New Research Breakthroughs at UHN

Breast Cancer: Reducing the Pain of Secondary Bone Disease

In a clinical study UHN researchers Drs. Mark Clemons and David Cole were the first to show that introducing a more potent form of a family of drugs called bisphosphonates to breast cancer patients with bone disease progression improves their quality of life.

In 65 to 75% of women with advanced breast cancer their cancer metastasizes, or travels, to their bone. In Canada, patients will usually be treated for this with bisphosphonates. Of the women that develop bone disease, two thirds of them experience a bone-related injury or progression of their bone disease. By switching to a more potent form of bisphosphonate both the quantity and quality of the patient's pain was reduced.

Working with their colleague George Dranitsaris, they correlated the patient's response with differences in substances in their urine samples that are associated with changes in bone. Clinicians could potentially use these data to determine if a patient is going to benefit from a switch in therapy.

"Currently, few innovative treatment strategies exist for women who develop complications from their bone disease despite standard bisphosphonate therapy," says Dr. Clemons. "Our prospective study has paved the way for a larger randomized trial—starting in the next few weeks—to compare the current treatment strategy to the proposed one."

J Clin Oncol. 2006 Oct 20;24(30):4895-900. [Pubmed abstract] *Research supported in part by Canadian Breast Cancer Foundation and Dairy Farmers of Canada.*

Stem Cells: Testing the Fates

UHN's Dr. John Dick, graduate student Joby McKenzie, research associates Drs. Olga Gan and Jean Wang, and senior technician Monica Doedens have discovered that the fate of human hematopoietic stem cells (HSCs) is highly variable—highlighting the importance of understanding how to manipulate them to achieve desired clinical outcomes.

When they divide, HSCs have the potential to either renew themselves or become different blood cell types, such as white and red blood cells. However, little is known about how an HSC's fate is decided.

A sophisticated method was used to track human blood cells that were transplanted into mice. Of the blood cells that were transplanted, there was a wide variation in their cell division and renewal properties.

"Establishing how the randomness of these paths is determined will be critical to using HSCs in regenerative medicine approaches," explains Dr. Dick. "And, changing the paths will be a powerful force driving stem cell-

based clinical applications."

Nat Immunol. 2006 Nov;7(11):1225-1233. [Pubmed abstract] *Research supported by Stem Cell Network of National Centres of Excellence, National Cancer Institute of Canada, Canadian Cancer Society, Terry Fox Foundation, Genome Canada, Ontario Cancer Research Network, Leukemia and Lymphoma Society, Canadian Institutes for Health Research and Canada Research Chair Program.*

Lung Cancer: Drug Improves Both Survival and Quality of Life

PMH investigators and their National Cancer Institute of Canada (NCIC) Clinical Trials Group colleagues report that administering erlotinib—a drug that blocks growth signals—to non-small cell lung cancer patients who have been previously treated with chemotherapy improves not only the length of survival for patients, but also their quality of life.

In 2005, Dr. Frances Shepherd reported in the *New England Journal of Medicine* on 731 patients enrolled in the trial. Patients given daily tablets of erlotinib had an improved one-year survival rate compared to patients who were taking an inactive pill (31% vs 22% one-year survival, respectively).

Dr. Andrea Bezjak, the quality of life coordinator for that trial, recently described the results of symptoms and quality of life analyses in the Journal of Clinical Oncology. The major tumour-related symptoms such as cough, shortness of breath and pain were controlled for significantly longer in patients treated with erlotinib and their overall physical function and quality of life remained stable for longer than patients in the control arm.

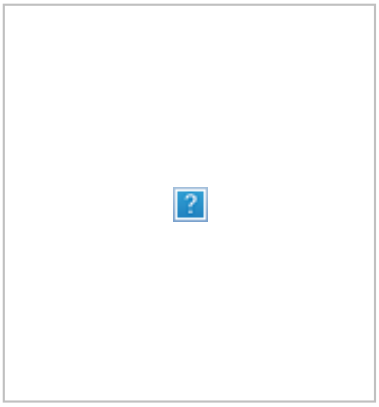
Says Dr. Bezjak, "As an oncologist, it is important to offer medications that not only extend survival but also alleviate tumour-related symptoms to improve the patient's quality of life. Erlotinib has emerged as a drug that advances both."

J Clin Oncol. 2006 Aug 20;24(24):3831-7. [Pubmed abstract]
N Engl J Med. 2005 Jul 14;353(2):123-32. [Pubmed abstract] *Research supported in part by a grant to NCIC-Clinical Trials Group from OSI Pharmaceuticals Inc.*

Arthritis: Predicting Probability of Joint Replacement Surgery

The need for improved patient education of people with arthritis is highlighted in new work by UHN researcher Dr. Elizabeth Badley, Dr. Gillian Hawker (from Women's College Hospital) and other Toronto-based researchers, who looked at factors underlying a patient's decision to undergo joint replacement surgery.

In a prospective study, the researchers recorded information about 3,307 seniors who were experiencing symptoms of arthritis in 1995-1997. In 1999, the researchers followed up with 2,103 respondents and found that—out of factors including education level, height, weight, socioeconomic factors, employment and living arrangements—the most important determining factor was willingness to have the surgery.



“Joint replacement surgery is a cost-effective treatment for debilitating arthritis of the hip and knee, and disparities in rates of surgery are troubling. Willingness to consider surgery as a treatment option results from improved patient understanding. This underlines the fact that we need to continue to develop and implement strategies to educate the community about arthritis and replacement surgery outcomes,” says Dr. Badley.

Arthritis Rheum. 2006 Oct;54(10):3212-20. [Pubmed abstract] *Research supported by Canadian Institutes of Health Research.*

Cancer: Forward Approach Reveals New Cancer Drug

A high-throughput method used by UHN researchers led by Drs. Fei-Fei Liu and Aaron Schimmer has identified a potential new anti-cancer compound.

Using robotic technology, the team was able to screen 2400 compounds from two compound libraries and assess their effects on human cancer cells. The new compound, benzethonium chloride, killed nearly 70% of cancer cells but less than 1% of normal cells. It prevented tumours from forming when injected into an animal model, and it added to the anti-tumour effects of radiation and chemotherapy. This novel anti-cancer agent appears have an effect for head and neck, lung, and colon cancer cells.

“This screening method is an example of the ‘forward chemical biology approach’, which means that we screened hundreds of compounds looking for novel agents, which produced the desired effect—in this case, cancer cell death. Ours is the first report of benzethonium chloride’s potential anti-cancer effects,” says Dr. Liu.

Clin Cancer Res. 2006 Sep 15;12(18):5557-69. [Pubmed abstract] *Research supported by Canadian Institutes of Health Research, Elia Chair in Head and Neck Cancer Research, and Natural Sciences and Engineering Research Council of Canada.*

Genetic Disorders: Advanced Technology Leads to “Record” Result

Just like a needle skimming across a record, atomic force microscopy (AFM) uses a tiny tip moving over a sample to measure changes in height only nanometres high.

This technique plus fluorescence microscopy was used by researchers led by UHN's Dr. Gil Privé and UT's Dr. Christopher Yip (Institute of Biomaterials and Biomedical Engineering) to investigate saposins—proteins that help breakdown fatty molecules in a cell.

Fatty molecule

They created a model of the cell's membrane with two layers of fatty molecules and treated them with saposins. Cavities formed after the saposins removed the upper fat layer.

"Using these data, we modelled how different types of saposins may affect the membrane. We think that saposins form a layer over the membrane and then change shape, allowing them to infiltrate and disrupt membrane organization," says Dr. Privé.

People born without functional saposin genes are not able to break down fatty molecules, a characteristic of some lysosomal storage disorders: a group of approximately 40 rare disorders estimated to occur in 1 out of 7000 births. The group includes Gaucher, Fabry and Niemann-Pick diseases, among others.

J Mol Biol. 2006 Oct 6;362(5):943-53. [Pubmed abstract] *Research supported by Canadian Institutes of Health Research and a grant from the Natural Sciences and Engineering Research Council.*

New Faces in UHN Research

W. Conrad Liles, MD, PhD

Senior Scientist, Division of Genomic Medicine
Toronto General Research Institute

Infectious disease expert and new TGRI Senior Scientist Dr.W. Conrad Liles is investigating the molecular immunopathogenesis of sepsis, malaria and other infectious diseases of public health importance. Specifically, he is elucidating the mechanisms responsible for tissue injury and organ failure in these diseases.

Dr. Conrad Liles

For example, one of the most frequent and severe pulmonary manifestations of sepsis is a form of diffuse acute inflammatory lung injury, clinically known as acute respiratory distress syndrome, which can lead to multiple organ dysfunction syndrome.

Dr. Liles is using mouse models to investigate the role of apoptosis mediated by the Fas/Fas ligand system and the involvement of MyD88-dependent inflammation in these diseases.

"A major theme of my research is to investigate important clinical problems in the laboratory in an effort to develop novel, rational therapeutic approaches that can be rapidly translated into clinical practice," says Dr. Liles.

The recent awardee of a Tier 1 Canada Research Chair in Inflammation and Infectious Diseases and member of the McLaughlin-Rotman Centre arrives at UHN from the University of Washington in Seattle.

Gang Zheng, PhD
Senior Scientist, Division of Biophysics & Bioimaging
Ontario Cancer Institute

Dr.Gang Zheng, holder of the Joey and Toby Tanenbaum/Brazilian Ball Chair in Prostate Cancer Research, is thinking “outside the box” to develop new ways to battle cancer.

“We are approaching the nanotechnology field by looking to nature to explain the best way to deliver therapeutics,” explains Dr. Zheng. “For example, we know that lipoproteins such as LDL and HDL are biocompatible and already set up to target specific tissues, a capability that we can manipulate. By packaging photodynamic therapy agents into these lipoproteins and optimizing their ability to target the prostate, we may be able to create a more effective treatment for prostate cancer.”

Dr. Zheng is also introducing a class of smart photodynamic therapy agents. These molecules are harmless to normal tissues but become potent cancer therapeutics once their activity is triggered by the prostate cancer-specific messenger RNA.

Dr. Zheng has been collaborating with Dr. Brian Wilson since 2003, giving him firsthand experience with the collegial atmosphere that eventually drew him to OCI from the University of Pennsylvania.

Update

Krembil Research Council Formed

Krembil announced its new Research Council members this month as follows:

Director
Dr. Peter St George-Hyslop

Division Heads
Dr. Rod Bremner, Genetics and Development
Dr. Peter Carlen, Fundamental Neurobiology
Dr. Karen Davis, Brain, Imaging & Behaviour Systems—Neuroscience
Dr. Marty Steinbach, Visual Science
Dr. Elisabeth Badley, Health Care & Outcomes Research
Dr. Jenny Heathcote, Patient Based Clinical Research

Vice President Research
Dr. Christopher J. Paige

Clinical Representatives
Dr. Michael Fehlings
Dr. Nizar Mahomed
Dr. Robert Inman

Site Representative
Kathy Sabo

Centre for Research Education and Training
Dr. Frances Skinner

The new division heads were nominated by Krembil scientists and appointed by a search committee. Krembil reorganization began just over a year ago and the new divisions were announced in August.

Breaking News from UHN Research

Prestigious HHMI Awards to Researchers at OCI and Krembil

UHN congratulates Dr. Peter St George-Hyslop, Krembil Director and Dr. Lea Harrington, a Senior Scientist at OCI and The Campbell Family Institute for Breast Cancer Research, who were among 39 chosen—out of a pool of 546 applications—as winners of the Howard Hughes Medical Institute International Research Scholar awards.

"From Blackboard to Benchtop to Bedside": Dr. Wilson Recognized

UHN's Dr. Brian Wilson received a lifetime achievement award at the Optical Imaging Workshop 2006 for his extraordinary pioneering contributions to translating optical technologies. The workshop was organized by the International Society for Optical Engineering and carried out at the National Institutes of Health (US).

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