

Bulletin

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

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50th
Anniversary



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2006

La Société canadienne de
biochimie, de biologie
moléculaire et cellulaire

2006

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CSBMCB Board for 2006-2007

PRESIDENT

Dr. Eric Brown
Department of Biochemistry and
Biomedical Sciences
McMaster University
Health Sciences Centre
Room 4h2
1200 Main St. W
Hamilton, ON L8N 3Z5
Tel: (905) 525-1940 ext 22392
FAX: (905) 522-9033
E-mail: ebrown@mcmaster.ca

PAST-PRESIDENT

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

VICE-PRESIDENT

Dr. Reinhart Reithmeier
Department of Biochemistry
University of Toronto
Rm 5216
Medical Sciences Building
1 King's College Circle
Toronto, ON M5S 1A8
Tel: (416) 978-7739
FAX: (416) 978-8548
E-mail: r.reithmeier@utoronto

TREASURER

Dr. Vincent Duronio
Department of Medicine
University of British Columbia
Jack Bell Research Centre
2660 Oak St.
Vancouver, BC V6H 3Z6
Tel: (604) 875-4707
FAX: (604) 875-4497
E-mail: vduronio@interchange.ubc.ca

SECRETARY

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

COUNCILLOR

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

COUNCILLOR

Dr. Dev Mangroo
Department of Molecular and
Cellular Biology
University of Guelph
Guelph, ON N1G 2W1
Tel: (519) 824-4120 ext 53432
FAX: (519) 837-1802
E-mail: dmangroo@uoguelph.ca

COUNCILLOR

Dr. John Orłowski
Department of Physiology
McGill University
3655 Promenade Sir-William-Osler
Rm 1112
Montreal, QC H3G 1Y6
Tel: (514) 398-8335
FAX: (514) 398-7452
E-mail: john.orłowski@mcgill.ca

COUNCILLOR

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

COUNCILLOR

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

COUNCILLOR

Dr. Frances J. Sharom
Department of Molecular and
Cellular Biology
University of Guelph
Guelph, ON N1G 2W1
Tel: (519) 824-4120 ext 52247
FAX: (519) 837-1802
E-mail: fsharom@uoguelph.ca

CHAIR, NOMINATING COMMITTEE

Dr. David Y. Thomas

BULLETIN EDITOR

Dr. Frances J. Sharom

CFBS HEAD OFFICE

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

CSBMCB President's Report

Dr. Eric Brown

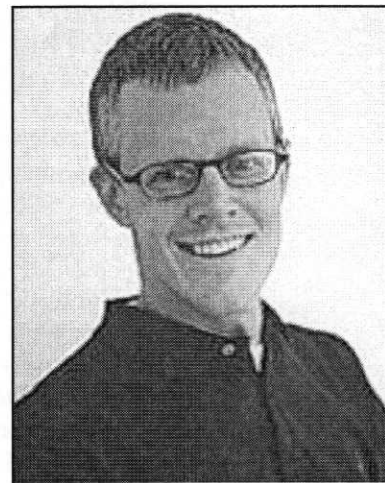
Introduction

It's a pleasure to provide the President's report for the 50th year of the CSBMCB for the 2006 edition of the Bulletin. The Bulletin, as it turns out, has been around almost as long as the CSBMCB, and the 50th anniversary has been an occasion to have a look back at some early and dog-eared issues of the society's yearly publication. What's been most fascinating about that look back for me is how little things have changed. The CSBMCB has apparently always concerned itself with communication among biochemists (and the like), putting on great meetings, celebrating top scientists' accomplishments and facilitating advocacy. It was regarding the latter, in particular the issue of science funding in Canada, that I was struck by how little had changed in many years.

It seems that Canadian scientists have always done much with very little, and frequently have written about their frustrations with science policy in this country. We have been grappling this past year with depressingly low success rates - about 16% - for the CIHR operating grants competition as a result of an indefinite freeze in research budgets by a new minority Conservative government. Particularly unsettling is that these freezes are in the face of huge federal financial surpluses. How this measures up historically is hard for me to say, but I would suggest that we are living and researching in a special time. It seems to me that Canada is faced today with an extraordinary opportunity to follow through with remedies that were begun in the late eighties to stem the brain drain, to shore up health research and to steady the growth of a knowledge-based economy.

In the past several years, the federal government has invested heavily in new science infrastructure through the Canada Foundation for Innovation, and in investigators through the Canada Research Chairs program. We are now poised to make good

on the vision for a strong research presence in Canada's health care system. We are in an excellent position to contribute to an innovative and knowledge-based economy that will sustain Canada in the face of increasingly cheap off-shore labour and a struggling manufacturing sector. And we can surely lead internationally in science and technology for the growing and world-wide environmental movement. What are needed, of course, are significant increases in CIHR and NSERC operating funds. This year has been a particularly busy one for the CSBMCB Executive, and much of the effort has been in advocacy, especially letter-writing, telephone calls, post-card campaigns and intense internal discussion about how best to get this message to the public, bureaucrats and politicians. While I am optimistic that we and others may be making some headway on this agenda, I am certain that biochemists, molecular and cellular biologists will always need to be vigilant about advocacy. So cheers to CSBMCB on its 50th birthday, and may its Bulletin continue to be a forum for dialogue, dissent and diatribe for the next 50 years.



Science Policy and Advocacy

The CSBMCB Executive has been very busy with advocacy efforts in the past year. A significant development in science policy in 2006 was a review of CIHR by a panel of international experts chaired by Regius Professor of Medicine John Bell of Oxford University. The report offered some considerable praise of the CIHR's accomplishments to date, as well as some very insightful observations, analysis and recommendations for the future of CIHR. The changes suggested are substantive and resonate, in my view, with much of the senti-

ment that exists at the grass roots of biomedical research in Canada. The CSBMCB Executive responded with a letter to president of the CIHR to underline the many the recommendations including, for example, addressing the deficit of basic researchers on Governing Council, abandoning the concept of pillars in recognition of the continuity of health research, and increasing the proportion of funding allocated to investigator-initiated grants.

By far the most important issue in advocacy this year for the CSBMCB Executive has been the freeze in federal research budgets that hit the CIHR particularly hard. This freeze meant that the funding available to last fall's competitions decreased by approximately 30%, drastically reducing both funding levels and success rates. The Executive wrote letters to the Prime Minister and Health Minister, and put out a call to the membership for grass-roots letter-writing. We posted a "how to" blurb on writing your MP on the CSBMCB website, and were copied on many letters written to government. Indeed, among the more enlightened and entertaining dialogue that I saw on this was from Alan Davidson at the University of Toronto, who suggested to his colleagues that they had better not complain for one second about not getting their grant if they hadn't written to their MP. Thanks to Alan and everyone else who wrote letters.

Perhaps the best news of the fall 2006 was the release of a report by the federal Standing Committee on Finance, which included a recommendation to increase the CIHR budget by \$350 million over three years. Most recently, and at the time of writing of this report (March 2007), it is looking unlikely that the government will act on this recommendation for the coming budget. In the past couple of weeks the CSBMCB has given a push to an effort that began in the Faculty of Medicine at the University of Toronto, to send post-cards to the Prime Minister and the Ministers of Health, Industry and Finance. The initiative has a goal of 10,000 cards from across Canada to encourage the government to move forward on its Standing Committee on Finance recommendations. Fingers crossed...

Relationship with Canadian Federation for Biological Sciences

The CSBMCB is not formally part of the Canadian Federation for Biological Sciences, but supports its efforts in advocacy on behalf of all of the biological sciences in Canada. To this end, the CSBMCB pays a per member levy and is afforded a seat at the table among CFBS's membership. In addition to the levy, the CSBMCB has had an office contract with the CFBS for its administrative needs. These dollars, along with those of other member organizations, support CFBS infrastructure, an Ottawa office including administrative assistance and a part-time professional advocate, Art Olson. The scale of the representation by CFBS in terms of membership is considerably greater than that of the CSBMCB and thus important when one considers the impact of advocacy efforts. Hence a coalition among biological scientists makes sense for advocacy. Nevertheless, a long-time concern among the Executive of the CSBMCB has been an emphasis by CFBS on running scientific meetings at the expense of attention to the administrative and advocacy needs of the CSBMCB. An argument can be made that the CFBS meetings serve a demand among much smaller member societies that could not put on meetings themselves. More importantly, however, the CFBS would not be sustainable in its current form without these conferences.

The CSBMCB Executive has frequently debated in recent years the merits of pulling out of the CFBS and seeking other avenues for satisfying its administrative needs and advocacy goals. These discussions reached a turning point this fall when the Executive approved a motion to terminate its office contract with the CFBS and seek alternative administrative arrangements. A remaining issue is therefore how to proceed on advocacy. Should the CSBMCB continue to fund the advocacy efforts of the CFBS? Are there other avenues for the best use of our advocacy dollars? In my own view, the best outcome would involve a workable plan for cooperation among a coalition of societies where the focus is solely on advocacy. In the past few

years, I have witnessed a tremendous amount of energy and resolve among the Executive and membership of the CSBMCB regarding advocacy, and I am confident that the right path will ultimately be taken. Now is clearly a good time for some measured rethinking of our approaches.

Upcoming CSBMCB Meetings

The 50th Annual Meeting will be held Thursday July 5 to Monday July 9, 2007 at McGill University. The theme of the meeting is "Systems and Chemical Biology" and it will feature a sizeable international presence in a variety of scientific sessions spanning systems and small molecule approaches in biology. This year the CSBMCB has plans for a particularly special meeting to commemorate the 50th anniversary of the Society. David Thomas (Past-President) and I are co-Chairs for this meeting, and have the support of a talented meeting planner, Nancy Dufour, and a lively organizing committee who have put together a really terrific program. The 2008 Annual Meeting will be held at the Banff Centre Thursday March 6 to Sunday March 9. The meeting has the tentative title "Chromatin Structure, Function and Dynamics" and will be Chaired by Jim Davie from the University of Manitoba. The 2009 meeting is scheduled for the Toronto area. Stay tuned for a date and a theme.

CSBMCB Awards

One of the most important roles of the CSBMCB, in my opinion, is to celebrate excellence among our members. In 2006, Joe Casey, University of Alberta, was the recipient of the Merck Frosst Prize. The prize is an early career award (less than 10 years as an independent investigator) that is given annually to a biochemist, molecular or cellular biologist who has made extraordinary research progress. Frances Sharom, University of Guelph, received the Jeanne Manery Fisher Memorial Award for scientific achievements by an eminent woman scientist. The awardees gave terrific talks at the 2006 meeting in Niagara-on-the-Lake, and are also featured later in this issue of the Bulletin for their outstanding contributions to research.

New CSBMCB Website

The CSBMCB has a new website. The website

project has been ongoing for some time and we are delighted that the new site has now become operational. It's a great new look and has terrific functionality that includes links for advocacy, meetings, society awards, on-line membership renewal and lots of other good stuff. Many thanks are owed to Vince Duronio, our Treasurer, who led this onerous initiative, and to all of the CSBMCB executive members who were contributors to the effort. With the new website in place, we are planning on a new membership drive for 2007.

Thank You(s)

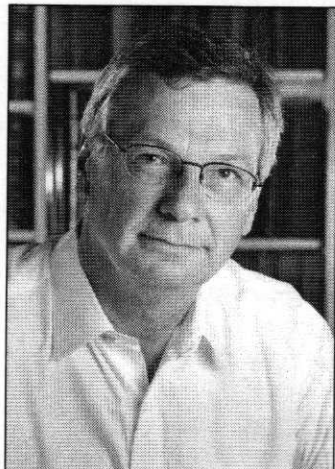
It's been a very rewarding year as President of the CSBMCB and I owe a debt of gratitude to number of people for their support. I am grateful for the administrative support of Wafaa Antonious, the CFBS Manager, and her Assistant Laila Raid. These activities are critical support for communications, finance, membership and annual meetings. Thanks also to Stephen Lau who was the point-person on our website changes. And many thanks to Nancy Dufour who expertly coordinated with all of these folks and others to help us prepare for the 50th Annual Meeting.

I am very grateful to have been handed this post with things in fine shape on account of the hard work of David Thomas, Past President. Indeed, as a relatively inexperienced leader, I have been particularly lucky to be sandwiched between David and Vice President Reinhart Reithmeier, and I have taken advantage of their experience and common sense on a regular basis. Vince Duronio has been huge asset in the past year doing his duties as Treasurer but also in spearheading the website overhaul. Frances Sharom has, as always, done an expert job in looking after the Bulletin and has been an experienced anchor on the organizing committee of the upcoming meeting in Montreal. I am grateful to Albert Clark for preparing meeting minutes and taking care of the awards details. Thanks also to Councillors Dev Mangroo, Linda Penn and John Orlowski - you folks have been great fun to work with. Finally I want to say a special thanks to Joe Casey (President 2004/2005), who left the Executive this fall after several stellar years of service.

Incoming Member of the CSMCB Executive Board 2006-2007

Reinhart Reithmeier, Vice-President

I was born in Germany and moved to Canada with my parents at the age of two. I grew up in the



countryside just outside Ottawa and attended a one-room schoolhouse for the first three years of my schooling. My parents were great nature lovers and encouraged my interest in biology. They also put up with my doing "chemistry experiments" in the basement.

With the help of a scholarship from a local golf course, where I worked for eight summers, I attended Carleton University and graduated in the first biochemistry class in 1972. Stan Tsai patiently supervised

my honours project on lysozyme catalysis and he got me interested in research. For two summers I worked at the NRC Labs in Ottawa with Mak Yaguchi and Lou Visentin. From Mak, I learned research was hard work, and from Lou that it was fun. I worked on the sequencing of ribosomal proteins purified from bacterial thermophiles and halophiles, and histones from plants (carrot cells grown in culture of all things!) and began to think of myself as a protein chemist.

Both Mak and Lou encouraged me to go to graduate school, so I applied to Toronto, Alberta and UBC. I didn't hear a thing until I was awarded an MRC Studentship, then the phone began to ring. I wanted to work with Gordon Dixon at UBC, a world expert in histones, but he was moving to England. Gordon passed my letter on the Phil Bragg who worked on bacterial membrane proteins. I had heard of the "fluid mosaic model" and thought that membrane proteins would be interesting. Little was I to know that membrane proteins would become my scientific life!

After graduating with a Ph.D. from UBC in 1976, and with the encouragement of Dennis Vance, who was on my supervisory committee, I started postdoctoral studies at the Biological Laboratories at Harvard University with Guido Guidotti. Guido had a large lab and you could do pretty much what you liked. I decided to work on human red cell proteins. He encouraged creative thinking and collaboration within the group. I worked with two great people, Lewis Cantley and Anjana Rao, who have gone on to spectacular careers. My MRC fellowship was for only two years (due to budget cuts!), so I decided to return to Canada and worked in David MacLennan's lab on the biosynthesis of muscle membrane proteins. David was an inspiring leader who demanded top quality work. Luckily, I was assisted by Stella DeLeon and Vijay Khanna, who made sure that my experiments were always up to David's high standards.

I really enjoyed the MacLennan lab and would have been happy to stay on forever, but David said that I was ready to start my own research group. That was in 1979 and there were no jobs, so I wrote to several biochemistry departments in Canada and asked them to sponsor me for an MRC Scholarship. John Colter, Chairman of the Biochemistry Department at the University of Alberta, was very keen to have me join his department, which had (and still has) a very strong protein structure group. I won the MRC Scholarship, so I was Alberta bound. The Alberta Heritage Foundation for Medical Research had just been set up, so money was available to set up my lab and to recruit students and post-doctoral fellows. I decided to return to work on the structure and function of red cell membrane proteins, which has continue to this day. John, and other members of the Department like Cyril Kay and Neil Madsen, were great mentors and were always available to guide me through the rough patches. The Department had a great sense of community and collaborations were the norm.

In 1986 I was recruited back to Toronto by Mel Silverman to join his Membrane Biology Group in the Department of Medicine. This group had a focus on kidney physiology and my group expanded to also work on kidney membrane transport proteins. I was fortunate to be supported by an MRC Scientist Award and an MRC Group Grant for many years. An MRC-CNRS Award allowed me to spend a sabbatical year in France with Jacques Pouyssegur where I learned about cell physiology and fine wine.

In 2002 I became Chair of the Department of Biochemistry at the University of Toronto, where I had held a cross-appointment and had been Graduate Coordinator. I am completing my first term this year and must say that this is the best job that I have ever had. Challenging to be sure, but in the Faculty of Medicine at the University of Toronto Chairs are given the resources and the mandate to build departments that meet the highest standards of international excellence in research and teaching. I have continued my

research program and have been busy as a CIHR Delegate, lobbying for increased research funding. I have been very involved in teaching and this year met the challenge of lecturing to 1,200 students in our introductory biochemistry class.

Over the years I have been very fortunate to have many excellent technicians, graduate students and post-doctoral fellows in my lab. Some have gone on to academic research careers of their own, others to medical or dental school, others to research administration and some into teaching. I am very proud of their accomplishments and the talent and energy they bring to the lab. My family has always been a constant source of support.

The CSBMCB is a vital organization driven by a talented group of dedicated people. The Society runs first-rate meetings and our advocacy efforts have had a real impact. I am very proud to serve as Vice-President of the CSBMCB as the Society enters its 50th year.

Minutes of the 49th Canadian Society of Biochemistry, Molecular and Cellular Biology Annual General Meeting

**White Oaks Conference Resort, Niagara-on-the-Lake
Saturday June 3, 17:30 – 18:30 h**

Chair: Dr. David Thomas, President CSBMCB

Board Members present: David Thomas, Joseph Casey, John Orlowski, Frances Sharom, Eric Brown and Albert Clark.

Thirteen other CSBMCB members present.

786. Approval of the Agenda

The agenda was approved as circulated (motion by Dr. Cass, seconded by Dr. Woodgett).

787. Approval of the Minutes of the 48th Annual General Meeting

The minutes of the 48th Annual General Meeting, held in Banff, March 18th, 2005 were approved as circulated (motion by Dr. Orlowski, seconded by Dr. Sharom). No changes were requested.

788. Business Arising from Minutes

Any items arising from the minutes will be discussed under later agenda items..

789. President's Report

Dr. Thomas's report centred on the relationships of CSBMCB with CFBS and with lobbying government.

Dr. Bruce Sells is retiring as Executive Director of CFBS and is being replaced by Art Olson, a former Assistant Deputy Minister in Ottawa. CSBMCB is an Associate Member i.e. not a member of CFBS and hence does not have a seat on the CFBS Board. Several other societies have left CFBS i.e. the Genetics Society; societies often leave because of the costs involved. Currently, the CFBS offices take care of CSBMCB office needs. CSBMCB has a contract with CFBS for these duties.

CFBS does a good job at lobbying government. In large part this has been achieved because of Dr. Sell's efforts and skills. CSBMCB's interests have been well-served by the efforts of CFBS in Ottawa. Some of the other societies are not as focused on biomedical research.

CFBS has financial problems, partly because some societies have left the Federation and partly because some of their recent meetings have lost money. CFBS is organizing 2 meetings per year in efforts to raise their profile and funds. CSBMCB, because it is the largest society, is a major contributor to CFBS. CSBMCB has signed a contract for a further year of association with CFBS.

The CSBMCB will continue to review its relationship with CFBS. While the work of CFBS is perceived as being very good to date, a more focused effort at advocacy might be more successful with government. The CSBMCB Board will be reviewing our work in this area - with CFBS and with other potential groups. A more unified approach might be more effective.

The Board has reviewed and approved a Sponsorship Policy with regards to CSBMCB support of meetings. A copy is attached to the minutes.

The 2007 meeting will be held in Montreal from July 5-9. The theme of the meeting will be systems biology. The meeting, which will be the 50th

annual meeting of CSBMCB, overlaps with the Montreal Jazz Festival.

790. CSBMCB and PENCE

PENCE (Protein Engineering Centre of Excellence) is no longer supported by the Canadian Centers of Excellence program. The members of PENCE wish to remain together as an organization in order to promote the discipline of protein science and further the networking among protein scientists in Canada.

PENCE has approached CSBMCB to become a division of our society. This would be called the Protein Division. This Division would have their own executive of which at least one and preferably two would also be members of the CSBMCB executive. Members of the Protein Division would have to be members of CSBMCB. The division would organize their own meetings as well as participating in CSBMCB meetings. The division would maintain their own separate funding, which would be managed by the CSBMCB Treasurer. They have left-over funds from PENCE which can be used to begin their separate activities.

The CSBMCB supports the initiation of this Division with assurances being incorporated into the agreement that protect CSBMCB from any financial liabilities.

791. Membership

Linda Penn, the Board Member responsible for membership was unable to attend the meeting. In the most recent report CSBMCB had 327 paid up members.

792. Communications

Dr. Frances Sharom had completed preparation of the annual CSBMCB Bulletin. She was complimented and thanked for her hard work. It is a major effort getting reports from the Departments across the country, etc. Also making a significant contribution to getting the Bulletin out to the members was Dr. Gene Tustanoff, past Secretary to CSBMCB.

793. Past President's Report

Dr. Joe Casey, Past President of CSBMCB has assumed a major responsibility on the Board to

promote and monitor advocacy. Major issues with regards to promoting the interests of the CSBMCB membership include the new government and what will be their priorities if any in research and developments and changing policies at CIHR concerning grant distribution. Proposed changes in policies on awarding of grants (similar percentage of awards by each panel as opposed to scores) could increase the number of grants for pillars 3 and 4 and fewer grants for basic science disciplines. CIHR is currently under review. Dr. Casey will prepare a presentation for this review on behalf of CSBMCB.

It was noted that advocacy takes time, but we continually need to remind politicians of how research pushes the economy. CSBMCB needs to develop specific targets with regards to advocacy. CIHR must be lobbied with regards to support for the basic sciences.

794. Treasurer's Report

The Treasurer, Dr. Vincent Duronio, was unable to attend the meeting. Dr. Duronio has provided a draft report for discussion purposes which indicated that the Society is in an excellent financial state. Unofficial current revenues over expenditures for 2005 were \$41,530 increasing net assets to \$424,063.00.

CSBMCB/SCBBMC Audit

Statement of Financial Position

December 31	2005	2004
ASSETS		
Current assets		
Bank	\$2,422	\$7,058
GST receivable	1,103	3,201
Sponsorships & accounts receivable	29,693	5,107
Meeting deposit 2006	5,000	-
	<u>38,218</u>	<u>15,366</u>
Meeting deposit 2008	7,000	-
Investments – at market value (Note 3)	400,480	385,719
	<u>\$445,698</u>	<u>\$401,085</u>

LIABILITIES AND SURPLUS

Current liabilities		
Accounts payable & accrued liabilities	\$7,407	\$14,253
Deferred sponsorship	7,500	-
Deferred membership fees	2,056	1,215
	<u>16,963</u>	<u>15,468</u>
Deferred membership fees	4,672	3,084
	<u>21,635</u>	<u>18,552</u>
Net assets	424,063	382,533
	<u>\$445,698</u>	<u>\$401,085</u>

STATEMENT OF CHANGES IN NET ASSETS

December 31	2005	2004
Net assets, beginning of year	\$382,533	\$358,165
Excess of revenues over expenses for the year	41,530	24,368
Net assets, end of year	<u>\$424,063</u>	<u>\$382,533</u>

STATEMENT OF REVENUE AND EXPENSES

December 31	2005	2004
Revenue from operations		
Memberships	\$17,108	\$15,743
Corporate contributions	15,500	66,812
Annual meeting & other	30,706	7,028
	<u>63,314</u>	<u>89,583</u>
Investment revenue		
Interest, dividends & other investment income	15,161	14,655
Realized & unrealized capital gains	16,769	21,561
	<u>31,930</u>	<u>36,216</u>
Expenses		
Annual meeting (Note 4)	17,594	65,385
Audit	3,000	2,875

Bank & credit card fees	914	1,073
Board meetings	6,848	8,139
Bulletin	6,093	6,079
Dues & subscriptions	379	1,317
Funding & other sponsorship	1,750	4,500
Gifts	-	1,700
Management fees	9,627	8,160
Newsletter	-	1,765
Office	-	275
Postage & courier	-	163
Printing	2,575	-
Publicity	385	-
Website	4,550	-
	<u>53,715</u>	<u>120,430</u>

Excess of revenues over expenses for the year

\$41,530 \$24,368

Canadian Society of Biochemistry and Molecular & Cellular Biology

Statement of Cash Flows

December 31	2005	2004
Cash flows from operating activities		
Cash received from members and events	\$48,657	\$80,038
Cash paid to suppliers	(70,463)	(89,110)
Cash flows from operating activities	<u>(21,806)</u>	<u>(9,072)</u>
Cash flows from investing activities		
Investment income	15,161	14,655
Proceeds from sale of investments	135,167	79,976
Purchase of investments	(115,036)	(62,291)
	<u>35,292</u>	<u>29,340</u>
Net change in cash and cash equivalents	13,486	20,268
Cash and cash equivalents, beginning of year	44,118	23,850
Cash and cash equivalents, end of year	<u>\$57,604</u>	<u>\$44,118</u>

Cash and equivalents is made up of:

Bank account\$	2,422	\$7,058
Cash held with investment broker	55,182	37,060
	<u>\$57,604</u>	<u>\$44,118</u>

December 31, 2005

3. Investments – at market value

Nesbitt Burns Canadian \$ account	2005	2004
Cash & short term investments	\$55,182	\$37,060
Fixed income	68,121	70,714
Common equity	270,396	224,790
Investment trusts	2,469	49,333
	<u>396,168</u>	<u>381,897</u>

**Nesbitt Burns U.S. \$ account
(in Canadian \$)**

Cash & short term investments	72	-
Common equity	4,240	3,822
	4,312	3,822
	\$400,480	\$385,719

Income Statement (Cash basis) 1/1/2006 to 11/16/2006

REVENUE

Membership Revenue

CSBMCB Membership Fees	12,739.83
CFBS Membership Fees	9,640.00

Membership Total

Annual Meeting Registration	22,379.83
Meeting Sponsors	20,753.66
Annual Meeting Registration	0.00
Exhibits Revenue	0.00
Meeting Miscellaneous Revenue	0.00

Meeting Revenue Total

PENCE Revenue

PENCE Meeting Revenue	23,485.30
PENCE Revenue Total	23,485.30

Other Revenue

TOTAL REVENUE	66,618.79
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EXPENSE

Bulletin Expenses

Bulletin Printing	5,137.34
Bulletin Mail out	901.41
Bulletin Editing	0.00
Bulletin Other Expenses	0.00
Total Bulletin	6,038.75

Annual Meeting Expenses

Exhibit & Facility Expenses	0.00
Receptions & Banquets	0.00
Speakers Travel & Expenses	622.30
J Manery Fisher Award	1,000.00
MendFrosst Awards	18,400.00
Roche Award	0.00
Awards Total	19,400.00
Meeting Supplies	0.00
Board Travel To AGM	1,954.60
Other Meeting Expenses	7,574.68
Meeting Total Expenses	29,551.58

PENCE Expenses

PENCE Facility Expenses	2,706.39
PENCE Receptions & Banquets	2,147.32
PENCE Speakers Expenses	15,053.65
Other PENCE Meeting Expenses	1,124.9
Total PENCE Expenses	21,032.27

Other Expenses

CFBS Fees	14,525.60
The Link Expenses	0.00

Other Meetings Sponsorship	6,082.20
Other Org. Mmb. Fees (IFCB & PABMB)	339.60
Board Meetings & Travel Expenses	0.00
CFBS Admin Contract	0.00
Other Expenses Total	20,947.40

General & Administrative Expenses

Accounting & Legal	7.00
Advertising & Promotions	0.00
Interest & Bank Charges	0.00
Office Supplies	0.00
Website Expenses	4,600.00
Miscellaneous	0.00
Telephone	0.00
Total General & Admin. Expenses	4,607.00

TOTAL EXPENSE	82,177.00
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NET INCOME	-15,558.21
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49th Annual Meeting of the CSBMCB:

Reinhart A. F. Reithmeier, Department of Biochemistry,
University of Toronto

The 49th Annual Meeting and Conference of the Canadian Society of Biochemistry and Molecular & Cellular Biology (CSBMCB) on "Membrane Proteins in Health and Disease" was held from May 31 to June 4, 2006 at the White Oaks Conference Resort and Spa in Niagara-on-the-Lake in Ontario. The Organizing Committee, consisting of Reinhart Reithmeier (Toronto), David Andrews (McMaster), Frances Sharom (Guelph), Joseph Casey (Alberta) and Jean-Yves Lapointe (Montréal) put together an excellent program featuring presentations by over 25 scientists from Canada and the United States. The talks were of uniformly high quality and they generated considerable discussion during the question period. The meeting was very popular, attracting close to 200 delegates, over half of whom were graduate students or post-doctoral fellows, from North America and as far away as Hong Kong.

The meeting began on Wednesday evening with a "Plenary Session" chaired by Joel Weiner. The first two speakers, Ron Kaback (UCLA) and Nobel Laureate, Peter Agre (Duke), set a high standard, as they engaged the audience in work they carried out that led to a detailed understanding of the molecular basis of membrane transport of sugars and water. The evening finished with a lively Mixer sponsored by Merck-Frosst Canada, which included a birthday celebration for Ron Kaback, who is now of an indeterminate age.

The second session on Thursday morning on the "Structural Biology of Membrane Proteins" was chaired by Reinhart Reithmeier. The four speakers covered various approaches that are used to determine membrane protein structures. Charles Deber (Sick Children's Hospital, Toronto) spoke on his work using model peptides to mimic transmembrane helix-helix interactions. Natalie Strynadka (University of British Columbia) described her work using crystallography to determine the structures of the key proteins involved in bacterial

pathogenesis. Michael Maguire (Case-Western Reserve) described a fascinating new membrane protein structure, that of the bacterial magnesium channel, CorA. Francesca Marassi (Burnham) described the use of solid state NMR to determine the structure of transmembrane proteins and their interaction with other membrane proteins. The final speaker, Robert Stroud (UC San Francisco), gave a fascinating talk on the structures of families of membrane proteins involved in ammonium/ammonia, glycerol and water transport.

The Thursday evening session chaired by Janet Wood (Guelph) on "Regulating Membrane Permeability" started with Michael Caplan (Yale) who spoke on membrane protein trafficking in polarized cells with a focus on polycystin 1 and interacting proteins. This was followed by a presentation by David Andrews (McMaster) on the regulation of membrane permeability by interaction and conformational dynamics of apoptosis proteins Bcl-2 and Bax. James Coulton (McGill) presented his studies on the structure of the TonB/FhuA complex, which appeared in *Science* the next day. John Collier (Harvard) spoke on his studies of anthrax toxin translocation across membranes.

The Friday morning session IV on "Dynamics of Membrane Proteins" was chaired by Christine Bear (Sick Children's Hospital, Toronto) and began with Frances Sharom (Guelph), this year's winner of the Jeanne Manery Fisher Award. Dr. Sharom was recognized for her innovative studies of the P-glycoprotein drug efflux pump, particularly for the use of fluorescence spectroscopy. Francisco Bezanilla (Chicago) spoke on the molecular basis of voltage-gated channels. Jennifer Baker, a Ph.D. student at the University of Toronto, gave an excellent presentation of her NMR studies of the intrinsically disordered R domain of CFTR. Eduardo Perozo (Chicago) continued with the channel theme and described the pore dynamics

and gating mechanisms of KcsA, a bacterial potassium ion channel.

Joseph Casey, this year's winner of the Merck-Frosst Prize, described his ground-breaking work on the role of anion exchangers in cardiac hypertrophy in Session V on "Membrane Proteins and Disease", chaired by Howard Young (Alberta). Dr. Casey presented compelling data on the linkage of carbonic anhydrase with bicarbonate transporters, and the role this interaction plays in regulating bicarbonate transport. Jean-Yves Lapointe (Université de Montréal) discussed the transport properties of a novel sodium-dependent monocarboxylate transporter. Shawn Li (Western) gave a short talk on a SH2 containing module, SAP, that regulates receptor signaling. The final talk was by John Orlowski (McGill), who spoke about sodium proton exchangers, interacting proteins and their role in cardiac physiology.

"Membrane Protein Trafficking" was the topic of Session VI, chaired by Carol Cass (Alberta). Mutations in the genes encoding membrane proteins often cause disease. These mutations may affect the functionality of the proteins directly, but often cause misfolding or trafficking defects. Art Johnson (Texas) provided a beautiful overview of how fluorescently-tagged nascent polypeptides can be used to characterize the machinery involved in translocating proteins across the ER membrane and into the lumen. Michel Bouvier (Université de Montréal) presented important findings from his group that mis-folded G-protein coupled receptors (GPCRs) can be rescued from ER retention and transported to the cell surface by the application of membrane-permeant antagonists. Ray Truant (McMaster) identified a membrane association signal in the protein huntingtin that can modulate vesicle targeting and nuclear entry. Benhart Reithmeier (Toronto) spoke about his group's studies of trafficking defects of the chloride/bicarbonate anion exchanger that are linked to diseases affecting the red cell and the kidney. The session finished with a presentation by Gergely Lukacs (Sick Children's Hospital, Toronto) who pointed out that the instability of mutant membrane proteins at the cell surface can cause rapid internalization, thereby reducing function.

Session VII was a "Workshop on Membrane Protein Crystallization", organized and chaired by Gilbert Privé (University Health Network, Toronto). This session was attended by many people who have, until now, only dreamed about determining the structure of their favourite membrane protein. The speakers engaged the audience as they talked about the challenges and successes they faced in this task. It was gratifying to know that persistence pays off, and the increase in the number of membrane protein structures paralleled the increase in the structures of soluble proteins, only off-set by about 50 years! Critical issues, such as the use of various expression systems (expression of mammalian membrane proteins remains a challenge), the precise design of the construct (removing the tag), the choice of detergent (dodecyl maltoside remains the clear winner), high throughput surveys (crystallize what you can express), etc. were highlighted by the panel of speakers: Gilbert Privé (UHN, Toronto), Joanne Lemieux (Alberta), Mark Dumont (Rochester), and Chris Koth (Vertex).

The workshop was followed by a panel discussion on "Biomedical Research Funding in Canada". The panel members included Joel Weiner (Alberta), David Thomas (McGill), Phil Branton (CIHR, McGill) and Jim Woodgett (SLRI, Toronto). This lively interchange highlighted the positive impact of the transition of MRC to CIHR with respect to the number and size of grants. There was however a consensus that the interests of basic biomedical sciences were not well represented at CIHR, particularly within the Governing Council. Also, too few resources were being devoted to open grant competitions, with the ever increasing numbers of RFAs. It was felt that our community must do more to reach out to key decision makers to inform them of the benefits of the basic biomedical research we do. We must also do a better job in engaging the public. The CSBMCB has made major strides in these directions lately. The various levels of government need to develop an integrated strategy with respect to research initiatives. "Research Canada", a new consortium of interested parties, may be useful in this regard. The CRC and CFI programs have provided salaries and equipment, but the granting agencies have not

been able to keep up with the growth in research. The Annual Meeting of the CSBMCB followed, with a record turnout of members. The meeting highlighted the success the Society had achieved in organizing high quality conferences every year, and in being a powerful advocate for biomedical research in Ottawa.

Saturday evening was devoted to a gourmet banquet and the awards presentations. The Merck-Frosst and Jean Manery Fisher Awards were presented to Joseph Casey and Frances Sharom, respectively by David Thomas (McGill), President of CSBMCB. Because of the generosity of the Society and the sponsors of the meeting, a large number of travel and poster awards were presented to trainees.

The meeting wrapped up with a session on Sunday morning on "Assembly and Disassembly of Membrane Proteins". Tom Rapoport (Harvard) revealed his ideas concerning novel pathways for the degradation of ER proteins. Membrane proteins do not fold in isolation, but are assisted by chaperones that act to prevent aggregation. David Williams presented compelling evidence for a direct chaperone effect for calnexin and calreticulin beyond their well-defined carbohydrate-binding properties, and described the regulatory roles for ATP and calcium ions. Graduate student Pekka Maattanen (McGill) presented the structure of ERp57, a protein disulfide isomerase that acts in concert with calnexin to recruit substrate proteins. Jeff Brodsky (Pittsburgh) discussed the use of yeast as a model system to study the ER associated

degradation (ERAD) of mammalian membrane proteins like CFTR, as well as plasma membrane-associated quality control systems. In the final presentation, Igor Stagljär (Toronto) told the audience about novel technology his laboratory has developed to detect membrane protein interactions in high throughput mode, providing a preview of the theme of the 50th Annual CSBMCB Meeting to be held in 2007 in Montréal.

A highlight of the meeting was the two poster sessions that featured the work of graduate students, post-doctoral fellows and senior investigators. The evening "Poster Pubs" provided plenty of opportunity for lively discussions of the over 100 posters presented, and they went well into the evening.

Many people took advantage of the Hillebrand Winery and Niagara-on-the-Lake tour on Thursday afternoon, and the Niagara Falls tour on Friday afternoon. Others found time to participate in tennis and swimming at the Resort, or golf at nearby courses. People were very impressed with the friendliness of the staff at White Oaks and their attention to detail. The "continuous" coffee breaks and snack tables were greatly appreciated.

The feedback on the meeting and the quality of the presentations has been overwhelmingly positive. It is very gratifying that a great deal of excitement was generated among the younger people at the meeting about research in the area of membrane proteins, suggesting that this important field will continue to prosper well into the future.

Travel and Poster Award Recipients for the 2006 CSBMCB Annual Scientific Meeting

Niagara-on-the-Lake, Ontario

POSTER PRIZES

AWARDEE	UNIVERSITY	SUPERVISOR
Roche Diagnostics Poster Prizes		
Leigh Ann Niven	Dalhousie University	Dr. Christopher McMaster
Fiona Cunningham	University of Toronto Hospital for Sick Children	Dr. Charles Deber
Jake Duerckson Poster Prize in Cell Biology		
Alina Ilie	McGill University	Dr. John Orlowski
CSBMCB Poster Prizes		
Mohammed Khan	University of Toronto	Dr. Russell Bishop
Matthew Henderson	McMaster University	Dr. David Andrews
Patrick Kim Chiaw	University of Toronto, Hospital for Sick Children	Dr. Christine Bear
Derek Ng	University of Toronto Hospital for Sick Children	Dr. Charles Deber
Dr. Ian Bates	McGill University	Dr. John Hanrahan
Dr. Saranya Kittanakorn	University of Toronto	Dr. Reinhart Reithmeier
Dr. Ariana Rath	University of Toronto	Dr. Charles Deber
CSBMCB Platform Presentation Prizes		
Jennifer Baker	University of Toronto, Hospital for Sick Children	Dr. Julie Forman-Kay
Veil-Pekka Maatanen	McGill University	Dr. David Thomas

TRAVEL PRIZES

AWARDEE	UNIVERSITY	SUPERVISOR
Merck Frosst 10 x \$750 awards		
Dr. Je Ding	University of Alberta	Dr. Larry Fliegel
Adam Elwi	University of Alberta	Dr. Carol Cass
Danielle Johnson	University of Alberta	Dr. Joe Casey
Heather McMurtie	University of Alberta	Dr. Joe Casey
Dr. Patricio Morgan	University of Alberta	Dr. Joe Casey
Robert Paproski	University of Alberta	Dr. Carol Cass
Dr. Jan Rainey	University of Alberta	Dr. Bruan Sykes
Hailey Standro	University of Alberta	Dr. Joe Casey
Emily Siepkov	University of Alberta	Dr. Larry Fliegel
Marian Ziomislic	University of Calgary	Dr. Peter Tieleman

Nunc and Nalgene \$600 award

Shannon Compton

Auburn University

Dr. Ellen Behrend

Amgen II x \$700 awards

Amy Curwin

Dalhousie University

Dr. Christopher McMaster

Leigh Ann Niven

Dalhousie University

Dr. Christopher McMaster

Dominique Gagnon

Université de Montréal

Dr. Jean-Yves Lapointe

Jean-Philippe Longpré

Université de Montréal

Dr. Jean-Yves Lapointe

Alina Ilie

McGill University

Dr. John Orlowski

Tushare Jinadasa

McGill University

Dr. John Orlowski

Dr. Viktoria Lukashova

McGill University

Dr. John Orlowski

Veli-Pekka Maatanen

McGill University

Dr. David Thomas

Valerie Walker

McGill University

Dr. Alvin Shrier

Hans Christian Zaun

McGill University

Dr. John Orlowski

Pascal Courville

INRA-Institut Armand

Dr. Mathieu Cellier

Frappier

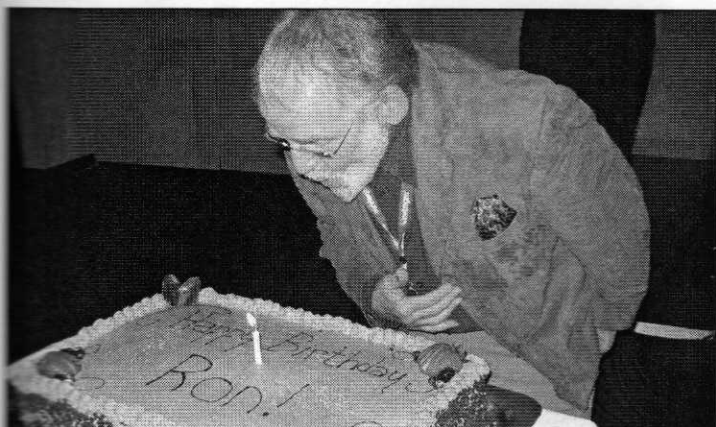
Scenes from the 2006 CSBMCB Annual Meeting



Rob Reedijk and Justin Thielman of the University of Toronto ran the Registration Desk



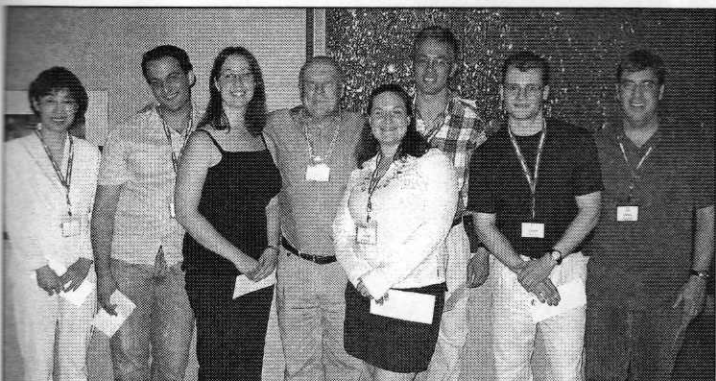
Dr. Joel Weiner, Session Chair (centre), flanked by the two Plenary Lecturers, Nobel Prize winner Dr. Peter Agre (left) and Dr. Ronald Kaback (right)



Plenary Lecturer Dr. Ronald Kaback blowing out the candles on his birthday cake



Dr. David Thomas, President of the CSBMCB (centre) with the Amgen and Nunc & Nalgene Travel Award winners



Dr. David Thomas, President of the CSBMCB (centre) with the Merck Frosst Travel Award winners



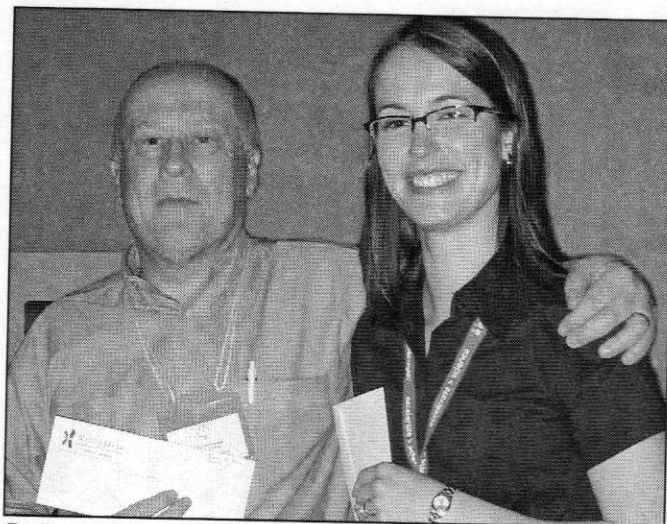
Dr. Frances Sharom, member of the local organizing committee, congratulates the winners of the CSBMCB Poster Prizes



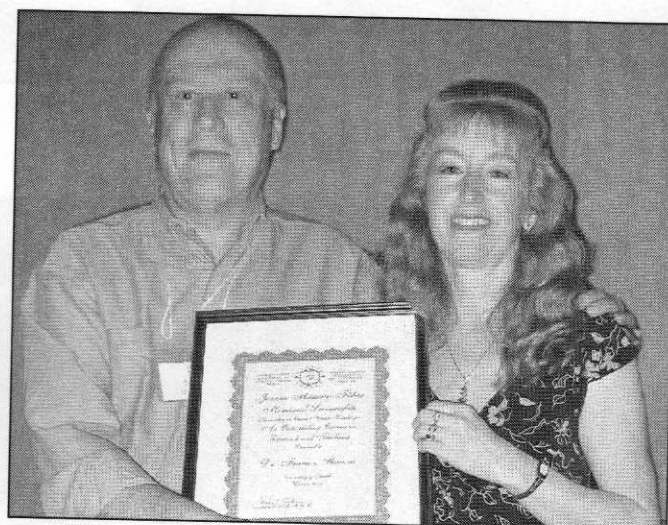
Dr. Frances Sharom, member of the Local Organizing Committee, congratulates the winners of the Roche Diagnostics Poster Prizes, Fiona Cunningham (left) and Leigh Ann Niven (not present), and the Jake Duerkson Poster Prize in Cell Biology, Alina Ilie



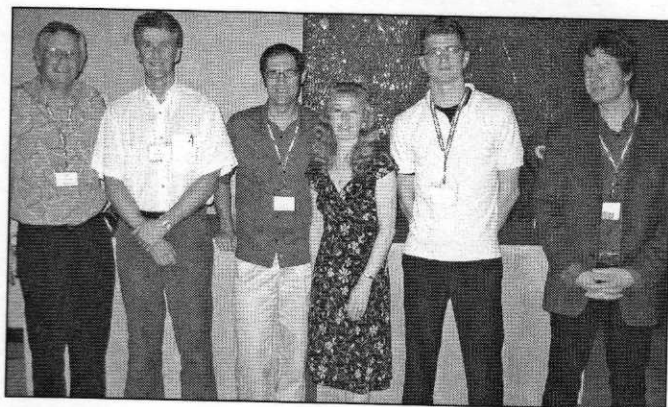
The 2006 winner of the CSBMCB Merck Frosst Prize, Dr. Joe Casey of the University of Alberta, receives his award plaque



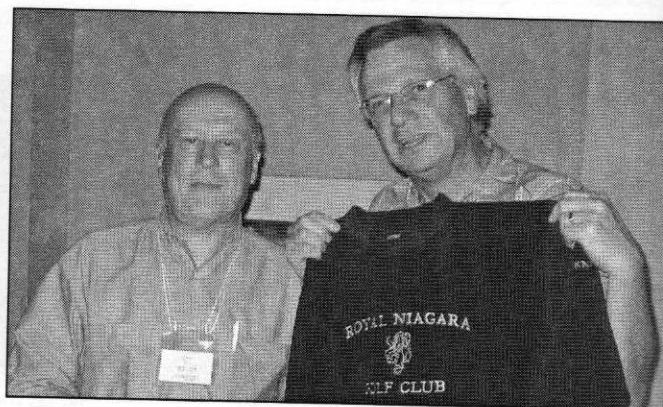
Dr. David Thomas, President of the CSBMCB presents awards to the two trainees selected for platform presentations, Jennifer Baker and Veli-Pekka Maatanen (not present)



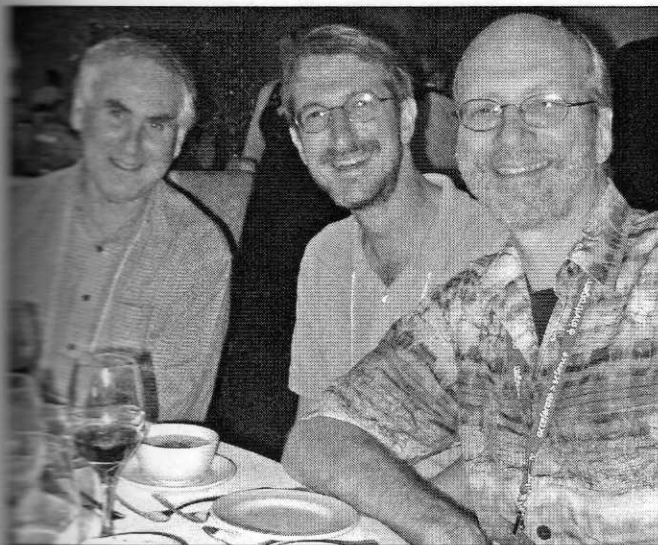
The 2006 Jeanne Manery Fisher Memorial Lecturer, Dr. Frances Sharom, receives her award plaque



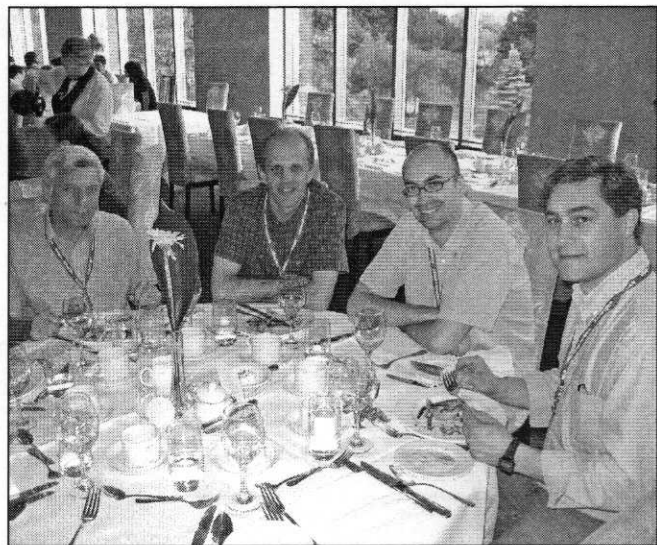
Members of the Local Organizing Committee (left to right), Dr. Reinhart Reithmeier, Dr. Jean-Yves Lapointe, Dr. Joe Casey, Dr. Frances Sharom, Justin Thielman and Rob Reedijk (not present, Dr. David Andrews and Dr. Victoria Ilgacs)



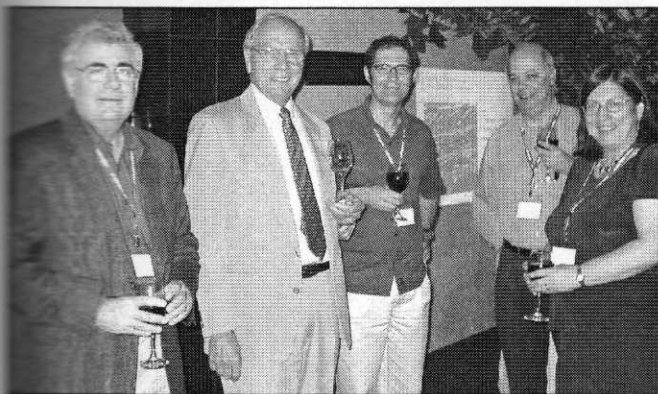
Dr. Reinhart Reithmeier, Chair of the Conference Organizing Committee, is presented with assorted "golf stuff" in appreciation for all his hard work



asey
 Drs. Tom Rapoport, Jeff Brodsky and David Williams enjoying the banquet.



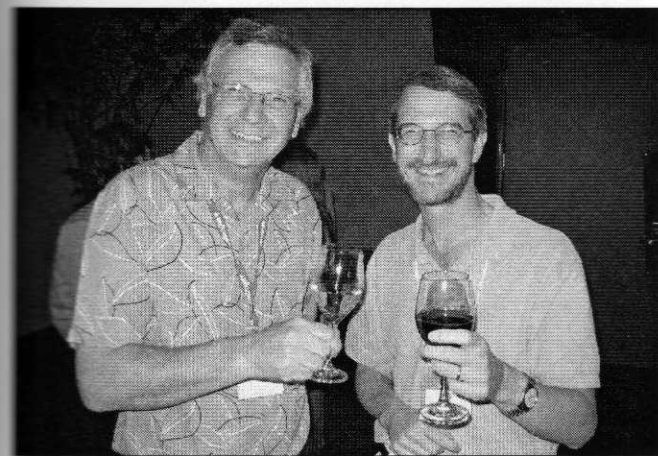
Lunch group



on
 Conference delegates enjoying wine and snacks at the Opening Mixer sponsored by Merck Frosst Canada



Relaxation at the end of the day



on
 Enjoying the Niagara region wine



Dinner group



Dinner group

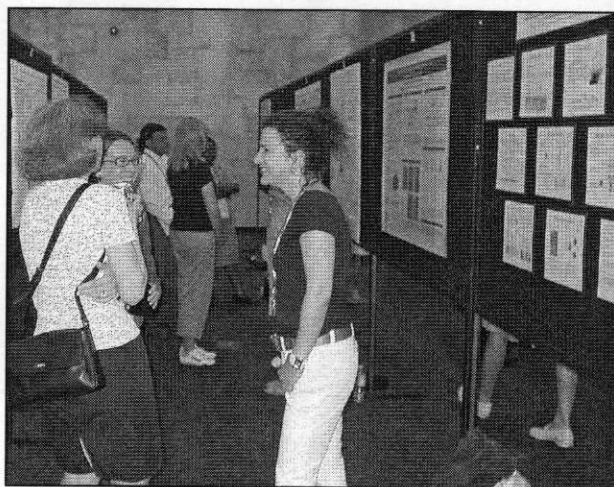
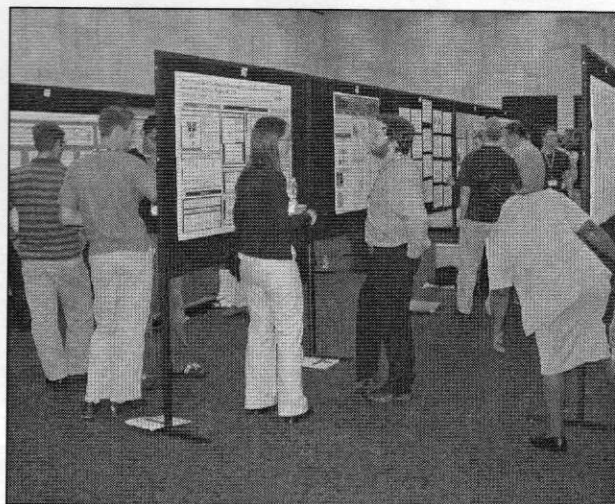
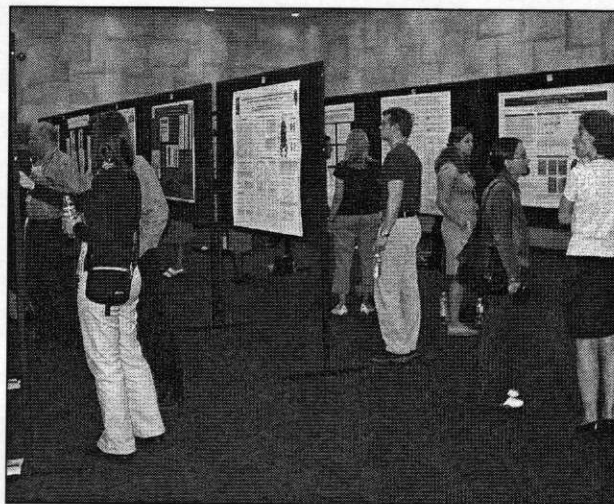


Dinner group



Dinner group

Poster Sessions



50th Annual Meeting and Conference of the CSBMCB "Systems and Chemical Biology"

Thursday July 5 - Monday July 9, 2007

New Residence Hall, McGill University

Scientific Program

Thursday July 5th, 2007

9:00-12:00 pm: Canadian Society for Systems Biology (CSSB) Annual Meeting

1:10-5:00 pm: Trainee's Mini-Symposium including invited speakers from the abstracts

Session I Plenary Lectures

Session Chair: Eric Brown, McMaster University

- 7:30 pm Ronald Breaker, Yale University, CT
Exploring the diversity of riboswitch structures and functions
- 8:15 pm Pamela Silver, Harvard Medical School, Boston
Designing biological systems
- 9:00 pm Opening mixer and exhibits

Friday July 6th, 2007

Session II Small Molecule Probes of Big Biology

Session Chair: Eric Brown, McMaster University

- 8:20 am Tom Silhavy, Princeton University, NJ
Chemical conditionality: an approach for understanding outer membrane biogenesis in gram-negative bacteria
- 9:00 am Jim Inglese, NIH Chemical Genomics Center, MD
Quantitative high throughput screening: discovery of investigational molecular probes through the biological activity profiling of chemical libraries
- 9:40 am Mike Tyers, Samuel Lunenfeld Research Institute, Toronto
In search of the magic shotgun: interrogation and manipulation of cellular networks by combinations of small molecules
- 10:20 am Coffee break with exhibitors
- 10:50 am Raymond Andersen, University of British Columbia
Bioactive marine natural products: drug leads and cell biology tools
- 11:30 am Peter Roy, University of Toronto
Using *C. elegans* as a platform for the discovery of small molecule tools for biological analysis
- 12:10 pm CSBMCB Board Meeting

Session III Chemical Biology of Nucleic Acids

Session Chair: Yingfu Li, McMaster University

- 1:20 pm Eric Westhof, Institut de biologie moléculaire et cellulaire du CNRS, France
Molecular recognition between antibiotics and RNA
- 2:00 pm Hiro Suga, University of Tokyo, Japan
Genetic code reprogramming
- 2:40 pm Bruce Sullenger, Duke University Medical Center, NC
Novel applications of aptamers: teaching an old dog some new tricks
- 3:20 pm Coffee break with exhibitors
-

- 3:50 pm Chuck Wilson, Chief Scientific Officer Archemix Corp, USA
Optimizing therapeutic aptamers through medicinal chemistry
- 4:30 pm Jean-Pierre Perreault, Université de Sherbrooke, Québec
Development of cleaving ribozyme with high fidelity
- 5:10-7:00 pm Poster Pub I and hors d'oeuvres
- 7:00-8:30 pm Award Lectures**
- 7:00-7:45 pm Roche Diagnostics Prize Lecture
- 7:45-8:30 pm Merck Frosst Prize Lecture

Saturday July 7th, 2007

Session IV Developments in Systems Biology

Session Chair: Daniel Figeys, University of Ottawa

- 8:20 am Janet Thornton, European Bioinformatics Institute, Cambridge, UK
The evolution of enzyme mechanisms and functional diversity
- 9:00 am Mathias Uhlén, Professor, Royal Institute of Technology, Sweden
A human protein atlas for normal and cancer tissues
- 9:40 am Shankar Subramaniam, University of California, San Diego
Systems biology approach to deciphering cellular networks in macrophages
- 10:20 am Coffee break with exhibitors
- 10:50 am Kristin Baetz, Ottawa Institute of Systems Biology
Integrated analysis of the histone acetyltransferase NuA4
- 11:30 am John Yates, Scripps Research Institute, CA
Driving biological discovery using mass spectrometry

Session V Genomics and Proteomics

Session Chair: Guy Poirier, Université Laval

- 1:20 pm N. Leigh Anderson, Plasma Proteome Institute, Washington DC
The plasma proteome: challenges for biomarker discovery and validation
- 2:00 pm Ronald Beavis, University of British Columbia
Informatics strategies for immune system surveillance
- 2:40 pm Arul M. Chinnaiyan, University of Michigan Medical School
Bioinformatics as an engine for oncology discovery
- 3:20 pm Coffee break with exhibitors
- 3:50 pm Benoit Coulombe, Institute des recherches cliniques de Montréal
A panorama of the protein complexes formed by the RNA polymerase II transcription machinery in mammalian cells
- 4:30 pm Akhilesh Pandey, John Hopkins Bloomberg School of Public Health, Baltimore
An integrated bioinformatics and proteomics approach to study kinases and substrates
- 5:10-7:00 pm Poster Pub II

Sunday July 8th, 2007

Session VI Frontiers in Chemical Biology

Session Chair: Gerry Wright, McMaster University

- 8:20 am Jon Clardy, Harvard Medical School, Boston
Genes, genetically-encoded small molecules, and biology
- 9:00 am Stephen Withers, University of British Columbia
Directed evolution as a strategy for the generation of new catalysts for glycoside assembly

- 9:40 am John Vederas, University of Alberta
Integrated approaches to discovery of new antimicrobial agents
- 10:20 am Coffee break with exhibitors
- 10:50 am Suzanne Walker, Harvard Medical School, Boston
Peptidoglycan biosynthesis and its inhibition
- 11:30 am Mike Marletta, University of California, Berkeley
Biological sensing of nitric oxide and oxygen: A problem in molecular recognition

Session VII Chemical Genomics and Cancer

Session Chair: Michael Hallet, McGill University

- 1:20 pm Albert Koong, Stanford University, CA
Inhibition of the unfolded protein response (UPR) as a cancer therapeutic strategy
- 2:00 pm Jerry Pelletier, McGill University, Montreal
Therapeutic potential of translation initiation inhibitors
- 2:40 pm Maya Schuldiner, University of California, San Francisco
Building a systems level view of the cell using genetic interaction maps
- 3:20 pm Coffee break with exhibitors
- 3:50 pm Stephen Michnick, Université de Montréal
Chemical biology on pins and needles

Session VIII CSBMCB 50th Anniversary Banquet and Awards Presentations

- 6:30 pm Cocktails with Dixieland Quartet at Faculty Club
- 7:30 pm Banquet and Awards Presentation
(Wine sponsored by Merck Frosst)

Monday July 9th, 2007

Session IX Systems and Synthetic Biology

Session Chair: Martin Latterich, Université de Montréal

- 8:20 am Robert Nadon, McGill University, Montreal
Statistical analysis of high throughput screening results
- 9:00 am John Bergeron, McGill University, Montreal
Systems biology of the cell via organellar proteomics
- 9:40 am Peter Swain, McGill University, Montreal
Stochasticity and designs of genetic networks
- 10:20 am Coffee break
- 10:50 am Anne-Claude Gingras, University of Toronto
Functional proteomics of serine/threonine phosphatases
- 11:30 am Jaclyn Vogel, McGill University, Montreal
Analysis of yeast PP1/Glc7 phosphatase networks using integrated genomic and proteomic approaches
- 1:10 pm Science Policy Meeting
- 2:10 pm CSBMCB Annual General Meeting
- 3:10 pm Coffee break
- 3:30 pm General discussion
- 4:00 pm CMC organizational meeting
- 4:30 pm Departure

Canadian Chemical Biology Network: biochemistry back to the future

Eric D. Brown¹ and David Y. Thomas²

¹Department of Biochemistry and Biomedical Sciences,
McMaster University

²Department of Biochemistry, McGill University

When the Canadian Society of Biochemistry was founded 50 years ago, there was a profound interest in the chemical principles that underpinned biology. Pauling and Corey had proposed alpha-helical and beta-sheet structures. Watson and Crick had just solved the structure of the DNA double helix and there was considerable excitement about how macromolecules would interact with small molecules. Studies of the action of small molecule hormones and second messengers in cells by the likes of Earl Sutherland captured the imagination of a generation of Biochemists. Work by Kendrew and Perutz on the structures haemoglobin and myoglobin were driven by a deep fascination for their interactions with oxygen and carbon monoxide. Meanwhile, isopropyl-thio- β -D-galactoside (IPTG) was the product of elegant investigations done in part by Monod and Jacob in *Escherichia coli* where a variety of synthetic galactosides were systematically tested for activity as either substrates or inducers of the *lac* genes for lactose utilization. The latter highlights the use of small molecules to perturb biological systems, that is the basis for renewed research efforts at the interface of chemistry and biology.

Small molecule-macromolecule interactions range from the exquisitely stringent, such as the biotin-avidin interaction, to the modestly specific, such as the interactions of penicillin with penicillin-binding proteins, to the non-specific, such as the effects of detergents on cellular membranes. Unlike genetic manipulations, small molecules can exert their effects in a time scale of seconds or less and be added or removed from the system at will. Thus small molecules are exquisite probes of biology. Despite these advantages, efforts to discover new

small molecules with biological activity have largely been limited to the private sector, where the goal is drug discovery, not new reagents to probe complex biology. Only relatively recently has small molecule screening emerged as a tool in academic biological research, and happily Canadian biochemists, molecular biologists and cell biologists are leading the charge.

The Canadian Chemical Biology Network (CCBN) is an expanding collection of chemists and biologists from across Canada who are working to develop a network in support of small molecule screening. These researchers recognize the value of small molecules as probes of complex biology and have taken on the challenge of setting up pharma-style facilities for systematically screening tens of thousands of small molecules. They include principals with screening operations at the University of British Columbia, the Samuel Lunenfeld Research Institute, McMaster University, McGill University and the Université de Montréal. In 2005, the CCBN was founded with a grant from the Canadian Institutes of Health Research to support the purchase of a national chemical library of 30,000 compounds, now housed, curated and distributed by the McMaster High Throughput Screening (HTS) Laboratory. Also supported is a grass-roots effort to amass a library of Canadian-synthesized molecules to be included in this national collection. Most recently, the CCBN has launched an informatics effort to network screening activities across the country. Here the focus is the Canadian Chemical Biology Database, (<http://www.ccbn-rcbc.ca/>), to analyze, store and integrate results of CCBN screening activities. The web-accessible database

open to all network participants and anyone with an interest in screening should join! The central database will house both curated screening data and up-to-date fully annotated descriptions of CCBN compound libraries.

Will the CCBN and similar efforts in other countries in fact lead to new drugs? The sceptics reasonably advance two main arguments. The first, and seemingly overwhelming argument that is the most widely discussed, is that the cost of development of a new drug is estimated to be more than \$800 million. The second is that medicinal chemistry is weak in academia. There is considerable dispute about the real costs of the research component of drug development but it is certain that drug development is an expensive process.

However, many drugs that are in clinical use were discovered in universities: the *Vinca* alkaloids and *HTC* are two good Canadian examples to add to our national protein, insulin. There is also an innovation deficit in large pharma resulting in a dearth of new drugs. Also there are few incentives to work on orphan and neglected diseases, but these impart enormous health burdens on individuals and society. The medicinal chemistry and

knowledge of drug development question is being addressed by biopharmaceutical companies, but innovative solutions to this rate-limiting step are also being explored by diverse initiatives across Canada. While it will be a challenge to bring to bear necessary resources in academe to the goal of discovering drugs, it is nevertheless clear that initiatives like the CCBN will take us some considerable steps closer.

So it seems that biochemistry may have found its roots again in the CCBN. At the interface of chemistry and biology, small molecule screeners across Canada will be searching for new probes with unique biological activity. And some of these molecules will surely have the right stuff to serve as leads for new efforts in therapeutic drug discovery. At a time when biochemists, molecular and cell biologists are working hard to have their academic research efforts recognized as relevant to economic and health agendas the CCBN provides a special and exciting opportunity.

Become a member of the CCBN. It's free!
<http://www.ccbn-rcbc.ca/?q=membership>

Biochemistry – The McMaster Way

Lori Dillon

Research Communications, Office of Research, McMaster University

Something amazing happened 40 years ago. And no, we're not talking about the last time the Leafs drank from Lord Stanley's Cup. What we're talking about didn't receive quite the same fanfare – no real celebrations, street parties or parades – but amazing, nonetheless.

It was in 1967 that McMaster's Department of Biochemistry was born. And while its birth was a fairly quiet event, what happened over the last 40 years has given much cause for celebration.

Over the last four decades, the department grew both in size and stature – indeed, it's recognized as one of the top centres for life sciences research in North America. Some 1600 students have graduated; more than \$100-million was awarded in research grants, hundreds of honours and accolades were awarded to faculty and students for their scientific contributions, and world-class, state-of-the-art laboratories now line the corridors.



A 1969 photo of the late Professor Thomas Neilson. Today, the Thomas Neilson Scholarship is awarded yearly to top McMaster Biochemistry graduate students on transfer to the Ph.D. programme.

So, how exactly did the department get its start? It was the year before, in 1966, that McMaster opened its flagship school of medicine. It was under the leadership of John Evans, the school's first dean, that a group of innovative educators developed an undergraduate medical program that stirred controversy and defied convention by emphasizing self-directed learning.

But McMaster was missing a key component common to all medical schools – a department of biochemistry. While the core work was taking place in the departments of chemistry and biology, a decision was made to form the department and bring the existing work together under the new banner.

After an exhaustive search, Dr. Ross Hall, a cell biologist who completed his doctorate in biochemistry from Cambridge University under Nobel Laureate Lord Todd, and his post-doctoral work under Nobel Laureate Gobind Khorana, was recruited from the Roswell Memorial Cancer Research Institute in Buffalo, New York, to become the department's founding chair.

Hall's first order of business was to build the department. He established a core group, with members coming primarily from chemistry, including Dennis McCalla, who was then the University's first dean of science, and then began his recruitment effort, securing the likes of Hara Ghosh, Louis Branda, Barbara Ferrier and Bill Chan. At the time, the department's primary focus was nucleic acids, but, like the department, the focus continued to grow.

When Karl Freeman (Ph.D Toronto, 1959) took over the reins as chair in 1973, budgets were tight, nothing unique to Biochemistry, rather a reality facing the entire university. But even with decreased budgets, Freeman managed to secure funding for two new recruits – Richard Epand, a

cell biologist who would go on to publish more than 300 papers (at last count) and whose name would become synonymous with McMaster biochemistry, and Gerhard Gerber, a membrane expert who had also studied under Khorana, and would eventually go on to become the department's fifth chair and co-founder of Fermentas – a world leader in the discovery, manufacturing and marketing of quality molecular biologicals – one of the University's most successful spin-off companies.

According to Freeman, regardless of budgets, these were exciting times in research, with lots of graduate students, particularly international graduate students. But, in terms of the educational component, there was always a great discussion on just how much the department contributed to Health Sciences education.

Thomas McCalla, the department's third chair, recalls the new medical school adding both excitement and consternation to McMaster. While the approach to learning was different from other medical schools and was receiving international attention, there were those at the university who considered the approach to be "not very academic." That would soon change as the benefits of this mode of learning became increasingly obvious, and the approach would eventually be adopted at medical schools around the world.

McCalla was focused on bringing in some new ones to build on the reputation the department was beginning to enjoy. He can take credit for recruiting research stars like Calvin Harley, who joined the University in 1994 to become the Chief Scientific Officer at Geron in California, and Evert Nijmmer, a toxicology and epidemiology expert who still calls McMaster home.

Collaborations were fairly rare back then, but McCalla saw the potential and power of partnering. Early on he did some work with Russell Bell (chemistry) and Tom Neilson (biochemistry), and a few years later he collaborated with chemist Brian McCarty, and their work had a profound effect on the lives of many Hamiltonians.

The occupational health group at Dofasco had witnessed a seven-fold elevation in lung cancer inci-

dents among crane operators and was looking for answers as to the cause – were chemicals responsible and, if so, what were these chemicals? They called on McMaster and collectively, McCalla and McCarty discovered the buckets of molten steel that were being carried by the operators were the root of the problem. The bucket molds were made of sand and glued together with an organic substance which, when in contact with the molten steel, produced and released carcinogenic chemicals. Their study and subsequent findings saved the lives of countless steelworkers.

The department continued to expand under the leadership of Tom Neilson and subsequently Hara Ghosh, who had also been trained under Khorana. Ghosh spent his early days trying to convince the University's administration of the critical and essential need for developing molecular biology and biotechnology. And convince he did. He went on to recruit four molecular biologists (Bruce Fletcher, now in Cold Spring Harbour, NY; Rick Rachubinski, now at the University of Alberta; John Capone and David Andrews) and two structural biologists (Daniel Yang and Vettai Ananthanarayanan). He was also instrumental in raising awareness of biotechnology, helping to create a President's Biotechnology Advisory Committee and, subsequently, the McMaster Molecular Biology Institute.

By the time Gerhard Gerber became chair in 1991, the department was in full swing, as was its focus on molecular biology. Wanting to expand the department's mandate while employing the philosophy of hiring individuals who were not only excellent scientists, but also strong, independent thinkers, Gerber recruited Harvard-trained Gerry Wright, now Canada Research Chair in Molecular Studies of Antibiotics and current chair of the department, and structural biologist Albert Berghuis, now at McGill.

When Gerber became the University's vice-president of research in 1996, John Capone, who had studied under Ghosh, took over as chair. And while the department was coming out of some tough times – the province's social contract and other cutbacks – there were some emerging oppor-

tunities for growth, part of which came with the strategic re-allocation exercise that the University was undertaking.

Under Capone's leadership, molecular biology was identified as a strategic priority for the University and new positions were granted to the department. The positions came in the form of Canada Research Chair in Chemical Biology Eric Brown, microbiologist Justin Nodwell and cell biologists Ray Truant and Dino Trigatti.

Around the same time, new linkages with the Faculty of Science were being made, particularly in Chemistry, two new joint-positions were created, and enzymologist Paul Berti and Canada Research Chair in Directed Evolution of Nucleic Acids Yingfu Li were hired. That same partnership model was extended to Physics and Astronomy, resulting in the joint hires of Canada Research Chair in Molecular Biophysics Cecil Fradin and Canada Research Chair in Biophysics Paul Higgs.

At the time, federal and provincial governments were investing heavily in university research – trying to maximize their investments in opportunities that would bring universities together with industry and government to create the infrastructure so desperately needed for Canada to compete on the world's research stage. The department scored high in these competitions, leading to the creation of new facilities including the High Throughput Screening Lab, which continues to provide screening expertise and service to researchers across Canada and around the world.

The momentum continued when Gerry Wright, the department's current chair, took over, resulting in further research collaborations and new joint undergraduate and graduate programs. His leadership led to strategic hiring, securing Canada Research Chair in Human Stem Cell Biology Mick Bhatia to head up the Cancer and Stem Cell Research Institute, housed in the new Michael G. DeGroote Centre for Learning and Discovery, and strategic partnerships, like those underway with engineering, physics and medicine. He also paved the way for the \$20-million Centre for Microbial Chemical Biology – a Canadian first, and a true

testament to the strategic investments McMaster has made in the chemical biology and infectious disease research and the \$12 million Biophotonics Imaging Facility – an international centre dedicated to live cell analysis.

There has been tremendous growth over the last four decades – from its humble beginnings with fewer than a dozen faculty to the now 43 faculty members; 27 of whom have their primary appointment within the department. It's grown so much it had to change its name – it is now Biochemistry and Biomedical Science – to reflect its breadth and depth. The research focus now encompasses six themes – structural biology and protein/nucleic acid structure and function; membrane biology and lipid biochemistry; metabolism and toxicology; cell biology and regulation; cancer biology; and microbiological biochemistry and antimicrobial research.

Its research institutes and centres – The High Throughput Screening Lab; the Antimicrobial Research Centre; the Centre for Gene Therapeutics; the Centre for Functional Genomics; the McMaster Biophotonics Facility; and the Stem Cell Research Institute – are internationally recognized and provide a fertile training ground for future generations of researchers.

So where does it go from here? Well, in keeping with the hockey analogy, Wright says they need to play like a team and take a page from Gretzky's playbook to stay on top of the research game. "Gretzky's success was based on his ability to skate to where the puck was going to be; not to where it had already been, and that's what needs to happen with research – we need to anticipate what's next," he says.

And what's next, according to Wright, is systems biology – the collaboration between the life and physical sciences. Genome sequencing has revolutionized biology – a revolution that will be felt for decades. This "new biology," as Wright calls it, means no more silos or single-streamed thinking. It means considering many things at the same time, in multi-disciplinary teams, with an emphasis on large-scale data management and analysis.

It also means that the department, under Wright's

leadership (he's in year one of a second five-year term), will build on areas that are not only relevant, but those that bridge the disciplines and emphasize collaboration. His track record to do so speaks for itself.

And while the department's research agenda grows, so do the opportunities for the students. "Active learning" is the department's motto and where we go to find the action and develop critical thinking and creative problem solving skills than state-of-the-art laboratories alongside first-class teachers.

The department will celebrate its 40th anniversary on October 13, 2007, with a great line-up of speaker sessions and tours of its new facilities.

Check out www.hsc/mcmaster.ca/biochem for more details.

Why Bicarbonate?

Joseph R. Casey

Membrane Protein Research Group, Department of Physiology and
Department of Biochemistry, University of Alberta, Edmonton, Alberta

Abstract

Bicarbonate is a simple single carbon molecule that plays surprisingly important roles in diverse biological processes. Among these are photosynthesis, the Krebs cycle, whole body and cellular pH regulation and volume regulation. Since bicarbonate is charged it is not permeable to lipid bilayers. Mammalian membranes thus contain bicarbonate transport proteins to facilitate the specific transmembrane movement of HCO_3^- . This review provides a wide-ranging view of the biochemistry of bicarbonate and its membrane transporters, revealing what makes the study of bicarbonate transport such a rewarding activity.

Introduction

This article will summarize my laboratory's studies of bicarbonate transport proteins, in the broader context of the literature. This seems an appropriate time also to pause and ask how my research got here. Why study the biochemistry of bicarbonate?

Since the start of my research career my focus has been the biochemistry and physiology of mammalian bicarbonate transport. Although bicarbonate is tremendously important in biology (especially in plants), the focus here will be on bicarbonate in mammals, in particular the transmembrane transport of the membrane impermeant anion, bicarbonate.

Biochemistry of bicarbonate

Chemistry of bicarbonate - There was considerable chance involved in deciding to study transmembrane movement of bicarbonate. Knowing what I know now, I have to wonder whether I would have chosen to study bicarbonate as a transport substrate. The chief difficulty in studying bicarbonate transport is that bicarbonate is a labile substrate. That is, the reaction $\text{CO}_2 + \text{H}_2\text{O} \leftrightarrow \text{H}_2\text{CO}_3$ occurs both spontaneously and catalyzed by carbonic anhydrase enzymes (see below). Further

complexity is added by the acid/base conversion properties of bicarbonate: $\text{H}_2\text{CO}_3 \leftrightarrow \text{HCO}_3^- + \text{H}^+ \leftrightarrow \text{CO}_3^{2-} + \text{H}^+$, reactions governed by pK_a s of 6.4 and 10.3, respectively. This chemistry makes it challenging to study bicarbonate transport since the substrate under investigation changes form, and alters pH as it does so. The situation becomes more complex because CO_2 (gas) \leftrightarrow CO_2 (dissolved), whose equilibrium varies with partial pressure of CO_2 , temperature and pH. Bicarbonate is indeed a "slippery" substrate to study, but this tendency to change chemical form is what makes bicarbonate biologically important, as described below.

Mitochondrial carbon dioxide production - The additional complexity to the study of bicarbonate transport is the fact that our cells continuously produce metabolic CO_2 as a waste product. Catabolism of proteins, carbohydrates and lipids ultimately results in formation of acetyl-CoA, which feeds into the Krebs cycle (Lehninger 1982). The Krebs cycle, the primary source of energy production in mitochondria, effectively oxidizes acetyl-CoA to carbon dioxide (Lehninger 1982). CO_2 is thus the primary waste product of respiratory oxidation.

RuBisCO and photosynthetic CO_2 fixation - Although the biochemistry of bicarbonate does not immediately seem of dramatic importance, in fact bicarbonate biochemistry is central to virtually all life. Ribulose-1,5-bisphosphate carboxylase/oxygenase (RuBisCO, EC 4.1.1.39) catalyzes the first reaction of photosynthetic CO_2 fixation: D-ribulose 1,5-bisphosphate + $\text{CO}_2 + \text{H}_2\text{O} \leftrightarrow$ 2 3-phospho-D-glycerate. Thus, RuBisCO provides the energy source for most other organisms, whose metabolism is based on consumption of plants/algae. In light of this central biochemistry RuBisCO comprises 30-50% of soluble protein in leaves (Dhingra *et al.* 2004) and has been suggested to be the most abundant protein of life.

Combustion and global warming - The chemistry, and biochemistry, of $\text{CO}_2/\text{HCO}_3^-$ is very much in the news with the unfortunate arrival of carbon dioxide induced global warming. Virtually all organisms ultimately rely on the energy provided by the fixation of CO_2 by RuBisCO (i.e. plants/algae fix the CO_2 and other creatures eat the plants). So too, our society's need for energy is in large part satisfied by oxidation of fossil carbon that was originally fixed by RuBisCO tens of millions of years ago. The overwhelming consensus is that the resulting elevation of atmospheric CO_2 traps heat, reducing nighttime loss and elevating mean earth surface temperature (Friedlingstein and Solomon 2005). There was hope that elevated atmospheric CO_2 levels would increase photosynthetic CO_2 fixation, thus mitigating some of the CO_2 rise. Unfortunately the most careful study to date suggests that there will be at best a modest increase of plant CO_2 fixation with increased levels of atmospheric CO_2 (Long *et al.* 2006). Engineering of RuBisCO to enhance CO_2 fixation in crop plants is an active area of investigation (Berry *et al.* 2003). With the advent of global warming as a significant threat to human survival, it is likely that the biochemistry of bicarbonate/carbon dioxide will receive increased attention in the future.

Physiology of bicarbonate

Bicarbonate and whole body pH regulation

Biochemical processes occur within narrow optimal pH range. Consequently our bodies have extensive pH buffering to restrict changes of intra and extracellular pH. Principal among these is the $\text{CO}_2/\text{HCO}_3^-$ system. As mentioned above $\text{CO}_2/\text{HCO}_3^-$ inter-convert; CO_2 is a conjugate acid and HCO_3^- is a base. While CO_2 is membrane permeant by diffusion across the lipid bilayer, HCO_3^- is charged and moves across membranes only with the assistance of specific transport proteins (see below). Because of the acid/base properties of $\text{CO}_2/\text{HCO}_3^-$ movement of CO_2 out of the cell will alkalinize the cell, while HCO_3^- efflux acidifies the cell. Under physiological conditions the majority of $\text{CO}_2/\text{HCO}_3^-$ is found as HCO_3^- (at levels around 25 mM) and metabolic acid will readily be consumed by conversion of HCO_3^- to CO_2 . Thus, $\text{CO}_2/\text{HCO}_3^-$ acts as a major physiological buffering system.

Excretion of $\text{CO}_2/\text{HCO}_3^-$ - CO_2 is produced as a metabolic waste product by the Krebs cycle. It is essential to continued body function that this acid load be excreted as the acid form, CO_2 . Yet the body has a problem in that the blood that flows through our kidneys contains high levels HCO_3^- . Secretion of renal HCO_3^- must be prevented as loss of this base from the body would cause dramatic, life-threatening acidosis. Not surprisingly our kidneys reabsorb virtually all of the HCO_3^- (amounting to about 500 g NaHCO_3 /day in each individual) that passes through them, using a series of bicarbonate transport proteins (see below). Rather than secrete HCO_3^- , our bodies exhale gaseous CO_2 using a remarkable and highly conserved system.

In the secretion of CO_2 from our bodies there is one major difficulty: CO_2 is poorly soluble in the aqueous medium of our blood. To maximize $\text{CO}_2/\text{HCO}_3^-$ carrying capacity, metabolically produced CO_2 diffuses out of our cells into the blood (Fig. 1). It then diffuses across the red blood cell (erythrocyte) membrane. Inside the erythrocyte the enzyme, carbonic anhydrase, is localized to convert CO_2 to HCO_3^- . HCO_3^- levels cannot be allowed to rise in the erythrocyte because the process would shut down, as a result of mass action. To prevent this erythrocytes express exceptionally high levels (about half the integral mem-

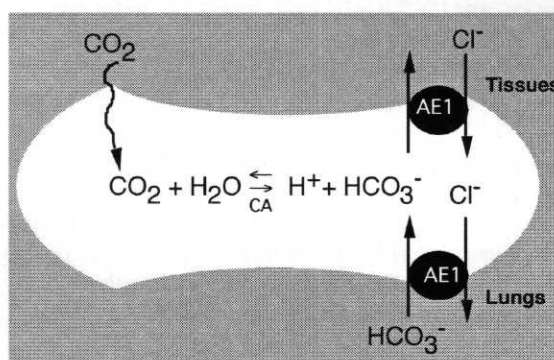


Figure 1 The role of AE1 in facilitating CO_2 efflux from the body. The body's tissues produce CO_2 as a waste product. CO_2 diffuses across membranes into the plasma and across the erythrocyte membrane. Inside the erythrocyte the enzyme, carbonic anhydrase (CA) catalyzes the conversion of CO_2 to HCO_3^- . The integral membrane transport protein, AE1, moves the HCO_3^- out of the cell into the plasma, in which the HCO_3^- is carried to the lungs. At the lungs the process reverses: AE1 carries HCO_3^- into the erythrocyte, where it is converted to CO_2 , and subsequently exhaled.

brane protein) the protein AE1 (Anion Exchanger 1). AE1 exchanges one intracellular HCO_3^- for one extracellular Cl^- , thus effluxing HCO_3^- into the plasma in an electroneutral manner. Upon reaching the lungs, the erythrocyte confronts an environment with low CO_2 levels. This drives dissolved CO_2 to leave the plasma, become gaseous and leave the body through exhalation. In turn, the low plasma CO_2 levels drive conversion of HCO_3^- to CO_2 : HCO_3^- is moved back into the erythrocyte in exchange for intracellular Cl^- , mediated again by AE1. Carbonic anhydrase converts the HCO_3^- to CO_2 , which diffuses across the erythrocyte membrane into the plasma, whereupon it is exhaled out through the lungs. With the assistance of AE1 secretion of acidic CO_2 is thus accomplished.

Bicarbonate transporters

Phylogeny of bicarbonate transporters - The examples of renal HCO_3^- reabsorption and the role of erythrocytes and the lungs in ridding the body of CO_2 illustrate two very different function of bicarbonate transport proteins. These proteins facilitate the movement of membrane-impermeant HCO_3^- across biological membranes. In mammals about 13 different genes encode bicarbonate transporters (Fig. 2), which function via a range of catalytic mechanisms, including $\text{Cl}^-/\text{HCO}_3^-$ exchange (e.g. AE1), $\text{Na}^+/\text{HCO}_3^-$ co-transport and Na^+ -dependent $\text{Cl}^-/\text{HCO}_3^-$ exchange. These bicarbonate transporters cluster into three separate branches upon phylogenetic analysis (Fig. 2): classical $\text{Cl}^-/\text{HCO}_3^-$ exchangers of the "AE" family, Na^+ /bicarbonate co-transporters of the NBC family and members of the SLC26 (Solute Carrier sub-family 26) family.

Cellular roles of bicarbonate transport

Bicarbonate transporters are involved in three fundamental processes: HCO_3^- metabolism/excretion, regulation of pH, and regulation of cell volume. By facilitating the movement of bicarbonate across membranes, bicarbonate transporters drive HCO_3^- metabolism. A good example of this function is the role of erythrocyte AE1, as described above. Since movement of HCO_3^- will acidify the region it leaves and alkalinize the opposite side of the membrane, HCO_3^- transporters are clearly involved in regulation of pH. A prime example of this activity is the role of the AE2 $\text{Cl}^-/\text{HCO}_3^-$ exchanger in the basolateral surface of acid-secre-

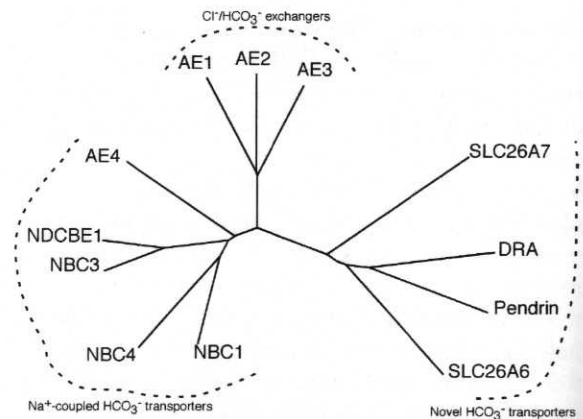


Figure 2 Phylogenetic relationships of human HCO_3^- transporters. Amino acid sequences for human bicarbonate transporters were analysed with the program Phylip. The degree of sequence similarity is represented by the length of line between proteins. The dashed curves enclosing the transporters indicate the three different clusters of bicarbonate transporters. Transporters analysed are: AE1 (Kopito and Lodish 1985); AE2 (Alper et al. 1988); AE3 (Kudrycki et al. 1990); NBC1 (Burnham et al. 1997); (Romero et al. 1997); NBC3 (Ishibashi et al. 1998); NBC4 (Pushkin et al. 2000); AE4 (Tsuganezawa et al. 2001); NDCBE1 (Romero et al. 2000); SLC26A3 (Schweinfest et al. 1993); SLC26A4 (Scott et al. 1999); SLC26A6 (Waldegger et al. 2001); and SLC26A7 (Lohi et al. 2002).

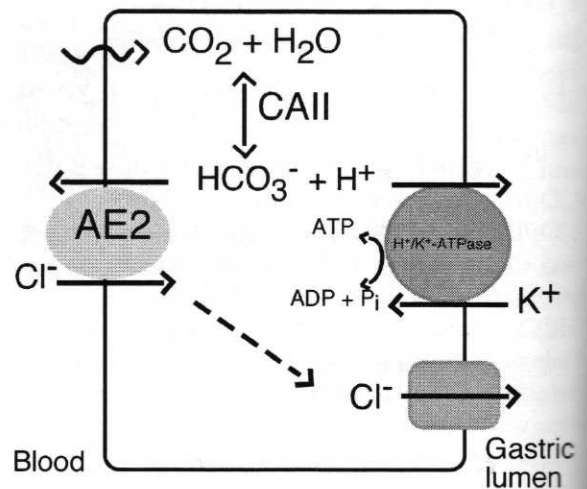


Figure 3 Essential role for $\text{Cl}^-/\text{HCO}_3^-$ exchange in parietal cell acid secretion. Basolateral AE2 provides both H^+ and Cl^- , required for HCl secretion. Similar physiology occurs for osteoclast acid secretion.

ing gastric parietal cells (Fig. 3). By efflux of HCO_3^- in exchange for influx of Cl^- , AE2 provides both the H^+ equivalent and Cl^- required for HCl secretion into the stomach lumen at the apical surface of the cell. The role of $\text{Cl}^-/\text{HCO}_3^-$ exchangers in volume regulation was first studied in lymphocytes (Mason *et al.* 1989), where it was found that cells exposed to hyper-osmotic challenge restore their fluid volume by loading with NaCl . They do so by coordinated activation of a $\text{Cl}^-/\text{HCO}_3^-$ exchanger and a Na^+/H^+ exchanger (which moves Na^+ in and H^+ out). Working together these transporters result in no change of cell pH, since the acid resulting from HCO_3^- efflux is balanced by H^+ efflux, so the net effect is cell loading with NaCl ; osmotic water movement restores cell volume.

Bicarbonate transport and the heart - Contractile activity of the heart is critically sensitive to pH. Consequently the heart expresses a wide range of pH-regulatory transport proteins, including HCO_3^- transporters (Alvarez *et al.* 2004). In addition to the need for HCO_3^- transporters to deal with the metabolic HCO_3^- load, HCO_3^- transporters have importance in two other physiological settings that have been studied by my laboratory: recovery from ischemic acidosis and cardiac hypertrophy. In ischemia reduced blood flow to cardiac muscle results in accumulation of waste products, including acid, and a shift to anaerobic metabolism. Upon restoration of blood flow, pH needs to be recovered to normal and HCO_3^- transporters are responsible for about 50% of pH recovery, through alkaline HCO_3^- influx (Vandenberg *et al.* 1993). Rapid recovery of pH by the cardiac NHE1 Na^+/H^+ exchanger can result in heart cell death, so that understanding the mechanisms of cardiac pH regulation is of great interest (Karmazyn 1988; Karmazyn 1996; Myers and Karmazyn 1996). A broad survey of bicarbonate transporter expression in the heart revealed that several HCO_3^- transporters are expressed in the heart (Alvarez *et al.* 2004). Predominant among these is the SLC26A6 protein, which carries out both $\text{Cl}^-/\text{HCO}_3^-$ and Cl^-/OH^- exchange (Alvarez *et al.* 2004). The role of AE in the heart is generally thought to be cellular acidification, by the efflux of HCO_3^- (Vaughan-Jones 1986). Indeed our recent data, using an inhibitory anti-AE3 antibody, showed that pH rises in rat cardiomyocytes treated with anti-AE3, leading to an increase of contractile force

(Cingolani *et al.* 2003). This suggests that under normal conditions AE3 significantly acidifies myocytes through HCO_3^- efflux.

We have proposed that cardiomyocyte acidification plays a significant role in the progression of cardiac hypertrophy, the enlargement of cardiomyocytes, leading to the compromised cardiac function found in heart failure. Our recent studies of $\text{Cl}^-/\text{HCO}_3^-$ exchange in the heart have led us to hypothesize that AE proteins contribute to the development of cardiac hypertrophy. Heart failure is marked by progressive enlargement of the heart, which contributes to the loss of cardiac function (Frey *et al.* 2004). Hypertrophic growth of individual cardiomyocytes underlies the heart expansion. Understanding the processes that regulate cardiomyocyte hypertrophic growth is thus of considerable importance. The cardiac NHE1 protein has a central role in the development of cardiac hypertrophy (Cingolani and Camilion De Hurtado 2002; Engelhardt *et al.* 2002) (Fig. 4). Hypertrophic signaling pathways converge by activation of NHE1; inhibition of NHE1 activation either through blockade of the signaling pathways that activate NHE1 (e.g. angiotensin converting enzyme inhibition (Camilion de Hurtado *et al.* 2002; Ennis *et al.* 1998; Fortuno *et al.* 1997)) or direct inhibition of NHE1 (e.g. with cariporide (Ennis *et al.* 2003; Kusumoto *et al.* 2001; Yoshida and Karmazyn 2000)) results in amelioration of cardiac hypertrophy. However, the fact that NHE1 action alkalinizes the cell and that NHE1 auto-inhibits at alkaline pH is under-appreciated (Counillon and Pouyssegur 2000). Thus, hyperactivation of NHE1 cannot be sustained in the absence of a balancing acid. Interestingly, under hypertrophic stimulation cardiomyocytes do not show an increase in steady-state pH (Perez *et al.* 1995), yet the increase of $[\text{Na}^+]_{\text{cytosolic}}$ verifies that NHE1 is hyperactivated (Cingolani and Camilion De Hurtado 2002; Perez *et al.* 2001). How is NHE1 hyperactivated without alkalinizing the cell? A parallel acidifying pathway, such as $\text{Cl}^-/\text{HCO}_3^-$ exchange, must be activated to balance the activity of NHE1 (Perez *et al.* 1995). We have found that AE3 η is the only AE protein whose activity is activated by PKC, the major kinase that integrates hypertrophic pathways (Alvarez *et al.* 2001) (Fig. 4). We thus hypothesize that AE3 η is essential for hypertrophic signaling pathways that act through NHE1. The mechanisms that couple NHE1 activation to hyper-

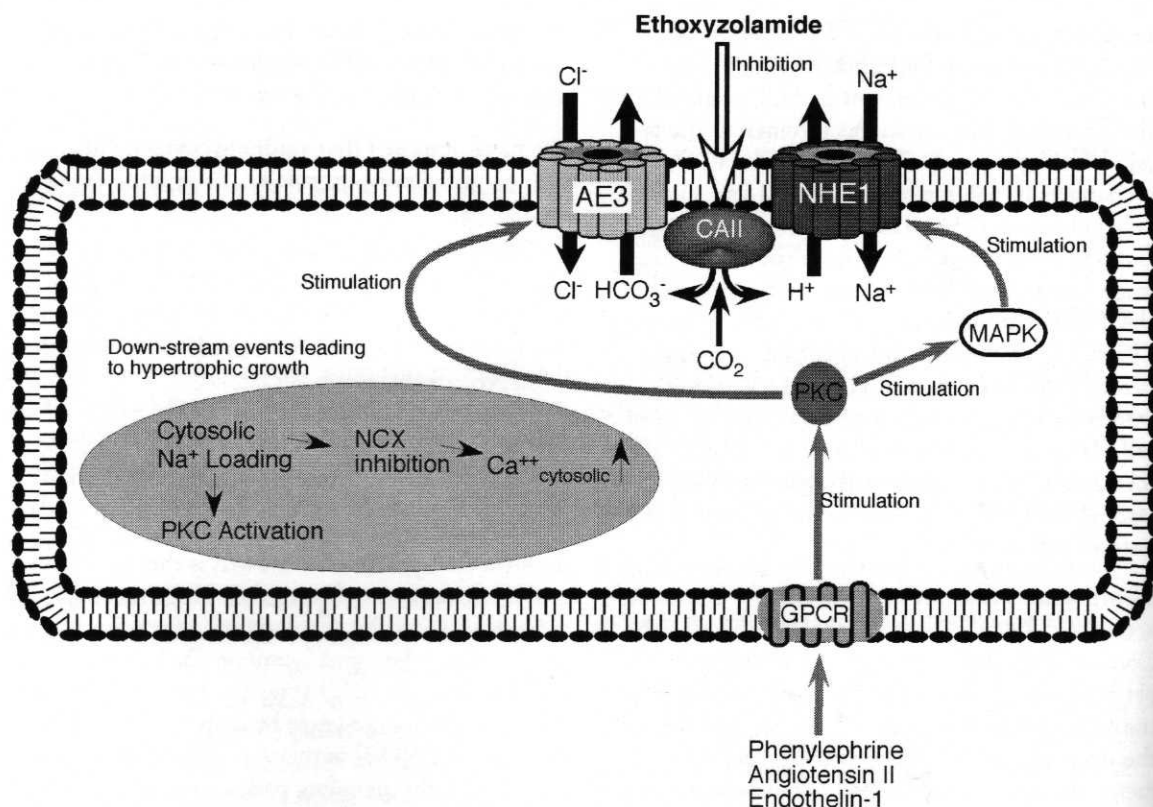


Figure 4 Hypertrophic growth in cardiomyocytes and the Hypertrophic Transport Metabolon. We propose that co-activation of the AE3 Cl⁻/HCO₃⁻ exchangers and the NHE1 Na⁺/H⁺ exchanger results in cellular NaCl loading, leading to stimulation of hypertrophic growth. CAII inhibition with ETZ limits substrate availability for AE3 and NHE1, thereby decreasing NaCl accumulation. MAPK= mitogen activated protein kinase; PKC= protein kinase C; GPCR= G-protein coupled receptor; CAII= carbonic anhydrase II.

trophic growth are not firmly established. The rise of cytosolic Na⁺ associated with NHE1 activation will, however, inactivate the Na⁺/Ca⁺⁺ exchanger and cause cytosolic Ca⁺⁺ elevation. In turn, elevated cytosolic Ca⁺⁺ activates the calcineurin/NFAT/transcription factor pathway to induce hypertrophic gene expression (Frey and Olson 2003).

We found that the cytoplasmic enzyme, carbonic anhydrase II (CAII) has a key role in cardiac pH regulation. Through hydration of CO₂, CAII produces H⁺ and HCO₃⁻ (Pastorekova *et al.* 2004). We have established that both AE proteins (Sterling *et al.* 2001b) and NHE1 (Li *et al.* 2002) bind CAII and that this binding event accelerates the respective transport rates of NHE1 and AE proteins, by maximizing the local concentration of transport substrates. We have termed the complex of a carbonic anhydrase with a bicarbonate transporter, the Bicarbonate Transport Metabolon, for

the linkage of metabolism and membrane transport (Sterling and Casey 2002; Sterling *et al.* 2001a; Sterling *et al.* 2001b). In a related way CAII, NHE1 and AE3 are linked (Fig. 4). The products of CAII action are effluxed by NHE1 and AE3, for a net cell-loading with NaCl. Co-activation of NHE1/CAII and AE3 is pathological as it is self-sustaining and NHE1 is not subject to inhibition by alkaline pH, since the co-activated transporters do not change pH_i. We propose that AE3, CAII and NHE1 form a functional and physical complex, which pathologically stimulates hypertrophic heart growth. We call this complex the Hypertrophic Transport Metabolon (Fig. 4).

Structure of bicarbonate transporters

The basic structure shared by bicarbonate transporters is a large cytoplasmic N-terminal domain of 40-80 kDa, followed by a membrane domain of

and a variable length cytoplasmic C-terminal region (Fig. 5). Erythrocyte AE1 has been subjected to an enormous number of studies since the protein's identification about 30 years ago (Cabantchik and Rothstein 1974) (reviews Reithmeier *et al.* 1993; Salhany 1990)). Little is known of the structure of other bicarbonate transporters has been reported, but topology of NBC1 has been studied (Tatishchev *et al.* 2003). The significantly a negative stain electron microscopy structure was determined for dimeric AE1MD at 20 Å resolution (Wang *et al.* 1993; Wang *et al.* 1994), which revealed each AE1MD as 46x50 Å rectangle. Many aspects of AE1 N-terminal cytosolic domain biology were explained by the 2.6 Å resolution crystal structure for the human (Zhang *et al.* 2000).

Topology - The topology of AE1MD, in particular the C-terminal portion, remains controversial (Fig. 5). Hydrophathy analysis for the first 9 transmembrane segments (TMs) is relatively clear and has been verified in large part experimentally (outlined in Tang *et al.* 1998; Zhu *et al.* 2003)). However, the remainder of AE1MD is not readily amenable to hydrophathy analysis and experimental evidence has been difficult to interpret. We performed a systematic scan of the AE1 TM8 region, clearly delineating the boundaries of the TM and identifying a two turn extension of helical structure into

the cytoplasm (Tang *et al.* 1998). Insertion of glycosylation acceptor sites revealed the presence of a re-entrant "T-loop" (transport loop) between TM9 and 10 (Popov *et al.* 1999), and helped to define topology in the remainder of the C-terminal region of AE1 MD. We mapped topology of the AE1MD by measurement of chemical reactivity of a series of individual introduced Cys mutants to membrane permeant and impermeant sulfhydryl reagents (Fujinaga *et al.* 1999; Zhu *et al.* 2003). This revealed the last two TMs as short (16 residues), suggesting that they are inserted into the protein's core structure and do not interact with lipid. N-terminal to the last two TMs is a region with puzzling structure. Much of the region is accessible to the extracellular medium, but it is difficult to model as either a conventional helical TM or as an extended β-structure (Fig. 5) (Zhu *et al.* 2003). We concluded that the region is extremely flexible, undergoing conformational transitions that allow it to extend across the AE1 transmembrane permeability barrier; the region likely forms a central portion of the transport site of AE1.

Oligomeric state - In the erythrocyte, AE1 exists as a mixture of dimers and tetramers (60:40 ratio) (Casey and Reithmeier 1991). The tetramers associate with the cytoskeleton, while the dimers do not. Proteolytic cleavage of the N-terminal cytoplasmic domain from AE1 reveals that the cyto-

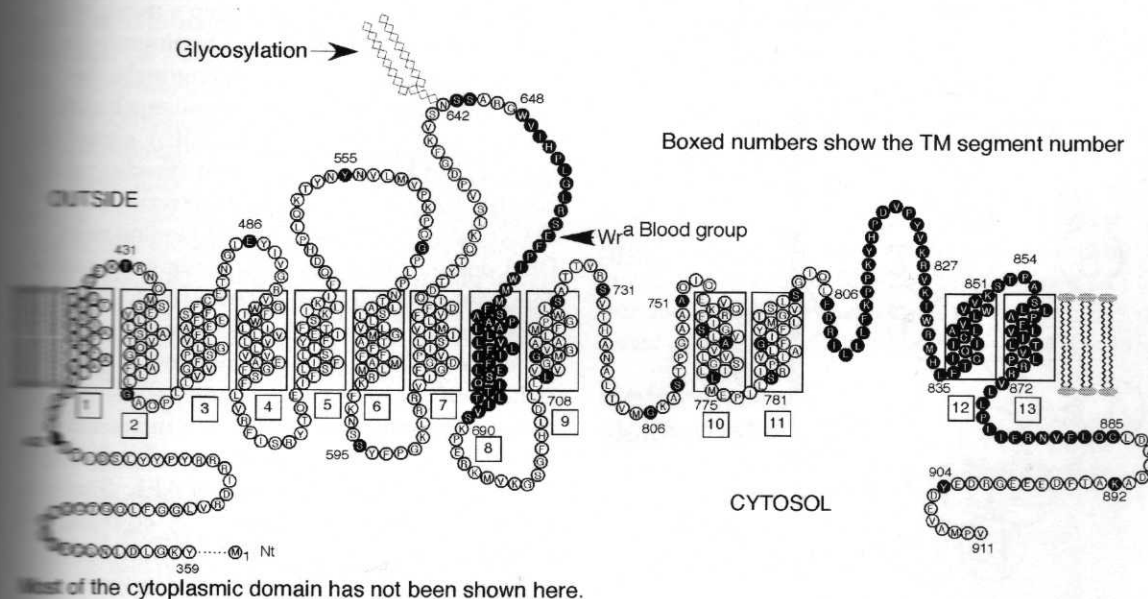


Figure 5 AE1 topology model, showing introduced cysteine mutants already constructed (filled circles). Topology model of AE1 was developed from several lines of evidence (summarized in Zhu, Lee and Casey, 2003).

plasmic domain is dimeric, as is the membrane domain (Casey and Reithmeier 1991; Zhang et al. 2000). Denaturation is required to separate AE1MD dimers to monomers, indicating a very strong association (Boodhoo and Reithmeier 1984). AE1 monomers function independently and each monomer has its own anion translocation pore (Jennings et al. 1998; Taylor et al. 2001). Oligomerically pure dimeric AE1MD can be readily purified following proteolytic separation from the cytoplasmic domain (Casey and Reithmeier 1991; Lemieux et al. 2002).

TM helical packing - Little data is available on the packing of AE1 TMs to form the membrane domain. Two studies designed to examine the region forming the AE1 dimeric interface developed limited models for AE1 TM packing. Tanner co-expressed separate portions of AE1MD to identify regions that were dispensable and those which could co-associate to form a functional transporter (Groves and Tanner 1999; Groves et al. 1998a; Groves et al. 1998b), which allowed him to propose a model for AE1MD helical packing (Fig. 6). Similarly, we cross-linked AE1 monomers to dimers, using AE1 introduced Cys mutants and a range of cross-linking reagents to determine a model for AE1MD (Fig. 6) (Taylor et al. 2001). The anion exchange inhibitor, H₂DIDS, covalently cross-links K539 and K851, and thus localizes these residues within 20 Å of each other (Okubo et al. 1994).

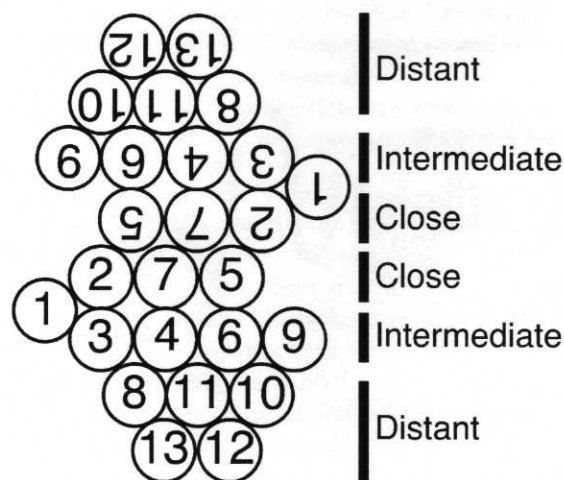


Figure 6 AE1 transmembrane segment packing in the dimeric unit. Numbers refer to transmembrane segment numbers. Adapted from (Taylor et al., 2001).

Carbonic anhydrases and bicarbonate transporters

The bicarbonate transport metabolon - A metabolon is a physical complex of enzymes in a linked enzymatic pathway (Srere 1987). Flux through the enzymatic pathway is accelerated by enzymatic co-localization, which increases the local concentration of substrate at the active site as the product of one reaction feeds into the next enzyme in the pathway. Likewise, flux is driven by reduced concentration of enzymatic product, when that product is removed into the active site of the next enzyme in the pathway. In the HCO₃⁻ transport literature, the initial indication of metabolon phenomena was the observation that carbonic anhydrase II (CAII) binds to the cytoplasmic C-terminus of the erythrocyte AE1 Cl⁻/HCO₃⁻ exchanger (Vince and Reithmeier 1998), mediated by an interaction between an acidic motif on AE1 (hydrophobic residue, followed by four residues, with at least two acidic) (Vince and Reithmeier 2000) and the basic N-terminus of CAII (Vince et al. 2000). We examined the functional significance of the AE1/CAII interaction and found that the direct interaction was essential for maximum transport activity, with transport activity ~40-60% lower if CAII was free in the cytosol, rather than tethered to AE1 (Sterling et al. 2001b). This led us to introduce the concept of a "transport metabolon," the complex between a transporter and the enzyme that produces or consumes the transport substrate (Fig. 7). Interestingly, the CAII binding motif is conserved among bicarbonate transporters (Sterling et al. 2001b), except for the SLC26A3 (DRA) transporter (Sterling et al. 2002b). Consistent with the observation that SLC26A3 does not have a CAII binding motif, DRA does not bind CAII and is not inhibited by dominant negative CAII (Sterling et al. 2002b). Subsequently we found that AE1 interacts with the enzyme, CAIV, which is anchored to the extracellular surface via a glycosylphosphatidyl inositol anchor (Sterling et al. 2002a); this interaction, too, accelerates the transport rate and is mediated by the fourth extracellular loop of AE1. Similarly, we have found that the Na⁺/HCO₃⁻ co-transporter (NBC) isoforms, NBC1 and NBC3, interact with and require CAII for full HCO₃⁻ transport activity (Alvarez et al. 2003; Loiselle et al. 2004).

The large and immediate impact of CAII upon

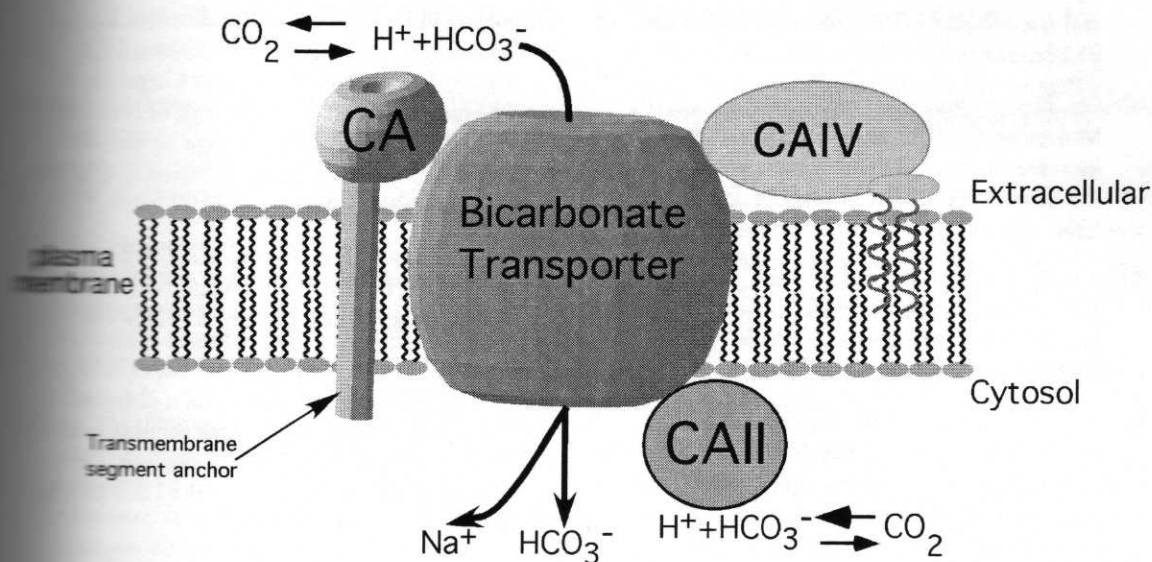


Figure 7 The Bicarbonate Transport Metabolon. We have shown that some Na^+ /bicarbonate co-transporters and $\text{Cl}^-/\text{HCO}_3^-$ exchangers directly bind both the soluble cytosolic enzyme, CAII, and the extracellular enzyme CAIV, anchored to the cell surface via a glycosylphosphatidyl inositol linkage.

HCO_3^- transport rate has led us to hypothesize that transport could be regulated acutely by modulation of the CAII/AE1 interaction, perhaps by phosphorylation. Recently this has been borne out: SLC26A6 transport activity is acutely inhibited following protein kinase-C mediated phosphorylation, leading to displacement of CAII from a site on SLC26A6 (Alvarez *et al.* 2005). This finding led us to introduce the concept of "metabolon disruption" as a mechanism that regulates transport. The combined action of intracellular CAII and extracellular CAIV work to maximize the size of the transmembrane $[\text{HCO}_3^-]$ gradient, which is the driving force for transport (Fig. 7). CAIX has a single TM, anchoring the catalytic site on the extracellular surface. Recently we showed that CAIX binds AE1-3 and accelerates the rate of cellular acid loading. The finding is significant as it reveals that CAIX/AE2 interaction plays a fundamental role in gastric acid secretion (Fig. 3) (Morgan *et al.* 2006).

Conclusions

So why study bicarbonate and its transport? HCO_3^- is involved in a very broad range of biochemical and physiological processes. This has allowed me to follow a broad range of fascinating projects from structural biology to physiology, even disease processes. It has allowed me to interact

with a wide range of outstanding scientists, which has been the best part!

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Shedding light on drug transport: structure and function of the P-glycoprotein multidrug transporter (ABCB1)

Frances J. Sharom

Department of Molecular and Cellular Biology,
University of Guelph, Guelph ON

Abstract

P-Glycoprotein (Pgp; ABCB1), a member of the ATP-binding cassette (ABC) superfamily, exports structurally diverse hydrophobic compounds from the cell, driven by ATP hydrolysis. Pgp expression has been linked to efflux of chemotherapeutic drugs in human cancers, leading to multidrug resistance (MDR). The protein also plays an important physiological role in limiting drug uptake in the gut and entry into the brain. Substrates partition into the lipid bilayer before interacting with Pgp, which has been proposed to function as a hydrophobic vacuum cleaner. Low and medium resolution structural models of Pgp suggest that the two nucleotide binding domains are closely associated to form a nucleotide sandwich dimer. Pgp is an outwardly-directed flippase for fluorescent phospholipid and glycosphingolipid derivatives, which suggests that it may also translocate drug molecules from the inner to the outer membrane leaflet. The ATPase catalytic cycle of the protein is thought to proceed via an alternating sites mechanism, although the details are not understood. The lipid bilayer plays an important role in Pgp function, and may regulate both binding and transport of drugs. This review focuses on the structure and function of Pgp, and highlights the importance of fluorescence spectroscopic techniques in exploring the molecular details of this enigmatic transporter.

Introduction

The ATP binding cassette (ABC) superfamily is one of the largest protein families distributed among all the kingdoms of life (Dassa and

Schneider 2001). They play a critical role in human health and are responsible for several important diseases (Borst and Oude Elferink 2002). These proteins are usually built from 4 modules, two transmembrane (TM) domains and two nucleotide-binding (NB) domains. In bacteria, these four modules may exist as separate subunits, while in mammals, ABC proteins often consist of a single polypeptide chain. Most ABC proteins are membrane transporters, either importing (bacteria) or exporting (mammals) their substrates, driven by the energy of ATP hydrolysis. The range of substrates transported by ABC proteins is astonishing, and includes chloride ions, amino acids, drugs, small peptides and large proteins. In recent years, significant advances have been made in determining the high resolution molecular structures of ABC proteins, which has in turn led to a better understanding of their possible mechanism of action (Jones and George 2004). However, many important details still remain to be uncovered.

P-Glycoprotein (Pgp; ABCB1, MDR1) is one of the most intensively studied ABC family members. This 170 kDa protein was first discovered in the plasma membrane of mammalian cells that had been selected for resistance to drugs (Gottesman and Ling 2006). Over a period of several years, it became clear that Pgp functions as an ATP-driven efflux pump for drugs. The protein has been implicated in the resistance of human tumour cells to multiple chemotherapeutic drugs (multidrug resistance, MDR), which is a major barrier to the successful treatment of many human cancers (Gottesman 2002).

This review is not intended to be a comprehensive presentation of all the available literature on Pgp, but is extensive. Rather, it focusses on the application of various fluorescence spectroscopic approaches to study this transporter.

Pgp substrates and modulators

Pgp interact with hundreds of structurally-diverse compounds. Transport substrates include natural products, chemotherapeutic drugs, steroids, fluorescent dyes, linear and cyclic peptides, neurotransmitters, etc. (see Fig. 1). Most are weakly amphipathic and relatively hydrophobic; many (almost all) contain aromatic rings and a positive-charged tertiary N-atom. There is little information in which, if any, of these substrates might be "physiological", although peptides, platelet-activating factor, lipids, steroid hormones, and small molecules are likely candidates. Direct measurement of transport has been carried out for only a few of these substrates. The majority were identi-

fied indirectly by resistance to cytotoxicity in cells overexpressing Pgp.

A second group of compounds, known as modulators (also called chemosensitizers, reversers or inhibitors), is able to reverse MDR in intact cells by blocking the drug efflux activity of Pgp (Tan et al. 2000). Most modulators appear to bind to Pgp at the substrate binding pocket, and compete with transport substrates in a complex fashion. Indeed, many modulators, including verapamil and cyclosporin A, are known to be transported by Pgp. Pgp modulators also belong to many different structural classes (see Fig. 1), and have similar molecular features to transport substrates (Wiese and Pajeva 2001). Cells are generally not resistant to killing by modulators, but a combination of MDR drugs and a modulator is highly cytotoxic.

Modulators are important clinically, since their co-administration with drugs that are Pgp transport

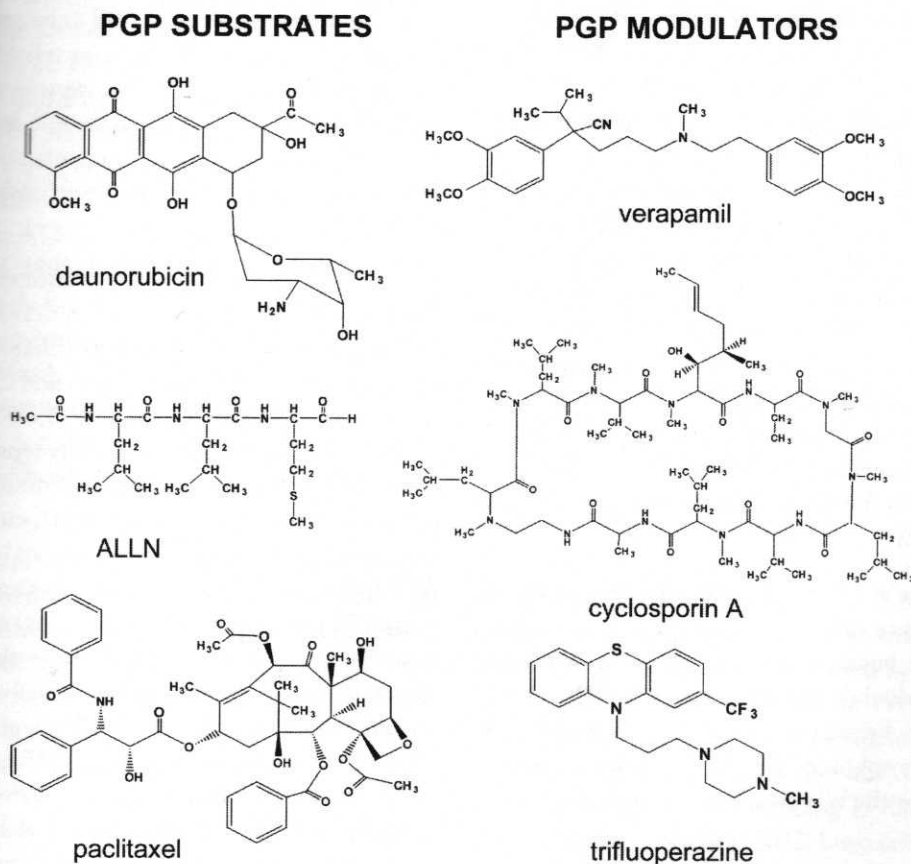


Figure 1 Structures of some Pgp substrates and modulators.

substrates has the potential to improve uptake in the gut and delivery to the brain (see below), and increase the cytotoxicity of anti-cancer drugs to tumour cells. Several promising "third-generation" modulators have progressed to clinical trials (for a review, see Modok et al. 2006). However, in general this approach has been disappointing, despite substantial evidence that treatment failure and patient survival are linked to Pgp expression in several malignancies (Polgar and Bates 2005).

Physiological role of Pgp

Pgp is now known to play a central role in the absorption and distribution of drugs in many organisms (Fromm 2003). It is expressed at the apical surface of epithelial cells lining the gastrointestinal tract, and also on the apical surface of the endothelial cells that line the brain capillaries, where it forms a major component of the blood brain barrier. Its physiological role appears to involve preventing entry of potentially toxic compounds from the gut into the blood (Zhang and Benet 2001), and protection of sensitive internal organs such as the brain from compounds that gain access to the circulation (Fromm 2004).

Transgenic knockout mice lacking Pgp are phenotypically indistinguishable from wild-type mice under normal conditions, however, they display a disrupted blood brain barrier, and are hypersensitive to drugs (Schinkel 1999). Many drugs that are used in the treatment of human disease are Pgp substrates. As well as anti-cancer drugs, these include immunosuppressive agents, HIV protease inhibitors, antibiotics, cardiac glycosides, and many more. Pgp can thus reduce the oral bioavailability of therapeutic drugs, and the targeting of such drugs to the brain tissue, limiting the efficacy of treatment.

A closely-related gene encodes a protein (ABCB4; 75% sequence similarity to Pgp) that is not a drug transporter, but an exporter of phosphatidylcholine (PC) into the bile (Ruetz and Gros 1994). This protein is believed to function as an outwardly-directed phospholipid flippase. ABCB4 is highly expressed at the bile canalicular membrane of hepatocytes.

Experimental systems for studying Pgp-mediated drug transport

Early work on MDR used mammalian cell lines selected for growth in high levels of drugs such as colchicine and vinblastine. However, simpler sub-cellular systems were soon developed to avoid the complexities of intact cells. Plasma membrane vesicles proved to be very useful, and allowed characterization of the transport process using radiolabelled drugs (for example, see Doige and Sharom 1992). Inside-out vesicles present in the preparation transport drug into the lumen when ATP and an ATP-regenerating system are added to the vesicle exterior. Purification of Pgp was necessary for further biochemical characterization of the protein. Several research groups succeeded in achieving this goal in the mid-1990s, using a variety of MDR cell lines and transfected cells as the source of protein (for a review, see Sharom 1997a). In general, expression in heterologous cells, such as bacteria, yeast and insect cells has proved to be problematical, and mammalian cells are most reliable as a source of active Pgp. However, expression in *Pichia pastoris* has been very successful, leading to the purification of milligram amounts of both wild-type and mutant Pgp (Lerner-Marmarosh et al. 1999).

Proteoliposomes containing reconstituted Pgp have also proved to be a powerful tool for characterization of the drug transport process (Sharom et al. 1993; Sharom et al. 1996; Shapiro and Ling 1995; Eytan et al. 1996; Ambudkar et al. 1998). They showed that transport is osmotically sensitive, active (generating a substrate concentration gradient across the bilayer of 5- to 6-fold), saturable at increasing substrate concentrations, and requires ATP hydrolysis. Other Pgp substrates and modulators block transport in a saturable manner. Real-time fluorescence-based assays can continuously monitor the transport of fluorescent substrates, such as Hoechst 33342 (H33342) (Shapiro et al. 1997) and tetramethylrhodamine (TMR) (Lu et al. 2001b), allowing direct estimation of initial rates of transport. The true kinetic parameters for drug transport have also been obtained for both the transport substrate and ATP (Lu et al. 2001c).

ATPase activity of Pgp

ATP hydrolysis by Pgp takes place at the two NB domains located on the cytoplasmic face of the protein. The NB domains of all ABC proteins are characterized by Walker A and Walker B motifs, and a signature C motif unique to the ABC superfamily. Mutational analysis has been very useful in defining the roles in catalysis of various amino acid residues in these three motifs (Loo and Clarke 1994; Erclet and Klein 2006). Studies with purified Pgp revealed that the protein displays high levels of constitutive ATPase activity, in the apparent absence of drug substrates. This behaviour is unusual; in most ATP-driven transporters, hydrolysis of ATP is tightly coupled to concurrent movement of substrate across the membrane. The basal ATPase activity of purified Pgp is as high as 3-5 $\mu\text{mol/min/mg}$ of protein, depending on the presence of lipids and detergents. The stoichiometry of ATP hydrolysis relative to drug transport is still a matter of controversy, mainly because of the high basal ATPase activity (Eytan et al. 1996; Ambudkar et al. 1997; Shapiro and Ling 1998a). Membrane-bound or purified Pgp shows a relatively high K_M for ATP hydrolysis, in the 0.4 mM range, and a divalent cation is also necessary (physiologically, this is Mg^{2+} , but Mn^{2+} and Co^{2+} also support ATP hydrolysis) (for a review, see Senior et al. 1995a). Sulfhydryl-modifying reagents, including N-ethylmaleimide, HgCl_2 , p-chloromercuribenzoate and 7-chloro-4-nitrobenzo-2,1,3-benzoxadiazole (NBD-Cl), inhibit Pgp ATPase activity by covalently modifying a Cys residue in the Walker A motif of each active site (Doige et al. 1992; al-Shawi et al. 1994; Loo and Clarke 1995a).

Ortho-vanadate (V_i), a phosphate analogue that inhibits several other ATPases, also inactivates Pgp in a reversible fashion. V_i can replace P_i in a single active site after ATP hydrolysis, leading to formation of a highly stable trapped complex that is thought to have the structural geometry of the transition state that exists transiently during ATP hydrolysis. The V_i -trapped complex, $\text{Pgp-ADP}\cdot\text{V}_i\cdot\text{M}^{2+}$, has no ATPase activity, despite the fact that one active site is unoccupied (Urbatsch et al. 1995). Slow dissociation of V_i

from the active site, followed by dissociation of ADP, leads to full restoration of ATPase activity.

Drugs and modulators affect Pgp ATPase activity in a complex fashion (Borgnia et al. 1996). Many drugs show biphasic modulation of activity, with stimulation at low concentrations and inhibition at high concentrations. Some substrates only stimulate activity, while others only inhibit it. At present, there is no satisfactory explanation for the different patterns that are observed. The biphasic pattern might arise from the presence of two drug-binding sites, a high affinity stimulatory site and a lower affinity inhibitory site (Gottesman et al. 1996). Results have been variable between different research labs, and the presence of various lipids and detergents also appears to affect the drug interaction patterns (Urbatsch and Senior 1995; Ambudkar 1995).

Pgp as a hydrophobic vacuum cleaner and drug flippase

Classical membrane pumps, such as lactose permease or the $\text{Na}^+\text{,K}^+$ -ATPase, transport polar or charged substrates across the membrane, by moving the substrate through a path within the protein that is lined with polar residues (Fig. 2). In this way, the substrate does not contact the hydrophobic interior of the lipid bilayer, which is a thermodynamically unfavourable event. However, Pgp substrates are relatively non-polar, and they are known to partition into lipid bilayers and accumulate to high concentrations. It was suggested that Pgp may function as a "hydrophobic vacuum cleaner" (Fig. 2), binding non-polar compounds that partition into the membrane and expelling them into the extracellular medium (Higgins and Gottesman 1992). Pgp can also be envisaged as a drug "flippase", moving its substrates from the cytoplasmic membrane leaflet to the extracellular leaflet, where they can partition into the aqueous phase (Fig. 2). This idea is supported by substantial experimental evidence (Sharom 1997a), including localization of the drug-binding sites of Pgp to the cytoplasmic membrane leaflet (Shapiro and Ling 1997a; Shapiro and Ling 1998b; Ferry et al. 2000; Qu and Sharom 2002; Lugo and Sharom 2005b).

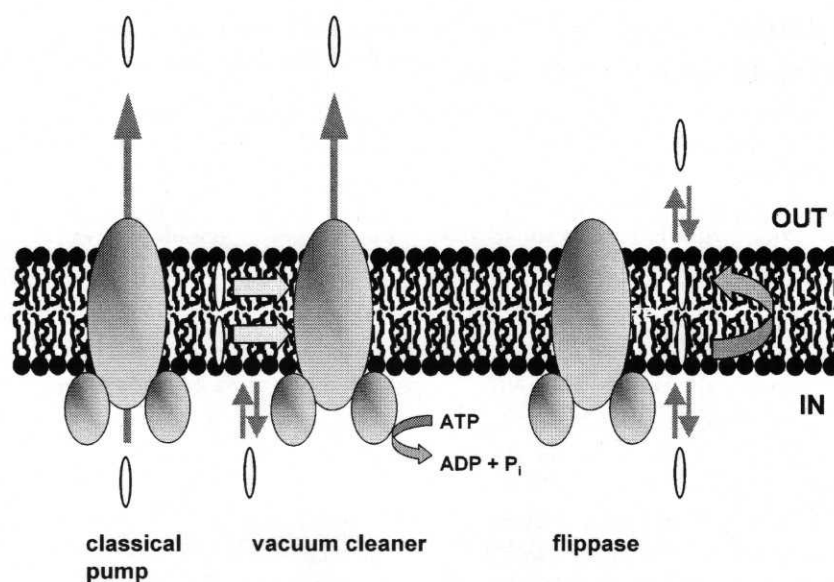


Figure 2 Classical pump, vacuum cleaner and flippase models of Pgp action. Classical pumps transport a polar substrate from the aqueous phase on one side of the membrane to the aqueous phase on the other side through a hydrophilic path formed by the TM regions of the protein. In the vacuum cleaner model, drugs first partition into the lipid bilayer, and interact with Pgp within the membrane. They are subsequently effluxed into the aqueous phase on the extracellular side. In the flippase model, drugs partition into the membrane, interact with the drug binding pocket in Pgp within the cytoplasmic leaflet, and are then translocated to the outer membrane leaflet, where they can partition into the extracellular aqueous phase.

Fluorescence approaches for studying Pgp structure and function

Fluorescence spectroscopic techniques have found increasing application to membrane proteins in recent years. They have the advantage of high sensitivity, so that only small amounts of protein are required, and can be used to explore many different aspects of protein structure and function. It is very difficult to study drug interactions with Pgp by classical biochemical techniques because of their nonpolar nature. Fluorescence approaches have circumvented these problems, and revealed important information that is not easy to obtain by other means. Using purified Pgp, it is possible to covalently link extrinsic fluorophores to specific residues on the protein, where they act as reporter groups. One very useful target in this approach has been Cys residues. The first fluorescence study of Pgp linked 2-(4-maleimidoanilino)naphthalene-6-sulfonic acid (MIANS) to the Cys residue that is present in the Walker A motif of each ATPase

active site (Liu and Sharom 1996). More recent studies have used intrinsic Trp fluorescence to examine the behaviour of the unmodified protein (Liu et al. 2000; Sonveaux et al. 1999). Pgp substrates include many fluorescent dyes, such as rhodamines, H33342 and LDS-751, and they have also been used in transport studies, and to probe the drug-binding pocket. Finally, Pgp can bind a variety of fluorescent nucleotides, including trinitrophenyl(TNP)-ATP, MANT-ATP and ϵ -ATP, which can yield useful information about the nucleotide binding site. Fluorescence studies have provided information on the following aspects of Pgp structure and function (for a review, see Sharom et al. 2001):

1. Binding of substrates and nucleotides; identification of substrates, quantitation of substrate and nucleotide binding affinities, estimation of nucleotide binding stoichiometry.
2. Probing of the local environment of the drug-binding pocket and the nucleotide binding site.
3. Transport kinetic studies; initial rates of drug

transport in real time, kinetic parameters of transport, flip-flop rates of fluorescent phospholipid and glycosphingolipid derivatives.

• Characterization of conformational changes taking place during the catalytic and transport cycle.

• FRET (fluorescence resonance energy transfer) studies; estimation of the distances between domains and regions of the protein, generation of a low resolution map of Pgp architecture.

Structure of Pgp

The topology of Pgp in the membrane was established using molecular biological approaches such as location of glycosylation sites (Kast et al. 1996) and *Cas* mutations (Loo and Clarke 1995b). It consists of two homologous halves, each with 6 TM segments and a cytosolic NB domain (Fig. 1B). Mutagenesis studies revealed that the drug-binding site is formed by the TM regions of both halves of Pgp, especially TM4, 5 and 6 in the N-terminal half, and TM9, 10, 11 and 12 in the C-terminal half (Loo and Clarke 2005). Substrates enter to this site from within the membrane. The NB domains of ABC proteins are highly conserved, and share several common motifs, including the Walker A and B motifs that are found in other ATPases, and the ABC signature, or C motif, that is unique to the protein family.

High resolution crystal structures for two bacterial ABC proteins, the DNA repair enzyme Rad50cd (Haghofer et al. 2000) and the vitamin B12 transporter BtuCD (Locher et al. 2002), showed that the two NB domains were closely associated, forming a dimeric structure in which the Walker A and B motifs of one NB domain and the C motif of the partner NB domain formed the ATP binding sites. This type of arrangement had previously been predicted by Jones and George (1999) based on biochemical and sequence considerations. This structure, now known as a nucleotide sandwich dimer, was also observed in the catalytically inactive E11Q mutant of the isolated NB domain of the ABC protein MJ0796, where two molecules of ATP are bound at the dimer interface (Smith et al. 2002). The process of tight dimerization of the

NB domains, induced by ATP binding, may be an important step in the catalytic cycle of the ABC proteins. Three high resolution structures have been published for MsbA, a homodimeric bacterial lipid A flippase (Chang and Roth 2001; Chang 2003; Reyes and Chang 2005). Far from clarifying the structure of this protein, three quite different dimer arrangements were observed, adding more uncertainty to the ABC protein field (Davidson and Chen 2005). The transmembrane regions of the MsbA dimer showed 12 TM helices, and it has thus been a popular basis for building homology models for Pgp (Stenham et al. 2003). However, the three MsbA structures were withdrawn in late 2006 when a data-processing error was discovered. A recent high resolution structure of the ABC protein Sav1866, shows a quite different arrangement of the 12 TM helices, in which the two halves are entwined with each other (Dawson and Locher 2006), raising doubt as to which structural model of the TM domains might best apply to eukaryotic proteins such as Pgp.

High resolution structural information for Pgp is still lacking. A low resolution structure determined by electron microscopy (EM) using single particle analysis showed a large 5 nm central pore in the protein, which was closed at the cytoplasmic side, and two widely separated lobes that were thought to be the NB domains (Rosenberg et al. 1997). This structure disagreed with biochemical studies and the other ABC protein structures described above, which showed close association between the NB domains. Further studies indicated that nucleotide binding causes a repacking of the TM regions of Pgp, opening the central pore to allow access of hydrophobic drugs directly from the lipid bilayer (Rosenberg et al. 2001; 2003), leading to the proposal that ATP binding, rather than hydrolysis, drives the conformational changes associated with transport. The vanadate-trapped complex of Pgp displayed a different conformation, suggesting that rotation of TM α -helices takes place during the catalytic cycle.

In contrast to these structures, a low resolution EM study of 2D crystals of Pgp, showed that the molecule was compact, with closely associated NB

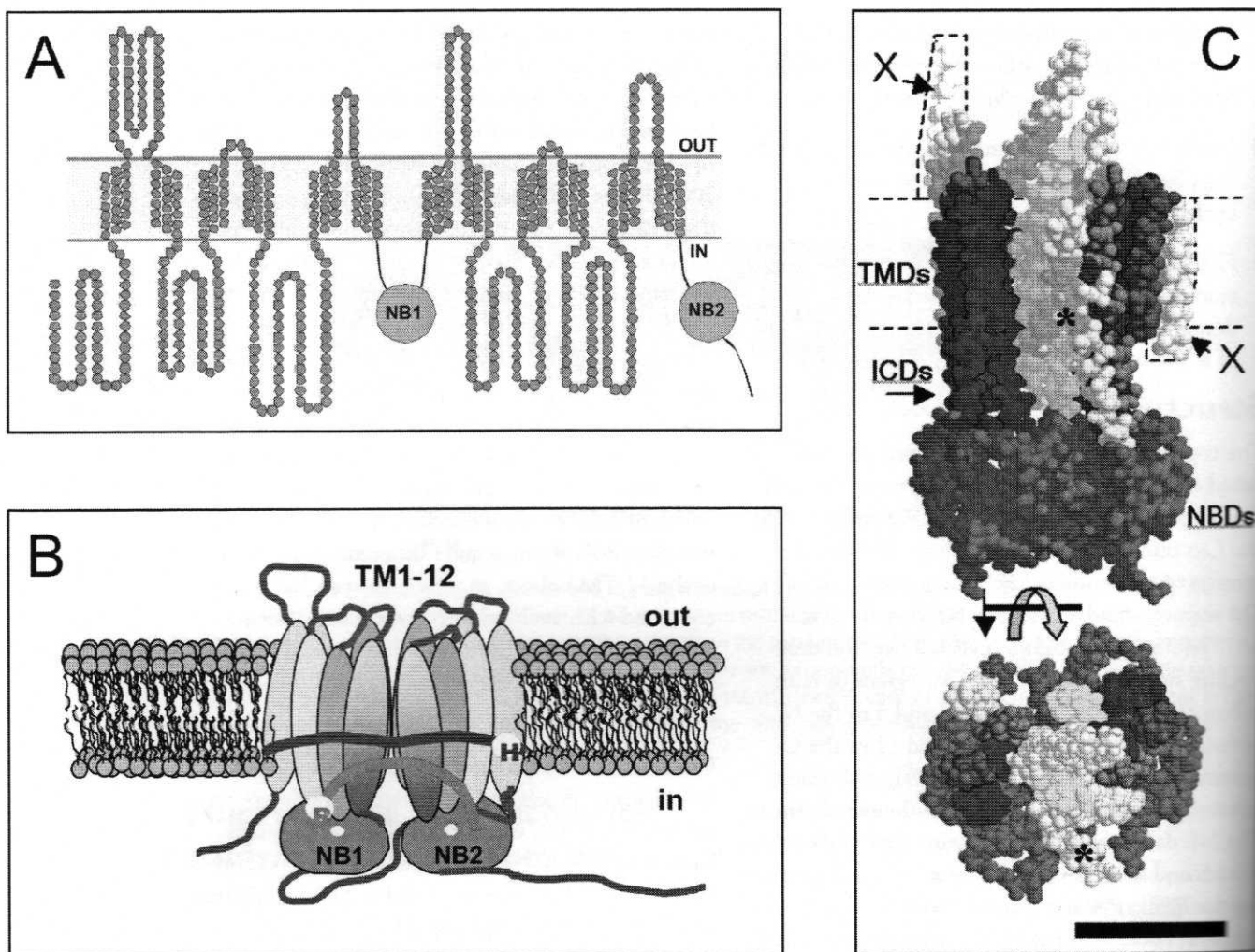


Figure 3 Topology and structure of Pgp. (A) Pgp is proposed to consist of two equivalent halves, each with 6 TM segments and a cytoplasmic NB domain. (B) Low resolution structural model of Pgp generated using FRET measurements of the distances separating key regions of the protein (Lugo and Sharom 2005b). The curves labelled H and R represent the boundaries of the binding sites for the dyes H33342 and LDS-751, respectively, as estimated by FRET analysis. (C) Medium resolution structural model of Pgp obtained from cryo-EM studies (Rosenberg et al. 2005). Top: a side view of the protein is shown with the NB domains at the bottom. The 12 putative TM α -helices are arranged in a pseudo-symmetrical relationship. * indicates the location of one of four helices without an obvious symmetry relationship; another (indicated by X) has a poorly defined location, and the other two are on the extracellular face of Pgp. Bottom: a view of Pgp looking down on the TM helices from the extracellular side of the membrane. The dashed lines indicate the putative boundary of the lipid bilayer (scale bar = 5 nm). Adapted from Rosenberg et al. (2005) with permission.

domains (Lee et al. 2002). FRET studies in which two different fluorescent probes were attached to the Walker A Cys residues also suggested that the two active sites are closely associated, compatible with the sandwich dimer model (Qu and Sharom 2001). FRET mapping of various intramolecular distances within the Pgp molecule led to a low resolution model of the protein structure (Lugo and Sharom 2005b) (Fig. 3B). A medium resolution EM structure of Pgp appeared recently (Fig. 3C), and showed closely associated NB domains and the existence of 12 TM seg-

ments, supporting the proposed topology (Rosenberg et al. 2005).

Fluorescence approaches for studying binding of nucleotides and drugs to Pgp

Photoaffinity labelling has been a popular approach to demonstrate interaction of azido-analogues of nucleotides and drugs with Pgp, both in native membrane vesicles and

protein. Competition experiments with labelled drugs and modulators have given a good indication of relative binding affinity. However, technical limitations, such as low labelling stoichiometry and variable labelling efficiency, complicate interpretation of the results, and quantitation of binding affinity is not possible using this approach.

Classical biochemical approaches using equilibrium binding are unable to quantitate ATP binding to Pgp, since it is of relatively low affinity. Fluorescence approaches can measure equilibrium binding without the need to separate Pgp-bound nucleotide from free nucleotide. Nucleotide binding was first characterized using MANS-labelled Pgp. ATP binding resulted in saturable quenching of the MANS fluorescence, likely as a direct result of a change in the local environment of the probe, which is located close to the site of ATP binding (Liu and Sharom 1996). Fitting of the data to an equation for binding to a single site led to an estimate for K_d of ~ 0.4 mM, similar to the K_M for ATP hydrolysis.

More recently, an intrinsic Trp quenching approach has been used to quantitate nucleotide binding. Trp residues are highly sensitive to their local environment, so that binding of substrates often leads to quenching of their fluorescence emission. Pgp has 11 Trp residues, but the blue-shifted nature of the fluorescence spectrum indicates that only a few, likely those in the TM segments, contribute to Pgp emission. Trp fluorescence was shown to be saturably quenched by binding of both unmodified and TNP-labelled nucleotides (Liu et al. 2000). Quenching of Trp residues appeared to arise from FRET to the bound nucleotide, suggesting that the NB domains are packed relatively closely with the TM regions of the protein.

Interaction of fluorescent nucleotides with Pgp results in a large enhancement of the fluorescence emission relative to aqueous solution, because of the relatively non-polar nature of the binding site (Liu and Sharom 1997). Work by the group of Di Pietro showed that in addition to this feature, intrinsic Trp fluorescence, could be used to monitor binding of fluorescent nucleotide derivatives to

the expressed C-terminal NB domain, which contains a single Trp residue (Baubichon-Cortay et al. 1994). The expressed N-terminal NB domain was also able to bind fluorescent nucleotides (Dayan et al. 1996). Binding of TNP-ATP/ADP to Pgp is of higher affinity compared to unmodified nucleotides ($K_d \sim 35$ – 45 μ M), because of additional interactions between the non-polar TNP group and the binding pocket. Fluorescence measurements were also used to determine the stoichiometry of TNP-nucleotide binding. Native Pgp binds two molecules of nucleotide under the conditions that exist in the cytosol (Qu et al. 2003b). V_1 -trapped Pgp, on the other hand, binds only one molecule of nucleotide at the unoccupied active site. A recent report of binding of a spin-labelled nucleotide derivative to Pgp supported these conclusions, showing a binding stoichiometry of 2 and a binding affinity of 0.2 mM (Delannoy et al. 2005).

Measuring binding of drugs and modulators to Pgp is especially challenging because of their lipophilic nature and high propensity to partition into membranes. Equilibrium binding studies have been carried out to quantitate the drug binding affinity and capacity of Pgp, but they are technically challenging, and only a few drugs can be studied using this approach (Taylor et al. 1999; Martin et al. 2000). Fluorescence approaches have been invaluable in demonstrating a direct interaction between Pgp and many different drugs, and also in quantitating their binding affinity. Studies using MANS-Pgp revealed that binding of drugs and modulators to the substrate binding pocket resulted in quenching of MANS in the ATPase active site. These results suggested the existence of conformational communication between the drug-binding site(s) in the TM regions and the active site in the NB domain, which alters the local environment of the MANS probe. This conformational change is also reflected in the observed stimulation of ATPase activity by drugs and modulators. Quenching by drugs is saturable, and can be fitted to a binding equation to extract estimates of the binding affinity (Liu and Sharom 1996). The K_d values measured by fluorescence quenching for a large number of drugs cover 4 orders of magnitude, from 158 μ M for the low affinity substrate colchicine, to 37 nM

for paclitaxel, a high affinity substrate (Sharom et al. 1999; Sharom et al. 2001). The binding affinity of a drug or modulator (as measured by the K_d value from fluorescence experiments) is highly correlated with its ability to inhibit Pgp-mediated transport of ^3H -colchicine in native plasma membrane vesicles, suggesting that all substrates make use of a common pathway and transport mechanism (Sharom et al. 1998; Sharom et al. 1999).

Intrinsic Pgp fluorescence can be used to examine drug binding more directly. Trp residues are also quenched saturably by binding of drugs and modulators, and these experiments give estimates of binding affinity very similar to those obtained using MIANS-Pgp quenching (Liu et al. 2000). The high degree of Trp quenching observed for some drugs suggests that these aromatic residues may be directly involved in binding substrates, perhaps via π - π stacking interactions. Aromatic residues are over-represented in the TM regions of Pgp, and their involvement in substrate recognition and binding by Pgp was previously suggested (Pawagi et al. 1994).

Several compounds, including H33342 and LDS-751, show greatly enhanced fluorescence emission on binding to the drug binding pocket of Pgp, which has hydrophobic character (see below). This phenomenon can also be used to directly quantitate their interaction with purified Pgp (Qu et al. 2003a; Lugo and Sharom 2005a; Lugo and Sharom 2005b). The measured binding affinities are in agreement with those estimated by both MIANS quenching and Trp quenching; thus the three different fluorescence approaches for measuring drug binding to Pgp all yield very similar quantitative information.

Probing the drug-binding pocket of Pgp

Much effort has been expended to try to understand how Pgp can interact with such a large number of structurally dissimilar compounds. Attempts to develop quantitative structure-activity relationships (QSAR) for Pgp substrates and modulators, to link their chemical and physical properties with their biological activity, have been fraught with difficulties. The best description of a substrate

appears to involve a set of structural elements required for interaction of a compound with Pgp (Seelig 1998; Seelig and Landwojtowicz 2000; Cianchetta et al. 2005), consisting of two or three electron donors (hydrogen bond acceptors), or hydrophobic units, arranged in a fixed spatial separation. Pajeva and Wiese have proposed a pharmacophore model consisting of two hydrophobic units, three hydrogen bond acceptors, and one hydrogen bond donor (2002). There have been suggestions of the existence of multiple separate drug-binding sites, but the current consensus is that Pgp probably possesses a single, large, flexible drug-binding pocket. Drugs are believed to interact with the amino acid residues lining this pocket by an "induced-fit" type of mechanism, involving multiple Van der Waal's and hydrophobic interactions which can be different for each compound. The principles of such multidrug binding have been well established for soluble bacterial transcriptional regulators (Schumacher and Brennan 2002), and it is likely that they also apply to mammalian multidrug transporters (Zheleznova et al. 2000; Loo et al. 2003). The drug-binding pocket is located within the membrane-bound regions of Pgp, and is made up from several TM segments. It appears to be funnel-shaped, and is narrower at the cytoplasmic side, where TM2/11 and TM5/8 come together (Loo and Clarke 2005). It may lie at the interface between the N- and C-terminal halves of the protein (Pleban et al. 2005).

There appear to be two "functional" transport sites within Pgp; the R-site, which interacts preferentially with rhodamine 123, and the H-site, which interacts preferentially with H33342 (Shapiro and Ling 1997b). These two sites interact with each other allosterically in a complex fashion. Binding of a drug to the H-site stimulates transport of an R-site drug, while inhibiting transport of other H-site drugs. Binding of an R-site drug has the reciprocal effect; it stimulates transport of an H-site drug, while inhibiting transport of other R-site drugs. It is not clear whether these functional sites have distinct physical locations within the protein.

What is the nature of the drug-binding pocket of Pgp? Fluorescence spectroscopy can again provide some answers that cannot be obtained by other

means. Suggestions that the drug-binding pocket was open to an aqueous chamber (Loo et al. 2004; Rosenberg et al. 2001) was not supported by fluorescence characterization. Large increases in fluorescence emission intensity, coupled with a blue shift in the emission wavelength, indicated that drugs bound to both the H-site and the R-site are in a very hydrophobic environment, with a polarity lower than that of chloroform (Qu and Sharom 2002; Lugo and Sharom 2005b). A detailed biochemical characterization of the R-site was recently carried out by our laboratory, using the fluorescent drug LDS-751 (Lugo and Sharom 2005a). We found that two drugs, rhodamine 123 and LDS-751, which compete with each other for transport by Pgp, can both bind to this site simultaneously. However, they compete with each other non-competitively, rather than competitively. Estimation of the binding parameters for each drug alone and in the presence of the other indicated that they have a 5-fold negative effect on each other's binding; bound LDS-751 reduces the binding affinity of rhodamine 123 by a factor of 5, and vice versa. The two drugs may bind to different overlapping regions, or mini-pockets, within the large flexible binding site. Steric interference would account for the observed reciprocal negative effect of each drug on the binding of the other.

Role of the lipid bilayer in Pgp function

The functioning of the Pgp molecule is inextricably linked to the lipid bilayer in which it is embedded, and from which it obtains its substrates (for a review, see Ferté 2000). The study of how Pgp is modulated by the membrane required reconstitution of the purified protein into bilayers of defined phospholipids with specific biophysical properties (Romsicki and Sharom 1997). Lipid is essential for catalytic function of the NB domains (Doige et al. 1993), and lipids also influence both basal ATPase activity and its stimulation or inhibition by drug substrates (Urbatsch and Senior 1995; Sharom 1997b). Purified Pgp was found to retain ~55 tightly bound phospholipids; whose removal led to complete loss of function (Sharom et al. 1995). The presence of cholesterol has also been

linked to Pgp function, both directly in model systems (Rothnie et al. 2001), and also indirectly in intact cells (Wang et al. 2000; Garrigues et al. 2002; Troost et al. 2004). Pgp is functional in a lipid environment that mimics sphingolipid/cholesterol-rich microdomains or "lipid rafts" (Modok et al. 2004), and various reports have suggested that the protein may be located in specialized regions of the plasma membrane in intact cells (Demeule et al. 2000; Hinrichs et al. 2004; Radeva et al. 2005; Orlowski et al. 2006).

The NB domains, which are usually thought of as separately-folded soluble domains, are surprisingly affected by the fluidity of the bilayer in which the protein is reconstituted. The kinetic parameters of ATP binding and ATP hydrolysis by Pgp differ, depending on the phase state of the host lipids (Romsicki and Sharom 1998). Lipids may modulate the function of the NB domains of Pgp indirectly by interacting with the TM regions of the protein, or the NB domains themselves may interact with the bilayer surface.

The bilayer also plays a major role in the interaction of drugs with the protein. Given their high lipid-water partition coefficients, P_{lip} , Pgp substrates will accumulate to very high levels in the membrane (Romsicki and Sharom 1999; Regev et al. 2005; Siarheyeva et al. 2006; Gatlik-Landwojtowicz et al. 2006). The actual drug concentration in the membrane may be 300- to 2000-fold higher than the concentration added to the aqueous phase. Thus Pgp may have a relatively low intrinsic affinity for its substrates; the role of the membrane is to concentrate the drug for presentation to the protein. The rate of transport of H33342 was shown to be proportional to its bilayer concentration, confirming that this substrate is removed from the membrane (Shapiro et al. 1997). The lipid composition of the host bilayer affects the ability of drugs to partition into the membrane. It was found that the apparent K_d value for drug binding correlated with the P_{lip} values (see Fig. 4); the higher the partitioning of a drug into the lipid, the lower the measured K_d value, in other words, the higher the apparent binding affinity (Romsicki and Sharom 1999). The interaction of a drug with

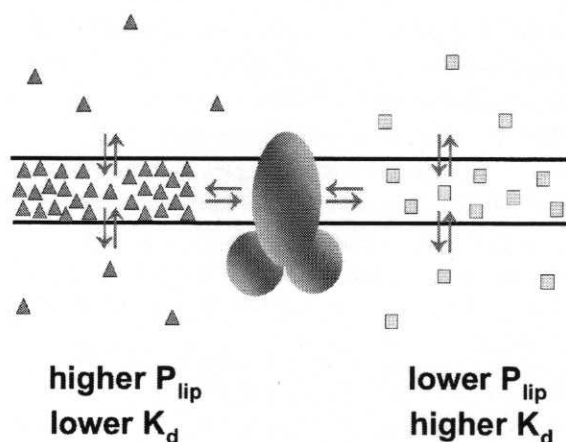


Figure 4 The binding affinity of Pgp for a particular drug substrate, K_d , is related to its lipid-water partition coefficient, P_{lip} . A drug with a high value of P_{lip} (left side) will accumulate to a high concentration within the membrane, favouring binding to Pgp and resulting in a low apparent K_d . In contrast, a drug with a low value of P_{lip} (right side) will have a lower membrane concentration, and a higher apparent K_d .

Pgp is thus strongly modulated by its lipid partitioning ability. Omote and Al-Shawi (2006) recently conducted a molecular dynamics simulation of the lipid bilayer partitioning and transbilayer movement of drugs by Pgp. They proposed that drugs are initially located in the interfacial region of the cytoplasmic membrane face, and are expelled to the exterior by a solvation exchange mechanism.

The fluidity of the host membrane also affects Pgp-mediated drug transport. When Pgp was reconstituted into proteoliposomes of differing fluidity, it was found that the initial rate of TMR transport measured by a real-time fluorescence assay showed an unusual biphasic temperature dependence (Lu et al. 2001a). The transport rate was high in the rigid gel phase, reached a maximum at the melting temperature of the bilayer, and then declined in the fluid liquid crystalline phase. Partitioning of organic compounds into lipid bilayers shows a similar pattern, suggesting that the rate of drug transport may be dominated by drug partitioning into the membrane.

Lipid flippase activity of Pgp

An early proposal suggested that Pgp might function as a drug "flippase", moving hydrophobic mol-

ecules from the inner to the outer leaflet of the membrane (Higgins and Gottesman 1992). Support for this idea came later, from the finding that the highly homologous protein ABCB4 is a flippase for PC, exporting it from the apical membrane of the liver canalicular cells into the bile (Ruetz and Gros 1994; Smith et al. 1994). Further studies in intact cells provided evidence that Pgp can translocate both short chain phospholipids and glycosphinglipids from the inner to the outer leaflet of the plasma membrane (van Helvoort et al. 1996; van Meer et al. 1999). The use of proteoliposomes containing reconstituted Pgp provided direct evidence of this flippase activity, and allowed its characterization (Sharom et al. 2005). Romsicki and Sharom (2001) used a fluorescence quenching technique to show that Pgp could flip a variety of NBD-labelled phospholipids and sphingomyelin, and this work was extended by Eckford and Sharom (2005), who found that fluorescent analogues of the simple glycosphingolipids, galactosyl- and glucosylceramide were also flipped at high rates. The process of lipid flipping resembles drug transport in that it requires ATP hydrolysis and is inhibited by ortho-vanadate. Drugs and modulators are able to compete with membrane lipids for flipping, and their inhibitory potency is highly correlated with their Pgp binding affinity as measured by fluorescence approaches, suggesting that the two types of molecule follow a similar route through the protein.

The fluorescent phospholipids, glycolipids and sphingolipids commonly used in flippase studies in intact cells and model systems usually (but not always) have one short acyl chain. Whether normal membrane lipids with two long acyl chains are good substrates for Pgp is still not clear, since it is very difficult to test flipping of normal unlabelled lipids in model systems. However, Pgp was able to translocate a fluorescent PE derivative with two 16-carbon or 18-carbon acyl chains. In addition, a large number of ABC transporters appear to translocate natural membrane lipids and sterols, and this may be a side activity of all proteins in this family (Borst et al. 2000; Kálin et al. 2004; van Meer et al. 2006). It is possible that Pgp plays a physiological role in translocating glucosylce-

side from the cytoplasmic to the luminal side of the Golgi membrane, a process which must take place during glycolipid biosynthesis (Lala et al. 2000). Pgp thus appears to be a broad specificity, unidirectionally-directed flippase for a variety of lipid analogues. The ability of Pgp to transport lipophilic drugs may have evolved from its lipid flippase function, since its close relative, ABCB4, can apparently transport lipophilic drugs at a low level (Smith et al. 2000).

The catalytic cycle of Pgp

The mechanism of transport by ABC proteins involves two distinct, but coupled cycles. First there is the catalytic cycle whereby ATP is hydrolyzed; this comprises ATP binding, formation of a putative nucleotide sandwich dimer, hydrolysis of ATP, dissociation of P_i , and dissociation of ADP. The energy derived from this cycle is coupled to movement of substrate across the membrane, although there are opposing views as to whether the energy is provided by ATP binding, or ATP hydrolysis (Higgins and Linton 2004; Hanekop et

al. 2006). Drug transport by Pgp involves entry of the substrate into the binding pocket, conformational changes, and drug release. It is assumed that dissociation of drug on the membrane exterior involves re-orientation of a drug-binding site from the cytosolic side of the membrane (likely in the inner membrane leaflet) to the extracellular side (possibly the outer membrane leaflet), with a concomitant switch from high to low drug-binding affinity. For a comprehensive recent review on this topic, see Callaghan et al. (2006). The drug-binding site and the active sites in the NB domains must communicate with each other, likely via conformational changes, so that drug binding activates ATP hydrolysis and initiates the transport cycle.

The approach of vanadate trapping has led to some important insights into the ATPase catalytic cycle. For the myosin ATPase, such trapped complexes have provided very useful structural information (Smith and Rayment 1996). V_i is trapped in only one of the NB domains of Pgp after a single cat-

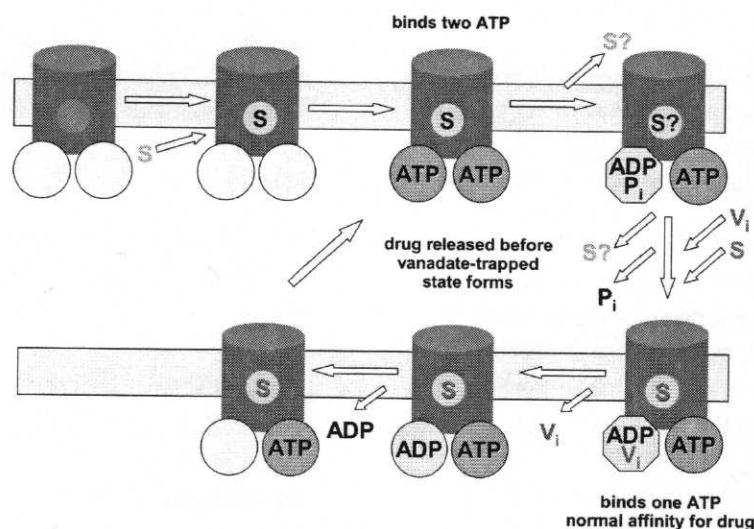


Figure 5 Vanadate trapping and proposed catalytic cycle of Pgp. The substrate, S, and two molecules of ATP bind to Pgp in a random order (Liu et al. 2000; Qu et al. 2003b). Following hydrolysis of ATP at one active site, dissociation of P_i and its replacement by V_i leads to formation of the stable vanadate-trapped complex, $\text{Pgp} \cdot \text{ADP} \cdot V_i \cdot M^{2+}$, which has no ATPase activity but retains one molecule of bound ATP (Qu et al. 2003b). Substrate is likely translocated across the membrane simultaneously with either ATP hydrolysis or dissociation of P_i , by switching of a high affinity cytoplasmic drug binding site to an outward-facing low affinity drug binding site. The vanadate-trapped complex has already regained high affinity drug binding (Qu et al. 2003a; Russell and Sharom 2006), and binds another substrate molecule. Following dissociation of ADP, rebinding of ATP to the vacant active site leads to another round of transport. According to the alternating sites hypothesis, ATP hydrolysis takes place at the other NB domain during this second round of transport (Senior et al. 1995b). It is not yet known how this cooperativity between the two active sites is achieved.

alytic turnover, yet all ATPase activity is lost (Urbatsch et al. 1995). Senior et al. suggested that the protein operates by an alternating sites mechanism, in which only one catalytic site can be in the transition state at any instant in time, and the two sites alternate in catalysis (Senior et al. 1995b). It is not yet known how this co-operation between the two active sites is achieved at the molecular level, or how ATP hydrolysis is coupled to drug transport (reviewed by Ambudkar et al. 2006). The alternating sites model implies that asymmetry between the two NB domains of Pgp must exist at some point during the catalytic cycle. Evidence for such asymmetry has been reported by Tomblin and Senior (Tomblin et al. 2005), who found a single occluded ATP molecule tightly bound in one NB domain of the double "catalytic carboxylate" mutant (E552A/E1197A). This catalytically-defective mutant conformation appears to represent a transient asymmetric intermediate. They proposed that after loose binding of two ATP molecules the sandwich dimer forms, and the tightly-bound nucleotide is then committed to hydrolysis and rapidly enters the transition state (Tomblin and Senior 2005).

The energy from ATP hydrolysis has been proposed to drive drug transport via relaxation of a high energy intermediate, with one ATP hydrolyzed for each drug molecule translocated (Senior et al. 1995b). There is still controversy as to whether one or two rounds of ATP hydrolysis are required in each transport cycle. An alternate model has been put forward by Sauna and Ambudkar (2001), in which two molecules of ATP are hydrolyzed per cycle, the first to transport the substrate molecule, the second to "re-set" the protein for another round of transport. The ATP binding stoichiometry, nucleotide binding affinity, and drug binding affinity are known at various stages of the catalytic cycle (Qu et al. 2003a; Qu et al. 2003b; Delannoy et al. 2005), and incorporation of these parameters into a proposed transport scheme is shown in Fig. 5. We have recently initiated rapid kinetic studies of the Pgp transport cycle, using fluorescence tools (Lugo et al. 2006), and we have also begun to measure thermodynamic constants for some of the steps (Lugo and

Sharom 2005a). More studies of this type will be needed to fully elucidate the transport mechanism of Pgp.

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2007 Society Award Designates

Dr. Nahum Sonenberg, from the Department of Biochemistry, McGill University, has been chosen to receive the 2007 Roche Diagnostics Award, which recognizes outstanding achievement in research in one or more of the fields of biochemistry, molecular or cellular biology undertaken in Canada by a Canadian scientist. This year, the Society decided to award the Merck Frosst Prize for meritorious research by a young Canadian scientist with ten years or less of independent research in the areas of biochemistry, molecular or cellular biology to Dr. Marco Marra, from the Department of Medical Genetics at the University of British Columbia. These awardees will be presenting Plenary Lectures at the 50th Annual General Meeting of the Canadian Society of Biochemistry, Molecular and Cellular Biology to be held July 5-9 2007 at McGill University.

The 2007 CSBMCB Roche Diagnostics Prize for Biomolecular and Cellular Research

Dr. Nahum Sonenberg

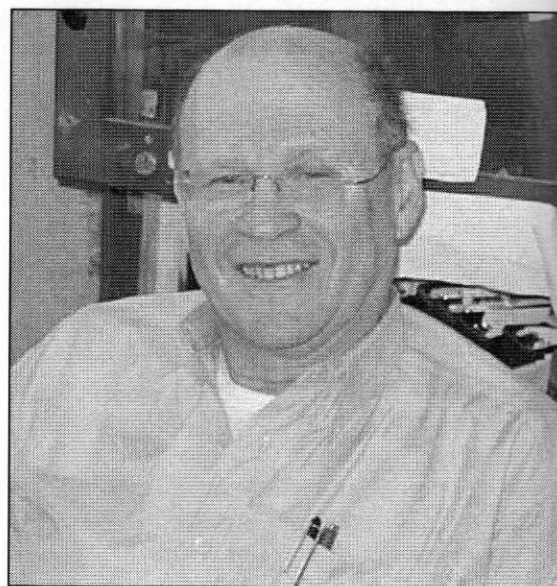
Dr. Sonenberg was born in Germany and educated in Israel, obtaining his B.Sc. and M.Sc. in Microbiology from Tel-Aviv University in Tel-Aviv, and his Ph.D. in Biochemistry from the Weizmann Institute of Science in Rehovot. Following completion of his Ph.D. degree, he was a post-doctoral fellow at the Roche Institute of Molecular Biology in Nutley, New Jersey, where he held the Chaim Weizmann Fellowship. He was appointed Assistant Professor in the Department of Biochemistry at McGill University and the McGill Cancer Centre in 1979, promoted to Associate Professor in 1983, and appointed Professor in 1987. In 1985-86 he was Visiting Professor at the Whitehead Institute for Biomedical Research in Cambridge, Massachusetts.

Dr. Sonenberg has received many honours and awards. These include Medical Research Council Distinguished Scientist Awards, the 1994 PMAC

Keynote Lecturer at the Annual Meeting of the Canadian Federation of Biological Societies in Montréal, an International Scholar Award from the Howard Hughes Medical Institute, the Robert L. Noble Prize from the National Cancer Institute, and a Killam Prize for Health Sciences. He has been elected to the Royal Society of Canada, the American Academy of Arts and Science and the Royal Society of the United Kingdom.

Over the past 25 years, Dr. Sonenberg has published over 300 papers in the field of regulation of protein synthesis. He is internationally recognized as one of the leading researchers in this area of research. His seminal observations about basic mechanisms in the regulation and control of protein translation have reshaped current knowledge in the area, and have been incorporated into current textbooks. In addition there are therapeutic applications to many of his discoveries, which have an impact on development of novel gene therapy approaches, novel drug targets for cancer treatment, and approaches to antiviral therapeutics.

His important contributions began while he was a post-doctoral fellow, when he identified protein complexes that bind the 5' cap structure of eukaryotic mRNAs. These eIF4F complexes and their individual components are now known to regulate,



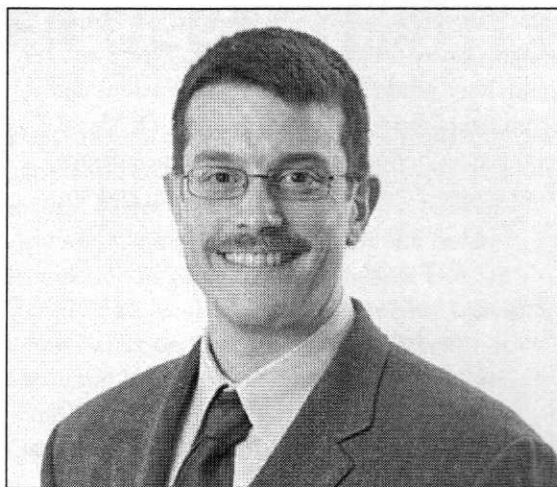
and be rate limiting, in protein translation. Regulation of eIF4F is altered in many human cancers. Dr. Sonenberg's laboratory has followed this initial discovery by linking several signal transduction pathways to translational control by means of phosphorylation of individual components of eIF4E. Over-expression of the least abundant component eIF4F leads to malignant transformation and hence it is a proto-oncogene. It is over-expressed in a number of cancers. He has shown that viruses can translate in a cap-independent manner; this has led to new targets for gene therapy. His contributions also include findings on the role of double-stranded RNA-dependent kinase PKR in growth control and apoptosis, and on the role of 5'-untranslated regions in the regulation of cellular and viral mRNA's. More recent research collaborations with groups at Rockefeller and Harvard Universities have focused on structural studies of translation factors. Very recent work has provided genetic evidence for the role of translational control in hippocampal-dependent synaptic plasticity, learning and memory.

Overall, Dr. Sonenberg's contributions have had a major impact in a number of areas. They have been extremely innovative and have changed the way others think.

The 2007 CSMCB Merck Frosst Prize

Dr. Marco Marra

Dr. Marco Marra, currently an Associate Professor in the Department of Medical Genetics at the University of British Columbia, obtained his education at Simon Fraser University – a BSc in Molecular and Cell Biology and a PhD in Genetics. Following his time at Simon Fraser University he was a post-doctoral Research Associate at Washington University School of Medicine in St. Louis, MO. In 1999 he returned to Vancouver, becoming a Senior Scientist and the Associate Director of the Genome Sequence Centre, Associate Member of the Michael Smith Laboratories, and a faculty member in the Bioinformatics Graduate Program of the University of British Columbia.



A major scientific achievement by Dr. Marra and his collaborators was the construction of a human genome map. This key resource allowed an International Consortium to efficiently complete and make publicly available the human genome sequence. This human genome sequencing project is a major scientific achievement. Through Dr. Marra's contributions, the sequencing data remained in the public domain. A specific contribution of his to the international project was development of a large-scale approach that resulted in the construction of a clone-based physical map of the human genome. His mapping approach, called "BAC fingerprinting", has been further refined in his laboratory and used to analyze more than 30 billion bases of genome DNA from 30 different diverse species, ranging from bacteria to plants to animals. The significance and uniqueness of these activities was recognized by an International Scientific Advisory Board, composed of individuals from the United States and the United Kingdom, which state "The...(mapping technology)...is in a dominant and unique worldwide position. There is no other group that has the equivalent expertise and throughput for BAC fingerprinting..."

Dr. Marra has also made significant contributions in the sequencing of the genome for the SARS coronavirus. The rapid generation of this sequence led to the "SARS Accelerated Vaccine Initiative" in British Columbia.

The Genome Science Centre has over the past 7

years competed successfully for over 100 million dollars of peer-reviewed grants. Dr. Marra and his group have produced over 100 publications and given over 75 invited presentations. Dr Marra received an honorary Doctor of Science degree from Simon Fraser University in 2004, and an

honorary Doctor of Laws degree from the University of Calgary in 2005. In 2004, his contributions to cancer research were recognized by the National Cancer Institute Terry Fox Young Investigator Award.

NEWS FROM MEMBER DEPARTMENTS

Dalhousie University

Department of Biochemistry and Molecular Biology

Correspondent: Mike Gray

The Department welcomed two new members in 2006. **David Waisman**, enticed from the University of Calgary to a Tier 1 Canada Research Chair in Cancer Biology, joined the Department as Full Professor in April. David's recruitment was supported by the Dalhousie Cancer Research Program, which funded renovations on the 11th floor of the Sir Charles Tupper Medical Building to provide new lab quarters for David's research team. In November, **Jan Rainey** arrived from the University of Alberta to take up his position as our newest Assistant Professor. Jan's lab occupies newly renovated space on the 10th floor of the Tupper Building. The Department is delighted to have these two additions to our research and teaching complement.

Meanwhile, **Barbara Karten**, who joined the Department in the Fall of 2005, has been very successful in competing for funding to establish her research program. Intramural support includes awards to Barbara from the Dalhousie Faculty of Medicine and the Dalhousie Medical Research Foundation (both an equipment grant and a New Investigator award). Extramural funding that Barbara has secured includes a substantial CFI Leaders Opportunity award, as well as operating grants from the Ara Parseghian Foundation, the Nova Scotia Health Research Foundation and CIHR. Our immediate challenge is to find additional space for Barbara's burgeoning research group.

Early in 2006, **Christina MacNeil** joined the Department as Administrator, replacing Dawn Schmidt, who moved with her family to Ottawa. The Department shares Christina with the Department of Physiology and Biophysics, but we certainly appreciate the time she devotes to us.

Departmental members continue to participate in extramural committee work. Recent appointments include **Roger McLeod** (Chair of the Scientific Advisory Committee of the Heart and Stroke Foundation of Nova Scotia), **Melanie Dobson** (NSERC Molecular and Developmental Genetics Grant Selection Committee, and **Michael Gray** (National Human Genome Research Institute (NHGRI) Working Group on Comparative Genome Evolution).

Our students garnered an impressive number of awards during 2006, including the W. Andrew MacKay Alumni Scholarship (Krystal van den Heuvel), Killam Predoctoral Award (Elke Uribe), Honorary Killam Scholarships (Ryan Gawryluk and Laura Hug), CIHR Canada Graduate (Doctoral) Scholarship (Jeremy Koenig), and Student Research Awards from the Nova Scotia Health Research Foundation (Kristin Bowden, Jessica Leigh and Tia Silver). At the Merck Frosst Biology Research Day in Kirkland, Quebec, Amin Majdalawieh was awarded first place for his presentation, a notable achievement considering that the organizing committee selected only 12 Ph.D. and postdoctoral finalists out of 135 applicants. Finally, at the 2006 Dalhousie Student Appreciation Night, the Dalhousie Biochemistry Students' Society was named Society of the Year in its category.

Department members in the Comparative Genomics, Proteomics and Molecular Evolution group are prominent participants in a number of protist genome projects currently underway in several U.S. genome centers. **Michael Gray** is a collaborator on the *Acanthamoeba castellanii* genome project being carried out at the Human Genome Sequencing Center, Baylor College of Medicine. **John Archibald** is the PI on a successful application to the Community Sequencing Program of the DOE Joint Genome Institute to sequence the genomes of two marine algae, *Guillardia theta* and *Bigelowiella natans*. Co-investigators on this project include **Chris Lane**, a postdoctoral fellow in the

Archibald lab, Michael Gray, Patrick Keeling (University of British Columbia) and Geoff McFadden (University of Melbourne). Gray is also the coordinator of UNICORN (UNICellular Opisthokont Research iNitiative), a ten-taxon genome sequencing project aimed at exploring the evolutionary roots of multicellularity in animals and fungi. Department member **Andrew Roger** and postdoctoral fellow **Iñaki Ruiz-Trillo** (recently re-located to the University of Barcelona) are key participants. This NHGRI-supported project is being carried out at the Broad Institute of MIT and Harvard, with DNAs supplied by the Roger lab and by co-investigators at Université de Montréal (Gertraud Burger and Franz Lang), University of California at Berkeley (Nicole King) and Oxford University (Peter Holland).

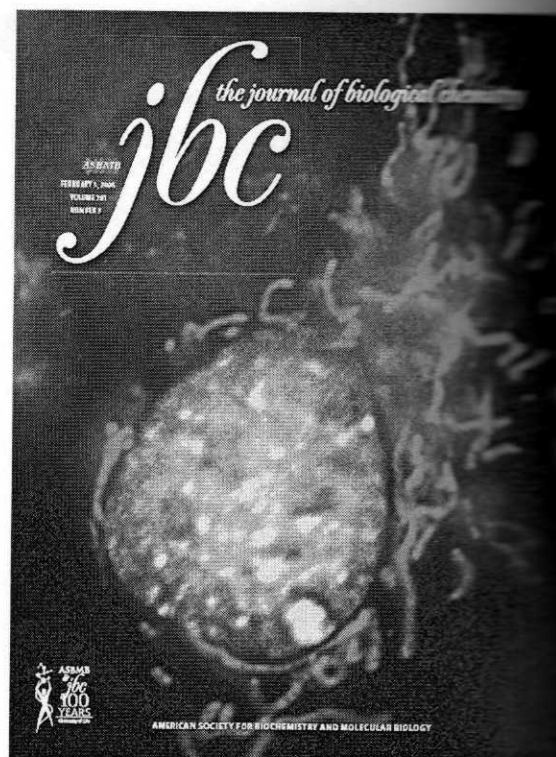
A most significant happening (at least as far as your correspondent is concerned) is the Survey/Search process that is well underway, which (hopefully) will lead to the installation of a new Head on July 1, 2007. While I have enjoyed my three years in the "top spot", I will not be unhappy to fade into the background and thus be able to devote more time to research.

McMaster University

Department of Biochemistry and
Biomedical Sciences

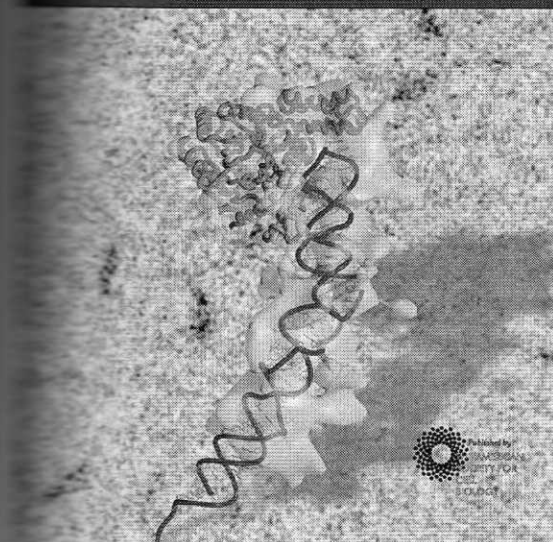
Correspondent: Alba Guarné

The year 2006 has been quite exciting for our Department. Just to kick-start the year, **Gerry Wright** and his team published their work on microbial resistance on the January 20th issue of *Science* (311:374-7), which resulted in a lot of international press for the Department. Many other relevant publications have followed. Notably, those from the Truant, the Ortega and the Andrews labs that have been featured on the cover of *J. Biol. Chem.* (281(5): 2730-9), *J. Mol. Biol.* (363(3): 648-59) and *Mol. Biol. Cell* (17(12): 5063-74), respectively.



Molecular Biology of the Cell

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During the year 2006, we welcomed seven new faculty members. **Mick Bhatia**, a McMaster alumnus, was appointed Professor in the Department of Biochemistry and Biomedical Sciences and the first Scientific Director of the McMaster Cancer and Stem Cell Biology Research Institute. Mick is a pioneer in Canada in the field of human hematopoietic stem cell biology and embryonic stem cells. **Lori Burrows** is one of our new Associate Professors and Joint Member with the Department of Pathology and Molecular Medicine. Her research area is in the study of microbial biofilms and how these impact health care and diseases. **Russell Bishop** (Associate Professor) comes from University of Toronto and brings to the Department expertise on integral membrane enzymes that modify the structure of a bacterial surface molecule. Russell is also enjoying his shortened commute from his home in Paris. **Brian Coombes** (Assistant Professor), who is also a research scientist with the Public Health Agency of Canada, focuses his research in the area of bacterial pathogenesis and evolution of virulence. **Bradley Doble** (Assistant Professor), a post-doctoral

fellow from the Ontario Cancer Institute (OCI), works towards understanding how GSK-3 regulates stem cell properties and cell signaling pathways linked to the genesis of cancer. Christopher Wynder joined the McMaster Stem Cell and Cancer Research Institute in June 2006 as an Assistant Professor in the Department of Biochemistry and Biomedical Sciences. Prior to his arrival, Chris completed his PhD at the Rockefeller University in New York and postdoctoral training at the Wistar Institute in Philadelphia. **Tony Collins** (Assistant Professor, Part-Time) manages our new CFI-funded Biophotonics facility. The main goal of this facility is to convert cutting-edge optical physics into mainstream biological applications.

Gerry Wright, was re-appointed Chair of the Department for five more years. Three new Assistant Chairs were created in Undergraduate Education (**Michelle MacDonald**), in Graduate Education (**Justin Nodwell**) and Research (**Eric Brown**) to absorb the increasing demands of our growing Department. Special thanks to our Assistant Chair of Research (Eric Brown) who filled the Chair's shoes for six-months while Gerry took a well-deserved sabbatical-leave. During his leave, **Gerry** had one of his CIHR grants renewed, published several papers, and led the team that was awarded \$7,824,028 from CFI to establish a new "Centre for Microbial Chemical Biology". **Gerry** was also part of a team awarded \$1,614,514 from CFI to create a "Systems Biology Centre of Host-Intestinal Bacterial Relationships in Health and Disease". Notably, he even found time to train and complete the Toronto Marathon. If this is what he can do in six months, we are looking forward to see what he will do during his second term in the Chair's Office!

Eric Brown renewed his CIHR operating grant in Bacterial P-loop NTPases and was awarded a new CIHR grant in Chemical Genomics. **Eric** also successfully renewed his Tier II Canada Research Chair. **Radhey Gupta**, **Boris Zhorov** and **Geoff Werstuck** were awarded CIHR grants. **Joaquin Ortega** and **Alba Guarné** were awarded Early Research Awards from the Ministry of Research

and Innovation. **Brian Coombes** won the ICAAC Young Investigator Award from the American Society of Microbiology. Congratulations to **Karen Mossman, Dino Trigatti** and **Ray Truant**, who received tenure and were promoted to Associate Professors.

Richard Epand presented a symposium talk on Protein-Induced Lipid Domains at the ASBMB meeting in San Francisco in April. His graduate student Armela Dicu also presented the results of her work on diacylglycerol kinase. Richard has written a chapter for the Wiley Encyclopedia of Chemical Biology on lipid domains, which is in press, as well as an invited review on protein-induced cholesterol-rich domains. The work of Dr. Epand's laboratory on antimicrobial peptides has received international recognition and has led to several publications. One of his research articles on this topic was classified by *Biochemistry* as a "hot" paper. In the past year, Richard has given invited talks at the University of Toronto, the University of Alberta, the University of Guelph, Columbus Children's Hospital, University College (London), Glasgow University, Edinburgh University, Université Libre de Bruxelles and the Centre de Biophysique Moléculaire Numérique de Gembloux. He continues in his role as Executive Editor of *Biochem. Biophys. Acta – Biomembranes*.

John Hassell received a grant from the OCRN focused on the Identification of Compounds that Target Breast Cancer Stem Cells. John presented his work at the AACR Workshop on Stem Cells in Virginia and has given invited talks at Sunnybrook Hospital in Toronto, Ohio State University and the MICB retreat.

Graduate education highlights

Our continuing growth is also reflected in the increasing number of graduate students accepted to the Biochemistry and Biomedical Sciences program. This year 25 new students were accepted, several of them supported by their own scholarships. A total of 26% of our graduate students were funded by rather competitive scholarships from NSERC, CIHR, Heart & Stroke, and OGS, a new departmental record that is a testament to the

exceptional quality of our students. The new Chemical Biology Program also accepted its first graduate students in 2006. Chris Delvecchio received the Thomas Nielsen Scholarship, the highest award offered by our Department. M.Sc. students Casey Fowler (**Li** lab) and Ye Xu (**Nodwell** lab) and Ph.D. students Jack Iwanczyk (**Ortega** lab) and Iva Bruhova (**Zhorov** lab) received the Karl Freeman Prizes, given to students who excel in our graduate seminar series. Eight Ph.D. candidates successfully defended their theses: Jonathan Cechetto (**Gupta** lab), Joe McCann (**Berti** lab), Iain Mainprize (**Andrews** lab), Aaron Kerman (**Ananthanarayanan** lab), Amit Bhavsar (**Brown** lab), Peter Pelka (**Whyte** lab), Marcus Eccelston (**Nodwell** lab) and Emma Griffiths (**Gupta** lab). Twelve more students graduated with a M.Sc. degree.

Graduate students Paul Sobol and Ryan Noyce (**Mossman** lab) published their first first-authored papers in *Journal of Virology*. Likewise, Sean Jackson (**Junop** lab) published the structure of the PH domain of pleckstrin in *Acta Crystallogr. D*. Jack Iwanczyk (**Ortega** lab) also published his first first-authored paper that was featured on the cover of *Journal of Molecular Biology*.

Tracey Campbell and Amit Bhavsar (**Brown** lab) presented award-winning talks at the Meeting of the Canadian Society of Microbiology in London, Ontario. Casey Fowler (**Li** lab) won one of the best poster awards at the Ribo-Club Conference in Sherbrooke, Quebec.

Undergraduate education highlights

In September, we hosted the traditional "Welcome Barbecue" to welcome back all of our students, including 106 new students to level II of our program. In October, the Department hosted a "Twist and Turns" event for the fifth year, as part of the Engineering and Science Olympics. Over 900 high school students converged on campus to participate in a variety of events to compete for McMaster University entrance awards.

As a result of the Undergraduate Faculty Education Retreat, the laboratory curriculum and inquiry-based approach to learning was one of the

main focuses of education development. Faculty members Michelle MacDonald and Paulina August, along with instructional assistant Adam Poir, have been instrumental in the implementation of a new 6-unit laboratory in second year where the students do not work from a prescribed manual, but rather conduct a laboratory research project based on a simulated study.

Facilities

The McMaster Biophotonics Facility was formally opened on May 30th 2006. Based in the Department of Biochemistry and Biomedical Sciences, MacBiophotonics is open to all. This facility was built with the help of an \$11-million grant from CFI, awarded to a team of investigators headed by **David Andrews**. MacBiophotonics houses a broad suite of state-of-the-art systems capable of a very wide range of fluorescence-based techniques. This suite includes advanced fluorescence, confocal and widefield microscopy, high-content screening, and cell sorting. The broad mandate of the facility is the study of the dynamic biochemistry of live cells using novel fluorescence based assays including time-lapse, FRET, FLIM, spectral imaging, FCS and FIDA. Currently researchers at the facility are using our systems to study protein biochemistry in *E. coli*, yeast, mammalian cells, nematodes, and fly larvae. Full details of the systems are available on the facility's website (www.macbiophotonics.ca). Contact Tony Collins (manager; tcollins@macbiophotonics.ca) for more details on how the facility can help with your research.

Finally, as the CSBMCB celebrates its 50th Anniversary, we will be celebrating the **40th Anniversary of the Department of Biochemistry and Biomedical Sciences**. So stay tuned for celebrations throughout the year!

Memorial University of Newfoundland

Department of Biochemistry

Correspondent: Sean Brosnan

....Forty Years of Biochemistry

Memorial's Department of Biochemistry was founded in 1967. We like to think of it as Newfoundland's Centennial project. The department was established in conjunction with the new Medical School. Ironically, the department has, since then, remained within the Faculty of Science. The first Head, LAW (Woody) Feltham, was a clinical biochemist who had initiated the teaching of Biochemistry within the Biology Department. Woody was a colourful character, and JM Sullivan's appreciative profile in the *Globe and Mail's* "Lives Lived" column only begins to do him justice. There can't be many Heads of Biochemistry whose resumé's include such derring-do, as a teenager, as skipping a schooner under sail to safe anchorage through the treacherous St. John's Narrows. The subsequent heads of the department were Charlie Bigelow, Salien Mookerjea, Kevin Keough, Gene Herzberg, Sean Brosnan, Phil Davis and, currently, Martin Mulligan. Early members of the faculty included Peter O'Brien, now at Toronto's School of Pharmacy, and Clive Little, who left us to become Chair of Biochemistry at the University of Tromsø, in Norway. Clive reported back that, at international meetings, he never had to buy dinner.... as chair of a department in a Scandinavian medical school, he was entitled to nominate for the Nobel Prize!

The 1970s brought an expansion of the department to about 12 faculty members. This was followed, in the '80s and '90s by expansion to its current complement of 18. This latter expansion focussed on Nutritional and Food Biochemistry. Early scientific successes included the discovery of antifreeze proteins in arctic and sub-arctic fishes by Choy Hew and Garth Fletcher, and their characterization, together with VS Ananthanarayanan. Willie Davidson reported some of the first sequenc-

ing of marine mitochondrial genomes. Kevin Keough carried out extensive work on lung surfactant and Sean Brosnan on renal metabolism. The department's strengths in nutritional biochemistry resulted in two Borden Awards from the Canadian Society for Nutritional Science, to Sean Brosnan and Gene Herzberg. In more recent distinctions, Sean Brosnan was awarded a D.Sc. by the National University of Ireland; Fereidoon Shahidi was notified by ISI that he is the 7th most cited food scientist in the world.

Members of our department have always played roles on the national stage. Two of our members have been President of CFBS (Margaret Brosnan and Kevin Keough), two have been President of CSBMCB (Kevin Keough and Sean Brosnan,) and one has been President of CSNS (Gene Herzberg). Kevin Keough went on to become Vice-President (Research) of Memorial, followed by a five-year stint as Chief-Scientist of Health Canada. He is currently President and CEO of Alberta Heritage Foundation for Medical Research.

At present the department is redefining its research foci as the old fogies begin to retire and hiring begins. We have done well from the Canada Research Chairs program. At present, we have two Tier 2 Chairs (**Rob Bertolo**, Human Nutrition and **Valerie Booth**, Proteomics). Rob has recently been awarded a Future Leaders Award by the International Life Sciences Foundation. We also have ties to two Chairs in the Ocean Sciences Centre: **Bill Driedzic** (Tier 1 Chair in Marine Biosciences) and **Matthew Rise** (Tier 2 Chair in Marine Biotechnology). Active research areas within the department include Developmental Biology, Protein Structure/Function, Nutritional Biochemistry/Nutraceuticals and Lipids.

We are a department that has always taken our undergraduate teaching seriously. We attract many of the brightest students in the university to our B.Sc. programs in Biochemistry and in Nutrition. This year, one of our students (Luke Pike) won a Rhodes Scholarship; this brought our Rhodes score to four over the last thirty years.

Queen's University

Department of Biochemistry

Correspondent: Albert Clark and Glen Jones

The Department is celebrating its 70th anniversary in 2007. In the past year, the Department has witnessed many notable achievements by students and faculty alike.

Among the recent Ph.D. graduates, Dr. **Chris Marshall** (from Peter Davies' lab) won a CIHR Jean-François St-Denis Fellowship in Cancer Research, while Dr. **Melanie Adams** (Zongchao Jia's lab) won a Governor General's Gold Medal and was nominated for an NSERC Doctoral Prize.

The Department welcomed the new appointment of Dr. **John Allingham** to a Tier II Canada Research Chair. John joined Queen's on January 1 2007, bringing with him grants of over \$1.1 M, including funds for a new X-ray diffractometer.

Dr. **Michael Boffa** received his first major operating grant from the Heart & Stroke Foundation of Ontario. Dr. **Andrew Craig** was awarded his first CIHR operating grant in the infamous September 2006 competition.

Dr. **Roger Deeley** was appointed as the Associate Dean of Research in the Faculty of Health Sciences. Dr. **Geoffrey Flynn** (Head 1990-1996) was appointed as Executive Director of the Office of Advancement in the Faculty of Health Sciences (fundraising). Dr. **Zongchao Jia** came off his two year spell as Steacie Fellow and resumed his role as Graduate Chair. Dr. **Marlys Koschinsky** stepped down as Graduate Chair and became Undergraduate Chair to add to her many key duties in granting agencies. Dr. **Glenville Jones** (current Head) was presented with a Lifetime Achievement Award by the 13th International Workshop on Vitamin D. Dr. **Alan Mak** stepped down as Director of Protein Function Discovery and will be replaced by Dr. **Peter Davies**. Dr. **Martin Petkovich** is on a two-year period of reduced responsibility which he is spending with the Queen's spin-off company Cytochroma Inc., which he co-founded. Dr. **Steven Smith** had a bumper year with a Faculty of Health Sciences

Teaching Award, Undergraduate Teaching Award and a CIHR Investigator Salary Award for his research. Finally, the ageless Dr. **Peter (Harry) Jellinck** (Head 1967-1978) continued his prolific research career with two new publications in the past year.

Simon Fraser University

Department of Molecular Biology and Biochemistry

Correspondent: Christopher Beh

Last year the report from the SFU Department of Molecular Biology and Biochemistry listed the Department's many accomplishments during the few short years since its founding. In this report, a select record of the past year's achievements is recounted. These successes include new faculty awards and awards to graduate students, as well as other research and teaching milestones.

Department highlights

This past year brought much-deserved awards to new and senior faculty members. **Dr. Edgar Young** received a Michael Smith Foundation for Health Research (MSFHR) Scholarship for his work on gated ion channels, and **Dr. Lisa Craig** received both MSFHR and CIHR New Investigator Awards for her research on the structure of bacterial pili and bacterial pathogenesis. **Dr. Michel Leroux** received a MSFHR Senior Scholar Award for recognition of his work on cilia and associated diseases such as Bardet-Biedl syndrome. **Dr. Peter Unrau** received a CIHR Senior Investigator Award for his research on ribozymes and microRNAs. These recent awards add to the many other awards received by the Department's faculty.

In addition to the awards to our faculty, our 85 graduate students continue to receive many accolades for their research. In particular, the Governor General's Gold Medal was awarded to **Dr. Jennifer Gardy**, a recent top SFU graduate who completed her PhD under the guidance of **Dr. Fiona Brinkman**. Together Drs. Gardy and

Brinkman developed a bioinformatics approach for accurately determining bacterial protein subcellular localization. Overall our graduate students were very successful in national and provincial awards claiming 10 NSERC, 6 MSFHR, 3 CIHR, and 11 SFU scholarships.

Our undergraduate program also has had many successes. The MBB Department continues to provide the largest undergraduate majors program in the SFU Faculty of Science and hosts many undergraduate students in its research labs. Successful initiatives include offering joint major programs with Computing Science and Business, allowing students to focus on bioinformatics or biotechnology. The challenge of our large undergraduate program has redoubled with the opening of the new SFU Surrey campus, which necessitated a further expansion of the Department's teaching mission. To manage the new complexities and emerging burdens associated with Department growth, **Dr. Esther Verheyen** accepted the newly formed position of Associate Department Chair. Dr. Verheyen will help facilitate and implement policies necessary for the Department's continued success, and hopefully the University will extend the term of the Associate Chair position. With University support, the research and teaching excellence of the MBB Department will continue and prosper.

New faculty

In the past year, **Dr. Jack Chen** (bioinformatics/neuroscience) joined us from Cold Spring Harbor Laboratories in New York, and he has now successfully established his research program at SFU. This year the faculty is seeking to hire an immunologist who, together with **Dr. Jamie Scott**, will add to the Department's core group in immunology. Dr. Scott holds a Canada Research Tier 1 Chair position recognizing her research in HIV vaccine development and phage display.

Research highlights

The immunology group complements our faculty's diverse research interests, which are broadly defined as cell biology & developmental genetics, structural biology, and bioinformatics. Of note is the group of researchers working on different but

complementary scientific approaches that have made important and unanticipated links between cilia and human disease. In the September 2006 American Society for Cell Biology (ASCB) Newsletter, **Dr. Lynne Quarmby** is featured and she discussed her life's work on cilia and the single-cell green alga, *Chlamydomonas*. Dr. Quarmby, together with **Drs. Leroux, Willie Davidson**, and **David Baillie**, have made the Department an international centre for cilia/flagella molecular and cell biology.

Sponsored scientific meetings

SFU faculty has been active in organizing meetings for scientific discussion and the exchange of ideas. This includes organizing sessions at large meetings such as the 2006 ASCB meeting in San Diego, where **Dr. Christopher Beh** co-organized a subgroup meeting on how membrane organization affects cell polarization, and also includes meetings held on the SFU Burnaby campus. **Dr. Norbert Haunerland** (an Associate MBB Department member) will co-organize the 6th International Conference on Lipid Binding Proteins to be held at SFU from June 3-5, 2007.

Université de Sherbrooke

Department of Biochemistry

Correspondent: Marcel Bastin

Our Chairman, **Jean-Pierre Perreault**, has received a new Tier 1 Canada Research Chair in genomics and catalytic RNA. Under his leadership, the Department is pursuing its interest in the study of protein and nucleic acid structure and function. Moreover, a new Division of Clinical Biochemistry has been established. It is presently headed by **Jean Dubé**. **Martin Bisaillon** has been appointed coordinator of our graduate program. Two new faculty members have recently joined us as Assistant Professors.

François Bachand

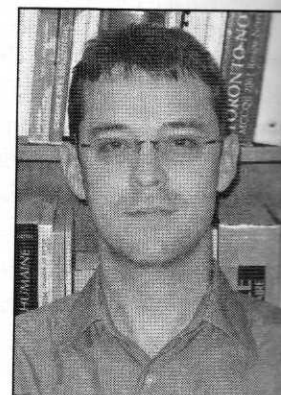
joined the Department in September 2005. He got his Ph.D. in Anatomy and Cell Biology from McGill University and completed his postdoctoral training at the Dana Farber Cancer Institute. François is interested in the biological significance of protein methylation and has already identified a number of physiological substrates for protein arginine methyltransferases. He is the recipient of a junior scholarship from the FRSQ.



François Bachand

François Corbin

obtained his Ph.D. in Molecular and Cellular Biology in 2000 and his M.D. degree in 2001, at L'Université Laval. He did a post-graduate fellowship (residency) in Medical Biochemistry at Université Laval and Université de Sherbrooke until he joined the Department in May 2006. His research interest deals with the biological role of the FMR1 protein. Mutations in the FMR1 gene lead to the fragile X syndrome, the leading cause of inherited mental retardation.



François Corbin

L'Université Laval

Correspondent: Guy Poirier

Dr Guy Poirier de la division biochimie est directeur du Centre Protéomique de l'Est du Québec a obtenu un nouvel octroi de la Fondation Canadienne de l'innovation pour l'étude des protéines fonctionnelles. En augmentant ainsi à 9 le

centre de spectromètres de masse incluant un QTRAP 2000, un LTQ-FTMS et un TOF-TOF, cette plateforme à l'Université Laval sera une des plus complètes de l'Est du Canada. Cette plateforme occupera 10% du nouveau Centre de génomique fonctionnelle (total 6 000 m²) en juillet 2007.

Dr Martin Simard a été recruté au pavillon Hôtel-Dieu de Québec (le plus vieil hôpital au Canada) de CHUQ. Dr Simard vient de terminer son stage postdoctoral avec Craig Mello, lauréat du prix Nobel, pour sa découverte sur les petits ARN.

De plus, l'Université Laval a démarré en septembre 2005 un programme d'études sous-graduées en bioinformatique qui évoluera en formation de biologie des systèmes.

Dr Guy Poirier, of the biochemistry division, at the Eastern Quebec Proteomics Centre has obtained a novel initiative grant from CFI for functional proteomics. This will bring the number of instruments in the mass spectrometry park to 9, including a QTRAP2000, a LTQ-FTMS and a TOF-TOF, making the Facility at Laval one of the most comprehensive in Eastern Canada. This platform will be moving to a new 7 000 sq ft laboratory in the 60 000 sq ft Quebec Genome Center in July 2007.

Dr Martin Simard has been recruited to the Hotel-Dieu (the oldest hospital in Canada) of CHUQ. Dr Simard has recently finished his postdoctoral training with Craig Mello, Nobel Prize Laureate for his small RNA discovery.

Laval University has also started a bioinformatics program that is moving towards systems biology training.

University of Alberta

University of Alberta

Correspondent: Bernard Lemire

The Department welcomed two new Assistant Professors in the past year. **Ing Swie Goping** received her Ph.D. under the supervision of Dr.

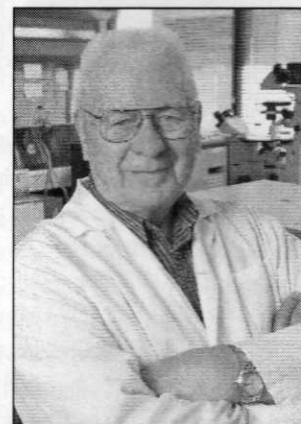
Gordon Shore at McGill University. She has been a postdoctoral fellow and research associate with Chris Bleackley (UofA) since 2000. Her lab is studying the role of mitochondria and the cytoskeleton in programmed cell death, why the apoptotic process malfunctions in cancer and how it can be artificially activated to eliminate tumour cells. **Richard Fahlman** comes to us from Dr. Chris Overall's lab at UBC. Prior to that, Richard received his Ph.D. with Dr. Dipankar Sen at Simon Fraser University. He joined Dr. Olke Uhlenbeck's lab, first in Boulder, Colorado and then in Evanston, Illinois when the lab moved. Richard has interests in understanding the roles and mechanisms by which microRNAs and tRNAs modulate the proteome in normal and in tumor development. It is always refreshing to see some new faces on the block and we wish both of our new recruits flourishing research programs.

The department was very successful in graduate recruitment this year, with 14 new students arriving in September and 2 more in January.

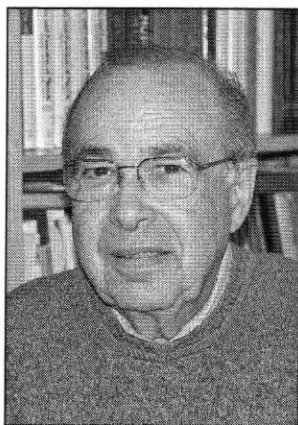
Past and present department members garnered a number of awards in 2006. **John S. Colter** received the Distinguished Alumni Award to recognize his leadership in the field of biomedical sciences. This award is the Alumni Association's most prestigious award. John was chair of our department from 1961 to 1987 and he is credited with building it into one of the best in North America. John played a leadership role at the Medical Research Council of Canada, the National Cancer Institute of Canada and at the Alberta Heritage Foundation for Medical Research. John also received an ASTech Award for Outstanding Contribution to the Alberta Science



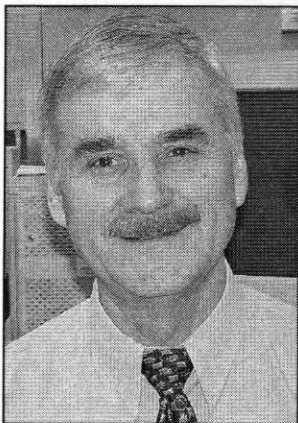
The new kids on the block in Biochemistry at the UofA. Richard Fahlman (top), Ing Swie Goping (bottom).



John Colter received the Distinguished Alumni Award to recognize his leadership in the field of biomedical sciences.



Dr. Cyril Kay, Professor Emeritus and winner of the 2006 ASTech Award for Outstanding Contribution to the Alberta Science and Technology Community.



William Wolodko retired after 30 years with the department and an incredible record of service.

and Technology Community in 1995. Following in John Colter's footsteps, **Cyril Kay** was awarded the 2006 ASTech Award at a ceremony at the Shaw Conference Center on November 3, 2006. Cyril has been a co-director of the MRC Group on Protein Structure and Function, a founding member of the Protein Engineering Network of Centers of Excellence (PENCE), co-chair of the Alberta Strategy Working Group to develop a plan for health research in Alberta, and Vice President Research for the Alberta Cancer Board. **Dennis Vance** was awarded the Avanti Award of the American Society of Biochemistry and Molecular Biology, which recognizes an outstanding investigator known for her/his seminal studies in lipid metabolism, lipid enzymology, or lipids in membranes. In addition, Dennis was appointed Editor-in-Chief of BBA and is looking forward to receiving your manuscripts. **Joel Weiner** was awarded the Distinguished Service Award of the International Union for Biochemistry and Molecular Biochemistry presented in Kyoto, Japan. **Brian Sykes** was awarded the Faculty of Medicine and Dentistry's Award for Excellence in Mentoring. **Larry Fliegel** was awarded a McCalla Research Professorship to recognize significant contributions to research, teaching and learning. **Mark Glover** was awarded a Killam Annual Professorship for his scholarly activities.

Luis Schang was made a Burroughs Wellcome Investigator in Pathogenesis of Infectious Disease. **Chris Bleackley** was awarded the Cinader Award from the Canadian Society of Immunology. He was also honored with the Bio Alberta Award for Scientific Achievement and Innovation to recognize his contributions to developing Bioindustry in Alberta. **Carlos Fernandez-Patron** was awarded the George Fodor Award for Young Investigators in Circulatory and Respiratory Health at the 3rd Annual CIHR National

Research Forum. **Charles Holmes** was appointed to the USA Presidential Task Force on Marine and Freshwater Toxins. **Leo Spyropoulos** was awarded a Heritage Medical Senior Scholarship. **Joe Casey**, who is cross-appointed to Biochemistry, was awarded the CSBMCB Merck-Frosst award and became an AHFMR Scientist. Congratulations to all.

William Wolodko retired after 30 years of service in the department. William was a central member of Dr. William Bridger's lab for many years. After Dr. Bridger left Edmonton, William became a Faculty Service Officer, a position in which he provided an invaluable service in running our ever-expanding undergraduate teaching program. William is greatly missed for his outstanding dedication, his humor and good cheer and his enological knowledge. Our undergraduate program continues to evolve and prosper, now under the direction of **Drs. Rachel Milner** and **Adrienne Wright**. The Department would also like to congratulate the following individuals for their years of service: 35 yrs, **Cliff Gibbs**; 30 yrs, **Sherry Maslyk**, **Paul Scott**, **Irene Shostak**, **Joel Weiner**, **Mae Wylie**; 25 yrs, **David Corson**, **Jozefa Marganski**, **J-C Soucy**. They were honored at a ceremony and reception on November 20 at the Myer Horowitz Theatre. We may be getting older but we are still getting better.

One of our two most notable visitors last year was Dr. Cynthia Kenyon of the Department of Biochemistry and Biophysics at the University of California, San Francisco. Dr. Kenyon delivered an exciting presentation entitled "Genes from the Fountain of Youth" as the 18th John S. Colter Lecturer in Biochemistry. We were also honored by the visit of Dr. John Moulton of the Center for Advanced Research in Biotechnology. He delivered the 2nd W.A. Bridger Lecture in Biochemistry on "SNPs, Protein Structure and Disease".

University of British Columbia

Correspondent: Chris Proud

During 2006, we were very pleased to welcome **Dr Eric Jan** as a new member of faculty from April 1, 2006. He joins us as an Assistant Professor. Previously, he was in the laboratory of Dr Peter Sarnow at Stanford University, where he developed a strong interest in the unusual mechanisms involved in the translation of certain viral mRNAs. He aims to pursue these interests in his new laboratory at UBC.

Dr Natalie Strynadka was elected to Fellowship of the Royal Society of Canada during 2006, and was also promoted to Full Professor. Natalie has a very strong international reputation for her work on the three-dimensional structures of glycosidases and, especially, her studies on components of type III bacterial secretion systems, involved in pathogenesis. These membrane proteins present great challenges for the X-ray crystallography, and her lab has enjoyed spectacular success in deriving their structures.

Dr Brett Finlay, a Peter Wall Institute Distinguished Professor who studies the molecular mechanisms of microbial pathogenicity, was awarded two very prestigious honours in 2006: he received the Flavelle Medal of the Royal Society of Canada, and was appointed to the Order of Canada. He also received a UBC Killam Research Prize. Both Brett and Natalie are International Scholars of the Howard Hughes Medical Institute.

Dr Ross MacGillivray (Director of UBC's Centre for Blood Research) was recognised for the high quality of both his teaching and his research through the award of a Killam University Teaching Prize and a Genome BC Award for Scientific Excellence.

Dr Lawrence McIntosh, who uses NMR spectroscopy to study macromolecular structure and dynamics (as applied to a range of biological systems), won a Killam University Research Prize.

Dr Leann Howe, who joined this Department just three years ago, received a New Investigator Award from CIHR to support her work.

Sabrina Cheng, the department's dedicated, and indeed irreplaceable, administrator very deservedly won the UBC Faculty of Medicine Applegarth Service Award.

The year 2006 also saw the departure of **Dr Arina Omer**, an instructor who ran our third year laboratory classes. Her successor in this role is **Dr Jason Read**, who joined us in summer of 2006.

Undergraduate Program

Our undergraduate courses in the faculty of Science have shown a further increase in enrolment, such that our Honours and Majors Programs are now among the largest in that faculty.

2006 was the 50th Anniversary of our first graduating class. A special event, linked to the 2006 graduation, was held to mark this on May 26th. We were very fortunate that four members of the original class were able to attend: Drs Anne Autor, Gray Scrimgeour, Huntley Blair and Ronald Somerville.

Graduate Program

A total of seven students graduated in 2006: Tanya Griffiths, Michael Johnston, Chris Sturgeon and Jose Villegas gained PhDs, while our Masters graduates were Daniel Grimes, David Martin, and Jed Shimizu. Twenty-eight of our graduate students held major fellowships including 11 with NSERC and 8 with CIHR awards.

Wilco Wu (Molday lab) won the Marianne Huyer Memorial prize (for best PhD thesis) and Michael Gretes (Strynadka lab) won the Zbarsky Award (for best graduate seminar).

Major seminars

Our two 'flagship' seminars are the Michael Smith Lecture and the Boehringer-Ingelheim (BI) Seminar. The former was delivered by Dr Peter Agre (Duke University) to a packed 300-seat lecture theatre, and was extremely well received by a very diverse audience. Dr Agre talked about his studies on aquaporins, selective membrane channels for water, for which he was co-recipient of the 2003 Nobel Prize for Chemistry. Dr John Kuriyan (Berkeley), another very eminent structural biologist, presented the BI Lecture.

University of Calgary

Department of Biological Sciences,
Faculty of Science

Correspondent: *Raymond J. Turner*

The past year has been a significant year of transition for members in our department. The restructuring of our department was finalized and implemented in August. The format moves from a division structure linked to the undergraduate programs, to three larger clusters where the biochemists now find themselves within the Biomolecules, Cells and Microbes cluster (BCM) and the two other clusters are: Organismal Biology, Ecology and Evolutionary Biology. The BCM group is the largest with 36 members of the 60 faculty in the department. To remind, in Calgary, Biochemistry faculty who are part of the faculty of Science teach the undergraduate program. There are other Biochemists in the Faculty of Medicine in the Department of Biochemistry and Molecular Biology (members of which also contribute lectures and courses to our program). The Cell Biologists and Microbiologists are also similarly dispersed in both faculties.

So in that I am also the chair of the BCM cluster, I would like to take this opportunity to introduce to you the members as the major focus of this report. The nature of the BCM cluster's research interests would find themselves as members of sister organizations such as the Canadian Society of Plant Physiologists and the Canadian Society of Microbiology. The formation of the BCM cluster has provided a more open environment for some of our plant biology members who are very good biochemists and cell biologists, yet just happen to take their samples from the green things about. These include CRC **Peter Facchini** (metabolic engineering of plants) and **Doug Muench** (mRNA targeting and metabolic engineering) and a new CRC addition of **Dae-Kyun Ro** (Plant and microbial metabolic engineering). Other plant science people include **David Reid** and **Trever Thorpe**, both plant physiologists. As part of the new organization the BCM cluster also welcomes the microbiologists: **Howard Ceri** (bacterial pathogenesis and biofilms), **Michael Hynes** (molecular biology of

plant-microbe interactions), **Doug Morck** (bacterial infections in veterinary medicine), **Ken Sanderson** (genomics of *Salmonella*), **Doug Storey** (molecular biology of *Pseudomonas aeruginosa*), **Gerrit Voordouw**, (sulfate-reducing bacterium and oil-field environmental microbiology), and **Sui-Lam Wong** (protein engineering in *Bacillus subtilis*).

Our BCM cluster now more closely reflects the CSBMB organization, with the cluster now incorporating the cell and molecular biologists: **Andre Buret** (immunopathogenesis and apoptosis), **Lashitew Gedamu** (molecular biology of *Leishmania*), **Dave Hansen** (genetics of stem cells), **Manju Kapoor** (gene regulation and chaperones in fungi), **Manfred Lohka** (cell cycle control and nuclear envelope assembly), **Carrie Shemanko** (mammary gland development and breast cancer), **Steve Zimmerly** (group-II introns in bacteria). The BCM cluster also includes physiologists and neural biologists: **Jeff Goldberg** (neural transmitters and neural developmental biology), **Hamid Habibi** (molecular endocrinology), and **Wic Wildering** (cell adhesion mechanisms and neuronal aging).

The biophysical chemists and biochemists of the BCM include the very valuable instructors **Elke Lohmeier-Vogel** (metabolism, protein purification & characterization), **Isabelle-Barrette-Ng** (bioinformatics and structural biology) and **Robert Edwards** (membrane proteins and tryptophan photochemistry). The five AHFMR scholars/scientists: **Marie Fraser** (X-ray crystallography and enzyme mechanisms), **Kenneth Ng** (X-ray crystallography on RNA polymerases and carbohydrate-binding proteins), **Elmar Prenner** (membrane architecture and environmental analytical methods), **Peter Tieleman** (computer simulations of membranes and membrane proteins) and **Hans Vogel** (NMR and spectroscopy studies of Ca-binding proteins, Fe uptake, antimicrobial peptides, and metabolomics by NMR). Other faculty includes **Greg Moorhead** (protein phosphatase and proteomics), **Raymond J. Turner** (membrane proteins, *in vivo* protein maturation, heavy metal resistance, proteomics, fluorescence), and **Vanina Zaremborg** (lipid mediated signaling and regulation of lipid metabolism) who presently holds an NSERC-UFA.

We also welcome **Sergei Noskov** (theoretical biophysics of ligand transport) who is part of the Institute of Biocomplexity & Informatics (IBI). The biochemists saw the retirement of **Gene Huber** (enzymology of disaccharide hydrolases), although a loss to the undergraduate program, we are fortunate to still have him around, as he will be maintaining his research program for a few years yet.

Recruitments. Within our department we have the Institute of Biocomplexity & Informatics, which is lead by **Stuart Kauffman** (systems biology). This institute has been very active the past fall recruiting faculty members. Thus we expect a regular faculty member and CRC tier I to join the department in the coming summer both of which are expected to be part of the BCM cluster.

Additionally, we have begun recruitments for an environmental microbiologist and plant developmental biologist and look forward to a positive recruitment and new faculty in place by the fall semester.

Recognition

Congratulations go to **Greg Moorhead** who was awarded the C.D. Nelson Award in August 2006 at the Joint Annual Meeting of the American Society of Plant Biologists and the Canadian Society of Plant Physiologists in Boston. This Award recognizes young plant physiologists whose "outstanding research contributions" show "originality and independence of thought".

Congratulations also go out to **Hans Vogel** his nomination in the Outstanding Leadership in Alberta Science category of the ASTECH Awards. **Howard Ceri** was also recognized receiving the faculty of science teaching excellence award.

Sabbaticals this year

Greg Moorhead was away in Dundee Scotland playing around with phosphatases for the winter semester. **Raymond Turner** was in Norwich England for January to March then to Italy to participate as an instructor in the European Union Bioremediation workshop then finally to University of Paris Sud for talks and to play in a lab there.

Other Highlights

Hans Vogel has been working hard to establish a Metabolomics centre as part of our BioNMR facility. We now have a dedicated NMR for such purposes and he culminated these efforts with a metabolomics mini symposium in December. Hans also spent some effort showcasing the BioNMR centre and the CFI funded CyberCell biophysical equipment suite.

Overall, an excellent year with our group with increase in our PDF and graduate numbers. It certainly is interesting living in a City with a growth rate only matched by two other cities in the world (Dhabi and Shanghai). With the cost of the average house increasing 40% in the past year gives extra challenges to recruitments of both students and faculty. Of course the most significant frustration of living in this boomtown is that the price of a pint of beer has now reached 6 \$!

For more information about our Biomolecules/Cells/Microbes cluster within the Department of Biological Sciences visit:
www.bio.ucalgary.ca/research/BCM.html.

University of Calgary

Department of Biochemistry and Molecular Biology

Correspondent: Leon W. Browder

The Department of Biochemistry and Molecular Biology in the Faculty of Medicine, the University of Calgary, is a diverse department with a highly productive research program. We also administer the genomics, proteomics and bioinformatics infrastructure that facilitates the research activities of biochemists and molecular biologists in Calgary and beyond. The department consists of 51 faculty members plus 20 adjunct appointees.

The department offers graduate training leading to Ph.D. and M.Sc. degrees in Biochemistry and Molecular Biology. Members of the department supervise more than 170 graduate students.

Transitions:

Dr. Randy Johnston completed his service as Interim President of Genome Alberta after serving for several years as President of Genome Prairie. Randy managed to retain a very productive and innovative research program while serving as President of these two organizations. Research will now be his major focus.

Dr. Jay Cross was named Associate Dean (Research) in the new Faculty of Veterinary Medicine. Jay will retain a joint appointment in Biochemistry and Molecular Biology, and will continue to oversee a large and highly productive research laboratory.

Dr. Joe Goren retired this year after 36 years' service and has been named Emeritus Professor. Joe joined the Faculty of Medicine as an Assistant Professor in the Division of Medical Biochemistry in 1970. He was promoted to Associate Professor in 1975 and to Full Professor in 1982. Joe made significant contributions to graduate education during his career, both as an educator and by serving as Coordinator of our graduate program. Joe was instrumental in helping to establish this program as one of the most rigorous graduate programs in the University of Calgary. Joe has had a distinguished research career, specializing in the study of Type II diabetes. He has maintained a small, but productive research program throughout his career and has continuously published in front-line biochemistry and diabetes journals.

Dr. David Waisman left Calgary this summer to accept a Canada Research Chair position at Dalhousie University. David has attained stature as an international leader in the annexin research community. His research has been well supported by grants from a variety of agencies, including CIHR. David has also served the biochemistry community as a member of the Editorial Board of the Journal of Biological Chemistry. He will continue to have a distinguished career in Halifax.

Dr. Derrick Rancourt is currently on sabbatical in Toronto. He is pursuing his interests in research management and leadership training in the MaRS Discovery District. Derrick has been a leader in

enriching the learning environment for students who intend to pursue careers in the biotechnology community. This sabbatical is an important step in this process.

Dr. Mike Walsh is currently on sabbatical at the Smooth Muscle Research Centre at the Dundalk Institute of Technology (DKIT) in Ireland. One of Mike's goals is to establish strong collaborative interactions between DKIT and the Smooth Muscle Research Group in Calgary. The Dundalk Institute has extensive expertise in calcium imaging, which will benefit Mike and his colleagues in Calgary.

New department members:

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

Dr. Sung-Woo Kim joined the department in July. Sung-Woo obtained his Ph.D. from Dalhousie University in 2000 and pursued his postdoctoral research at the Scripps Research Institute in San Diego. His research focuses on cellular and molecular mechanisms of tumor progression and metastasis.

Dr. Jennifer Cobb joined the department in December. Jennifer obtained her Ph.D. from the University of Tennessee in 2000 under the supervision of Dr. Daniel Roberts. Since that time, she was a Post-doctoral Fellow with Dr. Susan Gasser at the University of Geneva and the Swiss Cancer Institute. Jennifer studies the role of cell cycle checkpoint proteins in maintenance of genomic stability using *Saccharomyces cerevisiae*.

Dr. Jane Shearer first joined this department in 2004 as Core Director of the Centre for Mouse Genomics. She is currently completing a maternity leave and will join the Faculty of Kinesiology in March with a joint appointment as Assistant Professor in Biochemistry and Molecular Biology. Jane obtained her Ph.D. from Guelph before undertaking postdoctoral studies at Vanderbilt University with David Wasserman. She studies the mechanisms regulating glucose and fatty acid metabolism.

Dr. Cairine Logan has obtained a secondary

appointment in this department. Her primary appointment remains in Cell Biology and Anatomy. Cairine studies pattern formation within the developing central nervous system of the vertebrate embryo and the ontogeny of distinct neuronal systems, using the chick as model organism.

Dr. Blanka Kühnel has joined the department as an Adjunct Assistant Professor. Blanka received her Ph.D. training in the Department of Molecular Biology at the Swiss Institute for Experimental Cancer Research. Her degree was awarded through the University of Nijmegen, The Netherlands. She undertook postdoctoral training at the University of Colorado Health Sciences Center and the University of Calgary before joining Maurice Moloney's lab in Calgary as a Research Associate. This led to her being hired as Coordinator of the Student Internship Program and Research Scientist at SemBioSys, the biotech company founded by Maurice. Blanka currently serves as Practicum Coordinator for the Masters in Biomedical Technology Program in the Faculty of Medicine.

Training Opportunities:

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

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

Extraordinary Science in an Extraordinary Location!

University of Guelph

Department of Molecular and Cellular Biology

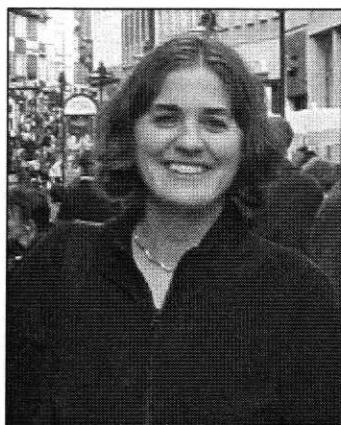
Correspondent: Frances Sharom

New Science Complex building update

The pace of the building schedule for the new \$144 million Science Complex has been proceeding rapidly over the past year. The Phase 1 research and teaching section was completed in July-October 2004. Its research wing now accommodates the research labs and offices of the former Microbiology Department and the Biochemistry group, who make up about 2/3 of the faculty in the Department of Molecular and Cellular Biology, which was formed in September 2004. Phase 2A opened on schedule in July 2006, and now accommodates the two Science deans, various seminar rooms, as well as new teaching labs for the biology undergraduate programs. The final part of the complex, Phase 2B, is scheduled to open in mid-2007, and will accommodate new administrative offices for our department, the research labs and offices of the remaining faculty in our department, primarily the molecular biologists and cell biologists, as well as all the members of the new Department of Integrative Biology. When all the moves are completed, the approximately 45 members of the department will all be housed together in the new 390,000 square feet complex, together with the 19,000 square feet Advanced Analysis Centre (AAC), which includes state-of-the-art NMR spectroscopy, X-ray crystallography, electron microscopy, confocal microscopy, and mass spectrometry instrumentation, as well as other analytical services such as DNA sequencing. The Science Complex will accommodate 150 faculty, 500 graduate students and 4,000 undergraduates.

New faculty additions

Nina Jones joined the Department as an Assistant Professor in the past year, strengthening the department's developmental biology group. Her research is focused on characterizing the molecular basis of cellular signal transduction, with an emphasis on studying the pathways required during blood vessel development. Dr. Jones's laboratory is



Nina Jones

investigating the function of a number of signaling adaptor proteins in vascular cells, including endothelial cells and kidney podocytes. Dr. Jones has returned to the University of Guelph, where she obtained her B.Sc. degree, after completing her PhD training at the University of Toronto in the Department of Medical Biophysics under the supervision of Dr. Daniel Dumont, and her postdoctoral training at the Samuel Lunenfeld Research Institute at Mount Sinai Hospital in Toronto, under the mentorship of Dr. Tony Pawson. Nina is currently hard at work setting up her new research space, and was awarded an NSERC operating grant, so her research program is off to a good start. She is also the recipient of an NSERC University Faculty Award (UFA).

The new department continues to grow by addition of faculty members transferring from other units. **Larry Peterson**, Professor Emeritus, and **Usher Pozlusny** have moved from Integrative Biology, and **Jaideep Mathur** has joined us from Plant Agriculture. All are plant cell biologists.

Congratulations!

Marc Coppelino was awarded an Early Researcher Award (ERA) by the Ontario government. These awards are directed to full-time Ontario researchers within the first five years of the start of their independent academic research career. The ERA will provide a welcome boost to the personnel in the Coppelino lab by providing salaries for graduate students, post-docs and technical staff.

John Dawson received the College of Biological Science Award of Excellence in Teaching in the spring of 2006. While John has made an excellent contribution in many areas, his innovative work on BIOC*4550, Biochemistry and Structure of Macromolecules, has received particular attention. The fourth year undergraduate students who take this course have an opportunity to research, write, and submit an article electronically to John's course journal, "Fold". They work in pairs, and

their manuscript is subjected to review by other members of the class, followed by revision, and resubmission of the revised version for final acceptance and publication. The process faithfully mimics the electronic submission and review processes of a typical scientific journal, and students are very proud when they see their "publication" finally appear!

Joe Lam was selected as the winner of the Canadian Society of Microbiology's top award, the CSM/Roche Prize.

Frances Sharom was the winner of the CSBMCB's Jean Manery Fisher Memorial Lectureship, and presented her award lecture at the 49th CSBMCB Annual Meeting in Niagara-on-the Lake.

Our Chair, Chris Whitfield, was elected a Fellow of the American Academy of Microbiology.

Several graduate students received awards and honour during the past year. **Veronica Kos** (Chris Whitfield lab) and **Erin Westman** (Joe Lam lab) received highly competitive Canada Graduate Scholarships from CIHR to support their PhD studies, while **Leslie Cuthbertson** (Chris Whitfield lab) was awarded an ICI Scholarship in Biotechnology.

Dr. **Susan Yates** (John Dawson lab) received a CIHR Post-Doctoral Fellowship, and headed off to Queen's University for the next step of her career.

PhD student **Abdi Musse** (George Harauz lab) received a travel award to attend the 2006 ASBMB meeting in San Francisco, to present his abstract entitled "Deimination of membrane-bound myelin basic protein in multiple sclerosis exposes an immunodominant epitope". A paper on this topic was published just prior to the meeting in the Proc Natl Acad. Sci USA March 21 2006 issue, where it was featured on the cover. Also accompanying Abdi's paper was commentary article entitled "Structural insight into the role of basic protein in multiple sclerosis", by Dr. C. Husted of the University of California. Abdi's poster at the conference presented new insights into the possible origins of autoantigens in MS and he was awarded a \$500 prize.

Muhammed Attiq Rehman (Joseph Yankulov lab) was awarded a Wood-Whelan Research Fellowship to expand his PhD studies through a visit to Dr. Hisao Masai's lab at the Tokyo Metropolitan Institute of Medical Science.

University of Lethbridge

Departments of Biological Sciences,
Chemistry and Biochemistry, and Physics

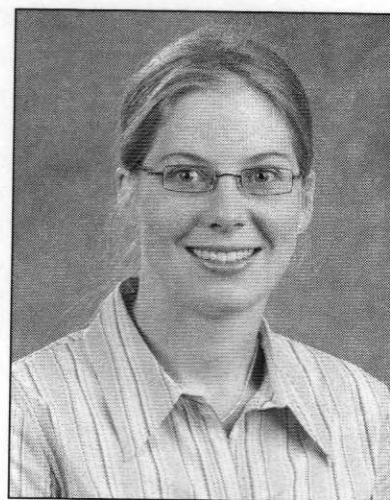
Correspondent: James E. Thomas

Biochemistry at the University of Lethbridge continues to grow. The program now has 135 majors with six Master's students. Biochemistry at the U of L is a multidisciplinary major delivered by several Departments. While much of our focus is on agricultural systems, new areas of research also are being explored in the areas of health and theory.

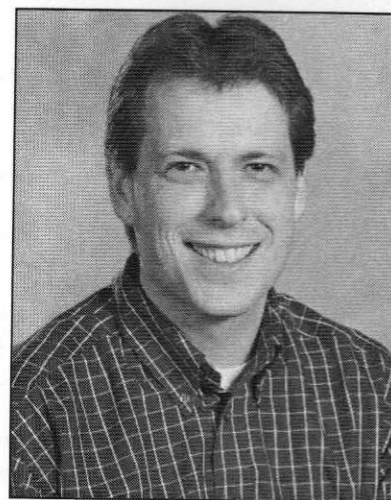
Dr. Ute Kothe joined the Department of Chemistry and Biochemistry at the University of Lethbridge in October 2006 as an Assistant Professor in Biochemistry. Ute has a strong background in biochemical and biophysical investigations of a large ribonucleoprotein, the prokaryotic ribosome. Her work has significantly increased our understanding of accurate decoding of messenger RNA by the ribosome; e.g., she identified a crucial mechanism of GTPase activation of elongation factors by the ribosomal L7/12 stalk (Cell (2005) 121(7): 991-1004). Additionally, her kinetic studies of ribosomal decoding elucidated the importance of tRNA modifications for efficient decoding which might be part of an evolutionary adjustment (Mol Cell 2007; 25(1), 167-174, 2007). In the future, Ute will use her biochemical and biophysical knowledge to study small ribonucleoproteins. Several of these particles have come into the focus of research only in the past five to ten years and fulfill crucial cellular functions, but are still only poorly understood. In particular, she is interested in understanding the molecular mechanisms and the building principles of ribonucleoprotein complexes - for example, in the early stages of ribosome biogenesis. Eventually, this research can lead

to the development of new nanomachines based on biomolecules such as RNA and proteins as well as to the identification of new drug targets.

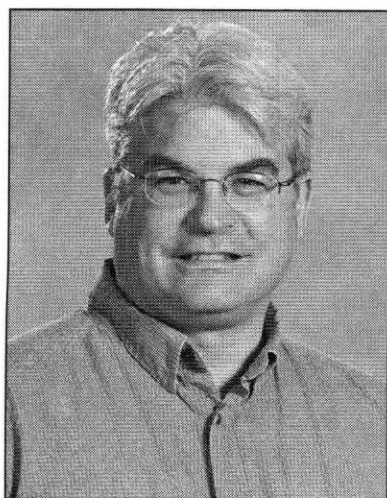
Dr. Hans-Joachim Wieden is also a member to the Department of Chemistry and Biochemistry. He joined the Department in January 2005 and was awarded a **Canada Research Chair in Physical Biochemistry**. HJ is studying the molecular mechanisms of antibiotics. With the steady emergence and spread of antibiotic resistant pathogens, the development of new antibiotics is increasingly important. This research program focuses on the study of antibiotic function in order to develop novel antibiotics, in particular antibiotics that target the cellular machinery of the pathogen that is responsible for translating genetic information into functional proteins, a process called translation. The detailed mechanistic understanding of the involved processes is of fundamental importance for the development of new types of antibiotics. In his research program, he approaches the problem of how antibiotics interfere with these processes, in order to inhibit translation, on the molecular level. His research group will identify the molecular requirements for the inhibition of translation and analyze how resistance mechanisms work. On the basis of these results we will develop novel tests that will allow us to search for chemical compounds that will effectively inhibit translation. The research will significantly contribute to our understanding of the structural and functional requirements of antibiotic function, providing the framework for rational inhibitor design.



Dr. Ute Kothe



Dr. Hans-Joachim Wieden



Dr. Brent Selinger

Other research is looking at the molecular dynamics of elongation factors. During translation, growth of the polypeptide chain is facilitated by consecutive binding of two elongation factors (EF), Tu and G, to the elongating ribosome. Protein molecules are intrinsically flexible, and typically undergo a wide variety of motions at normal temperatures. Crystal structures of the free EFs as well as cryoelectron microscopic studies of ribosome-bound EFs demonstrated a high degree of conformational flexibility to be

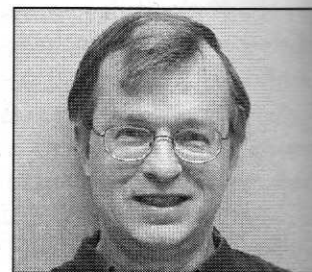
important for the function of these factors. The flexibility and dynamics of proteins such as elongation factors has been optimized by evolution for their activities and functions. In order to analyze the role of the dynamical properties on their function, and to bridge the gap between the static structural data and the huge amount of biochemical and kinetic information that is available, the conformational flexibility of elongation factors such as EF-Tu and EF-G is studied using molecular dynamics simulations and structural alignments.

HJ's work focuses around a unique combination of state-of-the-art biophysical techniques involving fluorescence spectroscopy, fast kinetics (quench flow/stopped flow), biochemistry, molecular biology, and molecular dynamics. He has two graduate students; Jeff Fischer is working on alternative elongation factors, while Adam Smith is working on the functional mechanism of RNase II (co-supervised by Dr. Steve Mosimann). HJ also is strongly committed to undergrad research and maintains an active undergrad research program. During the summer of 2006 four undergraduates researchers (funded through AHFMR, NSERC and Chinook stipends.) worked on individual research project in his lab.

(<http://people.uleth.ca/~hj.wieden/index.html>)

Dr. Brent Selinger is an Associate Professor in the Department of Biological Sciences and Coordinator of Agricultural Biotechnology at the

University of Lethbridge. Brent is interested in the genetics and biochemistry of microbial hydrolytic enzymes, microbial ecology of animal digestive tracts and surface waters and biological control of cattle ectoparasites. His research group is currently characterizing a unique family of phytate degrading enzymes related to protein tyrosine phosphatases (PTP). A large collection of PTP-like phytase genes is currently being used to address questions about the molecular and biochemical characteristics of this family as well as mechanisms of action, structure/function relationship and biological function. Two of his students recently completed their Master's degrees. Aaron Puhl worked on specificity of phytases related to protein tyrosine phosphatases. Jennifer Geddes worked with Brent and **Francois Eudes** (Agriculture and Agri-Food Canada, Lethbridge Research Centre), where she did proteomic analysis for *Fusarium* head blight resistance in barley. Carolyn Penniket, a Master's Student working with Brent and **André Laroche**, an Adjunct Professor with the University of Lethbridge and a Research Scientist at Agriculture and Agri-Food Canada, Lethbridge Research Centre, is working on the isolation and characterization of tissue-specific promoters in cereals using micro-arrays and two-dimensional protein gel electrophoresis.



André Laroche

A variety of techniques are used in Brent's research, including aerobic and anaerobic microbiology and molecular biology (e.g., gene cloning and overexpression, protein purification and characterization, and mutagenesis). Collaborations with **Steve Mosimann** and **Hans-Joachim Wieden** from the U of L and **Ralf Greiner** (Federal Research Centre for Nutrition and Food, Centre for Molecular Biology, Karlsruhe, Germany) have allowed questions on phytase structure/function relationships, molecular dynamics and dephosphorylation pathways to be addressed. Rob Gruninger is a Ph.D. student working on the structure/func-

tion relationships of PTP-like phytases under the supervision of **Steve Mosimann** and **Brent**.

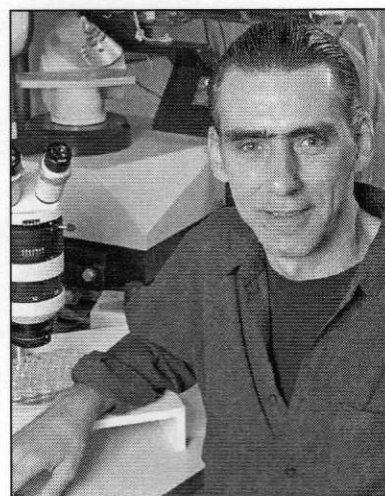
Dr. Steve Mosimann is an Associate Professor with the Department of Chemistry and Biochemistry at the U of L. Steve's research involves development of an understanding of the mechanism of mRNA turnover and the formation of long-lived mRNA species. One area of interest is in messenger RNA turnover in bacteria. The hallmark property of mRNA is its rapid turnover within the cell. Ultimately, it is the balance between the production and degradation of mRNA species that control the levels of proteins within a cell. Accurate, three-dimensional models of the enzymes, proteins and complexes responsible for 'general' mRNA turnover can reveal the recognition events that lead to degradation of a given mRNA species. The longer-term goals of this research program are an understanding of mechanism of mRNA turnover and the development of long-lived mRNA species. Other research involves ribosome biogenesis in Archaea. Ribosomes are assembled in a stepwise, vectorial process that involves a number of characterized RNA processing events. Archaeal ribosome biogenesis shares common features with eukaryotic ribosome biogenesis and can serve as a less-complex model for study. Structural studies of archaeal enzymes, proteins and complexes required for ribosome biogenesis will shed light on related processes in eukaryotes. Steve currently has a PhD Student, Rob Gruninger working with him, who is being co-supervised by **Brent Selinger** (Department of Biological Sciences, University of Lethbridge) and is working on the structure and functional relationships of phytases.

Much of Steve's research involves X-ray crystallography. Homogeneous samples of macromolecules and macromolecular complexes can be crystallized in aqueous solutions. The diffraction of monochromatic X-rays by these crystals can yield intensity data that is used to create a three-dimensional map of the electron density associated with the macromolecule(s) of interest and ultimately a three-dimensional structural model. As the structure and function of macromolecules are intimately connected, these models provide functional insights and lay the groundwork for an understanding of biological

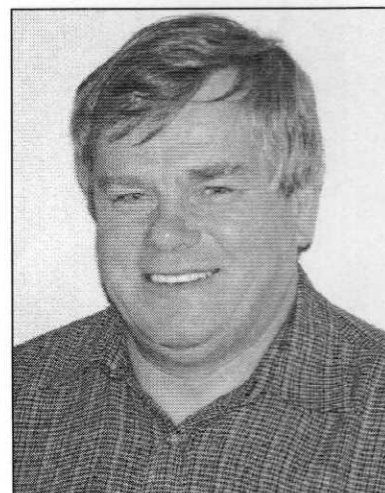
function at the molecular level.

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

Dr. Theresa Burg is a newly appointed Associate Professor in the Department of Biological Sciences at the University of Lethbridge. Her predominant research interests focus on how intrinsic and extrinsic factors influence the evolution of natural populations. Theresa uses a broad-scale, comparative phylogeographic approach to examine evolutionary patterns and processes in a wide range of organisms including fish, birds and mammals. In her research she has examined a diverse array of topics from mating systems in albatrosses to genetic structure of harbour seals. Current research projects include metapopulation dynamics of the wandering albatross complex, investigating temporal components of a range expansion in the northern fulmar and patterns of post-glacial population expansion in northern North American birds including chickadees and woodpeckers.



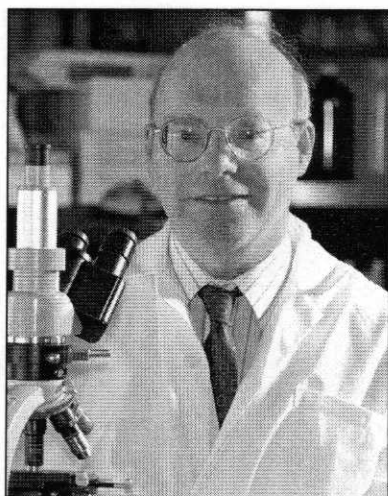
Dr. Steve Mosimann



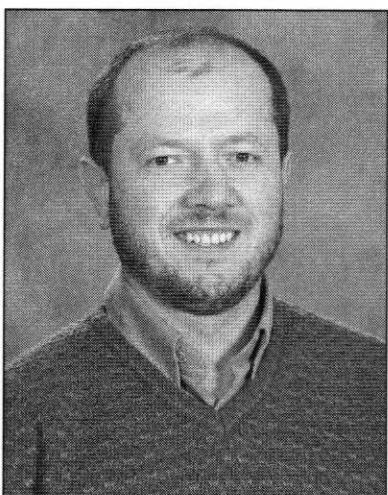
Dr. Roman Przybylski



Dr. Theresa Burg



Dr. James Thomas



Dr. Igor Kovalchuk

Dr. James Thomas is an Associate Professor in the Department of Biological Sciences, and Coordinator of Biochemistry at the University of Lethbridge. Part of his research focus is in the area of microbiology, looking at cause and effect associations in the occurrence of waterborne pathogens, in particular in relation to agriculture, ecology and urban/industrial activities. In collaboration with the Canadian Water Network, the Water Institute for Semi-arid Ecosystems and the Public Health Agency of Canada, he is using metabolic fingerprinting of environmental isolates of *Enterococcus* and *Salmonella* as a means of bacterial source tracking, and genomic characterization of environmental isolates of *E. coli* O157:H7 and *Campylobacter* to develop clinical assays for use in environmental testing. Part of this research has involved assessment of water quality within the Oldman River basin of southern Alberta using geographical information systems

to assess spatial and temporal distribution of the fecal coliforms, *E. coli* O157:H7 and, *Salmonella* within the watershed. This data is being related to land use, agricultural, urban and industrial applications. Three graduate students, Sara-Jo Paquette, Susan Ross and Jennyka Hallewell currently are being co-supervised by Jim and **Victor Gannon**, Adjunct Professor with the University of Lethbridge and a Research Scientist with the Public Health Agency of Canada, and are working on this research.

Jim also is working with **Surya Acharya**, Adjunct Professor with the University of Lethbridge and a Research Scientist with Agriculture and Agri-Food

Canada and, **Manjula Bandara**, Adjunct Professor with the University of Lethbridge and a Research Scientist with Alberta Agriculture Food and Rural Development in Brooks, Alberta to develop new forages for the livestock and dairy industries and, new value added food and nutraceutical crops to help diversify our agricultural industry. In 2004 ACE-1 PC rye (available through Kenneth Long Seeds Inc.), a new perennial cereal rye which is adapted for growth in semi-arid climates with reduced water, and has excellent feed characteristics as either silage, hay or pasture, was released through Agriculture and Agri-Food Canada. A recently graduated Master's student, Saikat Basu (co-supervised with Surya Acharya) also worked on development of new varieties of fenugreek which produce good forage and mature seed within the ~100 frost-free days for growth in southern prairie regions of Canada. The crop is an annual legume which can be used in crop rotations and, is adapted for growth on dry land or with limited irrigation. The plant produces diosgenin, a steroid hormone precursor which has potential to promote weight gain in livestock and increased milk production in dairy cattle. Another Master's student, Ee Lynn Lee (co-supervised with Manjula Bandara), currently is working to develop new varieties of fenugreek with enhanced production qualities for the food and pharmaceutical industries and, as a dietary supplement for the nutraceutical industry.

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

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

This work has potential to help with generation hardier more resistant crop and could provide an insight to the role of stress in plant evolution. The lab is the home for the following graduate students: Scott Greer (MSc), Franz Zemp (MSc), Lidia Luzhna (MSc), Alex Boyko (PhD), Palak Kathiria (PhD), Saikat Basu (PhD).

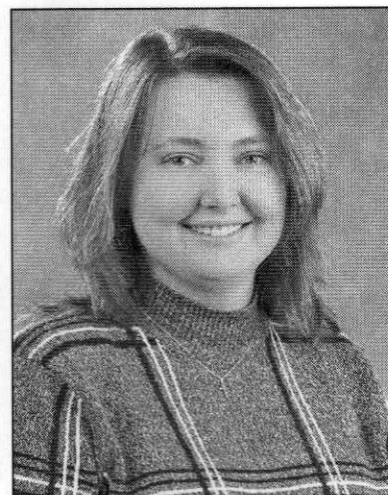
Dr. Olga Kovalchuk is an Associate Professor with the Department of Biological Sciences at the University of Lethbridge and the Associate Member (Fundamental Stream) of the Southern Alberta Cancer Research Institute. Dr. Kovalchuk is an active member of several professional societies and Editorial Board member of the *Mutation Research*. The Kovalchuk laboratory works in the rapidly evolving, challenging area of cancer research. Despite a plethora of research in the area, there is still no clear cut answer as to exactly why and how cancer arises. Many powerful cancer treatment modalities have been developed, but they cause serious side effects. Her research program is devoted to uncovering the molecular mechanisms of cancer development and new approaches to cancer prevention, diagnostics and treatment. The lab has a particular interest in the effects of radiation. Radiation is a double-edged sword – on one hand it is a powerful cancer treatment regiment, on the other hand it can cause cancer. The Kovalchuk laboratory works to minimize the harmful effects of radiation, while maximizing its therapeutic potential. The research program consists of several interconnected lines of research:

- Molecular and cellular mechanisms that underlie cancer development
- Epigenetic regulation in normal and cancer cells
- Radiation and cancer: why and how does radiation cause cancer in the exposed individuals and their unexposed progeny?
- Radiation and cancer: role of radiation in cancer treatment
- Radiation and cancer: mechanisms of radiation side effects

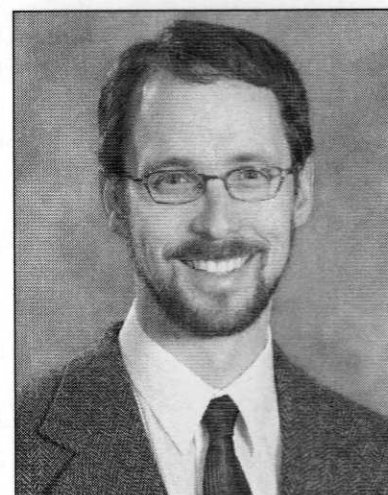
- Sex differences in radiation responses and cancer occurrence.

Amongst various cancer types they are specifically interested in breast, skin and blood cancers. Research in the Kovalchuk Laboratory is funded by the Canadian Institutes for Health Research, Alberta Cancer Board, Alberta Breast Cancer Research Initiative, NSERC and the USA Department of Energy. Dr. Kovalchuk's lab has built a rigorous collaborative network. They productively interact with Dr. Brian Hemmings (Friedrich Miescher Institut (Basel, Switzerland), Dr. Bevin Engelward (MIT Bioengineering Division, USA), Dr. Igor Pogribny (National Centre for Toxicological Research, USA), Drs. William Bonner and Olga Sedelnikova (Molecular Toxicology Laboratory at NCI/NIH, USA). They also collaborate with the researchers at the Department of Genetics, University of Leicester (UK), the Canadian Centre for Behavioral Neuroscience, Health Canada, McMaster University, University of Calgary, Savannah River National Laboratory, University of Georgia and William Beaumont Hospital Research Institute.

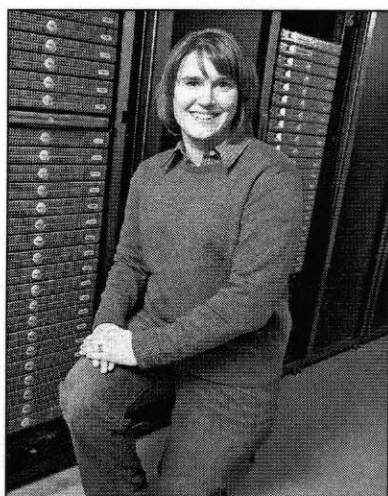
Marc Roussel is a mathematical chemist appointed to the Department of Chemistry and Biochemistry. His main research interests centre on the development of tools for the mathematical modeling of biochemical systems, from the smallest (subcellular) scales all the way up to the intermediate spatial scales represented by tissues. In addition to fundamental theoretical work, recent proj-



Dr. Olga Kovalchuk



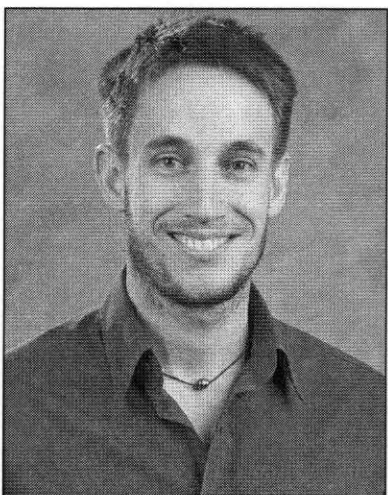
Marc Roussel



Dr. Stacey Wetmore

ects have included applied modeling research in developmental biology, and collaborative projects in which modern time-series analysis methods are applied to study physiological dynamics. The Roussel group has recently received an NSERC RTI grant to purchase some computer workstations and is thus well equipped to undertake a variety of projects in mathematical chemistry and biology.

Dr. Stacey Wetmore joined the Department of Chemistry and Biochemistry as an Associate Professor and Canada Research Chair in Computational Chemistry in July 2006. Dr. Wetmore comes to the University of Lethbridge from Mount Allison University where she established a research program with undergraduate students over a five year period. At the University of Lethbridge, her research program has expanded to include graduate students, where her current group includes two MSc students (Andrea Millen, Lesley



Dr. François Billaut

Rutledge), a PhD student (Ken Hunter), and two undergraduate students (Jennifer Przybylski, Brent Kamenz). Stacey's research uses calculations on computers to understand DNA damage and repair mechanisms, as well as the properties of modified DNA components that have a variety of biochemical and medicinal applications. Computational chemistry provides a unique approach to study these problems since information about short-lived, highly reactive, reaction intermediates can be obtained more readily than from experimental studies. Current areas of research in the Wetmore lab include understanding DNA damage due to phenoxyl radicals and the mechanism of action of enzymes involved in the base excision repair

process, where particular emphasis is being placed on understanding the glycosidic bond cleavage in damaged nucleotides catalyzed by DNA glycosylases. Although calculations on biological systems require significant computer resources, these calculations are possible at the University of Lethbridge due to the recent establishment of a high-performance computer cluster that is composed of 170 quad-core processors (680 cores in total). At the time of establishment, the computer cluster was one of the largest clusters in Western Canada dedicated to a single research group.

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

Dr. François Billaut joined the Department of Kinesiology and Physical Education at the University of Lethbridge in September 2006 as an Assistant Professor in Exercise Physiology. François has a strong background in biochemical (muscle samples through biopsy technique) and electrophysiological (electromyography analysis) investigations of the exercising human body. Specifically, he is looking at:

- metabolic and biochemical changes (substrates, muscle buffer capacity) that occur in the human body during high-intensity exercise,
- the effects of physical training on metabolic and electromyographic functions,
- and the impact of biological sex on exercise performances.

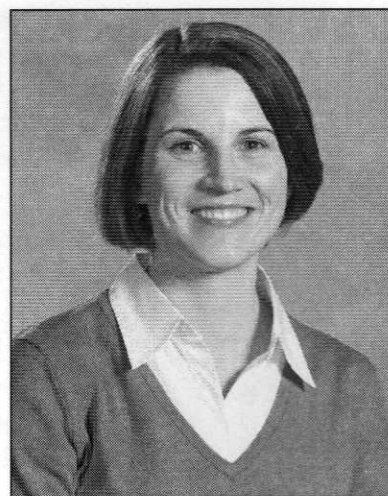
His work has significantly increased our understanding of the neuromuscular fatigue during exercise in human to optimise training methods, and develop health and wellness conditioning programs. In the future, François will use his biochemical knowledge to study muscle and arterial oxygenation trends (near-infrared spectroscopy and blood samples) during exercise in males and females.

Dr. Jennifer Copeland is an Assistant Professor in the Department of Kinesiology and Physical Education at the University of Lethbridge. Jennifer's research focus is in the areas of exercise physiology and endocrinology. Her primary objective is to understand the relationships between human aging, physical activity, and endocrine function, with emphasis on anabolic and catabolic hormones that play a role in tissue growth, repair and remodeling. She is particularly interested in the gonadal hormones, adrenal steroids, and growth hormone/insulin-like growth factor-1 as changes in these hormone axes have been implicated in the development of sarcopenia and some types of cancer. Jennifer will continue to investigate the role of body composition, physical activity, and nutritional status on age-related changes in endocrine function and this work will potentially lead to the development of evidence-based interventions to promote healthy aging. Jennifer's laboratory is one of three interconnected labs in Kinesiology that constitute the Southern Alberta Centre for Successful Aging.

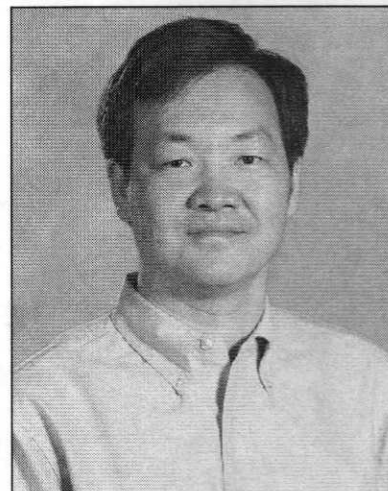
Dr. André Laroche is an Adjunct Professor in the Department of Chemistry and Biochemistry at the University of Lethbridge, and a Research Scientist in Plant Molecular Genetics with Agriculture and AgriFood Canada at the Lethbridge Research Centre. André currently is working in association with Genome Canada to look at stress biology in plants due to abiotic (e.g., low temperature) or biotic (e.g. fungi) factors. He is using functional genomic tools such as large scale sequencing; transcriptome profiling with DNA chips for screening large arrays of genes; real-time PCR to focus on specific genes, and transient and stable expression of candidate genes to assess their role and contri-

bution in a plant cell; and proteomic analyses using 2D-gel electrophoresis and protein sequencing. Within his multidisciplinary research group, he is looking to use this information to improve and accelerate the selection of germplasm toward the development of commercial cultivars. These tools provide complementary information to enable André and his team, to decipher plant responses to specific forms of stress in order to better understand plant responses and better devise strategies for plant protection and adaptation to unfavorable climatic conditions.

Dr. Oliver Lung is an Adjunct Professor with the Department of Biological Sciences. Oliver recently took a position with the Canadian Food Inspection Agency in Lethbridge. His research deals with identification and characterization of pathogenic viruses.



Dr. Jennifer Copeland



Dr. Oliver Lung

University of Manitoba

Department of Biochemistry and
Medical Genetics

Correspondent: Klaus Wrogemann



Hao Ding

Hao Ding, Canada Research Chair in Genetic Modeling, won the prestigious 2006 Young Investigator Award presented by Boehringer Ingelheim (Canada) Ltd. One award is presented each year to an outstanding researcher in the biological sciences who has been a faculty member at a Canadian university for less than five years. Hao won the award for his success in making mouse models, most notably for a gene called PDGF-C and its role in the development of medul-

loblastoma, the most common malignant brain tumor in children. Hao has created and studies numerous other models, including a knockout of Trim32, a gene responsible for both one of the limb girdle muscular dystrophies as well as one form of Bardet Biedl Syndrome.

University of Ottawa

Department of Biochemistry,
Microbiology, and Immunology

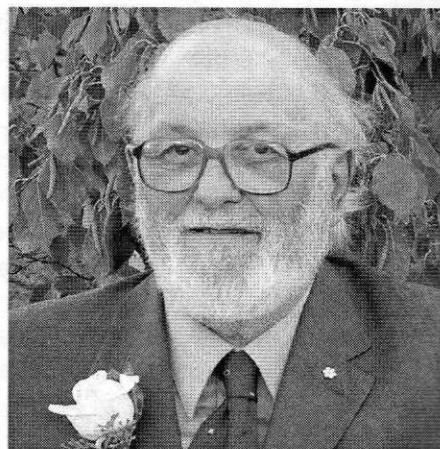
Correspondent: Zemin Zhao

The Department of Biochemistry, Microbiology, and Immunology (BMI) of the University of Ottawa (<http://www.medicine.uottawa.ca/micro-bio/bmi/eng/>) has experienced rapid growth in the last several years. Seven faculty members have been recruited since 2003 at various academic ranks. In the Fall of 2005, the state-of-the-art Biosciences complex was opened in the Faculty of Science on the downtown campus. The undergraduate biochemistry teaching labs at the second- and third-year levels are currently offered in these

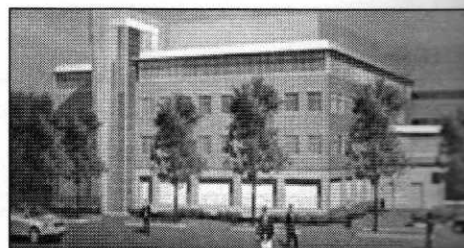
We mourn the loss of
John L. Hamerton O.C., 1929-2006

who passed away on February 9th, 2006. John was a very influential geneticist in Canada and internationally with an outstanding list of honors and awards. Details can be found at: www.umanitoba.ca/faculties/medicine/units/biochem/JohnHamertonNotice.htm

John created, and was the first head of, the Department of Human Genetics, which later merged with Biochemistry and Molecular Biology to form our current department.



new facilities. Our research facilities are also in the midst of a major expansion. Construction of the new addition to Roger Guindon Hall (Medical Science Building) is currently underway. The new addition is scheduled to reach completion in six months, and will house the Ottawa Institute of Systems Biology headed by **Dr. Daniel Figeys** who joined the Department as full professor in July 2004.



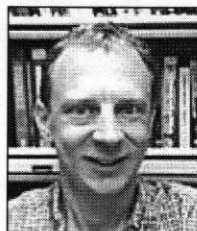
Dr. Thien-Fah Mah was recruited as Assistant Professor in January 2005. Dr. Mah completed her Ph.D. in Microbiology at the University of Toronto in 2000, and post-doctoral training at Dartmouth Medical School as a recipient of the Canadian Cystic Fibrosis Foundation post-doctoral fellowship. The research of Dr. Mah focuses on the antibiotics resistant of biofilms.



Dr. Kristin Baetz joined the Department in March 2005 as Assistant Professor, and was awarded the Tier II Canada Research Chair in Chemical and Functional Genomics. Dr. Baetz completed her Ph.D. at the University of Toronto in 2000 and post-doctoral training at the University of British Columbia as the recipient of Michael Smith Foundation and CIHR post-doctoral fellowships. Dr. Baetz' research centres on understanding chromosome imbalance using high throughput genomics in combination with biochemistry/molecular biology techniques.



Dr. Alain Stintzi was recruited as Associate Professor in July 2005. Dr. Stintzi was previously Assistant Professor at Oklahoma State University. He completed his Ph.D. in 1997 at the Louis-Pasteur University in Strasbourg and post-doctoral training at the University of California at Berkeley. Dr. Stintzi investigates mechanisms whereby human pathogens, such as the food-borne *Campylobacter jejuni*, colonize the host gastrointestinal tract.

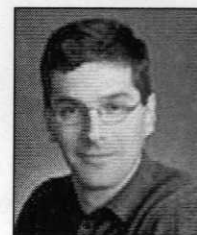


Dr. Ilona Skerjanc relocated her laboratory from the University of Western Ontario to BMI as full Professor in September 2004. Her research is focused on understanding transcription factors that control cell differentiation into car-

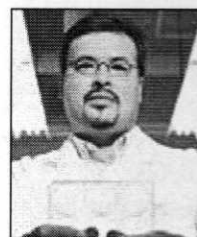


diac or skeletal muscle. Currently Dr. Skerjanc is the Director of the Biochemistry Graduate Program of BMI.

Appointed as the inaugural Director of the Ottawa Institute of Systems Biology, **Dr. Daniel Figeys** joined BMI as full Professor and the Tier I Canada Research Chair in July 2004. Dr. Figeys completed his Ph.D. in chemistry at the University of Alberta and undertook postdoctoral training in Seattle under the supervision of Dr. Ruedi Aebersold. Before taking on the OISB Directorship, Dr. Figeys was the Vice President of MDS Proteomics in Toronto. His current research centres on the development of new proteomic technologies to study post-translational modifications of proteins.



Dr. Jonathan Lee was recruited from McMaster University, as Associate Professor in September 2003. One of the research themes in Dr. Lee's lab concerns breast and ovarian cancer. Dr. Lee has discovered a new gene involved in cancer development; his work may lead to the development of new anti-cancer agents. Dr. Lee is also interested in cell cycle and the structural aspects of the actin cytoskeleton.



Dr. Martin Pelchat was appointed to BMI as Assistant Professor in July 2003, after postdoctoral training at the Université de Sherbrooke. The goal of his research is to characterize the components involved in small RNA pathogen replication. Understanding RNA replication may lead to inhibitors that can block small RNA virus replication.



Dr. Adam Rudner, our newest recruit, joined the Department in January 2007 as Assistant Professor. Dr. Rudner completed his Ph.D. in Genetics at

UC, San Francisco in 2000 as a Howard Hughes Pre-doctoral Fellow, and then had postdoctoral training at Harvard Medical School as a Jane Coffin Childs Memorial Fund Fellow. Dr. Rudner's research focuses on how cells assemble chromosomal structures and regulate chromosome dynamics. His work weds novel proteomic techniques with classical cell biological and genetic approaches.



Dr. Illimar Altosaar has just received a new 4-year CIHR grant to study mother's milk for innate immune system proteins. Understanding the fate and function of breast milk CD14 may help to protect mammary and newborn gastrointestinal mucosal epithelia. The project also extends Molecular Bio-Pharming platform development by funding the production of recombinant human proteins in transgenic rice flour. Breast milk is known to contain several immune proteins, such as CD14, that can reduce newborn gastrointestinal infections and help prevent mammary complications during lactation, such as mastitis and cracked nipples. CD14 plays an important role in the body's first line of defence by being the principal receptor for lipopolysaccharide (LPS or endotoxin), a major component of Gram-negative bacteria. By binding to LPS, CD14 activates the innate immune system to eliminate the bacteria and the subsequent infection. Recently, Dr. Altosaar's group showed that breast milk CD14 is undetectable in the stools of breast-fed newborns, however, it is not known whether CD14 is absorbed intact by the newborn intestine to provide beneficial immune protection, or if it is digested. Therefore, the aim of this research is to investigate the detailed fate and immune function of breast milk CD14 in the gastrointestinal tract of newborns. As CD14 may also reduce the incidence of bacterial infection in the mammary gland during lactation, the second aim of this project is to explore CD14 immune properties in mammary cells against mastitis infections. CD14 is absent from commercial infant formulas, and without the immune protection it provides, formula-fed newborns could be more susceptible to gastrointestinal

infection leading to intestinal injury. Therefore, the third aim of this research is to use rice plants as biofactories to produce CD14 for supplementing milk formulas and preventing gastrointestinal infections. This biotherapeutic could have a significant impact in reducing intestinal diseases of premature and newborn infants, and also in reducing the breastfeed transmission of HIV by preventing newborn intestinal injury with CD14-fortified formula and preventing mastitis with CD14-enriched creams.

University of Toronto

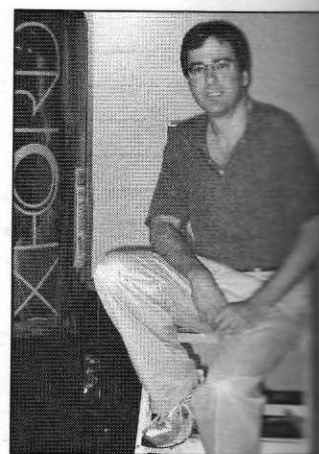
Department of Biochemistry

Correspondent: David Williams

The year 2006 witnessed a beehive of activity in the Department with the addition of two new faculty members and a search ongoing for a third, the growth of our graduate program to 130 students, and a host of scientific and social events. We maintain an up-to-date, image-rich "News and Events" page on our Departmental website at: <http://biochemistry.utoronto.ca/news>. We invite you to visit periodically and see what your friends and colleagues in Toronto are doing.

Faculty News

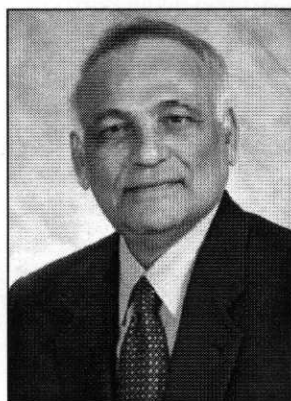
Lewis Kay's outstanding research accomplishments continued to garner recognition. He received the \$50,000 University of Toronto Dales Award in recognition of his development and application of novel NMR methods for the study of protein complexes and protein dynamics. He was also among five distin-



Lewis Kay

guished alumni of Yale University's Graduate School of Arts and Sciences who received the Wilbur Lucius Cross Medal which is the highest honour the Graduate School bestows on its alumni. To top things off, Lewis was elected to the Royal Society of Canada. His citation noted that Lewis is "internationally recognized as a leader in the development and application of nuclear magnetic resonance (NMR) spectroscopic methods for the study of protein structure and dynamics. He has pioneered novel approaches for the study of protein dynamics, developed new isotope labeling methods to facilitate structural studies of large biological complexes, and used innovative methods to examine membrane proteins. Dr. Kay is a superb mentor, a generous collaborator and a model citizen of the scientific community".

We also learned that the prestigious Priyadarajan Ray Memorial Award of the Indian Chemical Society was conferred on **Amu Sarkar** at Delhi University, India. He was recognized for his outstanding contributions in the field of Bioinorganic Chemistry and its application to human health and disease.

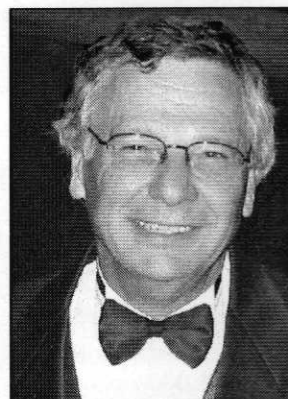


Amu Sarkar

His discovery of the treatment of Menkes disease, a fatal neurodegenerative disease of genetic origin is saving children around the world. His global health research to alleviate human suffering caused by deadly contamination of arsenic in drinking water from underground in the Bengal Delta of South Asia is bringing hopes to millions of people in the region".

Department Chair **Reinhart Reithmeier** was elected Vice-President of the CSBMCB. He also served as Chair of the Organizing Committee for the highly successful 49th Annual Meeting of the CSBMCB on "Membrane Proteins in Health and Disease" held May 31 - June 4, 2006 in Niagara-on-the-Lake, Ontario. The meeting featured 25

speakers from Canada and abroad, and attracted 200 participants, half of whom were graduate students and post-doctoral fellows. Along with Carol Cass and Joel Weiner, Reinhart was Special Editor of the *Biochemistry and Cell Biology* issue on "Membrane Proteins in Health and Disease" that featured reviews



Reinhart Reithmeier dresses up for his new role as CIHR Delegate

and papers from people who attended the meeting. Reinhart also became the CIHR Delegate for the University of Toronto starting January 2007. In this capacity he has been busy lobbying for an increase in the CIHR base budget, to ensure that the open grants competition is adequately funded, and that the peer-review system is strengthened. We've already seen the fruits of his efforts in the form of a nation-wide postcard campaign to support inclusion in the Spring Budget of a \$350 million increase in funding to the CIHR.

David Isenman was the inaugural winner of the "Excellence in Undergraduate Teaching In Life Science Award". David was recognized for the outstanding work he has done over many years as Coordinator of BCH 471, the Advanced Biochemistry Laboratory.

Amira Klip has been named the Editor-in-Chief of the *American Journal of Physiology - Endocrinology and Metabolism* for a 3-year term, the first time a Canadian has held this post.

Hue Sun Chan is co-organizing a workshop to be held in June 2007 at the Abdus Salam International Centre for Theoretical Physics (ICTP) in Trieste, Italy, entitled: Structure and Dynamics in Soft Matter and Biomolecules: From Single Molecules to Ensembles. The workshop will bring together experimentalists and theoreticians studying protein folding cooperativity, non-cooperative downhill folding, ultrafast folding, protein aggregation and amyloid formation, single-

molecule techniques, and intrinsically disordered proteins. Workshop website:
http://cdsagenda5.ictp.trieste.it/full_display.php?smr=0&ida=a06200

The Department bid a fond farewell to **Suzanne D'Alvise** who did an admirable job as our Business Officer for 21 years. Suzanne accepted the position of Business Officer in the Department of Medical Imaging. We are very pleased to welcome **Carol Justice** as our new Business Officer. Carol is no stranger to the Department since she started her career with us in 1973 as a Clerk and steadily rose up through the administrative ranks to the position of Administrative Assistant-Finance, a position she held for many years.



Carol Justice (left) with Suzanne D'Alvise

The Department also gathered to celebrate the 40 years that we have enjoyed having **Patricia Bronskill** as a colleague and friend in the Department. Pat obtained her M.Sc. degree in the Department with Prof. Jeffrey Wong and then spent 17 years as a sen-



Patricia Bronskill

ior technician in the Wong lab. She accepted the post of Senior Lecturer in 1989 where she co-coordinated our three laboratory courses, BCH370, BCH371, and BCH471. In all of the courses in which she taught, Pat was admired, respected and much loved by the students. Her knowledge, thoroughness, and compassion for students were a thing of legend. In 1999, Pat's excellence in teaching was recognized by the highest teaching honour in the Faculty of Medicine, the W.T. Aikins Award. Photos of the retirement party can be seen at:

http://biochemistry.utoronto.ca/news/news_archive/news_2006/bronskill_farewell.html

Events

100th Anniversary Celebration - our Department was founded in 1907-08, the first Biochemistry Department in Canada, with Archibald Byron Macallum serving as our first Chair from 1907-1917. In anticipation of our centenary, planning has begun for our 100th Anniversary Celebration which will culminate with a Symposium and Gala Banquet to be held May 28-30, 2008. We hope that many alumni of the Department will be able to join us for this reunion celebration.

Speaking of Archibald Macallum, Parks Canada recognized him on the anniversary of his birthday (April 7, 1858) as the "Father of Canadian Biochemistry" in their "This Week in History" series. He was designated a "National Historic Person" in 1938 with a plaque subsequently erected in his honour in 1947.

Our Annual Research Day held at the Old Mill Inn on May 30th was another great success with



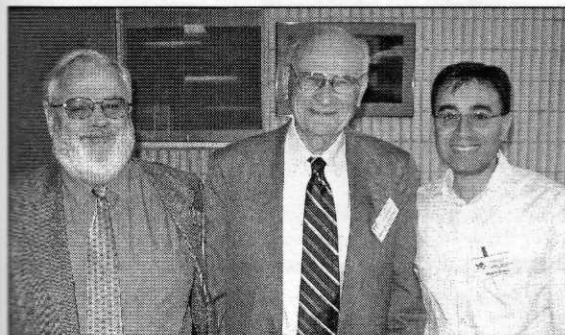
A bumper crop of biochemists gather at the 2006 Research Day

more than 200 participants. Oral presentations by faculty and students, numerous poster presentations, great food, and good spirits all combined to create a terrific experience for faculty and students alike. This is also the venue for our annual Theo Hofmann lecture which was presented by U. of T. alumnus **Mark Glover**, Department of Biochemistry, University of Alberta. Mark's lecture was entitled "BRCT domains - conserved phosphopeptide recognition modules in the DNA damage response."

For photos, go to:

http://biochemistry.utoronto.ca/news/news_archive/news_2006/research_day_06.html

The CIHR Training Program in Protein Folding: Principles and Diseases held its **Second International Symposium on Protein Folding** May 25th and May 26th. This Symposium, organized by John Glover, featured a stellar cast of speakers, as well as presentations by Program trainees. For program information and photos, go to: http://biochemistry.utoronto.ca/CIHR_folding/current_info.html



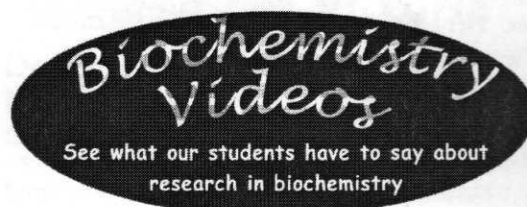
The Symposium reunited three generations of protein biochemists: Harold Scheraga (Cornell) with past grad. students: Vice Dean, Research, Peter Lewis and Walid Houry

The Department has come up with a couple of interesting ideas for graduate recruitment. For several years we have held an **Open House** in mid-January where prospective graduate students can visit and learn more about the Department and its programs. This year we decided to partner with Medical Genetics & Microbiology as an experiment to try to attract more students to Toronto. This turned out to be a very successful event,

bringing more than 120 students together for an afternoon of graduate student posters, short presentations on the respective Departments by their Chairs and Graduate Coordinators, some very enjoyable student-led tours of the campus and hospital research institutes, and lots of food! For some scenes of the event, go to:

http://biochemistry.utoronto.ca/news/open_house_07_photos.html

Another new initiative is our **Biochemistry Video Contest** where grad students submit videos on the topic of why they like being Biochemistry graduate students in Toronto. Modeled after American Idol, the videos, which were shown at our Year-End party, were critiqued by three celebrity judges and the winners were selected by popular vote. This proved to be a very entertaining event and the videos are now on the Departmental website where they can be viewed. They can be seen at: http://biochemistry.utoronto.ca/graduate_studies/biochem_student_videos.html <Biochemistry Video Contest>



Biochemistry Video Contest

Very enjoyable social events included our **Annual Ski Day** and **Annual Golf Day**, both of which are organized by graduate students. Photos can be found at

http://biochemistry.utoronto.ca/news/news_archive/news_2006/news_2006.html

Appointments

We were delighted to welcome two new Faculty members in 2006.

Simon Sharpe, a Scientist at the Research Institute of the Hospital for Sick Children, was appointed this year as Assistant Professor. Simon obtained his Ph.D. in Biochemistry from the University of Western Ontario and completed

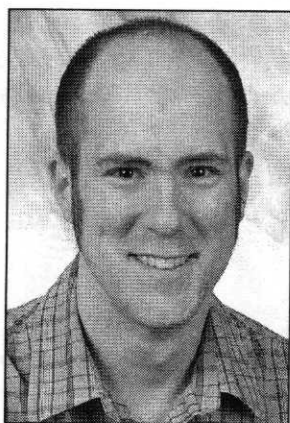
postdoctoral work with Robert Tycko at the NIH. His research focuses on the structural characterization of protein-protein and protein-lipid interactions at biological membranes, using solid state NMR methods.

This Fall, **Shana Kelley** arrived to take up a joint position between Biochemistry and Pharmacy as full Professor with tenure. Shana obtained her Ph.D. at Cal Tech and did postdoctoral work at Scripps before becoming a Professor at Boston College, a post she held for the past 6 years. Her group is dedicated to the development of biotemplated nanomaterials as well as new nanoscale sensors and organelle-specific peptidoconjugate probes for the detection and diagnosis of disease and the study of biological function.

We are also actively recruiting one additional Assistant Professor at this time.

Graduate Studies

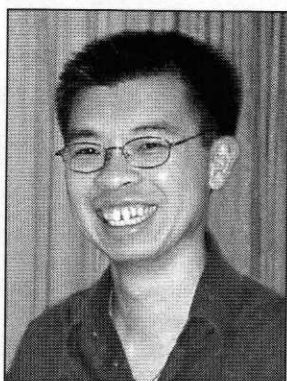
We were delighted to learn that **Jeff Lee**, a Biochemistry graduate student supervised by Lynne Howell, had been awarded the **Governor General's Gold Medal**. The Gold Medal is awarded to the student with the highest academic standing at the gradu-



Simon Sharpe



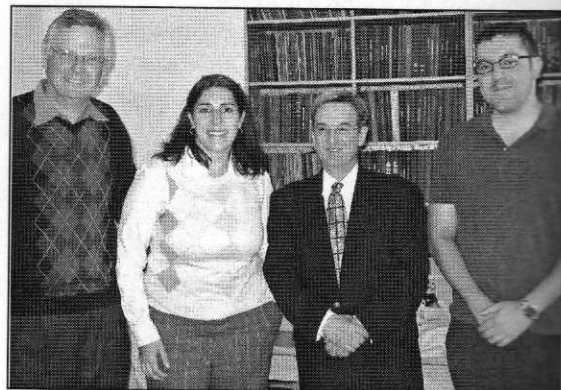
Shana Kelley



Governor General Awardee, Jeff Lee

ate level. Jeff's thesis was entitled "Structural and functional studies of 5'-methylthioadenosine/S-adenosylhomocysteine nucleosidase". Jeff published an incredible 9 papers during his Ph.D. studies and won three poster awards. Jeff is currently a post-doctoral fellow at Scripps in the Department of Immunology. Congratulations to Jeff (and Lynne)!

Our second annual **Benjamin Schachter Memorial Lecture** took place on May 16th this year. Named in honour of Benjamin Schachter, who conducted research in the Department from 1934-1939, this lectureship is organized by our graduate students who select a prominent graduate from our Department. This year's speaker was **Dr. Zayna Khayat**, from the Boston Consulting Group, who was a graduate student with Amira Klip and graduated in 2001. Dr. Khayat's lecture was entitled: "I have my grad degree... now what?!"

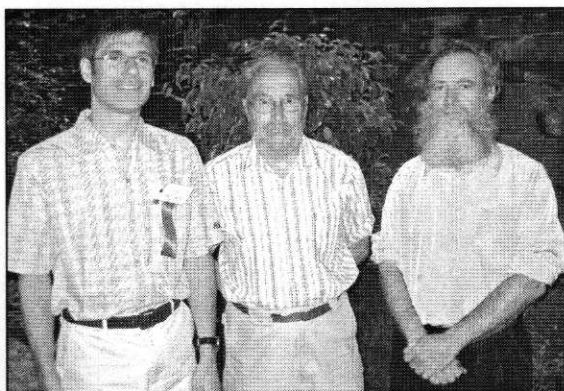


l to r, Chair, Reinhart Reithmeier; Dr. Zayna Khayat, Dr. Dan Schachter and BGSU president, Costin Antonescu

An integral part of the Department's Annual Research Day is its **graduate student poster competition**. Our guest poster judge was this year's Theo Hofmann Lecturer, **Mark Glover**, Professor, Department of Biochemistry, University of Alberta.

The following students (who receive cash awards) were chosen as poster winners:

Winners in the Ph.D. category were: **Ben Pinder** (Smibert lab): "Regulation of nos translation"; **Sean Reichheld** (Davidson lab): "Two-way inter-domain signal transduction in tetracycline repres-



Mark Glover (left) with Theo Hofmann and Ph.D. supervisor David Pulleyblank

sor"; **Wanyi Xiang** (Siu lab): "Normal formation of brain ventricles requires L1-mediated adhesion in zebrafish embryo"; and **Kassidy Huynh** (Grinstein lab): "Endosomal acidification terminates the activity of Rab5 and signals the transition to late endosomes".

Winners in the M.Sc. category were: **Jean-Philippe Julien** (Pai lab): "Escape from 2F5 neutralization by clade C HIV-1 fusion protein gp41: a structural analysis"; **Sarah Mansour** (Pomès lab): "Investigating the molecular basis for the aggregation and elastomeric properties of elastin"; and **Sian Patterson** (Reithmeier lab): "Interaction of wild type and mutant human $\text{Cl}^-/\text{HCO}_3^-$ anion exchanger 1 with molecular chaperones".

The winner in the postdoc category was: Yuri Lobsanov (Howell lab): "Arginine switch controls activity in Class I alpha-mannosidases: Structure of a fungal alpha-1,2-mannosidase in complex with-substrate analog".

Additional graduate awards:

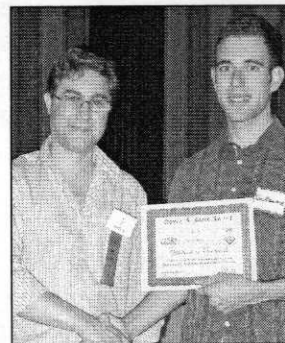
The winner of the **Beckman Paper of the Year Award for 2005** was: **Karen Rothfels** for her paper "Components of the ESCRT pathway, DFG16, and YGR122w are required for Rim101 to act as a corepressor with Nrg1 at the nega-



Karen Rothfels

tive regulatory element of the DIT1 gene of *Saccharomyces cerevisiae*." Rothfels, K., Tanny, J. C., Molnar, E., Friesen, H. and Segall, J. (2005) *EMBO J.* 23:150.

The annual **David Scott Prize** for outstanding all-round graduate student was awarded to **Guillaume Thibault** (Houry lab). Guillaume was selected on the basis of research excellence and outstanding contributions to the Department and fellow students.



Grad. Coordinator, James Rini (left) presents the Scott Prize to Guillaume Thibault

Congratulations to all winners on their achievements.

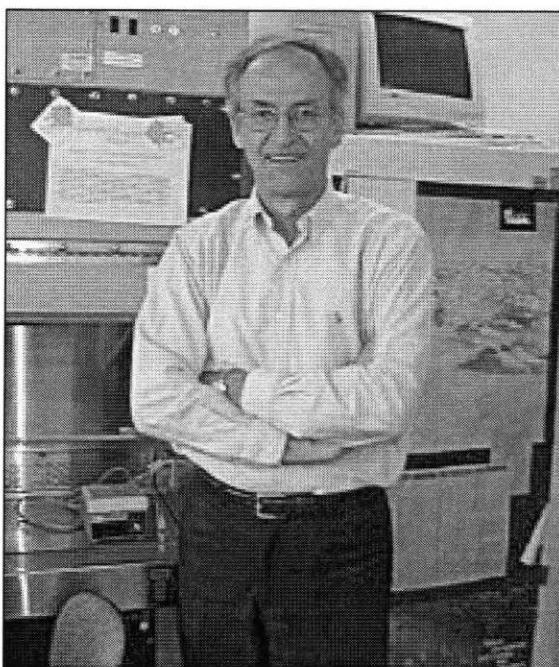
University of Victoria

Department of Biochemistry and Microbiology

Correspondent: Robert Burke

University of Victoria researcher leaves behind a strong legacy

After thirty years of devoted teaching and research, **Dr. William Kay** has retired as a Professor in the Department of Biochemistry and Microbiology. Before coming to the University of Victoria he was Director of Surgical Research and Associate Professor of Biochemistry at the University of Saskatchewan. He jokes that six years in the prairies was enough to make him look forward to leaving; but he adds that it was the opportunity to build something new that drew him to the University of Victoria. When Kay arrived, he made up a quarter of the faculty in the then Department of Bacteriology and Biochemistry. The rest comprised Jack Nichols, who was hired at the same time, Trevor Trust and Tom Buckley. Equipment and personnel were scarce, and facili-



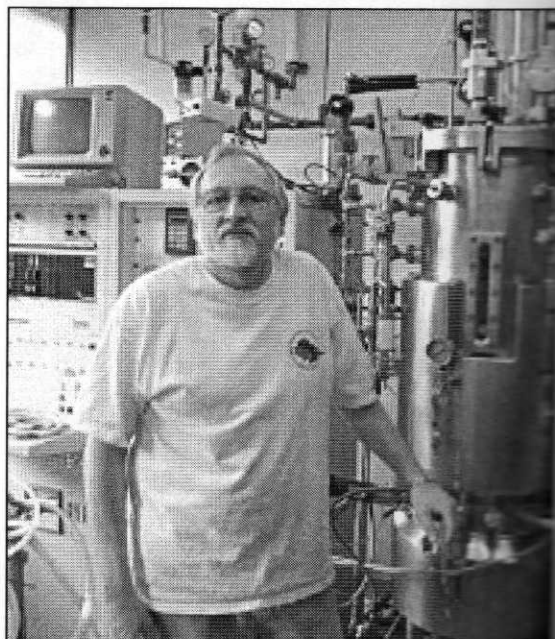
Dr. William Kay

ties extremely limited since the Department was housed in the huts. Research funding was difficult to come by because the Department was not part of a medical school, and yet a great department grew despite the odds. This he attributes in no small part to the excellent people who were here with him at the time.

Starting his own research at the University of Victoria, Kay focussed on membrane transport systems in bacteria such as *Salmonella*. At the University of Saskatchewan he had also been working on platelet research, but he didn't find much time to continue that in his new role. He did have the opportunity, however, to get into the pathogenesis of *Salmonella* and a variety of fish pathogens. Approaching the equally important task of teaching, Kay has made an impressive effort to encourage and stimulate his students. While he feels it is important to challenge them, but he also likes to make biochemistry and microbiology fun. An entertaining, and yet educational, lecture that he enjoys giving his fall classes has been the bioenergetics of Halloween. Enjoyed by all of the students, the lecture gives considerable insight into things that most people would probably never think to question. For example, the old vampire

myths probably originate from genetic defects causing iron deficiencies and sensitivity to garlic. This enthusiasm has been transmitted to countless students over the years.

In addition to a profound interest in the acquisition of knowledge, befitting a professor and researcher, Kay also has something of an entrepreneurial spirit. Working with people such as Trevor Trust, Edward Ishiguro and Santosh Misra, to name but a few, he has been involved in the creation of many companies. These have included such names as Microtek, Syngene and Stressgen. Kay was a cofounder of the Canadian Bacterial Disease Network, one of the first Centres of Excellence established in the country. Although he is now only actively involved with Microtek, his contributions to the growth of the biotech industry have been enormous. Although Dr. Kay officially left the University of Victoria in 2006, the benefit of his time in Biochemistry and Microbiology will continue. His work with aquaculture is ongoing, and he will still interact with the Department through his research at Microtek. Just as importantly, he leaves behind a legacy in the students who have benefited from the lessons he has taught them. He has impressed on them a love of knowledge that they will give to others. Already former



Albert Labossiere

students and post-docs of his at other institutions are contributing to a new generation of biochemists and microbiologists.

Head of Technical Services feels he is just getting started

Head of Technical Services in the Department of Biochemistry and Microbiology at UVic, **Albert Labossiere** has celebrated his thirtieth year in the Department. Labossiere's career started in a research lab at the University of Saskatchewan. Since moving to UVic, most of his work here has been focused on the logistics of keeping research and teaching equipment up and running, although there has been some room to participate in teaching along the way. He served as a lab instructor early on, teaching a protein chemistry section attached to Biochemistry 300. Labossiere marvels at the technical changes that have occurred since his own university days. Perhaps the biggest change relates to the scale on which biochemistry and microbiology are carried out. Advancing technology has catalyzed a move from large scale, bucket chemistry, requiring immense volumes of sample, to the development of analytical techniques that meet the same goal with a fraction of a drop. These processes can now be carried out in minutes instead of months. This speed and miniaturization have been made possible by the development of computers, which has changed the nature of technical services. It used to be that with a knowledge of basic electronics and physics, scientists could essentially fly by the seat of their pants. However, the increased complexity of the equipment has created a much greater need for the use of service manuals and specialized technical support. On the personnel level, this has resulted in the need for fewer people, with more sophisticated training, than in his early days. Labossiere has played an important role in the layout of Department space in the Petch Building. At the time Biochemistry and Microbiology planned to move into the building twenty years ago, he was drilled by the architect, George Redzich, on the nature of the job ahead of him. With responsibility for sixty-five rooms, Redzich stressed the importance of maintaining a balance between form and function. As

a result, Labossiere started to see the rooms as part of an organism, and the necessity for them to be properly laid out in order to function effectively. Only now does he feel that he has arrived where Redzich wanted him to be.

Although Labossiere has been in the Department for thirty years, it scarcely seems that long to him. The years have been full of challenges, and solutions that he can be proud of. Whether he is working on space planning for the new Science Building, a new layout plan for Biochemistry and Microbiology, or designing the security procedures for a level three containment lab, he approaches the task with great enthusiasm. Clearly his contributions to the form and function of the Department have made the faculty, staff and students all the richer for his presence.

The changing faces of our department

This year we have welcomed three new faculty members to the Department of Biochemistry and Microbiology. **Marty Boulanger** was granted a Ph.D. from UBC in 2002, did post-doctoral studies at Stanford until 2004. He then spent a couple of years as a Senior Research Scientist at Affinium Pharmaceuticals in Structural Biology and Protein Biochemistry before coming to Victoria. Marty is interested in the structural basis of molecular recognition that mediates host pathogen interactions. **Caroline Cameron** graduated from our Department with a Ph.D. in 1996 and went on to post-doctoral studies and then a Research Faculty appointment at the University of Washington. Caroline has a thriving research program in bacterial pathogenesis, specifically of *Treponema pallidum*; the causative agent of syphilis. Caroline was appointed at the University of Victoria as an Associate Professor and a CRC Chair. **Christoph Borchers** completed his doctoral studies in protein chemistry at the University of Konstanz in 1992. At the University of North Carolina, Chapel Hill, Christoph was the Director of the UNC Proteomics Core Facility. He brings that experience to his new role as Director of the University of Victoria-Genome BC Proteomics Facility. Christoph is recognized internationally for his work on the application of mass spectrometry, pro-

teomics, photoaffinity labelling and molecular modeling to determine structure-function relationships in proteins.

These are exciting changes for our Department and we are fortunate to have these accomplished young scientists contribute to our programs

University of Waterloo

Department of Biology

Correspondent: Bernie Duncker

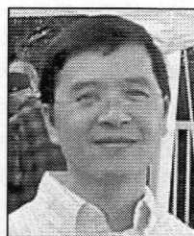
2006 was a year of continued expansion for the Biology Department at the University of Waterloo.

New faculty hires included **Dr. Susan Lolle**, formerly at Purdue University, whose groundbreaking work on a potential new form of genetic inheritance in *Arabidopsis* published in *Nature*, has sparked a lot of scientific debate recently; **Dr. Simon Chuong**, an expert in the molecular and biochemical mechanisms underlying photosynthesis, who recently completed his post-doctoral training at Washington State University; and **Dr. Heidi Engelhardt**, formerly at Brandon University, a reproductive physiologist studying the immunological relationship between mother and genetically 'foreign' embryo.

Along with these new arrivals, came the departure of one of our most respected colleagues, **Dr. Carol Peterson**, who recently retired after an impressive career as one of the world's foremost experts in plant root structure and function. **Dr.**



Dr. Susan Lolle



Dr. Simon Chuong

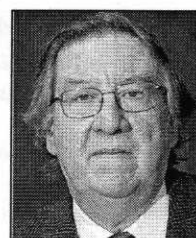


Dr. Heidi Engelhardt

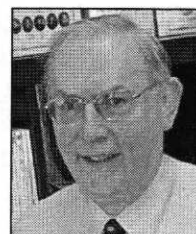


Dr. Carol Peterson

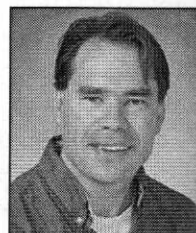
George Dixon, a toxicologist in our Department, and currently Dean of Science, has accepted an appointment as Vice President of University Research. Microbiologist, and current Director of the Science & Business program, **Dr. Owen Ward**, added to his already impressive resume, by winning the University of Waterloo Distinguished Teacher Award, while Biology graduate student Julie Gauley won the Distinguished Teaching by a Student Award. Finally, **Dr. David Spafford** was the recipient of a large CFI grant for "Development of New Biopharmaceuticals and Biomarkers for stress detection" and is one of the investigators in the newly established University of Waterloo Centre for Theoretical Neuroscience.



Dr. George Dixon



Dr. Owen Ward



Dr. David Spafford

University of Waterloo

Department of Chemistry

Correspondent: Guy Guillemette

Our newest biochemistry faculty member, **Thorsten Dieckmann**, is investigating the structure and function of ribonucleic acids using a variety of biophysical and biochemical methods. This includes structure determination by NMR spectroscopy as well as functional studies using kinetics and calorimetry. The lab focuses on catalytic RNA molecules and RNAs that are of interest as potential drug targets for the treatment of viral infections.

Gary Dmitrienko is exploring the synthesis and chemistry of bioactive natural products with a view to understanding their mode-of-action as anticancer agents (in collaboration with Dr. B.

Hasinoff in the Faculty of Pharmacy at the University of Manitoba), and to optimizing their potency. In addition, projects are under way aimed at the discovery of specific enzyme inhibitors as new antibacterial and antifungal agents with novel targets. A grant recently awarded by the Pharmaceutical Sciences committee of CIHR is funding efforts to discover broad spectrum beta-lactamase inhibitors to combat antibiotic resistance to beta-lactam antibiotics.

Guy Guillemette is investigating the regulation and mechanism of mammalian nitric oxide synthase enzymes as well as fungal and bacterial class II aldolases. Members of the lab characterize native and selectively mutated recombinant forms of the enzymes using a variety of biophysical techniques.

John Honek continues to pursue research in the area of carbon-sulfur biochemistry, metalloenzymes and drug design. He is currently an Associate Editor for *Biochemistry and Cell Biology* (NRC) and Regional Editor for *Letters in Drug Design and Discovery* (Bentham Press). He is also on the editorial board for the journals *Medicinal Chemistry* (Bentham Press), *BioMed Central-Biochemistry*, and *Current Medicinal Chemistry* (Bentham Press). He and Dr. T. Leung (Chemistry, University of Waterloo) were recently awarded an NSERC Nano-IP grant for the investigation of peptide-nanomaterial interactions. He is an organizer for the Enzyme Structure symposium at the Canadian Society for Chemistry annual meeting in 2007 (Winnipeg, Manitoba).

Research in **Elizabeth Meiering's** group is focused on protein folding, aggregation and engineering. She is on the editorial board for *Protein Engineering, Design and Selection*, and is on the scientific advisory board for the ALS Society of Canada. Research is funded by NSERC, CIHR, ALS Society, and MDC. Current projects include folding and aggregation of ALS-associated mutant superoxide dismutase, and the design, folding and function of beta-trefoil and beta/alpha proteins. A multidisciplinary approach is employed, including a range of biophysical techniques (including NMR, optical spectroscopies, calorimetry, light scattering)

and molecular biological techniques to overexpress and rationally modify proteins of medical and biological significance.

Michael Palmer's research focuses on protein-lipid interactions in biological membranes. There are three areas of research performed in the lab: structure and function of bacterial pore-forming toxins; development of fluorescence methods to study protein-protein and protein-membrane interaction; and lipid-mediated regulation of G-protein coupled receptors. These projects involve a range of methods including fluorescence spectroscopy, protein chemistry, molecular biology, and cell culture. The results of this work are of both theoretical and medical interest.

Scott Taylor's research interests cover a wide variety of topics such as catalytic antibodies, enzyme mechanisms, drug design and evaluation, pro-drug design and activation, polymer supported synthesis of small molecules, electrophilic fluorination and general synthetic organic chemistry.



Some of the biochemistry researchers within the Department of Chemistry at the University of Waterloo

University of Western Ontario

Department of Biochemistry

Correspondent: Eric Ball

In terms of physical location, 2006 marked the completion of renovations to the Medical Sciences Building after five years and four phases. The new quarters represent a vast improvement and it is a relief to escape the many trials of construction. Now, if only the temperature regulation can be fixed.

The Department was unable to match the new digs with a new Chair, however; and the search goes on. **Dr. Chris Brandl** stepped down in September after a year doing an excellent job as Acting Chair. In the meantime, **Dr. Ted Lo** was persuaded to return to the helm on an interim basis.

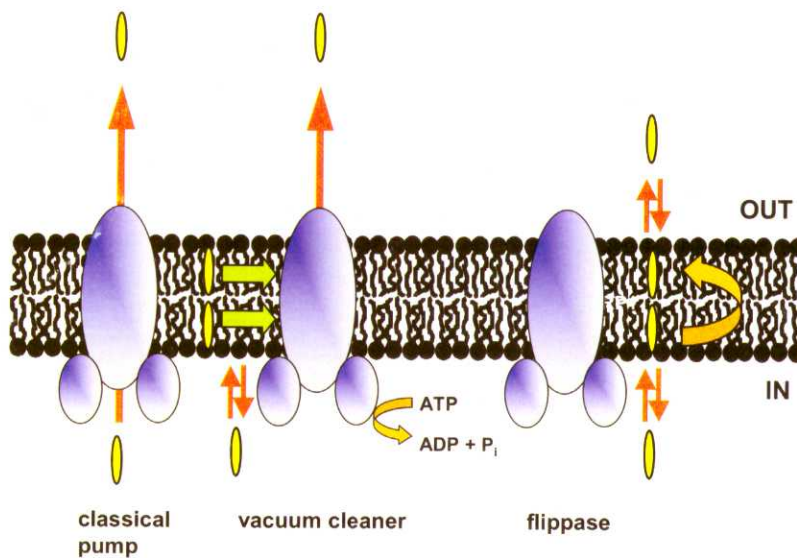
Two long-time Department members retired in the past year — **Dr. Robert Cook** and **Ted Jarvis**. Both had been members of the department over 35 years; Ted as Technical Officer and Bob as resident Enzymologist. We will miss Ted's stories about trucks and other subjects, but will have now more time to work. Bob's experience and expertise in enzymology, and his inimitable teaching style, will be missed. Another former Department Chair, **Dr. Bill Sanwal**, now officially retired some 10 years, is still found in his office every day (except when he's travelling the world), showing us one way to "retire".

Unfortunately two former members of the Department passed away during the year. **Dr. Ralph Henderson**, former chief of the University Hospital Clinical Biochemistry Division died on June 29, 2006. **Dr. Milt Haines**, former Chair of the Division of Clinical Biochemistry and Chief of Biochemistry for the London Health Sciences Centre passed away on December 22, 2006. A fund in the name of Milt Haines has been set up in his memory.

A number of faculty received awards over the past year: **Dr. James Choy**, **Dr. David Edgell** and **Dr. Mellissa Mann** received Early Researcher Awards.

Dr. Shawn Li was named a Canada Research Chair in Functional Genomics and Cellular Proteomics. **Dr. Robert Hegele** received the Genetics Society of Canada's William F. Grant and Peter B. Moens Award of Excellence. **Dr. James Choy** received a CIHR New Investigator Award for research on naturally disordered proteins using NMR spectroscopy.

The graduate and undergraduate programs of the Department have reached new heights as the "double cohort" of students passes through. New undergraduate initiatives in joint programs in Genetics and Biochemistry, Biochemistry and Cell Biology, and Biochemistry of Infection and Immunity have been added and are proving popular. With the prospect of a new Chair and new faculty on the horizon, the Department is looking forward to the coming year.



Guelph, ON N1G 2W1