Program

Inaugural Summer Cancer Research Symposium

Friday June 13, 2008
Room 1714 LLC, Ontario Veterinary College
University of Guelph

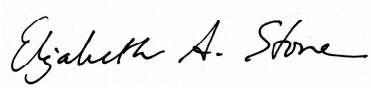
Introductory Remarks

Welcome to the University of Guelph Institue for Comparative Cancer Investigation **Inaugural Summer Cancer Research Symposium**. We appreciate your participation in this event and we trust you will find it informative and enlightening. In keeping with the mandate of the ICCI, we hope that this will be the first of an annual series of research meetings covering the exceptionally wide variety of topics of interest to those involved in cancer research at Guelph. As this is the first such symposium, we have asked several principal investigators on campus to present a brief overview of their research activities. We trust that informal discussions during break periods and at the closing reception will facilitate collaborative interactions between participants. Schedule constraints limited the number of speakers we could invite, so in subsequent years will hope to provide opportunities for additional presentations, including some from the many junior scientists and trainees at Guelph. We welcome any comments or suggestions concerning the format and speakers for future years. Last, but not least, we would like to thank the OVC Dean's Office and to the Arthur Willis Visiting Professorship Program for their financial support.

Co-Organizers
Brenda Coomber and Jon LaMarre.
Biomedical Sciences, University of Guelph

On behalf of the faculty, staff and students of the Ontario Veterinary College, I welcome you to the inaugural symposium of the U of G Institute for Comparative Cancer Investigation (ICCI). This event is but the first step in what I'm sure will be an exciting journey of discovery to understand and put an end to cancer in humans and in our animal companions. With the launch of the ICCI in 2007, the University and OVC made a bold statement about Guelph's unique potential to broaden the scope of cancer research and deepen our understanding of this complex and challenging disease. The ICCI represents our university's growing capacity for research and training in cancer studies and demonstrates that we are truly "changing lives, improving life."

Sincerely,



Dr. Elizabeth A. Stone
Dean, Ontario Veterinary College

Schedule
Guelph ICCI Inaugural Summer Cancer Research Symposium

June 13, 2008 Room 1714 OVC LLC

Morning Session

9:00 Greetings & Opening Remarks:
Ross Hallett, Interim Assistant VP Research
Gord Kirby, Associate Dean, Research and Innovation, OVC
Jonathan Lamarre, Professor, Biomedical Sciences, Event Co-Organizer

9:10 Guest Speaker: **Omar A. Coso**, Career Investigator, National Council of Sciences (CONICET) Argentina, Molecular Biology and Physiology Laboratory, School of Sciences. University of Buenos Aires. Arthur Willis Visiting Professor
Protein Phosphorylation Participates in the Regulation of Gene Expression at Multiple Levels

9:50 **Roger Moorehead**, Associate Professor, Biomedical Sciences, University of Guelph
Examining the Role of IGF-IR in Mammary and Lung Tumorigenesis; A Transgenic Approach

10:10-10:30 coffee break

10:30 **Nina Jones**, Assistant Professor, Cellular and Molecular Biology
Cell Signaling Pathways in Development and Disease

10:50 **Jim Petrik**, Associate Professor, Biomedical Sciences, University of Guelph
The roles of the Vascular Endothelial Growth Factor (VEGF) and Thrombospondin (TSP) Families in Epithelial Ovarian Cancer

11:10 **Kelly Meckling**, Associate Professor, Human Health & Nutritional Sciences
Nutrients and Phytochemicals as Adjuvant Anti-tumor Agents

11:30 **Geoff Wood,** Associate Professor, Pathobiology
Modeling Cancer Using Canine Clinical Cases and Genetically Engineered Mice

11:50 **Paul Woods,** Associate Professor, Clinical Studies, Co-Director, ICCI
Professional Killers: Dendritic cell vaccines for the treatment of canine oral melanoma

12:10-1:30 Lunch Break (on your own)

Afternoon Session

1:30 Thoughts and Reflections **Elizabeth Stone**, Dean, OVC

1:35 **Richard Manderville,** Associate Professor, Chemistry
DNA Modification by Phenolic Toxins: Opportunities for Cancer Treatment

1:55 **Praveen Saxena**, Professor, Plant Agriculture
Plant-based Medicines: Safety Consistency and Efficacy

2:15 **Olaf Berke**, Assistant Professor, Population Medicine
Cancer Registry for Companion Animals

2:35 **Linda Parker**, CRC in Behavioural Neuroscience; Professor, Psychology
Effects of Cannabinoids on Nausea in Rats and Shrews

2:55 **Michèle Preyde**, Assistant Professor, Department of Family Relations and Applied Nutrition
Psychosocial Oncology and Quality of Life

3:15 **Karen Houle**, Associate Professor, Department of Philosophy
Responsibility and Mourning

3:35 Guest Speaker: **Edith Kordon**, Independent Researcher, National Council of Sciences (CONICET) IFIBYNE-CONICET, Buenos Aires, Argentina. Arthur Willis Visiting Professor.
Pregnancy, Lactation and Mammary Gland Involution: Their Involvement in Tumor Development

4:15 Closing Remarks: **Brenda Coomber**, Professor, Biomedical Sciences, Co-Director, ICCI

4:20 Reception Room 1707C Cash Bar

Protein Phosphorylation Participates in the Control of Gene Expression at Multiple Levels.

Omar A. Coso, Career Investigator, National Council of Sciences (CONICET) Argentina. Molecular Biology and Physiology Laboratory, School of Sciences, University of Buenos Aires. Arthur Willis Visiting Professor.

Tight control of gene expression levels is required for healthy cells to maintain homeostasis. Therefore, studies that contribute to the characterization of mechanisms of regulation of gene expression provide clues to understand the transition to the development of pathologies such as cancer. We have been studying the molecular mechanisms that convey extracellular signals to the cell nucleus and control gene expression in living cells. We have mainly focused on signal transduction pathways that regulate Early Responsive Gene (ERG) expression through the mitogen-activated protein kinases (MAPKs). ERGs encode, among others, transcription factors belonging to the AP-1 family. Their expression levels rise quickly and transiently in response to both mitogenic stimuli and stress. Typical examples are the products of the proto-oncogenes *c-jun* and *c-fos* and prolonged expression or activation of these genes has been linked to cellular transformation.

MAPKs include the extracellular signal-regulated protein kinases ERK1/2, JNKs and p38s. These enzymes play an important role both as activators of ERG promoters and in the post-translational modification of its protein products, adding phosphate groups to key residues, as is the case for c-Jun and JNK. We have found that endogenous c-Fos becomes a substrate of p38 MAPKs acting concomitantly with the activation of c-Jun by JNK/ MAPKs and thereby contributing to the complexity of AP1-driven gene transcription regulation.

Regulation of gene expression by means of a limited number of proteins that are the targets of signaling cascades and bind to sequence specific motifs in a nucleic acid is not exclusive to the regulation of promoter activity. It has recently been shown also for exon inclusion and mRNA stability. Using ERGs like *c-jun* and *c-fos* as models, we are studying the role of signal transduction pathways that result in gene expression regulation at multiple levels, gene promoter activity, phosphorylation of the corresponding protein products, and stability of the corresponding mRNAs.

Examining the Role of IGF-IR in Mammary and Lung Tumorigenesis: A Transgenic Approach.

Roger Moorehead, Ph.D., Associate Professor, Biomedical Sciences, University of Guelph

The type I insulin-like growth factor receptor (IGF-IR) is a protein that is highly expressed in a number of cancers including those of the breast and lung. In cell lines established from human lung and breast tumours, activation of the IGF-IR increases cell survival and renders these cells resistant to chemotherapy and radiation therapy. However, animal models of IGF-IR overexpression are required to truly determine the role of IGF-IR in tumour initiation, progression and metastasis. In addition, these animal models can also serve as preclinical systems to test the efficacy of novel or existing therapeutic strategies. As an appropriate animal did not exist, my lab created transgenic mice that overexpress the IGF-IR specifically in the mammary glands or lungs. Using these mice we have shown that elevated IGF-IR expression promotes mammary and lung tumour development. We are now evaluating whether the IGF-IR represents a viable therapeutic target for cancer treatment.

Cell signaling pathways in development and disease

Nina Jones, Ph.D., Assistant Professor, Department of Molecular and Cellular Biology
University of Guelph, Guelph, Ontario

In multicellular organisms, communication between cells is required for the control of important cell processes such as growth, movement and survival. Cellular cues are received by receptor proteins expressed on the surface of the cell and through a complex network of interactions between proteins inside the cell, these signals are interpreted into biological responses. Understanding how protein-protein interactions are regulated in normal cells is of key importance in defining how particular mutations can contribute to diseases such as cancer. Research in our laboratory is focused on characterizing the signal transduction pathways that occur in endothelial cells during the process of blood vessel development (angiogenesis). A second focus within the lab involves the study of adaptor proteins in neuronal signaling pathways and classification of their expression in various brain tumours. Using mouse models and cultured cells, our laboratory aims to provide insight into how perturbations in cell signaling pathways arise in cancer.

The roles of the Vascular Endothelial Growth Factor (VEGF) and Thrombospondin (TSP) Families in Epithelial Ovarian Cancer

Jim J. Petrik, Ph.D., Associate Professor, Biomedical Sciences, University of Guelph.

Epithelial ovarian cancer (EOC) is the most common malignancy of the female reproductive tract and is the most lethal gynecological cancer. Ovarian cancer is detected at a late clinical stage in more than 80% of the cases partly due to diffuse, non-discrete clinical signs and the lack of appropriate screening techniques. We recently have generated a mouse model that closely replicates the human disease. As with other solid tumours, the growth and development of EOC is dependent on the formation of new blood vessels to provide nutrients and waste delivery. Our laboratory is interested in determining the roles of factors that promote blood vessel formation and those that inhibit this process. We hypothesize that treatment of tumour-bearing mice with a natural inhibitor of blood vessel formation will essentially starve the tumour and cause shrinkage. We have shown that the naturally occurring inhibitor TSP-1 opposes the vessel-promoting factor VEGF in the ovary. Thus, TSP-1 might be an important mediator of ovarian tumour development as it may prevent the blood vessel formation required for tumour development. Our preliminary results show that TSP-1 is a potent inhibitor of ovarian tumour growth and may be an important tool in increasing chemotherapy effectiveness and causing tumour regression.

Nutrients and Phytochemicals as adjuvant anti-tumor agents

Kelly A. Meckling, Ph.D., Associate Professor. Human Health and Nutrional Sciences, University of Guelph.

A variety of nutrients including omega-3 fatty acids, and the hormones, retinoic acid and 1,25 dihydroxyvitamin D_3 have potent activity as regulators of growth, differentiation, proliferation and apoptosis. We have shown that omega-3 fatty acids can cooperate with classical chemotherapeutic agents to increase efficacy of drugs against various tumor cell lines *in vitro* and some also *in vivo*. 1,25-D_3 and various analogues can act to modify cell fate through both traditional nuclear vitamin D receptor and through a non-classical membrane-bound receptor named MARRS (membrane activated rapid response to steroids) to induce differentiation or cell death depending on concomitant signals and tissue origin. Currently we are examining the activities of various plant extracts containing a variety of phytochemicals including polyphenolics, for activity as direct,and adjuvant, therapeutic agents against a variety of tumor cell lines while attempting to minimize toxicity to normal tissues. Recently we identified a compound isolated from the Osage Orange that has considerable selectivity against both ER+ and ER- breast cancer cells, leukemia cells and colon cancer cells. Molecular targets of its activity are being examined along with its *in vivo* activity alone and in combination with other compounds in rodent models.

Modeling Cancer Using Canine Clinical Cases and Genetically Engineered Mice

Geoff Wood, Associate Professor, Pathobiology, University of Guelph.

My lab is taking two related approaches to comparative cancer investigation; one makes use of canine clinical samples to perform multi-species oncogenomics, and the other uses a genetically engineered mouse model of prostate cancer to explore the relationship between inflammation and hormone signaling. The first approach is designed to determine which genetic changes are critical for malignant progression in cancer and which are merely bystander mutations. By comparing canine cancer cases with genetically engineered mouse models and human clinical samples, each species can act as a 'bio-filter' to identify the most important changes from within the genomic noise inherent to many cancers. The second approach uses mice engineered to develop prostate tumours that are initially hormone dependent and regress upon castration, but later re-grow as hormone-independent tumours. In humans there is an association between the emergence of hormone independent prostate cancer and inflammatory cell infiltration. My aim is to study this association by crossing the prostate cancer model to a mutant mouse that has heightened prostatic macrophage influx following castration.

Professional Killers: Dendritic cell vaccines for the treatment of canine oral melanoma

J. Paul Woods DVM MS Diplomate ACVIM (Internal Medicine, Oncology)
Associate Professor, Clinical Studies, Co-Director University of Guelph Institute for Cancer Investigation (ICCI)

Melanoma, the most common oropharyngeal cancer in dogs, is characterized by local invasion and early widespread metastases. Surgery and/or radiation therapy have been employed for local control; however, chemotherapy has not been successful at preventing systemic metastatic disease. Therefore, immunotherapy in the form of vaccines is being investigated for control of metastatic disease. Recent advances cloning tumour associated antigens (e.g. gp100) which are potential immunological targets and adoptive gene transfer techniques have led to new novel approaches to cancer therapy.
This study utlilized an autologous dendritic cell vaccine using xenogenic human gp100 antigen for the treatment of oral melanoma in dogs presenting to the Veterinary Teaching Hospital of the Ontario Veterinary College with histologically confirmed oral melanoma.

DNA Modification by Phenolic Toxins: Opportunities for Cancer Treatment

Richard A. Manderville, Ph.D., Associate Professor, Department of Chemistry, University of Guelph.

The double sword nature of covalent modification of DNA to form DNA adducts is illustrated by their involvement in the etiology and treatment of cancer. In some instances DNA adducts, that are not repaired by DNA repair enzymes, compromise the fidelity of DNA replication, leading to mutations and possibly cancer. Other DNA modifications such as interstrand cross-links are believed to be the source of cytotoxicity for many clinically used anticancer drugs. Our interest in covalent DNA adducts stems from research on DNA damage by the phenolic toxin, ochratoxin A (OTA); a fungal carcinogen that is a common contaminant of grains and cereal products. The toxin undergoes oxidative metabolism to form radical intermediates that attach covalently to deoxyguanosine (dG). The OTA-dG adduct belongs to a family of DNA adducts formed by a variety of chemicals and other natural products. We are interested in establishing the structural and biological properties of these adducts through their chemical synthesis and site-specific incorporation into oligonucleotides. While this effort is expected to uncover their mutagenic properties, we have found that phenolic adducts have potential to form interstrand DNA cross-links that may have therapeutic value. This evidence along with our new design ideas for modified dG bases as anticancer drugs will be presented.

Plant-based medicines: Safety consistency and efficacy

Praveen K. Saxena, Ph.D, Professor, Department of Plant Agriculture, University of Guelph

Plants synthesize, accumulate and use a bewildering range of secondary metabolites, many of which have been used as medicines for centuries. The secondary metabolite production of medicinal plants is affected by plant genetics and environmental conditions of cultivation, harvesting, processing and distribution. The widespread occurrence of chemical variability and compromised quality of medicinal plants often produce inconsistent results in clinical trials. Thus, the up-coming legislations requiring consistency and efficacy in many parts of the world would change how plant-based medicines are developed, manufactured, and marketed. We have developed an integrated process for the selection of elite lines of medicinal species such as Saint John's wort, Echinacea, and Scutellaria, with specific, consistent levels of medicinal metabolites. The effectiveness of the extracts of optimized Saint John's wort and Scutellaria lines was demonstrated using in vitro bioassays with HT-29 colon cancer cells and animal model systems.

Cancer Registry for Companion Animals

Olaf Berke, Assistant Professor, Department of Population Medicine, University of Guelph

Researchers at the OVC are starting to establish a population-based companion animal cancer registry. The registry project will begin as a pilot project focusing on all cancers within the dog and cat population in the city of Guelph.

Cancer registries are an integral part of human cancer research, however for companion animals such registries do not exist in North America. Population-based cancer registries enable epidemiologists to study the occurrence of cancer in the population and to make statements when, where and why the occurrence of cancer is more or less likely in the population. This specifically includes geographical and temporal comparisons.

The fundamental issue is that a population-based registry represents the entire population-at-risk and collects all cases. Therefore population-based registries are different from hospital registries, which collect information about certain patients without reference to the underlying population. Studies based on hospital records allow the investigation of treatment options and estimation of survival times, but the results are not necessarily representative for the general population.

The progress of the project to date and the next steps will be presented; major challenges for the future will be identified and discussed.

Effects of cannabinoids and ondansetron on the expression of anticipatory nausea in rats.

Linda Parker, Canada Research Chair in Behavioural Neuroscience and Professor of Psychology, University of Guelph.

Cancer patients undergoing chemotherapy treatments often report anticipatory nausea (AN) when they are re-exposed to contextual cues previously paired with treatment. AN is resistant to treatment with classical anti-emetic drugs such as ondansetron (OND). Although rats do not possess the mechanism to vomit, they do display conditioned gaping reactions elicited by an odour-laced context, previously paired with lithium-induced sickness—serving as a rodent model of AN. The primary constituents in marijuana, psychoactive Δ9 – tetrahydrocannabinol (Δ9- THC) and nonpsychoactive cannabidiol (CBD), are both effective in suppressing both the establishment and the expression of conditioned gaping in this model. Additionally, prolonging the action of the endogenous cannabinoid, anandamide (AEA), by inhibiting fatty acid amide hydrolase (FAAH), which rapidly deactivates AEA also suppresses AN in rats. On the other hand, as shown with humans, OND does not affect AN in this model. The conditioned gaping model in rats is an effective pre-clinical tool for assessing the potential of treatments to attenuate not only acute nausea, but also AN in human patients.

Psychosocial Oncology and Quality of Life

Michèle Preyde, PhD, Assistant Professor, University of Guelph, Pat Chevalier, MSW, RSW, Grand River Regional Cancer Centre, Jane Hatton-Bauer, Clinical Director, Supportive Care and Outpatient Clinics, Grand River Regional Cancer Centre

Patients with cancer often experience coping difficulties, grief, financial burden (e.g., costly medication, affect on ability to work), changes in their roles and abilities, and emotional distress. Research suggests that many patients with cancer and their families could greatly benefit from psychosocial oncology care that is specifically tailored to their unique needs. Our main research interest concerns how to effectively support patients while they are receiving medical treatment for cancer and their families, with a focus on their quality of life, and implications for the quality of work life for oncology staff and the support care team. My previous research in healthcare in areas such as the NICU and geriatric discharge planning inform the present focus in cancer. To date our cancer care research has taken the form of systematic reviews and surveys, with the hope of utilizing results to develop enhanced psychosocial oncology options, and testing the effectiveness with a RCT and process evaluation. Future research activities could include explorations of: care during other stages (diagnostic, remission, terminal), the perceptions of oncology medical staff, and environmental influences.

Responsibility and Mourning

Karen Houle, Ph.D., Associate Professor, Department of Philosophy, University of Guelph

One of the profound things about loss and death is the way that it opens up, or brings out of us, a possibility or an opportunity for action and response, for reflection and for insight, that simply cannot be generated in advance by the self, even a peaceful and wise self having made preparation for a loss or a death. Loss and death are a sort of absolute corner around which no human can see. In this presentation I focus on two ethical corollaries of this metaphysical claim. The first is that there is something *to do* after death which death itself calls us to do, and doing or not doing that, responding or not responding to whatever it is that death opens up, for us, to do, is an ethical moment, an ethical question. Responsibility is tied to mourning, and hence, since there are different ways of responding to loss and death, there are more or less ethical forms of mourning. This leads to the second corrolary, which asks us what kinds of deaths and losses we do, and do not, mourn. Given that animal lives and deaths are so intimately connected to human lives and deaths -- cancer research being absolute proof of this -- then we should begin to ask ourselves the difficult questions of what, if anything, animal lives and their losses, profoundly and uniquely, position us to do?

Pregnancy, lactation and mammary gland involution: Their involvement in tumor development

Edith Kordon, Independent Researcher, National Council of Sciences (CONICET) IFIBYNE-CONICET, Buenos Aires, Argentina. Arthur Willis Visiting Professor

It is well known that early first childbirth reduces the risk of developing breast cancer. However, epidemiological studies show that in pre-menopausal women there is a transient risk for developing breast cancer in the first 5 years following pregnancy. Tumors that appear in such a period are called pregnancy-associated breast cancers (PABC). There are not many animal models that are useful for studying the initiation and progression of mammary tumors in the context of pregnancy, lactation and involution of the mammary gland. The pregnancy-dependent mammary tumors induced by the retrovirus MMTV (mouse mammary tumor virus) offer that possibility. During the last 10 years, our group has studied the biology of these tumors, which are estrogen-dependent in their early stages to later progress to a hormone-independent behavior. We have demonstrated that this progression occurs associated with the loss of estrogen and progesterone receptor expression and to the selection of early occurring virus insertions. By inverse-PCR we were able to clone some of these MMTV insertion sites. Our most recent results are focused on the analysis of the biological activity and expression regulation of two genes found in those loci: *R-sponding 1* and *β1-integrin.* In addition, it has been indicated that it is not pregnancy nor parturition, but mammary involution that increases the risk of PABC. Therefore, we are analyzing different factors that play a role in the transition from lactation to involution and could also be relevant for breast cancer development. Our studies are mainly focused on inflammatory cytokines such as LIF and TNFalfa, transcription factors such as Stat3 and Stat5, and mRNA stability regulators such as TTP. In addition, we are investigating the role that mechanical stress can exert on mammary epithelial cells to trigger events that lead to either apoptosis or transformation of mammary epithelial cells.