

ADVANCED THERAPEUTICS

BCCA CANCER RESEARCH CENTRE

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Our Research Focus: We are a translational research department within the BC Cancer Agency, providing anticancer drug development capabilities which are focused on the critical need to rapidly establish the therapeutic value of emerging intervention strategies through validated assessments in preclinical models of cancer and in patients.

Scientists in Advanced Therapeutics provide three translational research platforms:

1. DISCOVERY RESEARCH PROGRAM

Advanced Therapeutics' anticancer drug development platform is driven by basic science to address the following critical goals: (i) To rapidly establish the therapeutic value and mechanistic actions of innovative medicines being developed for use in treating cancer; (ii) To concurrently identify and evaluate surrogate biological and imaging markers for predicting and monitoring tumor response to emerging cancer therapeutics; (iii) To promptly harness pharmacogenomic information for developing strategies for individualized cancer therapy, and ultimately to integrate them into clinical practice

2. INVESTIGATIONAL DRUG PROGRAM

The Investigational Drug Program (IDP) (Director: Dr. Dawn Waterhouse) expedites development of new and highly promising anti-cancer therapeutic agents up to the initial stages of clinical trials. IDP works with academic investigators and biotechnology companies. IDP has a wealth of expertise in murine models of human cancer, as well as critical ADME studies (absorption, distribution, metabolism and excretion), and completion of the documentation necessary to apply for a successful Investigational New Drug application (IND) in either Canada or the United States.

3. PHASE I/II CLINICAL TRIALS UNIT

Advanced Therapeutics participates in a rapidly growing Phase I/II/III clinical trials unit at the Vancouver Cancer Centre. These clinical trials are organized in collaboration with colleagues in Medical Oncology, other Canadian cancer treatment centres, co-operative oncology groups (e.g., NCIC) and pharmaceutical and biotechnology companies. Links have been established with US centres such as UCLA and the San Antonio Drug Development Institute.



Progress Highlights during 2005 and 2006:

Advanced Therapeutics scientists:

- were awarded four proof of principle grants (CIHR POP I grants).
- advanced one of the four CIHR POP I projects to the stage where a CIHR POP II application was written to develop a novel nano-formulation for irinotecan (Irinophore C™), which is progressing towards the final stages of development required to enter into a first-in-human Phase I clinical trial at the BC Cancer Agency
- collaborated with Dr. Aparicio to acquire two InCELL analyzers, which completed the department's efforts to establish a High Content Screening (HCS) center for cell based assays and the required fluid handling robotics to support HCS and assay development.
- worked with the Faculty of Pharmaceutical Sciences at UBC to recruit Dr. Sylvia Ng, who brings expertise in molecular pharmacology and angiogenesis.
- Dr. Bally was appointed as the co-head of the Division of Drug Evaluation with BC's Centre for Drug Research and Discovery (CDRD)

In addition:

- Dr. Yapp secured a rethink Breast Cancer career award and will lead the department's efforts in the area of non-invasive imaging, with a particular focus on PET and MRI based imaging technologies applied to gain a better understanding of treatment induced effects in models of breast cancer.
- Dr. Ng brought together the local pancreatic cancer community through the formation of the British Columbia Pancreatic Cancer Research Network – a team of local, prominent, pancreatic cancer clinicians and researchers (a private donation to the BC Cancer Foundation established the Betty Ergas Pancreatic Cancer Fund).
- Celator Pharmaceuticals, Inc., the BC Cancer Agency spin-off company, closed a \$40 million (U.S.) round of private equity financing with participation from several leading venture capital firms. The financing represented one of the largest venture capital investments in biotechnology in both Canada and the United States during 2005. The company initiated a Phase II clinical trial on its pharmaceutical drug product lead candidate at the BC Cancer Agency and McGill University. The company also entered into a Phase I clinical study on a second pharmaceutical drug product.



Key Research Staff

<i>Researcher name</i>		<i>Position & Cross-Appointments</i>
Marcel Bally	PhD Biochemistry	Head, Advanced Therapeutics Clinical Professor, Pathology and Lab Medicine, UBC Adjunct Professor, Pharmaceutical Sciences, UBC
Karen Gelmon	MD	Head, Investigational Drug Program Medical Oncologist, BCCA/VCC Chair, Breast Cancer Tumour Group Clinical Professor, Medical Oncology, UBC
Sylvia Ng	PhD, Medical Biophysics	Senior Scientist Assistant Professor, Pharmaceutical Sciences, UBC
Ellen Wasan	PhD, Pathology and Lab Medicine	Research Scientist Faculty, School of Health Sciences, BCIT Adjunct Professor, Pharmaceutical Sciences, UBC
Dawn Waterhouse	PhD Biochemistry, MBA	Cancer Specialist, Advanced Therapeutics Director, non-Clinical Studies, Investigational Drug Program Adjunct Professor, Pharmaceutical Sciences, UBC
Donald Yapp	PhD Chemistry	Research Scientist Adjunct Professor, Pharmaceutical Sciences, UBC

A.) Course Instruction

M Bally	UBC Path 500A
M Bally	UBC Path 535/635
M Bally	UBC Cancer Biology
S Ng	UBC Phar 514
E Wasan	UBC Phar 514/321
E Wasan	BCIT Pathology 6103 (Radiation Therapy Program)
D Yapp	UBC Phar 514

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>
20	5	7	8	0

C.) Current Students – Degrees Completed

<i>Name</i>	<i>Supervisor</i>	<i>Date Completed</i>
PhD		
Lincoln Edwards	M Bally	2006
MSc		
Aman Tagger	M Bally	2006

D.) Trainee Awards

<i>Name</i>	<i>Supervisor</i>	<i>Award Received</i>
Maite Verreault	M Bally	Les fonds de la recherche en sante du Quebec (FRSQ) (2005-2007)
Jesse Popov	M Bally	MSFHR Junior Graduate Studentship (2006) NSERC Canada Graduate Scholarship - Master's (2005)
Mihaela Ginja	D Yapp	Swiss National Science Foundation, PDF (2005-2006) Novartis Foundation, PDF (2005-2006)

Current Awards and Honours

Name	Distinguished Award/Honour
D Yapp	reTHINK Breast Cancer – Career Award (2006-2010)

Select Current Contributions

Name	Membership/Committee Involvement
M Bally	Co-Director, Centre for Drug Research and Development (CDRD)
	Member, Centre for Blood Research, UBC
	Co-Director/Member, Liposome Research Unit
S Ng	Leader, British Columbia Pancreatic Cancer (BCPCR NET)

Current Research Projects¹

1. Advanced delivery of agents targeting the endoplasmic reticulum in breast cancer	
PI: S Berger Co-I: E Wasan, D Waterhouse CBCRA \$85,317 (2004-2005)	The goal is to assess new ways to give the drug econazole in tiny lipid bubbles in which it can dissolve. If this approach works, it may lead to a new drug treatment that effectively kills breast cancer cells even when other drugs stop working.
2. Career salary award and material supply component	
PI: D Yapp reThink Breast Cancer \$46,838 (2006) \$93,676 (2006-2008)	The biological consequences of HER-2 overexpression in breast cancer are dire; this form of breast cancer is more virulent and prone to metastasis. There is thus a great need to define more clearly the impact of HER-2 overexpression on the tumour microenvironment and the proposed studies will use non-invasive positron emission tomography and magnetic resonance imaging in conjunction with molecular studies to evaluate physiological tumour functions and expression of molecular markers, such as HER-2.
3. Combining conventional therapeutics with molecular targeting: Strategies for the treatment of breast cancer	
PI: M Bally Co-I: K Gelmon, S Chia, P Gill NCIC \$92,155 (2005) \$316,073 (2002-2005)	This research focuses on two therapeutic agents (i) an ASO targeting bcl-2, an anti-apoptotic signal believed to be an important survival signal; and (ii) a siRNA sequence targeting integrin-linked kinase, which exemplifies a target that is capable of producing pleiotropic effects including stimulating cell growth and cell cycle progression as well as inhibiting apoptosis.

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)

4. Combining conventional therapeutics with molecular targeting: Strategies for the treatment of HER-2 positive relapsed and metastatic breast cancer	
<p>PI: M Bally Co-I: K Gelmon, S Dunn (UBC) CBCRA \$209,100 (2006) \$497,300 (2006-2009)</p>	<p>The goal is to assess drug combinations designed to overcome intrinsic and acquired Trastuzumab (Herceptin) resistance, identify parameters that contribute to achieving desired drug combination effects in vitro and in vivo and develop strategies that will optimize drug combination effects in vivo. Cell based high content screening assays are utilized to select drug combinations for further studies in orthotopic and systemic HER-2 breast cancer models.</p>
5. Creating opportunities for sequential therapies with liposomal CPT-11 in colorectal cancer	
<p>PI: D Yapp Cancer Research Society \$55,900 (2006) \$118,800 (2006-2008)</p>	<p>This project examine whether enhancements in tumour perfusion and oxygenation due to CPT-11 improves the penetration of a second drug and increases the tumour's sensitivity to radiation. The significance of the proposed work lies in the potential of sequential treatments, which take advantage of changes in the tumour, to improve the clinical management of colorectal cancer.</p>
6. Development of a novel formulation of liposomal econazole as an anticancer agent	
<p>PI: E Wasan Co-Is: SA Berger (UToronto), M Bally, D Waterhouse CIHR POP \$147,997 (2005-2006)</p>	<p>The goal of this project is to develop therapeutics from a known calcium influx blocker using advanced drug delivery technologies and test them in a panel of established human solid tumor models. This research builds upon a novel mechanism of cell death termed 'Activation-Enhanced Cell Death' (AECD). This mechanism involves stimulating a target cell with a growth or activation signal while concurrently blocking calcium influx blocker using advanced drug delivery technologies and testing them in a panel of established human solid tumor models.</p>
7. Imaging tumour vasculature non-invasively with positron emission tomography and cationic liposomes	
<p>PI: D Yapp CBCRA \$70,250 (2006-2007)</p>	<p>The goal of the project is to develop a non-invasive imaging tool based on Cu- labelled cationic liposomes and positron emission tomography (PET) to assess in situ tumour vasculature in breast cancer tumours.</p>
8. Enhancement of the efficacy of therapeutic antibodies via liposome conjugation in the treatment of cancer	
<p>PI: M Bally Co-I: D Natalie, E Ramsay CIHR \$150,000 (2005-2006)</p>	<p>We have developed a technology platform which involves the use of multiple antibodies attached to a liposome. Since antibodies are commonly used in combination with chemotherapy, the use of liposomes in this case offers the potential of delivering both the antibody and the anti-cancer drug in the same vehicle. Our goal is to develop a method for the scale-up production of these liposomal antibody formulations that prepares us for future pre-clinical and clinical studies. Furthermore, we will demonstrate whether the technology platform is applicable to other antibodies known to exhibit therapeutic effects.</p>

9. Fixed dose anticancer drug combination products: Pre-clinical testing for the specific fixed dose combination of gemcitabine and idarubicin in liposomal drug carriers	
<p>PI: D Waterhouse Co-I: M Bally, E Ramsay CIHR POP \$150,000 (2005-2006)</p>	<p>We have developed a new method of identifying optimal drug combinations prior to human testing using liposomal drug carriers and fixed dose drug ratios. Liposomal formulations that can retain the encapsulated drug for extended periods in the blood offer the potential to considerably improve the therapeutic effect. In our invention, liposomes are used as carriers for two drugs that are combined on the basis of non-overlapping toxicity, complementary mechanisms of action and proven anti-cancer efficacy.</p>
10. Intestinal lymphatic transport of water-insoluble drugs	
<p>PI: KM Wasan CIHR \$18,838 (2005) \$75,351 (2006) \$188,378 (2006-2009)</p>	<p>The overall objective of this project is to evaluate and characterize the contribution of lymphatic transport to the overall oral absorption of a poorly water soluble compound with very poor oral absorption, Amphotericin B. The drug will be formulated in lipid-based drug delivery systems to improve the absorption of the drug and administered orally in an instrumented rat model. Pharmacokinetics and antifungal activity will be evaluated as well as the role of lymphatic triglyceride transport in modulating drug transport from the GI tract.</p>
11. Lipid-based carriers for gene therapy: Applications for treatment of cancer	
<p>PI: M Bally CIHR \$121,506 (2005) \$364,518 (2003-2006)</p>	<p>A key challenge in drug development is the design of carriers that can efficiently deliver molecules in a manner that provides effective treatment of systemic disease. This study is focused on the development of such delivery systems.</p>
12. Liposome/vascular endothelium interactions: Development and characterization of drug formulations designed to promote tumour associated endothelial cell death	
<p>PI: M Bally CIHR \$125,344 (2005) \$119,930 (2006) \$365,204 (2005-2008)</p>	<p>This research will explore the development of drug combination products that affect new blood vessel structure and function as well as cancer cell populations within the tumor.</p>
13. Non-invasive monitoring of tumour microenvironment as a tool to optimize anti-cancer therapies	
<p>PI: D Yapp Cancer Research Society \$120,000 (2004-2006)</p>	<p>The overall goal is to examine whether changes in tumour microenvironment, as a tumour develops or responds to therapy, can be used to guide further treatment strategies. Specific goals are to (i) evaluate tumour hypoxia, perfusion, vasculature, pH and glucose metabolism in the HT-29 model before, during and after treatment with CPT-11, and (ii) evaluate levels of hypoxia, vascular density, proliferation and apoptosis at the cellular level with histology and flow cytometry in the same tumour.</p>

14. Novel compositions of liposomal anticancer drugs that exhibit improved drug retention and enhanced therapeutic potential	
<p>PI: M Bally Co-I: D Natalie, E Ramsay CIHR POP \$144,910 (2004-2005)</p>	<p>We have invented a novel method of preparing drug loaded liposomes that uses metal ions and an ionophore, or, channel forming protein. With this method, we are able to entrap the anticancer drug irinotecan with high efficiency into liposomes. Our goal is to develop this invention in a defined series of preclinical studies to the point at which it can be tested in humans in a Phase I clinical trial. Further we will establish whether the method is applicable to other anticancer drugs.</p>
15. The role of cancer associated fibroblasts in mediating treatment response in pancreatic cancer	
<p>PI: S Ng NCIC \$145,622 (2006) \$436,866 (2006-2009)</p>	<p>The goal is to identify key proteins critically involved in tumor–stroma interactions. The identified proteins have the potential to act as therapeutic targets for the development of new drugs or to contribute to new cocktails of existing targeted agents to be used in combination with the two chemotherapy regimens, leading to improvement in the prognosis of pancreatic cancer patients</p>
16. Translating target discovery into better health outcomes for women with breast cancer	
<p>PI: K Gelmon Co-Is: S Chia, S Dedhar, M Bally, J Lee, B Norris et al. CBCRA \$525,896 (2005) \$615,199 (2006) \$1,941,731 (2003-2007)</p>	<p>This research will explore three genetic changes to see whether they can be used to predict which cancers will return after treatment and which will respond to anti-cancer drugs. The group also plans to develop drugs targeted at cells containing these genetic changes.</p>
	<p><i>The research comprises the following projects:</i></p>
	<p><i>The role of protein elongation factor EEF1A2 in breast cancer</i> PI: JM Lee Co-I: D Huntsman, S Dedhar \$42,449 (05) \$130,074 (06) The overall goal is to test whether breast cancer patients whose tumors have more EEF1A2 genes do better or worse than those patients with normal copies of EEF1A2. We will also determine whether EEF1A2 can cause tumor formation in a mouse model of breast cancer.</p>
	<p><i>Preclinical studies designed to rapidly establish the utility of integrin linked kinase (ILK) inhibition to treat breast cancer</i> PIs: S Dedhar, M Bally \$142,400 (05, 06) The goal is to establish whether inhibition of ILK activity will lead to inhibition in tumour growth or progression.</p>
	<p><i>A comprehensive testing strategy for the integration of novel biomarkers into early breast cancer care</i> PI: B Norris, I Olivotto, P Ravdin(UTexas) \$127,232 (05) \$125,232 (06) This project will link the expression of novel biomarkers tested by immunohistochemistry on tissue microarrays with 10-year demographic, staging, treatment and outcome information collected, audited and maintained through Breast Cancer Outcomes unit.</p> <p><i>A Phase I pharmacokinetic and pharmacodynamic study of weekly and twice weekly OSI-774</i> PI: S Chia; Co-I: S. Glück, CB Gilks, M Hayes, M Bally, K Paton, D Katzenstein; CBCRA/ CIHR \$140,000 (05, 06) This study will look at a new drug OSI-774 which acts by blocking the activity of a protein known to be involved in breast cancer development, epidermal growth factor receptor (EGFR). Previous research has suggested that this drug could be useful against breast cancer, but it has not yet been thoroughly studied.</p>

17. Treating cancer with antisense oligonucleotides and small interfering RNAs	
<p><i>PI: M Bally</i> <i>CIHR</i> <i>\$53,270 (2006)</i> <i>\$532,640 (2006-2011)</i></p>	<p>One of the key challenges in drug development is the design of carriers that can efficiently deliver molecules in a manner that provides effective treatment of systemic disease. This study is focused on the development of such delivery systems.</p>
18. Triggered drug release from thermosensitive liposomes	
<p><i>PI: M Bally</i> <i>Co-I: E. Wasan</i> <i>Lotte & John Hecht Memorial</i> <i>Foundation</i> <i>\$144,950 (2004-2006)</i></p>	<p>Our goal is to optimize the lipid composition and the method of drug encapsulation to achieve desirable physical and biological properties of liposomes for hyperthermia-triggered drug release.</p>