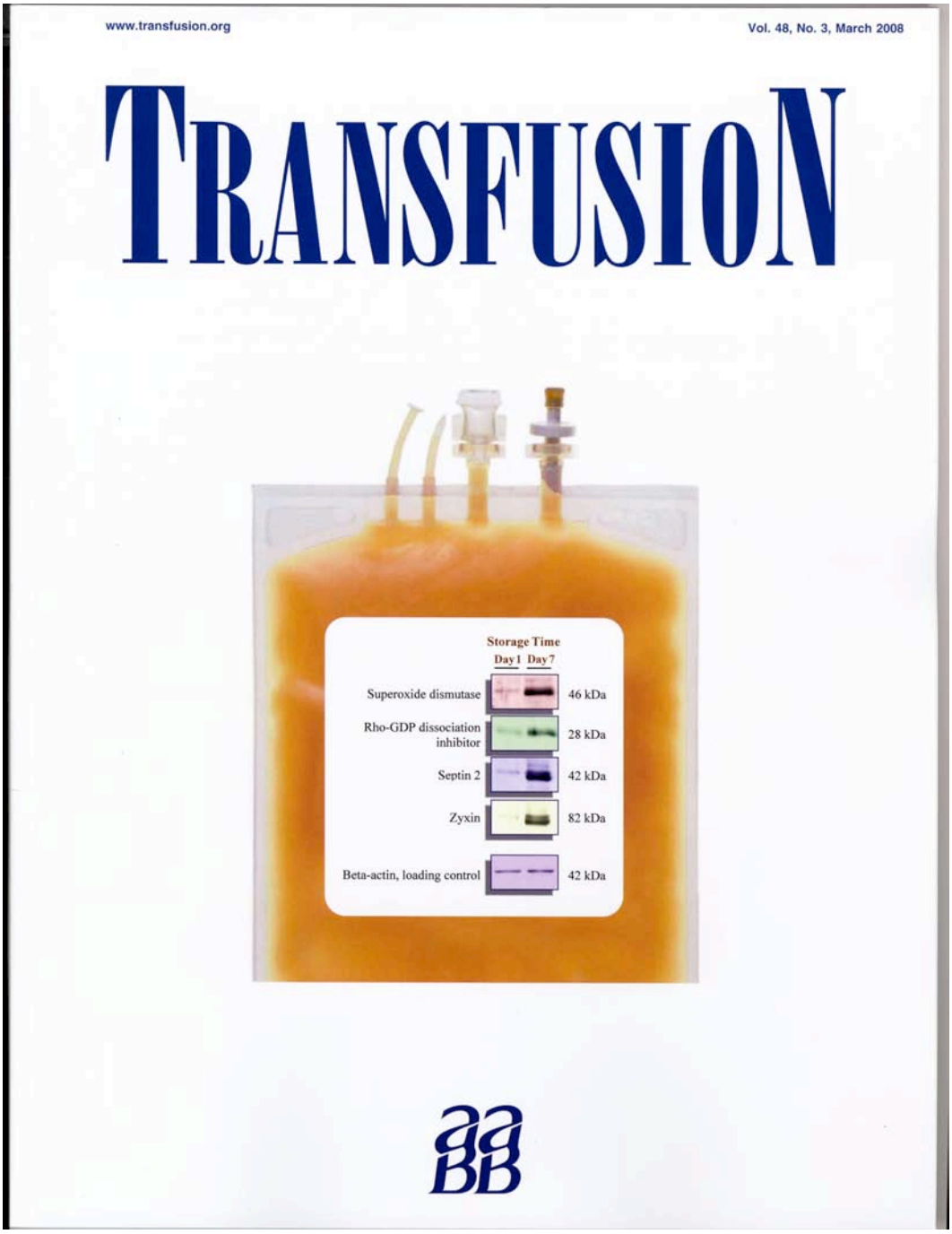
The Biomedical Research Centre
Annual Report 2007/2008



UBC Vancouver Coastal Health
Promoting wellness. Ensuring care

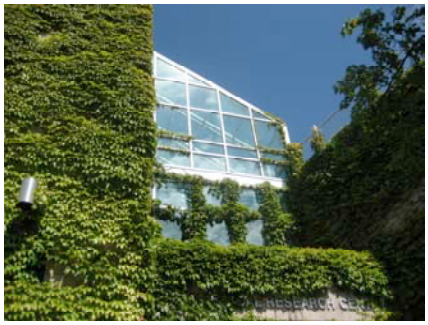
Front Cover

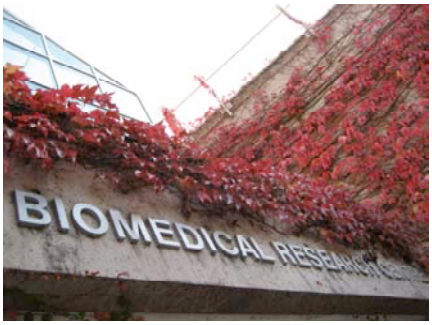
Shows a reproduction of the front cover of an issue of the journal *Transfusion* that featured an article in that issue that describes the use of proteomic techniques to study protein changes that occur during platelet storage, work done in a collaboration between the groups of Drs Dana Devine and Juergen Kast at the BRC. The importance of applying proteomics techniques to the field of transfusion and its potential to influence transfusion medical practice was discussed in an Editorial in the same issue.

Back Cover

Shows a reproduction of the front cover of the *Journal of Mass Spectrometry*. This shows a flow diagram of a chemical biology approach that involves chemical cross-linking of complexes of proteins in live cells to study their physiological interactions and was pioneered by Dr Kast at the BRC. Dr Kast was invited to review the current state of this field. The tutorial featured in this issue also describes the technique and its significance for the study of protein-protein interactions in cells.

TABLE OF CONTENTS





Mission of The Biomedical Research Centre

Our Vision

To provide British Columbia with an internationally recognized Centre for research in immunology and hemopoiesis and related fields that integrates:

- interactive and interdisciplinary research into the cells and molecular mechanisms that protect the body from disease, and repair and regenerate damaged tissues

- technological innovation and its translation into the discovery of new treatments for diseases such as arthritis, asthma, diabetes, multiple sclerosis and cancer

- education and training of young scientists by fostering creativity and critical thinking and by introducing them to state-of-the-art technology early in their careers

Aim #1: Research Program

The BRC will continue to maintain an internationally competitive program that focuses on the discovery and analysis of the proteins that regulate inflammation and specific immune responses and the repair and regeneration of damaged tissue. These proteins include the cytokines and adhesion molecules that orchestrate the growth, function and movement of blood cells, the antibodies that protect against infections, and the receptors, intracellular enzymes, adaptors and transcription factors that ultimately regulate genes. These cells include the stem cells that give rise to the blood and the immune system and cells that give rise to muscle, fat and cartilage. Using innovative technologies and interdisciplinary approaches, BRC researchers are increasing our understanding of these processes. In collaboration with industry they are working towards applying this knowledge to the treatment of common diseases such as arthritis, asthma, diabetes, cancer, multiple sclerosis, Alzheimer's disease and stroke.

Aim #2: Education and Training in Immunology and Tissue Regeneration

The Biomedical Research Centre provides a uniquely interactive, interdisciplinary environment for education and training in biomedical research. BRC faculty have been instrumental in establishing graduate courses in immunology and signal transduction. However their most important educational role lies not in formal teaching, but in introducing students to the ideas and techniques at the forefront of biological science. Undergraduate and graduate students learn to use state-of-the-art techniques, while experiencing the excitement of working along-side students and scientists from around the world. The BRC provides a unique opportunity for undergraduate students to experience first-hand the challenges and rewards of a career in research. The Biomedical Research Centre forms the hub of the Vancouver immunology community through collaborative research projects, graduate and undergraduate training programs in immunology, and by providing access to state-of-the-art technologies like fluorescence activated cell sorting, the generation of genetically modified mice and proteomics.

Aim #3: A Catalyst for Economic Growth

By providing state-of-the-art training in key disciplines and by fostering the creativity that is the basis of a knowledge-based economy, The Biomedical Research Centre has created an educational environment where cutting-edge science flourishes in partnership with industry. Entrepreneurship by The Biomedical Research Centre faculty has led to the founding of four new BC companies that have provided valuable career opportunities for young British Columbians. BRC faculty are actively participating in the Centre for Drug Research and Development. BRC graduates are in high demand in the biotechnology industry in Vancouver and across the globe. BRC faculty are valued by the financial community as a source of expert advice and commercially relevant research.

Aim #4: New Treatments for Arthritis, Asthma, Heart Disease, Cancer, Muscular Dystrophy and the promise of Regenerative Medicine

Research at The Biomedical Research Centre is expanding our knowledge of how the immune system and adult stem cell function. This will open the way for new approaches to the treatment of the many diseases that are caused by malfunction of the immune system, such as arthritis, asthma, diabetes and multiple sclerosis. It will also provide new treatments for diseases where the immune system can be harnessed for diagnosis or treatment such as cancer. A better understanding of adult stem cells is essential for progress towards regenerating tissues damaged by disease, for example, cartilage in the joints damaged by arthritis. Research at The Biomedical Research Centre is supported by the Canadian Institutes of Health Research and other government agencies such as NSERC and the Networks of Centres of Excellence (NCE) and by charities like the National Cancer Institute of Canada, The Arthritis Society and the Heart and Stroke Foundation.

The Biomedical Research Centre is an interdisciplinary research centre governed by a Steering Committee of Deans from the Faculties of Medicine, Science, Dentistry, Pharmaceutical Sciences and Graduate Studies together with the VP Research. Currently, it houses nine faculty members affiliated the Departments of Medicine, Medical Genetics, Pathology and Laboratory Medicine, Chemistry, Zoology and Microbiology and Immunology in the Faculties of Medicine and of Science. All work closely together in open-design, shared laboratory space, co-training their students, postdoctoral fellows and technicians. Their research focuses on the processes through which the body defends itself against microbes and cancer, and repairs and regenerates damaged tissues. The goal is to generate new knowledge about how the immune system and adult stem cells accomplish these vital tasks, and how disturbances in these processes result in disease. The aim is to translate this new knowledge into innovative treatments for chronic diseases like arthritis, Alzheimer's disease, asthma, diabetes, and cancer.

BRC researchers have adapted and extended many of the key technologies of modern biology including mass-spectrometry and proteomics, molecular genetics, the generation of recombinant monoclonal antibodies, and multi-parameter fluorescence activated cell sorting. The BRC is the home of the UBC Multi-user Flow Cytometry (FACS) Facility directed by Dr Fabio Rossi and the UBC Transgenic Facility directed by Dr Wilfred Jefferies and also serves as the focus of proteomics at UBC, housing the Collaborative Facility for Proteomics, directed by Dr Juergen Kast and the Global Proteome Machine Database, created by Dr Ronald Beavis. This diversity of approaches, coupled with the uniquely interactive environment and focus on the common goal of a better understanding of defense, repair and regeneration, generates powerful synergies. These have led to a series of novel discoveries, and a track record of spin-off companies and the creation of high-quality jobs for British Columbians.

The guiding principle of the BRC is that science flourishes when researchers from different disciplines share common research interests and work alongside each other, exchanging ideas and expertise. BRC researchers are focused on understanding how cells of the blood and immune system protect us from infections and cancer, but can also cause chronic inflammatory diseases like arthritis, asthma and diabetes. Their research also addresses fundamental questions about how stem cells function and can ultimately be used to regenerate damaged tissues.

The BRC provides an environment that not only fosters the informal interactions between researchers that often lead to new ideas, but also provides access to the technologies and expertise needed to test them. The BRC researchers pioneered the chemical synthesis of proteins, the application of the Cre-lox technology to the generation of mice in which the function of a gene was deleted in a single tissue, and a novel technology for the generation of monoclonal antibodies. These have led to the design of antagonists useful in treating arthritis or HIV infection and to spin-off companies that provide British Columbians with high-quality jobs.

The BRC provides an internationally competitive environment for training young scientists to think boldly and work rigorously. Many former BRC students and post-doctoral trainees now lead their own research groups in British Columbia and at Universities and companies around the world.

In its educational role, the BRC emphasizes hands-on experience at the laboratory bench, and one-on-one mentoring of under-graduate and graduate students by faculty and senior trainees. This has prepared students for the realities of a career in research. Students learn about selling their ideas and competing for funding and international recognition. They are also exposed to the challenges of translating research findings into commercially viable products or services.

Highlights of 2007-2008

A major highlight of 07-08 was the success recruitment back to Canada and to UBC - of an outstanding young investigator, Dr. Colby Zaph, who will establish here his research program in immunology of the got, bringing to the BRC and the UBC community increased strength in vaccine development and autoimmune diseases like colitis. We also welcomed to the BRC, Dr Michael Underhill of the Department of Cellular and Physiological Sciences, whose expertise in cartilage formation complements existing BRC interests in tissue regeneration and strengthens our research program in arthritis. This brings the total of BRC faculty members to nine.

The theme of BRC research is Immunology, inflammation, repair, and tissue regeneration. These are fundamental to the understanding of a wide range of diseases- from arthritis, cancer, diabetes, and asthma, to infectious diseases. There are strong conceptual and technical links between the system that protects against invaders and that which repairs and regenerates the damage. The best understood adult stem cell is the one that gives rise continuously throughout life to the differentiated cells of the blood and immune system. Antibodies, together with the sophisticated fluorescent activated cell sorting, have been a major tool in understanding these cells, and their application to other tissue has led to identification of stem cells in cancers and other tissues. Indeed at the BRC Dr Rossi has extended these techniques top the analysis of cells that give rise to muscle and fat.

The research program of the BRC continued to flourish. Despite the chilly funding climate, the seven BRC faculty won a total of 7 CIHR grants and an NSERC grant in 07-08.

RESEARCH

A proteome is defined as being the proteins expressed by an organism at a particular point in time. The study of the state and the temporal evolution of the proteome is now commonly referred to as proteomics. Proteomics is based on the idea that it is possible to effectively identify and track large sets of proteins in time or space. This idea has moved from the realm of pure speculation to an achievable reality by the availability of high-speed, low cost methods of identifying and quantifying proteins based on chromatography and mass spectrometry as well as complementary techniques for the analytical display of messenger RNA populations using cDNA-array technology.

Proteomics has become an important application of mass spectrometry to biological research and it is the fundamental enabling technology that has allowed proteomics to develop rapidly in the last five years. These protein identifications are based on the comparison of an experimentally determined list of masses and a database of protein (or translated nucleotide) sequences. These masses can be a list of parent ion masses or a list of fragment ion masses derived from a parent ion by tandem mass spectrometry.

The question of evaluating the validity of proteomics results is still a matter for active research and it has not been solved satisfactorily. A number of statistical approaches have been proposed. These studies have looked at the problem from different viewpoints, but they have not provided conclusions that can be directly applied to the common problem of estimating the confidence of experimental protein identifications in a simple and interpretable manner. The current software tools and scoring algorithms leave interpreting the results up to the user. Many practitioners have developed their own, pseudo-statistical tests for validating results based on the comparison of results from different scoring algorithms. A consensus similar to that used for evaluating sequence similarity scores must be reached for protein identification to become a truly mature technique.

Proteomics Data Repositories

A significant new strategy for understanding the results of proteomics experiments that will be the immediate focus of research is to collect a large number of peptide mass spectra obtained from proteomics experiments and store them in a repository. This research will be based on the informatics that have resulted from open source projects that have been generated by us under the generic name "The Global Proteome Machine". When a new mass spectrum-to-peptide sequence correlation is postulated, the repository could be queried to return a list of the best previously observed mass spectra that have been associated with that sequence. In a comparison of the existing exemplar peptide ion fragmentation patterns with the newly observed pattern, the repository would provide some of the same functions as a library of spectra obtained from synthetic peptides, with the proviso that the sequence annotation would be based on spectrum-to-proteome matching, rather than on known peptide analytes. This sort of repository structure allows the system to remain relevant as new instrumentation becomes available.

It also has the potential to provide additional confidence to particular assignments by having many redundant measurements of the same peptide sequence's fragmentation pattern under a variety of different experimental conditions, e.g., different parent ion charge states, fragment ion signal-to-noise ratios or mass spectrometer configurations.

Deeper Understanding of Proteomics
The repository may be used to compare the patterns of peptides that have been observed for a particular protein sequence (often referred to as the observed "coverage map" of a sequence). This pattern of observed peptide ions is naturally a property of the protein sequence and the physical properties of the peptides. It is also a function of the analytical sample workup protocols, the mass spectrometer's ion source and the fragmentation conditions for the peptides. This combination of characteristics makes it difficult to predict a priori which of the theoretical peptides for a protein sequence will actually be observed. However, by comparing an observed peptide coverage map with the best previously observed coverage maps, it should be possible to determine whether the observed pattern is consistent with previous results. This type of comparison becomes particularly important when only one or two peptides from a particular protein are observed, where knowing that these few peptides consistently produce the strongest signals would add considerable confidence to their assignment.

Merging protein, RNA and DNA information
To solve real biological problems, information about only proteins is often not enough: messenger RNA and genomic DNA information are also required. As practiced in most laboratories today, it is surprisingly difficult to tie together protein and mRNA concentration data. It is also often difficult to determine with any certainty which set of genes was responsible for a particular expression pattern. One of the goals of the laboratory is to provide a solid framework for transparently moving from proteomics data to mRNA and genomic information. This type of analysis is crucial to any understanding of how biological systems function.

Key Papers
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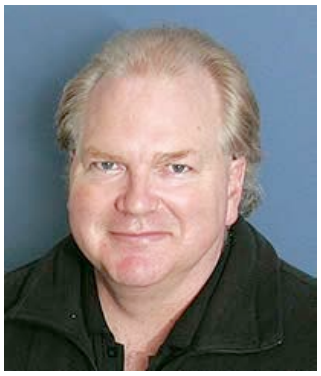
Craig R, Cortens, J and Beavis RC. The use of proteotypic peptide profiling in a practical system for protein identification. Rapid Comm. **Mass Spectrom**. 19:1844-1850 (2005)

Craig R, Cortens J and Beavis RC. An Open Source System for Analyzing, Validating and Storing Protein Identification Data, **J. Proteome Res**., 3:1234-42 (2004)

Craig R and Beavis, RC. TANDEM: matching proteins with mass spectra, **Bioinformatics**. 20(9):1466-7 (2004)

Craig R and Beavis RC. A Method for Reducing the Time Required to Match Protein Sequences with Tandem Mass Spectra. **Rapid Commun. Mass Spectrom.** 17: 2310-2316 (2003)



My lab has focused on three cellular processes.

First, we are interested in how machinery break down foreign pathogens by the cellular degradation and how they are then recognized by the host immune response. We have contributed to characterizing the function of the transporter associated with antigen processing (TAP), which transports peptides into the ER where they assemble with their receptors, the MHC Class I molecules. We have recently discovered a new intracellular compartment associated with antigen presentation by dendritic cells that is involved with crosspriming. In the future, we will define the peptide motifs that are effectively transported into the ER by the TAP molecules. We hope to test the hypothesis suggesting that protease components are directly linked to the peptide transport mechanism and have established new transgenic mouse models in order to study antigen processing and HIV pathogenesis.

Second, we carry out research on Adenovirus (Ad), which processes virulence factors that aid the virus to circumvent the host immune response. In our work on Adenovirus, we have concentrated on characterizing a viral protein E3/6.7K that acts to prevent apoptosis in host cells and appears to disregulate calcium channels in lymphocytes.

The *third* area of my research concerns a recently discovered method by which mammalian cells acquire iron. We have demonstrated that a cell surface protein belonging to the transferrin family of molecules, called melanotransferrin or p97, is able to directly bind and transport iron into cells. We have also found that this molecule exists as two distinct forms in humans: one is GPI-linked to the cell surface, and the other is a soluble form. In addition, p97 is uniquely expressed in human brain endothelium, suggesting that it may transport iron across the Blood Brain Barrier (BBB).
Furthermore, p97 is expressed on reactive microglia cells uniquely associated with deposits in brains of patients with Alzheimer's Disease. We have found soluble p97 to be present in elevated concentrations in AD serum and may be a biochemical marker of disease progression and recovery. In the future, we plan to examine the role of p97 in BBB transcytosis. Along with this, we are investigating the ability of other peptides to cross the BBB.

Key Papers

Lou Y, Basha G, Seipp RP, Cai B, Chen SS, Moise AR, Jeffries AP, Gopaul RS, Vitalis TZ, Jefferies WA. Combining the antigen processing components TAP and Tapasin elicits enhanced tumor-free survival. **Clinical Cancer Research**. 2008 Mar 1;14(5):1494-501.

Zhang QJ, Seipp RP, Chen SS, Vitalis TZ, Li XL, Choi KB, Jeffries A, Jefferies WA. TAP expression reduces IL-10 expressing tumor infiltrating lymphocytes and restores immunosurveillance against melanoma. **International Journal of Cancer**. 2007 May 1;120(9):1935-41.

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Dickstein DL, Biron KE, Ujiie M, Pfeifer CG, Jeffries AR, Jefferies WA. Abeta peptide immunization restores blood-brain barrier integrity in Alzheimer disease. **FASEB J**. 20(3):426-33 (2006)

Kotturi MF, Hunt SV, Jefferies WA. Roles of CRAC and Ca(V)-like channels in T cells: more than one gatekeeper? **Trends Pharmacol Sci**.27(7):360-7 (2006)

Lou Y, Vitalis TZ, Basha G, Cai B, Chen SS, Choi KB, Jeffries AP, Elliott WM, Atkins D, Seliger B, Jefferies WA. Restoration of the expression of transporters associated with antigen processing in lung carcinoma increases tumor-specific immune responses and survival. **Cancer Res**. 65:7926-33 (2005)

Setiadi AF, David MD, Chen SS, Hiscott J, Jefferies WA. Identification of mechanisms underlying transporter associated with antigen processing deficiency in metastatic murine carcinomas. **Cancer Res**. 65:7485-92 (2005)

Mass spectrometry - invented more than a century ago by Sir Joseph John Thomson (1906 Nobel prize in Physics) - has traditionally been used to study the composition of atoms and small molecules. The introduction of the soft ionization techniques electrospray and laser desorption (2002 Nobel prices in Chemistry awarded to John B. Fenn and Koichi Tanaka) in the late 1980's enabled the direct analysis of biological macromolecules such as DNA, RNA, and particularly proteins to determine their mass and monomer composition. Advances in instrumentation, DNA sequencing, and computer technology made possible the analysis of increasingly complex mixtures, and ultimately established mass spectrometry as a key analytical technique in proteomics - the study of the protein complement of an organism's genome expressed at a given time and condition. Mass spectrometry-based applications in proteomics can include high-throughput sequencing of peptides to infer the proteins in a proteome, differential incorporation of stable isotopes for quantitative comparisons between multiple states to gain insight into proteome dynamics, and targeted mass spectrometric experiments to trace individual peptides that carry protein-specific information with high specificity and sensitivity. Owing to its diversity, mass spectrometry has firmly established itself as the ultimate discovery and validation tool in proteomics.

It is now widely accepted that proteins are involved in almost all intra- and extra-cellular processes, and abnormal protein function has been shown to negatively affect human health. While some illnesses are caused by single gene mutations, most ailments are multi-factorial, hence involve many proteins. It is therefore not surprising that determining the entire protein complement of an organism's genome is considered a promising new approach for diagnosis and treatment. Indeed, it is believed that defining such proteomes for healthy cells and tissues will help identify changes that are characteristic for a particular disease, which in turn can be used for diagnostic purposes. Detected proteome alterations could also guide additional biochemical analyses to unravel the mechanisms that cause the transition from the healthy to the disease state. Likewise, the proteome can be utilized to monitor the efficacy of possible treatments, with detailed knowledge on the mechanisms providing much needed guidance.

There are four interdependent protein features that could be the root cause of any disease. Changes in protein abundance, localization, state of post-translational processing, or functional interactions with other molecules can each alter the complex interplay of proteins within and between cells in the human body that maintain human health. Our research focuses on the development and application of novel techniques to identify such changes. Recent highlights of our work include an increased depth of proteome coverage to up to 2000 distinct proteins, as well as new strategies for the comprehensive detection of post-translational modifications and the analysis of protein-protein interactions as they occur in living cells, both of which we have pioneered.

These optimized methods are being employed in current projects that involve proteome changes during storage of blood platelets that lead to loss of platelet function, changes in the interaction patterns of GTPases that play a role in increased metastatic potential of tumor cells, and post-translational protein modifications that are due to elevated glucose uptake or drug treatment. In addition to these health-related projects, we are also seeking to improve various aspects of the proteomic workflow such as affinity purification, interaction and post-translational modification analysis, and computational data processing.

Key Papers

Sutherland BW, Toews J, Kast J. Formaldehyde as an Alternative Cross-linking Reagent in the Study of Protein Interactions. ***Journal of Mass Spectrometry***. 2008; 43, 699-715.

Thon JN, Schubert P, Duguay M, Serrano K, Lin S, Kast J, Devine DV. Discovery of Protein Changes during Platelet Storage is Facilitated by Complementary Proteomics Approaches. ***Transfusion***. 2008; 48, 425-435.

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Schubert P, Hoffman MD, Sniatynski MJ, Kast J. Advances in the analysis of dynamic protein complexes by proteomics and data processing. ***Analytical and Bioanalytical Chemistry*****.** 2006; 386(3):482-93

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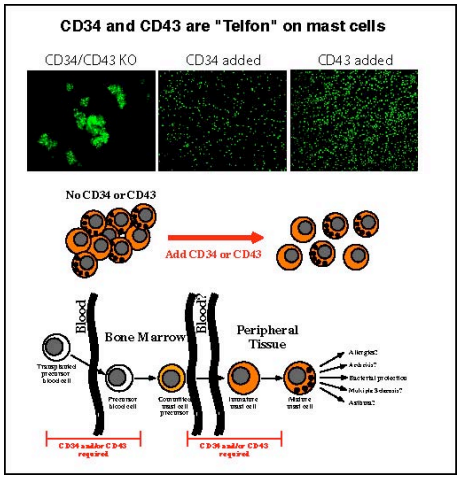
Vasilescu, J, Guo, X, and Kast, J. Identification of Protein-Protein Interactions Using In Vivo Cross-linking and Mass Spectrometry, ***Proteomics***. 2004; 4: 3845-54

My laboratory is interested in two aspects of hematopoietic stem cell biology: 1) the transcriptional and signaling network that regulates the commitment of multipotent progenitors to a specific lineage, and 2) the surface receptors expressed by HSC that regulate their interacts with their microenvironment.

Transcriptional and signaling networks

We are focusing on the regulatory mechanisms that govern mast cell and eosinophil production. These are relatively rare cells that are responsible for most of the pathology in chronic allergy and asthma and therefore may represent good targets for clinical intervention. We are using a number of transgenic mouse models to identify the factors that govern mast cell and eosinophil formation, homing and function and to perturb these processes during normal development.

Surface molecules expressed by HSC



We have focused predominantly on CD34-type proteins. CD34 is a cell surface sialomucin and the most widely used marker of hematopoietic stem cells and vascular endothelia. Recently we identified two novel receptors, Podocalyxin (also called MEP21, gp135, Thrombomucin and PCLP1) and Endoglycan that are also expressed by hematopoietic stem/progenitor cells and vasculature. We have shown that, together with CD34, these additional molecules comprise a gene family and that all three are probably derived from a common ancestral gene. Surprisingly, despite the extensive use of CD34 as a stem cell marker, virtually nothing is known of its function and it has alternatively be touted as a:

1) blocker of HSC differentiation
2) enhancer of HSC proliferation
3) bone marrow homing receptor
4) pro-adhesive receptor
5) anti-adhesive receptor

Targeted deletion of the ***CD34*** gene in mice has only fueled the debate concerning its function since these mice exhibit extremely subtle perturbations in normal hematopoietic function that could be used to support each of the above hypotheses. The discovery of two novel members of this gene family with overlapping expression patterns, has allowed us to: (1) re-evaluate these results in light of the potential for functional compensation and, (2) to generate compound mutant mice to test the true function of these receptors. In aggregate, these studies have allowed us to prove that the CD34 family of proteins function predominantly as anti-adhesion molecules, or "molecular Teflon". Thus, they enhance the mobility and invasiveness of hematopoietic cells and on non-hematopoietic cells, they are able to disrupt cell-cell junctional complexes between neighboring adherent cells (vascular endothelia or podocytes in the kidney, for example).

This is not a constitutive function, but is tightly regulated by a set of proteins that bind to the cytoplasmic tail of CD34-type proteins and regulate their sub-cellular localization and proximity to adhesion molecules. Preliminary data suggest that loss of CD34-type proteins leads to defects in hematopoietic function by preventing the HSC from entering the appropriate micro-environments (due to excessive adhesion). Similarly, we have shown that loss of these proteins can lead to dysregulation of blood pressure, presumably due to increased cell-cell adhesion and decreased vascular permeability. Finally, we have shown that these same "anti-adhesion" molecules are upregulated in an aggressive subset of epithelial tumors and lead to increased invasiveness and loss of cell polarity. They may, thus, prove to be excellent prognostic indicators of poor outcome tumors and provide a means of identifying these cancers early for aggressive therapy.

Key Papers

Blanchet MR, Maltby S, Haddon DJ, Merkens H, Zbytnuik L and McNagny KM. CD34 Facilitates The Development of Allergic Asthma. **Blood**. 2007; 110:2005-2012.

Nielsen JS, McCoy ML, Chellliah S, Vogl WA, Roskelley CA, McNagny KM. The CD34-related molecule, Podocalyxin is an inducer of microvilli formation. **PLoS One**. 2007*;* 2: 1-12.

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Hematopoietic stem cell migration

Transplantation of mobilized Hematopoietic Stem Cells (HSCs) is the best example of cellular therapy available today, and the only one to be routinely used worldwide. Yet, the mechanisms underlying the ability of HSCs, after their infusion in the bloodstream, to find niches that support their self-renewal are nearly completely unknown. Furthermore much of the current research is based on infusion of stem cells in lethally irradiated recipients, a poor model for the low-conditioning protocols in use in human patients. The elucidation of these homing mechanisms may lead to strategies to improve HSC engrafting efficiency and thus to a reduction of the number of stem cells required for transplantation. This would not only greatly improve the prospects for successful gene therapy by reducing the number of engineered stem cells required for engraftment. It may also enable us to use banked cord blood for transplantation of adult patients, which may in the future obviate the need for allogenic transplants. During the past year we have developed novel assays for stem cell migration that will allow us to study the molecular mechanisms underlying this important phenomenon. In collaboration with Dr. Ziltener's group at the BRC we have used these assays to demonstrate a role of P-selectin as the effector of a previously unreported feedback loop linking stromal niche availability with T-cell progenitor recruitment to the thymus. In the coming year we will expand these studies to hematopoietic stem cells.

Stem cell plasticity

Adult stem cells are present in every tissue and play a major role in the maintenance and repair of all the major body systems. Their tasks range from the daily production of the massive numbers of cells required for maintaining blood homeostasis to the occasional repair of injury in adult muscle. Recently, we and others have proposed that a subset of adult stem cells originating in one tissue may cross organ "boundaries" and "transdifferentiate" to participate in the repair of tissues different than the one they originate from. It is clear from work from a number of groups including ours that within the progeny of hematopoietic stem cells some cells are capable of integrating into damaged myotubes, potentially participating in their repair. It has been proposed that these cells enter the damaged myotube by fusion, and that only subsequently they are reprogrammed from to a myogenic fate. This suggests that, similarly to what take place during "cloning", nuclear reprogramming can take place in somatic cells in vivo. Despite this progress, several questions are left unanswered:

- Which lineage among the several that spawn from hematopoietic stem cells is responsible for this phenomenon?
- Is direct fusion into mature myotubes a requirement, or can circulating cells fuse into mononucleated precursors yielding a myogenic cell that can still expand?
- Can fusion be enhanced to the point that it becomes therapeutically useful?

The role of microglial cells in neurodegenerative disease

The early activation and proliferation of microglia is a hallmark of many neurodegenerative diseases, and in many cases it is evident prior to the beginning of overt symptoms. Microglial cells are the functional counterparts of tissutal macrophages in the central nervous system and they share the same origins from hematopoietic stem cells.

The role of microglia in the progression of these diseases is debated. While on one hand they clear potentially toxic debris through their scavenger action, they also produce pro-inflammatory molecules some of which, such as TNFα, have a direct deleterious effect on neuronal survival. Using a mouse model of amyotrophic lateral sclerosis we will assess the influence of microglia on the pathogenesis of this disease. Furthermore, we will take advantage of the recruitment of microglial precursors to deliver therapeutic neurotrophins locally to the ailing motorneurons

Chromatin organization and lineage choice

Ultimately, the fate that a given cell will acquire is controlled by the combination of transcription factors active in its nucleus. As more of these transcriptional regulators are identified, it now becoming clear they act in concert, instead of individually, to determine a cell's phenotype. A second level of transcriptional regulation is provided by the organization of chromatin in permissive or repressive domains. How is this organization achieved? It is currently thought that posttranslational modifications of histones may establish a combinatorial code of that ultimately controls the access of transcription factors to whole families of genes (transcriptional memory). To investigate the role of specific histone modifications in cell fate determination within hematopoiesis we are now beginning to use functional genetics and lentiviral mediated RNA interference. Our efforts are focused on SET domain-containing proteins. SET domains are associated with methyltransferase activity, and many members of this family can methylate histones as well as key transcription factors. As methylation is thought to be one of the most stable chromatin modifications, it is a good candidate to mediate the establishment and maintenance of "transcriptional memory" and thus for ensuring lineage fidelity.

Key Papers

Ajami B, Bennett JL, Krieger C, Tetzlaff W, Rossi FM. Local self-renewal can sustain CNS microglia maintenance and function throughout adult life. **Nature Neuroscience**. 2007 Dec;10(12):1538-43. Epub 2007 Nov 18.

Rossi FM, Corbel SY, Merzaban JS, Carlow DA, Gossens K, Duenas J, So L, Yi L, Ziltener HJ. Recruitment of adult thymic progenitors is regulated by P-selectin and its ligand PSGL-1. **Nat Immunol**. 6(6):626-34 (2005)

Corbel, S.Y., Lee, A., Yi, L., Duenas, J., Brazelton, T.R., Blau, H.M., Fossi, F.M. Contribution of hematopoietic stem cells to skeletal muscle. **Nat. Med**. 9: 1528-32 (2003)

Brazelton, T.R., Rossi, F.M.V., Keshet, G.I. and H.M. Blau. From marrow to brain: adult bone marrow-derived cells give rise to neuronal phenotypes in adult mice. **Science**, 290:1775-1779 (2000)

Rossi, F.M.V., Kringstein, A.M., Spicher, A., Guicherit, O.M. and Blau, H.M. Rheostat Mechanism of Transcriptional Regulation Converted to ON/OFF Switch. **Mol. Cell**, 6:723-728 (2000)

Blakely, B.T. *, Rossi, F.M.V. *, Tillotson, B., Palmer, M., Estelles, A. and Blau, H.M. EGF Receptor Dimerization Monitored In Live Cells. **Nature Biotechnology**, 18: 218-222 (2000) *Co-first authors

Our research has two major themes. One aims to understand the mechanisms through which messenger proteins called cytokines control the development and function of cells of the blood and immune system. The second aims to understand how evolution has shaped the antibodies that protect us against common viruses and bacteria and how monoclonal antibodies can be exploited as research tools or novel therapeutic agents.

Our work on cytokines is relevant to diseases caused by dysregulation of the immune system like rheumatoid arthritis and asthma. Because cells of the immune system and blood are regulated in large part by combinations of the same molecular mechanisms that control cells in other tissues, our research is also relevant to cancers like breast cancer and leukemia.

Our research on antibodies is directly relevant to combating two important human pathogens, human cytolomegalovirus (HCMV), a virus that is an important cause of birth defects, and the pneumococcus, which is a common cause of death from pneumonia. We are also exploring the use of human monoclonal antibodies to treat arthritis or cancer.

Our work on the regulation of hemopoietic cells has focused on M-Ras, a new member of the Ras family of proteins that is activated by most cytokines. The Ras proteins function as molecular switches that control many important biological processes. We identified M-Ras through bioinformatics approaches and went on to identify its binding partners using yeast-two hybrid screens or affinity-directed mass spectrometry. Activation of M-Ras-mediated signaling pathways in normal bone-marrow stem cells immortalized them and transformed them into cancer stem cells that give rise to leukemias. While expression of activated p21 Ras also resulted in the generation of myeloid leukemias, these resembled dendritic cells. These results raise the intriguing possibility that differences in the signals generated by the two Ras proteins determine the direction of differentiation taken by stem cells. We are investigating these ideas using transgenic mice and M-Ras knockout mice. We are also following up on clues that M-Ras may play a critical role in breast cancer and other human cancers. Expression of activated mutants of M-Ras in a mammary epithelial cell line resulted in epithelial- mesenchymal transition and tumorigenicity in vivo.

We are also studying another novel protein that we serendipitously discovered while studying the M-Ras pathway. This protein increases in levels when resting T- or B-lymphocytes were activated. We used mass spectrometry to identify the protein, which we call Caprin-1. Caprin-1 is also expressed in all dividing cells as well as in the brain. We have shown using gene-targeting that Caprin-1 is essential for normal cellular proliferation and used proteomic approaches to identify its binding partners. We showed that Caprin-1 heterodimerizes with an RNA-binding protein called G3BP-1. We have shown that Caprin-1 itself also selectively binds certain mRNAs. There is evidence that the Caprin-1/G3BP-1 complex promotes antigen-mediated activation of T lymphocytes and is involved with fundamental processes such as cellular adhesion and migration.

We generated a series of human monoclonal antibodies against HCMV using our novel technology. HCMV chronically infects most healthy humans, but can cause serious intra-uterine infections in the fetus and life-threatening illnesses in immunocompromised individuals. Our monoclonal antibodies were selected to bind a critical site on HCMV and, as expected, neutralized its ability to infect cells. Surprisingly, all known human antibodies against this part of HCMV, even those generated from different individuals, are encoded by genes derived from the same pair of germline V-genes. Given that these particular germline elements are well-conserved and are present in all humans, we hypothesized that they have co-evolved with HCMV to enable humans to reliably generate germline-based, primary immunoglobulins antibodies that would bind HCMV and trigger subsequent somatic mutation and affinity maturation. To test this idea, we recreated the germline-based ancestors of these antibodies, and confirmed that they indeed bound HCMV. In collaboration with Dr Emil Pai of the University of Toronto, we have compared dimensional structures of such a germline-based antibody and its somatically mutated, high-affinity progeny. We found that germline V-gene-encoded amino acids make critical contacts with the viral antigen. Moreover, somatic hypermutation and affinity maturation did not result in new side-chain contacts, but instead stabilized these germline-encoded contacts. These data show that germline V-genes sculpt the high-affinity binding sites of antibodies that protect us against HCMV. We have shown that the same germline V-genes are also used in primary immunoglobulins that bind pneumococcal polysaccharide. This suggests that these V-genes have evolved under selective pressure from multiple pathogens and "multitask". Germline V-genes thus form part of our innate immune system and embody an innate immunological memory that favors the generation of protective antibodies that target vulnerable, invariable sites on important pathogens.

Key Papers

Solomon S, Xu Y, Wang B, David MD, Schubert P, Kennedy D, Schrader JW. (2007) Free in PMC Distinct structural features of caprin-1 mediate its interaction with G3BP-1 and its induction of phosphorylation of eukaryotic translation initiation factor 2alpha, entry to cytoplasmic stress granules, and selective interaction with a subset of mRNAs. **Molecular Cell Biology**. 27:2324-42.

Schrader JW, McLean GR. (2007) Location, location, timing: analysis of cytomegalovirus epitopes for neutralizing antibodies. **Immunology Letters**. 112:58-60.

Guo X, Stratton L, and Schrader JW. (2006) Expression of activated M-Ras in hematopoietic stem cells initiates leukemogenic transformation, immortalization and preferential differentiation to mast cell. **Oncogene.** 13;25(30):4241-4.

David M, Cochrane CL, Duncan SK, Schrader JW. (2005) Pure lipopolysaccharide or synthetic Lipid A induces activation of p21Ras in primary macrophages through a pathway dependent on Src family kinases and PI3K. **J Immunol** 175(12):8236-41

Wang B, David M, Schrader JW. (2005) Absence of Caprin-1 results in defects in cellular proliferation. **J Immunol** 175(7): 4274-82

McLean GR, Olsen OA, Watt IN, Rathanaswami P, Leslie KB, Babcook JS, Schrader JW (2005) Recognition of HCMV by Human Primary Immunoglobulins Identifies an Innate Foundation to an Adaptive Immune Response. **J Immunology**. 174(8): 4768-78

Ward KR, Zhang KX, Somasiri AM, Roskelley CD and Schrader JW (2004) Expression of activated M-Ras in a murine mammary epithelial cell line induces epithelial-mesenchymal transition and tumorigenesis. **Oncogene**. 23(54): 8858

Ehrhardt A, David M, Ehrhardt GRA, Schrader JW. (2004) Distinct mechanisms determine the patterns of differential activation of H-Ras, N-Ras, K-Ras 4B, and M-Ras by receptors for growth factors or antigen. **Molecular and Cellular Biology**. 24:6311-23

CD43. A long-term interest of our research group has been the study of CD43, a member of the leukocyte mucin family of glycoproteins expressed on hemopoietic cells. CD43 is considered to be the most abundant cell surface molecule expressed on lymph-hemopoietic cells and is thought to paradoxically exhibit both anti-adhesive and pro-adhesive activities.

Mice genetically deficient in CD43 (CD43null) have been generated and reportedly displayed increased T cell adhesiveness and T cell hyper-responsiveness to mitogens and alloantigens. We therefore investigated whether T cell development was perturbed in CD43 deficient mice. Analysis of T cell development in mice that carried the CD43null mutation and a male antigen specific T cell receptor transgene (HY male antigen) revealed that neither positive T cell selection in female mice nor negative T cell selection in male mice were affected by loss of CD43. These observations were surprising in light of the reported hyper-responsiveness of CD43null T cells and we re-examined T cell responsiveness in CD43null T cells. We found that CD43+ and CD43null littermates on the C57Bl/6 background exhibited no differences in response to mitogen. The previous reports of a hyper-responsive CD43null phenotype is likely due to the mixed 129xC57Bl/6 genetic origin of these mice. In summary, we find it surprising that lack of CD43, a molecule of considerable bulk and negative charge, fails to affect T cell ontogeny.

CD43 was discovered some years ago to facilitate entry of *Mycobacterium tuberculosis* bacteria into macrophages. In a collaboration, led by the laboratory of Richard Stokes, we showed that *M. tuberculosis* binding and subsequent macrophage entry was CD43 gene dose dependent and lowest in absence of CD43. Interestingly, we found furthermore that *M. tuberculosis* bacteria, that enter macrophages in an CD43 independent way, survive better in infected cells, indicating that route of pathogen entry influences its subsequent growth.

Our laboratory has a longstanding interest in defining the in vivo relevance of CD43 ligands. Two laboratories have recently described CD43 as a ligand for E-selectin. These observations prompted us to query the in vivo relevance of relevance of CD43-E-selectin interaction using a novel competitive recruitment assay in an acute skin inflammation model. While we have been able to recreate the published in vitro observations, we have been unable to observe a role of CD43-E-selectin interaction in our competitive in vivo recruitment model.

Role of core 2 O-glycans in hemopoiesis

We have shown previously that over-expression of the enzyme core 2 N-acetylglucosaminyltransferase (C2GlNAcT-I) completely blocks development of myeloid lineages while T cell development is not impaired Some years ago we made the observation that in vivo overexpression of the core 2 glycosyltransferase blocks myeloid but not T cell development, indicating a differential role core 2 glycosyltransferase in myeloid and lymphoid cell development. To further elucidate the significance of C2GlNAcT-I in lymphohemopoiesis we have employed the parabiotic animal model.

This has led to a successful and extensive collaboration with the laboratory of my colleague Fabio Rossi an expert in stem cell biology. Our work showed that P-selectin and its ligand PSGL-1 are important components of thymic progenitor homing process and that thymic progenitor content regulates P-selectin expression in thymus, suggesting that P-selectin is a sensor for niche occupancy. Our data are the first to define the nature of the thymic homing receptors in steady state thymopoiesis. Our data are also the first to implicate a role of PSGL-1 in cell homing under non-inflammatory conditions.

Role of PSGL-1 in T cell development and T cell recirculation:
Analysis of T cell subset distribution in lymphoid organs of PSGL-1 deficient mice showed that PSGL-1 might be required for efficient homing of naïve T cells into lymph nodes. Close examination of the phenomenon uncovered a hitherto unknown chemotaxis enhancing function for PSGL-1. Our data show that the secondary lymphoid chemokines CCL21 and CC19, but not SDF-1, bind PSGL-1 on naïve T cells. This chemokine binding to PSGL-1 is associated with an approximate 100% increase in chemotactic response of resting T cells to CCL21 and CCL19, resulting in a significant enhanced homing efficiency into secondary lymphoid organs. The chemotaxis enhancing effect of PSGL-1 was not observed for B cells and the effect is lost on activated T cells in a C2GlcNAcT-I dependent mechanism. This C2GlcNAcT-I dependent loss of enhanced chemotactic response of activated T cells to CCL21 and CCL19 parallels loss of L-selectin shedding after T cell activation and we speculate that both these mechanisms are working together to reduce the potential for activated T cells to re-enter secondary lymphoid organs and direct them to the sites of inflammation. Our discovery of the bi-functional nature of PSGL-1 significantly expands the functional scope of this molecule and suggests reconsideration of previous analyses and conclusions of experiments using PSGL-1 knockout mice or PSGL-1 inhibition experiments.

Cytokine regulation of selectin binding sites
It has been shown that C2GlcNAcT-I activity is essential for formation of selectin binding sites recognized by P-selectin. However, other glycosyltransferases contribute essential components of the P-selectin ligand structure including fucosyltransferase VII (FucT VII), sialyltransferase and tyrosinesulfotransferase.

Cytokines have been implicated in regulating formation of functional selectin binding sites. These earlier studies have focused on FucT VII induction by IL-12 and TGFβ, while IL-4 has been found to inhibit this glycosyltransferase and consequently formation of functional P-selectin binding epitopes.

Observations in other laboratories had led investigators to conclude that C2GlcNAcT-I expression occurred as a direct consequence of T cell activation. In recent work our laboratory has established that in CD8 T cells the cytokine IL-2, not activation per se, is required to induce expression of C2GlcNAcT-I. We have also demonstrated that IL-2 is required to support formation of functional P-selectin binding epitopes. Our laboratory is now in the process of analyzing to what degree different cytokines modulate glycosyltransferase activities required for the formation of selectin ligands.

Key Papers

Carlow DA, Ziltener HJ. CD43 deficiency has no impact in competitive in vivo assays of neutrophil or activated T cell recruitment efficiency. **J Immunol.** 177(9):6450-9 (2006)

Rossi FM, Corbel SY, Merzaban JS, Carlow DA, Gossens K, Duenas J, So L, Yi L, Ziltener HJ. Recruitment of adult thymic progenitors is regulated by P-selectin and its ligand PSGL-1. **Nature Immun.** 6:626-634 (2005)

Randhawa AK, Ziltener HJ, Merzaban JS, Stokes RW. CD43 is required for optimal growth inhibition of *Mycobacterium tuberculosis* in macrophages and in mice. **J Immunol.** 175:1805-1812 (2005)

Carlow D, Williams M, Ziltener HJ. Inducing P-Selectin Ligand Formation in CD8 T Cells: IL-2 and IL-12 Are Active In Vitro but Not Required In Vivo. **J Immunol**. 174(7): 3959-66 (2005)

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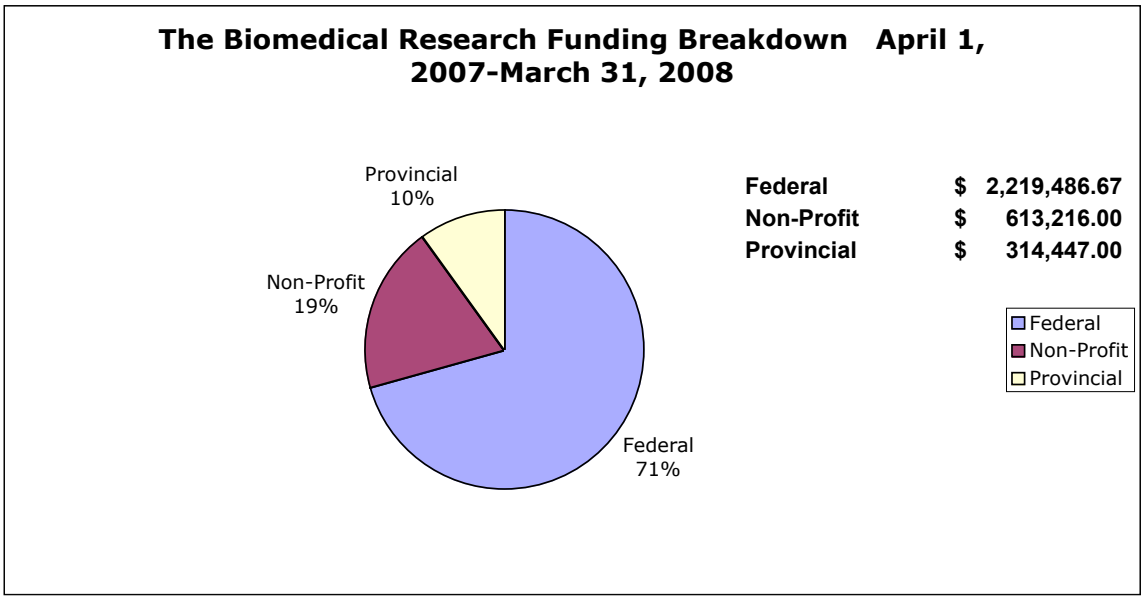
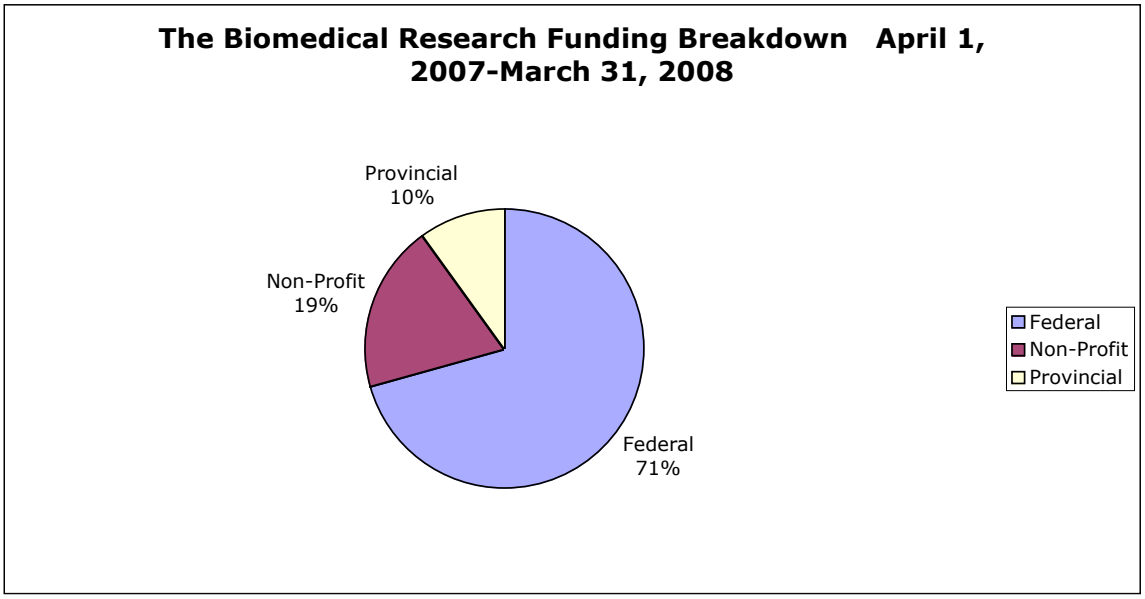
Veerman KM, Williams MJ, Uchimura K, Singer MS, Merzaban JS, Naus S, Carlow DA, Owen P, Rivera-Nieves J, Rosen SD, Ziltener HJ. Interaction of the selectin ligand PSGL-1 with chemokines CCL21 and CCL19 facilitates efficient homing of T cells to secondary lymphoid organs. **Nat Immunol.** 2007 May;8(5):532-9. Epub 2007 Apr 1. PMID: 17401367

GRANTS AND CONTRACTS

The Biomedical Research Centre
For the Period of April 1, 2007- March 31, 2008 **Total Funding $3,698,013.69**



Researcher	Funding	Body	Funding
Beavis, Ronald	National Institutes of Health: Research Grant	Federal	$129,178.00
Department of Medical Genetics	CRC: Canada Research Chair Tier I (CIHR)	Federal	$200,000.00
	CFI: Leaders Opportunity Fund	Federal	$114,750.00
	British Columbia Knowledge Development Fund	Federal	$114,750.00
		Subtotal	**$558,678.00**
Jefferies, Wilfred A.	CIHR: Operating Grant	Federal	$87,380.00
Department of Medical Genetics /	UBC VPR Research Development Fund	Non-Profit	$30,000.00
Zoology / Microbiology and	UBC VPR Research Development Fund	Non-Profit	$10,000.00
Immunology	MSFHR: Senior Graduate Studentship Award	Provincial	$208.00
	CIHR: Operating Grant	Federal	$104,133.00
	Genome Prairie	Provincial	$159,947.00
	MSFHR: Junior Graduate Studentship Award	Provincial	$2,500.00
	CIHR: Institute of Infection and Immunity Doctoral Research Awards	Federal	$1,000.00
	Multiple Sclerosis Scientific Research Foundation: Pilot Research Grant	Non-Profit	$35,000.00
	CIHR: Operating Grant	Federal	$28,354.00
		Subtotal	**$458,522.00**
Kast, Juergen	NSERC: Discovery Grants Program - Individual	Federal	$38,000.00
Department of Chemistry	Canadian Blood Services: Project Grant	Non-Profit	$115,332.00
	CFI: Infrastructure Operating Fund	Federal	$7,168.00
	CIHR: Student Award	Federal	$21,000.00
	CIHR: Student Award	Federal	$18,375.00
		Subtotal	**$199,875.00**
McNagny, Kelly	MSFHR: Scholar Award	Provincial	$80,000.00
Department of Medical Genetics	StemCell Technologies Inc.	Industry	$1,426.02
	Stem Cell Network (SCN) - NCE: Research	Federal	$21,500.00
	CIHR: Partnership for Health System Improvement	Federal	$94,304.67
	Allergy, Genes and Environment Network (AllerGen) - NCE: Research	Federal	$65,000.00
	Heart and Stroke Foundation of British Columbia and Yukon: Research	Non-Profit	$133,441.00
	CIHR: Operating Grant	Federal	$112,283.00
	MSFHR: Institutional Infrastructure Support Program	Provincial	$15,000.00
	Multiple Sclerosis Society of Canada: Postdoctoral Fellowships	Non-Profit	$39,000.00
	Allergy, Genes and Environment Network (AllerGen) - NCE: Research	Federal	$35,000.00
		Subtotal	**$596,954.69**



Rossi, Fabio	Canada Research Chair Tier II (CIHR)	Federal	$100,000.00
Department of Medical Genetics	MSFHR: Scholar Award	Provincial	$15,000.00
	CIHR: New Emerging Team Program	Federal	$75,443.00
	StemCell Technologies Inc.	Industry	$4,000.00
	Stem Cell Network (SCN) - NCE: Research	Federal	$40,666.00
	CIHR: CIHR Fellowship	Federal	$30,000.00
	CIHR: CIHR Fellowship	Federal	$5,000.00
	CIHR: Operating Grant	Federal	$95,495.00
	CIHR: Operating Grant	Federal	$98,116.00
	Canadian Breast Cancer Research Alliance	Non-Profit	$32,375.00
	MSFHR: Junior Graduate Studentship Award	Provincial	$1,458.00
	Stem Cell Network (SCN) - NCE: Graduate Studentship	Federal	$21,000.00
	Jesse's Journey Foundation	Non-Profit	$114,648.00
		Subtotal	**$633,201.00**
Schrader, John W.	Canada Research Chair Tier I (CIHR)	Federal	$200,000.00
Department of Medicine, Pathology and Laboratory Medicine, Microbiology and Immunology	CIHR: Operating Grant	Federal	$60,075.00
	CIHR Fellowship	Federal	$10,000.00
	MSFHR: Postdoctoral Trainee Fellowship	Provincial	$40,334.00
	CIHR: Operating Grant	Federal	$100,000.00
	CIHR: Proof of Principle Program	Federal	$150,000.00
	Arthritis Society: Research Operating Grant	Non-Profit	$103,420.00
	CIHR: Operating Grant	Federal	$18,628.00
	CIHR: Operating Grant	Federal	$22,888.00
		Subtotal	**$705,345.00**
Ziltener, Hermann	CIHR: Operating Grant	Federal	$147,088.00
Department of Pathology and Laboratory Medicine	CIHR: Operating Grant	Federal	$110,197.00
	Heart and Stroke Foundation of Canada: Research Fellowship	Non-Profit	$40,000.00
	Various Sources	Industry	$2,500.00
	CIHR: Student Award	Federal	$10,000.00
		Subtotal	**$309,785.00**
The Biomedical Research Centre	MSFHR: Research Unit Infrastructure Support Program	Provincial	$150,000.00
Centre Infrastructure Grants	UBC VPR Research Development Fund	Provincial	$32,000.00
	CFI: Infrastructure Operating Fund	Federal	$143,023.00
	CFI: Infrastructure Operating Fund	Federal	$18,445.00
		Subtotal	**$182,000.00**
	CIHR: Maintenance Grant for Multi-User Equipment	Federal	$53,653.00
		Subtotal	**$53,653.00**

ACTIVITIES

Ajami B, Bennett JL, Krieger C, Tetzlaff W, **Rossi FM**. Local self-renewal can sustain CNS microglia maintenance and function throughout adult life. *Nature Neuroscience*. 2007 Dec;10(12):1538-43. Epub 2007 Nov 18.

Blanchet MR, Maltby S, Haddon DJ, Merkens H, Zbytnuik L and **McNagny KM**. CD34 Facilitates The Development of Allergic Asthma. *Blood*. 2007; 110:2005-2012.

Erdman, SE, Gournaris E, Restaino C, Gurish MF, Friend DS, Lee DM, Zhang G, Shin K, Rao VP, Poutahidis T, Weissleder R, Gounari F, **McNagny KM*,** Khazaie K. Mast Cells Promote Polyposis. *Proceedings of the National Academy of Sciences*. 2007; 104: 19977-19982. ***Co-corresponding author.**

Grant JR, Moise AR, **Jefferies WA**. Identification of a novel immunosubversion mechanism mediated by a virologue of the B-lymphocyte receptor TACI. *Clinical Vaccine Immunology*. 2007 Jul;14(7):907-17. Epub 2007 May 30.

Hoffman MD, Rogalski JC, Locke J, **Kast J**. A Multiplexed Post-translational Modification Monitoring Approach on a Matrix-Assisted Laser Desorption/Ionization Time-of-Flight/Time-of-Flight Mass Spectrometer, *Rapid Communications in Mass Spectrometry*. 2007; 21, 2147-2156.

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Johansson CB, Youssef S, Koleckar K, Holbrook C, Doyonnas R, Corbel SY, Steinman L, **Rossi FM**, Blau HM. Extensive fusion of haematopoietic cells with Purkinje neurons in response to chronic inflammation. *Nature Cell Biology*. 2008 May;10(5):575-83. Epub 2008 Apr 20.

Junttila MR, Puustinen P, Niemelä M, Ahola R, Arnold H, Bottzauw T, Ala-Aho R, Nielsen C, Ivaska J, Taya Y, Lu SL, Lin S, Chan EKL, Wang XJ, Grenman R, **Kast J**, Kallunki T, Sears R, Kähäri VM, Westermarck J. CIP2A Inhibits PP2A in Human Malignancies. *Cell*. 2007; 130, 51-62.

Kelly MM, Brown GD, **McNagny KM,** Williams DL, van Rooijen N, Maxwell L, Gwozd C, Mody CH, Kubes P. The Pulmonary Microenvironment Responds to Zymosan in a Unique Manner Independent of TLRs, Complement and Dectin-1. *American Journal of Respiratory and Critical Care Medicine*. 2007; 38: 227-38.

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Setiadi AF, David MD, Seipp RP, Hartikainen JA, Gopaul R, **Jefferies WA**. Epigenetic control of the immune escape mechanisms in malignant carcinomas. *Molecular Cell Biology*. 2007 Nov;27(22):7886-94. Epub 2007 Sep 17.

Solomon S, Xu Y, Wang B, David MD, Schubert P, Kennedy D, **Schrader JW**.
Free in PMC Distinct structural features of caprin-1 mediate its interaction with G3BP-1 and its induction of phosphorylation of eukaryotic translation initiation factor 2alpha, entry to cytoplasmic stress granules, and selective interaction with a subset of mRNAs. *Molecular Cell Biology*. 2007; 27:2324-42.

Sutherland BW, Toews J, and **Kast J**. Formaldehyde as an Alternative Cross-linking Reagent in the Study of Protein Interactions. *Journal of Mass Spectrometry*. 2008; 43, 699-715. **(featured on Cover Page)**

Thon JN, Schubert P, Duguay M, Serrano K, Lin S, **Kast J**, Devine DV. Discovery of Protein Changes during Platelet Storage is Facilitated by Complementary Proteomics Approaches. *Transfusion.* 2008; 48, 425-435. **(Featured on Cover Page)**

Toews J, Rogalski JC, Clark TJ, **Kast J**. Mass Spectrometric Identification of Formaldehyde-Induced Peptide Modifications under In Vivo Protein Cross-linking Conditions. *Analytica Chimica Acta*. 2008; 618, 168-183.

Veerman K*, Williams MJ*, Uchimura K, Singer MS, Merzaban JS, Carlow DA, Owen P, Rivera-Nieves J, Rosen SD, **Ziltener HJ**. Interaction of the selectin ligand PSGL-1 with chemokines CCL21 and CCL19 facilitates efficient homing of T cells to secondary lymphoid organs. *Nature Immunology***.** 2007. 8: 532 – 539.

* equal contribution

Yang Y, **Rossi FM**, Putnins EE. "Ex vivo Expansion of Rat Bone Marrow Mesenchymal Stem Cells on Microcarrier Beads in Spin Culture". Biomaterials. 2007 Jul;28(20):3110-20.

Zhang QJ, Seipp RP, Chen SS, Vitalis TZ, Li XL, Choi KB, Jeffries A, **Jefferies WA**. TAP expression reduces IL-10 expressing tumor infiltrating lymphocytes and restores immunosurveillance against melanoma. *International Journal of Cancer*. 2007 May 1;120(9):1935-41.

	COURSES	COURSE NAME
Ronald Beavis	MEDG 520	Advances In Human Molecular Genetics
Wilf Jefferies	MICRO 402	Advanced Immunology
Juergen Kast	CHEM 333	Spectroscopic Techniques in Organic Chemistry
	CHEM 535A	Chromatography & Mass Spectrometry
	CHEM 449	Co-operative Work Placement IV
Kelly McNagny	MEDI 501	Molecular and Cellular Biology of Experimental Medicine
	MEDG 510	Advanced Immunogenetics
	MEDG 545	Current Topics in Medical Genetics Research
Fabio Rossi	MEDI 501	Molecular and Cellular Biology of Experimental Medicine
	MEDG 520	Advanced Immunogenetics
	FACS	SCN Advanced Flow Cytometry Workshop
Hermann Ziltener	PATH 302	Basic and Physical Biochemistry for Medical Laboratory Scientists
	PATH 500A	General Principles of Pathology

The major teaching by BRC faculty involves one-on-one, intensive mentoring of the students and trainees in the hands-on practice of science. These include not only graduate students (37) and postdoctoral trainees (24), but also undergraduate students (9) in Directed Studies courses and Co-operative Education and Summer Student programs.

The BRC also offers a weekly seminar program at which trainees present to the entire BRC, a seminar program of invited speakers and the Immunology Journal Club. In all of these activities the BRC faculty mentors play leadership roles.

BRC faculty mentors also sits on numerous graduate student advisory committees throughout the University and serve on examination committees.

Wilf Jefferies

Memberships of scholarly societies
British Biochemical Society
British Society of Immunology
Canadian Society of Immunology
Memberships of scholarly committees
TRID – Translational Research in Infectious Diseases
Memberships of UBC Committees
Centre for Disease Modelling Users Group
Biomedical Discussion Group
CANVAC, Principal Investigator
Transgenic and Knockout Facility, Director
Rederivation Facility, Director
Reviewer for
Biochemical Biophys. Act
Blood
European Journal of Immunology
FEBS Letter
International Immunology
Journal of Leukocyte Biology
Journal of Neuroscience
Nature Medicine
Pharmacology, Biochemistry & Behavior
Editorial Boards
International Journal of Cancer, Editor
Journal of Alzheimer's Disease, Editor
Canadian Institutes for Health Research
Canadian Network for Vaccines and Immunotherapeutics of Cancer & Chronic Viral Disease
CANFAR
National Cancer Institute of Canada
St. Paul's Hospital Foundation Grant

Juergen Kast

Membership of societies
American Society for Mass Spectrometry
Canadian Society for Mass Spectrometry
German Chemical Society
International Society for Mass Spectrometry
PENCE
Reviewer for
CIHR
NSERC
PNAS
Analytical Chemistry
Analytical and Bio-analytical Chemistry
Rapid Communications in Mass Spectrometry
Journal of Proteome Research
Proteomics

Kelly McNagny

Memberships of societies
American Association of Immunologists
Canadian Society of Immunology
Int'l Society for Exp Hematology (Membership Committee)
Int'l Society for Stem Cell Research (Junior Investigator Committee Chairman)
Stem Cell Network Centre of Excellence (Research Management Committee)
AllerGen Network Centre of Excellence
Stroke Network Centre of Excellence
Centre for Blood Research
Reviewer for
American Journal of Physiology
BLOOD
Cells, Tissues, Organs
Cell and Tissue Research
Cellular Immunology
Development
EMBO Journal
Experimental Hematology
FEBS Letters
Journal of Immunology
Molecular and Cellular Biology
Stem Cells
External Reviewer for
CIHR Operating Grants
Panel Reviewer for
Heart and Stroke Foundation of Canada (Deputy Chair – Committee V)
CIHR Operating Grants – Immunology and Transplantation Committee
NCIC Operating Grants

Fabio Rossi
Memberships of societies
Int'l Society for Stem Cell Research
NCE - Stem Cell Network
Reviewer for
Science
European Journal of BioChemistry
American Journal of Pathology
Journal of Biological Chemistry
Experimental Hematology
Gene
Stem Cells
PNAS
Panel Reviewer for
CRC application review panel
CIHR BMB grant panel
UBC Internal Review Committee

John Schrader
Memberships of societies
American Association of Immunologists
American Society of Hematology
Can Society of Immunology (Past Past President)
Int'l Society for Exp Hematology
Int'l Cytokine Society
Memberships of Scholarly Committees
Scientific Advisory Committee of the Int'l Cytokine Society,
Chair of the Interleukin Nomenclature Sub-Committee for the International Union of Immunology Societies
Editorial Boards
Cytokine
Reviewer for
Cytokine
Experimental Hematology
Journal of Biological Chemistry
Journal of Immunology
Oncogene
Memberships of UBC Committees
BioSafety Committee, UBC
Faculty of Medicine Nominating Committee
Faculty Planning and Priorities Commitee
External Reviewer for Grants or Salary Awards for
CIHR
CIHR IT Peer Review Committee (Invited Chair)

Hermann Ziltener
Memberships of societies
Canadian Society for Immunology (CSI) President
Int'l Cytokine Society for Glycobiology
American Association of Immunologists
Memberships of other committees
Vice-President CSI 2005 – 2007
Memberships of UBC Committees
Chair BioSafety Committee, BRC
Reviewer for:
Immunity
Blood
Journal of Biochemistry
Journal of Immunology
Reviewer for Grants or Salary Awards for
Panel Member CIHR Immunology/Transplantation review panel 2001 – 2004
Panel Member CIHR Doctoral Research Award panel 2005

Faculty		Country	Topic
Ron Beavis	*David Fenyo* Rockefeller University	USA	Proteomics Data Repository Development
	John Wilkins University of Manitoba	Canada	Biomarkers of Organ Rejection in Urine
	Susan Fisher UCSF	USA	Clinical Proteomic Technology Assessment for Cancer
Wilf Jefferies	*Barbara Seliger* *David Huntsman* UBC	Germany Vancouver, Canada	TAP molecules Tissue Micro-arrays
	Karen Gelmon UBC	Vancouver, Canada	Development of improved cancer treatments
	Steven Porcelli Albert Einstein College of Medicine, Yeshiva University	New York, USA	Identification of antigens recognized by T-cells
	Ann Hill Oregon Health Sciences University	Portland, USA	Interference with immune recognition by herperviruses
	Terry Pearson University of Victoria	Victoria, Canada	Trypanosomes and antigen-antibody reactions
	Francis Ouellette UBC	Vancouver, Canada	Bioinformatics
	Peter Cresswell Yale University	USA	Antigen processing

Faculty	Collaborator	Country	Topic
Juergen Kast	*Dana Devine*, UBC Centre for Blood Research	Vancouver, Canada	Proteomic analysis of platelet storage lesion
	Leonard Foster, Dept. of Biochemistry, UBC	Vancouver, Canada	Quantitative proteomics
	Charles Haynes, Michael Smith Laboratories, UBC	Vancouver, Canada	Chromatographic separation of post-translationally modified proteins
	Vince Duronio Jack Bell Research Centre, UBC	Vancouver, Canada	Characterization of cell signaling processes
	Robert Molday, Dept. of Biochemistry, UBC	Vancouver, Canada	Purification of Membrane Proteins
	Yves LeBlanc, MDS Sciex	Ontario, Canada	Novel MS/MS scan strategies
	Jukka Westermarck University of Tampere	Finland	Characterization of cell signaling processes
	Klaus Elenius University of Turku	Finland	Characterization of membrane protein complexes

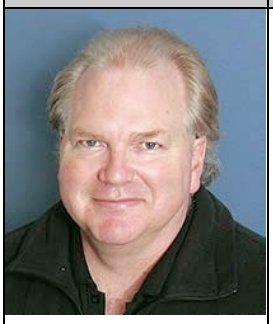
Faculty	Collaborator	Country	Topic
Kelly McNagny	**David Kershaw/ Ann Arbor** University of Michigan	Michigan, USA	Role of MEP21 in Kidney Development
	Atsushi Miyajima University of Tokyo	Tokyo, Japan	Podocalyxin and HSC homing
	Steve Rosen University of California	San Francisco, USA	CD34- family proteins In vascular biology
	Paul Kubes Univeristy of Calgary	Calgary, AB.	Origins, homing and function of mast cells and eosinophils
	Eduardo Soriano Inst. for Biomedical Research	Barcelona, Spain	Podocalyxin in brain development
	Calvin Roskelley Dept. of Anatomy, UBC	Vancouver, Canada	Podocalyxin in breast cancer progression

Faculty	Collaborator	Country	Topic
Fabio Rossi	*Charles Krieger* SFU	Vancouver, Canada	Role of microglia in the pathogenesis of ALS and neurotrophin delivery to the CNS via microglial cells
	Tom Oxland, Helen Burt, Don Brunette, Goran Fernlund UBC	Vancouver, Canada	Mesenchymal stem cells for bone regeneration in hip replacement
	Hermann Ziltener, BRC, UBC	Vancouver, Canada	Molecular Mechanisms of thymic progenitor recruitment

Faculty	Collaborator	Country	Topic
John W Schrader	*David Rose* **University of Toronto**	Toronto, Canada	Structural Studies of Caprin-1
	John Hamilton University of Melbourne	Melbourne, Australia	Human autoantibodies against GM-CSF
	Emil Pai Dept. of Biochemistry University of Toronto	Toronto, Canada	Structural Analyses of human antibodies
	Derek Kennedy Griffith University	Melbourne, Australia	The function of Caprin-1
	David Huntsman UBC Cancer Agency	Vancouver, Canada	Prognostic significance of M-Ras expression in human cancer
	Michael Roberge UBC Center for Drug Research and Development	Vancouver, Canada	Screening for compounds that inhibit M-Ras
Hermann Ziltener	*Jamey Marth* University of California	San Diego, USA	Core 2 enzyme knockout mouse model
	Richard Stokes UBC	Vancouver, Canada	Role of CD43 in mycobacteria infection
	Paul Crocker Wellcome Trust Biocentre	Great Britain	Co-stimulators of T cell activation
	Howard Petrie Scripps Florida Research Institute	Miami, USA	Thymic progenitor homing
	Steven Rosen UCSF	San Francisco, USA	Peripheral T cell homing to secondary lymphoid organs

Ronald Beavis

Beavis Informatics Ltd.
Dr. Beavis is the Founder of Beavis Informatics.
This company provides informatics consulting for academic and industrial groups interested in large scale proteomics. The company is located in Winnipeg, MB.



Wilf Jefferies

GeneMax Pharmaceuticals Canada, Inc
Dr. Jefferies is Scientific consultant for GeneMax Inc.
This is a spin-off company that is focused on taking an anti-cancer vaccine to market, based on Dr. Jefferies' work on the TAP molecule and it's role in antigen presentation in the immune system.

Fabio Rossi

Globe Biotechnologies
Dr. Rossi is Scientific consultant for Globe Biotechnologies**.**
This company handles assays for stem cell activity.

Hermann Ziltener

BioLegend
Sale of technology: The BRC granted an exclusive License to this company for any products produced from a CD43-specific monoclonal antibody.

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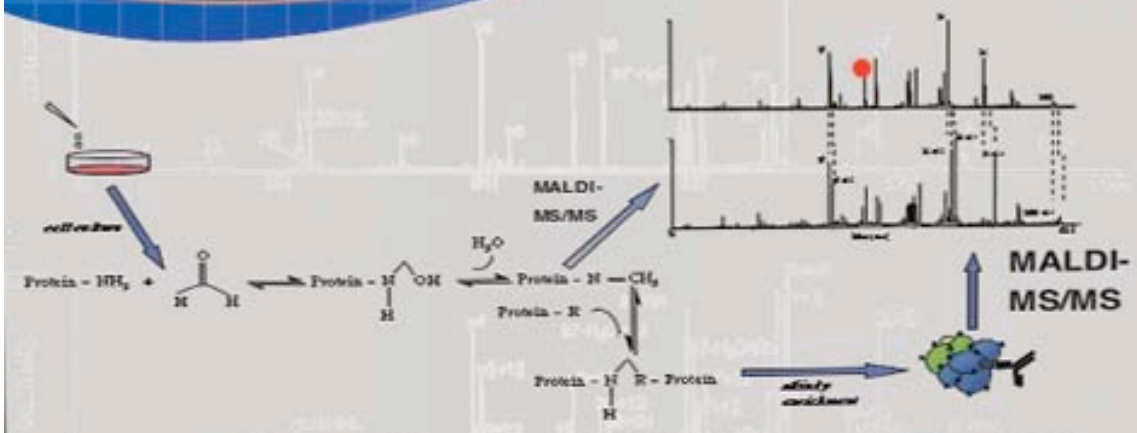

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