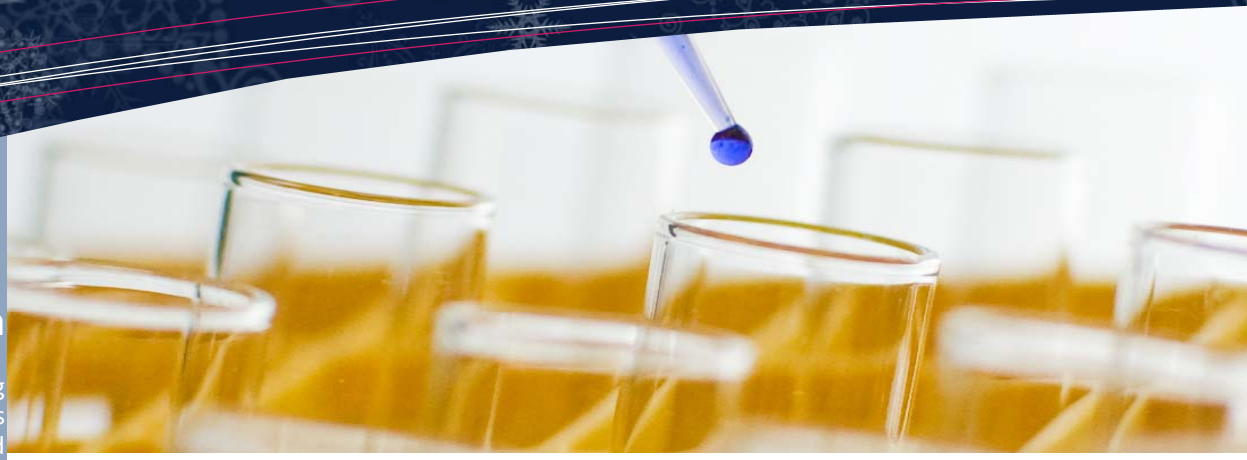
The ORT Times

A monthly newsletter featuring UHN Trainees



www.uhntrainees.ca

For information on UHN training courses, scholarships, seminars happening around the city and so much more, visit www.uhntrainees.ca.

Trainee Highlight

The Art and Science of a PhD!

By Melissa Hill

Recently, the Department of Medical Biophysics held its annual retreat. One of the traditions of the retreat is a session where PhD students that have either recently graduated, or are close to completion, give an 'exit talk' to discuss their experiences. As a PhD student near the end of my program, I accepted an invitation to give one of these presentations, but quickly realized that a great deal of reflection was required around the theme of the session, ***"My Journey."***

Looking back at what propelled me to do medical imaging research, I found that my interest really began in high school art class. Although art didn't quite fit in with my goal of being an engineer, I didn't want to drop a subject that I loved. In particular, my imagination was sparked by photography. Once I learned how to develop my own negatives and black and white photographs, I was hooked; hooked not only on photography as an art, but also as a science. During my undergraduate degree I studied Engineering Physics, which gave me a good background on the physical and chemical processes behind image formation. Incited by a particular interest in x-ray imaging, I joined Martin Yaffe's lab at Sunnybrook for my graduate studies to explore this subject further, specifically as it is applied to mammography.

Making a mammogram uses the same basic principles as exposing a photographic negative. Areas of tissue that are transparent to x-rays appear dark on an image, while regions of dense tissue that absorb x-rays remain white. The same principles behind mammographic image formation also present limitations for breast cancer detection in some women. These limitations come from the fact that there is little contrast between healthy glandular tissue and cancers. Also, tissues at different

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depths in the breast are superimposed in the 2D image, which can hide a cancer.

Picking up on the work of a former student in the lab, I considered the combination of a contrast agent with mammography to improve sensitivity. This technique, contrast-enhanced digital mammography (CEDM), can enhance the signal from cancers by the preferential diffusion of a radiopaque dye from leaky angiogenic vasculature. Clinical studies of this approach showed promise for revealing cancers, but with some limitations, including the fact that the standard x-ray contrast agents also diffuse into normal tissues. Based on measurements of patterns visible in clinical CEDM images, I have shown that the contrast agent uptake into normal tissues creates 'anatomical noise,' which may obscure small lesions.[1,2] To study the impact of this noise source on lesion detection, I extended a model of breast tissue structure to include contrast agent uptake.[3] This model allowed me to test lesion detection limits over a variety of imaging conditions, which demonstrated that normal tissue contrast enhancement is a limiting factor for lesion detection in CEDM.[4]

To overcome this constraint, and that of the 2D nature of mammography in general, investigators have proposed the use of breast tomosynthesis. This technique is a form of limited angle computed tomography that produces a series of 'slice' images. To understand the potential of tomosynthesis for imaging the effects of tumour angiogenesis, I collaborated with scientists at PMH and took advantage of the facilities at STTARR* to perform an animal model study. Using immunohistochemistry staining for markers of angiogenesis, we validated that the contrast-enhanced digital breast tomosynthesis (CE DBT) image signal is strongly correlated with blood vessel permeability.[5]

The technique of CE DBT promises to be a good approach to reduce anatomical noise and to provide clear images of signal enhancement due to the effects of tumour angiogenesis. As I near the end of my PhD program, I can't help but wonder with some amusement whether my grade 11 art teacher was right about his recommendation for my career: medical art.

*Spatio-Temporal Targeting and Amplification of Radiation Response (STTARR). STTARR promotes advanced medical research and translate outcomes to clinical applications in terms of new diagnostics and therapies. STTARR provides a wide range of support from single cell analyses through preclinical animal models to clinical studies in humans.

References

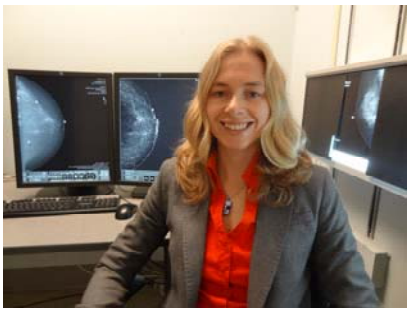
[1] Hill, M.L., Mainprize, J.G., Carton, A.-K., Muller, S., Ebrahimi, M., Jong, R.A., Dromain, C., and Yaffe, M.J. Anatomical noise in contrast-enhanced digital mammography: Part I. Single-energy imaging. *Submitted to* Medical Physics (2012).

[2] Hill, M.L., Mainprize, J.G., Carton, A.-K., Saab-Puong, S., Iordache, R., Muller, S., Jong, R.A., Dromain, C., and Yaffe, M.J. Anatomical noise in contrast-enhanced digital mammography: Part II. Dual-energy imaging. *Submitted to* Medical Physics (2012).

[3] Hill, M.L., Mainprize, J.G., Jong, R.A., and Yaffe, M.J. Design and validation of a mathematical breast phantom for contrast-enhanced digital mammography. Proceedings of SPIE 7961, 79615E (2011).

[4] Hill, M.L., Mainprize, J.G., and Yaffe, M.J. An observer model for lesion detectability in contrast-enhanced digital mammography. Lecture Notes in Computer Science 6136, 720–727 (2010).

[5] Hill, M.L., Liu, K., Mainprize, J.G., Levitin, R.B., Shojaii, R., and Yaffe, M.J. Pre-clinical evaluation of tumour angiogenesis with contrast-enhanced breast tomosynthesis. Lecture Notes in Computer Science 7361, 1–8 (2012).



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Continue the Discussion!

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success

recent awardees

CIHR Frederick Banting & Charles Canada Doctoral Awar

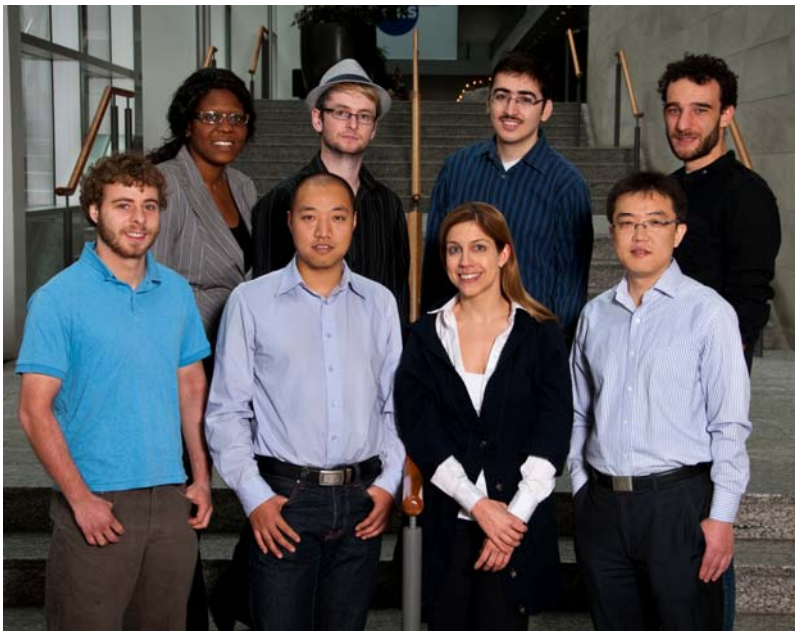
Congratulations to *Dr. Millar* who received a CIHR Fellowship for his research project entitled, **"Comparison of autonomic and vascular function late following repair of coarctation of the aorta by surgical and endovascular methods."**

Dr. Millar explains his research, "My project involves the study of adult patients with a successfully repaired congenital defect known as coarctation of the aorta. We aim to identify the possible autonomic, vascular or humoral disturbances that may be responsible for the continued risk of late hypertension following successful repair. We will also compare patients with successfully repaired defects via surgical versus endovascular methods."

Postdoctoral Fellow: Dr. Philip Millar

Supervisor: Dr. John Floras, TGRI

ORT Conference Travel Awardees



From Left to Right
Bottom Row: Joshua Moreau, Qi Wang, Alexandra Arnold-Oatley, Jinbo Zhao
Top Row: Odilia Osakwe, Peter Mullen, Ali Hussain, Andrea Ditadi

The ORT is pleased to announce the recipients of the November 1st, 2012 ORT Conference Travel Award.

MSc Program:
Joshua Moreau (OCI – Dr. Christopher Paige)

PhD Program:
Alexandra Arnold-Oatley (TRI – Dr. Robin Green)
Ali Hussain (OCI – Dr. Laurie Ailles)
Ben Xuhao Shao (TGRI – Dr. Eleanor Fish)
Sanaz Alali (OCI – Dr. Alex Vitkin)

Postdoctoral Fellow Program:
Andrea Ditadi (OCI – Dr. Gordon Keller)
Eszter Papp (TGRI – Dr. Lena Serghides)
Jinbo Zhao (TGRI – Dr. Mingyao Liu)
Odilia Osakwe (TGRI – Dr. Andre Siegel)
Peter Mullen (OCI – Dr. Linda Penn)
Qi Wang (OCI – Dr. Geoffrey Liu)
Yan Chen (OCI – Dr. Rama Khokha)
Zahi Touma (TWRI – Dr. Murray Urowitz)

conference reports

ORT Conference Travel Awardees

This section of The ORT Times includes research highlights from recent ORT Conference Travel Awardees. In this issue, learn about the latest developments in neuroscience, cancer research and sex and gender health research. In addition, read about interesting advances in back pain research and gerontology research.

Dr. Man Yu, a Postdoctoral Fellow in Dr. Ian Tannock's lab at OCI, recently presented his research entitled, **"Co-targeting multiple hallmarks of cancer: a future direction of cancer research"** at the *Cell Symposia: Hallmarks of Cancer* conference in San Francisco, CA.

Click here to read his report on the highlights of cancer stem cells.

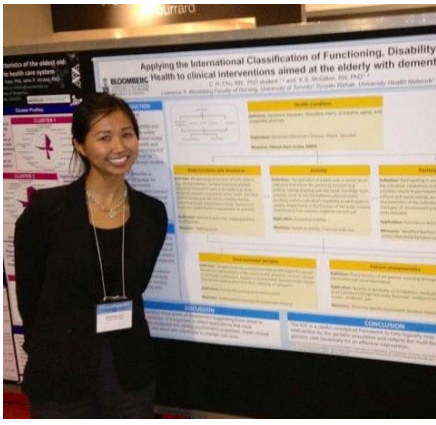
Want to know the latest project on aimed to characterize brain circuitry using the latest in-vivo neuroimaging methods?

Danielle DeSouza, a PhD student in Drs. Karen Davis and Mojgan Hodaie's lab at TWRI, recently attended the *Society for Neuroscience (SFN)* conference in New Orleans where she had the opportunity to present her research entitled, **"Abnormal peripheral nerve and brain white matter microstructure in trigeminal neuralgia."**

Click here to read her report.

Charlene Chu, a PhD student in Dr. Katherine McGilton lab at TRI, recently had the opportunity to attend the *Canadian Association of Gerontology (CAG)* conference where she was able to present three abstracts.

Click here to read her report on the latest research in population aging.

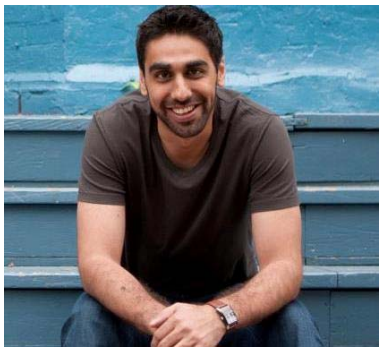


CONT'D…..ORT Conference Travel Awardees

Want to learn about the link between electrical stimulation and stroke victims?

Bimal Lakhani, a PhD student in Dr. William McIlroy's lab at TRI, recently attended the *Society for Neuroscience* conference where he presented his interesting research entitled, **"Priming' the brain to generate rapid upper limb movements."**

Click here to read his report.



Dr. Stephanie Xie, a Postdoctoral Fellow in Dr. John Dick's lab at OCI, had the opportunity to attend the *Cell Symposia: Hallmarks of Cancer* conference in San Francisco. Her abstract entitled, "**Determining metabolic requirements for stemness in human hematopoiesis and leukemia,"** was presented to key leaders in the field of cancer research.

Click here to read her report.

A PhD student in Dr. Shannon Dunn's lab at TGRI, Angela Zhang, recently attended the *Advancing Excellence in Gender, Sex and Health Research* conference in Montréal, QC. At the conference, she had the opportunity to present her research entitled, "**Mechanisms of sex-dependent repression of T helper 1 (Th1) immunity in humans by peroxisome proliferator-activated receptor (PPAR) – α."**

Click here to read her report on the latest findings on sex and gender health research.

CONT'D…..ORT Conference Travel Awardees

Want to know the latest advances in back pain research?

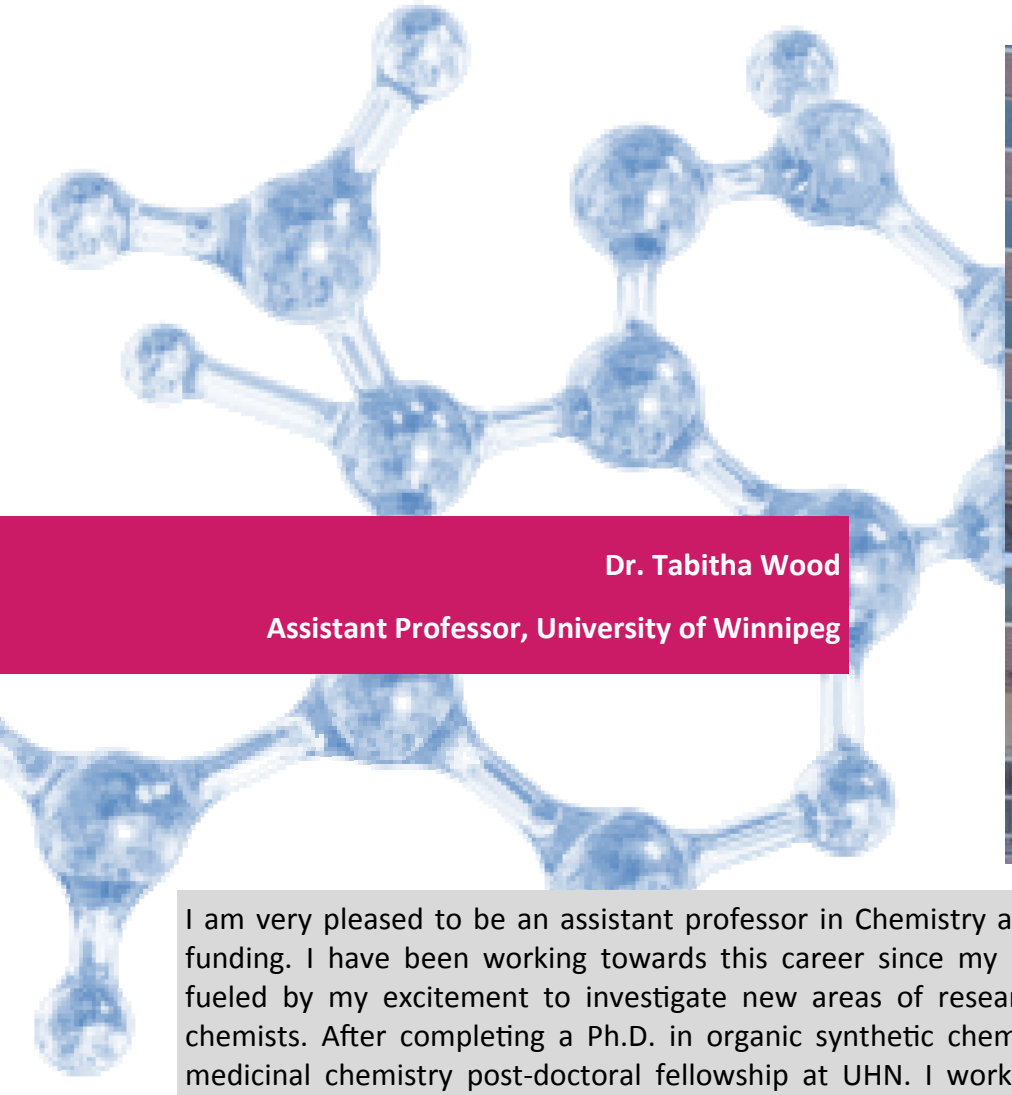
Maja Stupar, a PhD student in Dr. Pierre Coté's lab at TWRI, had the opportunity to attend the *Odense International Forum XII: Primary Care Research on Back Pain* held in Denmark. At the conference she was able to present her research on **"Exploratory factor analysis of the whiplash disability questionnaire in adults with acute whiplash-associated disorders (WAD)".**

Click here to read her report.

Vincy Chan, a PhD student in Dr. Angela Colantonio's lab at TRI, was able to present her research entitled, **"Factors associated with discharge destination from acute care among patients with acquired brain injury in Ontario, Canada,"** at the *Canadian Association on Gerontology* conference held in Vancouver.

Click here to read her report.

alumni focus



Dr. Tabitha Wood

Assistant Professor, University of Winnipeg

I am very pleased to be an assistant professor in Chemistry at the **University of Winnipeg**, with NSERC funding. I have been working towards this career since my undergraduate days—work that has been fueled by my excitement to investigate new areas of research and to pass my expertise on to new chemists. After completing a Ph.D. in organic synthetic chemistry at Dalhousie University, I took up a medicinal chemistry post-doctoral fellowship at UHN. I worked in this capacity at the Ontario Cancer Institute/Princess Margaret Hospital (OCI/PMH) under the supervision of Dr. Aaron Schimmer from January 2007 to June 2010. I am extremely grateful for the generous AMGEN/OCI Fellowship award that initially funded my work and to Dr. Schimmer who facilitated my move from synthetic to medicinal chemistry. The experience of working in the collaborative and multi-disciplinary Schimmer lab was great. ***I loved how for any experiment imaginable, there were experts somewhere in UHN willing to volunteer their equipment and expertise to collaborate.*** My time at UHN has helped my new career through exposing me to a research environment rich in collaboration, which allowed me to develop a healthy publication record and instilled in me the willingness to pursue challenging research questions. Being a trainee is an exciting and important time in your career. However, it is only a stage in your life-long development towards your ultimate career goal. So work hard and strive for accomplishment, but always look forward to the new challenges and opportunities for achievement that you will experience in the next stage of your career.

Regulation of podosome formation, microglial migration and invasion by Ca2+-signaling molecules expressed in podosomes.

Siddiqui TA, Lively S, Vincent C, Schlichter LC.

J Neuroinflammation. 2012 Nov 17;9(1):250. Toronto Western Research Institute (TWRI)

Microglia, key players in the immune response of the central nervous system (CNS), exhibit migratory activity during development and following CNS trauma. They are one of many cell types that migrate by adhering to and dissolving extracellular matrix (ECM). Podosomes, small structures that mediate this process of adhering and dissolving, are present in large numbers in the leading lamellum of migrating microglia.

A recent study by Siddiqui and colleagues (2012) examined the role of calcium-signaling machinery and mechanisms in rat microglial podosome expression and function. They used high-resolution immunocytochemistry to identify podosomes and pinpoint new molecular components related to calcium signaling. Specifically, models such as microglial invasion through Matrigel™-coated filters, trans-migration through filter pores, and migration into a scratch-wound were used to assess the roles of calcium-influx pathways and calcium ion channels in podosome expression and function.

The authors discovered new components of podosomes that relate to calcium signaling, including calcium release activated calcium (CRAC; Orai1) channels, calmodulin, small-conductance calcium-activated SK3 channels, ionized calcium-binding adapter molecule 1 (Iba1) and the Orai1 accessory molecule, STIM1.

They found that calcium influx and the CRAC and SK3 calcium channels are specifically required for podosome formation as well as for microglial migration and/or invasion, and that overall, microglial podosomes serve as a focal point for calcium signaling events that regulate ECM degradation and cell migratory activity. Click here to read the full article.

FIRST AUTHOR Q&A:

ORT: What technical aspects of this work do you find most interesting?
TAS: The evidence that podosomes are expressed in microglia was a very significant discovery made by our lab. However, there is a knowledge gap in the scientific literature regarding how microglia migrate in the brain, a phenomenon that occurs during brain development or after injury. These previous findings have allowed our laboratory to hypothesize that microglia use podosomes to navigate through the unique brain environment that they dwell in and fiercely protect. Being able to study and investigate these unique structures has been extremely fascinating and rewarding. In the current paper, we provide evidence for a novel regulatory pathway involving calcium and specific ion channels that govern the formation of podosomes in microglia as well as microglia migration/invasion using tissue culture, pharmacology and microscopy techniques. We have thus taken the first step to further our understanding of microglia migration, providing key information that may lead to the development of better therapeutic strategies to treat debilitating brain diseases.

ORT: What new skills did you learn during the course of this work?
TAS: I had the opportunity to learn many different techniques through various courses that I took at Toronto Western Hospital's Wright Imaging Facility, graduate school and the AOMF microscopy course at Princess Margaret Hospital. I developed microscopy techniques such as widefield microscopy in combination with post-acquisition deconvolution and learned scientific protocols including different cell fixation methods for immunocytochemistry. Learning these skills and gaining practical knowledge of these techniques was imperative for the proper design of experiments to test hypotheses as well as troubleshooting for optimization purposes. I am grateful to Dr. Schlichter for supporting me in learning these skills.

ORT: What challenges did you encounter along the way and how did you overcome them?
TAS: Microglial cells are immune cells found in the brain that are sensitive to changes in their environment. Our lab takes pride in the fact that we work with microglia that are directly isolated from animals and are genetically unmodified, allowing us to gather physiologically relevant data without perturbing any of the internal cellular machinery. However, this makes working with them challenging, since experimental treatments usually induce cytotoxicity, thereby rendering the experiment a failure. However, these failures drove me to be creative and troubleshoot my experiments. One example was when one of the experimental treatments was severely acidifying my cell culture medium. This was problematic because healthy cells prefer residing in a slightly basic environment. I had to borrow a method typically used in electrophysiology. The process allows electrophysiologists to take cells out of their ideal, nutrient-rich growth culture medium and have the cells survive for about an hour while experiments are performed. They do so by bathing the cells in a solution that contains essential electrolytes and glucose as an energy source. A key aspect of this solution that interested me was its buffering capacity (the solution's ability to resist changes in pH). Since my experiments were short-term in nature, I was able to utilize the same solution to perform my studies and overcome the problem of acidification. The experimental results provided key evidence for my Master's project. This work seems to be well matched to my personality as I am curious and like to continually learn new things. To quote Bill Nye, "everyone you will ever meet, knows something you don't."

UPCOMING EVENTS & FUNDING CALENDAR:

12/12 **Fundraising Event.**
The TWRI Training Affairs Committee (TAC) will join the Annual Krembil Neuroscience Centre Holiday Food Drive, spearheaded by the Fehlings' lab. Raffle tickets can be obtained at the TWRI Admin office (14-324) and the Fehlings' lab (MP 12-308) in support of the Daily Bread Food Bank.

12/17 **Call for Abstracts.**
The National Postdoctoral Association (NPA) invites Postdoctoral Fellows to submit an abstract for their 2013 Annual Meeting held between March 15-17 in Charleston, SC. Click here for more details.

12/20 **Funding Opportunity.**
American Association for Cancer Research (AACR) is pleased to offer Basic Cancer Research Fellowships open to Postdoctoral and Clinical Research Fellows. The Letter of Intent is due December 20th; Full Application is due on February 13th. See link for more details.

01/07 **Funding Opportunity.**
The AACR is offering a Millennium Fellowship in Lymphoma Research conducted by Postdoctoral and Clinical Research Fellows. Click here for more details.

01/07 **Funding Opportunity.**
The AACR is offering a Millennium Fellowship in Prostate Cancer Research conducted by Postdoctoral and Clinical Research Fellows. Click here for more details.

QUESTIONS?

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Toronto Rehab's 8th Annual Research Day, November 23rd

Photo credits: James Austin, M. Fehlings' Lab, TWRI

11th Annual Charles H. Tator - Barbara Turnbull Lectureship Series in Spinal Cord Injury, November 30th

"Piled Higher and Deeper" by Jorge Cham
www.phdcomics.com