

MEDICAL BIOPHYSICS

BCCA CANCER RESEARCH CENTRE

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Our Research Focus:

Radiation therapy is the cornerstone of treatment for many patients' tumours. As improving radiation and drug treatment of solid tumours is an important focus in the department, our research programs include studies into the biology and vasculature of solid tumours, basic studies on endothelial cell biology and signaling, and studies on new methods of treating solid tumours and predicting their response to treatment.

Methods development plays a key role in scientific advancement. Development and validation of methods for analysis of tumour hypoxia (starvation of oxygen supply to tumour cells) and tumour cell proliferation, new ways to measure DNA damage and repair (comet assay, DNA repair complex formation), development of the multilayer cell culture model for drug penetration studies, and characterization and validation of proteomic approaches have all led to new insights into cancer cell behavior and response to therapy.

Progress Highlights during 2005-06

- Demonstration that radioresistant hypoxic cells in human tumours are capable of cell division *during* therapy.
- Demonstration of the critical importance of pre-analytical and analytical variables when using proteomic approaches to identify cancer biomarkers.
- Demonstration that the hypoxic cell cytotoxin tirapazamine also causes vascular dysfunction.
- Demonstration that retention of DNA repair complexes can be used to predict response of xenografted tumours to fractionated irradiation, paving the way for studies with clinical samples.

Key Research Staff

<i>Researcher name</i>		<i>Position & Cross-Appointments</i>
Ralph Durand	PhD Biophysics	Head, Medical Biophysics Associate Vice-President, Research, BCCA Honorary Professor, Pathology and Lab Medicine, UBC Associate Member, Physics and Astronomy, UBC Director, Interdisciplinary Oncology Program, UBC
Aly Karsan	MD	Senior Scientist Hematopathologist, Dept. of Pathology, BCCA Associate Professor, Pathology and Lab Medicine, UBC
Andrew Minchinton	PhD Radiation Biology	Senior Scientist Honorary Assistant Professor, Pathology and Laboratory Medicine, UBC
Peggy Olive	PhD Biochemistry	Senior Scientist Adjunct Professor, Physics and Astronomy, UBC Honorary Professor, Pathology and Laboratory Medicine, UBC

Training

A.) Course Instruction

R Durand	UBC PATH548/ ONCO 502
R Durand	BCCA-Radiobiology to Radiation Oncology Residents
A Karsan	UBC MEDG 521/ PATH 531
A Karsan	UBC PHAR545
A Karsan	BCCA Basic Science of Oncology to Medical Oncology Residents
A Minchinton	UBC PHYS 405/ 436
A Minchinton	BCCA-Radiobiology to Radiation Oncology Residents
P Olive	UBC PATH548/ ONCO 502
P Olive	BCCA-Radiobiology to Radiation Oncology Residents
P Olive	UBC-MEDG 521/ PATH 531

B.) Summary of Trainees

<i>Total No. of Current Students</i>	<i>Post-doctoral</i>	<i>Post-graduate</i>	<i>Undergraduate</i>	<i>Clinical</i>
48	19	13	16	0

C.) Current Students – Degrees Completed

<i>Name</i>	<i>Supervisor</i>	<i>Date Completed</i>
PhD		
Michelle Wong	R Durand	2006
Kevin Leong	A Karsan	2005
MSc		
Bojana Jankovic	P Olive	2005
Solmaz Sobhanifar	P Olive	2005

D.) Trainee Awards

<i>Name</i>	<i>Supervisor</i>	<i>Award Received</i>
Linda Chang	A Karsan	MSFHR Trainee Award (2005-2006)
Shauna Dauphinee	A Karsan	MSFHR Trainee Award (2006-2007) CIHR Doctoral Research Award (2006-2009)
YangXin Fu	A Karsan	MSFHR Postdoctoral Trainee Fellowship (2005-2006) NCE/Stem Cell Network Postdoctoral Fellowship (2005-2006)
Iva Kulic	A Karsan	MSFHR Trainee Award (2006-2008) NSERC Trainee Award (2005-2007)
Kevin Leong	A Karsan	DOD Studentship (2001-2005)
Kyle Niessen	A Karsan	MSFHR Trainee Award (2005-2007)
Michela Nosedà	A Karsan	MSFHR Postdoctoral Trainee Fellowship (2002-2005) CIHR Postdoctoral Fellowship (2002-2005)
Audi Setiadi	A Karsan	NCE/Stem Cell Network Research Student Award (2005-2006)
Daniel Starczynowski	A Karsan	MSFHR Postdoctoral Trainee Fellowship (2006-2009)
Lynsey Huxham	A Minchinton	MSFHR Trainee Award (2005-2007)
Alastair Kyle	A Minchinton	CIHR Doctoral Research Award (2003-2005) MSFHR Trainee Award (2001-2005)

Current Awards and Honours

<i>Name</i>	<i>Distinguished Award/Honour</i>
A Karsan	MSFHR Scholar Award (2001-2006) MSFHR Senior Scholar Award (2006-2011)

Select Current Contributions

<i>Name</i>	<i>Membership/Committee Involvement</i>
R Durand	Vice-Chair, NCIC Advisory Committee on Research Ad Hoc Reviewer, National Institutes of Health grant panel Member, U.S. Army Breast Cancer Review Program
A Karsan	Member, Tobacco Related Diseases Research Program (administered through University of California) – Cardiovascular panel Member, National Cancer Institute of Canada, Grant panel B1 Cancer Progression and Metastasis Member, UBC Dept. of Pathology Research Programs Committee Member, UBC MD/PhD Advisory and Admissions Committee Member, Heart and Stroke Foundation Telephone Thank You Campaign
A Minchinton	Member, MSFHR Research Trainee Program Panel Member, Pathology and Laboratory Medicine Graduate Awards Committee Member, Canadian Breast Cancer Foundation (BC & Yukon) Grants Committee Member, Canadian Breast Cancer Foundation (Ontario) Grants Committee
P Olive	Vice-President Elect, International Association for Radiation Research Member, Panel SC15, NCRP Lunar Missions Radiation Risk Evaluation Member, Canadian Association for Radiation Oncology task force on translational research Co-Chair, NCIC Grant Panel E Advisory Board, RTOG Translational Research Program

Current Research Projects¹

1. Benzotriazines as antivascular anticancer drugs	
PI: A Minchinton CIHR \$56,615 (2006) \$169,844 (2006-2009)	This study aims to elucidate the mechanism by which Tirapazamine causes vascular dysfunction and to explore analogues of Tirapazamine as potential new anticancer agents targeting the tumour vasculature.
2. Cardiovascular and respiratory stem cell plasticity	
PI: J Galipeau (McGill) Co-I: A Karsan, P Lansdorp, P Liu, L Megeney, J Stewart CARE/NET-CIHR, Stem Cell Network, Heart & Stroke Foundation \$29,040 (2005) \$29,040 (2006) \$130,680 to Karsan (2004-2009)	The goal of this large interdisciplinary project is to study the use of adult stem cells as repair material for damaged hearts, lungs, and blood vessels.
3. Control of cell proliferation in solid tumours and implications for therapy	
PI: R Durand CIHR \$129,325 (2005) \$129,325 (2006) \$567,779 (2003-2007)	This project examines tumour cell growth in patients during their treatment. The aim is to determine how many and how well each patient's tumour cells respond to therapy, which in turn provides the ability to individualize therapy and to offer timely suggestions of different treatment options for some patients.
4. Development of technologies for the derivation, propagation and differentiation of hESC	
PL: J Piret (UBC) Co-I: M Bhatia, A Nagy, A Karsan et al Stem Cell Network	For project description see Terry Fox Laboratory.
5. Dissecting gene expression networks in mammalian organogenesis- Genome Canada Comp III	
PL: M Marra, P Hoodless Co-I: A Karsan, S Jones, C Helgason Genome Canada/Genome BC	For project description see Terry Fox Laboratory.
6. DNA repair complexes and tumour responses to ionizing radiation	
PI: P Olive NCIC \$149,920 (2005) \$149,920 (2006) \$449,760 (2004-2007)	A cell's sensitivity to radiation is known to be related to its ability to repair the damage to its DNA caused by radiation. The repair of radiation-caused DNA damage is carried out by substances called repair complexes, which can be identified under a microscope. This study will investigate the possibility that the rate at which these complexes disappear after radiation treatment is related to the cell's ability to repair the damage.

¹ Key to abbreviations: PI = Principal Investigator, Co-I = Co-investigator; CIHR* = Funding Institution; \$150,000 (2005-2007) = Total Project Funding for Given Years (*see pages 16-17 for a list of acronyms)

7. Endothelial to mesenchymal transformation	
<i>PI: A Karsan</i> <i>Co-I: P Hoodless</i> CIHR \$116,075 (2005) \$116,075 (2006) \$522,338 to Karsan (2003-2008)	The goal is to understand how the cardiac cushion develops using the process of endothelial to mesenchymal transition.
8. Evaluation of novel peptides to revert epithelial-to-mesenchymal transition in tumour progression	
<i>PI: A Karsan</i> CIHR \$150,000 (2005-2006)	The purpose is to examine inhibitory activity of Notch peptides.
9. Lipopolysaccharide signaling in endothelial cells	
<i>PI: A Karsan</i> CIHR \$111,479 (2005) \$111,479 (2006) \$501,656 (2003-2008)	The goal is to understand endothelial signaling in response to Toll-like receptor activation.
10. Maintenance support for a flow cytometry facility	
<i>PI: R Durand</i> CIHR \$54,000 (2005) \$270,000 (2001-2006)	This grant provides essential support to keep flow-cytometry and cell-sorting facilities operational for researchers.
11. Mechanisms of ischemic neovascularization	
<i>PI: A Karsan</i> <i>Heart & Stroke Foundation</i> \$104,782 (2005) \$108,470 (2006) \$538,662 (2004-2009)	The goal is to determine whether Notch activation in endothelial cells plays a role in arteriogenesis by promoting endothelial transformation to smooth muscle cells.
12. Mechanisms of tumour angiogenesis	
<i>PI: A Karsan</i> NCIC \$140,107 (2005) \$424,324 (2003-2006) Project Funding Renewed: \$104,648 (2006) \$523,240 (2006-2011)	The goal is to understand the role of Notch signaling in tumour angiogenesis.
13. Microregional assessment of the anticancer activity of trastuzumab (Herceptin)	
<i>PI: A Minchinton</i> CBCF \$96,899 (2005) \$193,798 (2004-2006)	The goal is to study the role of extravascular penetration in the activity of Herceptin.
14. Microregional effects of pyrimidine analogues in tumours	
<i>PI: A Minchinton</i> CIHR \$103,878 (2005) \$103,878 (2006) \$431,562 (2004-2007)	The goal is to examine the role extravascular penetration plays in the activity of pyrimidine analogues.

15. Molecular mechanisms of endothelial survival/apoptosis	
<i>PI: A Karsan</i> <i>Heart & Stroke Foundation</i> \$91,770 (2005) \$129,747 (2006) \$274,778 (2003-2006) Renewed: \$648,735 (2006-2011)	The goal is to determine whether Notch4 can protect endothelial cells from death triggered by glucose, homocysteine and oxidized lipids. Phase II is designed to understand mechanisms of viability in response to cytokine exposure.
16. Quantitation of hypoxic tumour cells	
<i>PI: P Olive</i> <i>CIHR</i> \$104,107 (2005) \$104,107 (2006) \$491,428 (2003-2008)	This project examines tumour hypoxia in xenografts and clinical samples using flow cytometry and fluorescence imaging with chemical and endogenous markers for hypoxia.
17. Radiosensitization by pharmacocyclic histone deacetylation complex (HDAC) inhibitors	
<i>PI: P Olive</i> <i>Varian Biosynergy</i> \$66,250 (2006-2007)	This grant examines the potential of a pharmacocyclic HDAC inhibitor to sensitize human tumour cell lines to ionizing radiation and the mechanisms for this effect.
18. Solid tumour progression research unit	
<i>PL: C Roskelley (UBC)</i> <i>Co-I: S Dedhar, R Anderson, A Karsan, A Minchinton, M Roberge</i> <i>MSFHR</i> \$44,157 (2005) to Minchinton \$44,157 (2006) to Minchinton \$179,028 (2003-2007) to Minchinton	This research unit aims to develop and evaluate novel compounds that control or prevent solid tumour metastasis. This research will encompass the development of cell-based screening assays to identify key molecules involved in three processes underlying tumour spread: tumour cell invasion, metastatic apoptosis and endothelial cell sprouting, compound development and pre-clinical testing.
19. The role of vascular endothelial growth factor (VEGF) in hematopoiesis	
<i>PI: A Karsan</i> <i>CIHR</i> \$109,462 (2005) \$109,462 (2006) \$328,386 (2005-2008)	The goal is to determine the role of VEGF signaling in malignant and normal hematopoiesis using mouse bone marrow transplant models and proteomic techniques.