

The CEO, the Researcher and the Surgeon

Dr. Robert Bell | Mak Tak PhD | Dr. Jonathan Irish
Great Minds in Dialog. January 30, 2008. University of Toronto

Dr. Robert Bell

CEO & President

University Health Network

Orthopaedic surgeon, healthcare executive, clinician-scientist and educator, Dr. Bell brings more than 20 years of experience in healthcare to his role. Since 2000, he



served as Vice President and Chief Operating Officer of UHN's Princess Margaret Hospital where he was responsible for leading the strategic vision and operation of Canada's largest comprehensive cancer centre. Since 2003, he has served as Regional Vice President and Chair of the Clinical Council of Cancer Care Ontario.

Dr. Bell earned a Doctor of Medicine from McGill University in 1975 and a Masters of Science from the University of Toronto in 1981. Dr. Bell is a Fellow of the Royal College of Physicians and Surgeons of Canada. He recently completed an Advanced Management Program at the Harvard Business School.

Clinical Studies Resource Centre Member Ontario Cancer Institute (OCI)

Research Interests

Dr. Bell is involved in team-based research related to clinical trials in sarcoma management and understanding the molecular basis of sarcoma oncogenesis.

The Sarcoma Group at PMH has collaborated in developing an extensive MSK Tumor Bank linked to clinical trials grade information. The Sarcoma Group is interested in the interaction of radiation and surgical management of sarcoma and cell therapy following radiation is a major research interest.

In collaboration with researchers at TRI, the Sarcoma Group has developed an extensive outcomes database that permits both description of and enhancement of functional outcomes following musculoskeletal oncology surgery.

Tak W. Mak, PhD

Director

Advanced Medical Discovery Institute

Director

The Campbell Family Institute for Breast Cancer Research

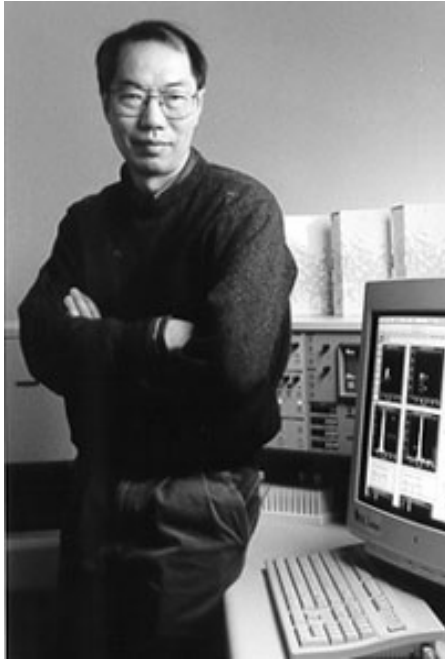
Senior Scientist

Division of Stem Cell and Developmental Biology

Advanced Medical Discovery Institute/Ontario Cancer Institute

Research Interests

Our research is concentrated on gaining fundamental knowledge of the biology of cells in normal and disease settings. We have chosen to focus on the mechanisms underlying immune responses and tumorigenesis. With this broad agenda in mind, we have initiated



several complementary programs. Many of these projects have evolved from the production and analysis of genetically engineered mouse strains.

Biology of the Immune System

The various compartments of the immune system make up what is perhaps the most intriguing and intricate cellular network aside from the nervous system. Through the targeted mutation of individual genes, our laboratory has endeavoured to dissect the function of its various components, one molecule at a time.

To achieve this goal, we have generated mice lacking the key receptors, co-receptors and signaling molecules that participate in T cell development, activation and differentiation. To understand signal transduction through the TCR complex, animals lacking the tyrosine kinase Lck, the tyrosine

phosphatase CD45, or the adaptors Bcl-10 or MALT1 have been generated.

Lck is essential for the transduction of receptor proximal signals, while CD45 promotes Lck activity. Bcl10 and MALT1 appear to cooperate in a signaling complex that specifically links antigen receptor engagement to activation of the cell survival transcription factor NF- κ B. The activation of NF- κ B depends on the degradation of an inhibitory binding protein called I κ B. We generated mice lacking NEMO, a scaffolding subunit of the IKK complex responsible for phosphorylating I κ B and promoting its degradation. NEMO-deficient mice die of severe liver damage due to a lack of NF- κ B-driven transcription of protective genes.

To gain further insights into the co-stimulatory signaling essential for normal T cell activation, mice lacking the positive regulator CD28 and the negative regulator CTLA4 have been studied. Animals lacking the inducible co-stimulator ICOS or its counter-receptor B7RP-1 have also been generated, revealing the multiple layers of control of T

cell differentiation and effector function. Recent work in this area has established that B7-H3 is a selective negative regulator of Th1 responses.

Differentiation of effector T cells also requires the receipt of certain cytokine signals, as clarified by study of mice deficient for subunits of the interleukin-2 receptor. In the absence of IL-2R β , mice exhibit dysregulated T cell activation and autoimmunity. Mice lacking WSX-1, a cytokine receptor homologous to IL-12R, show a delay in the mounting of Th1 responses. Members of the IRF family of transcription factors also have regulatory effects on immune responses. We identified IRF2 as a lymphocyte-specific family member that is essential for both B and T cell activation and for the development of NK and Th1 cells. In contrast, IRF-4 is required for the expression of the transcription factor GATA-3 that governs Th2 responses.

Biology of Programmed Cell Death

Apoptosis is the process of programmed cell death essential for normal embryonic development, resolution of immune responses, and defence against tumorigenesis. We have generated mice with defects in several molecules associated with apoptotic pathways, including TRAF-2, FADD, Apaf-1, caspase-3 and caspase-9.

Analyses of these mutant animals have revealed roles for these molecules in lymphocyte ontogeny, activation, effector function and cell death, as well as for susceptibility to autoimmune diseases. In addition, it has become clear that multiple apoptotic pathways exist that are stimulus- and tissue-specific. These pathways show differential requirements for Apaf-1 and the caspases. Study of mice deficient for TNFR revealed that, depending on the adaptors recruited to the cytoplasmic tail of this receptor, signaling for either survival or apoptosis can be transduced. We have also examined molecules involved in the regulation of apoptosis. SMAC/DIABLO binds the 'inhibitor of apoptosis' proteins and thus is thought to have an anti-apoptotic function. However, mice lacking this molecule show no phenotypic defects. These animals demonstrate the redundancy built into essential pathways governing cellular homeostasis.

The Pathogenesis of Cancer

Genetic susceptibility factors are associated with most types of cancer, but few of these genes have been identified. We have generated mutant mouse strains with engineered modifications of genes shown to be strongly linked to cancer. In addition to mice with null mutations, we have used the Cre-loxP or FLP systems to generate mice with conditional mutations. We have also adopted DNA microarray screening and a Drosophila screening method to isolate novel genes that interact with genes linked to cancer.

One of our earliest mutants was a mouse lacking MSH2, a component of the DNA mismatch repair machinery. MSH2-deficient mice spontaneously develop tumours early in life, making them a useful model for the study of tumorigenesis, carcinogens and anti-cancer agents.

More recently we have concentrated on tumour suppressor genes (TSGs). Studies of mice lacking the breast cancer susceptibility genes Brca1 or Brca2 suggest that these proteins have roles in pathways controlling DNA damage repair and the maintenance of genome stability. Loss of Brca1/2 function in cells that have already acquired one tumorigenic 'hit' may lead to uncontrolled proliferation of cells with damaged DNA, ultimately leading to oncogenesis. The phenotypes of mice bearing tissue-specific

mutations of Brca1/2 have generally supported this hypothesis. Similarly, null mutation of the SMAD4 gene in mice leads to dysregulation of apoptosis, an event that likely contributes to tumorigenesis. At least some IRFs may also act as TSGs under certain conditions. Functional inactivation of IRF1 renders a cell highly prone to transformation.

One of the most important TSGs for human cancer is p53, a multi-functional protein that induces apoptosis or cell cycle arrest in cells with damaged DNA. We identified Chk2 as a kinase that phosphorylates p53 and stabilizes it, allowing it to carry out its anti-tumorigenic functions. We also generated mice lacking HIPK1, a kinase that binds to p53 and appears to modulate its transcriptional activity. HIPK1 may promote oncogenesis if dysregulated. Functional inactivation of the TSG p53 leads to an accumulation of p53 that blocks embryonic development.

Our most recent TSG work has focussed on PTEN and genes with which it interacts. Studies of mice lacking PTEN indicated that PTEN negatively regulates the PKB/AKT cell survival pathway. PTEN-deficient cells are resistant to agents inducing apoptosis, becoming immortal and thus susceptible to acquiring additional mutations that lead to tumorigenesis. Loss of heterozygosity for PTEN in heterozygous mice results in a high incidence of tumours, especially T cell lymphomas.

We have undertaken the analysis of gene expression in the absence of PTEN function using DNA microarray screening and phenotype rescue experiments in *Drosophila* to identify novel genes acting either upstream or downstream of PTEN. The functions of these newly isolated genes are under investigation in the hopes of identifying new targets for cancer drug therapy.

Findings of Clinical Relevance

Our DNA microarray screening of 950 genes expressed by tumors revealed that the Reed-Sternberg cells of Hodgkin's lymphomas depend on autocrine production of IL-13 for growth. IL-13 and IL-13R are now under investigation as therapeutic targets for this malignancy. Our studies of mice and cells lacking the T cell signaling adaptors Bcl10 and MALT1 have provided rational explanations for how translocations involving these genes lead to the formation of MALT lymphomas.

Ongoing studies of the above and other gene-targeted mutant mice and examination of the expression levels of various gene products in normal and mutant cells should yield a wealth of information on the biology of normal and cancerous cells.

Dr. Jonathan Irish - Surgical Oncologist
Chief of Surgical Oncology, University Health Network and Mount Sinai Hospital
Clinical Studies Resource Centre Member, Ontario Cancer Institute (OCI)

Research interests are centred around the following themes:

Utilization of molecular biological techniques for prediction of clinical outcomes:

Currently our work in collaboration with Dr. Suzanne Kamel-Reid is concentrating on



the utilization of microarray analysis to predict patient outcome in head and neck malignancy. One project is looking at comparing the microarray profiles between 'young' patients with no risk factors for head and neck malignancy to a group of patients with risk factors. Our group is also comparing microarray instability in this young, low-risk group to the high-risk older patient group. Investigations in oral cancer and laryngeal cancer tumorigenesis is a major focus of our basic science collaboration with Dr. Kamel-Reid with the constant theme of relating molecular biological descriptors to clinical outcome parameters such as overall survival, regional disease failure rates and local disease behaviour characteristics.

Quality of life outcome in head and neck cancer:

Our work collaborates with the Psychosocial Oncology group at the Princess Margaret Hospital. An NCIC-funded randomized trials is ongoing which investigates the effect of an intensive psychoeducational intervention for oral cancer patients awaiting surgery compared to a group of patients receiving 'usual care' with 6 months follow up. Quality of life outcomes in skull base malignancy, maxillofacial surgery with prosthetics and other cancer groups have been studied using validated quality of life outcome scales.

3-D ultrasound analysis of patients undergoing glossectomy: Our work collaborates with the University of Toronto Speech-Language Pathology laboratory under the direction of Dr. Tim Bressmann. We are currently running a CIHR-funded trial investigating 3-D ultrasound analysis of patients undergoing glossectomy for oral cancer. We hypothesize with application of this technique and using this technique's ability to predict tongue volume changes as well as structural changes pre- and post-operatively will allow a prediction of oral function (speech and swallowing function) after oral cancer surgery.

Population-based outcomes in head and neck cancer: Our work continues to concentrate on describing patient outcomes (survival, local/regional/systemic disease control, functional outcomes) after head and neck cancer surgery. Some of this work is CIHR and NCIC funded in collaboration with Dr. Patti Groome at Queen's University. This work looks at population-based differences in practice and patient

outcomes between populations. Our group has concentrated on comparing Ontario patient outcomes to the U.S. SEER population outcomes to determine and describe differences in practice and potential effects on patient outcome in cancers of the larynx and oral cavity.

Guided Therapeutic (GTx): A multidisciplinary team comprised of scientists, physicists, surgeons, interventional radiologists have resulted in the creation of the GTx Program. This program is dedicated toward developing and testing new technologies in imaging merged with developing and applying new physical therapies such as laser, photodynamic therapy and high intensity focused ultrasound (HIFU). Research is directed in collaboration with Dr. Jeff Siewerdsen.

Additional Appointments

- Professor, University of Toronto
 - Chief of Surgical Oncology, University Health Network and Mount Sinai Hospital
 - Head of Surgical Services, Princess Margaret Hospital
 - Lead, Access to Care and Strategic Funding Initiatives, Cancer Care Ontario
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For more information contact Lina Lopez at llopez@longwoods.com.

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