave enlightenment to a new approach to study membrane proteins, when production of the entire protein and its crystallization is problematic.

Dr. Etana Padan of the Hebrew University of Jerusalem talked about “NhaA Based Modeling of the Eukaryotic Exchanger NHE1 and NHA2”. She outlined differences in the functional aspects of NhaA and NHE1, including differences in affinity and regulation by pH. She explained how a new model of NHE1 was developed based on a comparison with NhaA. This model shows critical differences in topology from a previous model of NHE1 based on cysteine scanning accessibility. Dr. Padan outlined some inconsistencies in the previous model as some intracellular located residues were accessible to reagents that are impermeable to the plasma membrane. A new model of NHA2 was presented based on comparison with NhaA. Structural based mutagenesis studies were used to identify residues critical to the activity of the protein. This very sophisticated lecture showed new insights into how topology of membrane proteins can now be predicted and used to plan structure-based mutagenesis.

Dr. Masa Numata of the University of British Columbia spoke about “Membrane Dynamics and Tumor Metastasis - Potential Role of NHE7”. He explained the comparative effects of expression of NHE7 and NHE1 in causing metastasis. His studies examined the effects of their expression in a metastatic breast cancer cell line, MDA-MB-231. He described effects measured by use of cell overlay and cell infiltration assays. Cells with elevated NHE7 expression demonstrated greater saturation compared to controls or NHE1-containing cells. In cell invasion assays increased expression of NHE7 enhanced colony formation. Preliminary experiments in nude mice suggest NHE7 expression may enhance tumor formation and metastasis.

After a lively discussion and break Dr. Pavel Dibrov from the University of Manitoba gave a talk entitled “Peculiar Features of Na⁺/H⁺ Antiporters of NhaP Type in *Vibrio cholerae*”. Dr. Dibrov reviewed the alternating access model of NhaA transport. He outlined the many isoforms of Na⁺/H⁺ antiporter that exist in *Vibrio cholerae* and how some arose from gene duplication. He described work on vcNhaP2, which showed that chromosomal deletion of this isoform caused growth impairment at pH 6.0 in medium containing KCl. This isoform was also expressed in *E. coli* and its activity was characterized in vesicles using acridine orange. It exhibited transport in response to KCl addition and to a lesser degree in response to NaCl, but not in LiCl.

The results were explained in terms of an interesting model describing how these ions bind to the putative cation binding sides.

Dr. Todd Alexander of the University of Alberta gave a talk entitled “NHE3 is Necessary for Renal and Intestinal Calcium Absorption”. Dr. Alexander described the proposed mechanism by which NHE3-mediated Na⁺ flux might drive paracellular Ca²⁺ flux across renal and intestinal epithelia. To test this he employed NHE3 null mice. The knockout animals had normal serum calcium and parathyroid hormone levels but increased vitamin D levels. Functional studies on calcium flux across the small intestine revealed decreased flux in the knockout mice. Similarly the knockout animals had increased urinary calcium excretion. These combined observations contributed to a decreased bone mineral density in the null animals. Dr. Alexander inferred from these findings that NHE3 plays a significant role in calcium homeostasis.

The final talk of the session was given by Grant Kemp, a graduate student in the Department of Biochemistry at the University of Alberta. Grant Kemp described a yeast based expression system that he developed to express milligram quantities of the NHE1 protein. The protein was used with electron microscopy and single particle reconstruction of negatively stained NHE1 to produce a molecular envelope for the protein. The envelope showed that NHE1 is dimeric, each monomer with a size and shape consistent with a general 12 membrane segment protein, similar to NhaA. Experiments were shown that demonstrated that the protein produced by yeast can be phosphorylated in vitro. Reconstitution of NHE1 demonstrated that it had a typical profile of inhibition with NHE1 inhibitors. Future experiments will further examine the structure of the protein.

Overall, the symposium gave a very state of the art summary of Na⁺/H⁺ exchanger proteins spanning from the *E. coli* and *Vibrio cholerae* proteins, to mammalian Na⁺/H⁺ exchanger isoforms. The discussions that followed were lively and many scientists received constructive comments from their colleagues.

Scenes from the 53rd Annual Meeting, Banff, Alberta 2010



▲ A busy time at the poster sessions.



▲ Delaine Ceholski takes visitors through her poster.



▲ Marek Duszyk and Gergely Lukacs consult during the difficult task of judging posters



▲ Reinhart Reithmeier and Joe Casey visit with guest Gunnar von Heijne.



▲ Research Canada President, Deborah Gordon-El-Bihbey, describes advocacy efforts at the Annual General Meeting



▲ Michel Chretien receives the Arthur Wynne Gold Medal for his lifetime scientific achievements and for promoting biomedical science in Canada



▲ Hans Vogel (U. Calgary) receives the Senior Investigator Award from David Williams



▲ Senthil Muthuswamy (Ont. Cancer Inst) is honoured with the Young Investigator Award



▲ Cheryl Arrowsmith (Ont. Cancer Inst.) joins a select group of outstanding women scientists as the 2010 Jeanne Manery Fisher Memorial Lecturer



▲ CSBMCB President, David Williams, thanks outgoing Secretary, Albert Clark, for his years of service to the Society



Enjoying dinner in the fantastic setting of the Banff Centre



▲ Oh yes, there was skiing...amazing skiing... in an amazing setting! Just ask Susan Bustos, Sian Patterson and Reinhart Reithmeier who normally drive 2 h from Toronto just to ski down a 720-foot bump.



▲ The CSBMCB Board with Deborah Gordon-El-Bihbety and Michel Chretien

Reinhart Reithmeier presents Meeting Organizer, Joe Casey, with an Oilers
▼ jersey as a thank you for his efforts in putting together a superb meeting



Poster Award Winners 53rd Annual Meeting

Pamela Bonar. *Overexpression and Purification of Functional Human AE1 Expressed in Saccharomyces cerevisiae, Suitable for Protein Crystallization.* Departments of Physiology and Biochemistry, University of Alberta. Supervisor: Joe Casey

Kyle Legate. *A novel role for PtdIns(4,5)P₂ in force coupling integrins to the cytoskeleton.* Departments of Molecular Medicine, Max Planck Institute of Biochemistry. Supervisor: Rienhard Faessler
(Biochemical Journal Poster Prize)

Gonzalo Villas. *Structural Characterization of SLC4A11, a Membrane Protein Mutated in Some Corneal Dystrophies.* Departments of Physiology and Biochemistry, University of Alberta. Supervisor: Joe Casey

John Paul Glaves. *A Functional, Pentameric Form Of Phospholamban Is Required For Two-Dimensional Crystallization With The Sarcoplasmic Reticulum Calcium Pump.* Department of Biochemistry, University of Alberta. Supervisor: Howard Young

(Jake Duerksen Poster Award)

Christian Scholz. *Expression, purification, characterization and reconstitution of recombinant human transporter associated with antigen processing in Pichia pastoris.* Inst. of Biochemistry, University Frankfurt. Supervisor: Robert Tampé

Tara Winstone. *Twin-arginine translocase substrate specific chaperone interaction with the targeting leader sequence.* Department of Biological Sciences, University of Calgary. Supervisor: Raymond Turn

Harris Huang. *Mechanism of silencing of the catalytic domain by the regulatory membrane lipid-binding domain of an amphitropic protein, cytidyltransferase.* Department of Molecular Biology and Biochemistry, Simon Fraser University. Supervisor: Rosemary Cornell

(Biochemical Journal Poster Prize)

David Langelaan. *MC-HELAN: A Monte Carlo method for helix and kink characterization in proteins.* Department of Biochemistry & Molecular Biology, Dalhousie University. Supervisor: Jan Rainey



▲ CSBMCB President David Williams (bottom left) with 2010 Poster Awardees

Travel Award Winners 53rd Annual Meeting

Nicole Alcolado. Dept. of Physiology & Biophysics, Dalhousie University.
Supervisor: Valerie Chappe

Huan Bao. Dept. of Biochemistry, University of British Columbia.
Supervisor: Franck Duong

Damien Biot-Pelletier. Dept. of Microbiology and Immunology, McGill University.
Supervisor: James Coulton

Jennifer Chiang. Dept. of Biochemistry, University of Toronto. Supervisor: Emil Pai

Fiona Cunningham. Hospital for Sick Children, Dept. of Biochemistry, University of Toronto. Supervisor: Charles Deber

Hamed Ghanei. Dept. of Medical Biophysics, University of Toronto. Supervisor: Gil Prive

Alister Gould. Dept. of Biochemistry, University of Western Ontario. Supervisor: Brian Shilton

Harris Huang. Dept. of Molecular Biology and Biochemistry, Simon Fraser University. Supervisor: Rosemary Cornell

Tushare Jinadasa. Dept. of Physiology, McGill University. Supervisor: John Orlowski

David Langelaan. Dept. of Biochemistry & Molecular Biology, Dalhousie University. Supervisor: Jan Rainey

Nicole Nivillac. Dept. of Biology, York University. Supervisor: Imogen Coe

Jamie Park. Dept. of Physiology and Pharmacology, University of Western Ontario. Supervisor: James Hammond

Sian Patterson. Dept. of Biochemistry, University of Toronto. Supervisor: Reinhart Reithmeier

Hannah Pierson. Dept. of Biochemistry, University of Saskatchewan. Supervisor: Oleg Dmitriev

Durga Sivanesan. Dept. of Biology, McMaster U. Supervisor: Christian Baron

Jamie Snider. Depts. of Molecular Genetics and Biochemistry, University of Toronto. Supervisor: Igor Stagljar



2010 Travel Awardees receive their cheques from CSBMCB President David Williams.

Our thanks to New England BioLabs for sponsoring two of the travel awards.

2010 Jeanne Manery Fisher Memorial Lectureship

Toward Chemical Probes of Chromatin Biology



Cheryl Arrowsmith

Peter J. Brown¹ and Cheryl H. Arrowsmith^{1,2}

¹Structural Genomics Consortium, University of Toronto and

²Ontario Cancer Institute, Campbell Family Cancer Research Institute, and Department of Medical Biophysics, University of Toronto

Background

One of the major problems that limit the discovery of new medicines is identifying a specific cellular protein that is causally linked to a given disease, so that this protein can be targeted for drug development. Often pharmaceutical companies learn after more than a decade of research and hundreds of millions of dollars that the drug target is not related to the disease in the manner originally thought, and therefore candidate drugs do not alleviate the disease. As a result, the pharmaceutical industry is reticent to embark on drug discovery programs for novel, “un-validated” targets. The ideal way to validate a target is to show, in humans, that an inhibitor has a therapeutic effect; however, this is impractical in most cases for ethical reasons. Among the next best strategies is to develop an inhibitor for the protein and show in animal, and human cell and tissue models that its inhibition has the appropriate effects. These inhibitors, termed “chemical probes”, are valuable not only in disease association studies, but also in studies of basic human biology. Chemical probes are complimentary to genetic methods of target validation. Furthermore, if the probes are well-characterized and specific to the target, they also form the starting point for new, potentially more successful drug discovery programs.

We have embarked on a program to generate a “chemical map” of the druggability of proteins involved in epigenetic gene regulation. Our goal is to develop high quality chemical probes and make them available to the broader research community free from restrictions on their use. This will enable the scientific community to gain a deeper understanding of the role of epigenetic regulatory proteins in human physiology and disease. In addition, scientists and organizations engaged in drug discovery will have access to a plethora of chemically tractable molecular targets for the development of new medicines.

Why Epigenetics?

Although all cells in an organism inherit the same genetic material, their ability to maintain the unique physical characteristics and biological functions of specific tissues and organs is due to epigenetic changes in their DNA and chromatin structure. As such, epigenetics underpins the fundamental basis of human physiology. It explains why our genome sequence is static, yet each cell type or tissue is different from each other. It explains why the process of cellular differentiation is stable over multiple generations, while stem cells retain the ability to differentiate into multiple cell types. It explains the effects of environmental factors on aging, such as why identical twins can be different as they grow older. The importance of epigenetics is further underscored by evidence linking it with disease such as cancer, where epigenetic mechanisms account for up to half of all genetic alterations [1] or the effect of maternal nutrition on the development of diabetes and cardiovascular disease in her offspring [2].

Over the past decade we have seen an explosive growth in our understanding of the molecular mechanisms of epigenetics, such that it is now clearly an area of potential therapeutic relevance for many diseases. While many aspects of epigenetics are still not understood, we now know the basic complement of regulatory proteins that mediate many aspects of epigenetic signaling, in particular the readers, writers and erasers of chromatin marks. Recent insights from structural biology have revealed the molecular mechanisms by which specific enzymes and recognition domains modify and read the epigenetic state of a cell. Chemical Probes that specifically target these epigenetic proteins will be valuable tools for understanding their role in human physiology and disease and essential reagents to identify which epigenetic targets are the most promising for pharmacological modulation of disease states. Ultimately, the availability of such probes will lead to new medicines.

Epigenetic signaling

The concept of epigenetics was first introduced by Waddington [3] in 1939 to describe “the causal interactions between genes and their products, which bring the phenotype into being”, and was later defined as heritable changes in gene expression that are not due to alterations in DNA sequence [4]. The physical correlate of

these heritable changes is found in chromatin, composed of DNA, histones and other protein factors. Direct modification of DNA by methylation of the sequence CpG has been known for many years. DNA methylation is associated with inactivation of genes and the DNA methylation state of the genome changes during cellular differentiation and development of an organism. Aberrant methylation of DNA is a hallmark of cancer cells [5].

Over the past decade it has become clear that post-translational modification of histones also plays a central role in regulating information that is stored within DNA. The majority of histone modifications are found on the N-terminal histone tails that protrude from the globular core of the nucleosome and include phosphorylation, acetylation, ribosylation, ubiquitylation, and methylation. To regulate post-translational histone modifications, a corresponding class of enzymes has evolved that can remove histone modifications. For example, acetylation, methylation and phosphorylation “marks” are dynamically removed by deacetylase, demethylase and phosphatase enzymes. Of particular interest are the recent advances in our understanding of histone arginine and lysine methylation, and the lysine acetylation systems. Each modification can affect chromatin structure, but the state of the chromatin is ultimately determined by a combination of these and other modifications, which play important roles in maintaining genome integrity, regulating transcription, and contributing to epigenetic memory [6-9]. Mechanistically, proteins interacting with chromatin are divided into modifying enzymes that “write or erase” histone “marks” (such as methyltransferases/demethylases) and “reader” proteins that recognize specific chromatin marks (such as Bromo domain containing proteins which recognize histone lysine acetylation).

The Structural Genomics Consortium (SGC) is investigating the human proteins from these classes with the goal of understanding the structural basis of substrate recognition, selectivity and inhibition by small molecules (Table 1).

Epigenetics in human biology, health and disease

The past two decades have seen an explosion of epigenetic-related clinical and molecular biological discoveries,

Family		Number of domains	Pure in SGC	Assays established in SGC	Structures deposited [SGC/Total]
Lysine demethylase (KDM)		29	19	16	8/11
Bromodomain (BRD)		56	40	41	28/33
R O Y A L	Tudor domain	58	35	5	8/22
	Chromo domain	43	34	9	10/18
	MBT domain	9	8	3	5/7
	PWWP domain	26	15	0	8/14
PHD		127	34	4	1/30
Histone acetyltransferase (HAT)		17	8	6	5/7
Histone methyltransferase (HMT)		60	43	21	16/24
TOTAL		425	236	105	89/166

Table 1 Human protein families associated with epigenetic regulation

highlighted by global hypomethylation of DNA in human tumors, hypermethylation of tumor suppressor genes, and inactivation of microRNA genes by DNA methylation [10-12]. These discoveries have led to the development of DNA methyltransferase inhibitors that appear promising in oncology therapy settings. Early development, and subsequent susceptibility to disease, is determined epigenetically. Maternal behavior can influence epigenetic programming, and hence the HPA axis and glucocorticoid signaling in the fetus. Phenotypical features such as susceptibility to cardiovascular diseases might also be determined early in life [13, 14]. The regulatory pathways that underpin the maintenance of stem cell pluripotency also rely on chromatin based epigenetic memory systems. Epigenetic factors are commonly disrupted in debilitating mental retardations, and almost all cancers show abnormal epigenetic features. Taken together, this suggests that the ability to modulate epigenetic signaling pathways will have important implications in disease and regenerative medicine/ stem cell therapy.

There is a close relationship between the DNA methylation status of a given gene or region of chromatin and the spectrum of histone marks in that region. These related epigenetic states are maintained by a complex network of signaling between epigenetic factors in the cell. The recent success of DNA methyltransferase and histone deacetylase inhibitors in

oncology clinical trials [15] suggests that modulation of this signaling network is a fruitful approach to cancer therapy. Thus, it may be possible to reverse aberrant methylation status in cancer cells by inhibition of related epigenetic factors, offering the opportunity to target cancer in a tumor specific manner. Well characterized Chemical Probes will be excellent tools to discover which factors may trigger such an outcome.

The need for chemical probes

The potential for inhibitor based therapeutic intervention in epigenetic conditions appears very promising; DNA methyltransferase inhibitors, azacytidine and decitabine, and histone-deacetylase (HDAC) inhibitor, vorinostat, have been approved for treatment of certain cancers and additional compounds are at advanced stages of clinical trials. This strongly suggests that pharmaceuticals that modulate other proteins and enzymes that read, write, or erase chromatin marks thereby modifying the state of chromatin and gene expression, may also be good therapeutic targets. However, our current level of knowledge is not sufficient to know which of the hundreds of epigenetic signaling proteins to target. Recently, Shi et al, [16] published the first demonstration of the use of an epigenetic probe that inhibits the histone methyltransferase called “G9a”, and whose 3-dimensional structure we have solved. This exciting result showed that a compound was able to help induce human skin cells to revert into a stem cell. The ability to chemically induced pluripotent stem cells (IPS) using chemicals agent instead of protein factors [17] has tremendous potential in regenerative medicine.

The focus of our Chemical Probe project is to design specific inhibitor molecules to probe epigenetic signaling. Chemical probes are complementary tools to molecular genetic methods such as transgenic/knockout animals or RNAi experiments. Chemical inhibition can better probe a specific activity of multifunctional proteins and does not eliminate the entire protein which may disrupt protein complexes or networks. A further advantage of chemical probes lies in their cell permeable properties, systemic distribution and ease of administration. These properties make them attractive reagents for cellular and in vivo experiments.

In total, we are targeting the majority of readers, writers

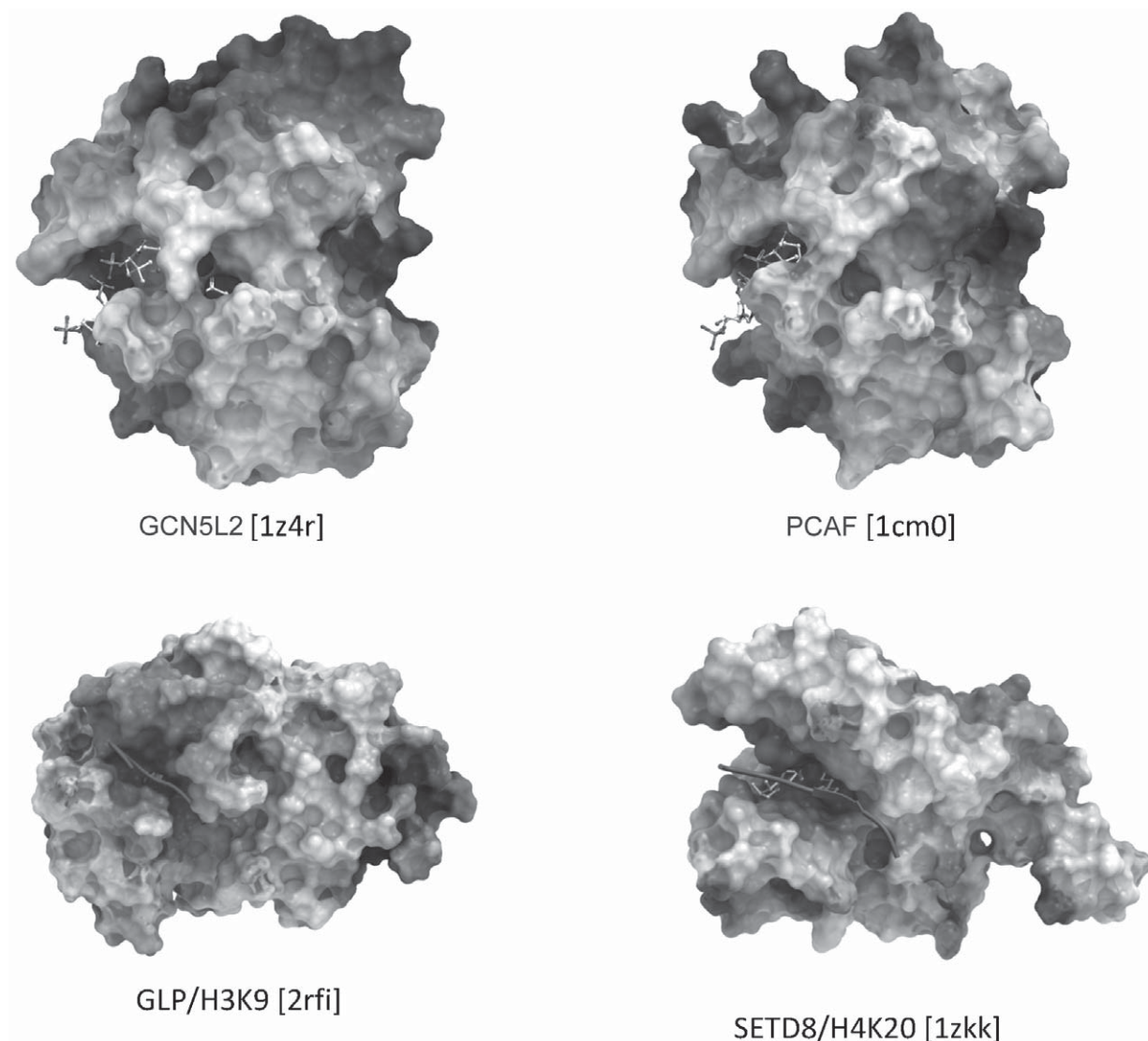


Figure 1.

Examples of 3D structures of acetyltransferases GCN5L2 and PCAF, and histone methyltransferases GLP and SETD8 bound to substrate peptides.

and erasers of epigenetic marks in the human genome. This broad group of factors includes several hundred proteins of potential but unknown therapeutic value, and constitutes excellent targets for such an undertaking for several reasons. First, we have been able to produce, purify and solve the 3D structures of a large proportion of these proteins in laboratories of the Structural Genomics Consortium (SGC), leading to significant “structural coverage” of these protein families (Table 1). Our protein structures and those of others indicate that each of the protein families appears to be druggable; they each have defined “pockets” on their molecular surface that could accommodate small drug-like

molecules and displace the histone peptides to which they normally bind. The combined ability of the SGC to make and assay hundreds of proteins together will be partnered with medicinal chemistry expertise of a network of collaborators.

We estimate that the epigenetics field is currently at a similar state of knowledge to that of the nuclear receptor (NR) and kinase fields in the early-mid 1990s. Although, the field of epigenetics is likely to be far more complex, there are key lessons that can be learned from the NR field. For example, over the past 15 years researchers at GSK (and its predecessor companies) have developed chemical probes

to orphan NRs using principles of medicinal chemistry and structure-based drug design. As such, they have been able to map the “chemical tractability” of each orphan NR – the ability of the protein to bind to, and be inhibited by, a drug-like small molecule. They have gone on to provide chemical probes to academics leading to a rapid expansion in new knowledge of orphan NR signaling and the discovery of new links to human diseases and physiological processes [18-25]. Importantly, this new knowledge combined with the availability of chemical probes and 3D protein structural information has led to the generation of clinical candidates for many of the orphan nuclear receptors that are chemically tractable [26, 27].

Key lessons learned from this experience that can be applied to the chemical biology of epigenetics

- A “protein family” strategy is an efficient approach for identification of innovative drug targets
- Chemical tractability is the most important issue for the success of a class of proteins as targets
- Scan the protein family with small compound arrays (or fragments) to map tractability. This approach is likely to speed the rate of discovery by a factor of 3-10X compared to more traditional high throughput screening of a single target at a time.

- Synthetic ligands are powerful tools for discovery of new biology if they are well-characterized, potent, and selective for one or a subset of targets within a protein family and they are used in bioassays that are able to distinguish physiology from phenomenology.
- Smart experimental strategies often beat brute force
 - o Knowledge-based chemical library design
 - o The use of 3D structures for biological and chemical insight

We are applying these principals to the chemical biology of epigenetic proteins to reveal novel mechanisms of epigenetic signaling, disease association, and eventually to spur the development of new medicines.

The first target upon which we focused our attention was EHMT2 (G9a) which catalyses the mono- and dimethylation of lysine 9 of histone 3 (H3K9) and also the dimethylation of lysine 373 of p53, a tumor suppressor. The only known ligand for G9a is BIX-01294, which was reported in 2007 [28] (Figure 2). BIX-01294 was shown to reduce H3K9 dimethylation in cellular assays, however, the wide spread use of this compound in cell-based assays is limited by its toxicity. In collaboration with medicinal chemists at the University of North Carolina Center for

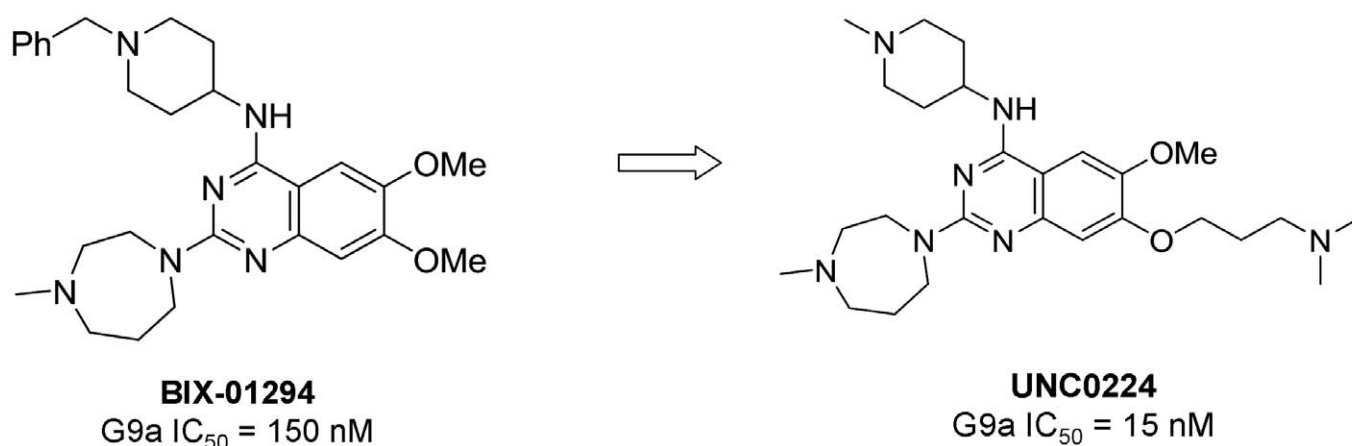


Figure 2. Structures and in vitro activities of quinazoline analogs.

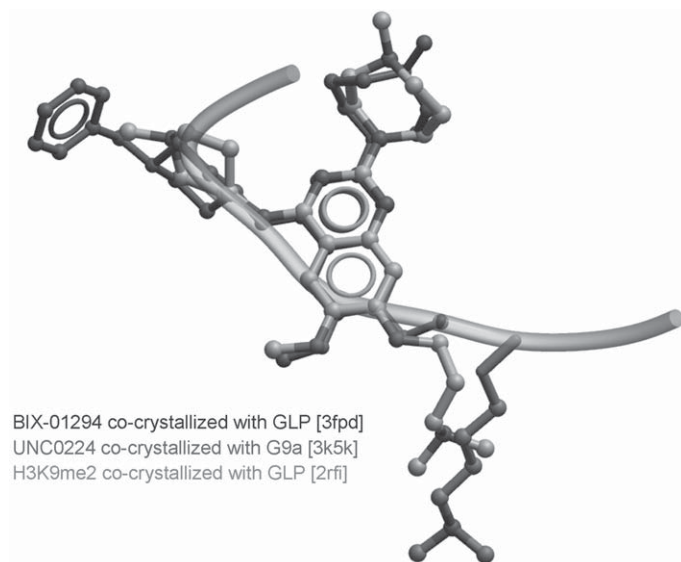


Figure 3. Superposition of the inhibitory compound UNC0224 when bound to G9a, with BIX-01294 and histone 3 substrate peptide when bound to the highly similar enzyme, GLP.

Integrative Chemical Biology and Drug Discovery (CICBDD), we set out to discover more potent analogs of BIX-01294, in both in vitro and cellular assays.

Our initial studies focused on the relatively easy chemistry of varying the 2- and 4-substituents around the quinazoline ring system, however, with no resultant increase in inhibitory potency. During the course of this work, the structure of BIX-01294 bound to EHMT1 (GLP; 80% sequence homology to G9a) was published [29] which clearly showed that BIX-01294 bound at the histone peptide binding site, but did not interact with the lysine channel. Thus it was hypothesized that adding a lysine tail to the 7-methoxy group might increase binding affinity. Indeed this is the case as UNC0224 inhibits G9a with 10-fold potency enhancement over BIX-01294 with a concomitant increase in binding as measured by ITC [30] (Figure 2).

In addition, the interaction of the dimethylaminopropoxy side-chain with the lysine-binding channel of G9a was confirmed by X-ray crystallography, resulting in the first X-ray structure of G9a with a bound ligand (PDB 3k5k). The overlay of three structures below clearly shows that UNC0224 binds in a similar manner to BIX-01294 and that the side-chain of UNC0224 extends into the lysine-binding pocket (Figure 3).

Our excitement that UNC0224 was ten-fold more potent than BIX-01294 in vitro was tempered by the fact that this difference did not translate into increased potency in cell-based assays, which is probably due to decreased cellular permeability. However, rapid evaluation of SAR focused on optimization of cellular activity resulted in the identification of molecules which are superior in cellular assays as well as less toxic at higher doses [31]. These compounds are currently being characterized in multiple cell-lines.

We have also started to assess the tractability of protein sub-families by screening a 2000-member fragment set of compounds in order to find starting points for medicinal chemistry. Figure 4 outlines the progress to-date indicating that, as expected, some protein families are more tractable than others.

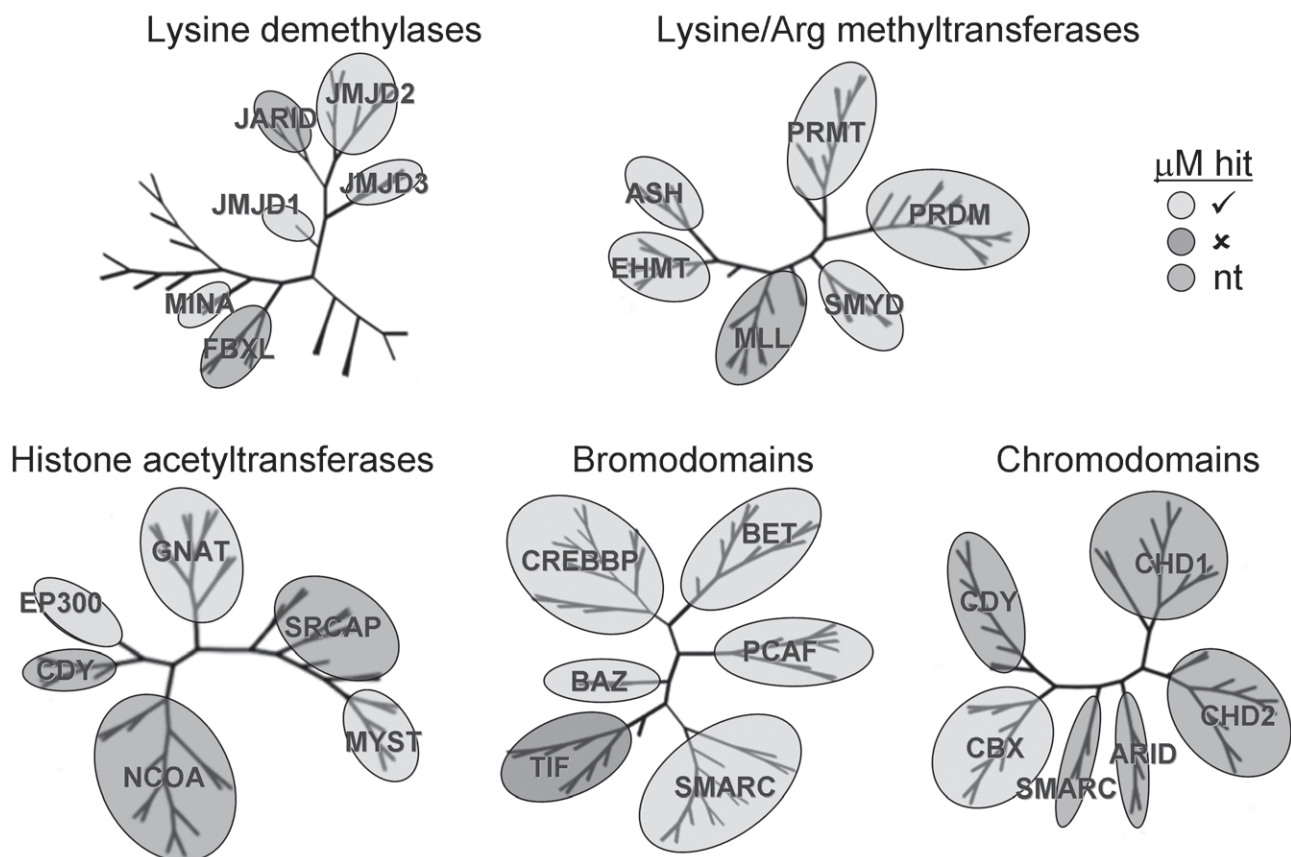


Figure 4. Phylogenetic trees of several human protein domain families involved in epigenetic gene regulation.

Summary

While the prospect of finding chemical probes for epigenetic targets is daunting, considering how little is known about ligands for this protein family, we have made considerable progress on one target, G9a, and have indications of chemical tractability in many others. The histone code is complex and combinatorial in nature [32], however, chemical probes for individual enzymes/proteins will help elucidate how histone signaling controls gene expression, cell differentiation and plasticity, and will point the way for future targeting of these proteins for new medicines.

Acknowledgements

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2010 Arthur Wynne Gold Medal Awardee



Dr. Michel Chrétien

Article by Dr. Reinhart Reithmeier

Michel Chrétien was selected as the 2010 winner of the CSBMCB Wynne Gold Medal. The Medal was presented to Dr. Chrétien by President David Williams at the 53rd Annual Meeting of the Canadian Society for Biochemistry, Molecular and Cellular Biology held in Banff, Alberta. David summarized the career of Michel Chrétien, who is an internationally renowned researcher, with a record of inspired leadership and commitment to science in Canada.

Michel is best known for his ground-breaking work on hormone peptide processing and the role of convertases in this as well as other biochemical processes. With over 500 publications to his name, Dr. Chrétien was the 7th highest cited Canadian scientist during his most productive period of 1981-1990. He has given 100s of seminars around the world on his research and other topics such as commercialization.

During his post-doctoral studies with Dr. C. Li in California Dr. Chrétien published a classic paper in the *Can J. Biochem.* in 1967 on the isolation of lipotropic hormone where they developed the pro-hormone hypothesis in parallel to the work of George Steiner on pro-insulin. Michel relayed how Dr. Li wanted to send the paper to *Nature*, but Dr. Chrétien insisted it go to a Canadian journal since he was funded by the Medical Research Council of Canada. This work set Dr. Chrétien down his life-long path to study the proteases that cleave at dibasic residues involved in this processing pathway, leading to the discovery and cloning of proprotein convertases beginning in 1990. Chrétien and his close collaborator Nabil Seidah discovered 7 of the 9 human convertases and have dominated the field. These enzymes are now known to be involved in Alzheimer's, cholesterol homeostasis and the processing of viral envelope glycoproteins.

Dr. Chrétien has many honours to his credit. An Officer of the Order of Canada, Dr. Chrétien was recently elected as a Fellow of the Royal Society (London), and is a Fellow of the American Association for the Advancement of Science and the Royal Society of Canada. He holds five honorary degrees. Dr. Chrétien won the Boehringer-Mannheim Award from CSBMCB, the McLaughlin Medal of the Royal Society of Canada, the Izaak Walton Killam Memorial Prize, the Henry Friesen Award from the Royal College of Physicians and Surgeons, and the Award of Distinction from the Manning Foundation.

Dr. Chrétien founded the Laboratory of Molecular Neuroendocrinology (CRIM) in Montréal and was its Director from 1967 until 1999, when he moved to Ottawa to be the Scientific Director of the Loeb Health Research Institute. In 2005 he founded the University of Ottawa Institute of Systems Biology and helped procure the funding for a new building to house the institute. During his research career he trained over 100 graduate student and post-doctoral fellows, many of whom are national and international leaders in their fields.

Michel Chrétien has been active in many societies including CSBMCB where he served as President from 1983-84 and a member of Council from 1981-86. He is on the board of numerous organizations, funding agencies and corporations. Dr. Chrétien was on the board of Directors of PENCE during its entire existence (1994-2006). He was on the editorial boards of 10 journals.

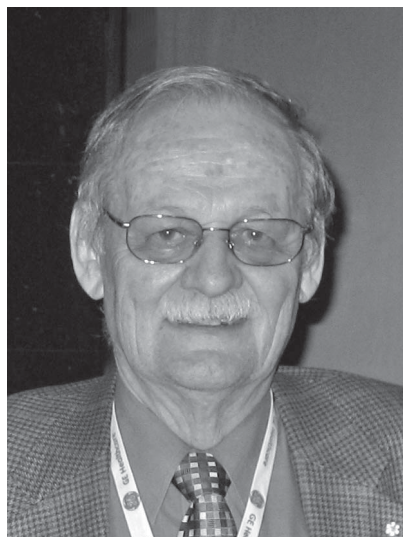
Michel Chrétien continues to be active, particularly in the field of AIDS and anti-virals. In 2008 he was the co-founder and Scientific Director of the Foundation on Anti-Virals (FAV) and was co-founder of ICAV, the International Consortium on Anti-virals in 2004.

Michel gave a very gracious and inspiring after-dinner speech at the banquet where he highlighted the role serendipity played in his personal career. The youngest

of 19 children, Michel told humorous tales of encounters with the public who often mistake him for his (perhaps more famous) brother Jean, John Turner, and even the Australian singer Roger Whittaker.

Beginning with his publication of his post-doctoral work done in California in the *Can J. Biochem.* Michel Chrétien has been a tireless advocate for the recognition of excellence in Canadian science. His outstanding research has brought him and Canada international fame. Michel has always been a strong support of CSBMCB. Recognizing his achievements by the awarding of CSBMCB Arthur Wynne Gold Medal seems most fitting as “*recipients of this life-time achievement award typically have attained an international profile in research, have played a major role in the development and promotion of the discipline in Canada, and have a long-standing record of service to the academic community*”. This notation describes Michel Chrétien perfectly.

My Road to Damascus: How I Converted to the Prohormone Theory and the Proprotein Convertases



Michel Chrétien MD, FRS

Professeur de recherche émérite, Institut de recherches cliniques de Montréal

Professeur émérite, Université de Montréal

Emeritus Scientist, Ottawa Hospital Research Institute

Professor, Department of Medicine, and Department of Biochemistry, Microbiology, and Immunology, Faculty of Medicine, University of Ottawa

Abstract

My desire as a young endocrinologist to improve my clinical skills through a better knowledge of hormone chemistry led me to serendipitous discoveries and unexpected horizons. The first discovery, published in 1967, revealed that peptide hormones are derived from endoproteolytic cleavages of larger precursor polypeptides. It was the foundation of the prohormone theory. Initially thought to apply to a few hormones, the theory rapidly extended to many proteins, including neuropeptides, neurotrophins, growth and transcription factors, receptors, extracellular matrix proteins, bacterial toxins, and viral glycoproteins. The endoproteolytic activation mechanism has become a fundamental cellular process, affecting many biological functions. It implied the existence of specific endoproteolytic enzymes. These proprotein convertases were discovered in 1990. They have been shown to play a wide range of important roles in health and disease. They have opened up novel therapeutic avenues. Inactivation of PCSK9 to reduce plasma cholesterol is currently the most promising. To make this good thing even better, I recently discovered in a French Canadian family a potent PCSK9 (Gln152His) mutation that significantly lowers plasma cholesterol and should confer cardiovascular longevity. The discovery helped me to complete the loop: "From the bedside to the bench and back to the bedside."

Résumé

Comme jeune endocrinologue, l'idée d'améliorer mes compétences cliniques par une meilleure connaissance de la chimie des hormones m'a conduit à des découvertes inédites et inattendues. La première, publiée en 1967, révélait que les hormones peptidiques résultent de coupures endoprotéolytiques de précurseurs inactifs. Elle constituait la base de la théorie des prohormones. Initialement proposée pour quelques hormones, avec les années, cette théorie s'est révélée applicable à un large éventail de protéines : neuropeptides, neurotrophines, facteurs de croissance et de transcription, récepteurs, protéines de la matrice

extracellulaire, toxines bactériennes, glycoprotéines virales, etc. L'endoprotéolyse activatrice, devenant un mécanisme général en biologie, présageait l'existence de protéases spécifiques : les convertases des proprotéines, qui furent découvertes en 1990. Depuis lors, l'importance de ces enzymes dans divers aspects de la santé et de la maladie s'est confirmée. Elles ont trouvé des applications cliniques et ont mené à des percées thérapeutiques, dont l'inactivation de la PCSK9 pour réduire le cholestérol plasmatique. Comble de chance, mes activités cliniques m'ont permis de découvrir, chez une famille canadienne française, la mutation Gln152His de la PCSK9, qui abaisse de façon significative le cholestérol plasmatique et devrait conférer une grande protection cardiovasculaire. Ainsi ai-je bouclé la boucle «du malade au laboratoire et de retour au malade ».

Introduction

One always hesitates when asked to write one's own biography, particularly in a scientific field. As the 1969 Nobel Laureate Salvador E. Luria once commented: "I have found most biographies of scientists remarkably uninteresting and their autobiographies even more so"¹ I was lured into making the effort by Dr. David Williams, former President of the Canadian Society of Biochemistry, Molecular and Cellular Biology, when I was awarded the 2010 Arthur Wynne Gold Medal by the Society. Following my acceptance talk, during which I described the "*Fil d'Ariane*" that became the thread of my scientific career, David suggested that I put it in writing and publish it in *Biochemistry and Cell Biology*, formerly the *Canadian Journal of Biochemistry*. In 1967, I published my first scientific article as first author in this journal (Chrétien and Li 1967b). That article determined my career path. The current autobiographical article, published 45 years later, in the same journal, is my report card of some sort.

I have chosen to write this short autobiography in a narrative mode, hoping that Luria would have found it more interesting this way, had he lived to see it. I leave it to the readers to make their own judgment on the validity of my hope. In my narrative, I try to illustrate how, except for the training years, the career of clinician scientist cannot be

programmed in advance. For newly graduated physicians, it requires additional years of hard training; otherwise, they may be stricken by PAIDS i.e. Paralyzed Academic Investigator's Disease Syndrome. The PAIDS phenomenon was first described by Dr. Joseph Goldstein in his 1986 Presidential Address to the American Society of Clinical Investigation in Washington, DC. Commenting on the short-lived career of too many clinician scientists, Goldstein rightfully recommended that, to achieve longevity and success as researchers, physicians must strengthen their knowledge of basic science and demonstrate "technical courage", i.e. the capacity to use new techniques as they emerge (Goldstein 1986). My scientific itinerary has been, I hope, in line with these recommendations. I tried hard to be spared from PAIDS. If I have been successful, I have many people to thank for it. My personal thirst to understand the chemistry of peptide hormones would not have been quenched without the inspiration, the encouragement, the opportunities, the assistance, and the collaboration of these generous individuals. This short biography is my chance to pay tribute to their influence on my scientific life.

1936-1955: The Early Influences

I was born in 1936, in the village of La Baie-de-Shawinigan, Québec, the youngest of a family of 19 children. This means that, growing up, I had many people to look after me and, when I decided to prolong my postgraduate training, many on whom to count. My father, Willie Chrétien, worked for 50 years as a mechanic at the local paper mill, while earning some extra revenue as the part-time village Secretary-Treasurer. My mother, Marie Boisvert, single-handedly managed the household, including balancing the family budget. I surmise that they were an inspiration for my brother Jean, when, years later, he faced budgetary challenges as Prime Minister of Canada.

My parents were ahead of their time in many ways. To them, education for their children was a non-negotiable priority. Unlike most boys and girls growing up in our small village, who, skipping most of high school, joined the town mills, all nine of the Chrétien children, who survived infancy, went on to a Junior or Technical College, and six completed university degrees. Socially, my father was a strong defender of the rights of women, long before

1 (In: "A slot machine and a broken test tube. An autobiography. S.E. Luria 1984 Harper Colophon Books)

they were allowed to vote. Indeed, when, in 1920, he was elected Director of the *Association Canado-Américaine* (ACA), a small insurance coop under the influence of the Catholic Church, he complained to the Board about the exclusion of women from institutional activities (Robert 1946). Many women, including my own mother, were later elected members of the ACA *Légion d'honneur*.

From 1941 to 1955, I attended boarding schools: first in my hometown, under the Dominican Sisters; and then at the reputed *Collège de Joliette* (then known as *Séminaire de Joliette*), headed by the *Clercs-St. Viateur*. This 160-year educational institution is well renowned in Québec for its excellent programs in the Arts and the Sciences. Two teachers at the *Collège* left me with lasting impressions: Father Raoul Duchesnes, who awakened my interest in Mathematics; and Father Emile Lavigne, who got me enamored of Physics and Chemistry. When, at the end of my Junior College in 1955, I had to choose a career, I hesitated between Chemistry, Medicine, and missionary Priesthood. I finally decided to walk in the footsteps of my eldest brother Maurice, an obstetrician and gynecologist: I chose to become a physician.

1955-1964: My Attraction for Biochemical Endocrinology

All living cells derived their energy from the same fundamental chemical reactions.

(LOUIS PASTEUR)²

In 1955, I was accepted as a medical student at the *Université de Montréal*. The first two semesters were devoted to basic sciences. The chemistry of life caught my attention. Like Pasteur in the 19th century, my biochemistry teachers stressed the fact that cells were highly sophisticated chemical laboratories. In my third year, I became fascinated by endocrinology, following a series of lectures given by Professor Henri Bricaire, Head of the Endocrine Service at the *Hôpital Cochin*, in Paris, France. Dr. Bricaire had a unique talent for explaining endocrinology. I still remember how captivating his lectures were on the cascade of suspected chemical signals secreted by the hypothalamus into the pituitary gland,

inducing the latter to secrete peptide hormones targeted at peripheral endocrine organs. Because of Dr. Bricaire and my biochemistry teachers, I decided that, for my residency, I would join a program that included clinical endocrinology and the chemistry of hormones. This, I thought, would improve my skills as an endocrinologist. I had not yet embraced the idea of a research career.

Moving into my residency years, I was accepted by Dr. Jacques Genest, who had just created a clinician scientist program at the *Hôpital Hôtel-Dieu*, in Montréal. Dr. Genest was an outstanding physician and scholar. Trained in three sub-specialties, - endocrinology, nephrology and internal medicine - he had also gained extensive laboratory experience at the Rockefeller Institute, Harvard, and John Hopkins Universities. He agreed to let me divide my time between the clinic and the bench. I also registered as a M.Sc. student in the Department of Investigative Medicine of McGill University with, as co-supervisor, Professor John S. L Browne, a Canadian pioneer in reproductive endocrinology. Through the mentorship of these two eminent clinician scientists, I took my first timid steps into the world of biomedical research. Besides my clinical duties on the wards, I spent time in the laboratory with Dr. Roger Boucher, a young organic chemist, who, with patience and understanding, introduced me to his discipline.

Dr. Genest was a world-recognized pioneer and expert on the role of the renin/angiotensin/aldosterone system in human hypertension. Under his supervision, I carried out the first ever angiotensin II infusions in human subjects. With Dr. Boucher, I participated in the development of the first quantitative assay for blood angiotensin II. Those early studies demonstrated that angiotensin II is a potent aldosterone-stimulating agent in human and an important factor in the pathophysiology of arterial hypertension (Biron et al. 1962, Chrétien 1962, Genest et al. 1964).

Along the way, I became more and more fascinated by the chemistry of hormones. For example, I was amazed by the fact that a two-amino acid difference between angiotensin I and II increased by many fold the vasoactive effect of the latter peptide; and the fact that minor chemical modifications on the steroidal cyclopentano-perhydrophenanthrene ring defined the biological properties of steroid hormones. I became drawn even more to chemistry

2 In: *Louis Pasteur: Free Lance of Science*, by René J. Dubos, Little Brown and Company, Boston, 1950.

and wanted to improve my knowledge of it. I began to contemplate a career in research. However, I still had two more years of clinical residency to complete.

My work on the angiotensin/aldosterone system attracted the attention of Professor George W. Thorn, Chair of Medicine at the Peter Bent Brigham Hospital (PBBH), in Boston, MA. He invited me to join his hospital as a Junior Resident in Internal Medicine and a Fellow in Endocrinology. Dr. George Cahill was the Chief of the Endocrine Service. This successful clinician scientist, with a highly productive laboratory research program, had a strong influence on my career. To this day, he has remained a close mentor.

At the PBBH, Dr. Thorn had inherited a large cohort of patients treated by Dr. Harvey Cushing, the famous neurosurgeon, who first described the syndrome now bearing his name. Cushing's Syndrome is caused by excessive secretion of adrenocorticotrophic hormone (ACTH) by pituitary tumors. Dr. Thorn also had many patients suffering from Addison's disease and Nelson's syndrome. These pathologies also have in common the release of large amounts of ACTH by the pituitary gland. I became interested in the chemistry of this hormone in humans, and I spent my spare time away from the clinic trying to isolate it from patients' urine. I was unsuccessful. This failure reinforced my conviction that my eventual success in this effort would depend on my acquiring a better expertise in peptide hormone chemistry.

While at the PBBH and its affiliated institutions, I also greatly benefited from my academic and clinical interactions with outstanding professors: Lewis Dexter, Sam Levine, David Littman (the inventor of the Littman stethoscope), Bernard Lown (the first to combine defibrillation and cardioversion), and Joseph E. Murray (Nobel Laureate, 1990, who pioneered kidney transplant procedures).

1964-1967: My Years at UC Berkeley and UCSF: The Birth of the Prohormone Theory

The secret of success is in prolonged efforts through perseverance. In a field of investigation, one succeeds in acquiring what I am inclined to call the instinct of truth.

(LOUIS PASTEUR)³

In late 1963, while visiting a friend at the Rockefeller Institute in New York, I met by chance Professor Lyman Craig, the inventor of the counter-current phase distribution technique (Craig et al. 1945). When I mentioned to him my wish to learn the chemistry of peptide hormones, he immediately phoned the illustrious peptide chemist Dr. Chao Hao Li of the University of California (UC) at Berkeley, who, a few years before, had elucidated the amino acid sequence of bovine ACTH (Li et al. 1958, Li et al. 1961). This fortuitous 30-minute encounter with Dr. Craig was a major turning point of my career. To this day, I am still puzzled as to why Dr. Li accepted me into his team, which was uniquely composed of protein chemists. Even more intriguing to me was his suggestion that I apply for a Fellowship of the Jane Coffin Childs Memorial Fund for Medical Research, which had its headquarters at Yale University. I was invited to New Haven for an interview. My English at the time was rather hesitant. The Chair of the Selection Committee was Dr. Cyril N. H. Long, of whom I had never heard. He was so hard on me during the interview that I came out of it discouraged and told my wife Micheline to forget about California. I did not know at the time that Dr. Long was an expert in ACTH experimental physiology (Long 1956), walking in the footsteps of Dr. Cushing who, in 1933, had moved from Harvard to Yale. Thus, by mere coincidence, he and I were interested in the same hormone. The ACTH trail worked in my favor: I was awarded a two-year fellowship at the Hormone Research Laboratory, then located at UC Berkeley. Thanks to a Medical Research of Canada (MRC) fellowship, I extended my stay to three years.

Dr. Li had many research projects. I was attracted by two in particular: the elucidation of the amino acid sequence of human growth hormone (hGH) using the manual Edman degradation method, and the chemical synthesis of ACTH. These were complex and challenging undertakings at the time. As an endocrinologist, I hoped that Dr. Li would ask me to join Jonathan S. Dixon on the hGH project. He thought otherwise. He assigned me a minor project, as my training ground in protein chemistry. He handed me

3 In: *Louis Pasteur: Free Lance of Science*. by Rene J. Dubos, Little Brown and Company, Boston, 1950.

a small vial containing a fluffy white powder of so-called β -lipotropic hormone (β -LPH), a yet to be sequenced 90-amino acid peptide he had isolated from sheep pituitary glands (Birk and Li 1964; Li 1964). He teamed me up with Dr. Livio Barnafi, a Chilean visiting scholar, and asked us to derive the full sequence of the peptide. I was responsible for one-half of the molecule, and Livio for the other half.

Dr. Li insisted that I do everything by myself. As an example, I asked him one day if he could purchase for my use an expensive instrument that had just been developed to conduct polyacrylamide gel electrophoresis. He immediately agreed, but rather gave me an old power supply and a platinum wire, and suggested that I build my own; which I did. Dr. Li placed me under the supervision of David Chung, his trusted chief laboratory assistant. Dave advised me all along, but never interfered. I owe him a great debt of gratitude for his mentorship.

Besides conducting my experiments, I regularly conferred with two brilliant organic chemists, Jonathan Dixon and John Ramachandran, who have remained good friends to this day. I also attended lectures by illustrious UC Berkeley Professors: Melvin Calvin, Howard K. Schackman, and Frederick H. Carpenter.

Manual sequencing was a painstakingly slow technique; it took a week of intense labor to determine the sequence of 3 amino acids. While pursuing the sequencing of β -LPH, I processed sheep pituitary extracts in search for other bioactive peptides. I isolated one, which exhibited minimal lipolytic activity. Dr. Li suggested that it be named γ -LPH and gave me the task to determine its complete amino acid sequence. It took more than two years, to complete the sequencing of β -LPH and γ -LPH (Li et al. 1965, Chrétien and Li 1967a, Chrétien and Li 1967b).

The results were astonishing and seminal; they shaped my entire scientific career. They showed (Figure 1) (i) that the middle portion of β -LPH contained the sequence of β -melanocyte-stimulating hormone (β -MSH), a peptide isolated and sequenced by Dr. Li's team a few years before (Geschwind et al 1957); (ii) that γ -LPH was a truncated form of β -LPH with β -MSH as its C-terminal fragment. These chemical homologies led us to conclude that β -LPH could be the precursor of γ -LPH and β -MSH, with γ -LPH

being an intermediate product and β -MSH, the end-product. Of note was the presence of pairs of basic amino acids at the junctions between these peptides.

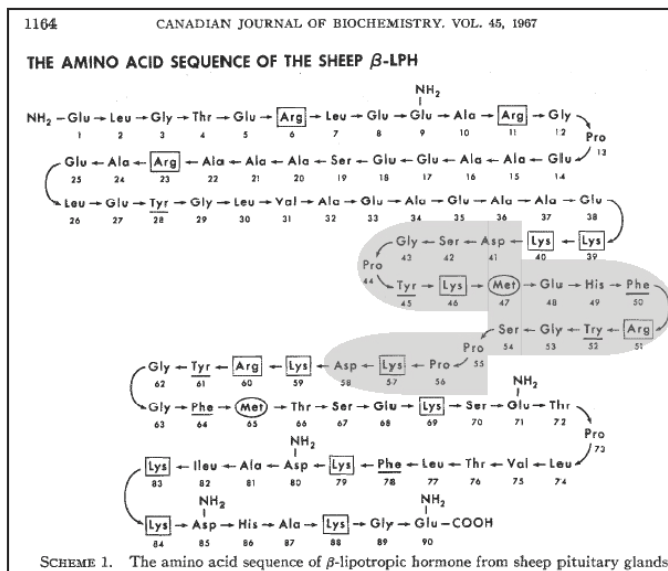


Figure 1. Sequence of β -LPH as published in my 1967 Canadian Journal of Biochemistry (reprinted with permission). In the β -LPH sequence, γ -LPH represents the segment 1-58 and β -MSH (shaded), the segment 41-58. Note the presence of the internal pairs of basic residues flanking these peptides. Residues (Arg, Lys, and Met) targeted for specific cleavages to generate sub-fragments for manual sequencing are either boxed or circled. Already apparent in the β -LPH sequence were pairs of basic residues which were later shown to constitute canonical junctions between active peptides within prohormone and proneuropeptide sequences.

I presented our results as an abstract in January 1967, at the Annual Meeting of the Canadian Society for Clinical Investigation (CSCI) in Toronto, ON (Chrétien and Li 1967a). By then, we had already submitted a manuscript to the Canadian Journal of Biochemistry for publication. In it, we concluded:

“The results raise the interesting possibility that the pituitary glands synthesizes *de novo* a number of peptides having identical sequences, or, alternatively, that the pituitary produces one large molecule that is subsequently broken down into smaller fragments. If the latter possibility does occur, the question then arises

as to whether the breakdown occurs in the pituitary or during the isolation procedure as the result of chemical and (or) enzymatic degradation”

To my pleasant surprise, the manuscript, my first as lead author, was accepted with these most encouraging comments:

“This paper is acceptable, as it stands. I have found this paper by Chrétien and Li most interesting. **It is work of considerable importance**, clearly and convincingly documented and well written. I have no hesitation therefore in recommending that it be published by the Journal without change.”

The article was published in July 1967 (Chrétien and Li 1967b). To this day, I have no idea who the reviewers were; but their positive comments have certainly entrenched my destiny in the exploration of the new prohormone paradigm. If, as a Chrétien, I could be forgiven a self-indulging analogy to a story found in the Bible, I would say that the highly flattering comment by the mysterious reviewer was like the blinding light and mysterious voice that overwhelmed Saul, the Hebrew zealot, in his road to Damascus and converted him to the Christian faith; except that my road went through California, the mysterious voice was from Canada, and my conversion was to basic biomedical research. Since then, like Saul for Christianity, I have put my zeal for the chemistry of peptide hormones into “converting” others to the new paradigm.

That same year, Donald F. Steiner reported the existence of an insulin precursor, that he called proinsulin (Steiner et al. 1967, Steiner and Oyer 1967). One year later, Donald Chance published the amino acid sequence of proinsulin, also revealing the presence of pairs of basic amino acids at inter-peptide junctions (Chance et al. 1968).

In 1967, I was in my 7th year of post-graduate training. Still, I wanted to spend one more year in Melbourne, Australia with Dr. Pehr V. Edman, who had just developed an automated sequencing instrument, capable of elucidating the sequence of 13 residues per day (i.e. 30-40 times faster than manual sequencing!). I applied to the Medical Research Council of Canada for an extension of my post-doctoral fellowship. I was bluntly turned down,

with the following comments: “It is about time for you to come back to Canada”. Although my wife Micheline never told me so, I believe she was pleased that, at last, I could begin to earn a decent salary. Micheline has always gracefully accepted the many sacrifices that my medical and scientific pursuits imposed on her and on our two daughters, Marie and Maria-Lyne. I am forever indebted to them for their loving generosity.

Coincidentally, at the CSCI meeting in Toronto, I met Dr. Jacques Genest who had attended my 10-minute presentation. He offered me a research position at his newly created *Institut de recherches cliniques de Montréal* (IRCM). I accepted.

1967-1979: The First Decade in Montreal: POMC, a Predestined Prohormone

The probability of the correctness of a hypothesis rises with the number of facts brought forward that fit into it. (KONRAD LORENZ ⁴)

I arrived at the IRCM on July 1 1967. Two months later, I had my laboratory up and running. In my first series of experiments, I demonstrated that: (i) β -MSH was likely to be a biosynthetic peptide rather than a degradation product generated by extraction and purification procedures (Gilardeau and Chrétien 1970); (ii) LPH molecules have no *in vitro* or *in vivo* lipotropic activity in human (*unpublished*). Soon after, I was joined by Mrs. Suzanne Benjannet, a talented cell biologist, and Dr. Xavier Bertagna, a French post-doctoral fellow. Together, we demonstrated that β -LPH and γ -LPH were genuine cellular products of the pituitary gland (Bertagna et al. 1974, Chrétien et al. 1976a). Xavier went back to *Hôpital Cochin*, in Paris, France, where he is now Chair of the Endocrine Service, once run by Dr. Bricaire, my former professor. Suzanne has remained with the group and has continued to make many valuable contributions.

In the early 1970's, I thought that it was important to identify which pituitary cells produce these chemically related molecules. To clarify this point, I turned for advice to Pr. Marc Herlant, a Belgian expert on the microscopic morphology of the pituitary gland. Like his colleagues,

⁴ In: Lorenz K. *Civilized Man's Eight Deadly Sins*. Harcourt Brace Jovanovich, New York, 1974.

Pr. Herlant viewed the pituitary as a “confederation” of complementary and specialized endocrine cell types, each dedicated to the production of specific hormones: somatotrophs, lactotrophs, gonadotrophs, thyrotrophs and corticotrophs producing, respectively, growth hormone, prolactin, gonadotrophins, thyroid-stimulating hormone, and ACTH. Thus, in this gland, the hormonal contents of a particular cell type would be associated with common functions. We raised a polyclonal antibody against β -LPH (Desranleau et al. 1972), and established by immuno-histochemical analysis that that β -LPH was present in the ACTH-producing pituitary corticotrophs (Dessy et al. 1973). Retrospectively, this co-localization was the first indication that LPH and ACTH could be functionally related. We confirmed this observation in collaboration with Jacob Furth (Furth et al. 1975). With George Pelletier, we later demonstrated, in human and rat pituitaries, that they were in the same secretory granules. We then concluded that both hormones were released together during granule extrusion (Pelletier et al. 1977).

It is during this period that many peptide hormones (e.g. parathyroid hormone, calcitonin, glucagon) were shown to be generated through cleavages of their biosynthetic precursors at selected basic residues (Potts et al. 1971, Lernmark et al. 1976).

In the mid-seventies, my research activities attracted the attention of a group of highly gifted and motivated Ph.D. graduates. First I recruited, as an Associate Member, Nabil G. Seidah, a young dynamic physical chemist who wanted to move into biology. Soon after, Philippe Crine, Guy Boileau, and Christina Gianoulakis joined in as post-doctoral fellows.

The interest in the LPH/MSH precursor model was amplified by one order of magnitude when John Hughes and Hans Kosterlitz serendipitously noted that their met-Enkephalin decapeptide was identical to residues 61-65 of β -LPH (Hughes et al. 1975). This observation launched a fierce competition for the isolation of suspected endogenous opiates, which had been named endorphins by Eric J. Simon (Simon 1976). The long list of competitors included prestigious biomedical investigators: Roger Guillemin, Solomon H. Snyder, Avram Goldstein, Lars Terenius, Derek

G. Smyth, Laszlo Graf, and my former mentor, C.H. Li.

A latecomer into the fray and an obvious underdog, I decided to concentrate our efforts on two aspects: a) the isolation of endorphins from human pituitary glands, and b) the study of their in vitro biosynthesis from β -LPH. For the first project, I had the advantage of having at hand thousands of human pituitaries collected at autopsy as part of a Canadian special program of hGH purification for the treatment of GH-deficient children. This tissue supply allowed us to be first to purify and sequence human β -endorphin (Chrétien et al. 1976b). For the second project, we repeated the biosynthetic experiments we had performed before for β and γ LPH (Bertagna et al. 1974, Chrétien et al. 1976a), and demonstrated that, in pituitary tissues, β -endorphin is a genuine intracellular product of β -LPH cleavage at the expected sites identified by radioactive microsequencing (Crine et al. 1977a, Crine et al. 1977b). To my knowledge, this was the first demonstration of intracellular biosynthesis of β -endorphin. Coincidentally, in collaboration with Frank LaBella, we showed the presence of lipotropins in the brain (LaBella et al. 1977), indicating that the brain possessed the same capacity as the pituitary gland to make endorphins from its β -LPH precursor. The Guillemin's group independently came to a similar conclusion, following experiments showing that incubation of β -LPH with brain extracts produced opiate-like activity, but they did not characterize the biochemical process leading to this activity (Lazarus et al. 1976).

While the β -LPH/ β -endorphin story unraveled, the ACTH molecule resurfaced when Rosalyn Yalow and a few others observed “big-ACTH” forms in plasma and pituitary extracts (Yalow 1976) (review). Eipper and Mains in Edward Herbert's laboratory, better defined their molecular weights (Eipper and Mains 1975). For the following years, several laboratories, including ours, described in detail the biosynthetic cascade of events that leads to the production ACTH, MSHs, LPHs and β -endorphin. Collectively, the results demonstrated the existence of a larger precursor from which were sequentially derived LPHs, ACTH, MSHs, and β endorphin (Mains et al. 1977, Roberts and Herbert 1977a, Roberts and Herbert 1977b, Crine et al. 1978, Seidah et al. 1978, Chrétien et al. 1979, Crine et al. 1979,

Gianoulakis et al. 1979, Benjannet et al. 1980, Herbert and Uhler 1982, Douglass et al. 1984). This chapter was completed with the nucleotide sequence of the cloned cDNA of the common precursor in which was confirmed the presence of lysine and arginine residues at all cleavages sites (Nakanishi et al. 1979). The marriage of “big-ACTH” and LPH was finalized and the wedding ring was a pair of basic amino acids.

Because its bioactive end-products are ACTH, α - and β -MSHs, as well as β -endorphin, the precursor became known as pro-opio-melanocortin (POMC) (Chrétien et al. 1979). A few years later, during a seminar given at the IRCM, Xavier Bertagna, my former French post-doctoral fellow, jokingly noted that the POMC acronym could alternatively mean Polypeptide Of Michel Chrétien. This unexpected and unscientific decrypting was somewhat flattering to me, considering the place this molecule has occupied in my scientific career.

1980-1989: The Second Decade in Montreal

PART ONE: FROM PROHORMONES TO PRONEUROPEPTIDES
What one is interested in, in science, is to arrive at statements that are of very wide generality. (FRANÇOIS JACOB)⁵

Proneuropeptides and brain functions

The early 1970s were a florid period for the identification of numerous hypothalamic factors and other important neuropeptides (Guillemin 1978, Watson et al. 1982, Douglass et al. 1984). The question rapidly arose as to whether all those neurohormones followed similar biosynthetic pathways as β -endorphin (Lazarus et al. 1976). With the advent of molecular biology, their corresponding full-length cDNA were cloned and sequenced. The deduced open reading frames revealed that the sequences of these neurohormones were contained within larger polypeptides and flanked by basic residues. Thus, the prohormone theory, which initially applied to peptide hormones, held true for brain peptides and neurotrophins as well. It implied that the brain could produce wide variety of active substances from a limited number of genes.

With such an unforeseen extension of the prohormone

theory to neurobiology, I felt the need to improve my understanding of the brain functional systems. In 1979, I received a Josiah Macy's scholarship and took a sabbatical year. I spent the first half of it at Cambridge University, Cambridge, U.K, in Les Iversen's Molecular Pharmacology Laboratory; and the second half at the Salk Institute, in La Jolla, CA, with Roger Guillemin's group.

I returned to the IRCM convinced more than ever that the identification of the prohormone/proneuropeptide-cleaving enzymes was the obligatory next step in the field of the neuroendocrinology of peptidergic systems. I conveyed my thoughts to the ever-present Nabil Seidah and Suzanne Benjannet. I gradually attracted to the IRCM additional scientists of complementary expertise: Claude Lazure, a peptide chemist; Majambu Mbikay, a molecular biologist; Mycieslaw Marcinkiewicz, a neuroanatomist; and Ajoy Basak, an organic chemist.

In 1983, Nabil Seidah was promoted Laboratory Director at the IRCM. Our two laboratories constituted the IRCM Neuroendocrinology Group. We continued to apply for joint grants and to pursue complementary research objectives. I stayed as team leader until 1987, i.e. for three years after I had taken on the duties of IRCM Scientific Director. I suggested to Nabil that he take over the PI role of the MRC group grant. He accepted. Since then, our laboratories have reached new heights in terms of scientific achievements and finally unraveled the mystery of proprotein convertases.

PART TWO: THE SEARCH AND THE DISCOVERY OF PROPROTEIN CONVERTASES

Success is going from failure to failure with renewed enthusiasm. (WINSTON CHURCHILL)

In research projects, change the approach to the problem; don't change the problem. (LINUS PAULING)

In the early 1980's, there were various avenues being investigated in search for the elusive precursor convertases (Lazure et al. 1983). Over a period of ten years (1980-1990), we failed many times to isolate them, repetitively coming up with promising proteases, which later turned out to anything but the right enzymes (Cromlish et al. 1985, Cromlish et al. 1986a, Cromlish et al. 1986b, Seidah et al. 1986, Cromlish et al. 1987, Seidah et al. 1989). This was a

5 Cited in *The Eighth Day of Creation*, by H.F. Judson, Cold Spring Harbor Laboratory Press; Expanded edition, 1996.

decade of great frustration and multiple disappointments.

In 1986, I convinced Nabil to spend a sabbatical year in Dr François Rougeon's laboratory at the Pasteur Institute in Paris, France. Dr Rougeon gained notoriety in 1975 for the first cloning of a cDNA, during his post-doctoral fellowship under Professor Bernard Mach at the University of Geneva, Switzerland (Rougeon et al. 1975). Since then, he has made numerous trend-setting contributions to the field of molecular immunology. In addition, Pasteur Institute happened to be an excellent training ground for molecular biologists.

Soon after Nabil's return to Canada, our two laboratories joined efforts to unravel the nature of the convertases. It had become clear by then that these enzymes were most likely serine proteases structurally related to yeast Kexin (Fuller et al. 1989). Using polymerase chain reactions (PCR) (Mullis et al. 1986) and mRNA from mouse pituitary gland and the AtT20 POMC-producing cell line, Nabil was able to amplify cDNA fragments, which encoded internal canonical residue signatures of serine proteases. These fragments were used as probes to screen full-length cDNA libraries swiftly constructed by Majambu from the same mRNA. Intensive manual DNA sequencing by a group of technicians, students, and post-doctoral fellows resulted in our successful cloning of two mammalian prohormone convertases, PC1 and PC2. When we confirmed the exclusive expression of their mRNAs in endocrine and neural tissues, a 5-liter bottle of Champagne was opened in celebration. Every member of team signed his John Hancock on the bottle, in memory of these emotionally charged moments. We reported our discovery in the August 1990 issue of *DNA and Cell Biology* (Seidah et al. 1990). Independently of us, Dr Donald Steiner's team at the University of Chicago had achieved the same feat a few months earlier by cloning the cDNA of PC2 (Smeekens and Steiner 1990)⁶.

Thus, it took some 23 years after the prohormone theory

was enunciated for the first two PCs to be elucidated. Soon, we confirmed their authenticity as POMC convertases (Benjannet et al. 1991). The discovery was heralded as seminal by Jean Marx in a comment that appeared in the May 10, 1991 issue of *Science*:

Biologists will be greatly aided in their quest to understand brain function and the developmental pathways that the embryo follows – two of life's most fundamental mysteries...One of them might play a role in the maturation of viruses, including those that cause AIDS and influenza, and might therefore be a target for antiviral drugs".

Soon after, the Gordon Research Conferences asked me to organize the first symposium on Hormonal & Neural Peptide Biosynthesis, which was held in 1994. The biyearly symposium is currently known as Proprotein Processing, Trafficking & Secretion.

The saga that led to the discovery of nine PCs is vividly and exhaustively recounted by Nabil (Seidah 2011) in an issue of *Methods in Molecular Biology*, entirely dedicated to Proprotein Convertases (PCs) (Mbikay and Seidah 2011) as well as by Seidah and Prat (2012) in a recent review. The enzymes are now collectively called proprotein convertases or proproteins convertases subtilisin/kexin type (PCSKs). They are calcium-dependent serine endoproteases, structurally related to bacterial Subtilisin and to yeast Kexin. Out of the nine identified so far in mammals, seven were discovered by our group (Figure 2). They are PC1/3, PC2, Furin, PC4, PC5/6, PACE4 (paired basic amino acid cleaving enzyme-4), PC7, SKI-1/S1P (subtilisin/kexin isozyme-1/Site-1 protease) and PCSK9 (PC Subtilisin-Kexin type 9). PC5/6 is expressed in two isoforms, A and B, resulting from alternative splicing of its primary gene transcript. The first seven PCs belong to the Kexin-like clan; their catalytic domains are very homologous (>55%); they cleave their physiological substrates after an Arg or a Lys residue. The remaining two convertases, SKI-1/S1P and PCSK9, belong to the pyrolysins and proteinase K clan respectively and cleave at non-basic residues.

6 I must note that the chronological overlap, but experimental independence of the discoveries by Don and I has been one of the most remarkable coincidences in this field. It is as though our scientific careers have followed two parallel roads of similar interests and common destination [Seidah, N.G. and Chrétien, M. 1992. *Trends Endocrinol Metab.* 3(4): 133-140].

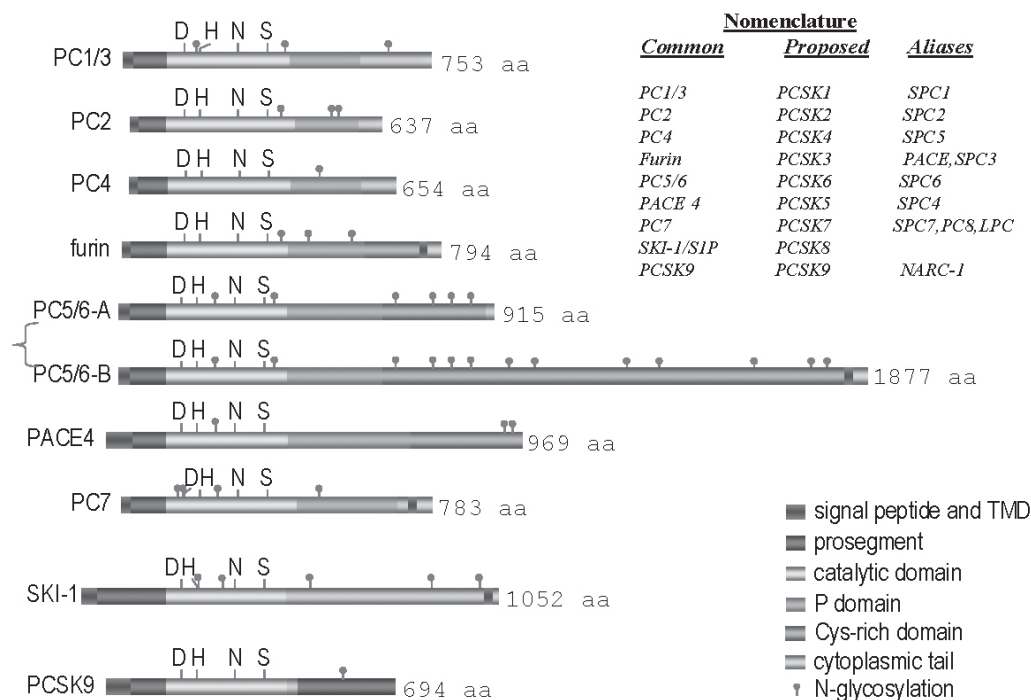


Figure 2. Diagrammatic structure of members of the human proprotein convertase family. Their typical successive domains are identified by shading. Their alternative names are provided.

PCs are biosynthesized in the endoplasmic reticulum (ER) as secretory multi-domain zymogens. They are made of a prodomain, a relatively conserved catalytic domain, a P (protease) domain, and a variable carboxyl-terminal domain, which may contain a transmembrane domain. They self-activate by autocatalytic removal of the prodomain. Their final destination can be the Golgi (SKI-1/S1P), the trans-Golgi network (TGN), (Furin and PC7), secretory granules (PC1/3, PC2, and PC5/6A), the plasma membrane (PC4, Furin, PC5/6B, and PC7), the cell surface and the extracellular matrix (ECM) (PC5/6A and PACE4), endosomes (Furin, PC7, and PCSK9), or the extracellular space (PCSK9) (Figure 3). They are expressed in all nucleated cells, in varying levels and combinations. Based on the ease of detection of their transcripts in various tissues, their expression is considered to be either ubiquitous (furin, SKI-1/S1P and PC7), widespread (PC5/6 and PACE/4); limited PC1/3, PC2 and PCSK9) or restricted (PC4).

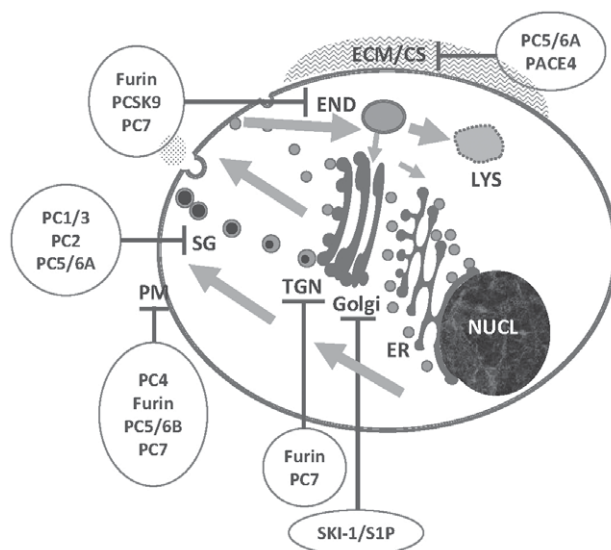


Figure 3. Sub-cellular location of proprotein convertases. Produced in the endoplasmic reticulum (ER), proprotein convertases navigate through the secretory pathway to their final destination, which is, either the golgi, the TGN, secretory granules (SG), endosomes (END), the plasma membrane (PM), the extracellular matrix (ECM), the cell surface (CS). Other abbreviations: NUCL, nucleus; LYS, lysosome.

The variety of proteins and peptides activated through the action of the PCs suggests that these enzymes are active participants in many aspects of physiology, in health and disease. Their overlapping expression and activities, as demonstrated by *in vitro* and *ex vivo* studies, made it difficult to define their relevance in normal development and physiology. Animal models of abnormal expression of PC genes were needed to address this concern.

1990-2000: The Third Decade: Biological and Clinical Relevance of Proprotein Convertases

If chance offers you a clue, follow the trail. You may not discover what you were looking for, but what you discover may be more interesting (CHRISTIAN DE DUVE)⁷

As years passed, it was found that a vast range of non-neuronal and non-hormonal secretory proteins and peptides were produced through a similar mechanism. These included growth factors, membrane receptors, transcription factors, zymogens, EMC proteins, bacterial toxins, and viral glycoproteins (Seidah and Chrétien 1999, Thomas 2002) (Table 1). In his 2002 *Nature Reviews* article on furin, Gary Thomas concluded: “This irreversible post-translational modification is now recognized as a fundamental mechanism of regulating cellular and physiological functions, comparable in importance to the phosphorylation cascade” (Thomas 2002).

By the mid 1990s, the number and the variety of PC substrates led us and others to predict that these enzymes were not only involved in important biological phenomena, but could be implicated in the pathophysiology of many human diseases, e.g. cancer, atherosclerosis, obesity, diabetes, Alzheimer, hypertension, arthritis, viral and bacterial infections (Chrétien et al. 1995, Thomas 2002). As recently summarized (Chrétien et al. 2008), several groups, including our own, have confirmed many of these predictions. Their accuracy was further supported and amplified by PC gene inactivation studies in mouse (Taylor et al. 2003), and the discoveries of human genetic mutations in PC1/3 (O’Rahilly et al.

1995, Jackson et al. 1997, Jackson et al. 2003, Farooqi et al. 2007).

In view of the critical need of having in-house capacity of molecular genetics including homologous recombination, Majambu Mbikay accepted to spend a sabbatical year (1993-1994) in Dr. Elizabeth E. Simpson’s laboratory at The Jackson Laboratory in Bar Harbor, Maine. He led the group in the mapping the chromosomal loci of several PC genes (Mattei et al. 1990, Mbikay et al. 1995) and in the production of mouse models of PC deficiency. A PC4 knockout (KO) mouse was the first model to be produced. Described in the June 1997 issue of the *Proceedings of the National Academy of Sciences* of the United States of America (PNAS), the mouse exhibited severely impaired male fertility, consistent with the predominant expression of this enzyme in testicular germ cells (Mbikay et al. 1997). A PC2 KO mouse showing multi-hormonal abnormalities was reported in the same issue of the journal (Furuta et al. 1997). The group’s mouse genetic program has greatly expanded since Dr. Annik Prat joined Nabil Seidah in the year 2000.

So far, PC gene inactivation in mouse has yielded phenotypes that varied from embryonic lethality (furin, PC5/6, PACE4, and SKI-1/S1P), to metabolic deficiencies (PC1/3, PCSK8, and PCSK9), to delayed liver regeneration (PCSK9) (Zaid et al. 2008), or to no obvious phenotype at all (PC7) (Scamuffa et al. 2006, Creemers and Khatib 2008) (*reviews*). In humans, heritable morbid phenotypes have been linked to PC1/3 loss-of-function mutations (O’Rahilly et al. 1995, Jackson et al. 1997, Jackson et al. 2003, Farooqi et al. 2007), and PCSK9 gain-of-function mutations (Abifadel et al. 2003, Abifadel et al. 2009). Inversely, and to the greatest excitement of the biomedical community, PCSK9 loss-of-function mutations was found to lower LDL-C and to confer cardiovascular longevity (Cohen et al. 2006).

Based on the sum of *in vivo*, *ex vivo* and *in vitro* studies, it is evident that PCs play critical functions a) in health: growth & development, reproduction, tissue homeostasis, glucose and lipid homeostasis, endocrine and

⁷ *My love affair with Insulin* by C. de Duve in J. Biol. Chem. 279:21 679-688, 2004.

TABLE I Diversity of PC Substrates: Our Contributions

Processing Products	Primary PC	References
Adrenocorticotrophic hormone	PC1/3	(Benjannet et al. 1991)
α -Melanocyte-Stimulating Hormone	PC2	(Benjannet et al. 1991)
β -Endorphin	PC2	(Benjannet et al. 1991)
Dynorphins	PC1/3	(Dupuy et al. 1994)
Brain-Derived Growth Factor	Furin, SKI-1/S1P	(Seidah et al. 1996a); (Seidah et al. 1999)
Nerve Growth Factor	Furin	(Seidah et al. 1996b)
Neurotrophin-3	Furin	(Seidah et al. 1996a)
Insulin-like Growth Factor 1 Receptor	Furin	(Stawowy et al. 2004a)
Platelet-Derived Growth Factor A	Furin	(Siegfried et al. 2003b)
Platelet-Derived Growth Factor BB	PC5	(Stawowy et al. 2002)
Transforming Growth Factor	Furin	(Stawowy et al. 2004c)
Vascular Endothelial Growth Factor C	Furin, PC5, PC7	(Siegfried et al. 2003a)
Integrin α	Furin, PC5A	(Lissitzky et al. 2000)
Integrin α_v	PC5	(Stawowy et al. 2004b)
Membrane Type 1-membrane metalloprotease	Furin	(Stawowy et al. 2004c)
Chikungunya Virus E3/E2 protein	Furin, PC5, PACE4	(Ozden et al. 2008)
Cremean Congo Hemorrhagic Fever Virus gp*	SKI-1/S1P	(Vincent et al. 2003)
Ebola Virus gp	Furin, PC5, PC7	(Basak et al. 2001)
Hemorrhagic Fever Lassa Virus	SKI-1/S1P	(Basak et al. 2002)
Hong Kong Virus gp	Furin, PC5, PC7	(Basak et al. 2001)
Human Immunodeficiency Virus	Furin	(Vollenweider et al. 1996)
Respiratory Syncytial Virus gp	Furin, PC5, PC7	(Basak et al. 2001)
SARS* Coronavirus proS	Furin, PC5B, PC7	(Bergeron et al. 2005, Basak et al. 2007)
BACE1*	Furin	(Wickham et al. 2005)
BR1 ₃ *	Furin	(Wickham et al. 2005)
Hepcidin	Furin, PAC4, PC5, PC7	(Scamuffa et al. 2008)
Pan-neuronal PC2 Chaperone 7B2	Furin	(Paquet et al. 1994)

*Extracellular Matrix Proteins**Growth Factors & their Receptors**Neurotrophins**Other Proteins**Peptide Hormones/Neuropeptides**Viral Infectivity Proteins*

* Abbreviations: *BACE*, β -secretase β site APP cleaving enzyme; *BR1₃*, brain protein I3; *gp*, glycoprotein, *SARS*, Severe Acute Respiratory Syndrome

neuroendocrine regulation; b) in disease: atherosclerosis, diabetes, obesity, viral and bacterial infections, cancer, Alzheimer's disease, infertility and congenital anomalies (Figure 4). Their discovery can be seen as a major scientific advance that could lead to the development of novel therapeutic strategies aimed at altering their bioavailability. Conceptually, these strategies could also aim at increasing their activities to restore or improve health, but the foreseeable therapeutic approach will be to reduce, directly or indirectly, these activities.

The Fourth Decade: The Serendipitous Discovery of a Role for SKI/SIP and PCSK9 in Cholesterol Homeostasis

Serendipity is the ability to make discoveries not purposely searched for. (HORACE WALPOLE)⁸

In 1998, I moved my laboratory to the Loeb Research Institute (now called Ottawa Hospital Research Institute, OHRI in short) in Ottawa, Ontario, where I was appointed Scientific Director, in replacement of Dr. David Grimes whose health had rapidly deteriorated. Majambu Mbikay and Ajoy Basak joined me a year later. We continued our close collaboration with Nabil under joint group grants.

In Ottawa, I opened a protein chemistry laboratory and made it a regional facility. In anticipation of the explosive developments in proteomics, I convinced the Faculty of Medicine (Dean Peter Walker and Biochemistry Department Chair Zemin Yao) to create a Systems Biology Institute, and proposed that it recruit Daniel Figeys as its director. Daniel is a young and dynamic physical chemist who had led the research that unraveled the yeast interactome in 2000 (Ho et al. 2002). He has recently invented a "Rare Cell Proteomic Reactor", an integrated processing and analysis system that facilitated the elucidation of the proteome of small number of cells (Tian et al. 2011). Together, we have begun to characterize

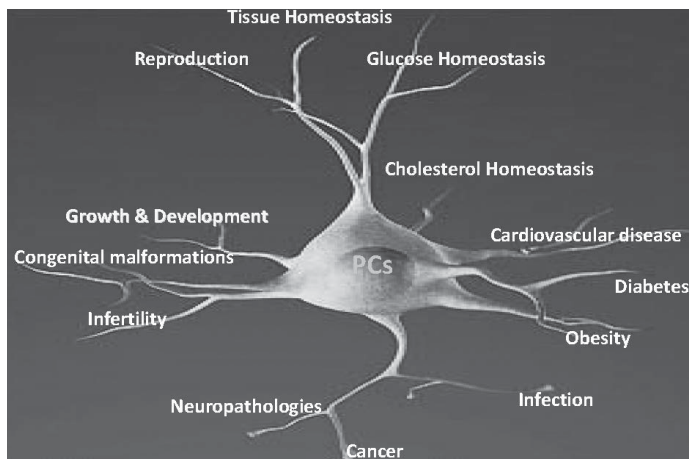


Figure 4. Dendrifcation of the roles of proprotein convertases in physiological processes, in health and disease.

PC interactomes in selected cell lines (Denis et al. 2011). The elucidation partner molecules may eventually lead to the identification of functional complexes that could be dubbed "convertosomes". With Majambu, and Dr. Janice Mayne, a new recruit to the team, we have explored the role of the PCs in the GI tract, (Gagnon et al. 2009, Gagnon et al. 2010), while Ajoy characterized interesting inhibitory motifs within PC sequences (Basak et al. 2011).

This move to Ottawa coincided with our discovery of SKI-1 (Seidah et al. 1999). SKI-1 was the first PC lacking a multi-basic motif at the activation cleavage site of its zymogen. This cleavage occurred after a RSLK↓ or a RRLL↓ motif (Seidah et al. 1999, Toure et al. 2000). Pro-Brain-derived neurotrophic factor (BDNF), which carries an RSLT motif at its activation site, was shown to be cleavable by SKI-1 at this site (Seidah et al. 1999). SKI-1 has been implicated in the infectivity of the hemorrhagic fever lassa virus (Basak et al. 2002), reinforcing the established view that PCs mediate the infectivity of various viruses.

We never anticipated that SKI-1 would be involved in sterol homeostasis. This came about following a series of elegant studies by Joseph Goldstein's and Michael Brown's team at The University of Texas Southwestern Medical Center, in Dallas, Texas (Cheng et al. 1999, Espenshade

⁸ The word serendipity was coined in 1754 by Horace Walpole based on the Persian tale *The Three Princes of Serendip*.

PCSK9 was the last PC to be discovered (Seidah et al. 2003); it is also involved in lipid metabolism. It is secreted by the liver, and circulates in the bloodstream as an inactive enzyme. This inactivity is due to the permanent non-covalent binding of its propeptide to the mature enzyme, following the autocatalytic cleavage of the zymogen after the prodomain in the ER. No PCSK9 substrate other than its zymogen has been identified to date. The role of PCSK9 in cholesterol metabolism also occurred by pure serendipity. This time, it took the sagacity of Nabil Seidah who noted that the *PCSK9* gene mapped on a region of human chromosome 1 implicated in familial hypercholesterolemia (FH) in some French families devoid

HF is caused by severe reduction of the surface density of hepatocyte low-density lipoprotein receptor (LDLR), leading to impaired clearance of blood LDL-Cholesterol (LDL-C), hypercholesterolemia and potentially lethal cardiovascular complications. Studies in cell lines and experimental animals showed that PCSK9 is a negative modulator of LDLR levels. FH-causing mutations accentuate this property. Mechanistically, circulating PCSK9 attaches to the LDLR at the cell surface, gets co-endocytosed in a complex, prevents its recycling to the cell surface, rerouting it to lysosomes, where it is degraded (Benjannet et al. 2004, Maxwell and Breslow 2004, Horton et al. 2009).

The *PCSK9* gene is highly polymorphic (Leigh et al. 2009). The finding that PCSK9 gain-of-function (GOF) variants cause hypercholesterolemia and cardiovascular

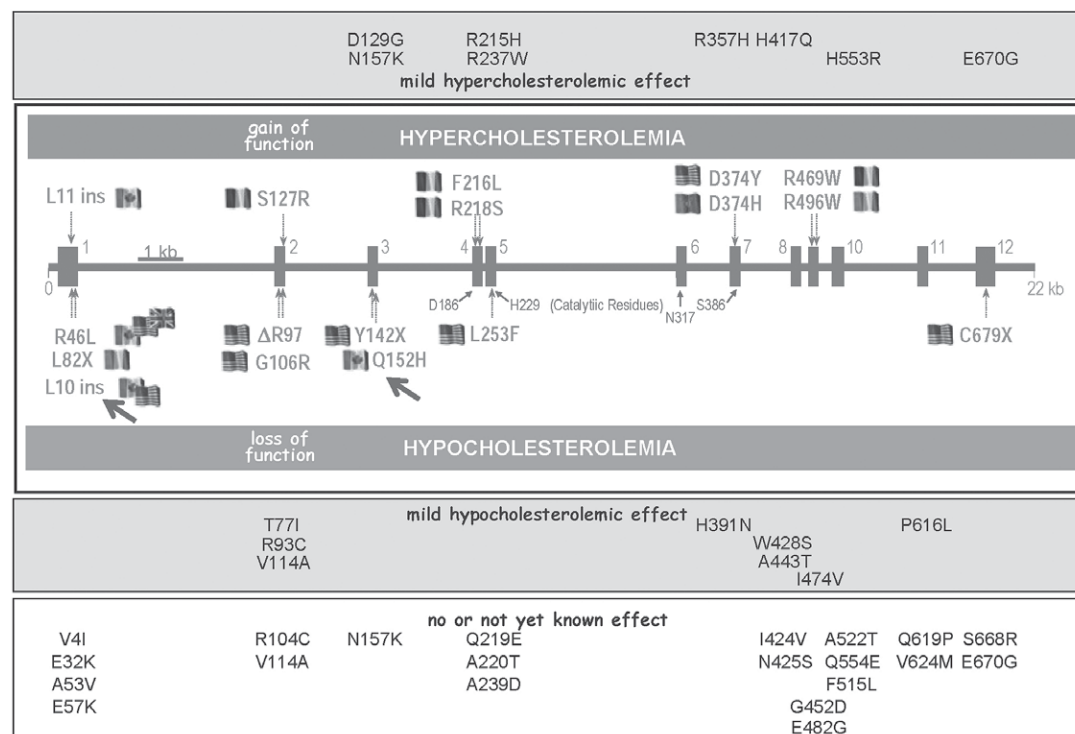


Figure 5. *PCSK9* genetic variations. Arrows indicate variations of which we have studied the segregation in 2 French Canadian families (see Figure 6).

disease (CVD) (Abifadel et al. 2009) was as surprising as the retrospective observation that loss-of-function (LOF) variants cause hypocholesterolemia and protect from CVD (Figure 5). The cardioprotective function of LOF PCSK9 variations was definitely validated in a large retrospective study conducted by Cohen et al. (Cohen et al. 2006). The study showed that African Americans, who were heterozygous for two nonsense variations, had plasma LDL-C 28% below average, and an 88% protection from coronary artery disease (CAD); while Caucasians who were heterozygous for a missense variation causing an Arg46Leu (R46L) amino acid substitution had their plasma LDL-C and CAD risk reduced by 15% and 47%, respectively. These observations indicated that reduction of PCSK9 levels or activity would be a valuable therapy that may complement statins for the control of circulating LDL-C levels (Brown and Goldstein 2006, Chrétien et al. 2008, Seidah 2009).

As mentioned above, the involvement of proprotein convertases in lipid metabolism was totally unforeseen. On a personal note, this outcome was extremely rewarding. As a clinical endocrinologist, I had participated since 1967 in the IRCM *Clinique de Nutrition métabolisme et athérosclérose* led by Dr. Jean Davignon (Davignon and Roy 1993). An internationally renowned internist and lipidologist, Jean has conducted extensive genetic studies on a large cohort of French Canadians suffering from clinical dyslipidemia, including FH due to LDLR mutations (Hobbs et al. 1987, Ma et al. 1989, Leitersdorf et al. 1990, Davignon and Roy 1993).

In Montreal, Jean joined efforts with Nabil to study his cohort and observed that statins, while inhibiting intracellular cholesterol biosynthesis, stimulates PCSK9 expression. Because this stimulation could attenuate the anti-cholesterol effect of statins, they suggested that therapeutic intervention to inhibit PCSK9 would enhance this effect (Dubuc et al. 2004, Dubuc et al. 2009, Davignon et al. 2010).

In Ottawa, I maintained a limited clinical activity, including a small cohort of dyslipidemic patients, with Dr. Teik-Chye Ooi, a clinical lipidologist. In 2005, I had the referral of a subject with an extremely low plasma LDL-C level. Logically, I suspected that this patient might carry a LOF PCSK9 variation. We sequenced his *PCSK9* gene. It turned out to carry a single-nucleotide polymorphism that specifies an R46L amino acid substitution (Mayne et al. 2007). Before we could determine the cellular impact of this variation, Cohen et al. (Cohen et al. 2006) described its strong association with hypocholesterolemia.

In the meantime, we noticed that one of our control subjects carried a 10-Leucine repeat instead of the common 9-Leucine repeat in the PCSK9 signal peptide. This L10ins variant was already known to be associated with mild hypocholesterolemia in Caucasians. Its presence had not yet been examined in the Canadian population. The *propositus* in our cohort belonged to a large French Canadian family. This motivated us to sequence the *PCSK9* exons of 51 living relatives (39 by blood and 12 by marriage), and to derive possible association of the L10ins variation with their plasma lipid profiles. The results (Figure 6) revealed that 19, 15 blood relatives and

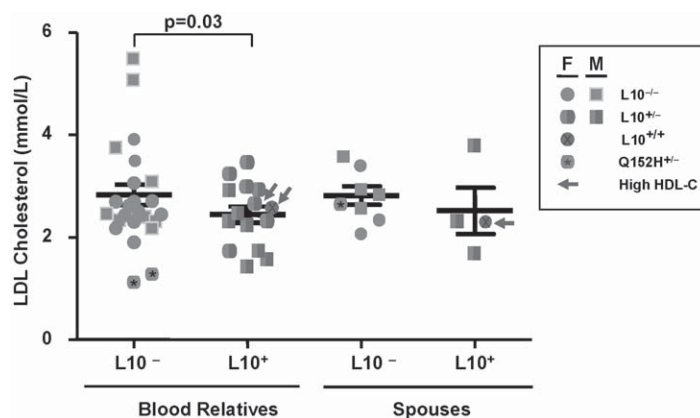


Figure 6. Genetic studies over 3 generations of a large French-Canadian family including their spouses. The *propositus* was serendipitously found to be PCSK9 L10 variant. One L10^{+/+} spouse and her L10^{+/+} and L10^{+/+} daughters showed a noticeably high HDL-C (2.5 – 4.1 mmol/L), a rare cardio-protective combination (arrow). One spouse and her 2 daughters carried the Q152H mutation (indicated by *. See figure 7).

4 spouses, out of the 51 participants (37.3%) carried the L10ins variation with a minor allele frequency of 20.3; and that the carrier status correlated with 19.3% lower plasma cholesterol.

Most interestingly, in the course of this study, we discovered a Gln152His (Q152H) variation in another spouse (see Figure 6). This novel variation occurs at the prodomain cleavage site; it prevents the autocatalytic maturation of the proPCSK9, causing ER retention, not only of the variant enzyme, but also of its normal isoform, through a dominant negative effect (Mayne et al. 2011). We studied the lipid profiles and sequenced the *PCSK9* exons of 14 of her relatives, 10 by blood and 4 by marriage. The two daughters and one brother of the *propositus* carried the Q152H variation (Figure 7). The plasma levels of LDL-C in carriers of the Q152H PCSK9 variant are 25% below normal (Mayne et al. 2011). Thus, this variant may be as cardioprotective as the nonsense African variants (Cohen et al. 2006). The absence of a morbid phenotype in these subjects suggests that blocking the proPCSK9 autocatalytic cleavage could be a good therapeutic target. Moreover, nine out the 15 genotyped subjects (including

the *propositus*) in this pedigree, had the L10ins variation; two of these were double heterozygotes for the R46L and L10ins variations (see Figure 7).

The two pedigrees combined (Figures 6 and 7) formed 18 distinct French Canadian branches; 8 of these branches (44.4%) carried at least one LOF PCSK9 variation. These intriguing results strongly suggest that PCSK9 LOF variants may be frequent in the French Canadian population.

In Conclusion

Derived from the 1967 Prohormone Theory, precursor endoproteolysis in the secretory pathway is now recognized as a fundamental mechanism of cellular physiology. Initially limited to peptide hormones, it is now applicable to a wide variety of bioactive proteins, e.g. neuropeptides and neurotrophins, incretins and enteropeptides, growth factors and their membrane receptors, transcription factors, bacterial toxins and viral glycoproteins. The identification of PCs was the final piece of the puzzle in this theory. Over the last 22 years, PCs have been shown to regulate an ever-expanding number of functionally important

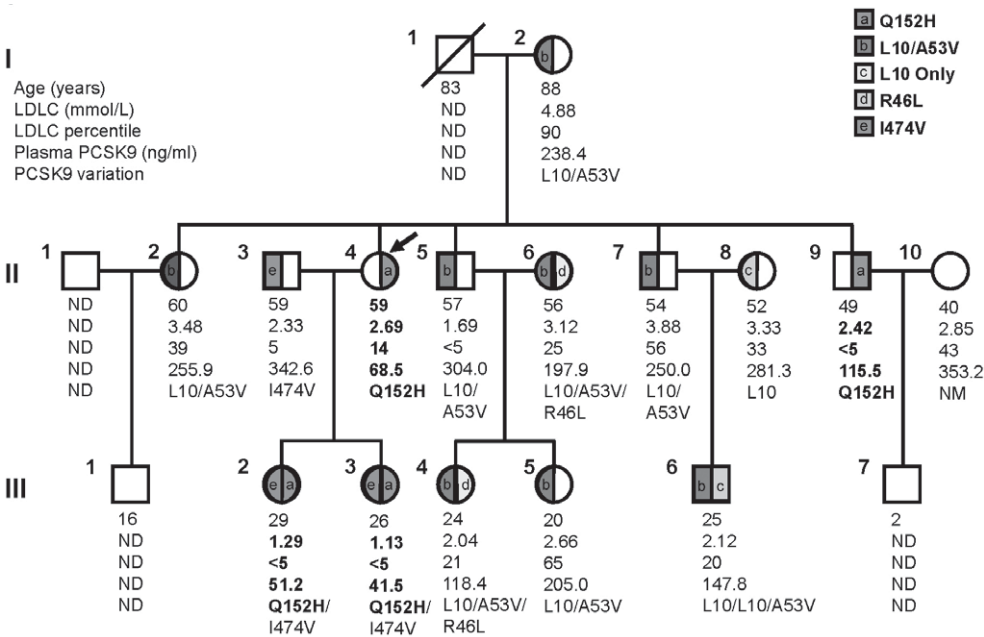


Figure 7. Segregation of the Q152H PCSK9 variation in a French Canadian family. Plasma from participants was tested for the levels of LDL-C. The percentile positions of participants' level are indicated. The levels of plasma PCSK9, as expected, is remarkably low. Numerous *PCSK9* gene variations were found in this family. Only one member carried no variation.

proteolytic events, depending on their time, site, and level of expression. Their physiological relevance has expanded with the discovery of SKI-1/S1P and PCSK9, two key players in cholesterol metabolism. The fact that PCSK9 plays a non-enzymatic role of a destructive chaperone in LDLR catabolism, adds a new dimension to this functional diversity. Current evidence suggests that PCs play roles in the pathophysiology of pain, mood disorders, diabetes, obesity, cardiovascular disease, cancer, and infectious diseases. They are potential targets for a new *armamentarium* of drugs. Among them, PCSK9 best lends itself to bench-to-bed translation, as a therapeutic target in hypercholesterolemia and a genetic marker of CVD risk (O'Donnell and Nabel 2011).

As a young medical graduate, I wanted to be a clinical endocrinologist. To improve my knowledge of endocrinology, I diverged to peptide chemistry. For most of my scientific career, I was a bench scientist with limited clinical activities. Now, late in my professional life, PCSK9 gave me the opportunity to apply my basic and clinical expertise to an important human health issue of the day: CVD risk. In a way, my biomedical career has taken me “from the bedside to the bench and back to the bedside”.

Through luck, serendipity and longevity, I feel blessed beyond measure to have been at the central stage of the exciting developments around the Prohormone Theory and the Proprotein Convertases. I am deeply grateful to each and all who have accompanied me in this long and rewarding journey.

“Follow the trail”, said de Duve. I did so and I will go on doing it. Stay tuned.

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CSMB Board for 2011-2012



The CSMB Board at its annual meeting in Toronto, November 2011.

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Back row from left: President Jim Davie (Manitoba), Vice President Art Hilliker (York), Andrew Simmonds (Alberta), Jan Rainey (Dalhousie), Secretary Randy Johnston (Calgary), Treasurer Vince Duronio (UBC). Photographer: CSMB Secretariat Wafaa Antonious.

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President's Report – 2011-2012

Dr. James Davie

During my tenure as President, it has been exciting to be part of the transition to change our Society name to the Canadian Society for Molecular Biosciences (CSMB). It is considerably better than our previous name - the Canadian Society for Biochemistry and Molecular & Cellular Biology (CSBMCB). With the recent the recent amalgamation with the Canadian Society for Genetics, we were faced with either extending our Society's name or simplifying the name. We are pleased with the participation of our membership in selecting our new name. CSMB is one of the largest scientific societies in Canada, with over 1000 members, and our new name better reflects our inclusive nature. I urge you to visit our Web site to appreciate the rich history of the Society.

I have been most impressed with the dedication and commitment of the CSMB Executive team in strategic planning and the promotion of the society. We are in a period of unprecedented change, with the restructuring and changes in priorities of the life sciences granting agencies. Agencies providing operating grants in the \$60 - 70K per annum range have seen a major increase in the number of applications. Clearly, our members are looking at all sources of funding to keep their research operations viable. Your society is actively involved in advocacy, towards stabilizing the life sciences funding. We count on your continued participation as well as encourage you to persuade your colleagues to join the society. There is a strength in numbers, which will aid us in our mission to have your collective voice heard.

Advocacy Remains a Priority - A Request for Your Involvement

Many of our members are concerned with the CIHR proposed reforms on open programs and peer review. But at the same time, our members supported by NSERC grants have also experienced the consequences of program revisions. These changes in strategic planning, in programming and in peer review should never be viewed as standalone as funding for the life sciences is interdependent. Provincial

Health Research funding organizations, for example, will to a certain extent craft their suite of programs to improve the competitiveness of their provincial researchers to secure CIHR operating grants. As with biological systems, which we are all familiar with, radical changes in one component of the food chain have consequences throughout the system.

On our Society Web site, we posted letters responding to the CIHR reforms. Without doubt, there is major concern with the proposed reforms, particularly around the changes to peer review. *We strongly request that the membership sends us the comments and letters you sent into CIHR as we would be pleased to include this correspondence on our Web site.*

In moving forward, it is our understanding that the University Delegates will continue to be involved in discussions on the CIHR proposed peer review changes with a Face-to-Face meeting in Ottawa in June. I will continue to participate in the discussions with CIHR, providing input towards the adoption of a peer review process that we can all be proud of. The current CIHR peer review system will clearly be revamped so the status quo is not an option. *We are putting a call out to our membership to challenge your creativity in proposing a plan for restructuring the CIHR peer review.* We will post these plans on our Web site.

We will continue to advocate vigorously in the areas of science policy, public awareness and research funding to help maintain a favorable environment for the research community. Our membership in Research Canada will help to get the message that research matters heard in Ottawa and across the country.

Membership

Our Society continues to provide a forum to voice your collective opinions on important issues such as the proposed CIHR reforms, and supporting outstanding scientific conferences and graduate student activities. I urge you to visit our Web site to review our wide range of activities, many of which will be of interest to you. *I also seek your aid in our membership recruitment drive.* There are many benefits to being a member, but importantly there is strength in num-

bers. This is so important in a time when we are in a period of unprecedented restructuring of national and regional life science research funding agencies.

Annual CSMB Meeting

We have just completed a very successful Scientific Conference, conducted this year in Whistler, British Columbia, which I had the pleasure of organizing. Attendance was very good with many national and international speakers devoted to the theme of epigenetics and genomic stability. Also presenting at the conference was Dr. Jane Aubin, Chief Scientific Officer/Vice-President of the Canadian Institutes of Health Research, to update us on the status of the CIHR proposed reforms on open programs and peer review. There will be more about that later but just to say now there was lively debate about the proposed reforms for peer review.

At the Whistler meeting, we awarded Dr. Henry Friesen the Society's Arthur Wynne Gold Medal. Dr. Friesen told us about his experiences in transforming the Medical Research Council to the Canadian Institutes of Health Research and the genesis of Genome Canada. An important take home message from his presentation was a reminder that each of us should thank the Minister of Health for funding we do receive for health research. When was the last time that you wrote a letter thanking your MP or the Minister (provincial or federal) for receiving an operating grant, postdoctoral fellowship, or graduate studentship? Believe me these letters will be read and will have a positive impact.

Annual General Meeting of CSMB

Our Annual General Meeting was held in conjunction with the Scientific Conference. In the coming month, Jean-Pierre Perreault will have completed his term as Past-President of the Society, I will move from President to Past-President, and Arthur Hilliker will move from Vice-President to President. Andrew Simmonds will be the incoming Vice-President.

CSMB and Canadian Science Publishing

We have formalized an agreement with the Canadian Science Publishing (formerly NRC Research Press). Two of their journals, *Biochemistry and Cell Biology* and *Genome*, publish original manuscripts and reviews. These journals have special issues, which have a collection of reviews from speakers at our Society's sponsored scientific meetings.

These journals welcome your original manuscripts and reviews. Canadian Science Publishing has been a strong advocate of Canadian publishing in the life sciences and has contributed financially to our scientific conferences.

Goals

With your participation, we have several important goals over the coming year. First, we will continue to support excellent science through our annual Scientific Conference and through other national and international meetings that we co-sponsor (see our website for details). A reminder that our 56th Annual Meeting on Cellular Dynamics during Development, Regeneration and Cancer will be held at Niagara-on-the-Lake, Ontario from June 4 to 7, 2013. Second, we will maintain our efforts to grow our membership among researchers and trainees, who are eligible for a variety of awards that are described in the website. Third, we will keep the membership informed as we learn more about the changes being planned by CIHR and NSERC. Fourth, and perhaps most importantly, we will advocate vigorously in the areas of science policy, public awareness and research funding to help maintain a favorable environment for the research community.

Thanks

Thanks to all the Society Board members for your dedication and service. In particular I would like to thank Randy Johnston, CSMB secretary. Randy has had many tasks including revising the by-laws, drafting correspondence and many, many other tasks. The secretary position is, in my opinion, one of the most demanding positions in our Society. Randy's commitment to improving the society has been noted, and I thank him for all of his hard work. I would also like to thank Vince Duronio (UBC) for keeping our finances in order. You have done a fantastic job. Thanks to Art Hilliker, Vice-President, and Jean-Pierre Perrault, Past-President, for your help and insights. Thanks also to our councillors John Orlowski, Alba Guarne, Andrew Simmonds, Frances Sharom, Jan Rainey and Josée Lavoie. And last but certainly not least, I thank David Williams and Reinhart Reithmeier not only for your exemplary management of the Bulletin but also for your advice throughout my term.

Thank you for your ongoing support for our Society. We look forward to your continuing engagement.

Minutes of the 2011 Annual General Meeting

Orford, Quebec - September 2011

1. Greetings from the President (Jean-Pierre Perrault)

Jean-Pierre Perrault welcomed the attendees.

2. Approval of quorum and agenda

Jean-Pierre Perrault declared a quorum and called the meeting to order. Martin Bisaillon made a motion to approve the agenda, seconded by Christian Baron, agenda approved.

3. Approval of the Minutes of 53rd Annual General Meeting

Vincent Duronio made a motion to approve the minutes, seconded by Randall Johnston, all in favour, minutes approved.

4. Business Arising from the Minutes

Randall Johnston reported that all business arising from the minutes were included in the agenda.

5. Update on Merger of GSC with CSBMCB

Randall Johnston stated that the GSC would have to submit a letter requesting the revocation of its charitable status. One of the terms of the merger agreement was that two members of the GSC would serve on the CSBMCB board. He added that the GSC awards would be offered in the 2012 CSBMCB Whistler conference.

6. Secretary's Report - Randall Johnston

a) Membership Report

Randall Johnston reported that the CSBMCB had run a vigorous membership campaign in the last 12 months. The society secretariat is cleaning up the database to remove members

who have not renewed their membership for some time. The CSBMCB has over 560 members, making it one of the biggest scientific organizations in Canada. There are around 40 members from outside Canada. Duronio added that only students who renewed their information in 2011 were included in these figures and therefore the number of active members is even greater than 560.

b) Approval of Revised Constitution and By-laws

Randall Johnston recounted the history of the By-Laws, the rules about how we recruit our members and communicate with them over the years. Accumulating change over time in the scope of our Society and its strategies meant that we had to revise the bylaws to reflect present day practices and communication media. He added that CSBMCB engaged in advocacy through its partnership with other organizations, including Research Canada, and that the former Canadian Federation of Biological Societies no longer existed. Some of the changes that were recommended for the By-Laws were in the process of election and nomination of the society board members. The indemnification clauses were added to protect the board members since the society was growing in number through merger with other organizations, and especially that the CSBMCB was planning to be involved in the 2016 international conference in Vancouver. A draft of the revised By-Laws had been posted on the Society website for comment and several minor changes suggested by members had been incorporated. Vincent Duronio made a motion to accept the revised by laws, seconded by Randall Johnston, all in favour. Revised Bylaws approved.

c) Approval of New Name for Society

Randall Johnston said that the Executive proposed to change the name of the society as a result of the merger with the Genetics Society of Canada. It was agreed not to add another word to the society name and thus another letter to the acronym. Email notices were sent out to the membership asking first if they wanted to change the name and to provide us with suggestions. Over 40 suggestions were received; these were narrowed down to 3 popular names that were suggested multiple times, then a second email notice was sent out to all the members to vote. 80% voted to choose Canadian Society for Molecular BioSciences (CSMB).

Johnston made a motion to approve the new name, seconded by Ute Kothe, all in favour, new name approved. Vincent Duronio then gave a history of the name and how it came to be CSBMCB. Jim Davie added that it would take over a year to have the name officially adopted with a new logo posted on the website. He expressed the Executive's thrill with the response received regarding the society name change and we would like to keep the momentum of communications with the members.

7. Treasurer's Report - Vincent Duronio

a) Presentation of the Auditor's Financial Report.

Vincent Duronio explained that in the last two years the CSBMCB financial books had been undergoing a review of engagement conducted by an auditor. The Review of engagement is less rigorous than an audit but is consistent with the needs of not-for-profit corporations. He reported that the investments had increased substantially from 2009 to 2010.

b) Presentation and Approval of Budget 2011 – 2012

2011 / 2012 budget was circulated. Duronio stated that although the Ribo club covered most of the expenses related to the conference the CSBMCB still had to pay for travel awards and some of the board travel to the conference. He estimated an operating deficit of \$70,000 for 2011, explaining that in the previous year the Society had an influx of funds from Pence and GSC. He assured the members that the Society's finances were in good condition since the CSBMCB had an investment account which was supporting its activities and securing its future. In general, the finances of the society are very strong. Originally this investment account started with \$100,000 from an international meeting in Toronto, and the funds have grown since then.

A question was raised if the CSBMCB was planning to meet again with the Ribo Club, as it provided exposure. Duronio replied that they were planning to increase the involvement of the society in other meetings and sponsoring other events. He added that the society had invested over \$50,000 in the 2012 Whistler meeting.

Christian Baron voiced his concern that the meetings were narrowly focused and only a fraction of Society members would attend any given meeting. Perrault replied that we were currently sponsoring more than one meeting with various partners, and that the meeting theme and location varied each year so that over time, most members could eventually attend and benefit.

c) Acceptance of the financial Report

Martin Zion moved to accept the presented financial report, seconded by Jim Davie, all in favour, financial reports accepted.

8. Board Membership for 2011 - 2012

Jean-Pierre Perrault advised that Linda Penn had been responsible for the membership for over 6 years and was leaving the board. He added that this year Art Hilliker who was a former GSC member was nominated for the position of VP. He further noted that we would like to ask if someone from the floor would like to be nominated for the position of VP, but no nominations were received. Dr. Perrault made a motion to approve the nomination of Art Hilliker for the VP position. Dr. Johnston seconded the motion, all in favour. Dr. Johnston added that the following year there would be two or three positions to be filled, including the next VP and councillors.

9. Current and future meetings

Jim Davie made a presentation about the CSBMCB 2012 Whistler meeting. The meeting will end on Saturday evening and delegates will then be leaving on Sunday or Monday. The program information will be posted on the CSBMCB website the following week. He went then through the highlights of the program. He reported that they had been contacting exhibitors, and the response was very positive. The exhibitor registration is a good source of financial support for the meeting.

Vincent Duronio added that the 2013 CSBMCB meeting would be held in the Niagara-on-the-Lake and the proposed theme was Cellular Stress, Metabolism and Disease.

10. Canadian Science Publishing Presentation (NRC Research Press)

Jim Davie stated that the Society currently had two journals through the NRC Research Press.

Kelly Bogh from the Canadian Science Publishing (NRC Research Press) gave a presentation: The NRC Research Press was privatized last year. A new non-profit corporation, Canadian Science Publishing, was created to take over the NRC Research Press operations, and the brand name "NRC Research Press" was licensed to Canadian Science Publishing. Many

things remain the same under the new company: the Press is still a not-for-profit publisher; it still publishes the same 15 titles, including "Biochemistry and Cell Biology" and "Genome"; it still offers the same benefits to authors (i.e., there are no charges for publishing in the NRC Research Press journals, authors retain their copyright, and NRC Research Press is compliant with the open-access policies of the funding agencies); and we have maintained wide access to the journals for Canadians (articles published up until Dec. 31, 2010 remain open access, and we have license agreements with the Canadian Research Knowledge Network and the Federal Science eLibrary). In the new company, however, the Press has more flexibility and can better promote the content it publishes, for example by issuing press releases. The Press was able to launch a new, state-of-the-art website and was also able to transition to Scholar One Manuscripts. Finally, the Press has developed partnerships with 12 Canadian societies, in which each Society is affiliated with a particular journal and supports that journal, and Canadian Science Publishing sponsors and promotes the Society.

Jim Davie added that Art Hilliker and he were looking for mini-reviews and encouraged the attendees if they had an idea to put it in a mini-review and send it to them.

Randall Johnston asked about the impact factor and Kelly replied that it was just under 3, which has increased over the years from lower levels.

11. Other business / Adjournment

No other business. Jim Davie made a motion to adjourn seconded by Jean-Pierre Perrault, all in favour, meeting adjourned.

CANADIAN SOCIETY OF BIOCHEMISTRY, MOLECULAR AND CELLULAR BIOLOGY

Financial Statement

STATEMENT OF FINANCIAL POSITION

AS AT DECEMBER 31, 2011
UNAUDITED

	2011	2010
ASSETS		
CURRENT		
Cash	\$ 7,369	\$ 20,261
Accounts receivable – CSBMCB	2,541	3,078
Accounts receivable – GSC (note 4)	741	-
Conference deposit	66,714	32,060
	<u>77,365</u>	<u>55,399</u>
INVESTMENTS (note 5)	419,048	465,076
	<u>\$ 496,413</u>	<u>\$ 520,475</u>
LIABILITIES		
CURRENT		
Accounts payable and accrued liabilities	\$ 12,265	\$ 9,304
Deferred membership fees and subscription fees	4,405	5,435
Deferred conference income	5,036	-
	<u>21,706</u>	<u>14,739</u>
LONG TERM		
Deferred membership fees	<u>5,594</u>	<u>2,391</u>
UNRESTRICTED NET ASSETS	469,113	503,345
	<u>\$ 496,413</u>	<u>\$ 520,475</u>

STATEMENT OF OPERATIONS AND CHANGES IN NET ASSETS

FOR THE YEAR ENDED DECEMBER 31, 2011

UNAUDITED

	2011	2010
REVENUE		
Memberships dues	\$ 28,931	\$ 25,783
Corporate contributions	8,750	20,828
Annual meeting	-	57,840
PENCE transferred funds	-	10,682
Other	1,075	1,351
	<u>38,756</u>	<u>116,484</u>
Investment income	8,539	7,327
	<u>47,295</u>	<u>123,811</u>
EXPENSES		
Secretariat	15,390	21,930
Annual meeting (note 6)	15,030	84,822
Board meetings	9,275	13,021
Meeting sponsorship	7,542	1,500
Website	3,900	4,255
Membership drive	3,159	2,593
Professional fees	2,191	2,100
Bank and credit card fees	2,178	1,382
Science advocacy	1,757	7,703
Bulletin	1,246	5,640
Office	272	649
Miscellaneous	-	4384
Dues and subscriptions	-	-
	<u>61,940</u>	<u>149,979</u>
NET (EXPENSES) FOR THE YEAR	\$ (14,645)	\$ (26,168)
Unrestricted net assets at beginning of year	\$ 503,345	\$ 447,504
Balance before items affecting net assets	488,700	421,336
Gains (losses) from sale of investments (realized and unrealized) (note 5)	(16,566)	30,240
Transfer of assets to the CSBMCB (note 4)	-	51,769
Unrestricted net (deficit) transferred from GSC	<u>(3,021)</u>	<u>-</u>
UNRESTRICTED NET ASSETS AT END OF YEAR	<u>\$ 469,113</u>	<u>\$ 503,345</u>

STATEMENT OF CASH FLOWS

FOR THE YEAR ENDED DECEMBER 31, 2011
UNAUDITED

	2011	2010
CASH PROVIDED BY (USED FOR)		
OPERATING ACTIVITIES		
Cash from operations		
Net revenue for the year	\$ (14,645)	\$ (26,168)
Non-cash portion of investment income	(8,539)	(9,327)
	<u>(23,184)</u>	<u>(35,495)</u>
Net change in non-cash working capital balances		
Accounts receivable	(204)	37,238
Conference deposit	(34,654)	(32,060)
Accounts payable and accrued liabilities - CSBMBC	2,961	(7,164)
Accounts payable and accrued liabilities - GSC	(3,020)	-
Deferred membership and subscription fees	2,173	(8,160)
Deferred conference income	5,036	
	<u>(50,892)</u>	<u>(45,641)</u>
INVESTING ACTIVITY		
Transfer of funds from investment account	38,000	-
Transfer of assets to the CSBMBC (note 4)	-	51,769
	<u>38,000</u>	<u>51,769</u>
(DECREASE) INCREASE IN CASH	<u>(12,892)</u>	<u>6,128</u>
 Cash, beginning of year	 <u>20,261</u>	 <u>14,133</u>
CASH, END OF YEAR	\$ <u><u>7,369</u></u>	\$ <u><u>20,261</u></u>
 CASH POSITION		
Cash	\$ <u><u>7,369</u></u>	\$ <u><u>20,261</u></u>

NOTES TO THE FINANCIAL STATEMENTS

December 31, 2011
UNAUDITED

I. PURPOSE OF THE ORGANIZATION

The Canadian Society of Biochemistry, Molecular and Cellular Biology (CSBMCB) was incorporated without share capital in 1979 under Part II of the Canada Corporations Act and is recognized as a not-for-profit organization for income tax purposes. The main objective of the Society is to foster research and education in Biochemistry, Molecular Biology and Cellular Biology in Canada.

2. SIGNIFICANT ACCOUNTING POLICIES

- (a) Capital assets
Capital assets purchased at a cost of less than \$2,000 are expensed in the year of purchase. The Society does not own capital assets at this time.
- (b) Basis of Accounting
Revenue and expenses are recorded on the accrual basis, whereby they are reflected in the period in which they have been earned and incurred respectively, whether or not such transactions have been finally settled by receipt or payment of money.
- (c) Revenue Recognition
CSBMCB follows the deferral method of accounting for contributions. Restricted contributions are recognized as revenue in the year in which the related expenditures are incurred. Unrestricted contributions are recognized as revenue when received or receivable if the amount to be received can be reasonably estimated and collection is reasonably assured.
- (d) Use of estimates
The preparation of the financial statements in conformity with generally accepted accounting principles requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities at the date of the financial statements and the reported amounts of revenues and expenses during the reported period. Actual results may differ from those estimates.
- e) Financial Instruments
CSBMCB's cash is recorded using the held-for-trading method. These financial assets are measured at fair value at the balance sheet date. Any changes in fair value, both realized and unrealized, are recorded as adjustments to revenue and expenses. CSBMCB's accounts receivable and accounts payable and accrued liabilities are accounted for at amortized cost using the effective interest rate; they include all loans and receivables and all financial liabilities. Investments are classified as available for sale and are carried at market value and any changes in market value, both realized and unrealized, are recorded as adjustments to net assets under the available for sale method.

3. FINANCIAL INSTRUMENTS

CSBMCB's financial instruments consist of cash, accounts receivable and accounts payable and accrued liabilities. The fair value of these financial instruments approximates their carrying values, unless otherwise stated. It is management's opinion that the organization is not exposed to significant interest, currency or credit risks arising from its financial instruments.

4. TRANSFER OF ASSETS AND LIABILITIES FROM GSC

After December 31, 2010, the Canadian Society of Biochemistry and Molecular and Cellular Biology merged with the Genetics Society of Canada (GSC). This merger had been negotiated and agreed upon by the Boards of both organizations during fiscal 2010. The majority of the GSC's assets were transferred to the CSBMCB's bank account prior to December 31, 2010, all remaining GSC assets and liabilities will be merged with the CSBMCB's during fiscal 2011.

5. INVESTMENTS (at Market Value)

CSBMCB investments are recorded at market value. Any actual gains or losses on the disposal of investments during the year are included with the unrealized gains or losses on the portfolio as a whole at December 31 and recorded as "Gains (losses) from sale of investments, realized and unrealized".

BMO Nesbitt Burns Canadian Account

	2011	2010
Cash and short term investments	\$ 24,546	\$ 85,400
Fixed Income	64,608	64,914
Common equity	245,828	235,797
	<u>334,982</u>	<u>386,111</u>

BMO Nesbitt Burns US Account (in \$ Canadian)

Cash and short term investments	80	253
Common equity	83,986	78,712
	84,066	78,965
	<u>\$ 419,048</u>	<u>\$ 465,076</u>

6. ANNUAL MEETING EXPENSES

	2011	2010
Exhibits and facility	\$ -	\$ 31,531
Organizing and planning	-	18,509
Travel and Expenses	4,878	16,984
Awards	10,104	11,856
Supplies and other	48	5,942
	<u>\$ 15,030</u>	<u>\$ 84,822</u>

7. CAPITAL DISCLOSURES

CSBMCB defines the capital that it manages as unrestricted net assets. CSBMCB's objectives when managing capital are to generally match the structure of its capital to the underlying nature and term of the assets being financed, and to hold sufficient funds to enable that organization to withstand negative unexpected financial events, in order to maintain stability in the financial structure. CSBMCB seeks to maintain sufficient liquidity to enable it to meet its obligations as they become due.

There were no changes in CSBMCB's approach to capital management during the year ended December 31, 2011.

Meeting Report: The 54th Annual Meeting of the CSBMCB, Orford, Québec, 2011

Studying RNA one molecule at a time

Correspondents: Drs. Sherif Abou Elela, Jean-Pierre Perreault, Raymund Wellinger and Benoit Chabot, Université de Sherbrooke



The 54th Annual Meeting of the Canadian Society of Biochemistry, Molecular & Cellular Biology (CSBMCB) in partnership with the RiboClub Annual Meeting 2011 was held at the Hôtel Chéribourg at Orford from September 19th-21st. The RiboClub annual meeting is an international congress for RNA scientists. The meeting covers different topics related to the chemistry, structure and biology of RNA. The meeting format is designed to encourage collaborations between the different labs and to stimulate the interest of young scientists in this research area. Moreover, students have the opportunity to present their research in a poster session or, in selected cases, to give a talk at the meeting. The theme of this year's meeting was "Studying RNA, one molecule at a time".

For the opening of the meeting, we heard from keynote speaker, Dr. Gary Ruvkun (Harvard). He talked about his new data in the field of *C. elegans* small RNAs and how they target particular classes of mRNAs and genes.

The first session was on RNA-dependent regulation of translation, chaired by Dr. James E. Dahlberg (University of Wisconsin, Madison). Dr. Dahlberg talked about how Ago proteins restrict RNAi during *X. laevis* early development. Dr. Paul Fox (Cleveland Clinic) showed us his research on the GAIT system and the "translational trickle" control mechanism. Afterwards, Xianying Cui (University of Toronto) presented her research investigating ribosome-independent mRNA targeting and maintenance on the endoplasmic reticulum. Prasad Padmanabhan (University of Laval, Québec) defined the role of antisense ribosomal RNA processing in translational arrest during stress and apoptosis-inducing conditions in leishmania. Gabrielle Todd (University of Michigan, Ann Arbor)

described her work on the role of mRNA structure during translation bypassing of bacteriophage T4 gene 60. Finally, Guillaume Desnoyers (Université de Sherbrooke) demonstrated a new mechanism of non-canonical repression of translation initiation through small RNA recruitment of the RNA chaperone Hfq.

The second session dealt with splicing decisions under stress, chaired by Dr. Benoit Chabot (Université de Sherbrooke). Dr. Chabot's research characterizes the regulation of Bcl-x splicing under stress. Jiuyong Xie (University of Manitoba) described distinct ways in which alternative splicing is controlled by external factors. Dr. David Wassarman (University of Wisconsin, Madison) presented his research on the control of alternative splicing by signal-dependent degradation of splicing regulatory proteins. To close the session, Dr. Martin Duterte (University of Lyon) proposed that camptothecin alters the coupling between transcription and splicing by decreasing the interaction between EWS, an RNA polymerase II-associated factor, and YB-1, a spliceosome-associated factor.

Session three was on the RNA-dependent regulation of viral infection, chaired by Dr. Andrew K. White (York University, Toronto). Dr. White's research provides the beginnings for building a comprehensive RNA structural model for the tombusvirus genome that includes different types of RNA-based structures that control diverse viral processes. Dr. Biao Ding (Ohio State University, Columbus) proposed that specific RNA-protein interactions may play a major role in infectious RNA trafficking across various types of cells. Dr. Martin Pelchat (University of Ottawa) presented the involvement of PSF in the recognition of HDV RNA promoters by RNA polymerase II. Mark A. Ditzler (University of Missouri, Columbia) gave us a fresh look at HIV reverse transcriptase aptamers using high-throughput sequencing techniques combined with in vitro selection. Lara Ajamian (McGill) discussed her work which revealed that UPF1 promotes nucleocytoplasmic export of HIV-1 vRNA. Finally, Erin L. Garside (University of Alberta) presented her latest

structural and functional analyses of Cse3, an endonuclease involved in processing of the RNAs transcribed from CRISPR loci.

An after-dinner highlight was an exciting talk by Dr. Peter B. Moore (Yale), who described the history of the work done to determine the three-dimensional structure of RNAs from the 1960s to the present.

RNA molecules associated with genome stability was the topic of the fourth session, chaired by Dr. Andrés Aguilera (University of Sevilla). Dr. Aguilera provided evidence and possible mechanisms by which transcription and mRNP biogenesis can cause recombination-mediated genome instability. Dr. David C. Zapulla (John Hopkins, Baltimore) characterized the limits of flexibility within the 1157-nt telomerase RNA. Jason Kuehner (Tufts University, Somerville) presented his work on the coupling of RNA 3'-end processing with the DNA damage response. Evan P. Booy (University of Manitoba) provided evidence that the RNA helicase DHX36 (RHAU) regulates telomere maintenance by binding to a G4-Quadruplex in the 5' region of human telomerase RNA.

Session five was on the structure and behavior of regulatory RNA, chaired by Dr. Frédéric H-T Allain (ETH Zurich). Dr. Allain presented his structural work on guanine recognition by Lin28 zinc-binding domains and SR protein RRM. Dr. Robert T. Batey (University of Colorado, Boulder) outlined his studies which reveal that regulation of riboswitches is achieved through a series of ligand-induced tertiary structural changes in the RNA that serve to stabilize a helix that forms part of a secondary structural switch with the expression platform. Dr. Kalle Gehring (McGill) presented evidence that interdomain allostery promotes assembly of the mRNA complex with PABP and eIF4G. Dr. Ute Kothe (University of Lethbridge) showed for the first time a detailed kinetic study of pseudouridine synthases. Shyam S.S. Panchapakesan (Simon Fraser University, Burnaby) demonstrated that 6S RNA transcriptional regulation is controlled by a phylogenetically conserved hairpin switch. And, to close this session, Lydia A. Burns (York University, Toronto) described for the first time the regulation of ribosome inactivating proteins (RIPs) by a small RNA

and a pseudogene, which also supports the notion that pseudogenes are functional components of the genome.

The sixth session dealt with nuclear RNA degradation, chaired by Dr. Domenico Libri (University of Strasbourg). Dr. Libri gave a comprehensive analysis of exosome targets in the yeast *S. cerevisiae*. He provided the first transcriptome analysis of cells deprived of both Dis3 and Rps6 catalytic function. Dr. François Bachand (Université de Sherbrooke) unveiled an unanticipated role of the THO complex in the control of snoRNA expression by a mechanism of THO dependent co-transcriptional recruitment of the TRAMP complex to 3' end of snoRNA. Dr. Françoise Stutz (University of Geneva) provided her ongoing results on the characterization of antisense mediated transcriptional gene silencing. Julie-Anna Benjamin (Université de Sherbrooke) showed evidence for a new mechanism of regulation, which depends on iron states. It appears that *acnB* mRNA is regulated both by the small RNA RyhB and the Fe-dependent mRNA binding protein Apo-AcnB. Jamie Van Etten (University of Wisconsin, Madison) demonstrated that human PUF-mediated deadenylation regulates protein expression and mRNA degradation.

At the end of the day, the RiboClub student representatives presented the best student seminar award of the year. The award was given to Dr. Dariel Ashton-Beaucage (Université de Montréal), who described his work on the characterization of the control of the exon junction complex on the splicing of MAPK and other long intron-containing transcripts in *Drosophila*.

At the beginning of the third day, the laureates of the CSBMCB annual awards were unveiled; these were Dr. Gerardo Ferbrege (Université de Montréal) and Dr. Benjamin J. Blencowe (University of Toronto). Gerardo Ferbrege used an algorithm that they devised, MultiTar, to design artificial micro RNA to target selected groups of genes. He gives hope to exploiting therapeutically the natural ability of micro RNAs to target multiple genes. Benjamin Blencowe gave us a review of the work done on characterizing alternative splicing and presented his recent work on the discovery and characterization of alternative splicing events that control transcriptional networks.

The seventh session was entitled "Studying the dynamics of a single RNA molecule in vitro" chaired by Dr. Joseph Puglisi (Stanford). Dr. Puglisi discussed their investigation of translation initiation in both prokaryotic and eukaryotic organisms using real time single-molecule methods to probe conformational and compositional dynamics. Dr. David Rueda (Wayne State University, Detroit) talked about the RNA folding memory effects. Due to the high barrier height of interconversion, RNA can remain trapped in intermediate forms for a long time. They use a combination of laser-induced temperature jump kinetics and single molecule detection to monitor the interconversion between the subpopulations of hairpin ribozyme and to calculate the corresponding energy barriers. Patrick St-Pierre (Université de Sherbrooke) gave us a better understanding of the influence of RNA-ligand interactions in the context of purine riboswitches. Satoko Yoshizawa (University of Tokyo) presented us with a method, on-chip digitalized cell-free protein synthesis (d-CFPS), which allows a further step towards the miniaturization of protein chips for the generation of arrays with extremely high densities in the micro or submicrometer scale.

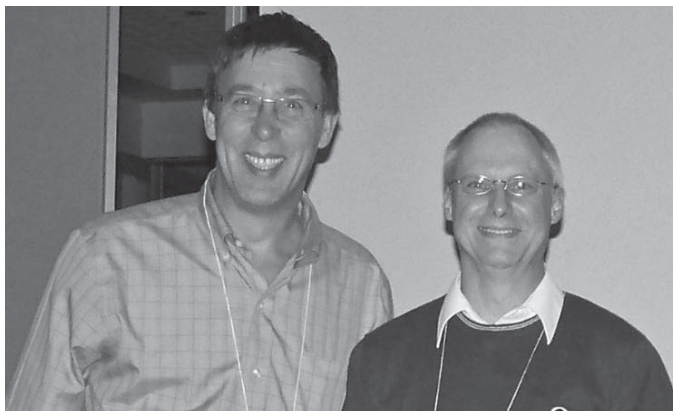
The final session dealt with single molecule RNA studies in vivo chaired by Dr. Robert Singer (Albert Einstein, New York). Dr. Singer revealed to us a novel regulatory mechanism of mRNA decay and mitotic division. He showed that SWI5 and CLB2 mRNA decay was regulated by the promoter sequence through mitotic exit network kinases. Dr. David Grünwald (Delft University) presented us with his ongoing work on mRNA export, both in yeast and mammalian cells using super-registration microscopy and the first data on fast 3D imaging to reveal the routes taken by RNA to reach the nuclear periphery. Dr Daniel Zenklusen (Université de Montréal) summarized recent advances in single molecule RNA imaging approaches that have facilitated single molecule studies in cells and has also illustrated how we can apply different single molecule techniques to determine the mechanism and kinetics of different processes along the gene expression pathway, in particular transcription and mRNA export. Dr. Raymond J. Wellinger (Université de Sherbrooke) presented his work on the monitoring of TLC1 transcription, localisation, dynamics and degradation during the cell cycle and also

assessing the different factors involved in these crucial events.

To close the meeting, Dr. Jennifer A. Doudna (University of California, Berkeley), recipient of the RiboClub student choice seminar award, discussed their recent work uncovering the molecular basis for small RNA production and targeting in bacteria. She showed exciting new molecular structures of the clustered regulatory interspaced short palindromic repeats (CRISPR) machinery for targeting nucleic acids.

Additional highlights of the meeting were the poster sessions, the banquet, the award presentation, the musical interludes, and the dance night.

Scenes from the 54th Annual Meeting, Orford, Québec 2011



▲ Past-President and Meeting Organizer Jean-Pierre Perreault with CSMB President Jim Davie



▲ The 54th CSMB Meeting was held jointly with RiboClub, which is a yearly meeting of RNA scientists from Canada and the Eastern US. There was an excellent turnout for this year's theme: "Studying RNA One Molecule at a Time"



▲ Breakfast was also a great opportunity to catch up with colleagues and friends



▲ Fiona Fitzgerald presents the GE Healthcare New Investigator Award to Gerardo Ferbeyre (U. de Montréal)



▲ Benjamin Blencowe (U. Toronto) receives the Senior Investigator Award from Jean-Pierre Perreault



▲ CSMB Board Members gather for a photo-op. From left: Randy Johnston, Jean-Pierre Perreault, Jim Davie, Wafaa Antonious and Vince Duronio



▲ Scenes from the gala banquet



▲ Scenes from the gala banquet



▲ Scenes from the gala banquet



▲ Relaxing during the poster sessions



▲ Meeting attendees enjoying the setting of Hotel Chéribourg at the foot of Mont Orford, Québec

Poster Award Winners 54th Annual Meeting

Lara Ajamian

McGill University
Dept. of Exp. Medicine
Supervisor: Andrew Mouland
First Prize

Xianying Amy Cui

University of Toronto
Dept. of Biochemistry
Supervisor: Alex Palazzo
Jake Duerkson Poster Award

Kohila Mahadevan

University of Toronto
Dept. of Biochemistry
Supervisor: Alex Palazzo
CSMB Poster Prize

Hubert Salvail

Université de Sherbrooke
Dept. de Biochimie
Supervisor: Eric Masse
Second Prize

Chantal Brosseau

Université de Sherbrooke
Dept. de Biologie
Supervisor: Peter Moffett
CSMB Poster Prize

Eileen Shaw

McGill University
Dept. of Exp. Medicine
Supervisor: Anne Gatignol
CSMB Poster Prize

Maxime Simoneau-Roy

Université de Sherbrooke
Dept. de Biologie
Supervisor: Daniel Lafontaine
Second Prize and Sherbrooke-Innople prize

Cristina Gareau

Université Laval
Supervisor: Rachid Mazroui
CSMB Poster Prize

Maude Tremblay-Létourneau

Dept. de Biochimie
Université de Sherbrooke
Supervisor: Martin Bisaillon
CSMB Poster Prize

Jacqueline B. Pierce

University of Guelph
Supervisor: Dev Mangroo
Biochemical Journal Prize

Mathieu Lavoie

Université de Sherbrooke
Dept. de Microbiologie
Supervisor: Abou Elela Sherif
CSMB Poster Prize



Happy Poster Award Winners receive their cheque

Travel Award Winners 54th Annual Meeting

Caijie Zhao City University New York

Supervisor: Nancy Greenbaum
(RNA Society Award)

Jamie Van Etten University of Michigan

Supervisor: Aaron Goldstrohm
(RNA Society Award)

Erin Garside University of Alberta

Supervisor: Andrew MacMillan
(RiboClub Award)

Julia Claverol Scripps Institute

Supervisor: Martha Fedor
(RiboClub Award)

Katherine Cleroux IRCM

Supervisor: Marlene Oeffinger
(CSMB Award)

Arnold Dopgwa Université de Montréal

Supervisor: Christian Baron
(CSMB Award)

Christina Gareau Université Laval

Supervisor: Rachid Mazroui
(CSMB Award)

Evelina de Laurentiis University of Lethbridge

Supervisor: Hans Joachim Wieden
(CSMB Award)

Laura Keffer-Wilkes University of Lethbridge

Supervisor: Ute Kothe
(CSMB Award)

Shanker Panchapakesan Simon Fraser University

Supervisor: Peter Unrau
(CSMB Award)

Samir Rahman Université de Montréal

Supervisor: Daniel Zenklusen
(CSMB Award)

Lara Ajamian McGill University

Supervisor: Andrew Mouland
(CSMB Award)

Our sincere thanks to New England BioLabs for sponsoring four awards and Fisher Scientific for one award.

2011 GE Healthcare New Investigator Award

Downregulation of E2F target gene expression during oncogene induced senescence: mechanisms and therapeutic potential.



Gerardo Ferbeyre

Département de Biochimie
Université de Montréal

Gerardo Ferbeyre, Véronique Bourdeau, Mathieu Vernier, Marie-France Gaumont-Leclerc and Olga Moiseeva.

Abstract

Senescence is a permanent cell cycle arrest where cells remain viable. The molecular mechanisms that prevent these cells from re-entering the cell cycle and remain viable are beginning to emerge. The retinoblastoma family of proteins forms complexes with E2F transcription factors repressing the expression of genes required for cell cycle progression. This event characterizes both a transient cell cycle arrest and senescence. However, senescent cells are refractory to growth factors and other proliferation signals that induce E2F-gene targets. We found that the promyelocytic leukemia protein PML organizes Rb/E2F repression complexes during senescence and inhibits the expression of a particular subset of E2F target genes, with a bias for DNA repair and DNA replication genes. This process has two consequences: first Rb/E2F complexes in PML bodies are protected from the disruptive action of CDK dependent phosphorylation, which largely occurs in the nucleoplasm and can be reversed by phosphatases that localize to PML bodies. Second, the repression of a subset of E2F targets generates an imbalance in the normal E2F transcriptional program leading to DNA damage and p53-dependent transcription of proteins that further reinforce the senescence program. Drugs mimicking the PML-dependent suppression of E2F-target gene expression may help to reinstall the senescence program in tumor cells. Since drugs capable of targeting multiple proteins are not yet feasible, we designed an RNA based strategy to target multiple genes, suggesting the possibility of RNA based therapy to induce senescence in tumor cells.

Introduction

The transformation of normal cells into tumor cells requires genetic or epigenetic changes leading to activation of oncogenes and inactivation

of tumor suppressor genes¹. Tumor suppressors curtail cell transformation by detecting oncogenic threats and organizing intrinsic tumor suppression programs that include apoptosis and cell senescence². One general mechanism by which oncogenes signal to tumor suppressors is the DNA damage response³⁻⁶. However, the full spectrum of metabolic and gene expression activities linking oncogenic action to tumor suppressors remain to be identified^{5,6}. For example, oncogenes can activate the retinoblastoma protein independently of the DNA damage response⁶, or activate p53 via p19ARF^{7,8}. In addition, the gene expression signature of cells forced to senesce after oncogene expression revealed a pattern that clearly indicates the activation of a program of cytokine signaling, which includes the expression of many cytokines, cytokine receptors and signaling molecules⁹⁻¹¹. How the DNA damage response, p53, Rb and cytokine signaling work together during oncogene induced senescence is not known.

One critical component of the senescence tumor suppression response is the interferon responsive gene PML. PML is activated by oncogenic stress and interacts with both p53 and the retinoblastoma protein to regulate senescence^{9,12-19}. Our recent studies revealed that PML, Rb and p53 are interlinked in positive feed-back loops that sustain the functions of each other and inhibit the expression of E2F target genes²⁰. Here we present a unifying model of cell senescence based on our results and discuss its therapeutic implications.

PML, a cytokine signaling gene regulating senescence

The promyelocytic leukemia protein, PML, was discovered as a gene rearranged and inactivated in promyelocytic leukemia. The links between PML, senescence and regulation of the tumor suppressors p53 and Rb were recently reviewed¹⁰. In particular, PML not only serve as a convenient marker to follow the senescence process but also is sufficient to trigger senescence. It was previously thought that PML was induced via p53 after oncogene expression. Since p53 is induced by the DNA damage response in this situation, that places PML downstream of DNA damage. Intriguingly, Vernier, Bourdeau and

colleagues in my laboratory found that PML is also capable of activating the DNA damage response leading to modification of p53 catalyzed by DNA damage-dependent kinases²⁰. They also revealed a positive feedback loop between PML and p53 that reinforce their mutual activation. They also worked out the mechanism by which PML induces the DNA damage response. Large-scale gene expression analysis of PML-expressing cells revealed a defect in the expression of genes in all major DNA repair pathways (Figure 1). On closer inspection, all these genes are recognized E2F targets and a role for E2F target gene expression has been recognized before^{21,22}. Several E2F targets that play a role in DNA replication were also downregulated in PML expressing cells but many other E2F targets were not decreased. We concluded that PML expression lead to a decreased expression of a subset of E2F targets²⁰. A similar pattern of E2F target gene downregulation was observed during senescence induced by oncogenic ras²³. Hence, senescence involves a repression of E2F target genes and PML, Rb and p53 converge their functions for silencing these genes.

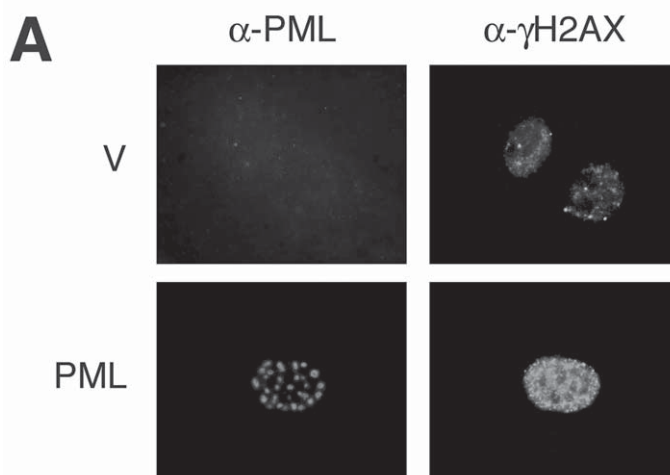
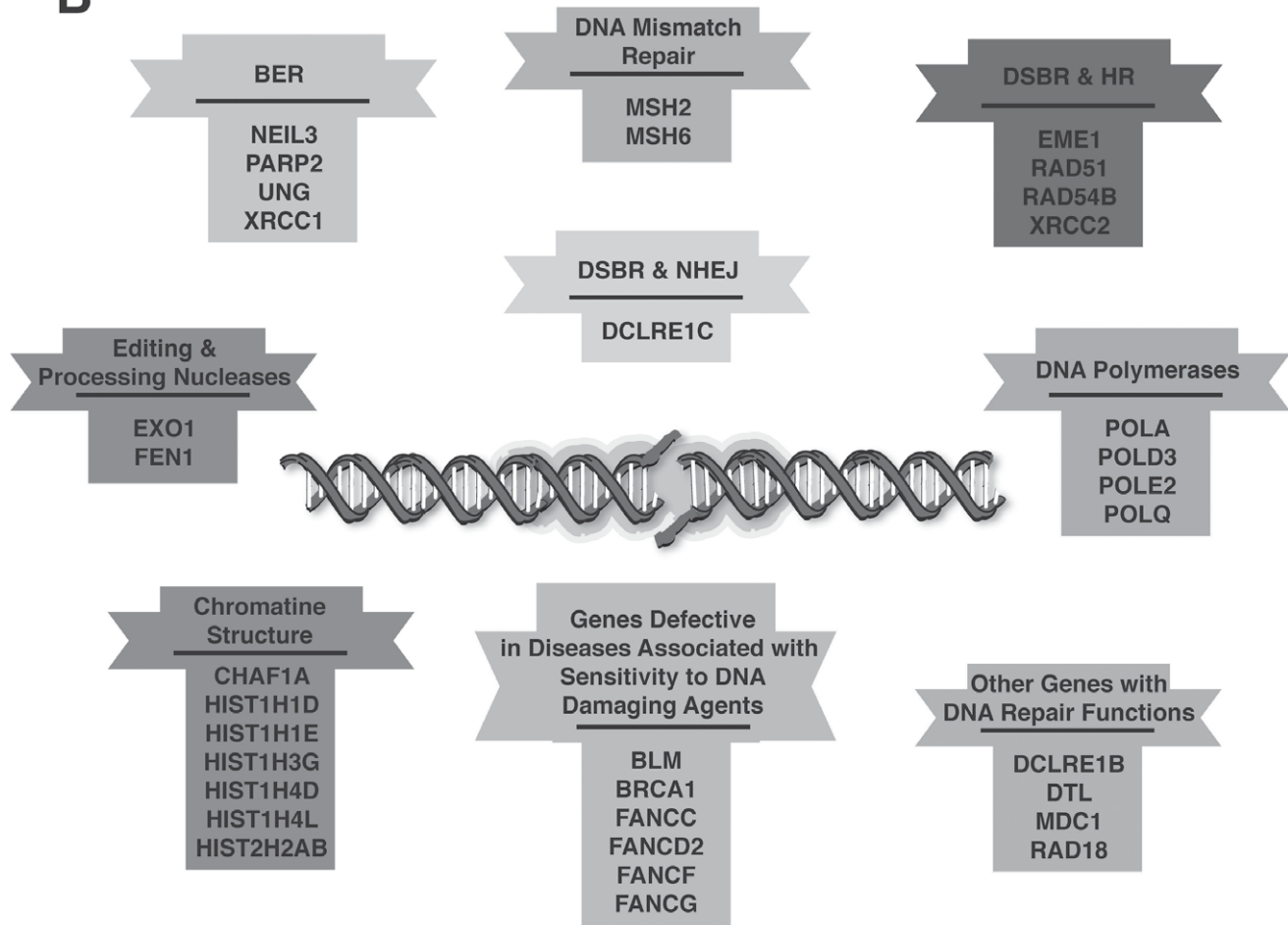


Figure 1. DNA damage and repression of multiple DNA repair genes by PML. A) Immunofluorescent images showing accumulation of DNA damage foci in PML-expressing cells. B) DNA repair pathways affected by PML: BER (base excision repair), DSB (double stranded break repair), HR (homologous recombination), and NHEJ (non homologous end joining).

B

Localization of Rb/E2F complexes in PML bodies during cellular senescence

The ability of PML to regulate E2F target genes was accompanied by a remarkable colocalization of E2F1, E2F2 and E2F3 in PML bodies. The Rb tumor suppressor and the heterochromatin protein HP1 were found localized in the same compartment using confocal microscopy. This suggests that during senescence Rb/E2F/HP1 complexes function in association to PML bodies. Inactivation of Rb using the oncoprotein E7 disrupts the PML/E2F complexes and reversed the repression of E2F targets and the senescence phenotype. Unlike oncogenes that increase the ability of human tumor cells to form tumors, PML can also trigger senescence in tumor cells lines via the same

mechanisms - localization of Rb/E2F complexes into PML bodies and repression of E2F target genes²⁰. In addition to putting together Rb and E2F in PML bodies, PML recruits the protein phosphatase PP1A, which dephosphorylates the retinoblastoma protein protecting it from the inactivating phosphorylation catalyzed by the cyclin dependent kinases²⁰.

The repression of E2F targets by PML could be the consequence of sequestration of E2Fs into PML bodies away from their target binding sites. Alternatively, the promoters of E2F-genes could be recruited to the vicinity of PML bodies by the E2F/Rb complexes. We used chromatin immunoprecipitation of E2F and PML during

senescence and revealed that they were both associated with the promoters of E2F target genes found repressed in senescent cells²⁰. This suggests that PML helps to organize Rb/E2F mediated repression during senescence by a direct interaction with the promoters of E2F target genes.

Consistent with a role of PML in E2F targets repression, the heterochromatin proteins HP1²⁴ the histone variant MacroH2A²⁵ and the histone chaperones ASF1 and HIRA¹⁹ localize to PML bodies shortly after oncogene expression in primary cells but not at later times. This suggests that these proteins transit through PML bodies to form a repressive heterochromatin on E2F promoters. Why PML-organized gene silencing involves moderate silencing of only a fraction of E2F targets is not yet known. However, the process is sufficient to trigger senescence because overexpression of E2F or disruption of Rb restore the expression of E2F targets and induce cell proliferation. The association of moderate silencing of multiple genes and cell phenotypes is typical of miRNA actions²⁶ suggesting that PML-organized gene silencing may involve nuclear-acting miRNAs or a similar RNA based silencing mechanism.

Benign tumors of the prostate express high levels of PML bodies and low levels of E2F targets

PML bodies are mostly absent from most human malignant tumors^{27,28}. PML is an inducible protein^{14,29}, so the number of PML bodies in resting tissue is very low. A comparison of tumor tissues with normal tissues is not very informative because PML bodies are not abundant in non-stressed cells. However, it has been proposed that benign neoplasms represent the *in vivo* counterpart of the process of oncogene-induced senescence^{30,31}. We therefore compared samples from benign prostatic hyperplasia with normal prostate tissues and prostate adenocarcinomas using tissue microarrays developed in the laboratory of Fred Saad and Anne Marie Mes-Masson. We found that BPH samples were strongly stained for the senescence marker p16INK4a and contained abundant PML bodies. Normal cells contained just a few PML bodies (less than 4) and most malignant tumor cells lacked PML bodies. In the few malignant tumors we observed PML bodies,

their number was that of normal cells and never reached the number found in BPH²⁰. Consistent with the ability of PML to repress a subset of E2F targets, we found a reduced expression of this gene class in several published microarrays of BPH samples in comparison with tumor cells²⁰.

Senescence by downregulating E2F functions: RNA mediated anticancer therapy

To mimic PML actions we need compounds that can target simultaneously several E2F targets. There are no obvious structural identities between the set of E2F genes repressed in senescence and the chemistry for designing chemical agents that target several proteins is not yet developed. On the other hand, natural miRNAs seems to have evolved to do just that, downregulate multiple genes using rules of RNA-RNA recognition²⁶. A problem with this strategy is that natural miRNAs targeting a subset of E2F targets are not yet discovered and they may not exist at all. MiRNAs control development and differentiation and whether they have been optimized to regulate senescence is not known. To circumvent this problem we decided to use the known rules of miRNA action to design artificial miRNAs that can potentially target a desired gene set. The algorithm was named MultiTar and first tested *in silico*. When MultiTar is presented with a set of genes known to be regulated by a natural miRNA it finds this miRNA among its solutions³². To obtain an experimental validation, we decided to design artificial miRNAs against E2F1, 2 and 3. We tested these miRNAs in human fibroblasts and found that they reduced E2F1-3 mRNA levels and E2F target gene expression. They were also capable of inducing senescence in a significant fraction of the cells. In addition, our artificial miRNAs reduced the proliferation of prostate cancer cells³². Future studies will involve the generation of artificial miRNAs against subsets of E2F genes downregulated in senescent cells and upregulated in cancer cells. We expect to validate combinations of E2F targets that need to be inhibited to induce senescence in human tumors.

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2011 CSMB Senior Investigator Award Article

An exon-centric perspective



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Setting the stage for exon-resolution exploration on a genome-wide scale

The completion of the draft version of the human genome sequence in 2001 led to the surprising revelation that metazoan organisms with vastly differing complexity have comparable numbers of protein coding genes. In particular, the nematode worm *C. elegans*, which consists of around 1000 different cells, was shown to contain approximately 19,000 protein coding genes, whereas humans, which have over 50 trillion cells, including thousands of distinct types of neurons, were estimated to have on the order of 20,000-25,000 protein coding genes (Consortium, 1998; Lander et al., 2001; Venter et al., 2001). It was immediately appreciated that processes capable of greatly diversifying the repertoires of functional RNAs and proteins must account for the dramatically increased biological complexity associated with the evolution of vertebrate species. Alternative splicing, the process by which pairs of splice sites in precursor mRNA are differentially selected to produce distinct mRNA and protein isoforms, was proposed to play a major role in establishing such complexity.

Although researchers in the '80's and 90's had identified and characterized many biologically important alternative splicing events, the prevalence and general importance of this process was far from clear. With the generation of sequence data from human and mouse genomes and large collections of full length and expressed sequence tag (EST) cDNAs, it began to emerge that alternative splicing was far more widespread than previously appreciated (Modrek et al., 2001). With this realization, we became interested in developing profiling technologies that would enable the large-scale discovery and characterization of alternative splicing events. Our goals were several-fold: (1) To systematically discover and quantify cell, tissue and condition-specific alternative splicing events, (2) To determine whether sets of genes containing co-regulated alternative splicing events function in common processes and pathways, (3) To

use information from quantitative alternative splicing profiling data and computational modeling to reliably predict combinations of cis-regulatory elements - or the “splicing code” - that controls splicing, and finally (4) To use alternative splicing profiling data to identify alternative exons that have key functions in development and disease.

Our vision at the time was to combine information from high-throughput experimental and computational strategies in ways that would ultimately facilitate an exon-level resolution, or “exon-centric”, understanding of gene function and regulation, and also to apply this knowledge in useful ways. This review provides an account of research efforts from our group and others during the past decade that have strived to reach these goals.

A system for the global-quantitative profiling of alternative splicing

Around 2001, we began to explore different methods for profiling alternative splicing on a global scale. After extensive testing of various platforms and “home brew” approaches, and after running into all manner of technical hurdles, our work towards developing an effective system finally began to take shape in 2003. Our project was given a major boost by the arrival of Qun (Sandy) Pan, a talented bioinformaticist who joined my group in 2002, and by forging collaborations with Tim Hughes, who had been recruited to the Banting and Best Department of Medical Research (BBDMR) from Rosetta Inpharmatics (later acquired by Merck) in 2001, and with Brendan Frey, a machine learning researcher in the Department of Electrical and Computer Engineering at the University of Toronto.

As a postdoctoral researcher at Rosetta, Tim had played a major role in the development of high density oligonucleotide microarrays fabricated using an ink-jet printing process (Hughes et al., 2001). This reliable and highly flexible system was subsequently licensed to Agilent Technologies, and we chose to employ it in our work on alternative splicing. Tim worked with us to design sets

of oligonucleotide probes optimized for the detection of exons and splice junction sequences. A collaboration with Brendan and his group members, Ofer Shai and Quaid Morris (now a faculty member in the BBDMR), led to the development of a Bayesian network model that accurately predicted alternative exon inclusion levels from signals produced by fluorescently-labeled cDNA hybridized to probes on our microarrays (Pan et al., 2004; Shai et al., 2006). Initial tests of our assembled system indicated that it worked very well. By designing a microarray containing sets of probes for monitoring over 3,000 cassette alternative exons in mouse cells, we then used our system to profile the inclusion levels of these exons across ten physiologically diverse mouse tissues (Pan et al., 2004) (Figure 1).

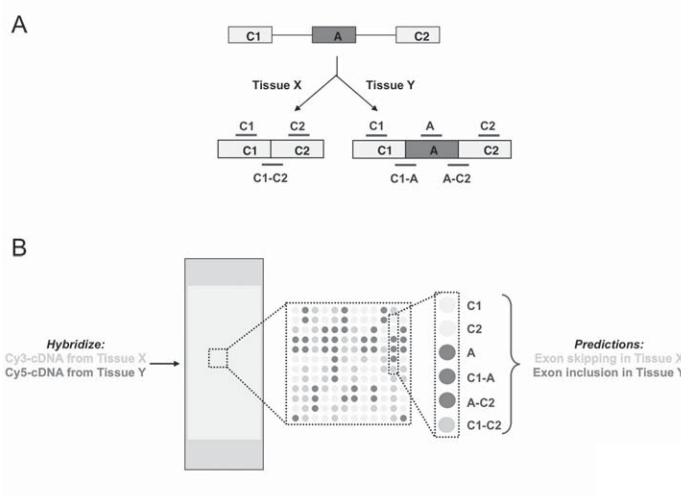


Figure 1. Microarray Profiling of Alternative Splicing (AS) (A) A set of six oligonucleotide probes, one each targeted to constitutive (C1 and C2) and alternative (A) exons, and three targeted to splice-junction sequences (C1-A, A-C2, and C1-C2), permits the quantitative profiling of a cassette alternative exon between two different tissue types (X and Y). In the example shown, the cassette alternative exon is skipped in tissue X and included in tissue Y. Figure adapted from (Pan et al., 2004). (B) Hypothetical hybridization pattern obtained from microarray profiling of AS using Cy3-labeled tissue X cDNA (light grey) and Cy5-labeled tissue Y cDNA (dark grey). Light grey and dark grey spots indicate detection of signals from probes hybridized to the labeled cDNA from tissues X and Y, respectively. White spots indicate detection of signal from splice junctions that

are expressed in both tissues X and Y. Data processed using a suitable algorithm from this microarray format can permit the accurate prediction of AS levels for thousands of cassette-type alternative exons (Pan et al., 2004; Shai et al., 2006). Figure adapted from (Blencowe, 2006).

Excitingly, we finally had a system in place that could simultaneously generate thousands of quantitative measurements for alternative splicing levels in mammalian cells. This technical achievement, together with the parallel development of other microarray based systems ((Johnson et al., 2003; Ule et al., 2005); see below) by our colleagues, opened the door to entirely new types of investigation in the splicing field.

Alternative splicing as a discrete regulatory layer

From profiling diverse mouse tissues our first experiment revealed thousands of new tissue-dependent and tissue-independent alternative splicing events. It also demonstrated that the level of inclusion of alternative exons in major tissues is strongly influenced by their evolutionary history. Notably, species-specific exons tend to be weakly included whereas conserved alternative exons typically display variable inclusion levels across tissues. We also observed that widely expressed genes that contain tissue-specific alternative splicing events, in addition to often being conserved, tend to be associated with specific functions; for example, genes with brain-specific alternative splicing events were found to be often associated with neural-specific functions (Pan et al., 2004).

Prior to our initial microarray profiling experiments, an accumulation of evidence had supported the notion that most splicing occurs co-transcriptionally, and research primarily from the work of Alberto Kornblihtt and colleagues in Buenos Aires had demonstrated that at least some alternative splicing events in nascent RNA are influenced by the rate of elongation of RNA polymerase II (Kornblihtt et al., 2004). We were therefore surprised to find from our initial tissue profiling experiments that the

majority of alternative exons that are regulated in a tissue-dependent manner are located in genes that, by and large, do not overlap the genes that are differentially regulated between the same tissues at the transcriptional level (Pan et al., 2004). This finding, which was published within days of similar observations from Christopher Lee's group at UCLA (Le et al., 2004), suggested that differential alternative splicing and differential mRNA expression act largely as a separate layers of gene regulation to establish cell- and tissue-type characteristics (Figure 2).

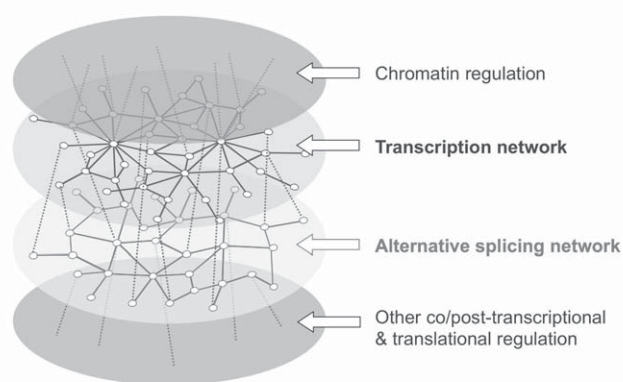


Figure 2. Layers of Coordinated Gene Regulation
Different subsets of genes are regulated at the levels of transcription and AS to define cell-, tissue- and condition-specific patterns of gene-expression. These subsets of genes comprise “layers” of regulatory networks that coordinate specific cellular functions. The dotted lines depict hypothetical interconnections that serve to integrate these and the other layers of gene regulation that are shown. Figure adapted from (Blencowe, 2006).

Within a few years immediately following this work, the deployment of our own and other microarray-based systems for profiling alternative splicing led to the discovery of large sets of differentially regulated exons in discrete groups of genes in a variety of physiologically-normal and disease contexts (Ben-Dov et al., 2008; Calarco et al., 2007a; Moore and Silver, 2008). For

example, by using a microarray containing junction-spanning oligonucleotides manufactured by Affymetrix, Robert Darnell and colleagues at Rockefeller University demonstrated that the neural-specific splicing regulator Nova controls alternative splicing events concentrated in genes with important functions in the synapse and in axon guidance (Ule et al., 2005). By profiling increased numbers of alternative splicing events across a larger set of mouse cell and tissue types and conditions, we found that, overall, brain-specific exons are most highly enriched in genes that function in GTP-based regulation (Fagnani et al., 2007), whereas exons that are differentially regulated in response to T cell activation are most highly concentrated in genes associated with cell cycle control (Ip et al., 2007). Consistent with our initial findings, these studies confirmed that subsets of tissue-dependent exons are significantly enriched in functionally-related genes. They also provided support for the concept of “mRNP operons” proposed previously by Jack Keene and his colleagues, namely, that specific RNA binding proteins post-transcriptionally regulate-functionally related sets of genes (Keene and Tenenbaum, 2002).

Our experiments were thus providing a glimpse into a vast new landscape of conserved regulation organized into “exon networks”. Moreover, in addition to providing a basis for follow-up studies of exon function (see below), we were also beginning to generate a quantity of data that would facilitate computational inference of a splicing code.

Deciphering and applying a splicing code

In 2005, Brendan Frey and I were fortunate to recruit a very talented postdoctoral fellow, Yoseph Barash (now an Assistant Professor at University of Pennsylvania), who had trained at Hebrew University under Nir Friedman, a leading machine learning researcher. Yoseph’s thesis research focused on the computational modeling of transcriptional networks in yeast. With his background in machine learning research and knowledge of gene regulation, he immediately grasped the potential of applying inference-based methods to our alternative

splicing data as a route to deriving a predictive code for RNA splicing, and he began work on this problem in earnest in 2006. At the time, researchers in the field, notably Chris Burge (MIT), Larry Chasin (Columbia University), and Robert Darnell, had devised clever schemes for the computational mining of cis-regulatory sequences in exons and introns that act as enhancers or silencers of splice site selection (Fairbrother et al., 2002; Ule et al., 2006; Zhang and Chasin, 2004). What the field was lacking, however, was an approach to predict the combinations of these and other types of cis-elements that control cell-, tissue- and condition-dependent classes of regulated alternative splicing events.

The computational strategy that Yoseph developed involved two main stages (Figure 3A). The first stage identified confidence-ranked changes in the levels of thousands of alternative exons in data we had generated from microarray profiling 27 diverse mouse tissue types (Barash et al., 2010a; Fagnani et al., 2007). Next, from sequence analysis of these and other splicing events, and from a literature-based survey, a compendium of over one thousand experimentally-defined and putative cis-acting features associated with splicing was assembled. In the second stage, combinations of cis-acting features in the compendium were assembled in an iterative manner to define the specific combinations that are maximally predictive of tissue-dependent alternative splicing changes defined in the first stage of the strategy. After several years of intensive work and countless meetings between our groups, Yoseph and Brendan had developed a computational approach that appeared to reliably predict tissue-dependent alternative splicing patterns in our profiling data (Barash et al., 2010b). Globally, the inferred combinations of cis-regulatory features, or splicing code, revealed that critical cis-elements are often located deeper into introns than previously appreciated, and that complex combinations of cis-elements are generally required to control individual tissue-dependent alternative splicing events. The next phase of the project was to experimentally test predictions produced by the code, and also to use it to discover new biology.

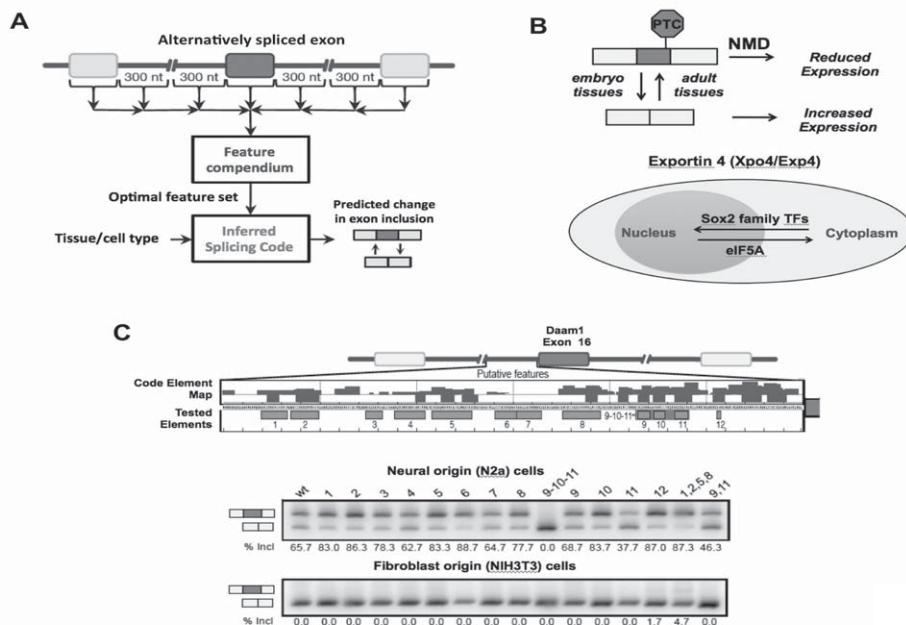


Figure 3. Assembling and Applying a Splicing Code

(A) The code extracts RNA features (e.g., known/new/short motifs and transcript structure features) from any exon of interest (dark grey), its flanking exons (light grey), and from the intervening intronic sequences (dark grey). It then predicts whether or not the exon is alternatively spliced, and whether its inclusion level is increased or decreased in a given tissue, relative to others tissues. (B) The code correctly predicts a class of premature termination codon (PTC)-introducing exons that activate nonsense-mediated

mRNA decay (NMD) when included in adult tissues, but which allow mRNA expression when skipped in embryonic tissues. *Exportin4* (*Xpo4*, also known as *Exp4*), a nuclear export receptor for the translation initiation factor eIF5A46 and nuclear import receptor for SRY-related HMG-box (Sox) family transcription factors, is an example of a gene containing this type of exon (refer to main text for details). (C) The code correctly predicts a set of regulatory elements in the intron upstream of exon 16 of the *Daam1* gene to be associated with the neural-specific increased exon inclusion. Code-selected cis-elements from the feature compendium and also from an unbiased motif set (dark grey blocks) were selected for testing (medium grey blocks). Fifteen minigene reporters with single or combined segment substitutions were constructed and transfected into neuroblastoma (N2A) and epithelial (NIH-3T3) cells. RT-PCR assays were performed using primers specific for exons 15 and 17 of *Daam1* to assess the effects of the substitution mutations on inclusion of exon 16 in the N2A and NIH-3T3 cell lines. (Figures in A-C adapted from (Barash et al., 2010b))

John Calarco, a very talented graduate student working in my group (now a Bauer Fellow at Harvard University), set about to test various inferences made by the code. He confirmed that it performed well in predicting tissue-specific alternative patterns in transcripts that had not been analyzed in our profiling data, and that it also accurately pinpointed combinations of critical cis-regulatory elements in intronic sequence that direct individual tissue-specific alternative splicing events (Barash et al., 2010b) (Figure 3B). John further confirmed a class of regulatory alternative splicing events predicted by the code, namely a small subset of cassette exons that introduce premature termination codons that elicit nonsense mediated mRNA

decay in adult tissue transcripts, but which are skipped during embryogenesis to allow increased mRNA expression (Barash et al., 2010b) (Figure 3C). John's experiments demonstrated that this mode of regulation is important for controlling the differential expression of *Xpo4*, a nuclear import/export receptor that regulates the nuclear to cytoplasmic levels of key transcription and translation factors during development, and which has been shown to trigger cancers if inappropriately expressed in adult cells (Zender et al., 2008).

Inferring programs of gene regulation from genomic sequence alone is widely considered to be a holy

grail in biology. Such knowledge would transform our understanding of the complex, interconnecting mechanisms that control gene expression during development and in response to environmental and experimentally-induced perturbations. An obvious application of this approach is the prediction of the effects of genomic sequence variation and disease mutations on gene regulation and function, which in turn would likely facilitate the development of new strategies for disease diagnosis and treatment. While it was satisfying for our team to decipher part of the overall genomic regulatory code, and demonstrate that the problem of regulatory “code cracking” is tractable given the right combination of experimental data and inference modeling, our success was facilitated by the concentration of splicing regulatory elements within the relatively short lengths (average of ~120 nucleotides) of exons, and the immediate ~ 300 nucleotides of flanking intronic sequence (Barash et al., 2010b), which greatly reduced the computational complexity of the problem. By contrast, extending similar strategies to solving a transcriptional regulatory code in mammalian species does not appear to be currently feasible given that there are often tens to hundreds of thousands of nucleotides of DNA sequence surrounding critical regulatory elements, and insufficient *a priori* knowledge, or the computational capacity, to model the location and activity of these elements.

Our initial work directed at deciphering a predictive splicing code represented a new phase of research for our groups. Improvements to computational inference methods coupled with the availability of much larger alternative splicing profiling datasets (see below) from a wider spectrum of cells, tissues, and conditions, is facilitating the development of more accurate and complete codes. At the time of writing, we are close to inferring and characterizing codes for humans and several other species.

Transcriptome profiling by high-throughput RNA sequencing

While we were enjoying the fruits of the hard work that went into establishing our microarray-based system for profiling alternative splicing, rival technologies were being developed at a rapid rate. Suddenly, high-throughput, massively parallel short-read sequencing was on the scene in 2008. Short read sequence data generated by a new generation of sequencing machines was offering the possibility of not only providing unambiguous and unbiased detection of expressed RNA sequences, but also a more accurate method (based on simple read counting) for quantifying relative levels of different transcripts. We were therefore very eager to try out this new technology. After a phone call to Illumina Inc., a company based in San Diego that was manufacturing commercial sequencers based on Solexa technology, Gary Schroth, the highly enthusiastic Senior Director of Research Applications, was kind enough to share some of his group’s recently generated human tissue RNA sequencing (RNA-Seq) data for us to analyze.

Within several frenetic months, Sandy Pan in my group had developed a computational pipeline for the detection and quantification of alternative splicing using short read data. This pipeline included a searchable reference library comprising all splice junction sequences represented in human cDNA and EST collections, in addition to hypothetical splice junction sequences formed by the simulated joining of all possible 5’ to 3’ combinations of annotated splice sites (Figure 4). It also included an effective method, developed in collaboration with Ofer Shai and Leo Lee (a postdoctoral fellow in Brendan’s group), for discriminating true- from false-positive splice junction-spanning reads. By combining information from the detection of splice junctions from the human tissue RNA-Seq data and from cDNA/EST data, we were able to determine that approximately 95% of human multi-exon genes produce alternatively spliced transcripts, and that most of the resulting isoforms display variable expression across tissues. We also demonstrated that RNA-Seq data can indeed provide a reliable method for quantifying

exon inclusion levels. Thanks to some behind the scenes coordination by Nature journal editors, our results were published on the same day as similar observations from Chris Burge's group (Pan et al., 2008; Wang et al., 2008).

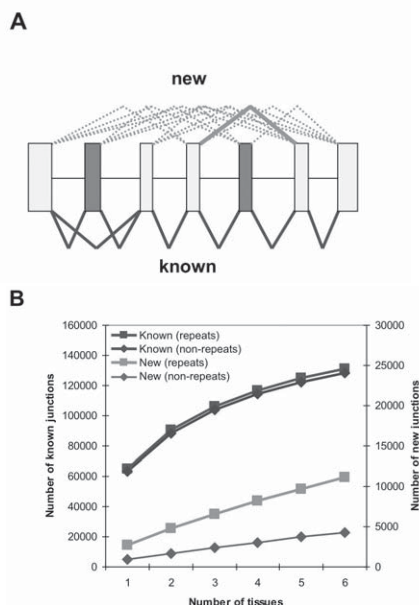


Figure 4. Assessing Human Alternative Splicing Complexity Using RNA-Seq Data
(A) Diagram showing a gene with 'known' splice junctions (black grey lines) supported by cDNA-EST evidence. Dashed grey lines represent all hypothetically possible 'new' splice junctions, and the solid grey lines indicate a new junction detected using Illumina RNA-Seq data. Alternative exons are indicated in dark grey. (B) Numbers of known and new splice junctions detected using RNA-Seq data from human tissues. Each point in the four plots indicates the mean number of junctions detected when comparing data from all possible combinations of the specified numbers of tissues. The above dark grey and below black grey plots show the numbers of detected known junctions when junction sequences that are repeated elsewhere are either included or excluded, respectively. The light grey and medium grey plots show the numbers of new junctions detected when including or excluding repeated sequences. Based in part on these data, it can be estimated that transcripts from over 95% human multi-exon genes contain one or more AS event. From (Pan et al., 2008).

We were soon generating and analyzing RNA-Seq data to identify and characterize networks of alternative exons that are differentially regulated across a variety of physiologically-normal and disease states, as well as networks of exons controlled by specific RNA and chromatin regulatory factors (Luco et al., 2010; McIlwain et al., 2010; Saltzman et al., 2011; Voineagu et al., 2011). However, despite having uncovered enormous alternative splicing complexity, that different subsets of exons form co-regulated networks in functionally related genes, and key features of the splicing code that predict different classes of regulated exons on a genome-wide scale, we were still far from being able to address one of our major original goals: to use alternative splicing profiling data to identify and characterize important functional roles for alternative splicing events.

Work from several groups including our own had shown that despite the human and mouse genomes sharing essentially the same repertoire for genes, most alternative splicing events detected in the two species are not conserved (Modrek and Lee, 2002; Pan et al., 2005; Sorek et al., 2004; Thanaraj et al., 2003). Moreover, alternative splicing profiling work from John Calarco in my group had shown that although human and chimpanzee protein coding genes share over 99% identity, surprisingly, 6-8% of alternative exons are differentially spliced in physiologically-equivalent tissues in these two species (Calarco et al., 2007b). Collectively, these observations implied an important and widespread role for alternative splicing in the evolution of species-specific differences. Indeed, over the years, interesting examples of alternative splicing events that control species-specific characteristics have been uncovered (eg. (Gracheva et al., 2011; Terai et al., 2003)). However, to begin to address the question of exon function on a large-scale, we focused our attention on conserved alternative splicing events that we had identified in specific co-regulated exon networks. Since this work is in progress, I will finish this account by summarizing a few of our most recent findings, as well as possible future directions in this area.

Surprising new functions for alternative splicing events

By applying our transcriptome profiling tools and data to identify alternative splicing events that are differentially

regulated between embryonic stem cells (ESCs) and differentiated cells, Mathieu Gabut, a gifted postdoctoral fellow in the group, discovered a highly conserved exon in the forkhead family transcription factor FOXP1 that is included specifically in ESCs, but skipped in differentiated cells (Gabut et al., 2011) (Figure 5). Inclusion of this exon was predicted to change critical amino acid residues in the forkhead DNA binding domain that recognizes the FOXP family consensus binding site GTAAACA. Indeed, using dsDNA binding microarrays produced in Tim's group, we were able to show that inclusion of the ESC-specific exon in FOXP1 changes its DNA binding preference such that it recognizes a distinct consensus sequence. Mathieu went on to show that the FOXP1 ESC-specific splice variant, "FOXP1-ES", but not the canonical isoform

of FOXP1, is required for stimulating the expression of several key pluripotency transcription factor genes, including OCT4 and NANOG, and that it is also required for the maintenance of the self-renewing, pluripotent state of mouse ESCs (Figure 5). In work performed in collaboration with local colleagues Jeffrey Wrana and Andras Nagy (Samuel Lunenfeld Research Institute, Mount Sinai Hospital and University of Toronto), we also demonstrated that FOXP1-ES is required for the efficient reprogramming of somatic cells to induced pluripotent stem cells (iPSCs) (Gabut et al., 2011). Remarkably, therefore, a single AS "switch" can regulate the core transcriptional network required for controlling transitions between pluripotent and differentiated states of ESCs.

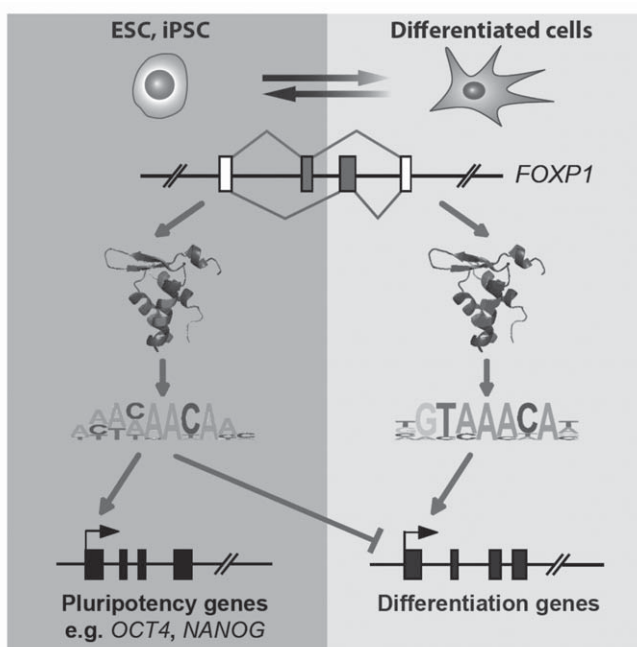


Figure 5. An AS Switch Regulating Embryonic Stem Cell Pluripotency and Reprogramming

In pluripotent embryonic stem cells (ESCs) or induced pluripotent stem cells (iPSCs), inclusion of exon 18b in FOXP1 transcripts results in the expression of "FOXP1-ES", which preferentially binds to a distinct set of DNA motifs. This event promotes the expression of key transcription factors including OCT4 and NANOG required for the maintenance of pluripotency, and it represses genes required for ESC differentiation. During differentiation, exon 18b is entirely skipped, resulting in the exclusive inclusion of exon 18 and expression of the "canonical" FOXP1 isoform. This leads to a change in DNA recognition, a consequence of which is reduced expression of pluripotency genes and increased expression of genes required for differentiation. Adapted from (Gabut et al., 2011).

In parallel work, members of my group including John Calarco, Bushra Raj and Jonathan Ellis, were busy characterizing a network of mostly conserved brain-specific exons regulated by nSR100/SRRM4, a new neural-specific splicing factor that we had identified and characterized a few years previously (Calarco et al., 2009). Our work had shown that nSR100-regulated exons are concentrated in genes involved in various aspects of neuronal differentiation, and that proteins encoded by these genes are predicted, based on Jonathan's mining of published literature and available proteomics data, to form a highly interconnected protein-protein interaction network (Ellis et al., in press). Most of the nSR100-regulated exons were predicted to overlap disordered regions in proteins, which are known to often form interaction surfaces. Accordingly, Jonathan, together with Miriam Barrios-Rodiles in Jeff Wrana's group, set about using LUMIER, an automated co-immunoprecipitation assay developed in Jeff's group, to systematically determine whether nSR100 regulated exons can modulate interactions with one or more partner proteins in the modeled network. This project, which has just been completed, has indeed provided evidence that many brain-specific exons regulated by nSR100 control interactions between proteins with critical functions in neuronal development (Ellis et al., in press).

Finally, Bushra Raj, another very gifted graduate student in the group, discovered that nSR100 also regulates a neural-specific exon in transcripts from the gene encoding REST, a key transcriptional repressor of genes required for neurogenesis that is active in non-neural cells, but which is inactive in neural cells (Raj et al., 2011) (Figure 6). Bushra's experiments demonstrated that nSR100 directly activates splicing of the neural-specific exon in REST transcripts, and that this alternative splicing switch leads to the expression of a truncated isoform of the protein that lacks repressive activity, thereby allowing expression of neurogenesis genes and neuronal differentiation (Raj et al., 2011).

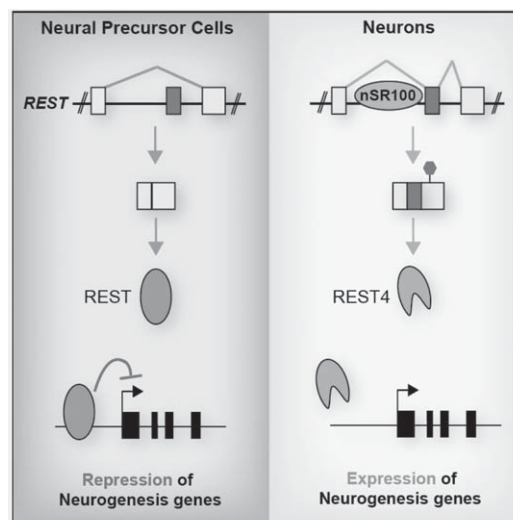


Figure 6. An AS Switch Regulating Mammalian Neurogenesis

The neural-specific Ser/Arg repeat-related protein of 100 kDa (nSR100/SRRM4) negatively regulates REST (also known as NRSF), a transcriptional repressor of genes required for neurogenesis. nSR100 directly promotes alternative splicing of REST transcripts to produce a REST isoform (REST4) with greatly reduced repressive activity, thereby activating expression of REST targets in neural cells. Conversely, REST directly represses nSR100 in non-neural cells to prevent the activation of neural-specific splicing events (not shown). Consistent with a critical role for nSR100 in the inhibition of REST activity, blocking nSR100 expression in the developing mouse brain impairs neurogenesis. Adapted from (Raj et al., 2011).

Similar to the ESC-specific alternative splicing switch in FOXP1 transcripts, the alternative splicing switch controlled by nSR100 in REST transcripts provides another remarkable example of how a single splicing event can function to re-wire transcriptional networks with key roles in vertebrate development. These observations are reminiscent of classic discoveries made a few decades ago of splicing regulators that differentially control the expression of splice isoforms of transcription factors with pivotal roles in the control of sex determination in *Drosophila* (Graveley, 2011; Salz, 2011). These and related findings that have emerged recently (Irimia and Blencowe,

2012), have further demonstrated the tremendous opportunities afforded by combining powerful new transcriptome profiling technologies with computational and experimental methods, to facilitate timely, exon-centric discoveries in biomedical research.

Conclusions

The past ten years has been a period of remarkable progress in the understanding of the complexity and regulation of transcriptomes. Innovation in microarray and sequencing technologies, coupled with advances in computational and experimental biology, have generated detailed global surveys of the expression of mRNA isoforms (as well as non-coding RNAs) across diverse cell and tissue types, developmental stages, and conditions. What has emerged is entirely new insight into exon and other types of co-regulated RNA networks that operate in conjunction with transcriptional and additional layers of gene expression control. Interesting examples of how these layers are coupled and cross-regulate each other are also emerging from these studies. The enormous datasets generated by transcriptome profiling are further providing the raw material to train advanced algorithms designed to infer the complex combinations of sequence features that govern splicing and other RNA processing events. Of critical importance in future studies will be to harness these technologies, together with high-throughput experimental methods, to provide a detailed, exon-centric view of gene function, regulation and evolution. These studies are expected to further facilitate advances in our understanding of human diseases, as well as improved strategies for disease diagnosis and treatment.

Acknowledgements

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Incoming Members of the CSMB Executive Board



James (Jim) R. Davie, President and Past Vice-President

Jim Davie received his B.Sc. and Ph.D. degrees from the University of British Columbia. His post-doctoral training in the area of chromatin structure and function was done in the lab of Dr. Ken van Holde at Oregon State University. Dr. Davie is presently the Scientific Director of the Manitoba Health Research Council, Leader of the Terry Fox Research Institute Prairie Node, and Professor in the Department of Biochemistry and Medical Genetics at the University of Manitoba. He serves on several Editorial Boards of journals publishing in Biochemistry, Cell Biology and Molecular Biology and is Editor of the journal *Biochemistry and Cell Biology*. He has served as a Chair and panel member on CIHR and NCIC/CCSRI Peer Review Committees. His research interests include epigenetic regulation of gene expression in normal and disease (cancer) cells, nuclear matrix structure and function, sub-cellular trafficking of transcription factors and chromatin remodeling complexes, signal transduction pathways, chromatin structure and function, and biomarkers in the early detection of disease. He currently holds a Canada Research Chair in Chromatin Dynamics (Tier 1). Dr. Davie is the current President of the Canadian Society for Molecular Biosciences.

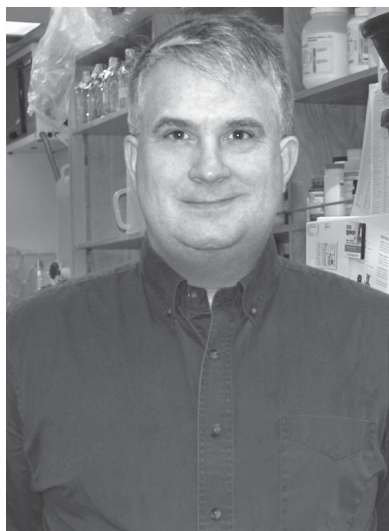


Randall Johnston, Secretary

Dr. Randy Johnston received a BSc degree (1975) from the University of Victoria and his PhD (1980) and postdoctoral training from Stanford University. He has been a faculty member of the University of Calgary since 1984, where he was recruited with funding from the Alberta Heritage Foundation for Medical Research.

For 10 years, he was appointed as the Terry Fox Professor for Cancer Research at The University of Calgary, together with the positions of Director, Southern Alberta Cancer Research Centre and Associate Director (Research), Tom Baker Cancer Centre. He then was appointed as the Associate Vice-President (Research) for the University of Calgary, and subsequently as President of Genome Prairie/Alberta (a not-for-profit corporation dedicated to genomics research as part of the Genome Canada program), before returning full-time in 2006 to his academic position at the University in the Department of Biochemistry and Molecular Biology and his new role as Secretary for the Canadian Society for Molecular Biosciences.

Dr. Johnston's research focuses on cancer genomics and novel viral therapies for cancer that show great promise and are currently being used in clinical trials.



Andrew Simmonds, Councillor

I received the majority of my academic training within Canada. I received my B.Sc. in Honours Genetics from the University of Western Ontario in London. Following this I travelled west to obtain my Ph.D. in Molecular Biology and Genetics from the University of Alberta in Edmonton. Following this, I travelled back east for my postdoctoral training with Dr. Henry Krause at the Banting and Best Department of Medical Research at the University of Toronto. In 2002 I was recruited as an Assistant Professor to the Department of Cell Biology, University of Alberta, Edmonton as both an AHFMR Scholar and a CIHR New Investigator (2002-2007). In 2007 I received an AHFMR Senior Scholar award (2007-2015) and was promoted to the rank of Associate Professor.

Since establishing my research group at the University of Alberta almost ten years ago, my primary research interests are how regulated cytoplasmic localization of mRNAs affects key cellular processes including cell division and cell signalling. My group primarily uses the genetic model system *Drosophila melanogaster* to study these processes as they occur in the cells within developing animals like flies. My group also studies how alternative complexes of the Vestigial-like and TEAD transcription factor proteins regulate genes necessary for the process of cell specification during early embryonic muscle development. Recently, we have undertaken a new project to determine the developmental consequences of mutations that affect assembly or function of motile cytoplasmic organelles involved in lipid metabolism – the peroxisomes. As an “all-Canadian” trained researcher, I have been quite active within the Canadian research community, most recently serving as vice-president of the Genetics Society of Canada. In 2009 I was the main organizer of the 10th Canadian *Drosophila* Research Conference, which attracted over 100 attendees.



Jan Rainey, Councillor

I was born and raised in Kingston, Ontario as a first-generation Canadian (my parents moved to Kingston from Belfast, Northern Ireland in the height of the troubles, and have been there ever since.) From an early age, I played with computers, electronics and chemistry sets. Thanks to a very dynamic high school biology teacher, I found out about this field called biochemistry that seemed to most nicely combine my like of chemistry and my desire to understand living organisms vs. microchips or plain-Jane non-biological molecules. My goal at this point was to become a veterinarian, but I felt that studying biochemistry would be much more suited to my interests than something like animal science.

I decided to go to Guelph for my undergraduate degree – in part because they gave me the best scholarship (just by a hair), in part because the vet school was there,

and probably mostly because I received a personal call from a Math professor at Guelph inviting me to join an amazing, now-defunct, intensive first year program called MPC² (Math, Physics, Chemistry & Computers) that had a maximum enrollment of ~30. After MPC², I went into the Biochemistry co-op program, which was strongly chemistry-based, and spent my first two co-op work-terms at DuPont Canada's Research & Business Development Centre in Kingston. In particular, my second work-term, working with Dr. Geoff Whitfield, provided me with a really amazing and independent research project, awakening me to the potential excitement of research as a career.

During this work-term, a University of Toronto Chemistry faculty member who had recently won an award from DuPont, Dr. Cynthia Goh, came to give a seminar and was nice enough to meet with a lowly 3rd year co-op student from Guelph. (For my project at DuPont I was using some atomic force microscopy (AFM), a technique that Cynthia was and is expert in.) During the course of our meeting, I asked if she ever took co-op students. She said, "No, but I'll hire you" (or something along those lines.) This sealed my third work-term, and I happily spent a fall in her lab at Toronto, using AFM to study self-assembly of collagen. This resulted in my first peer-reviewed paper, with PhD student Matthew Paige (now on the faculty at Saskatchewan) and Cynthia. I was interested in neurochemistry, so set up my fourth workterm at Cornell University where I did whole-cell electrophysiology, molecular biology and cell culture with Dr. George Hess. The result of all of these great co-op work-terms, and an honours thesis in physical organic chemistry with William Tam, was that I fell in love with research well before my finishing my BSc in Dec. 1998. Vet school therefore went absolutely out the window, and I seriously shopped around for graduate programs.

The great experience I'd had in the Goh lab as a co-op student, both in terms of the rapport that Cynthia and I had and in terms of the great lab environment, led me back to U of T for graduate work in Experimental Physical Chemistry. My MSc project, focusing on collagen self-assembly, took advantage of some of my organic chemistry background, involved lots of AFM and was my first exposure to NMR spectroscopy as a research tool. I also got married to an economist named Mary Ellen right after

I handed in my MSc thesis, which was a good deadline for completion! During my PhD, I developed computational methods to predict collagen triple-helix structure for improved understanding of our AFM results. I loved the nature of AFM as an experimental technique, but felt limited by our inability to resolve our biomolecular images at an atomic level. This led me to search out a postdoctoral position in biomolecular NMR, and I applied to work with Dr. Brian Sykes at the University of Alberta. I wasn't sure if an NMR spectroscopist of Brian's caliber would even bother to respond to an e-mail from a naïve grad student from outside of the field, but Brian did indeed respond very favourably (and very fast!) and was nice enough to fly me to Edmonton for an interview (in February, of all months, which still didn't deter me!) and offer me a position.

In January 2003, my wife and I moved to balmy Edmonton, where I joined the Alberta Node of the Protein Engineering Network of Centres of Excellence (PENCE) and where she rapidly found work with Alberta Revenue. It was here that I began to study membrane proteins. A fruitful and stimulating collaboration with Dr. Larry Fliegel led to the first structural data on the mammalian Na⁺/H⁺ exchanger (NHE1), where we made use of segmental approaches to study individual transmembrane domains of NHE1. Brian also set me loose on developing methods for study of membrane proteins by solid-state NMR, particularly in lipid bilayer environments. I was really fortunate to have nearly dedicated access to a wide-bore 300 MHz spectrometer with solids capabilities and to have excellent interactions with a great electronics technologist, Jeff DeVries, who could readily modify NMR probes to handle different sample types and perform my desired experiments! Working in Brian's lab gave me a great grounding in both solution- and solid-state NMR spectroscopy, as well as a strong appreciation for membrane proteins and just how little we really know about them. When PENCE's mandate (and funding) finished, I moved, on paper, to Brian's group in Biochemistry at Alberta. Our first son, Donovan, was born around the time that PENCE ended. Flying to job interviews, in Canadian winter, with a wife in the final trimester certainly added to the stress, but I was delighted to receive an offer from Dalhousie University's Department of Biochemistry & Molecular Biology.

In October 2006, Mary Ellen, Donovan and I moved to Halifax. My research program at Dalhousie combines the interest I developed as a graduate (and undergraduate) student in collagen structure and self-assembly with that I developed as a postdoctoral fellow in membrane proteins. My lab uses a variety of NMR and optical spectroscopy methods, and we are also now (thanks to CFI funded infrastructure) adding AFM methods to the arsenal of biophysical characterization tools that we routinely use. We produce our peptide and protein samples in-house by solid-phase peptide synthesis or cloning and expression methods, as appropriate. I have really enjoyed the collegial and research active environment at Dalhousie, as well as at the neighbouring National Research Council Institute for Marine Biosciences (which houses a nice new 700 MHz NMR spectrometer). Thanks to operating funding from NSERC, CIHR and the Nova Scotia Health Research Foundation, I have been able to develop an active research program studying three major protein systems and supporting a number of trainees at levels from first year undergraduate to postdoctoral fellow. I have also enjoyed introducing and developing a new 4th year/graduate course covering biophysical methodology and teaching in the graduate seminar course that we offer for incoming students. All of my spare time these days seems to be taken up by Donovan and his little brother Malcolm, who was my birthday present in the wee hours of the morning in 2008.

I joined the Board of the then CSBMCB as a Councillor in January 2010. To me, it is critical to support the CSMB's mandate of giving Molecular Biosciences researchers a voice in Ottawa. One way of doing this is to promote increased membership, since our lobby power is proportional to our membership numbers! I have also thoroughly enjoyed attending three Annual Meetings, so far, and feel that these provide a unique forum for the cohesion of our membership (both at the trainee and PI levels) across the country.

News from Member Departments

University of Alberta

Department of Cell Biology

Correspondent: Paul LaPointe

The Cell Biology department at U of A is comprised of 20 primary and cross-appointed investigators whose research interests span a variety of areas in cell biology and with a strong molecular focus in each case. Our Chair, **Rick Rachubinski**, and the entire department of Cell Biology are pleased to welcome our new faculty member, **Ben Montpetit**, who joins us after a successful postdoctoral experience at the University of California at Berkeley. His focus on the mechanism of mRNA export from the



Ben Montpetit

nucleus will broaden the spectrum of research interests in our department which already includes neuroscience, *Drosophila* development, organelle biogenesis and inheritance, protein folding, mitochondrial biology and metabolism, protein and lipid transport, nuclear pore function, the RNAi system, and virology.

Several of our investigators have been recognized in the last year for excellence in their research; Canada Research Chairs were recently awarded to Drs. **Tom Hobman** (Tier I: RNA Viruses and Host Interactions), **Joel Dacks** (Tier II: Evolutionary Cell Biology) and **Sarah Hughes** (Tier II: Cell Adhesion and Proliferation). Dr. **Paul LaPointe** also received an Alberta Innovates - Health Solutions Scholar award. All told, members of our department were successful in attracting nearly \$6 million in operating grants, training awards and visiting speaker awards from provincial and national sources. Our department has 36 graduate students who have been successful in obtaining prestigious fellowships including the Vanier and Dr. Fred Banting and Dr. Charles Best CIHR Graduate Fellowships.



Tom Hobman



Joel Dacks



Paul LaPointe



Sarah Hughes

The Department of Cell Biology hosted a number of high calibre speakers over the last two years. In 2010, Robert Mullen (University of Guelph), Stephen Polyak (University of Washington), Natalie Ahn (University of Colorado), John Archibald (Dalhousie), Mary Baylies (Cornell), John Bertram (University of Calgary), Greg Jedd (National University of Singapore), Scot Leary (University of Saskatchewan), Mo Motamedi (Harvard), William Shain (Seattle Children's Institute), Molly Soichet (University of Toronto), Danny Welch (University of Alabama at Birmingham), and Carmel Hensey (University College Dublin) gave wonderful talks and participated in important discussions with our faculty and trainees. In 2011, we hosted visits by Stephen Robbins (University of Calgary), Eric Jan and Ivan Robert Nabi (UBC), Susan Harkema (University of Louisville), Leonard Neckers

and Jane Trepel (National Cancer Institute), Julie Brill (Hospital for Sick Children), Darren Boehning and Christopher Sullivan (University of Texas), Nevan Krogan (UCSF), and Howard Worman (Columbia). These visits contributed greatly to the already vibrant environment of the Cell Biology Department here at the University of Alberta.

After a difficult transitional period, the Alberta Heritage Foundation for Medical Research has been relaunched as Alberta Innovates - Health Solutions which we hope will continue to support basic and clinical research here in Alberta. Also, the coming months and years promise to bring many changes to how research is funded in Canada. Our faculty members look forward to working through the CSMB to promote basic research across the country at the provincial and national levels; and ensure that the CIHR continues to equitable and adequately fund the important work being done in the Canadian research community.

University of Calgary Department of Biochemistry & Molecular Biology

Correspondents: Drs. Jonathan Lytton & Randy Johnston

The past two years have been a busy and successful period for the Department of Biochemistry & Molecular Biology in the Faculty of Medicine at the University of Calgary. There are 29 primary members plus 30 more joint appointees in the Department, whose research interests range broadly and encompass molecular mechanisms of complex biological processes associated with developmental biology & genetics, cancer biology, immunology, infectious diseases, cardiovascular and neuronal biology. In the most recent year our primary members brought in about \$15 million in operating, infrastructure and training grant funds.

In 2009, **Dr. Jonathan Lytton** took over as Head of the Department, replacing **Leon Browder** who will retire in 2012 after more than 42 years of service to the University of Calgary, the most recent 14 years in the Faculty of



Jonathan Lytton



Leon Browder

Medicine. Leon's contributions to research, education, mentorship and service will be sorely missed, but never forgotten.

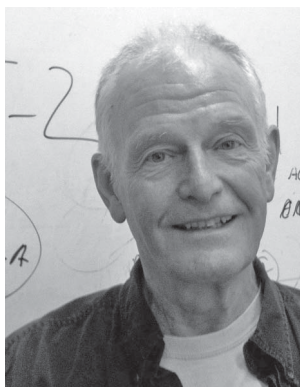
There have also been several important achievements during the past two years. Our newest recruit is **Dr. Aaron Goodarzi**, who joined the Department in early 2011 as a member of the Genomic Instability and Aging Group within our Faculty's Southern Alberta Cancer Research Institute. Aaron has already been very successful at CIHR and CFI and is starting an innovative research program investigating DNA repair in the context of chromatin remodeling.



Aaron Goodarzi

In partnership with another of the Faculty's research institutes, the Alberta Children's Hospital Research Institute for Child & Maternal Health, we have recently established a new genomics core facility that features two next generation sequencing instruments, which we think will be transformational for the research efforts of many Department members.

Drs. Jim McGhee and **Dave Schriemer** were each successful in 2010 in obtaining large CFI grants to support a new STORM imaging platform and new mass spectrometry instrumentation, respectively.



Jim McGhee



Dave Schriemer

Our members have been very active in service to the academic community. In 2010, **Dr. Steve Robbins** became Director of the Faculty's Southern Alberta Cancer Research institute, while in 2011 **Derrick Rancourt** was appointed Deputy Director of the Faculty's McCaig Institute for Bone & Joint Health, **Dr. Jay Cross** was appointed Associate Vice-President Research and **Dr. Randy Johnston** became General Secretary of the CSMB.



Steve Robbins



Derrick Rancourt



Jay Cross



Randy Johnston

In education, **Dr. Mayi Arcellana-Panlilio** took on an important leadership role in the Faculty's Bachelor of Health Sciences undergraduate program delivering molecular, biochemical and cell biological content for which she won teaching excellence awards from the Students' Union in both 2011 and 2012! As well, Mayi coordinated a team of undergraduate students who won the Best Environment Project award at the international Genetically Engineered Machines world competition for their modified bacterial biosensor to monitor oil sands toxins.



Mayi Arcellana-Panlilio

Among our research achievements, **Dr. George Chaconas** won the 2011 Murray Award for Career Achievement from the Canadian Society for Microbiology, while **Dr. Yan Shi** won the New Investigator Award of the Canadian Society of Immunology. Last, but far from least, in 2010 **Dr. Susan Lees-Miller** was elected to membership in the Royal Society of Canada. This is a deserving honour for one of the Department's most distinguished scholars.



George Chaconas



Susan Lees-Miller



Yan Shi

The Department continues to build on our strengths in 2012 with ongoing new recruitment in developmental biology, bioinformatics and cancer biology. Please visit our website at www.ucalgary.ca/bmb/ for more information about the Department.

University of Calgary

Department of Biological Sciences

Correspondent: Vanina Zaremborg

The Biological Sciences Department at the University of Calgary is currently organized in four clusters based on general research and teaching interests. They include Biochemistry, Microbiology, Cell Development & Physiology and Ecology & Evolutionary Biology. **Marie Fraser** was the chair of the Biochemistry cluster for a two-year term and has been replaced by **Elmar Prenner** in 2011. **Greg Moorhead** was chair of the biochemistry program during 2010 and has passed the torch to **Ken Ng** last year.

Teaching undergraduates is one of our priorities and we take great pride in our program. The Biochemistry program has set high standards and continues offering excellent courses and good quality lab experiences to our students despite recent budget cuts and class size expansions. A special recognition goes to our instructors **Robert Edwards**, **Elke Lohmeier-Vogel** and **Isabelle Barrette-Ng** for their outstanding work in this regard. Elke Lohmeier-Vogel spent a six month sabbatical in Lund Sweden at the Technical Microbiology Department studying metabolism of the probiotic bacterium *L. reuteri* and teaching part of a Microbial metabolism course. Several members of our cluster are also involved in teaching other programs at the U of C, like **Elmar Prenner**, who contributed several courses and labs to the minor in Nanoscience program launched in 2009 by the Faculty of Science.

Research in our department is exciting at all levels and several colleagues have been recognized with distinctions/awards for their contributions or have received important funding to support future or ongoing projects. **Ken Ng** was the recipient of the Brockhouse Canada Prize for

Interdisciplinary Research in Science and Engineering as part of a team of five researchers (3 from U of A and 2 from U of C) collaborating in the Alberta Glycomics Centre. **Hans Vogel** was awarded the Lance Armstrong Chair in Molecular Cancer Epidemiology by the Faculty of Medicine to help extend our metabolomics research into the area of cancer diagnostics, prognosis and treatment follow-up. He also spent a very productive sabbatical leave in Lund Sweden for the first half of 2011.



Hans Vogel

Credit: Riley Brandt

Peter Tieleman was awarded an Alberta Innovates Health Solutions Scientist award, salary support for 2010-2017. At the same time, the end of this program and major changes in provincial research bodies were announced, which are still playing out at the moment. Peter has developed a coarse-grained MARTINI model with Prof. Siewert-Jan Marrink at the University of Groningen. MARTINI has become the most popular model for biomolecular simulation, with particular strength in lipid simulations. His research has been supported by a prestigious NSERC Steacie Fellowship (2009-2011). He wrote an excellent review published in TIBS in 2011 on hydrophobicity scales and their relevance in understanding membrane protein folding and insertion, which drew on concepts developed in simulations of interactions of charged and polar molecules with membranes. **Sergei Noskov** received tenure and finally got his laboratory finished.

Raymond Turner has been recruited to a number of university leadership roles from a VPR advising committee to Associate Director of the Institute of Environmental Toxicology, and has been the Microbiology Cluster Chair for the past year. He was involved in the faculty strategic planning directions leading a direction on Environmental and Applied Microbiology as well as co-leading others including Environmental Toxicology and Water Quality and supporting a number of others. He has been instrumental in the past year bringing the diverse group of microbiologists on campus together. Beyond this, Raymond's research program has

been strong revolving around microbes and metals, protein chaperones, and drug transporters. He has seen two patents issued, his work on a couple of journal covers, and top downloads, and several of his graduate students recognized for the Dean's Research Excellence Awards (Sean Booth, Thorin Leach, Michelle Stan), and thesis awards (Vy Tran) and top poster awards (Matt Workentine, Tara Winstone). He also maintains a student exchange with the University of Bologna, Italy. At the end of 2011 his research around bioremediation of Alberta oil sands tailings water attracted significant media attention with over 30 interviews and news articles. **Dea-Kyun Ro** renewed his Canada Research Chair Tier 2 in Plant Bioproducts (2011-2016), and his research will be supported by NSERC Discovery Accelerator Supplements Program (2012-2014). **Elmar Prenner** continues his research in the areas of biophysics and biomembranes. His collaborative work with industry was supported by grants by the Canadian Institute of Photonics Innovation. Moreover, his group participates in a new Genome Canada initiative "Hydrocarbon metagenomics" initiated by **Gerrit Voordouw** from our Department and CIHR sponsored group grant on antimicrobial peptides led by Hans Vogel. **Greg Moorhead** just finished his 3rd and final year of NSERC panel and is currently a co-organizer of the European Proteomics Assoc. meeting in Glasgow this summer. **Vanina Zaremborg** started a sabbatical leave in 2011 and has established a very productive collaboration with Karin Athenstaedt (Graz University of Technology, Austria) studying regulation of lipid fluxes in yeast. The work of her student Nancy Marr was presented at the Gordon Research Conference on Molecular & Cellular Biology of Lipids. She has renewed an NSERC discovery grant (2011-2016) to further support these studies. Vanina is also involved in supervision of PhD students from the University of Buenos Aires, Argentina, supported by the Emerging Leaders in the Americas Program (Canadian Bureau for International Education).

Overall, the Biochemistry group in the Department of Biological Science (Faculty of Science), although a small group, has displayed considerable leadership and strength on campus over the past two years.

To finalize, the UofC is hosting the 95th Canadian Chemistry Conference and Exhibition (May 26-30, 2012), and several members of the group have been organizing sessions for the meeting:

Steve Zimmerly, Andrew MacMillan (Nucleic Acid Chemistry in Memory of M. O'Neill)

Elmar Prenner, M. Khajepoor (Biophysical Chemistry)

Ray Turner, Lisa Gieg (Microbial Chemistry of Fossil Fuels)

Ken Ng, Mark Glover (Macromolecular Crystallography)

Hans Vogel, Neeloffer Mookherjee (Antimicrobial and Host-Defense Peptides)

Sergei Noskov, Dennis Salahub (Multiscale Bio/Physical/Chemical Modeling)

For more information about our activities in the Department of Biological Sciences please visit:

<http://www.bio.ucalgary.ca/research/index.html>

Dalhousie University

Department of Biochemistry & Molecular Biology

Correspondent: David Byers

The Department of Biochemistry & Molecular Biology at Dalhousie University welcomes the impending arrival of new faculty member **Thomas Pulinkunnil**, who will be joining us in July to help establish a cardiovascular research team based in Saint John N.B., part of our recent medical school expansion (Dalhousie Medicine New Brunswick). Thomas is currently completing a PDF at the University of Alberta, and will strengthen and expand our research in metabolic biochemistry in the areas of cardiac triacylglycerol metabolism, insulin resistance, obesity and diabetes. His appointment will present many new research opportunities and collaborations, along with the challenges of communication and interaction with a "remote" campus.

Our Department has also grown recently through the cross-appointments of **Graham Dellaire** (epigenetics and chromatin structure) and **Roy Duncan** (structure and function of viral membrane fusion proteins). New adjunct appointments include **Ray Syvitski** and **Tobias Karakach** from the National Research Council Institute of Marine Biosciences; they bring depth in protein NMR

and metabolomics, respectively. This summer, we say goodbye to **Barry Lesser**, who has provided much of our undergraduate teaching to science, nursing and pharmacy students over the past decade. Barry, you will be missed...

Andrew Roger was appointed in 2010 as the Canada Research Chair (Tier I) in Comparative Genomics and Evolutionary Bioinformatics. He currently leads the internationally renowned Dalhousie Institute of the same name and hopes to move into his newly renovated and expanded lab facility within the next month or so. Other notable faculty awards within the past two years include those to **Paul Briggs**, who has just received a Dalhousie University Outstanding Student Advisor Award, and to **Ford Doolittle** (Professor Emeritus), inducted into the Nova Scotia Discovery Centre Hall of Fame last fall. **Barbara Karten**, **Paola Marignani** and **Jan Rainey** have all been promoted to Associate Professor (with tenure) during this period, while **John Archibald** has just been promoted to Full Professor. Congratulations all!

Several retired and emeritus members of our Department have also been very active recently. In 2010, former department head **Michael Gray** (Professor Emeritus) established the Schnare-Spencer Prize in honor of two long time research associates in his lab. This annual award recognizes a staff member or trainee for technical excellence, innovation, and willingness to assist others in the Department. Our first two recipients have been technicians **Joyce Chew** and **Lynn Thomas**. More recently, John and **Catherine Lazier** (herself a former President of the Canadian Biochemical Society in 1986-87) have endowed the Beth Gourley Travel Award for students and postdocs in our department. This award honours John's aunt, a pioneering clinical chemist with a long and influential career at the Montréal Neurological Institute and the Children's Hospital in Winnipeg. Former graduate **Faye (Naugle) Sobey** (B.Sc. '53) has established a \$1-million endowment to support summer research experiences for Dalhousie undergraduate science students. **Robert Chambers** (our department head from 1981-88) has written a novel online textbook "The Chemical Basis of Metabolism": check it out at his website (www.biochemistrybob.com). Finally, **Harold Cook**, who retired from Dalhousie as Dean of Medicine in 2010, has resurfaced as the Acting Dean and Principal of Dalhousie's new Faculty of Agriculture, created by the

recent merger with the Nova Scotia Agricultural College in Truro, NS (quite a commute from his beautiful new home in Yarmouth).

We continue to celebrate the success of our students and postdoctoral fellows, many of whom are supported by national and local salary awards. Most notable are the recent recipients of the departmental Patrick Prize for outstanding research by a recent Ph.D. graduate (**Jessica Leigh** in 2010 and **Gerrit Volkmann** in 2011), and of the Doug Hogue Award for persistence and dedication to research: **Peter Murphy** in 2010 and **David Langelaan** in 2011.

Our alumni (and anyone else interested) are invited to find out about the latest news and events of the Department of Biochemistry & Molecular Biology at www.biochem.dal.ca/. As I prepare to join the pantheon of former department heads in July, I reflect on both the state of our discipline and of our Department, where I received my undergraduate education so many years ago. The former is stronger than ever, as evidenced by its importance in the new revised MCAT structure. The latter, established in 1924, continues to be a leader in research and education in our region and a source of pride for past and present students, faculty and staff.

University of Guelph Department of Molecular and Cellular Biology

Correspondent: Frances Sharom



Nina Jones

New Canada Research Chairs

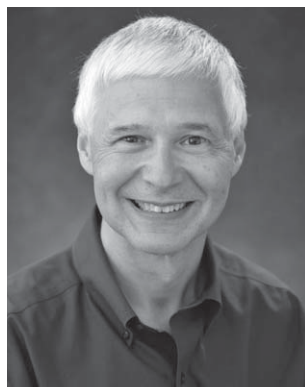
Dr. Nina Jones was awarded a Tier 2 Canada Research Chair in Eukaryotic Cellular Signalling, effective August 2011. Experiments in the Jones laboratory focus on mammalian cell communication pathways, using the mouse as a model organism to understand protein

interactions in both normal and diseased cells. Current areas of research include: signalling pathways in kidney podocytes, cell migration pathways in cardiovascular development, and characterization of the neuronal adaptor protein, ShcD. This research is funded by the Kidney Foundation of Canada, CIHR and NSERC, respectively, and Dr. Jones has also received support from CFI for infrastructure, in addition to an Ontario Early Researcher Award. Prior to assuming the CRC, Dr. Jones was a New Investigator in The Kidney Research Scientist Core Education and National Training (KRESCENT) Program, created through a special contribution of The Kidney Foundation of Canada, the Canadian Society of Nephrology and CIHR-INMD, as well as the recipient of an NSERC University Faculty Award. Trainees in the Jones laboratory have been awarded competitive external scholarships, including CIHR-Vanier, CIHR-CGS and NSERC-CGS, in addition to funds from the Heart and Stroke Foundation and the Ontario Ministry of Research and Innovation.



The Jones Research group (Dr. Nina Jones, far left)

Dr. George Harauz was awarded a Tier 1 Canada Research Chair in Myelin Biology on 1 July 2011 (announced officially 12 October 2011). The Harauz lab works on



Dr. George Harauz

unraveling the structure of central nervous system myelin and how it is affected in multiple sclerosis. They use biophysical and cell biological tools, ranging from solution and solid-state NMR spectroscopy, to live-cell imaging. The goal of this research is a better understanding of this enigmatic and debilitating

disease, which has a disproportionately high incidence in Canada. The group has been funded by CIHR, NSERC, and the Multiple Sclerosis Society of Canada via Doctoral Studentships (to **Ian Bates**, **Abdi Musse**, **Graham Smith**, **Miguel De Avila**), and Postdoctoral Fellowships (to **Drs. Vladimir Bamm** and **Kenrick Vassall**).



The official announcement of Dr. George Harauz' CRC, October 2011 at the NMR Centre, University of Guelph. Front row (left to right): Miguel de Avila (Ph.D. candidate); Lauren Seymour (B.Sc. project student); Caroline Velte, Diplomandin; Dr. Suzanne Fortier, President, NSERC Canada; Dr. Robert Davidson, Vice-President, Canada Foundation for Innovation. Back row (left to right): Harold Albrecht, MP, Kitchener-Conestoga; Dr. George Harauz, Professor and CRC I; Hon. Dr. Gary Goodyear, Minister of State (Science and Technology); Dr. Kevin Hall, Vice-President (Research); Sergio Jaramillo-Tatis, M.Sc. candidate.

Faculty news

Dr. Emma Allen-Vercoe was featured in a new documentary on autism which aired December 8th 2011 on the CBC-TV program *The Nature of Things*, hosted by David Suzuki. *The Autism Enigma* includes interviews with Dr. Vercoe, and footage filmed in her research laboratory. The documentary looks at the various and often conflicting hypotheses about autism, focusing on a new "microbial theory." The gut bacteria in children with regressive autism appear to differ from those in healthy individuals. About 70% of children with this type of autism exhibit severe gastrointestinal symptoms, prompting the question as to whether this disease begins in the gut. Dr. Allen-Vercoe is among several international scientists featured in the documentary. She studies normal gut microflora in healthy and ill people, including people with inflammatory bowel disease (Crohn's and ulcerative colitis), disease associated with *Clostridium difficile* and regressive autism. Her laboratory is one of the few places in Canada where this research can be done. Using a computer-controlled "robo-

gut” that mimics the environment of the large intestine, Dr. Allen-Vercoe has been able to culture certain microbes for the first time. Her research group can study the potential links between specific bacteria and regressive autism, and how those bacteria behave among other microbes. They hope to learn more about microflora in autistic patients and whether bacterial products may help cause autism. This collaborative program is carried out with researchers at



the University of Western Ontario and UCLA. The Allen-Vercoe lab also provides novel gut bacteria to the Human Microbiome Project, whose researchers are cataloguing the genomes of all microbes found in or on the human body.

Dr. Emma Allen-Vercoe and her lab team working on the “robo-gut”

Dr. Allen-Vercoe is also collaborating with **Dr. Cezar Khursigara’s** laboratory, whose primary focus is to develop and use novel cryo-electron microscopy, cryo-electron tomography and correlative light-electron microscopy techniques to advance understanding of how bacteria perform complex cellular processes and multi-cellular interactions. Specifically, his team is pursuing two distinct yet complementary themes. The first investigates the organization and structures of macromolecular protein complexes involved in bacterial cell division and seeks to determine the molecular architecture of the bacterial “divisome”, both *in vitro* and *in vivo*. As part of the second theme, Dr. Khursigara’s team aims to characterize the organization and architecture of bacterial biofilms. Here the group is divided into two camps, one that investigates the potential therapeutic aspects of probiotic biofilms in



Dr. Khursigara’s team using the cryo-electron microscope

collaboration with Dr. Emma Allen-Vercoe, and one that investigates the pathogenic effects of *Pseudomonas* biofilms in the context of the cystic fibrosis lung. Dr. Khursigara’s research is generously supported by the National Science and Engineering Research Council, the Canadian Foundation for Innovation, Cystic Fibrosis Canada, and the Ontario Ministry of Farming, Agriculture and Rural Affairs.

University Professor Emeritus **Dr. Derek Bewley** was the 2010 recipient of the Charles Reid Barnes Life Membership Award. Presented annually by the American Society of Plant Biologists, the award recognizes his contributions to the field of plant biology. Dr. Bewley moved to Guelph in 1985, where he has been Chair of the Botany Department and Director of the Plant Biology Program. Over the course of his 40-year career, he has written several influential books and is a fellow of the Royal Society of Canada. Dr. Bewley is a past recipient of the Gleb Krotkov Award, the CSPP Gold Medal and the C.D. Nelson Award from the Canadian Society of Plant Physiologists. He currently serves as Associate Editor of Seed Science Research and is President of the International Society for Seed Science (ISSS). Over the years, he has also been involved in many national and international committees, and has acted as a consultant to the biotech industry.

Retirements

Dr. Usher Posluszny retired in 2011 after a long and distinguished career at the University of Guelph. Dr. Posluszny received his Ph.D. from McGill University, where he specialized in the area of developmental plant morphology. He continued his research on the structure, development and evolution of aquatic plants during postdoctoral work at Harvard University and as a Life Science Fellow at the Hebrew University in Jerusalem, Israel. After being elected a Fellow of the Linnean Society of London in 1976, he began his academic career at the University of Guelph in 1977 in the Department of Botany and Genetics. When this department was reorganized in 1984, he remained in the Department of Botany, and later joined the new Department of Molecular and Cellular Biology. Dr. Posluszny worked with freshwater and marine plants, as well as members of the grape family, the *Vitaceae*. During his career at the University of Guelph, he developed and taught a number of ethnobotanical

courses including “Plants and Human Use”, and “Plants, Biology and People”. Dr. Posluszny’s goal is to use plants evident in everyday life to develop a deeper appreciation of their important role in human history, and the biological basis for this importance. Dr. Posluszny also taught Plant Anatomy and graduate courses in Plant Morphology. He was active in the Canadian Botanical Association and received the Mary E. Elliott Award for his contributions to the society. Dr. Posluszny has a passion for bonsai, and is one of the founding members and current President of the Guelph Bonsai Club.

Sabbatical leave visitors and visiting scientists

Dr. Jose Casaretto, an Associate Professor from Universidad de Talca in Chile and researcher at the Institute for Plant Biology and Biotechnology, has been collaborating with **Dr. Steven Rothstein’s** group since June 2011 on a project related to regulation of plant metabolism in crops grown under different conditions. The Rothstein lab also hosted **Dr. Mahmoud Yaish**, a Professor in the Department of Biology at Sultan Qaboos University in Muscat, Oman. Dr. Yaish worked on review articles on the role of epigenetics in flowering and also a techniques paper on how to assess this. Several visiting students from China, **Qingnan Hao**, **Dan Mei Liu**, **Pengfei Peng**, **Chao Yu**, and **Yong Ping Zhao** also worked in the Rothstein lab during 2010 and 2011.

Dr. Anthony Clarke’s lab hosted **Ana Branco Maranhã Tiago**, a visiting doctoral student from Coimbra University in Portugal. Ana spent 10 weeks working on the expression of a gene encoding an acyltransferase, and the production and initial characterization of the protein product. A protocol to provide sufficient quantities of the protein was worked out, and an HPLC-based assay was developed to monitor the acylation of glucose-glycerate, a cell wall component of a species of *Mycobacterium*, as a model for *M. tuberculosis*.

Dr. Cecilia Pini, a Visiting Scientist from the Research Institute Estacion Experimental Del Zaidin (Granada, Spain) received an EMBO fellowship to travel to the University of Guelph. She spent three months (Nov. 2010-Feb 2011) working in **Joseph Lam’s** lab studying

biophysical changes on the cell surface of a strain of *Pseudomonas putida* that has a mutation causing a defect in cyclopropane fatty acid. This mutation causes changes in the phospholipid composition of the cytoplasmic membrane, and the bacteria become drug-resistant and solvent-tolerant. Dr. Pini learned how to operate the Atomic Force Microscope in **Dr. John Dutcher’s** lab (Department of Physics) and in collaboration with Dr. Lam and his former Ph.D. student **Dr. Peter Lau**, she collected a large amount of data on cell morphology and force (adhesiveness).

Dr. Xiu-Ping Gao, a Professor of Plant Stress Physiology at the Dryland Agricultural Research Centre of the Shanxi Academy of Agricultural Sciences, China, visited the lab of **Dr. Janet Wood** from February 2011 through October 2012 to benefit from their understanding of the molecular basis for bacterial osmotic stress tolerance.

The labs of **Dr. Derek Bewley** (2010 and 2011) and **Dr. Jaideep Mathur** (2011) played host to a Visiting Scientist, **Dr. Elwira Sliwinska**, who runs the Laboratory of Molecular Biology and Cytometry in the Department of Plant Genetics and Biotechnology at the University of Technology and Life Sciences, Bydgoszcz, Poland. Her studies at Guelph were on the cellular and nuclear changes associated with germination and collet hair formation in *Arabidopsis*, using laser scanning confocal microscopy and flow cytometry.

Karen Solomon, an exchange student from Brigham Young University in Idaho, joined **Emma Allen-Vercoe’s** lab, where she did a 3 month placement working on isolating and characterizing the microbial flora from human fecal samples.

From May-August 2011, **Dr. Ian Tetlow’s** lab hosted **Caitlyn Burns**, an exchange/visiting student from the University of Manchester, who was involved in plant biochemistry lab work and field harvesting of maize plants.

George Harauz’s lab hosted two international exchange students in 2011, **Caroline Velte** from Mainz (April-October, Diplom-Biologie), and **Marie-Lise Jobin** from Bordeaux (June-September, Ph.D.).

Université Laval

Department of Molecular Biology, Medical Biochemistry and Pathology

Correspondent: Josée Lavoie

The Department of Molecular Biology, Medical Biochemistry and Pathology (BMBMP) was established on June 2009 in a reorganization affecting four departments of the Faculty of Medicine: the Departments of Medical Biology, Anatomy, Physiology, Psychiatry and Medicine. The Department BMBMP is chaired by **Dr Pierre Leclerc**, M.D., F.R.C.P.C. and co-chaired by **Dr Robert Tanguay**, PhD and its inception brought together within the same department molecular biologists, the majority of whom came from the Departments of Medical Biology and Medicine. The aim was to bring together faculty members with related research interests, who directed students in the programs of Cellular and Molecular Biology (MSc and PhD) and were responsible for teaching in these programs. The Master and Doctorate programs in Cellular and Molecular Biology regroup close to 150 graduate students and are headed by **Dr Jacques Landry**, a member of our Department. The Molecular Biology Division of the Department is composed of 29 professors. In 2010-2011, two have reached the rank of Associate Professors : **Drs Anime Nourani** and **Martin Simard**, and four became Full Professors : **Drs Jean-Yves Masson, Michel Lebel, Darren Richard** and **Masahiko Sato**. Congratulations to all of them!

Several professors of our Department have been involved in the new undergraduate program in Biomedical Sciences, one of whom, **Dr Michel Vincent**, is heading the program. This 6-sessions program was launched in the fall 2010 and will host its third cohort in September 2012. It was designed to develop qualities and skills sought by research laboratories and biotechnology and pharmaceutical companies. The first half is devoted to acquiring basic science knowledge and involves a close collaboration between the professors of the Faculty of Medicine and those of the Faculty of Science and Engineering. The second half of the program, and this is

its main point of originality, brings students workplace in biomedical sciences, placing them progressively in a dynamic learning, problem solving and knowledge integration. For instance, the fourth session is devoted to the approach of major health problems (oncology, obesity and cardio-respiratory diseases, neurosciences, infectious diseases, endocrinology) through series of 2- to 3-weeks intensive courses on each subject, which have been conceived and are headed by researchers in these fields. During the following summer, a research training is mandatory for all students to introduce them to laboratory work. The fifth session is devoted to two research internships in rotation that students choose among a dozen fields of immersion. In small groups, they perform a series of mandatory activities under the supervision of a team of professors in a research environment of network teaching hospital affiliated with Laval University. The last session consists of an individual internship search during which the student performs the steps of a scientific method of experimental type, under the supervision of a teacher-researcher.

In 2010-11, we welcomed two new faculty members : **Drs Marc-Étienne Huot and Nicolas Bisson**, who have recently established their labs at the Cancer Research Center of Laval University, at the Hôtel-Dieu de Québec, CRCHUQ.

Dr Marc-Étienne Huot trained as a Masters and PhD student at Laval University under the supervision of Dr. Édouard W. Khandjian. During that period, he acquired a unique expertise on the molecular mechanisms modulating mRNA translational control by RNA-binding proteins. After a successful PhD, he joined the group of Dr. Stéphane Richard at the Segal Cancer Center (Jewish General Hospital, McGill University) as a postdoctoral fellow, where he worked on different aspects of the RNA-binding protein Sam68. For instance, he discovered that



Marc-Étienne Huot

changing Sam68 expression level affected the regulation of Src activity and caused dramatic effects on cell polarity, adhesion and migration. By investigating the phenotype of the Sam68^{-/-} mice, he found that loss of Sam68 impaired mTOR mRNA splicing and normal production of the full-length mTOR protein. Since August 2010, he joined the Cancer Research Center at the Hôtel-Dieu de Québec. His research program seeks to uncover the mechanisms that regulate the involvement of RNA-binding proteins in adhesion and migration processes.



Nicolas Bisson

Dr Nicolas Bisson trained as a molecular and cellular biologist at Université Laval, and as an embryologist at the Marine Biological Laboratory (Woods Hole). He obtained his Ph.D. in 2007. During his training, he studied the function of the p21-activated kinase (PAK) and the mixed-lineage kinase (MLK) family of kinases during early embryonic development,

using both *Xenopus* and mouse as model systems. Dr Bisson's work led to important publications in the fields of embryology, biochemistry and molecular biology. Furthermore, he received scholarships from NSERC and The Terry Fox Foundation, as well as several awards for the excellence of his work. Dr Bisson completed his postdoctoral training in 2011 with cell signaling leader Dr. Tony Pawson at the Samuel Lunenfeld Research Institute in Toronto. During his post-doc, he developed an innovative targeted mass spectrometry-based strategy, namely AP-SRM (affinity purification-selected reaction monitoring), to quantify signaling network dynamics. His work suggested that capturing a key hub protein by AP and dissecting its interactions by SRM is an approach that can be extended to obtain a truly quantitative view of dynamic intracellular protein interactions and network assembly activated by different classes of extracellular signals, in both normal and cancer cells. These findings led to a seminal publication in *Nature Biotechnology* (Bisson *et al.* 2011). Dr Bisson was recruited to Université Laval and the CRCHUQ-HDQ in 2011-2012. His laboratory

seeks to understand how normal cells use adaptor proteins to coordinate their response with extracellular cues, and to define how this becomes deregulated in cancer. The long-term objective of his lab is to employ signaling networks as predictive tools to follow pathogenesis, and to target them for therapeutic purposes in complex diseases, such as cancer, for which conventional drug development strategies have often failed.

Their research programs further expand and complement the spectrum of research taking place at the Cancer Center on cellular and molecular mechanisms of tumor progression, which already includes gene expression and genome stability, development, cell signaling and apoptosis. Finally, several professors of our Department have succeeded in obtaining funding from CIHR, NSERC and CRS. Congratulation to all of them!

University of Lethbridge Molecular Life Sciences

Correspondent: Ute Koth

RiboWest Conference 2010 & 2012 in Lethbridge

"I had a phenomenal experience networking with other students and getting a glimpse of the many exciting directions that RNA research is taking off into!" This statement of a RiboWest 2010 participant clearly describes this event. Eighty researchers from western Canada (and the US), representing more than 20 research labs, enjoyed sharing their passion for RNA when they met in 2010 at the University of Lethbridge in southern Alberta, Canada. It's hard to describe the feeling when all of the sudden everybody gets excited. Maybe it's best to cite the keynote speaker, Dr. Reinhard Lührmann, who spontaneously encouraged all students at the conference dinner to stay in RNA research because "it is so much fun and people are so friendly". He certainly contributed tremendously to the success of the RiboWest 2010 meeting. Reinhard was able to convey his excitement for RNA through his keynote

lecture, highlighting the advances in the splicing field over the last 25 years, as well as in the career workshop, where the students learned how he became an RNA Scientist.



Participants of the 2010 RiboWest Conference

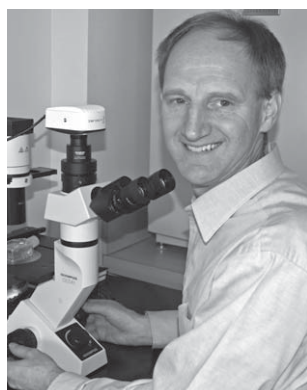
The other highlight of this meeting was the invited lecture by Dr. Jean-Pierre Perreault who showed us how sophisticated investigations on ribozymes can lead to a multitude of fascinating applications. Last but not least, a wide range of RNA research was presented in five sessions and many posters. Notably, the students judged each other in addition to the traditional PI judging which made the poster sessions very lively and interactive for everybody. Now, we are looking forward to the next RiboWest Conference which will take place from June 10-13th 2012 at the University of Lethbridge. We are expecting Dr. Marina Rodnina as keynote speaker as well as Dr. Raymund Wellinger and Dr. Wolfgang Wintermeyer as invited speakers. This event is organized every other year at the University of Lethbridge by **Drs. Ute Kothe, Hans-Joachim Wieden and Steven Mosimann**.

Alberta RNA Research and Training Institute
To represent the growing expertise in RNA research at the University of Lethbridge, The Alberta RNA Research and Training Institute was established in late 2011. The core institute members are **Drs. Hans-Joachim Wieden (Director), Tony Russell (Associate Director), Ute Kothe, Marc Roussel and Steven Mosimann** from the Departments of Chemistry & Biochemistry and Biological Sciences. RNA research is one of the fastest growing fields in the life sciences, with implications for many diseases, our understanding of evolution, as well as biotechnological applications and has enormous economic potential. The Alberta RNA Research and Training Institute is dedicated to foster and facilitate RNA research and training

excellence, to contribute to the multidisciplinary research and teaching community at the University of Lethbridge, its surrounding communities and beyond, ultimately facilitating transfer of leading-edge knowledge into the private sector as well as academia. ARRTI constitutes a coordinated team effort advancing RNA research initiatives in complement to the excellence in the research, teaching, and training programs that already exist at the University of Lethbridge. Members of the Institute operate several focus laboratories including the laboratory for structure and function of small noncoding RNAs, the laboratory for biomolecular design and engineering, the laboratory for systems biology and mathematical modeling, and the laboratory for synthetic biology.

UofL iGEM team succeeds all expectations
The U of L's International Genetically Engineered Machines (iGEM) team is the top team in Canada, and has made it to the top eight per cent of all teams competing at the International Genetically Engineered Machines competition in Boston, Massachusetts, in November 2011. The team presented their research about a petrochemical-eating bacteria the group has designed and how it could be used to help clean up water in tailings ponds – a byproduct of the bitumen refining process in which water that cannot be recycled is deposited into large ponds to settle. The team was the only Canadian team to place in the top 16 teams among 66 final competitors from around the world. The group has already won an Alberta-wide competition and were one of the four finalists at the "Americas" regional competition in Indianapolis, IN, where they placed with Brown-Stanford, the University of Washington and Yale University in the final four. In part, this tremendous success of the UofL's iGEM team can certainly be contributed to its faculty supervisor, **Dr. Hans-Joachim Wieden**. The International Genetically Engineered Machine Competition (iGEM) is the premiere Synthetic Biology competition and currently the largest Synthetic Biology conference in the world. Working at their own schools over the summer, participants use standard biological parts to design, build, and operate biological systems in living cells. They add their new parts to the Registry of Standard Biological Parts for the students in the next year's competition.

Canada-wide Science Fair 2013 in Lethbridge
Next year, the University of Lethbridge will attract even more brainpower when more than 400 of Canada's best young scientists visit the city for the Canada-Wide Science Fair, May 11-18. Youth Science Canada, along with federal, provincial and City representatives, announced recently that Lethbridge would host the 52nd annual Canada-Wide Science Fair (CWSF) through its local host organization, Southern Alberta Technology Council (SATC). The weeklong event will be presented at the University of Lethbridge and University of Lethbridge Biological Sciences researcher, **Dr. Roy Golsteyn**, has volunteered to be the Chief Judge. "This is a great opportunity to showcase our facilities and technology to Canada's top-level students and their families," says Golsteyn. "Like many of us, I still fondly recall that my first steps into science started at school science fairs. The values of the Canada-Wide Science Fair are perfectly aligned with our values of education, mentorship and research. I am looking forward



Roy Golsteyn

Awards

Dr. Roman Przybylski from the Department of Chemistry and Biochemistry received two very prestigious awards in 2011 and 2012.

First, he is the 2011 winner of the Alberta Food for Health Award – a Premier's Award in the Alberta Food and Nutrition Researcher Category. The Premier's Award is intended to recognize the important role that individuals, industry and the research community have in promoting the health benefits from food. Dr. Przybylski was recognized for his important research in lipid chemistry, lipid quality and the processing and functionality of oils. Przybylski

was selected as the Healthy Alberta food and nutrition researcher for contributing to leading edge research in the development of Omega-9 canola oil, a high-quality frying oil suitable for the same uses as traditional oils. The conversion of Omega-9 canola oil from hydrogenated oil helps to remove unhealthy trans and saturated fats from the North American diet. Providing this alternative can positively impact health problems such as heart disease, obesity and diabetes. Dr. Przybylski's research is helping to improve Alberta's food oil industry's processing and preparation practices while improving nutrition.

Second, Dr. Roman Przybylski was recognized by the American Oil Chemists' Society for his contribution to the research on chemistry of vegetable oil components as related to food application and preparation. He received the 2012 Timothy L. Mounts Award from this professional organization, which is given yearly for recognition of important contribution into Application Technologies of Lipids in Foods.

Dr. Roy Golsteyn received an Alberta Innovates New Faculty Award in 2010 to set up the Cancer Cell Laboratory in the Department of Biological Sciences. The laboratory focuses in cell division in cancer cells and training students in cancer cell biology. Specifically, Dr. Roy Golsteyn is studying how cancer cells divide even though they may have damaged DNA- a process known as checkpoint adaptation. This phenomenon is important in the biology of cancer treatments and involves projects in collaboration with the pharmaceutical industry and biotechnology companies.

Similarly, **Dr. Theresa Burg**, Department of Biological Sciences, has also been awarded an Alberta Innovates New Faculty Award in 2009. She uses molecular markers to study various evolutionary and ecological aspects of natural populations and how they relate to physical (e.g. glaciers) and non-physical (e.g. foraging patterns) barriers. Much of her research focuses on vertebrates examining a range of topics from mating systems, hybridization, population structure and systematics.

In 2011, **Dr. Hans-Joachim Wieden**'s tremendous achievements in teaching, in particular in supervising

the iGEM team, were recognized with the Distinguished Teaching Award by the University of Lethbridge. Dr. Hans-Joachim Wieden works diligently to provide students with enriched learning experiences. He has transformed the learning environment for biochemistry students at the U of L, as he succeeded in building an “extended family” of biochemistry students, by deliberately creating the circumstances for this to happen and nurturing it. This idea of a learning community is a recurring theme in his approach to teaching. Dr. Wieden believes strongly in informal, self-directed learning, and strives to provide opportunities for students to explore areas of interest. One example of this is Dr. Wieden’s leadership of the U of L team at the International Genetically Engineered Machines competition, iGEM. Under Dr. Wieden’s mentorship, the U of L iGEM team works by consensus, with students responsible for the organization, conceptualization, and lab work. He encourages students to become involved in iGEM and supports and mentors them in their iGEM experience. It is the epitome of Dr. Wieden’s teaching philosophy: give the students a sense of belonging and ownership; create opportunities for them to direct their own learning; and encourage them to be ambitious and confident in their abilities.

Dr. Ute Kothe has received the Minerva Mentoring Award 2011 of the Alberta Women’s Science Network after being nominated by her own graduate students. This award recognizes her involvement in a number of outreach programs at the University of Lethbridge e.g. Let’s Talk Science, Bridges of Science and Operation Minerva in addition to the mentoring that she provides to her M.Sc. and Ph.D. candidates. In particular, Dr. Ute Kothe has played the lead role in establishing a new science outreach program at the University of Lethbridge since 2010 which is based on graduate student volunteers and operates in partnership with the national Let’s Talk Science organization. The special focus of the Lethbridge Let’s Talk Science Team is high-quality science outreach for high school students in southern Alberta.

Dr. Felix A. Aladedunye was recently awarded an Alexander von Humboldt Foundation prestigious German post-doctorate scholarship. Felix did his graduate work at the University of Lethbridge under supervision of Dr.

Roman Przybylski. The main goal of his graduate work was the chemistry of food components and the formation of toxic compounds during food preparation using frying. As result of his meticulous work, Felix developed new high capacity antioxidants for protection of oil and food components from oxidative degradation. Additionally, he developed a new frying protocol which: (1) improve nutritional quality of fried foods; (2) prevent oxidative degradation of frying oil and food ingredients; (3) limit the amount of toxic compounds formed from thermo-oxidative degradation during frying. As result of his graduate work Felix published 11 papers in reputable journals.

University of Manitoba

Department of Biochemistry and Medical Genetics

Correspondent: Klaus Wrogemann

2010 / 2011 have been busy years in the Department of Biochemistry and Medical Genetics with many changes in faculty and support staff. **Louise Simard** was renewed for a second term as Head of the Department and **Barbara Triggs-Raine** was appointed as Associate Head, filling the vacated position of Klaus Wrogemann. Barbara has been a member of the Department for more than 20 years and has research interests that bridge the area of biochemistry and genetics.

Klaus Wrogemann retired in 2011 after 41 years of service. Klaus has been awarded Professor Emeritus status and continues to be active in the Department, Faculty, and University. He has developed a keen interest in the application of next generation sequencing



Professor Emeritus Klaus Wrogemann with President David Barnard and Chancellor Harvey Sector

to the study of monogenic diseases as a result of his recent sabbatical at the Max Planck Institute for Molecular Genetics in Berlin.



Mark Nachtigal

Mark Nachtigal joined the Department as Associate Professor, coming from Dalhousie. He works on ovarian cancer, the fifth leading cause of cancer death in women, and the most deadly form of gynecologic disease. Mark has cross-appointments in the Department of Obstetrics, Gynecology and Reproductive Sciences and also holds an

appointment as Senior Scientist at the Manitoba Institute of Cell Biology. The focus of his research for the past 13 years has been on the ovarian cancer microenvironment, in particular on autocrine factors that contribute to ovarian cancer cell biology. This research has led to a number of novel discoveries regarding the role of the transforming growth factor beta and bone morphogenetic protein superfamily of secreted growth factors. His laboratory is currently investigating multi-kinase inhibitors as potential therapeutics for naïve and drug-resistant ovarian cancer. Importantly, in collaboration with the Manitoba Tumor Bank, Cancer Care Manitoba, and the Division of Gynecologic Oncology they have now established the Manitoba Ovarian Biobank Program that will produce a collection of normal and tumorous ovarian tissues that can be accessed for research purposes.



Kirk McManus

Another new face in the Department is **Kirk McManus** who joined as Assistant Professor, coming from the Michael Smith Labs at UBC. He studies tumorigenesis as a result of genomic instability. Mark and Kirk expand the strong pre-existing expertise in the Department in breast cancer and chronic lymphocytic leukemia.

This year **Jim Davie** stepped down as Director of the Manitoba Institute of Cell Biology. **Leigh Murphy** resumed the position on an “acting basis” for two years and now **Spencer Gibson** has been appointed Director. Many of the members of the Manitoba Institute of Cell Biology have their home in Biochemistry and Medical Genetics making cancer a major focus of the research in the Department.



Spencer Gibson

Jim Davie, Professor in the Department of Biochemistry and Medical Genetics and current President of our society, had his Tier 1 Canada Research Chair in chromatin dynamics renewed for another seven years. In December of 2011, he moved his lab from the Manitoba Institute of Cell Biology to the Manitoba Institute of Child Health (MICH). Exciting to his research program and to investigators at the University of Manitoba, Jim has established a Next Generation DNA Sequencing Facility in MICH which will be used for both genetic and epigenetic research. The Facility was acquired through funds from CFI, the Provincial Government of Manitoba, Cancer Care Manitoba and the University of Manitoba, Faculty of Medicine.

The Department celebrated the much anticipated opening of the new Regenerative Medicine labs. Regenerative medicine is an emerging field of medicine focused on repairing and replacing damaged cells and tissues. Often, this involves harnessing the power of stem cells, which can renew themselves and differentiate into many other cell types. The Regenerative Medicine Program (RMP), with the considerable support of the Faculty of Medicine, the affiliated hospital research institutes and the University of Manitoba, was initiated in 2008. **Geoff Hicks**, a Canada Research Chair, was appointed as Director of the Program. The RMP moved into their new 24,000 sq ft state-of-the-art research space on the 6th floor of the Basic Medical Sciences Building. A key component of the new program is a recruitment strategy for six new tenure-track positions, including the deployment of two Canada



Mojgan Rastegar

Research Chairs. **Mojgan Rastegar**, Ph.D. (Université Catholique de Louvain, Belgium), was appointed as Assistant Professor. Her research focuses on neurological disorders with an emphasis on Rett Syndrome, HOX targets in neural stem cells, and epigenetic control of embryonic stem cell neurogenesis. **Tamra Werbowetski-Ogilvie**, Ph.D.

(McGill), Assistant Professor, focuses her research on the earliest regulation in brain tumour progression and invasion of brain tumor stem cells. **Soheila Karimi**, Ph.D. (Saskatchewan), was appointed as Assistant Professor of Physiology. Her lab focuses on spinal cord repair and regeneration and therapeutic application of neural stem/progenitor cells in spinal cord injury. **Afshin Raouf**, Ph.D. (University of Toronto) has his academic home as Assistant Professor in Immunology. His research focuses on the application of cancer stem cells to the development of preventative breast cancer therapies. Recruitment of the final two positions is currently underway. **Donna Wall**, MD (Manitoba), Professor of Pediatrics and Child Health, is a significant complement to the new recruitments. She focuses on the understanding the aging process of stem cells for more effective bone marrow and cord blood transplant therapies.

Some student awards deserve special mention: **Ju-Yoon** (MD/PhD) received the CIHR Banting & Best Award as well as the University of Manitoba Tri-Council Top-Up Award. Aside from his academic excellence, Ju-Yoon Yoon is the VP Internal (elect) of the Clinician Investigator Trainee Association of Canada. **Alexandra Kuzyk** (MD/PhD) received one (of 2) of the University of Manitoba's nominations for the National competition - Mackenzie King Open Scholarship. She also received the Nancie J. Mauro Graduate Scholarship in Oncology and the Sheu L. Lee Family Scholarship in Oncology Research. **Yan Yi** (PhD) received the CIHR Banting & Best Award for three years. **Sumit Sandhu** (PhD) received the NSERC - PGS D3 Award. **Biswajit Choudhury** (PhD) was awarded the President's Graduate Scholarship in Human Genetics. He

also received an MHRC scholarship.

Tamra Ogilvie was successful in obtaining a Tier II Canada Research Chair in regenerative medicine, making her one of 4 CRC Chairs in the Department. Professor Emeritus **Patrick Choy** became the first member of our Department to be awarded the Order of Manitoba. **Malcom Xing** was awarded the Dr. Moore House Fellowship by the Diabetes Foundation of Manitoba, and **Francis Amara** was a recipient of the Dr. and Mrs. Ralph Campbell Outreach Award.



Tamra Ogilvie

McGill University

Department of Biochemistry

Correspondent: Kalle Gehring

The Department was awarded a NSERC CREATE grant, which has led to the establishment of the CREATE Training Program in Bionanomachines. This training initiative offers summer research stipends to undergraduates and 2-year stipends to graduate students in a number of laboratories in Montreal, Québec City, Calgary and Saskatoon. Select students from the first round of applicants have been admitted to the program, and another application period will be announced in fall 2012. Bionanomachines is a young and developing field at the intersection of structural biology, supramolecular chemistry and biophysics that seeks to understand how biological machines function at the molecular level, and to harness their power for applications in health, chemistry and physics. For more information visit <http://bionano.ca> or contact the CTPB Coordinator at bionano.med@mcgill.ca.

Drs. **Kalle Gehring** and **Albert Berghuis** were also successful in renewing funding for the GRASP group

(Groupe de Recherche Axé sur la Structure de Protéines) which brings together nearly 50 Quebec research groups to promote exchanges and collaborations in order to better understand the molecular basis of diseases and to develop new therapies. GRASP is sponsored by the Quebec provincial Fonds de Recherche du Québec – Santé (FRQS), and was ranked highly in the renewal competition, due to the high productivity of its members, and their frequent collaborations within the group. For more information, please visit <http://grasp.mcgill.ca>.

The CIHR-Institute of Infection and Immunity (III) has selected **Dr. T. Martin Schmeing**, a new Assistant Professor at McGill University, as its first laureate for the Bhagirath Singh Early Career Award in Infection and Immunity. This award was established to honour the outstanding work of III's inaugural Scientific Director, Dr. Bhagirath Singh. To recognize the excellence of research being done in Canada, this prize is awarded annually to a new investigator in the field of Infection and Immunity. Dr. Schmeing's research project entitled Structural and Function Studies of Nonribosomal Peptide Synthetases, was highly ranked in the 2010 March competition, and proved to be the highest among both open competitions of the year 2010 for the CIHR New Investigators Competition. The project is very innovative and has the potential to find novel ways to synthesize new bio-active molecules that may impact infectious and immunological diseases.

Dr. Nahum Sonenberg was promoted to Officer of the Order of Canada in 2010 for his contributions to cellular biochemistry, notably for advancing scientific knowledge on the regulation of protein synthesis. Dr. Nahum Sonenberg was previously named the 2009 Health Researcher of the Year in Biomedical and Clinical Research by the CIHR for his pioneering study and analysis of translation control mechanisms, the process by which the genetic information stored in our DNA is turned into proteins. His research has opened the door to new treatments for diseases such as cancer and HIV/AIDS. Dr. Sonenberg was also awarded the Lewis Rosentiel Award, recognizing his distinguished work in basic medical research. He will be awarded a medal and \$30,000 at Brandeis University, Massachusetts.

Dr. Philip E. Branton, past chair of the Department of Biochemistry at McGill, is the recent recipient of the Award for Exceptional Leadership in Cancer Research for his outstanding contributions to the development of the cancer research community and inter-agency research collaboration in Canada through the founding of the Canadian Cancer Research Alliance.

Dr. Bernard Brais of the Montreal Neurological Institute was awarded a "New emerging team grant" along with Biochemistry Department members **Drs. Jason Young** and **Kalle Gehring** on Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay (ARSACS): From models to treatment strategies. The award is valued at \$2.5M over the next five years, and is part of an initiative by the federal government to focus on rare diseases. ARSACS is a debilitating hereditary and progressive childhood neurological disease that has serious consequences on mobility.

Drs. Morag Park, William Muller, Vincent Giguère and Michel Tremblay were all also recently honoured, having been appointed as Fellows of the Royal Society of Canada.

Several other researchers in the department passed important career milestones. **Drs. Thomas Duchaine, Bhushan Nagar** and **Jason Young** were promoted to Associate Professors, with tenure. **Drs. Robert MacKenzie, Walter Mushynski** and **Rhoda Blostein** retired in 2010 and were appointed as Professor Emeriti.

It is also with much sadness that we report the passing of **Dr. Rose Johnstone**. Rose was an accomplished researcher and was the chair of McGill's Department of Biochemistry from 1980-1990. Her work involved exosomes and their function in health and disease. Beyond her research, Dr. Johnstone had many accomplishments, including being the Treasurer of the Royal Society of Canada from 1991 to 1994, and she was also the Past Chair of the Canadian Biochemical Society.

The Rosalind and Morris Goodman Cancer Centre of McGill was awarded \$3.8M from the Terry Fox Foundation for a three-year program to study molecular links between cancer and obesity, diabetes and



Four generations of Chairs of the Dept. of Biochemistry at McGill University. Left to right: Angus F. Graham (1970-1980), Phil Branton (1990-2000), David Thomas (2001-), Rose M. Johnstone (1980-1990)

cardiovascular disease. This funding is a part of the New Frontiers Program Project Grants, which aim to fund team science and research excellence. The program is operated in collaboration with CIHR.

Several renovation initiatives have enhanced the facilities for research within the Department. The McGill Cystic Fibrosis Translational Research Centre (CFTRc) was created and had its official opening on October 17th, 2011. The goal of the centre is to find a cure for cystic fibrosis. CFTRc provides a platform for basic CF research and the development of therapies that target the basic defect underlying this disease, as well as others that involve protein trafficking. It is part of a larger McGill initiative on orphan and neglected diseases.

Additionally, the Department was awarded substantial funding from the Canada Foundation for Innovation (CFI), Knowledge Infrastructure Program (KIP) and the Quebec Ministère du développement économique, innovation et exportation (MDEIE). With a total value of \$26.5M, funding helped cover renovation costs and the purchase of new equipment for many groups within the Biochemistry Department. This involved the complete demolition and rebuilding of nearly 26,000 square feet of laboratory space, and upgrades to ventilation, electrical

and other mechanical systems. This was the first major renovation of the McIntyre Medical Sciences building since it was constructed nearly 50 years ago, and the drastic improvements now offer modern and attractive research areas for numerous McGill groups.

McMaster University

Department of Biochemistry and Biomedical Sciences

Correspondent: Alba Guarné

In the last two years research from several laboratories in the Department of Biochemistry and Biomedical Sciences, as well as the Institute for Infectious Diseases Research (IIDR), has resulted in several high-profile articles that have received much attention from the scientific and lay press. The **Bhatia** laboratory found the key to turn human fibroblasts into blood progenitors (Nature, 2010). The **Magarvey** laboratory discovered a key controller of weaponry in the superbug *Staphylococcus aureus*. The **Guarné** laboratory unveiled one of the critical steps in the correction of DNA replication errors and its link to cancer development (Molecular Cell, 2010). The **Brown**, **Coombes** and **Wright** laboratories found that combination of antibiotics with nonantibiotic drugs enhance antimicrobial efficacy (Nat. Chem. Biol., 2011). The **Truant** laboratory found how kinase inhibitors modulate huntingtin toxicity (Nat. Chem. Biol., 2011). The **Wright** and **Poinar** laboratories found that antibiotic resistance is ancient (Nature, 2011) and, soon after, a collaborative effort led by the **Poinar** laboratory sequenced the genome of *Yersinia pestis* from victims of the Black Death, allowing them to track changes in pathogen evolution and virulence over time (Nature, 2011). Stay tuned for more interesting stories coming out soon.

Despite the current funding climate, our Faculty has continued to secure operating dollars. Notably, **Ray Truant** got considerable funding support from the Krembil

Family Foundation for his competitive research program in Huntington's disease and **Mick Bhatia** and his colleagues captured a large \$11.5 million investment from the Ontario provincial government to develop stem-cell based therapies. **Alba Guarné** and **Murray Junop** received an infrastructure grant from the CFI Leaders Opportunity Fund to renovate the crystallization and X-ray diffraction facilities. The caliber of our Faculty has continued to be recognized nationally and internationally: **Gerry Wright**, director of the IIDR, received the prestigious Killam Research Fellowship, **Mick Bhatia** received the newly minted McMaster University Innovator of the Year Award, **Brian Coombes** was named one of Canada's Top 40 Under 40, and **Yingfu Li** was recently awarded the W.A.E. McBryde Medal from the Canadian Society of Chemistry.

The students in our program have also done extremely well in securing scholarships including **Soumaya Zlitni** (Brown lab) who got one of the prestigious Vanier Scholarships awarded to McMaster University students. In 2010, 43% of our PhD and 26% of our MSc students held competitive external awards. Similarly, 40% of all our students were supported by external scholarships in 2011. In the last two years, our trainees have published 124 articles in leading journals in their fields. That is more than one per week!

These two years have also been marked by new faces: **Kristin Hope** joined the Stem Cell and Cancer Research Institute in 2010 and, last year, **Jonathan Schertzer**



Mary Margaret Strong addressing the audience during her retirement reception at the McMaster University Club

came to strengthen our core of faculty interested in metabolism. We also welcomed **Gregory Steinberg** and **Michael Surette**, who hold joint appointments with the Department of Medicine, as well as **Tim Gilberger** (joint with Pathology and Molecular Medicine) and **Deborah Sloboda** (joint with Obstetrics and Gynecology). There have also been important changes in our administrative office.

Mary Margaret Strong retired after 41 years of service and is now spoiling her granddaughter full-time. **Dale Tomlinson** took an administrative manager position in the Department of Anesthesia after 35 years in Biochemistry. **Donna Marfisi** and **Julie Paul** took positions at the Department of Family Medicine and the IIDR, respectively. Meanwhile, we welcomed **Lorraine Curtis** (Manager of Operations), **Jodi Biro** (Administrative Assistant), **Vicki Cometto** (Administrative/Finance Assistant), **Mizan Graham** (Undergraduate Program Administrator), and **Liz Theriault** (Chair's Assistant), who keep the office running like a well-oiled machine.

Of course, it was not all work. The artists in the **Ortega** laboratory prevailed at our Annual Pumpkin Carving Contest with their Pumpkin Phage Creation, the **Coombes** lab won the Halloween Group Costume Contest award, the hidden biochemistry musical talents surfaced at the IIDR Holiday Reception, and **Murray Junop** turned up to be the killer at the Murder Mystery Organized by the Undergraduate Biochemistry Society. Who knew that our most inspiring teacher had such a dark side...



Pumpkin Phage (Ortega laboratory). Winner of the 2011 Departmental Pumpkin Carving Contest

Memorial University of Newfoundland

Department of Biochemistry

Correspondent: Valerie Booth

Two new faculty members joined us in 2010. **Sherri Christian** became part of the Department in May; her current research involves trying to figure out how one cell-surface receptor, CD24, decides if a cell should live or die or change into a different type of cell. Dr. Christian was not the “newbie” for very long though, as **Rob Brown** took up his appointment in the Department in September. Dr. Brown is studying “the balance between the good HDL cholesterol and the bad LDL cholesterol and the enzymes that influence those in the circulation.”



Sherri Christian

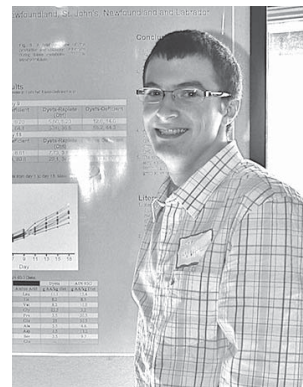


Rob Brown

In August 2011, the first Biochemistry Summer Student Symposium was held at the Fluvarium. The competition was intense, but in the end undergraduate poster awards went to **Timothy Hynes** (first place) and **Luke MacMillan** (runner-up), and graduate oral presentation awards went to **James Pius** (first place) and **Nicole Smith** (runner-up). Dr. Simon Sharpe, a graduate of the Department and now a faculty member in the Dept. of Biochemistry at U. of T. and a scientist at the Hospital for Sick Children, Research Institute, Toronto, travelled home to Newfoundland to give the keynote address.



Timothy Hynes



Luke MacMillan



James Pius



Nicole Smith

Honours to departmental faculty in 2010 and 2011 included **Sean Brosnan's** appointment as a Fellow of the Royal Society of Canada, **Fereidoon Shahidi's** recognition by the International Society for Nutraceuticals and Functional Food via an establishment of a fellowship in his name, as well as Tier II Canada Research Chair renewals to **Rob Bertolo** (Human Nutrition) and **Valerie Booth** (Membrane Proteins).

Dr. Martin Mulligan, our department head since 2004, stepped down at the end of 2010. **Dr. Phil Davis** is currently our acting head, and a committee has been struck to search for a new, external head.

Université de Montréal

Département de biochimie

Correspondent : Christian Baron



Daniel Zenklusen

Appointments

Faculty renewal is a key challenge for every academic Department and in 2010 three Assistant Professors joined Biochemistry. **Daniel Zenklusen's** laboratory is on the main campus and he will conduct a research program on the regulation of transcription using cutting-edge single molecule microscopic approaches.

Éric Lécuyer established his RNA Biology laboratory at the Université de Montréal-affiliated IRCM (Institut de recherches cliniques de Montréal). Similarly, **Marlene Oeffinger** who is an expert in proteomics and ribosome assembly established her group at the IRCM where she will direct the Ribonucleoprotein Biochemistry laboratory.



Eric Lécuyer

Operating and infrastructure funds

The training grant proposal piloted by **Christian Baron** in the NSERC CREATE program competition succeeded, and since 2010 the program on the "Cellular dynamics of macromolecular complexes" (CDMC) is operational.

This innovative Canada-wide program includes 10 co-



Marlene Oeffinger

PIs from the Université de Montréal (Pascal Chartrand, Benoit Coulombe, Nicolas Lartillot, Stephen Michnick, James Omichinski, Jurgen Sygusch), from McGill (James Coulton and Jackie Vogel), from UBC (Franck Duong) and from the University of Toronto (Sachdev Sidhu) as well as 18 collaborators. The funds of \$1,650,000 will primarily be allocated to the funding of graduate students.

Our faculty members were equally successful at other **NSERC** competitions in 2010 and 2011. Five of them received a Discovery grant for the first time (Grandvaux, Lécuyer, Legault, Oeffinger, Zenklusen). Drs. Brisson, Legault, Omichinski and Sygusch led groups who succeeded in the RTI (Research tools and instruments) competition providing the addition and renewal of much-needed smaller research equipment for the Department. Times are difficult at **CIHR** competitions, but our faculty proved to be very competitive in general, and as an example, several of them obtained operating grants in a single 2011 competition, which is quite a spectacular success these days (DesGroseillers, Drouin/IRCM, Ferbeyre (2 grants!), Lécuyer/IRCM, Legault, Michnick, Moreau/St. Justine and Zenklusen).

Genome Québec and the government of Québec announced the allocation of major grant support for genomics research in collaboration with private partners. One of these grants was obtained in 2010 by **Alain Moreau**, Professor in the Biochemistry and Stomatology Departments, and his colleagues at the Université de Montréal-affiliated Ste-Justine Research center (Andelfinger, Kibar and Rouleau). In 2011, Genome Québec funded a major environmental genomics project (**Reclaiming polluted land sites**) piloted by **Franz Lang** with his co-PI Mohamed Hirji (Biological Sciences) on the process of phytoremediation, the application of plants and microorganisms for soil decontamination. The results of this research may improve the decontamination of sites impacted by mining activities, by oil extraction or by other industrial activities and will thereby help to protect the environment and population health. These successes underline the excellence of the researchers in our Department in genetics and genomics.

Research highlights

Researchers of our Department continued to publish their work in high impact journals. In 2010, **Hervé Philippe** published a genomic study in *Science* that changes the understanding of the link between genome architecture and phenotype, **Pascal Chartrand** described a new molecular mechanism at the basis of cell fate in *Genes & Development* and **Martine Raymond** presented a potential novel approach against fungal infections in *Nature Medicine*. The year 2011 was equally good for **Hervé Philippe** and collaborators who published an evolutionary study that disproves living missing link theories in *Nature*, **Gerardo Ferbeyre** and his colleagues at the CHUM research center published a study on the malignancy of cancer cells in *Genes and Development*, and **Pascal Chartrand's** work on the observation of telomerase in living cells was published in *Molecular Cell*.

Awards

Michel Bouvier received the Michel Sarrazin prize of the Club de recherches cliniques (CRCQ) in 2010, and in 2011 he received the Adrien-Pouliot Prize from ACFAS (Association francophone pour le savoir). His professional activities and multiple contributions testify that he is a key proponent of biomedical research in Québec and this is also shown by his appointment as CEO of the NCE-funded commercialization center IRICoR. **Gerardo Ferbeyre** received the GE Healthcare prize for new researchers from the CSMB for the excellence of his scientific work. **Philippe Crine** received the CP Leblond prize for research and bone health from the FRQS Network for Oral and bone health research for his work on the identification, development, and clinical assays of an enzyme replacement therapy for the treatment of hypophosphatasia. Finally, **Alain Moreau** received the 2011 distinction from the Foundation Biotech Montréal for the best business presentation of a biomarker for the diagnostics of Osteoarthritis.

Ryerson University Department of Chemistry and Biology

Correspondent: Roberto Botelho

The Dept. of Chemistry and Biology encompasses multi-disciplinary interests in research and teaching. Our Chemistry research programs are generally focused on macromolecular, synthetic and medicinal chemistry. The research interests in Biology enjoy strengths in ecology and environmental biology, microbiology and biofilms, cellular microbiology, protein biochemistry, developmental biology and intracellular signaling. The breadth and variety of research interests creates a unique environment that permits cross-pollination of research ideas and an open-concept milieu for learning and teaching.

In the last two years, we have grown by three new faculty members. In 2010, **Dr. Lesley Campbell** began her academic position in our Department. She is investigating evolutionary processes and properties of plants including hybridization and genetic diversity in invasive plants. In 2011, **Dr. Bryan Koivisto** joined our Department to study solar fuels, photovoltaics and redox-active chromophores. Also in 2011, **Dr. Costin**

Antonescu began his academic position in our Department. His research focuses on the reciprocal regulation of membrane trafficking and cell signaling. Dr. Antonescu did his Ph.D. in Biochemistry at the University of Toronto with Dr. Amira Klip, followed by a post-doctoral position with Dr. Sandy Schmid at the Scripps Institute in San Diego, California.



Costin Antonescu

Importantly, our Department has maintained the research momentum built over the last five years by enjoying continued success in NSERC and CFI funding applications and increased research output. Perhaps, the most significant change to our Department was the inauguration of the Ph.D. program in Molecular Sciences

at Ryerson University in 2011. This will greatly facilitate our ability to increase our research output particularly in areas relevant to CSMB. Along with these changes, our Department will become a founding member of the new Faculty of Science at Ryerson in July 2012. This new unit will help foster and promote scientific research within Ryerson including in CSMB-related areas.

With this, we expect our Department to continue growing its research footprint and visibility within Canada and the international stage.

University of Saskatchewan Department of Biochemistry

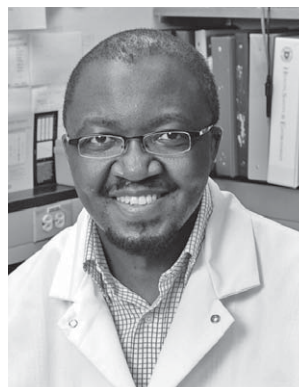
Correspondent: Scot Leary

Our Department has experienced tremendous change over the course of the last three years. In 2009, **Suzanne Laferté** and **Lambert Loh** both retired after 22 and 26 years on Faculty.



Suzanne Laferté & Lambert Loh

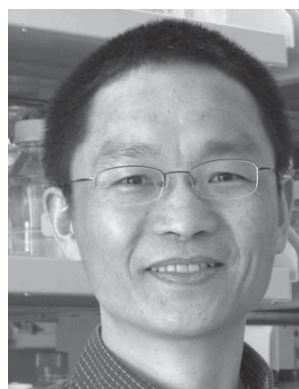
While they are both sorely missed, their retirement facilitated the recruitment of two junior Faculty in July of that same year; **Kiven Erique Lukong** (Université de Montreal) and **Scot Leary** (Montreal Neurological Institute). Two additional Faculty have since been hired. **Yuliang Wu** (NIA/NIH) joined us as an Assistant Professor in January, 2011, while **Mirek Cygler** arrived in October, 2011. As many of you know, Mirek was recruited from the NRC in Montreal to fill the position vacated by **Louis Delbaere**, who unexpectedly passed away in the Fall of 2010. Mirek is a Full Professor and a Tier I Canada Research Chair, and we are excited to welcome him and his considerable expertise aboard.



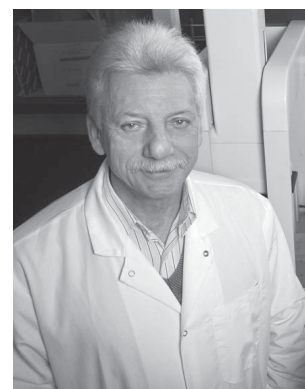
Kiven Erique Lukong



Scot Leary



Yuliang Wu



Mirek Cygler

In addition to the considerable turnover in Faculty, **Bill Roesler** assumed headship of the Department in July, 2011. We are very grateful to our previous Head, **Ramji Khandelwal**, for his strong presence and steady leadership throughout his eight year tenure in this position. Not surprisingly, Bill possesses these same qualities, and we look forward to his stewardship for many reasons, but in particular as we transition over the next year or so from traditional, stand alone lab space to open



Bill Roesler



Ramji Khandelwal

concept labs that are composed of researchers with diverse Departmental affiliations.

The provincial economy continues to grow in strength relative those of our national brethren. However, in 2010, the Government of Saskatchewan substantially cut its budget allocation to the Saskatchewan Health Research Foundation (SHRF), which awards extramural grants to junior investigators and research groups. In spite of the associated challenges, our junior Faculty continue to do well in these competitions, with **Erique Lukong** and **Yuliang Wu** submitting the highest scoring grants in 2010 and 2011, respectively. It remains to be seen if and how SHRF will be able to sustain its group grant program over the long term.

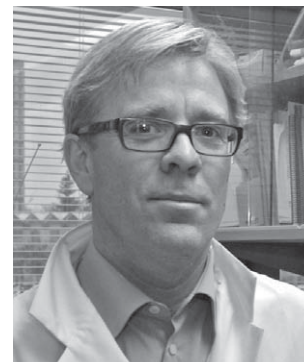
Nationally, we continue to build research momentum. **Stan Moore, Scot Leary, Yu Luo, Ron Geyer, Jeremy Lee** and **Hong Wang** have all been awarded NSERC Discovery grants over the last three years. **Kiven Erique Lukong** now holds both an Operating grant (2010) and a salary award (2011) from the CIHR. **Scot Stone, Scot Leary, Mirek Cygler** and **Ron Geyer** also have operating funds from the CIHR. Recently, **Scot Leary** received two years of funding through the Champions of Genetics grant program, which is a partnership between the Canadian Gene Cure Foundation and the CIHR Institute of Genetics.

It is worth expanding on the recent research initiatives and accomplishments of two of our Faculty in particular. **Scott Napper**, whose lab is located within the Vaccine and Infectious Disease Organization (VIDO), receives considerable funding from a large number of industry and government sources to develop therapeutics for the effective treatment of diseases caused by protein misfolding. A tangible example of the impact of this work is the recent licensing by a commercial partner of a prion vaccine his research group has developed, which is now going through clinical trials. The last year has also seen **Ron Geyer** launch the Saskatchewan Therapeutic Antibody Resource (STAR). STAR is a research group comprised of a dozen scientists that represents the Western arm of a national consortium established in partnership with the Toronto Recombinant Antibody Centre at the University of Toronto. The ultimate goal of this consortium is to produce synthetic antibodies for diagnosing and fighting cancer. However, the wealth of antibodies produced by such a high throughput facility will also offer unique opportunities to collaborate with

infectious disease researchers at VIDO, among others.



Scott Napper



Ron Geyer

This past year saw an expansion of the breadth and depth of our Departmental seminar series, thanks to talks given by a greater number of external speakers including Drs. Mark Akesson (UC Santa Cruz), Albert Berguis (McGill University), Adelaine Leung (Harvard Medical School and MGH), Andrew MacMillan (University of Alberta), Filip Van Petegem (UBC) and Peter Davies (Queen's University at Kingston). We value their willingness to contribute to the education of both our undergraduate and graduate students, and we hope to secure sufficient funds from the College of Medicine to ensure the sustained contributions of invited speakers in the coming years.

We would be remiss not to acknowledge two of our M.Sc. graduate students who garnered fellowships this past year: Kristen Marciniuk (Napper) received a Frederick Banting and Charles Best Canada Graduate Scholarship from the CIHR, while Chris Christensen (Lee) was awarded an NSERC PGS-M. Lastly, we would like to send out heartfelt congratulations to **Scot Stone** for being awarded tenure and promotion to Associate Professor, and **Oleg Dmitriev** who was promoted to Full Professor.



Oleg Dmitriev



Scot Stone

Université de Sherbrooke

Department of Biochemistry

Correspondent: Marcel Bastin

2011 was a year of changes for the Biochemistry Department. Following the appointment of **Dr. Pierre Cossette** as the new Dean of the “Faculté de médecine et des sciences de la santé”, **Dr. Jean-Pierre Perreault** joined the Cabinet as Vice-Dean for research. Stepping into Dr. Perreault’s large shoes, **Dr. Martin Bisaillon** was appointed Chairman of the Department and Director of the undergraduate Biochemistry program. The Department also recruited a few new members with a strong focus on bioinformatics.



Rafael Najmanovich

Rafael Najmanovich, Ph.D.

Dr. Najmanovich got a Bachelor’s degree in Molecular Sciences and a Master’s degree in Statistical Physics from the University of São Paulo, Brazil. He then obtained a joint Physics and Biology PhD degree from the Weizmann Institute of Sciences in Israel, working on small-molecule/protein docking simulations.

The PhD was followed by Postdoctoral and Research Assistant positions at the European Bioinformatics Institute in Cambridge, United Kingdom in the group of Professor Janet M. Thornton. He joined our Department as an Assistant Professor in April 2009 with a cross-appointment in the Department of Informatics, Faculty of Sciences. His group focuses on Molecular Recognition, bringing together different aspects from bioinformatics, chemo-informatics, systems biology and structural computational biology.

Michelle Scott, Ph.D.

Dr. Scott completed an undergraduate degree in Biochemistry at the Université de Montréal in 1998 and a MSc in Biochemistry and Molecular Biology at the University of Calgary under the supervision of Dr. Karl Riabowol. She then moved on to studies in computer engineering and a PhD in Bioinformatics at McGill University under the supervision of Drs Mike Hallett



Michelle Scott

and David Thomas. Her PhD studies centered on the computational characterization and prediction of protein subcellular localization with an emphasis on the secretory pathway. After completing her Ph.D. in 2005, she joined the Computational Biology group of Professor Geoff Barton at the University of Dundee in Scotland, as a CIHR and later a

Caledonian Research Fellow. At the University of Dundee, she pursued her interest in protein localization and protein networks with a focus on the nucleolus and its diverse and dynamic protein content. She also delved into the world of small RNAs, participating in the characterization of an evolutionary relationship between small nucleolar RNAs and miRNAs. She joined our Department as an Assistant Professor in September 2011, where she is currently building a multi-disciplinary group with both computational and biochemical interests.



Luigi Bouchard

Luigi Bouchard, Ph.D., MBA.

Dr. Bouchard pursued his Ph.D. studies at the Université Laval (genetic epidemiology) and his masters and undergraduate degrees in biochemistry (Université de Montréal (M.Sc.) and the Université du Québec à Montréal (B.Sc.)). He also holds two postdoctoral fellowships from the Université

Laval and the University of Toronto. He joined our department in September 2010 as an assistant professor and is pursuing his research as a chercheur-boursier junior 1 of the FRSQ at the Centre hospitalier affilié universitaire régional, CSSS de Chicoutimi. His research focuses on transcriptomics and epigenetic events on cardiovascular diseases. He is, furthermore, characterizing the impacts of fetal exposure to gestational diabetes mellitus on DNA methylation profiles and the role of epigenetics in dyslipidemia.

Simon Fraser University

Department of Molecular Biology and Biochemistry

Correspondent: Christopher Beh

In the past few years, the MBB Department at SFU has seen notable changes including its partnership with the BC Genome Sciences Centre (operated by the BC Cancer Agency). Our ranks have now expanded to include 27 research faculty and >100 graduate students and post-doctoral fellows. In this report, some of our recent successes are recounted along with details about other research and teaching achievements.



Mark Brockman

Department highlights

During the past year, several notable research honours and awards have been bestowed on our faculty. MBB Department Associate Professor **Dr. Mark Brockman** has taken a shared appointment with the SFU Faculty of Health Sciences (FHS), which sponsored his successful Canada Research Chair

(CRC) Tier 2 award in viral pathogenesis and immunity. The award supports Dr. Brockman's many collaborations including those involving the BC Centre for Excellence in HIV/AIDS and projects with colleagues in Africa. Dr. Brockman and SFU colleagues recently received funding from the Global Health Research Initiative for HIV/AIDS prevention trials in Sub-Saharan Africa. This project will enable African researchers to apply cross-disciplinary approaches to study HIV. Also, in recognition for her work on HIV, MBB Professor **Dr. Jamie Scott** successfully renewed her CRC Tier 1 award. **Dr. Lynne Quarmby**



Lynne Quarmby

was named by the *Vancouver Sun* as one of the 100 most influential women in British Columbia, and a "woman of influence" in BC science and medicine.

Dr. Rob Holt, a MBB faculty member and BC Cancer Agency scientist, made *Time Magazine's* top 10 list of medical breakthroughs in 2011 by discovering a link between human colorectal cancer and *Fusobacterium* infection. **Dr. Steven Jones**, a MBB Professor and head of the BC Cancer Agency's Genome Sciences Centre, was recognized for his work in genomics and named as a fellow of the Royal Society of Canada. Congratulations also to **Dr. David Voadlo**, an associate MBB faculty member, for his award of a NSERC E.W.R. Steacie Memorial Fellowship, which recognizes his research in the therapeutic targeting of O-linked glycosylation and chemical glycobiology. All of these notable distinctions are in addition to the many grants and awards obtained by MBB faculty from CIHR, NSERC, CCSRI, and MSFHR. We applaud all these efforts to bring excellence in research to SFU.

Faculty promotions

We congratulate **Dr. Nicholas Harden** on his promotion to Full Professor and **Dr. Sharon Gorski** for her success in obtaining tenure. Dr. Harden's research program has provided important insights into the signaling of Rho family small GTPases during dorsal closure in the *Drosophila* embryo. Dr. Gorski's work has focused on identifying regulators of autophagy and understanding their relationship to cancer development and therapy.

Teaching and student achievements

In addition to the MBB Department's strengths in research, we are particularly proud of our on-going mission to foster the advancement of our graduate and undergraduate students. As a superb example, Dr. Quarmby was nominated by her students for a well-deserved SFU Excellence in Teaching Award. As a notable example of the success of our graduate students, **Ms. Suraj Aulakh**, received a first place award in the SFU Business Concept Competition where Ms. Aulakh created a website (www.LabTricks.com) that helps other students understand lab techniques. This award follows Ms. Aulakh's win the previous year at the Gene Screen BC film competition for a short film on issues involving gene sequencing.

University of Toronto

Department of Biochemistry

Correspondent: David Williams

The past two years have been busy ones in the Biochemistry Department and have witnessed considerable growth in our Faculty and Graduate Student complement. So much so that its been a challenge to capture everyone in our annual Departmental photo. The shot below was taken at our 2011 Research Day at the Old Mill Inn, Toronto.



Faculty News

A number of Biochemistry Faculty received prestigious awards over the past two years. We were delighted to learn that **Shana Kelley** was awarded the \$10,000 NSERC Steacie Prize in 2011. This follows on the heels of Shana's Steacie

Fellowship which she received in 2010. The Fellowship takes the form of a \$250,000 research grant which will be used to further her studies on the development of chip-based sensors that can detect trace quantities of DNA, RNA and protein analytes in samples, and that have already been applied for early diagnosis of cancer.



Shana Kelley

Last August, **Harry Schachter** was honoured with The Austrian Cross of Honour for Science and Art First Class, a prestigious state designation from his birth country. Harry received the award for his seminal scientific achievements in glycobiology and also for his collaboration with scientists at BOKU: University of Natural Resources and Life Sciences, Vienna. The award was particularly poignant for Harry since, in 1938, his father foresaw the future for Jewish people in Vienna and moved his family to Trinidad in September 1938. This was just a few weeks before Kristallnacht – the Night of Broken Glass, a night of terror for many of the remaining Jewish people in Europe. In his presentation speech, Josef Glössl, the current Vice-Rektor of BOKU, not only spoke about Harry's science but also acknowledged the traumatic events in Austria of the late 1930s.



Harry Schachter receives the Austrian Cross from Josef Glössl

The Canadian Society of Atherosclerosis, Thrombosis, and Vascular Biology (CSATVB) honoured **Khosrow Adeli** with its Scientific Excellence Award at the annual meeting of the Society in Vancouver, October, 2011. Khosrow won the award for his research on the critical factors that coordinate lipid homeostasis in normal and insulin resistant states. Khosrow has also been very active in organizing a number of major conferences including taking on the role of Chair of the International Federation of Clinical Chemistry

Symposium (Toronto, Sept. 2011) and being a member of the organizing committees of the China-Canada Atherosclerosis Symposium, (Beijing, October 2011) and the International Congress in Pediatric Laboratory Medicine (Berlin, May 2011). He was also the Chair and Organizer of the CALIPER Investigators Workshop, (Toronto, October 2011)



Roula Andreopoulos

Senior Lecturer **Roula Andreopoulos** won the 2011 Faculty of Medicine Excellence in Undergraduate Teaching in Life Sciences Award. This award is presented each year to a faculty member in recognition of sustained excellence in the teaching, coordination and development of undergraduate

courses in Arts and Science offered by the Basic Sciences Departments in the Faculty of Medicine. Roula is coordinator and lecturer in our 1200-student Introductory Biochemistry Course BCH210 as well as coordinator and lecturer in BCH311, Nucleic Acids and Biological Information Flow, and Director of our new Online Biochemistry course.

Biochemical research seems to correlate well with longevity as evidenced by the number of our Faculty who were honoured with University service awards. **David Williams** and **Reinhart Reithmeier** received 25-year Awards and **Charles Deber** and **Roy Baker** received 35-year Awards. Charles, Reinhart and Roy are also well known at U. of T. as their alter-egos, the "Pro-Teens", a 50's era Doo-Wap group that entertains students annually with their geeky



Earnest academics by day....

but endearing science parody songs.

We were also pleased to learn that Professors **Amira Klip** and **Julie Forman-Kay** were successful in the renewal of their Tier I Canada Research Chairs. **Larry Moran** finished work on the 5th edition of his biochemistry textbook (Moran, L.A., Horton, H. R., Scrimgeour, K.G., and Perry, M.D., Principles of Biochemistry, 5th edition, Pearson/Prentice Hall, Upper Saddle River, NJ USA) and copies began rolling off the presses in late August 2011. The book is one of the most popular introductory biochemistry textbooks at colleges and universities in the United States and Canada.

Several of our colleagues have retired after long and distinguished careers. Having spent 32 years at the University of Toronto, **Annelise Jorgensen** retired June 30, 2010. Annelise joined the Biochemistry Department in 2002 after many years as a member of the Department of Cell Biology and Anatomy. She revitalized our undergraduate Cell Biology course offerings and, together with Angus McQuibban and Chi-Hung Siu, developed our current BCH445 (Organelles and Cell Function) and BCH446 (Membrane Dynamics of the Cell Surface) courses. Although retired, Annelise keeps her scientific interests alive by working on a web-based Histology Atlas as a resource for faculty and students. It is comprised of images collected over 60 years by the Division of Histology. **Roy Baker** also elected to take early retirement effective January 1, 2012. Roy started at U. of T. in the Department of Medicine in 1976 and switched his primary appointment to Biochemistry in 1998. Roy ran an active research program on lipid metabolism for many years. An award-winning lecturer, Roy taught countless medical and Arts & Science undergraduates every year. Since 2003, in



... "Pro-Teens" by night.

his role as Undergraduate Coordinator, Roy played a large part in the creation of our Major Program, a research-intensive Specialist Program, and an on-line Biochemistry course. He has also served as a most able and trusted Associate and Acting Chair.

After a career spanning more than four decades at the University of Toronto (beginning as an undergraduate student in 1968), **David Isenman** decided to take early retirement. David's former trainees, international collaborators and local colleagues gathered to celebrate at a Symposium in his honour on June 6th, 2011. David graduated from the Biochemistry Specialist Program in 1972 and stayed on as a graduate student with Dr. Robert Painter, finishing his Ph.D. in 1976. After post-doctoral fellowships at Scripps and the Weizmann, David returned to the Department as an MRC Scholar and Assistant Professor in 1979. He was promoted to Associate Professor in 1984 and Full Professor in 1991. A dedicated teacher, David won the Faculty of Medicine Aikins Teaching Award in 1996 and the Excellence in Life Science Undergraduate Teaching Award in 2006. David served as Course Coordinator for BCH471Y and JBI428H for many years, Graduate Coordinator from 1991-1993, Acting Chair for 6 months in 2002, Associate Chair from 2002 until 2008, and on numerous departmental and university committees. David's research interests lie in structure-function studies of the complement system and he has published a steady stream of papers on this topic. Following a successful sabbatical leave in 2010, David capped off his career with a co-authored paper in *Science* on the crystal structure of the complex between human complement receptor 2 and its ligand C3d, solving a 10-year controversy in the field.

Brenda Bradshaw, the Department's Secretary for Undergraduate Affairs retired following a 30-year career at U. of T. She began in 1981 as a mail sorter at the Banting and Best Institute and then worked in the purchasing division of MedStores from 1986 to 2000. Brenda then joined the Biochemistry Department in 2000. Brenda's outgoing personality served her well in this position and a decade of undergrads benefitted from her sound advice and good humour. At an afternoon gathering over cake and coffee, a string of testimonials from Chair Reinhart Reithmeier, past Chair Peter Lewis, Undergrad Coordinator Roy Baker and Business Officer Carol Justice described Brenda's accomplishments and noted the many lives she touched during her time here. Brenda will be greatly missed but we are delighted that she will be enjoying her retirement doing the gardening, reading and relaxing that there never seemed to be enough time to do before.

Finally, Faculty, Staff and Trainees gathered on May 2nd, 2011 to celebrate the retirement of our Business Officer **Carol Justice** (Avola) and also to thank her for her many years of dedicated and exceptional service to the Department. Carol started in Biochemistry in the old Medical Building in 1966 as a Clerk-typist (100 + wpm!) and moved into the Medical Sciences Building when it opened in 1968. With a few breaks to raise her family Carol remained in the department for over 40 years, filling many roles and moving up the ranks to Business Officer. Her work ethic, dedication and loyalty were inspiring to all around her. Carol considered Biochemistry her second family. We all wish Carol well in her retirement, which will allow her to spend more time with her real family. Carol will be greatly missed!



Retired Colleagues (left to right: Annelise Jorgensen, Roy Baker, David Isenman, Brenda Bradshaw and Carol Justice)

Events

Biochemistry Launches New Online Course

In 2010, the Department of Biochemistry, together with the School of Continuing Studies (SCS), laid the framework for the generation of a new online biochemistry course, SCS-2472: Biochemistry with a Medical Perspective. SCS-2472 consists of 54 1-hour illustrated video lectures and complementary medical vignettes, which were recorded over a span of 12 months. The team of instructors for SCS-2472 included award-winning professors from within the Department, **Dr. Reinhart Reithmeier**, **Dr. Roy Baker** and **Dr. Shana Kelley**, as well as **Dr. Robert Murray**, an emeritus biochemistry professor and medical doctor. This online course was successfully launched in January 2011, and is administered and supported by **Dr. Roula Andreopoulos** (Course Director) and **Dr. Sian Patterson** (Course Coordinator). SCS-2472 is offered three times annually to Canadian and international students, professionals, and individuals with an interest in biochemistry. The majority of students enrolled in the first four sessions have found the course ideal as preparation for entrance into professional health science programs including medicine, pharmacy, nursing, and dentistry. Students appreciated the flexibility of being able to take the course based on their schedules while viewing the video lectures at their own convenience. The logical and succinct progression of the course material enables all students, irrespective of their science background, to develop a real sense of engagement and interest in biochemistry.

BIOCHEMISTRY WITH A MEDICAL PERSPECTIVE

ONLINE COURSE FROM THE UNIVERSITY OF TORONTO
DEPARTMENT OF BIOCHEMISTRY, FACULTY OF MEDICINE

For more information regarding SCS-2472: Biochemistry with a Medical Perspective, check out our website at: www.onlinebiochemistrycourse.com

Our **Annual Research Days** were held on May 26th, 2010 and May 17th, 2011 at the Old Mill Inn in Toronto. The day highlighted work by our students and postdocs in the form of posters and oral presentations. Selected talks from some junior faculty also added to the mix. This has become

the traditional venue for our annual **Theo Hofmann lecture** which was presented in 2010 by **Joanne Lemieux**, University of Alberta, who took us on a structural tour of transmembrane proteases with a talk entitled "*Making the cut: a structural study of rhomboid proteases*". In 2011, our Theo Hofmann lecturer was **Kalle Gehring**, McGill University, who presented an eclectic selection of research vignettes entitled "*Tales from the Dewar*". Terrific science and good spirits combined to make both research days memorable experiences. For some photos of the events, go to:

http://biochemistry.utoronto.ca/news/news_archive/news_2010/Research_Day_10.html

http://biochemistry.utoronto.ca/news/Research_Day_11.html



Theo Hofmann with Joanne Lemieux and Kalle Gehring

Other events were our ever-popular **Golf Day**, **Ski Day** and **Year-End Party**. For some photos, visit: <http://biochemistry.utoronto.ca/news>

New Appointments

We are pleased to welcome **Roman Melnyk** to the Department. Roman is a Scientist in the Division of Molecular Structure and Function at the Research Institute of the Hospital for Sick Children and was appointed to the Department of Biochemistry in 2011 as an Assistant Professor. Roman obtained his Ph.D. with Charles Deber at SickKids, Toronto, completed postdoctoral training with John Collier at Harvard Medical School and then worked as a Senior Scientist in the small



Roman Melnyk

molecule drug discovery program at the Merck Frosst Centre for Therapeutic Research before accepting the position at SickKids. Roman's primary research goals are directed towards understanding the structure and function of key virulence factors implicated in bacterial pathogenesis to guide the design of novel therapeutics.



Frank Sicheri

The Department was also delighted to welcome **Frank Sicheri** who was cross-appointed in 2011 as a Professor in the Dept. of Biochemistry. Frank is a Senior Investigator of the Samuel Lunenfeld Research Institute at Mount Sinai Hospital. He uses X-ray crystallography as a means to understand protein kinase regulation with a focus towards the underlying structural mechanisms that imparts specificity to signaling function.

Congratulations also to **Grant Brown** who was promoted to the rank of Full Professor, and to **Ahlia Khan** who was promoted to Senior Lecturer.

Graduate Studies

Each year, our graduate students organize the **Benjamin Schachter Memorial Lecture** and they select a prominent graduate from our Department to address current students as a means to gain insights and advice on diverse career choices. The lectureship is named in honour of former graduate student Benjamin Schachter, who conducted research in the Department from 1934-1939. In 2010, the Biochemistry Grad Students Union invited back alumnus **Fraser Wright**. Fraser's talk was entitled "*From Academia to Industry, and Back: One Biochemist's Adventures*". Fraser discussed how his career took many twists and turns along the way, following various industrial and academic opportunities as they presented themselves. Both environments contributed to learning about the immunological challenges facing viral-mediated gene therapy, ultimately culminating in recent success in treating blindness associated with Leber's Congenital Amaurosis which has a defect in the RPE65 gene.

In 2011, our Benjamin Schachter Lecturer was **Tony Cruz** who gave a talk entitled "*From Academia to Biotech in Business: An Easy Transition!*". In a fascinating retrospective, Tony described his path from graduate school, to postdoc, to academic, to biotech CEO, emphasizing the unexpected events that he capitalized on to influence his directions. He provided an insider's view of the factors that influenced the success of many of his start-up companies as well as the failures. Most importantly, Tony offered advice to students to take risks at an early stage when the consequences of failure are minimal, to seek opportunities for exposure to different facets of research, industry and business, and not to be afraid to seize opportunities when they arise.



Members of Benjamin Schachter's family with Fraser Wright (left) and Tony Cruz (right)

An integral part of the Department's Annual Research Day is its **graduate student poster competition**. Our Theo Hofmann Lecturers, **Joanne Lemieux** and **Kalle Gehring**, served as guest judges and with other Faculty judges struggled with the challenge of deciding between many worthy posters. In the end, the following students (who receive cash awards) were chosen as poster winners:

2010

Winners in the Ph.D. category were:

Lindsay Baker (Rubinstein lab) "*The structure of ATP synthase from bovine heart mitochondria by single particle electron cryomicroscopy reveals the organization of the membrane-bound F_o region*", **Gong Chen** (Siu lab) "*Functional Analysis of Heterophilic Cell Adhesion Molecule LagC and its Partners during Dictyostelium discoideum Development*", **Jay Yang** (Brown lab) "*hTOPO IIIa is a single-stranded DNA decatenase that is stimulated by BLM and RMI1*", **Angela Yu** (Houry lab) "*Functional Interaction between the Molecular Folding Chaperone Trigger Factor and the ClpXP Degradation System in Escherichia coli*" and **Usheer Kanjee** (Houry lab) "*Linkage between the Bacterial*

Acid Stress and Stringent Responses: The Structure of the Inducible Lysine Decarboxylase".

Winners in the M.Sc. category were:

Dustin Little (Howell lab) "*Understanding the role of partial N-deacetylation of poly- β -1,6-N-acetyl-D-glucosamine in biofilm formation*", **Eric Zholumbetov** (Trimble lab) "*Role of Septin 5 in Exocytosis*" and **Alan Wong** (Rini lab) "*Structural and Biochemical Characterization of Human Coronavirus 229E Spike Glycoprotein and its Cellular Receptor Human Aminopeptidase N*".

The winner in the postdoc category was:

Yoshito Kakihara (Houry lab): "*Pih1/Nop17 is an adaptor regulating snoRNP biogenesis and rRNA synthesis in response to cell growth phase through a novel dynamic relocalization mechanism*"

2011

Winners in the Ph.D. category were:

Mahboubeh Ghoryshi (Parkinson lab) "*Elastin Polymorphisms Associated with Increased Risk of Thoracic Aortic Aneurysm and Dissection (TAAD)*", **Angela Yu** (Houry lab) "*Functional Interaction between the Molecular Folding Chaperone Trigger Factor and the ClpXP Degradation System in Escherichia coli*", **Lindsay Baker** (Rubinstein lab) "*The structure of ATP synthase from bovine heart mitochondria by single particle electron cryomicroscopy*", **Wioletta Glowacka** (Rotin lab) "*The lysosomal transmembrane protein LPTM5 is a positive regulator of proinflammatory signaling pathways in macrophages*" and **Lori Rutkevich** (Williams lab) "*Assessing the relative contributions of ER oxidases during the oxidative folding of human secretory proteins*".

Winners in the M.Sc. category were:

Tina Sing (Brown lab) "*Characterizing the role of the RSC Complex in DNA damage response and ploidy maintenance*", **Antoinette Bugyei-Twum** (Chakrabartty lab) "*A structure-guided design of a novel antibody selective for misfolded transthyretin*", and **Dustin Little** (Howell lab) "*Structural insights for the N-deacetylation of poly- β -1,6-N-acetyl-D-glucosamine*"

The winner in the postdoc category was:

Charles Calmettes (Moraes lab) "*Structural variations within the transferrin binding site on transferrin binding protein B, TbpB*".

Additional graduate awards:

The winner of the **Beckman Coulter Paper of the Year Award** for 2009 was: **Sean Reichheld** (Davidson lab) for his paper "*The induction of folding cooperativity by ligand binding drives the allosteric response of tetracycline repressor*" Reichheld, SE, Yu, Z and Davidson AR. PNAS (2009) 106:22263

The 2010 winner of the **Beckman Coulter Paper of the Year Award** was: **Wilson Lau** (Rubinstein lab) for his paper entitled "*Structure of intact Thermus thermophilus V-ATPase by cryo-EM reveals organization of the membrane-bound V(O) motor*." Lau, WC and Rubinstein JL PNAS (2010) 107:1367



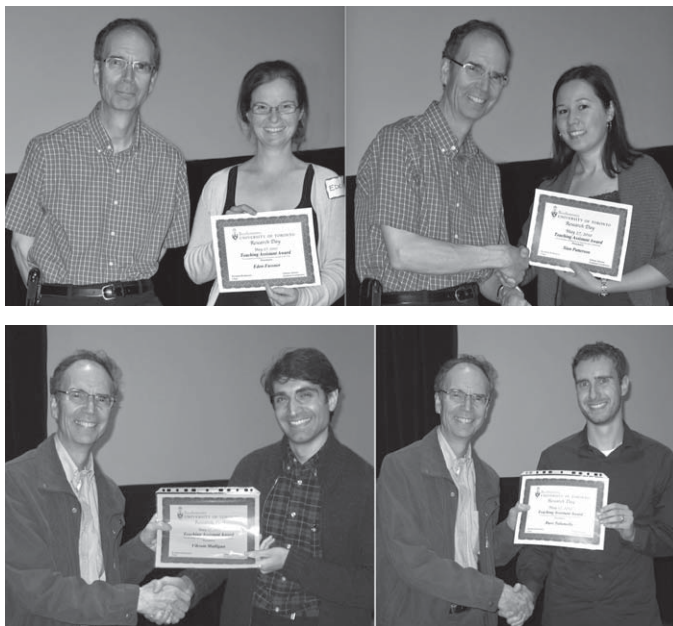
Sean Reichheld (left) and Wilson Lau present their Beckman Papers of the Year at Research Day

The annual **David Scott Prize** for outstanding all-round graduate student was awarded jointly in 2010 to **Eden Fussner** (Bazett-Jones lab) and **Sian Patterson** (Reithmeier lab) and in 2011 to **Wes Errington** (Privé lab). Award winners are selected on the basis of research and teaching excellence and outstanding contributions to the Department and to fellow students.



(left) Grad Coordinator Lil Attisano presents the Scott Award to Sian and Eden; (right) Wes receives his award from Roy Baker

In 2010, **Outstanding Teaching Assistant** awards went to **Eden Fussner, Sian Patterson** and **Patrick Walsh**. The outstanding TAs in 2011 were **David Tulumello, Vikram Mulligan, Priya Sharda** and **Ryder McKay**. Awards are given to acknowledge exceptional performance as teaching assistants in our BCH371, BCH 370, BCH471 and BCH210 courses.



Undergraduate Coordinator, Roy Baker, presents TA awards to Eden (left) and Sian and to Vikram (left) and David.

Congratulations to all winners on their achievements.

University of Toronto

Department of Cell and Systems Biology

Correspondent: Tony Harris

The Department of Cell and Systems Biology is a major contributor to research and teaching at the University of Toronto. Groups in the Department combine high-throughput, cell imaging, physiological and bioinformatics methods to characterize and understand cellular and physiological processes in both model (*Arabidopsis*, *Drosophila*, Mouse, Zebrafish, *Xenopus*) and non-model organisms. The Department's major strengths are its groups studying plant molecular biology, its labs focused on animal cell biology and tissue morphogenesis, and its groups studying neurophysiology. The Department is also home to the Centre for the Analysis of Genome Evolution and Function, a CFI-funded centre for genomics and proteomics research, in addition to a state-of-the-art imaging centre.

Our labs have made numerous exciting discoveries over the past two years. A few examples are highlighted here. Disordered protein regions are often enigmatic, but in a paper published in *Science Signaling* the lab of **Alan Moses** revealed how functionally relevant elements can be predicted. In *PLoS Pathogens*, the labs of **Darrell Desveaux** and **David Guttman** showed how a bacterial effector protein impacts the microtubule cytoskeleton to infect plant cells. In the *Journal of Neuroscience*, **John Peever's** group linked deficiencies in glycine and GABA transmission to REM sleep behaviour disorder, a predictor of neurodegenerative disease onset. Also in the *Journal of Neuroscience*, **Vince Tropepe's** lab showed how dopamine signaling can impact neural development in the zebrafish brain. In *PNAS*, **Rudi Winklbauer's** group revealed the large-scale mechanical properties of tissues and how they drive development of the *Xenopus* embryo. Also in *PNAS*, the labs of **Les Buck** and **Melanie Woodin** revealed how turtle brains naturally avoid damage in low oxygen conditions, suggesting strategies to protect the human brain from low-oxygen insults. This sampling highlights the vibrant research environment in the Department.

Our graduate program has also excelled. We welcomed 90 new students in 2010 and 2011, and congratulate 67 students on their graduation over the last two years. Currently we have 169 graduate students in the Department. We are very proud of our students' success in earning scholarships and travel awards. For example, our students won 21 NSERC Graduate Scholarships and 48 Ontario Graduate Scholarships in the last two competitions.



Sergio Peisajovich

In the last year, **Sergio Peisajovich** joined the Department as an Assistant Professor. Dr. Peisajovich studies synthetic and systems biology of regulatory networks, in addition to how networks evolve and how they can be engineered. In 2010, **Keiko Yoshioka** and **Nicholas Provart** were promoted to Associate Professor. In 2011,

Darrell Desveaux and **Tony Harris** were promoted to Associate Professor. **Patricia Romans** is now an Emeritus Professor in the Department. **Ulrich Tepass** has been Chair of the Department since 2009.

University of Toronto - Scarborough Campus

Department of Biological Sciences

Correspondent: Rongmin Zhao

The Department of Biological Sciences at the University of Toronto Scarborough grows steadily since its split from the former Department of Life Sciences in 2007. As of 2011, there are 31 full time faculty members in the Department. In 2010 and 2011, four new (Drs. Weir, Stehlik, McGowan and Treanor) and two cross-appointed (Drs. Zhang and Kerman) members joined the faculty to expand and complement the research profile and instructional offerings of the Department. Particularly, **Dr.**

Jason Weir's interest in conservation ecology and evolution fosters his search for key factors that drive the build-up of biodiversity in tropical and temperate regions. **Dr. Patrick McGowan** studies the interaction between the genome and environment. **Dr. Bebhinn Treanor** is the newest addition to the department (2011). She is interested in exploring how cell-surface scaffolding proteins modulate the interaction, function and turnover of immune cell glycoproteins by using advanced optical microscopy techniques. Together with the Biological Sciences' faculty, cross-appointed professors **Drs. Xiaonan Zhang** and **Kegan Kerman**, from the Department of Physical and Environmental Sciences (DPES) at UTSC are interested in Chemical Biology and Neuroscience. They are actively collaborating with colleagues in developing biosensors.



Dr. Bebhinn Treanor, an immunologist, who studies the cellular and molecular mechanisms of immune cell activation

The Department of Biological Sciences maintains a very successful record of attracting external research funding. Almost every faculty member holds an NSERC Discovery Grant; additionally, three CFI/LOF grants (**Drs. Cadotte, Welch and Kerman**) were secured in 2010 and 2011. The Department currently has four Canada Research Chairs (**Drs. Aarts, Brown, Andrade and Kronzucker**). **Dr. Malcolm Campbell** received a Discovery Accelerator Supplement award and a Strategic Project Research grant from NSERC to investigate the effect that early environment can have on gene expression in trees. **Dr. Patrick McGowan**, who studies epigenetic changes in brain systems, recently received a Connaught New Researcher award and a grant from the Chronic Fatigue and Immune Dysfunction Syndrome (CFIDS) Association of America. **Dr. Ian Brown** was awarded an NSERC Discovery Grant in 2010 and his grant was scored in the top two percentile in Canada in the "Genes, Cells and Molecules" Evaluation Group.

Graduate students in the Department also made significant achievements in the last two years. Three NSERC Canada

Graduate Scholarships (Doctoral) were brought to the Department (**Michael Prouse**, **Noushin Nabavi** and **Devrim Coskun**). **Sherri Thiele** received a Scholarship from the Parkinson Society of Canada. Moreover, Ph.D. student **Eric Lewallen** performed molecular studies and confirmed that the wide variety of flying strategies found in fish around the world are all the result of a single evolutionary chain of events, and his study attracted major media attention.

Colleagues in the Department were also well recognized for their contributions to teaching. **Dr. Rene Harrison** was recognized as the “Professor of the Year” in 2010 by The Underground UTSC, an official student publication. **Dr. Clare Hasenkampf**, who leads a research group in studying the structure and function of eukaryotic chromosomes, won the Ontario Confederation of Faculty Associations Teaching Award, and she was inducted into the 3M National Teaching Fellowship in 2010, acquiring the highest teaching honour for a University faculty member in Canada.

In July 2010, **Dr. Dudley Williams** retired. Dr. Williams has been recognized for his contribution in aquatic invertebrate population and Ecology, and he was awarded an NSERC Certificate of Excellence in 2010 for 25 years of continuous funding. The Department **Chair Dr. Greg Vanlerberghe**, also held a joint Departmental retreat with the Department of Environmental and Physical Sciences at UTSC in December 2011. The two Departments introduced their current research programmes and discussed potential collaboration in the field of environmental stresses.

Ontario Cancer Institute Princess Margaret Hospital

Correspondent: Linda Penn

In 2010:

Senior Scientist **Dr. Mitsuhiro Ikura** has been recognized by the Canadian Cancer Society with the 2010 Robert

L. Noble Prize, given for outstanding achievements in cancer research. A Tier I Canada Research Chair in Cancer Structural Biology, Dr. Ikura is being recognized for his groundbreaking findings in the field of cancer signaling protein structural biology. Over the course of his career, Dr. Ikura's research has significantly expanded our understanding of signaling proteins and processes involved in human diseases such as cancer, neurological disorders and heart disorders.



Mitsuhiro Ikura

Dr. Catherine O'Brien joined the Ontario Cancer Institute as a Scientist and PMH Cancer Program Member. Catherine came to UHN following a surgical oncology fellowship at the University of Toronto and doctoral studies on cancer stem cells in colon cancer under the supervision of Drs. John Dick and Steven Gallinger. Her research is focused on the biology and pathways that regulate colon cancer stem cells in translational medicine.

The OCI welcomed **Dr. Rodger Tiedemann**, a New Zealand-trained hematologist/oncologist and expert in multiple myeloma, as a Scientist at the Ontario Cancer Institute. Rodger comes to Toronto via Scottsdale, Arizona's Mayo Clinic where he held an Assistant Professorship of Medicine. His laboratory is engaged in high-throughput genome-scale RNA interference screens in multiple myeloma to identify vulnerable novel therapeutic targets.



Rodger Tiedemann

2011:



Ernest McCulloch

Dr. Ernest McCulloch (1926-2011) On January 20, 2011, Dr. Ernest “Bun” McCulloch passed away. Dr. McCulloch was an esteemed Senior Scientist and former Head of Biology at the Ontario Cancer Institute/Princess Margaret Hospital and a University Professor Emeritus at the University of Toronto. This pioneer of stem cell science, along with Dr. James Till, is

renowned for establishing an entire field of study with the 1961 discovery of blood-forming stem cells.

Dr. Richard (Dick) Hill received the 2011 Henry S. Kaplan Distinguished Scientist Award from the International Association for Radiation Research in recognition of his scientific achievements in basic and practical radiological sciences. **Dr. Bradly Wouters** was awarded the Klaas Breur Gold Medal Award from the European Society for Therapeutic Radiology and Oncology (ESTRO). The Klaas Breur Award, the most prestigious prize awarded by ESTRO, acknowledged Dr. Wouters’ major scientific contributions to the field of radiotherapy.



Richard Hill



Bradly Wouters

Hospital for Sick Children Cell Biology, Developmental and Stem Cell Biology, and Molecular Structure and Function Programs

Correspondents: William Trimble, Najeeb Siddiqui and Lynne Howell

Excitement continues to mount for SickKids researchers as the new Research and Learning Centre approaches completion (see news below). The new building will significantly enhance interactions among an already vibrant research group at SickKids. In addition, many of our biomedical researchers have made the news or received national and international recognition for their contributions over the past two years.

Awards

Dr. Elizabeth Frank presented the 2011 Commission on Accreditation (ComACC) service award to **Dr. Khosrow Adeli**, the training program Director at the University of Toronto at the National Academy of Clinical Biochemistry Awards Ceremony in Atlanta, Georgia. The Commission on Accreditation is an independent non-profit organization that accredits training programs in clinical chemistry at the masters, doctoral, and postdoctoral level. The purpose of granting accreditation to training programs is to foster their excellence, to provide recognition to accredited programs, and to attract qualified individuals to training centers of excellence. This process is intended to assure the trainee that the standards of education and training are consistent with the progress in medicine and clinical laboratory sciences.



Khosrow Adeli receives the ComACC award from Elizabeth Frank

Dr. Darius Bagli was recently recognized as the 2012 Distinguished Mentor by the American Urology

Association. This distinction honours those with a strong record of mentoring research scholars in the field of Urology. Dr. Bägli is currently investigating extracellular matrix biology as it pertains to wound healing and biomechanically-mediated injury in the lower urinary tract.



John Brumell

John Brumell received the 2012 GE Healthcare New Investigator Award from the CSMB, joining an impressive list of previous recipients. John, who completed his PhD with Sergio Grinstein (SickKids) and postdoctoral work with Mike Tyers (Mt. Sinai Hospital) and Brett Finley (UBC), continues to

make significant advances into understanding the mechanisms by which pathogenic bacterial cells subvert normal cellular processes to proliferate and spread.



Amira Klip

Amira Klip was elected as Fellow by the Canadian Academy of Health Sciences in 2011. CAHS Fellows are prominent scientists who have a history of outstanding performance in the academic health sciences in Canada. In addition, Amira renewed her Tier I Canada Research Chair in Cell Biology of Insulin

Action. Amira's research focuses on understanding

how muscle and fat cells respond to insulin in healthy individuals, and how this insulin-responsiveness is lost during type II diabetes.

Dr. Freda Miller became a Fellow of the American Association of the Advancement of Science (AAAS) in recognition to her scientific accomplishments in the area of neuroscience. Dr. Miller also recently renewed her Tier I Canada Research Chair in Neuroscience.

Dr. Norman Rosenblum received the 2011 Kidney Foundation of Canada Medal for research excellence. This medal is given to one individual every year for their scientific research excellence in the area of nephrology.

Daniela Rotin was named a Woman of Action by the Israel Cancer Research Fund in 2011. Daniela also renewed her Tier I Canada Research Chair in Biochemistry and Signal Transduction in 2011. Daniela's research centers on protein degradation and phosphorylation and how these affect human diseases such as cancer, inflammatory bowel disease, hypertension and cystic fibrosis.



Daniela Rotin

Jim Rutka was elected as Fellow to the Royal Society of Canada. Jim becomes the 10th active SickKids Research scientist to become a RSC Fellow, one of the highest honours available for academics in Canada. Jim is a neurosurgeon in the Division of Neurosurgery at SickKids, Director of the Arthur and Sonia Labatt Brain Tumour Research Centre at SickKids and is also the Chair of the Department of Surgery at the University of Toronto. Jim's research focuses on the molecular biology and genetics of malignant brain tumours with particular focus on the regulation of the cytoskeleton by Rho family GTPases and its role in cell migration and tumour invasion.



Jim Rutka signs the RSC membership book with Daniel Wayner, Honorary Secretary, RSC

Dr. Simon Sharpe wins a 2010 Early Research Award from the Ministry of Research and Innovation. Researchers will receive up to \$140,000 each through the program. Simon Sharpe, a Scientist in Molecular Structure & Function at SickKids, and Assistant Professor at the



Simon Sharpe

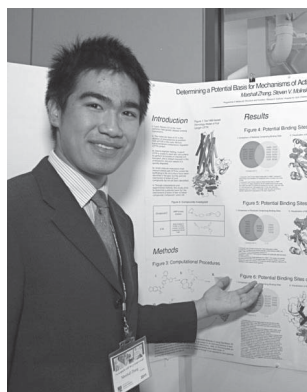
University of Toronto is researching the interaction between tetherin and the HIV-1 virus. The protein tetherin protects our bodies by preventing cells infected by certain viruses from releasing new virus particles into the rest of the body. Some viruses, however, can fight back. The HIV-1 virus, for instance, has a protein that can overcome tetherin's protective effect.

Sharpe's research could lead to new antiviral therapies.

The Early Researcher Award (ERA) program helps promising, recently-appointed Ontario researchers build their research teams of undergraduates, graduate students, post-doctoral fellows, research assistants, associates, and technicians. The goal of the program is to improve Ontario's ability to attract and retain the best and brightest research talent.

Mentorship

Marshall Zhang, a grade 12 International Baccalaureate student at Bayview Secondary School in Richmond Hill, Ontario, mentored by Dr. Christine Bear and her graduate student Steve Molinski, won the 2011 National Sanofi-Aventis BioTalent Challenge award. His research focused on the mechanism of how two small effector molecules act to correct molecular defects in the protein that causes cystic fibrosis, research that may one day have important implications in the development of novel therapeutics for the disease. Zhang also represented Canada at the International BioGENEius Challenge in Washington D.C. in July 2011.



Marshall Zhang with his winning poster

Recruitments and Departures

Dr. Roman Melnyk, a former graduate student of the Biochemistry Dept. at UofT, joined SickKids as a Scientist in March 2011. Following a PDF at Harvard Medical School, where he helped define the molecular mechanism of translocation through the anthrax toxin pore, Roman spent 4 years at Merck Forst Canada in Montreal. His current research program uses chemical biology and targeted drug discovery approaches, coupled with molecular biophysics and structural analysis, to identify and validate host and toxin targets and discover small molecule hits for further exploration and development.



Roman Melnyk

Dr. Shoshana Wodak retired in April 2012 after 8 years at SickKids and The University of Toronto. Dr. Wodak obtained her PhD degree from Columbia University, New York. She was a professor at the Free University of Brussels for over 20 years, where she founded and co-directed the Centre of Structural Biology and Bioinformatics and started a Master's program in Bioinformatics with colleagues in 2001. Dr. Wodak is best known for her pioneering work on many computational methods for the analysis, prediction and simulation of protein structures and protein interactions. While at SickKids, she was the Scientific Director of the Centre for Computational Biology and held a Tier 1 Canada Research Chair in Computational Biology and Bioinformatics. Her research in the last decade has focused on developing advanced database tools for the representation and analysis of protein-protein interaction networks and biochemical pathways, as well as computational methods for protein design and the analysis of protein-protein and protein-DNA interactions.



Shoshana Wodak

News

Dr. Benjamin Alman's research has resulted in the development of a cream that can dramatically reduce scar formation. This groundbreaking discovery was recently reported in the *Globe & Mail*: (<http://www.theglobeandmail.com/life/health/new-health/health-news/canadian-discovers-method-to-radically-minimize-scars/article2424537/>)

Dr. Michael Taylor received the \$10 million Large Scale Applied Research Project grant from Genome Canada for RNA-seq and whole genome sequencing analysis of over 1000 human medulloblastomas.

Topping off Ceremony marks construction milestone for the new SickKids Centre for Research and Learning.

Work continues apace on the New SickKids Centre for Research and Learning. On May 4, 2012, two years to the day after the shovels first hit the ground, SickKids celebrated the fact that concrete construction had reached its highest point with a Topping off Ceremony. The Tower is a 750,000 square foot, 21 storey building, designed by Diamond and Schmitt Architects Inc. In the Fall of 2013, it will become the home to more than 2000 SickKids scientists, trainees and child health research staff. The SickKids Centre for Research and Learning has been designed to achieve LEED® Gold Certification, the second highest level of the rigorous qualifications developed by the Canadian and U.S. Green Building Council, and will set the standard for energy efficiency and sustainable infrastructure in Toronto's Discovery District.



The new Centre for Research and Learning rises behind other SickKids buildings at the corner of Bay and Elm Streets, image by Craig White

The building will cost \$400M to build and equip and is one of the single largest capital projects dedicated to pediatric research in the world. \$200M was raised by the Hospital through long term bonds guaranteed by the Foundation, while \$91.1M was provided by the CFI Hospital Fund Large Scale Institutional Endeavours. The remainder will be raised by philanthropic donations through a special fundraising campaign and, to start this off, the Government of Ontario provided up to \$75M to match donations made toward the building. In addition, a transformative donation of \$40M was provided by Peter Gilgan, Founder and CEO of Mattamy Homes, so we are well on our way to reaching our goal.



Forty SickKids researchers and patient ambassadors join Mary Jo Haddad, President and CEO, SickKids; Tim Hockey, SickKids Campaign Cabinet Chair; and Dr. Janet Rossant, Chief of Research, SickKids (centre right to left), to thank Peter Gilgan

(at podium) who announced his \$40 million donation to SickKids Centre for Research and Learning March 7, 2012 at The Hospital for Sick Children (CNW Group/SickKids Foundation)

University of Victoria

Department of Biochemistry and Microbiology

Correspondent: Robert Burke

The Department of Biochemistry and Microbiology leads in teaching and research of biomedical science and molecular biology at the University of Victoria. With 15 faculty, 40 graduate students and 11 post-doctoral fellows, our programs emphasize our expertise in structural biology and proteomics, microbial pathogenesis, and gene regulation. Our undergraduate and graduate teaching integrate biochemical and microbial approaches to problems in health and the environment.

The past few years have seen continuous growth in our undergraduate programs. We continue to emphasize hands on learning, which means our undergraduates spend a lot of time at the bench where they acquire individual skills and experience. In spite of Canada's economic woes, the Coop program thrives, in part because our courses are designed to give students skill-sets that are attractive to employers. The Coop coordinator, **Rozanne Poulson** placed about 180 students in Coop jobs last year and has introduced a new Internship program. The Honours program, which consists of two terms in a research lab, seminars, and a thesis examination, is an essential program for students who want to become involved in research. The growing numbers of Honours students emphasizes the interest that students have in research. We are developing new curricula in Epigenetics and Proteomics, both areas supplemented by new Faculty appointments. **Chris Nelson** arrived with his expertise in yeast and mammalian systems to study epigenetic signaling in 2009 and we are currently interviewing candidates for a faculty position in proteomics. **Doug Briant** was added to the faculty in 2011 as a Senior Instructor and we have benefitted from his enthusiasm for, and expertise in, effectively teaching large classes.

Steve Evans, the Graduate Advisor, has transformed our graduate program into a structured training program that provides students with the background, opportunities, and challenges necessary for them to thrive as independent scientists. The growth in our graduate programs is steady and fulfills important roles for our research and teaching programs.

A number of faculty have been recognized with awards over the past couple of years. **Terry Pearson** was awarded the Craigdarroch Gold Medal for Career achievement and **Caren Helbing** was recognized with a Craigdarroch Award for Innovation and Entrepreneurship. The University of Victoria Genome BC Proteomics Centre has thrived under the capable leadership of **Christoph Borchers**, who has been honoured with a Research Chair from the Leading Edge Endowment Fund. This year **Marty Boulanger** received the Faculty of Science Research Excellence Award and **Al Boraston** was recognized with an NSERC Staacie Fellowship. We are very proud of all of their accomplishments!

The Department continues to move forward with innovative and distinctive programs that are based on a history of excellence in research and teaching. The fundamentals of learning by doing and the captivation of imaginative research serve us well in ensuring the success of our students and our programs.



The Salish "Welcoming Totem" stands in front of the Petch building, arms outstretched to welcome all to the University of Victoria. Biochemistry and Microbiology expanded its space to the first and second floors of the Petch building in 2010

University of Waterloo

Department of Biology

Correspondent: Bernie Dunker

During the past two years, the impressive influx of talented new faculty members to the Department of Biology at the University of Waterloo has continued. **Matt van der Meer**, a neuroscientist who joined us after completing his postdoc at the University of Minnesota, studies decision making through the development of computational models based on recordings of electrical signals from multiple brain structures in rats. Long-time CSMB member **Moir Glerum** moved her research lab here from the University of Alberta; she studies mitochondrial myopathies



Matt van der Meer

and biogenesis, as well as assembly of cytochrome oxidase in yeast and humans. We were also excited to recruit **Todd Holyoak**, who moved his lab from the University of Kansas. Todd is a structural biologist who uses steady state kinetics and x-ray crystallography to study phosphoenolpyruvate carboxykinases and IgA proteases.

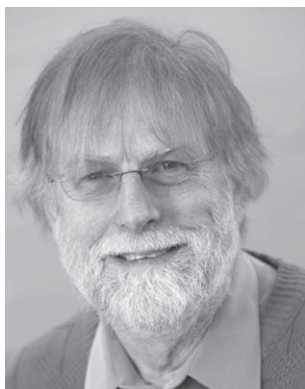


Moira Glerum



Todd Holyoak

The numerous awards recently received by UW Biology faculty include a Tier 1 CRC Chair to **Brian Dixon**, a Tier 2 CRC chair to **Matt van der Meer**, and a Lifetime Achievement Award from the Society of In Vitro Biology to **Niels Bols**. Finally, we were excited to hear that the green light has been given for the construction of a large new Science building in which Biology will be a major tenant!



Niels Bols

University of Waterloo

Department of Chemistry

Correspondent: Guy Guillemette

Biochemistry and Molecular Biology at the University of Waterloo are key areas of focus in the Departments of Chemistry and Biology. The Institute of Biochemistry and Molecular Biology (IBMB) was established to coordinate these areas of activity at UW. Together, we operate a strong undergraduate program in Biochemistry; one of the flagship programs of our faculty. We have a large number of graduate students carrying out research in Biochemistry and Molecular Biology.

In the past year, a multinational team led by **Gary Dmitrienko** of the Department of Chemistry was awarded funding to investigate bacterial resistance to antibiotics. A description of the program has been provided by Gary Dmitrienko.

On November 14, a special event was held in the Dmitrienko research laboratory. The Minister of State for Science and Technology, the Right Honourable Gary Goodyear, and Dr. Marc Ouellette, Scientific Director of the CIHR-Institute of Infection and Immunity, as well as Dr. **George Dixon**, UW's VP of Research, Dr. Maureen Mancuso, University of Guelph's VP (Academic), and several local dignitaries, were in attendance for the formal announcement of funding (approximately four million dollars from CIHR in Canada and two million pounds from MRC in the UK) for two new research teams, assembled to battle the serious clinical problems posed by bacterial resistance to antibiotics. The two research teams have been funded through the Canada/UK Partnership on Antibiotic Resistance, a collaboration between the Canadian Institutes of Health Research and the UK Medical Research Council. The partnership takes advantage of research strengths that exist in both Canada and the UK in the area of antibiotic research.

One team led by **Professor Gary Dmitrienko** of the University Waterloo and **Professor Tim Walsh** of the University of Cardiff will focus on hospital acquired infections with the aim of developing a new treatment for infections caused by bacteria resistant to beta-

lactam antibiotics (e.g. penicillins, cephalosporins and carbapenems). Another team led by Professor **Anthony Clarke** of the University of Guelph and **Professor Chris Dowson** of the University of Warwick will focus on increasing our understanding of bacterial cell wall growth and production with the aim of identifying new targets for the development of new antibiotics.

Both Dr. Dmitrienko and Dr. Clarke spoke briefly about their respective research teams and, through the wonders of Skype (and the computer skills of Dr. **Nan Chen** in the Dmitrienko group), two key team players on the UK side, Dr. Jim Spencer from the University of Bristol, and Professor Chris Dowson from the University of Warwick, were able to speak to the gathering about the team participants in the UK components of the Dmitrienko team (at Bristol, Cardiff, Leeds and Oxford) and the Clarke team (at Bristol, Birmingham, Leeds, Sheffield and Warwick).

Dr. Dmitrienko commented that, “although research can often involve complex hypotheses and sophisticated scientific instrumentation, it is for the most part about people and I will concentrate on people in my remarks this morning. I believe we have assembled an exceptional collection of extremely talented and dedicated researchers both in Canada and in the UK to cooperate in tackling the very serious problem posed by antibiotic resistance.”

He went on to identify the key members of the Canadian component of his team. These included Professor **William Lubell** in the Department of Chemistry and Biochemistry, at the Université de Montréal, Dr. **Don Low** at the University of Toronto and Mount Sinai Hospital, Professor **Stefan Siemann** in the Department of Chemistry at Laurentian University in Sudbury, Professor **Jeuwen Liu** here at Waterloo, Dr. **Johann Pitout** and Dr. **Dylan Pillai** at the University of Calgary and finally Professor **Natalie Strynadka** at the University of British Columbia.

He added, “I would like to acknowledge the fine efforts of members of my own research group that allowed us to put together a credible and ultimately fundable research proposal. In particular, I thank **Valerie Goodfellow** (B. Sc. Hon. Co-op Chem. UW, 1981; M.Sc. GWC2 1992) for fine efforts in the area of microbiology and biochemistry, Dr. **Laura Marrone** (B. Sc. Hon. Co-op Biochem.(1993)

and Ph.D. (1997) UW) for her research in enzymology, and the members of the organic chemistry component of my group, Dr. **Ahmad Ghavami**, Dr. **Anthony Krismanich** (Ph.D. UW Chem. 2008), Dr. Nan Chen (Ph.D. UW Chem. , 2010), Dr. **Ahmed Desoky** (Ph.D. UW Chem, 2011), Dr. **Glenn Abbott** (Ph.D. UW Chem, 2011) and Dr. **Jarrold Johnson** (Ph.D. UW Chem, 2011) who is now a postdoctoral fellow at Notre Dame in the US, working on antibiotic research. Also with us is **Carol Tanner**, who is an undergraduate biochemistry research student working on this project.”

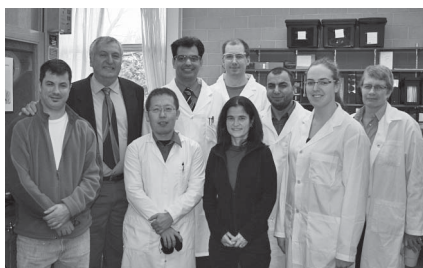
He went on to say, “I also must acknowledge the efforts of members of the Office of Research here at Waterloo, who have gone to extraordinary lengths over a number of years in supporting our efforts to secure funding for research in the antibiotic resistance area. In particular, I thank Leslie Copp who is our resident expert in all things related to CIHR and Scott Inwood, Waterloo’s Director of Commercialization, who provided much guidance to my research group in regard to intellectual property protection and who has agreed to continue in that role for the team effort going forward.”

Dr. Dmitrienko concluded by saying, “Finally I would like to make note of the contributions of someone who is not with us this morning physically but who I am sure is here in spirit. I have posted here a picture of Professor **Thammaiah Viswanatha** who was for many years the heart of biochemistry teaching and research here at Waterloo. He was a mentor both to me, when I was a young postdoctoral fellow, and to Professor Clarke when he was a Ph.D. student here at Waterloo and to many others over his long and illustrious career. It was he who first introduced me and Professor Clarke to biochemistry and to the field of antibiotic resistance and he served as an inspiration to the both of us and to our research group members for many years until his untimely death in 2008. I feel that it is fitting that he be included in this event.”

Leslie Copp, (currently Senior Manager, Grants & Government Research Contract in UW’s Office of Research), who was in attendance and who worked with Professor Viswanatha as a summer research assistant while she pursued her Honours B.Sc. in Biochemistry here at UW some years ago, commented in an e-mail message after the event, “it was wonderful to have TV mentioned,

I saw his picture right away when I came in – and it is exactly how I remember him! And to be the mentor for both successful teams in this initiative is extraordinary and shows what a major influence he was.”

All in all, this felt like a rather good day for Chemistry at UW and, hopefully, this is a sign of good days ahead. For additional comments and a few pictures of this event and related issues, go to the following links:
<http://www.bulletin.uwaterloo.ca/2011/nov/15tu.html>
<http://www.cihir-irsc.gc.ca/e/44519.html>
<http://www.therecord.com/news/local/article/625038--uw-joins-two-nation-team-to-fight-super-bugs>
http://www.research.uwaterloo.ca/watco/ipmg_news_watpharm.asp



Dr. Gary Dmitrienko (second from left) and his research group at the University of Waterloo

Chemistry and Biochemistry Reunion

As part of the year of celebrations in 2011 associated with the International Year of Chemistry, the faculty of science at the University of Waterloo hosted a Chemistry and Biochemistry reunion on September 24, 2011. **Sharon McFarlane** the Science Alumni Services Coordinator has written a summary of the event. Some returned with light-hearted stories of first year chemistry labs gone horribly wrong while others joked about the home-made beer they tried to sell in residence. Others marveled at the transition of the University campus and the rise of so many buildings and development of academic programs

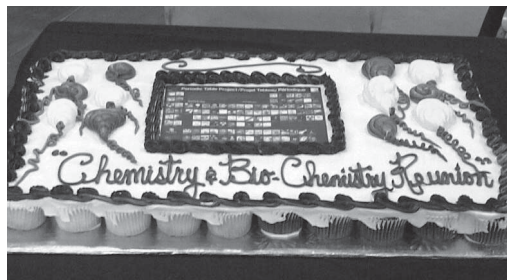


Attendees at the Chemistry and Biochemistry Reunion 2011

since they graduated. This Fall, a wave of enthusiastic biochemistry and chemistry alumni returned to campus to reunite at their alma mater during Reunion Weekend.

The day started off with tours of existing chemistry and biochemistry labs, showcasing some of the Department's up and coming research as well as providing a nostalgic flood of emotions for many. University of Waterloo President, Feridun Hamdullahpur along with Dean of Science, **Terry McMahon** and Chemistry Chair, **John Honek** all welcomed our alumni back with open arms, "It's a tremendous honour for us," said Terry McMahon as he addressed the forty or so alumni, "to hear of your successes upon graduation knowing in some way we helped you along your current path."

Shortly after the welcome session, the department unveiled the impressive Periodic Table Project. Alumni helped themselves to a special cupcake dessert before making their way to watch the Warrior football game in the alumni VIP tent.



Periodic Table Project Dessert

The final event of the night was a sit down dinner with some current and retired faculty at the University Club. It was a great opportunity for old friends to reconnect. Bob Wells and Bruce Fraser were friends and lab partners over thirty years ago and had not seen each other since graduation, "This guy got me through! I can't tell you how happy I am to see him after all these years," grinned Bruce. "He even offered free haircuts back in the day to those guys with the long hair. His residence room had a line up right out the door when it was time for co-op interviews too."



Bob Wells and Bruce Fraser

Alumni received a commemorative plaque of a special periodic table element, and during what was supposed to be an entertaining game of word scramble using chemistry tiles nearly came to good natured fisticuffs as Alumni Advancement Officer, Sharon McFarlane, tried to control the ensuing mayhem! A big thanks to Ray Clement ('81) for his thoroughly enjoyable stint as the evening's Master of Ceremonies and to Enrico Seminario ('84) and Terry McCurdy ('84) for their tireless work getting people to return home for the reunion.

Chem 13 News Periodic Table Project

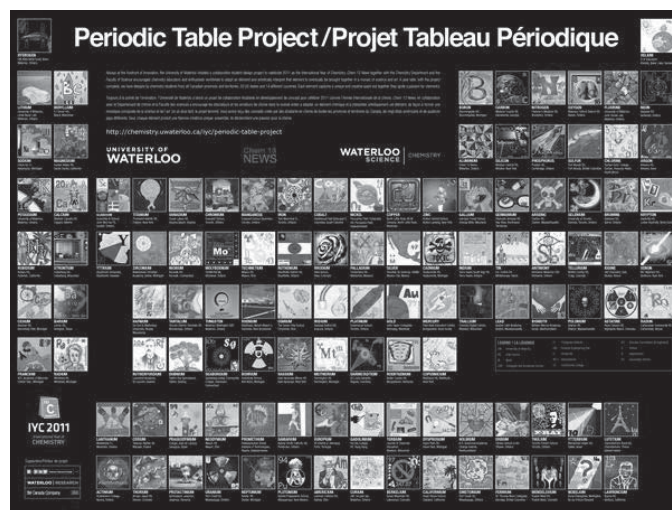
Chem 13 News is an informal magazine published monthly by the Department of Chemistry at the University of Waterloo for teachers of introductory chemistry courses, especially at the high school and Year 1 college levels. Approximately 3000 teachers subscribe from 30 countries. Many of our authors are high school teachers. As part of the IYC, *Chem 13 News* initiated a special periodic table project as summarized here by **Jean Hein** the editor of the magazine.

The International Year of Chemistry (IYC) is coming to a close. *Chem 13 News* together with the Chemistry Department and the Faculty of Science encouraged chemistry educators and enthusiasts worldwide to adopt an element and artistically interpret that element. The project would create a Periodic Table as a mosaic of science and art. A small version of the final project is displayed above. You can go online to see the project and read about the creative process of each tile at: <http://chemistry.uwaterloo.ca/iyc/periodic-table-project>

Thank you to all the teachers and students who participated in the collaborative Periodic Table project. Students from all Canadian provinces and territories, 20 US states and 14 countries researched, created and designed the elemental tiles. We would like to thank 3M Canada and the University of Waterloo for providing support to the project. We have more exciting plans for the project beyond the International Year of Chemistry. One goal is to have a large (25' by 18') wall mural display of the project on the University of Waterloo campus.

You may be wondering where the final classroom-sized Periodic Table posters (36" by 27") are displayed. The University of Waterloo has helped us mail out complimentary posters to all participants, all *Chem 13 News* readers and all high schools in Canada. We have been celebrating the project by handing out complimentary Periodic Table posters at conferences during IYC: the 94th Canadian Society for Chemistry in Montreal, Quebec; Chem Ed 2011 in Kalamazoo, Michigan; American Chemical Society High School Day in Denver, Colorado; 61st Canadian Chemical Engineering, London, Ontario and the STAO conference (Science Teachers' Association of Ontario) in Toronto, Ontario. Thanks to Chem Ed 2011 and STAO for giving us the opportunity to display our large travelling version of the Periodic Table Project.

To order a poster and have it shipped to you, contact Spectrum Customer Service: 1-800-668-0600 and reference Product # 9003M, or order online at <http://www.education.spectrum-nasco.ca>; search for product # 9003M.



Periodic Table Project

University of Western Ontario

Department of Biochemistry

Correspondent: David Edgell

The Dept. of Biochemistry at Western strives for excellence in research and teaching. During 2010 and 2011, our multidisciplinary community continued to advance our research programs, educate undergraduate students, and train graduate students and post-doctoral scholars.

Faculty News

Nathalie Berube, **Melissa Mann**, and **James Choy** were promoted to Associate Professor. **Shawn Li** was promoted to Full Professor. Sabbaticals include **Hong Ling** (2010-11), **James Choy** (2011-12), and **Shawn Li** (2011-12).

Greg Penner was appointed in September 2010 as an Adjunct Professor in the Dept. He is President and CEO of NeoVentures Biotechnology Inc., a biotech company located in The Stiller Centre in London, ON. This company specializes in the development and commercialization of agricultural biotechnology.

Professor Emeritus **William (Bill) McMurray** passed away on 2 Aug 2011 at the age of 80. He was the former Chair of Biochemistry from 1983-93, retiring in 1996 with 36 years of service. He led the recruitment of molecular biologists for the Dept., opening the way for an interdisciplinary graduate program in Molecular Biology and a new Biochemistry/Chemistry Honors program.

Several of our primary faculty and cross-appointees received research, service, and teaching awards at the University and Faculty levels. The Faculty Scholar Award was given to **Greg Gloor** (2011) and **Rob Hudson** (2010). The Dean's Award of Excellence for Faculty was awarded to **David Haniford** (2011), **Chris Brandl** (2010), and **David Edgell** (2010). **David Litchfield** (Chair of Dept.) received Western's Division of Experimental Oncology Award of Excellence in Research & Teaching (2011). **Lars Konermann** won the Florence Bucke Prize in the Faculty of Science (2011). **Rob Hegele** received his renewal for the

Jacob J. Wolfe Distinguished Chair in Human Genetics (2010). In 2011, **Derek McLachlin** earned Western's Award of Excellence in Undergraduate Teaching, as well as the Schulich Educator Award. He, **Gary Shaw**, **Greg Gloor**, and **Lars Konermann** were named to the University Students' Council Teaching Honour Roll (2009-10).

External research awards included a CIHR New Investigator Award for **Walter Siqueira** (2011) and the CLC Senior Scientist Award for Excellence in Lipid and Lipoprotein Research in Canada for **Murray Huff** (2010). **Gary Shaw** received a renewal for his Canada Research Chair (CRC Tier I) in Structural Neurobiology (2010). **Shawn Li** received his CRC Tier 2 renewal in Functional Genomics and Cellular Proteomics (2010).

Biochemistry faculty published about 175 papers per year for 2010 and 2011. Citations for career publications of our faculty members reached 106,500 by the end of 2011. Notable contributions are listed below.

Fred Dick and **Nathalie Berube**, with graduate student **Courtney Coschi** as first author, showed that retinoblastoma protein's contribution to mitotic chromosome condensation suppressed tumour formation [Genes Dev. 2010, 24(13), 1351]. This paper was highlighted in a PERSPECTIVE article in the same journal [Genes Dev. 2010, 24(13), 1329].

David Edgell, with graduate student **Ewan Gibb** as first author, discovered temporal control of the splicing of the intron of homing endonuclease I-TevI and I-TevI translation [Mol Microbiol. 2010, 78(1), 35]. A commentary in Molecular Microbiology outlines the importance of this paper [Mol Microbiol. 2010, 78(1), 1]. **David Edgell** and collaborators also showed how ribonucleotide reductase protein remains functional even when its gene contains a mobile genetic element [Nucleic



David Litchfield receiving Western's Division of Experimental Oncology Award of Excellence in Research

Acids Res. 2011, 39(4), 1381]. This paper was chosen as a Featured Article by the journal. Such articles represent the top 5% of publications in Nucleic Acids Research in terms of originality, significance, and scientific excellence.

Rob Hegele, Murray Huff, and collaborators published in Nature Genetics [2010, 42(8), 684]. This article describes the use of genome-wide association studies to study hypertriglyceridemia.

Murray Huff, with graduate student **Erin Mulvihill** as first author, showed that nobletin decreased lipoprotein secretion and atherosclerosis in insulin-resistant models [Diabetes 2011, 60(5), 1446].

Graeme Hunter, Harvey Goldberg, and collaborators published an Invited Feature Article that appeared on the cover of Langmuir [2010, 26 (24), 18639]. Their research showed that electrostatic interactions mediate the binding of proteins (such as osteopontin) to biomaterials.

David Litchfield, Shawn Li, Greg Gloor, and graduate student **James Duncan** (as first author) published in Science Signaling [2011, 4(172), ra30]. Their work suggests a role for CK2 in caspase signaling.

Geoff Pickering, with graduate **Matthew Frontini** as first author, showed that FGF9 mediated wrapping of smooth muscle cells around blood vessels during angiogenesis [Nat Biotechnol. 2011, 29(5), 421].

Trainee Accomplishments

Many of the Dept.'s graduate students and post-doctoral scholars have received recognition for their research talent. Some of their accomplishments are highlighted here.

Courtney Coschi (Dick lab) was awarded a CIHR Institute of Cancer Research Publication Prize for her publication in Genes & Development [2010, 24(13), 1351]. She also received the Faculty's 2011 Drs. Madge and Charles Macklin Fellowship for Publication.

Matt Cecchini and **Courtney Coschi** (Dick lab) won talk/poster awards at Western's Oncology Research Day in 2011. **Justin Crawford** (O'Gorman lab) won a 2010

Young Investigator's Award at the European Tissue Repair Society (ETRS) for his seminar on periostin.

Chris Hughes (former student in Lajoie lab) received a prestigious 2011 EMBL Interdisciplinary Postdocs Award.

Christopher Johansen (Hegele lab) received the 2010 Graduate Student Award for Best Oral Presentation at the Canadian Lipoprotein Conference. **Kristin Kernohan** (Berube lab) won the Faculty's 2010 Drs. Madge and Charles Macklin Fellowship for Publication [first author on Dev Cell. 2010, 18(2):191]. She also won the 2010 Zhogbi Prize Graduate Student Award for Poster at the 11th Annual Rett Syndrome Symposium, Virginia.

Christina Raykha (O'Gorman lab) received a 2011 IGF Society Award for the 5th International Congress of the GRS and IGF Society, NY. **Joe Ross** (Haniford lab) and **Jennifer Ruizhe Li** (Berube lab) won poster awards at the Faculty's 2011 Research Day. **Sue Safadi** (Shaw lab) received the Dept.'s 2010 Dr. William Zaharia Award for excellence in the PhD Program.

Don Spratt (Shaw lab) was awarded a 2011 CIHR Postdoctoral Fellowship. Amer Youssef (Han lab) participated in the CIHR National Student Research Poster Competition.

Events

The Dept. hosted a Research Showcase for Biochemistry Students in Jan of 2010 and 2011. This annual event features posters of research highlights from Biochemistry 4th-year thesis undergraduate students and 1st-year graduate students. Our trainees appreciated the opportunity to practice their presentation skills and interact with other researchers in the Dept.

The Biochemistry Undergraduate Summer Research Program took place during the summers of 2010 and 2011. Fifteen 2nd- and 3rd-year students from Western and other Ontario universities worked on specific research projects in our Biochemistry labs each summer. The program featured pizza lunches at which faculty talked about their research, a prize draw, a group photo, and a poster session with judging and prizes. Participating students appreciated the experience of doing research for

the first time. Many students wanted to continue with research in the future.

The *First Canadian Conference on Epigenetics: Epigenetics, eh?* took place in London in May 2011. The event was organized by **Nathalie Berube**, **Melissa Mann**, and **David Rodenhiser**. Attendees listened to Canadian and international speakers and attended a poster session.

Western's Molecular Biology Laboratories (MBL) turned 50 years old on 22 Nov 2011. Thanks to the National Cancer Institute, MBL first opened in 1961 as the Cancer Research Laboratory, under the direction of Professor Cameron Wallace. In 1989, the building was renamed the London Life Molecular Biology Laboratories. Today, MBL houses part of the Biochemistry Dept., including the offices and labs of 4 faculty members.



Members of the Molecular Biology Laboratory gather in honor of the building's 50th anniversary in 2011

CSMB-Sponsored Events

The CSMB provides financial support to graduate student societies for a variety of activities related to biochemistry, molecular biology, cell biology or genetics. Examples of supported activities include (but are not restricted to) the following:

- Scientific Symposium Days, with invited scientists speaking on subjects in the areas of biochemistry, molecular biology or cell biology.
- Student Research Conferences, where students display their research work as posters, or give oral presentations.
- Career Fairs or Career Workshops in areas related to biochemistry, molecular biology or cell biology.

The society will support several events each year, to a maximum of \$500 per event, on a first-come, first-served basis. Student organizations seeking financial support under this program should contact the Society Secretary, Dr. Randall Johnston, with a short description of the planned event and the amount of funding requested. A short report is required following the event for inclusion in the Bulletin.

Journée Scientifique des Étudiants 2011 (JSE 2011)

Cancer Research Centre, Université Laval

August 24, 2011

Correspondent: Gabriel Bossé, Graduate Student

For 14 years the students of the Cancer Research Centre of Université Laval in Québec City have organized the “Journée Scientifique des étudiants (JSE)”. During that day all the students from the Center are invited to present their research by poster or oral presentation. The best presentations are rewarded with travelling fellowships that enable the students to attend international meetings. A guest speaker is also invited to participate in the day’s activities.

This year, the Journée Scientifique des Étudiants 2011 (JSE 2011) was held on August 24th. Events actually began the preceding day when Dr. Luc Sabourin from the University of Ottawa gave a talk as the invited speaker. More than 120 people were in attendance at JSE 2011 and 72 students presented their work. At the end of the day, \$6500 in fellowships was awarded to more than 15 students.

The contribution of the CSMB was greatly appreciated and was acknowledged in the official program, in the all-day PowerPoint presentation and by our Chairman of the Day.

In Memorium: W. C. (Bill) McMurray 1913-2011

Ian Walker



Bill was a professor of biochemistry at the University of Western Ontario, London, Ontario and chairman of that Department from 1983-1993. He was internationally recognized for his research on phospholipid synthesis in animal cells. Early in his career while working in the laboratory of Henry Lardy at the University of Wisconsin he notably described the inhibitory effects of oligomycin on oxidative phosphorylation which stimulated a large burst of activity in the ox-phos field. His interest in inherited diseases of the nervous system led to his discovery of citrullinuria, hypercitrullinemia and hyperammonemia in a young patient with severe mental retardation.

Bill served on a number of committees of the Medical Research Council. He initiated and organized the Rossiter research conferences which were held at Lake Couchiching, near Orillia, Ontario. At the University of Western Ontario he was a highly regarded teacher and award winner. He wrote and published the text book "Essentials of Human Metabolism", which went through several editions. When not occupied with research, administration and teaching duties he found time for other activities which included tennis, hockey and wood and soap stone carving. He also wrote three mystery stories with an academic setting. These have been recently published as E-books. Bill is sorely missed but fondly remembered by his many friends, students and colleagues.

Bill McMurray - A Personal Memoir

Jane Wilson, PhD student of Bill McMurray's, 1976-1981

I graduated with a B.Sc. in Honours Biochemistry from the University of Western Ontario in 1975. After a year at the University of Toronto, I returned to Western to find a home at the Department that had developed my love of biochemistry, to do graduate work. Bill McMurray had an opening in his lab for a graduate student, and I jumped at the opportunity. I knew he was well thought of by students and faculty. My graduate years are full of positive memories and respect for Dr. McMurray. I'd like to share with you some reminiscences of my experience working with WC (a graduate student nickname for Bill McMurray).

In an article for the Western News Supplement in 1979, Bill McMurray described his feelings about his chosen career: “My day-to-day life is exciting and fun. I look forward to going to work”.

He was always a gentleman when dealing with graduate students. Although he would never say so, and there would be a small smile as he passed by, I’m sure he enjoyed our quirks and pranks. These included taping a lab coat to the ceiling of the lab, which was there for a long time, so visiting scientists had to walk under it to get to his office.

In the lab, there was encouragement and freedom to explore a variety of research avenues. Studies and directions morphed, as we graduate students discerned which paths yielded positive results versus those that were dead-ends. Bill was always there for needed consultation about problems and experiments. Outside of the lab there was some competition amongst graduate students and Bill on the tennis court!

My first major research paper with Bill McMurray was cited for over 10 years. My training allowed me to secure post-doctoral work at Harvard University and the University of Calgary. I came back again to Western for a couple of years as an Honorary Lecturer in Biochemistry. Bill McMurray strived to be the best lecturer and teacher he could be. His texts were part of that goal, to make biochemistry more palatable and interesting for the medical students. After all, it is a fascinating area of science, isn’t it?

I envied Bill’s mastery of the written word, and was ever thankful for the editing he would do for our papers and my thesis. Reflecting his sense of humour, he provided me with an alternative version of my thesis acknowledgments which, as mentioned in it, “will keep me chuckling into old age”. To give you a taste, the last line was “The research in this thesis was supported by a grant from the Medical Research Council to Dr. W.C. McMurray, and anything that could be moved from other laboratory areas.”

Sadly, I can’t enlist his editing help for this piece, but I will always be grateful for the memories.

