



# **cancer biology**

***Graduate Program in Cancer Biology***

***University of North Texas Health Science Center***

***Alakananda Basu, Ph.D., Graduate Advisor***

***Jacklyn Crisp: Graduate Secretary***

***RES-416M***

***817-735-2131***

# **1. Description of the Cancer Biology Program**

## **1.1. General description and goals:**

The Cancer Biology program is an interdisciplinary program that offers both M.S. and Ph.D. degrees. The goal of this program is to provide students with rigorous education and training in biomedical sciences with a specialty in Cancer Biology. The students will receive training through original research, formal classroom education, problem-based learning, seminars and journal clubs. The program includes faculty members from several departments. Our faculty members are engaged in various aspects of cancer research, including signal transduction, apoptosis, cell proliferation and differentiation, cancer immunology, drug resistance, tumor invasion & metastasis, DNA damage and repair, gene delivery, cancer therapeutics, molecular carcinogenesis, and nanotechnology/imaging. The research projects employ state-of-the-art molecular, cellular & biochemical techniques that include genomics, proteomics, mass spectrometry, molecular cloning, gene targeting, FACS analysis, advanced fluorescence spectroscopy, and optical imaging.

A major advantage of this program is that the students will have the freedom to choose faculty advisors from any department according to their research interests. In addition, students will be able to utilize the resources and expertise of faculty members with diverse background from several departments. During the first year, the students will acquire sufficient background in biological sciences, including biochemistry, molecular biology and genetics, cell biology, pharmacology, physiology, microbiology and immunology. The students will have the opportunity to rotate in research laboratories in any department prior to selecting their thesis advisors. The students will take advanced courses, such as Molecular Aspects of Cell Signaling and Molecular and Cell Biochemistry of Cancer. The students will be able to select additional elective courses from any department based on their needs and interests. Ph.D. candidates are admitted to candidacy after successful completion of their preliminary oral qualifying examinations and defense of an NIH-style research grant proposal. M.S. candidates are expected to graduate in 2 years whereas Ph.D. candidates may require 5 years to complete their degree.

## **1.2. Graduate Faculty and Specific Research Programs**

### **Sanjay Awasthi, M.D., Ph.D.**

The mercapturic acid pathway has been of central importance in cancer, implicated in carcinogenesis, and chemotherapy drug-resistance through its rate-limiting enzyme, glutathione S-transferase (GST). The thioether glutathione-electrophile conjugates (GS-E) that originate from GST-catalyzed reactions of glutathione (GSH) with foreign toxic electrophilic compounds (xenobiotics), cytochrome-P-450 mediated electrophilic derivatives of xenobiotics, as well as lipid-peroxidation derived endogenous electrophiles. The GS-E efflux pump, the necessary next step after GST-mediated conjugation has been conclusively identified as the multi-specific and multifunctional protein, RLIP76 (encoded by the human gene RALBP1). Because of the known inhibition of GST by GS-E, and the toxic/pro-apoptotic nature of many endogenously derived GS-E, we predicted that inhibiting RLIP76 would have a uniformly toxic effect in cancers. We have recently confirmed this postulate in studies showing striking, consistent and very broad-spectrum antineoplastic activity of this approach in cell and animal models. The present focus of our basic research is on chemical and biochemical studies of mercapturic acid pathway in the pathobiology of diseases including cancer, radiation poisoning, diabetes, atherosclerosis and neurodegenerative disorders. Our clinical focus is the development of mercapturic acid pathway modulators to be used in translational clinical studies for therapy for these diseases.

### **Yogesh Awasthi, Ph.D.**

We have an active and productive research program focusing on glutathione-linked cellular detoxification mechanisms (exclusion/transport of xenobiotics and their biotransformation). These studies have a relevance to diseases such as cancer, atherosclerosis, cataractogenesis, and retinopathy, where chronic oxidative stress and environmental factors such as exposure to UV and toxic xenobiotics are involved in the mechanisms of pathogenesis. Currently our research is focused on two inter-related projects: 1) Protective role of Glutathione S-transferases (GSTs) against the toxicity of environmental pollutants and carcinogens and also against endogenously generated toxic Lipid peroxidation products such as 4-hydroxynonenal (4-HNE). Our central hypothesis is that 4-HNE and perhaps other lipid peroxidation products play a major role in stress-induced cellular signaling and GSTs by regulating the intracellular concentrations of these products can modulate stress-mediated cell cycle signaling. 2) We have discovered a novel multi-specific transporter ( RLIP76 or Ralbp1 ) which is the major transporter of various glutathione-conjugates (GS-E) as well as cationic chemotherapeutic agents such as doxorubicin and is involved in the mechanisms of multi-drug resistance of cancer cells. We are studying the protective role of this transporter against toxins and also against ionizing radiation and its functions as a stress-response multi-functional protein involved in stress-mediated

signaling. We have shown that in animal models as well as in cultured cells inhibition of RLIP76 function leads to apoptosis of cancer cells and that its over expression protects against ionizing radiation and toxicants. These studies are relevant to cancer and diabetes.

### **Alakananda Basu, Ph.D.**

Dr. Basu's research interest is in signal transduction, especially in the context of cancer chemotherapy. The ultimate goal of cancer chemotherapy is selective eradication of malignant cells. Currently used anticancer agents are of limited value due to their toxicity to normal tissue and development of resistance by malignant tissue to these anticancer agents. One area of research is to investigate how signal transduction pathways regulate anticancer drug sensitivity and to elucidate the molecular mechanism(s) of drug resistance. Another area of research focuses on tumor necrosis factor- $\alpha$  (TNF) signaling in breast cancer. TNF induces apoptosis, a genetically programmed cell death and autophagy, a process by which a cell recycles its own components to survive under stressful or nutrient-derived conditions. While lack of apoptosis contributes to cancer, it is not clear if autophagy promotes or prevents cancer. A major effort is to understand how various signaling pathways, such as mTOR/p70 ribosomal S6 kinase, Akt/protein kinase B and mitogen-activated protein kinases regulate apoptosis and autophagy. Three-dimensional cell culture model is being used to dissect the role of various signaling pathways in breast carcinogenesis. A third area of research is to study the regulation of protein kinase C isozymes that play important role in cell survival and cell death. The ultimate goal is to exploit intracellular signaling systems to benefit cancer therapy.

### **Patrick Cammarata, Ph.D.**

Human lens epithelial cells survive the entire life of the host and undergo consistent mitotic activity. As such, the lens epithelium represents a cell type capable of controlled active cell division. Interestingly, the lens has never been documented to show a tumor, making the lens unique in that it is *cancer-free* the life of the host. From a biological point of view, the lens epithelia are fascinating because they represent an experimental system highly prone to resist apoptosis, but in a continual state of limited mitosis and at the same time, remains non-tumor forming.

Past work in my laboratory (Flynn et al., Am J Physiol Endocrinol Metab. 294: E589, 2008; Flynn et al., Am J Physiol Endocrinol Metab. 295:E637-647, 2008) has concentrated on the fact that estrogen has been shown to be mitoprotective in human lens epithelial cells, as well as, breast carcinoma, prostate carcinoma and neurodegenerative diseases, stabilizing mitochondria against oxidative stress-induced depolarization. But the biological and clinical significance of estrogen in visual systems is highly controversial. Instead, we have altered the direction of our experimental strategy in that recent work in my laboratory has identified the endogenous protein machinery that regulates mitochondrial stability in the lens epithelium without the need to utilize estrogen. My laboratory is actively identifying the critical signal transduction pathways and protein-receptor complexes that are involved in

this protective mechanism without resorting to the use of estrogen.

**Hriday Das, Ph.D.**

Presenilin-1 (PS1) is a transmembrane protein which functions as ER Ca<sup>2+</sup> leak channel and also is the catalytic subunit of the PS1/\_-secretase complex. PS1/\_-secretase is involved in the proteolytic processing of type I membrane proteins including amyloid precursor protein (APP) and Notch-1 receptor. Mutations of the PS1 gene cause early-onset familial Alzheimer's disease by altering PS1/\_-secretase mediated processing of APP. Some pathogenic mutations of the PS1 gene also potentiate IP3R-mediated Ca<sup>2+</sup> liberation from ER to cytoplasm. Transcriptional regulation of the PS1 gene appears to modulate both PS1/\_-secretase activity and ER Ca<sup>2+</sup> leak channel. We have shown that PS1 expression can be regulated by JNK signal transduction pathway involving tumor suppressor protein p53. Therefore, the long term goal of this research is to understand how wild type p53 and cancer causing mutations of p53 differentially regulate the processing of APP and Notch1 as well as PS1-mediated ER Ca<sup>2+</sup> leak channel.

**Erb4** is a transmembrane receptor tyrosine kinase that regulates cell proliferation and differentiation. Erb4 undergoes ectodomain shedding by PS1/\_-secretase cleavage to produce Erb4ICD, which translocates to the nucleus and activates the transcription of target genes. Because the Erb4ICD retains a tyrosine kinase domain, it is possible that nuclear substrate may be phosphorylated by Erb4ICD leading to novel mechanisms of action of this receptor. Since overexpression of PS1 increases the generation of Erb4ICD fragment, we are studying how regulation of PS1 may control cell growth and proliferation.

**Dan Dimitrijevič, Ph.D.**

As a result of our activities in Tissue Engineering, we are interested in control of proliferation and differentiation of normal human cells *in vitro*, with particular emphasis on epithelial cells. Extending proliferation without initiating cancerous phenotype suits our requirements. To date we have employed ectopic expression of human telomerase reverse transcriptase for this purpose and are also studying 14-3-3 proteins in this context. Both have resulted in generation of several cell lines with extended life span, but intact p53 and pRb expression. Our goal may also be achieved by delaying differentiation of epithelial cells. This is a more difficult task to accomplish as the early events in initiation of differentiation are not well understood. Since most of the human cancers are of epithelial cell origin, understanding epithelial cell proliferation and early differentiation signals are also important in cancer where the proliferation is uncontrolled and differentiation is inhibited. Because telomere maintenance is a global mechanism, involving vast majority of somatic cells, our interests in 14-3-3 proteins is related to the possibility of studying epithelia cell specific mechanism of cell cycle regulation (or dysregulation in the case of cancer cells). We also have experience and expertise in three-dimensional tissue constructs using human cells which has yet to be translated into *in vitro* models for evaluation of cancer chemotherapeutic agents.

**Art Eisenberg, Ph.D.**

Dr. Eisenberg is a pioneer in the development of DNA Identity testing. He is a world-renowned molecular geneticist who helped develop many of the procedures, techniques and quality-control standards currently used in human identification. As director of the DNA Identity lab, Dr. Eisenberg has been responsible for developing a state-of-the-art clinical reference laboratory using DNA technology for the determination of paternity, forensic casework analysis, the identification of missing persons, cancer diagnostics and the analysis of genetic diseases. His research on the analysis of DNA polymorphisms has been in the development of tests for the detection of several types of leukemia and lymphoma. Dr. Eisenberg is considered one of the top DNA advisors for the Federal Bureau of Investigations Laboratory Division. He was appointed chairman of the United States DNA Advisory Board, which recommended standards to the Director of the FBI for quality assurance and for proficiency testing of forensic laboratories throughout the United States. He currently serves on the Histocompatibility and Human Identification committee for the College of American Pathologists. The committee evaluates the performance of laboratories that are using the analysis of genetic polymorphisms to monitor residual disease following a bone marrow transplant for the treatment of certain forms of leukemia.

**Anuja Ghorpade, Ph.D.**

The research in my laboratory focuses on the inter- and intra-cellular signaling mechanisms implicated in inflammation, HIV-1 and other neural injury. Cytokines, including [tumor necrosis factor (TNF)- $\alpha$ , interleukin (IL)-1 $\alpha$ , IL-1 $\beta$ , IL-6, and tumor growth factor (TGF)- $\beta$ 1], have all been associated with both HIV-1-associated dementia (HAD) and are implicated in a variety of cancers. Thus, inflammation that begins with the injury in the brain, is amplified through interactions with other neural cells, will likely serve as a model for better understanding of a variety of diseases. More specifically, several distinct pathways are currently under investigation. These include, but are not be limited to, role of matrix metalloproteinases and their tissue inhibitors, other chemokines such as CXCL8 and CCL2, molecules upregulated in activated astrocytes such as CD38 and molecules that are involved in microglial infection and activation. We believe that the role of signaling molecules such as NF- $\kappa$ B, STAT3, SHP-2, all implicated in both inflammation and cancer biology will improve our understanding of the cellular mechanisms involved in neural injury and also facilitate our understanding of the mechanisms involved in brain tumors.

**Zygmunt “Karol” Gryczynski, Ph.D.**

Dr. Zygmunt Gryczynski and his colleagues have established a Center for Commercialization of Fluorescence Technologies (CCFT) with support from Emerging Technology Funds (EFT) of Texas. His early work at the University of Maryland was focused on ultrafast time-resolved fluorescence spectroscopy, intrinsic fluorescence of hemoproteins as well as the thermodynamics of ligand binding and the allosteric mechanism of O<sub>2</sub> binding in hemoproteins. He has pioneered the use of multi-photon

excitation and light quenching in time-resolved fluorescence spectroscopy. His focus has been on applications of fluorescence spectroscopy to study biological systems using time-resolved fluorescence, anisotropy, and FRET. He also pioneered novel fluorescence sensing methods for biomedical applications in tissue and blood. His interest includes modern optical imaging methods with focus on fluorescence microscopy. For the last six years his interests expanded to nanotechnology and applications of novel plasmonic effects induced by light in metallic nanostructures to fluorescence spectroscopy. He pioneered metal enhanced fluorescence and surface plasmons coupled emission phenomena for biomedical and diagnostics application. His current focus is to explore quantum-level interactions to study the dynamics of biophysical and biochemical processes at the molecular level. He is an author of over 140 peer-review publications and 8 book chapters.

**Ignacy Gryczynski, Ph.D.**

Fluorescence spectroscopy and microscopy progressed recently towards a nanotechnology. The technological advances in optics, computers, surface science and engineering made possible single molecule detection and overcame the diffraction limit. Dr. Gryczynski's research focuses on fluorescence enhancements near metallic surfaces and particles. The enhanced fluorescence is being applied to sensing devices and bioassays. He also has a joint appointment in the Department of Molecular Biology and Immunology, where he co-manages the time-resolved fluorescence laboratory. This laboratory carries basic spectroscopy research and is open to the needs of researchers from both departments.

**YiWei Jiang, Ph.D.**

A key question in eukaryotic differentiation is whether there are common regulators or biochemical events that are required for diverse types of differentiation or whether there is a core mechanism for differentiation. The unicellular model organism *S. cerevisiae* undergoes filamentous differentiation in response to environmental cues. Since conserved cell cycle regulators, the mitotic cyclin-dependent kinase Clb2/Cdc28 and its inhibitor Swe1, were found to be involved in both nitrogen starvation- and short chain alcohol-induced filamentous differentiation, they were identified as components of the core mechanism for filamentous differentiation. We have discovered that slowed DNA synthesis also induces yeast filamentous differentiation through conserved checkpoint proteins Mec1 and Rad53. The mechanism for Rad53 activation in filamentation is distinct from the classic phosphorylation by Mec1 in response to DNA damage or replication block. Swe1 and Clb2 are also involved in this form of differentiation, and the core status of Swe1/Clb2/Cdc28 in the mechanism of filamentous differentiation has therefore been confirmed. Slowed DNA synthesis also induces differentiation in mammalian cancer cells, and such stimulus conservation may indicate that the core mechanism for yeast filamentous differentiation is conserved in mammalian differentiation. Therefore, yeast filamentous differentiation may be an excellent model for cancer development and therapeutics. The human homologues of

MEC1 and RAD53 (ATM/ATR and CHK2 respectively) are indeed known tumor suppressor genes. Our studies of yeast differentiation may help shed light on human cancer development and the discovery of novel anticancer drugs.

**Harlan Jones, Ph.D.**

There is increasing evidence that psychological stress is an important risk factor in the initiation and progression of chronic disease (e.g. cancer, atherosclerosis, and chronic infectious disease). Dr. Jones' research interest include the investigation of how stress affects host immune mediation of chronic disease states with the intention of facilitating comprehensive therapeutic approaches against stress-induced disease pathogenesis.

**Myoung Kim, Ph.D.**

Dr. Kim's research is focused on understanding the mechanism of RNA polymerase II transcription and how the transcriptional activator, Oct-1 protein, stimulated transcription from MMTV promoter. As a post-doctoral fellow she studied the transcription termination occurring during the micro-delta Ig heavy chain gene switching and the role of matrix metalloproteinases in the tumor invasion. Currently her lab investigates the prostate cancer development and metastasis using *in vitro* cell culture and *in vivo* animal models.

**Andras Lacko, Ph.D.**

Dr Lacko's research involves a novel drug delivery model utilizing synthetic/ reconstituted high density lipoproteins (rHDL). This drug delivery formulation has shown the promise during preliminary studies to reduce toxic side effects and diminish drug resistance encountered with cancer chemotherapy. Accordingly, the paclitaxel (PTX) containing, rHDL nanoparticles have been found to kill cancer cells with a 5-20 fold higher efficiency than the free drug. Furthermore, during animal studies a 2.3-fold and 1.4-fold higher dosage of rHDL/PTX nanoparticles were substantially better tolerated by female mice than conventionally used chemotherapeutic agents (Taxol® and Abraxane® respectively). Currently animal studies are under way to evaluate the tumor suppressing capabilities of the rHDL drug delivery model. It is anticipated that when completed, these studies will substantially improve the efficacy of cancer chemotherapy and thus the prognosis for cancer patients.

**Porunelloor Mathew, Ph.D.**

Natural killer (NK) cells are a subpopulation of lymphocytes that play an important role against tumor metastasis and various viral and bacterial infections. NK cells are also involved in the rejection of allogeneic bone marrow transplants. The molecular basis of NK cell recognition and activation by target cells is poorly understood. NK cell functions are controlled by a balance between positive and negative signals through various receptors. We have identified, cloned and characterized several receptors expressed on NK cells. One of the receptors, 2B4, is a member of the immunoglobulin superfamily and is involved in

killing cancer cells and virus-infected cells by NK cells. We have determined CD48 as the counter-receptor for 2B4 in both mice and humans. Recently, we have generated 2B4 knockout mice and this will allow us to study the biology of this molecule in the immune system. We are investigating the signal transduction pathway via 2B4. We have also identified two other novel receptors called LLT1 and CS1. The functional role of LLT1 and CS1 in regulating immune responses is being investigated. The major objective of Dr. Mathew's laboratory is to decipher the molecular basis of tumor cell recognition by NK cells. The information obtained in these studies will be utilized towards developing new strategies for eliminating tumor cells.

### **Laszlo Prokai, Ph.D.**

Dr. Prokai is recognized nationally and internationally for his work on discovery, bioorganic and medicinal chemistry of central nervous system agents, as well as on neuropeptides, proteomics and mass spectrometry. His cancer research interests focus on (i) prevention of estrogen-related malignancies associated with hormone therapy by discovering and developing compounds with improved safety and selectivity compared to current estrogen products, (ii) proteomic assessment of (a) the impact of oxidative stress in cancer and during chemotherapy, and (b) signaling events associated with cancer.

### **Abha Sharma, Ph.D.**

My interest in Cancer Research was initially sparked during my doctoral studies during which I investigated the energetics of DNA repair mechanisms in UV-damaged normal and chronic myeloid leukaemic peripheral blood leukocytes for the optimization of radiation therapy of cancer. Currently my research interests are focused on the protective role of glutathione S-transferases (GSTs) against toxic compounds, both external and formed within the cell. Failure of cellular defense mechanisms (detoxification) can turn a normal cell into a cancer cell which then may give rise to a clinically significant tumor. Basically, the core of my studies is based on understanding tumor biology and the process of carcinogenesis as it relates to detoxification. Another critical factor in tumorigenesis is the malfunction of the tumor suppressor p53, whose suppressive function is regulated by various post-translational modifications such as phosphorylation, acetylation and ubiquitylation. Presently, we are investigating the role of hydroxynonenal (4-HNE), a stable and toxic end-product of lipid peroxidation on the p53-mediated intrinsic apoptotic pathway in human retinal pigment epithelial cells (RPE), and its modulation by GSTs and associated cellular redox factors. Results from these studies will advance our understanding of the tumor suppressive function of p53 and establish viable targets for preventive and therapeutic strategies for various types of cancer.

### **Rajendra Sharma, Ph.D.**

Our current research interests are focused on three interrelated themes: 1) Detoxification of xeno- and endo-biotics through biotransformation and active transport; 2) Role of lipid

aldehyde, 4-hydroxynonenal in stress-induced signaling; 3) Mechanisms of drug resistance in cancer cells. Studies in our laboratory have demonstrated that exogenous and endogenously generated electrophilic compounds are metabolized in cells through GST catalyzed conjugation with glutathione and are transported across the membrane through ATP-dependent transport mechanism mediated by RLIP76, a Ral-binding GTPase activating protein. This novel multi-specific transporter (RLIP76 or RalBP-1) was first identified by our research group and has been shown as the major transporter of various glutathione-conjugates (GS-E) as well as cationic chemotherapeutic agents such as doxorubicin and is also involved in the mechanisms of multi-drug resistance of cancer cells. Studies on the metabolism and transport of xeno- and endo-biotics have relevance to various chronic diseases including cancer where chronic oxidative stress and environmental factors such as exposure to harmful radiations and toxic chemicals are involved in the pathogenesis of these chronic diseases. Additionally, we have recently demonstrated that the intracellular concentration of the lipid peroxidation product 4-hydroxynonenal (4-HNE) exerts opposing effects on key components of the signaling cascade which governs various cellular processes including cell cycle, proliferation and apoptosis. 4-HNE is therefore, a common denominator in stress-induced signaling. Our recent studies have indicated that 4-HNE induces apoptosis in cells through Fas-mediated extrinsic pathway which is independent of Fas-L and DISC formation. Furthermore, 4-HNE also self limits apoptosis by facilitating export of transcription repressor Daxx from nucleus to cytoplasm where it binds to Fas. These novel findings will help us to understand the mechanisms of death receptor mediated apoptotic signaling and to develop new preventive and therapeutic strategies for cancer.

#### **Wolfram Siede, Ph.D.**

Work in our laboratory concerns DNA damage responses in the yeast *Saccharomyces cerevisiae* as a model organism. Specifically, we are interested in the mechanisms of checkpoint arrest and mutagenesis following UV radiation, oxidative damage, inhibitors of replication and cisplatin. The yeast pathways have been shown to be highly conserved in human cells. We also have ongoing projects in anti-cancer drug screening using yeast.

#### **Meharvan Singh, Ph.D.**

The research interests of my laboratory relates to understanding and characterizing novel mechanisms by which gonadal steroids, including androgens, elicit their effects. Within this context, we have recently described a novel membrane androgen receptor that is associated with the promotion of cell death. Our data, therefore, suggest that within a given cell type, there may be two competing pathways by which androgens elicit their effects: one that promotes cell survival (through the classical androgen receptor), and the other that promotes cell death (through activation of the membrane androgen receptor). Thus, we argue that androgens may exacerbate the growth of certain androgen-sensitive tissues or cancers depending on the relative abundance of the two receptor mechanisms. As such, we

believe that the more complete characterization of the membrane androgen receptor may be valuable in defining a novel cellular target that can be exploited for the development of safer and more effective treatments for androgen-sensitive neoplasms (such as prostate cancer).

**Sharad Singhal, Ph.D.**

Our laboratory is interested in glutathione metabolism and its role in stress-defense, carcinogenesis, drug-resistance, radiation-resistance, and cell-signaling mechanisms. Recently, we have demonstrated that RLIP76 (RALBP1, ral binding protein) is the major glutathione-electrophile conjugate (GS-E) and drug-transporter in mammalian cells. RLIP76 is a crucial stress-protective protein which regulates signaling in the Ral, Ras, EGF, Insulin, and other pathways. Inhibition or depletion of RLIP76 causes cancer cell apoptosis in cell culture, and regression of melanoma, lung and colon cancer in xenograft. "RLIP76 is a membrane associated non-ATP binding cassette (ABC) multi-specific transporter of chemotherapeutic drugs as well as of glutathione-electrophile conjugates (GS-E) and involved in signaling pathways. This transporter is ubiquitously expressed in human as well as in rodent tissues. It is frequently over-expressed in malignant cells, and plays a prominent anti-apoptotic role selectively in cancer cells through its ability to control cellular concentration of pro-apoptotic oxidized lipid byproducts. Inhibition of RLIP87, using antibodies, or depletion of RLIP76 using either siRNA or anti-sense phosphorothioate oligonucleotides kills cancer cells or caused apoptosis in malignant cells preferentially.

**Jamboor Vishwanatha, Ph.D.**

Dr. Vishwanatha's research interest is in regulation of cell proliferation and DNA replication in cancer cells. The objective of his research is to understand the mechanisms that regulate normal and cancer cell proliferation. His lab is particularly interested in the molecular changes accompanying progression of prostate and oral cancers. They have identified novel genes and proteins associated with cancer progression. The long-term objectives of the laboratory are: (i) to understand mechanism of regulation of cell proliferation and DNA replication in normal and cancer cells, and (ii) to utilize nanotechnology to deliver drugs and bioactive compounds for cancer therapy. These long-term objectives are addressed by the following independent, but related, research projects: 1. Nucleo-cytoplasmic shuttling of annexin II and its impact on cell proliferation; 2. Modulation of nitric oxide-mediated apoptosis by nicotine in oral epithelia; 3. Studies on the genetic alterations in the progression of prostate, breast and oral cancer; 4. Nanoparticle mediated sustained gene delivery in breast and prostate cancers.

**Robert Wordinger, Ph.D.**

Glaucoma is a leading cause of blindness worldwide and is characterized by a defect in the ability of aqueous humor to drain efficiently through the trabecular meshwork. This abnormality results in elevated intraocular pressure resulting in death of retinal ganglion

cells and subsequent blindness. Our laboratory studies gene and protein expression of growth factors and neurotrophins by human trabecular meshwork cells and cells of the human optic nerve head. We wish to understand the role these factors play normally and in the pathophysiology of glaucoma. Modern cell and molecular biology techniques are utilized by graduate students and research associates. Ultimately, we wish to discover new and innovative methodologies for the diagnosis, management and treatment of glaucoma.

**Shoahua Yang, Ph.D.**

Estrogen receptors (ERs) are believed to be ligand-activated transcription factors belonging to the nuclear receptor superfamily, which upon ligand binding translocate into nucleus and activate gene transcription. To date, two ERs have been identified: estrogen receptor alpha (ERalpha) and estrogen receptor beta (ERbeta). ERalpha plays a major role in the estrogen-mediated genomic actions in both reproductive and non-reproductive tissue, while the function of ERbeta is still unclear. We and other laboratories recently demonstrated the localization of ERbeta in mitochondria, suggesting the involvement of ERbeta in mitochondrial function. Down regulation of ERbeta in various cancers has been well demonstrated, suggesting the anti-cancer property of ERbeta. My current research interests are to determine the mechanism underlying the ERbeta's anti-cancer effect, with a focus on mitochondrial function.

## 2. Course Offerings

### M.S. Degree plan for Cancer Biology

#### Year 1: Fall

BMSC 6301	Integrative Biomedical Sciences I: Principles of Biochemistry	4 SCH
BMSC 6302	Integrative Biomedical Sciences II: Molecular Cell Biology	4 SCH
BMSC 5135	Introduction to Faculty Research	1 SCH
BMSC 5150	Laboratory Rotation	2 SCH
BMSC 5160	Biomedical Ethics	1 SCH
		<b>12 SCH</b>

#### Year 1: Spring

*At least two of the following*

BMSC 6303	Integrative Biomedical Sciences III: Physiology	3 SCH
BMSC 6304	Integrative Biomedical Sciences IV: Pharmacology	2 SCH
BMSC 6305	Integrative Biomedical Sciences V: Immunology and Microbiology	3 SCH
	<i>And</i>	
BMSC 5135	Introduction to Faculty Research	1 SCH
MOLB 6250	Molecular and Cell Biology of Cancer	2 SCH
BMSC 5998	Individual Research for MS Students	1-4 SCH
		<b>12 SCH</b>

#### Year 1: Summer

BMSC 5400	Biostatistics for Biomedical Sciences	4 SCH
BMSC 5998	Individual Research for MS Students	2 SCH
		<b>6 SCH</b>

#### Year 2: Fall

BMSC 5998	Individual Research for MS Students	4-5 SCH
	Electives*	3-4 SCH
	Journal Club/Current Topics**	1-2 SCH
		<b>9 SCH</b>

#### Year 2: Spring

BMSC 5998	Individual Research for MS Students	3 SCH
BMSC 5395	Thesis	3 SCH
		<b>6 SCH</b>

**Total** **45 SCH**

### PH.D. Degree plan for Cancer Biology

**Year 1: Fall**

BMSC 6301	Integrative Biomedical Sciences I: Principles of Biochemistry	4 SCH
BMSC 6302	Integrative Biomedical Sciences II: Molecular Cell Biology	4 SCH
BMSC 5135	Introduction to Faculty Research	1 SCH
BMSC 5150	Laboratory Rotation	2 SCH
BMSC 5160	Biomedical Ethics	1 SCH
		<b>12 SCH</b>

**Year 1: Spring**

*At least two of the following*

BMSC 6303	Integrative Biomedical Sciences III: Physiology	3 SCH
BMSC 6304	Integrative Biomedical Sciences IV: Pharmacology	2 SCH
BMSC 6305	Integrative Biomedical Sciences V: Immunology and Microbiology	3 SCH
<i>And</i>		
BMSC 5135	Introduction to Faculty Research	1 SCH
BMSC 6998	Individual Research	1-3 SCH
MOLB 6250	Molecular and Cell Biology of Cancer	2 SCH
		<b>12 SCH</b>

**Year 1: Summer**

BMSC 5400	Biostatistics for Biomedical Sciences	4 SCH
BMSC 6998	Individual Research	2 SCH
	Oral Qualifying Exam	0 SCH
		<b>6 SCH</b>

**Year 2: Fall**

MOLB 6435	Molecular Aspects of Cell Signaling (offered alternate years)	4 SCH
BMSC 5310	Scientific Communication	3 SCH
BMSC 6998	Individual Research	4-6 SCH
	Electives*	2-4 SCH
	Journal Club/Current Topics**	1-2 SCH
		<b>12 SCH</b>

**Year 2: Spring**

BMSC 6310	Grant Writing	3 SCH
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BMSC 6998	Individual Research	4-6 SCH
	Electives*	2-4 SCH
	Journal Club/Current Topics**	1-2 SCH
		<hr/>
		<b>12 SCH</b>

**Year 2: Summer**

BMSC 6998	Individual Research	6 SCH
		<hr/>
		<b>6 SCH</b>

**Year 3: Fall**

BMSC 6998	Individual Research	3-5 SCH
	Electives*	0-3 SCH
	Journal Club/Current Topics**	1-2 SCH
		<hr/>
		<b>12 SCH</b>

**Year 3: Spring**

BMSC 6998	Individual Research	4-5 SCH
	Journal Club/Current Topics**	1-2 SCH
		<hr/>
		<b>6 SCH</b>

**Year 3: Summer**

BMSC 6998	Individual Research	6 SCH
		<hr/>
		<b>6 SCH</b>

**Year 4: Fall**

BMSC 6998	Individual Research	3 SCH
BMSC 6395	Doctoral Dissertation	3 SCH
		<hr/>
		<b>6 SCH</b>

**Year 4: Spring**

BMSC 6395	Doctoral Dissertation	6 SCH
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		<b>6 SCH</b>

<b>Total</b>		<b>90 SCH</b>
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**\*Elective Courses (6-8 SCH) from the following:**

MOLB 6220	Cellular and Molecular Fluorescence	2 SCH
BMSC 5203	Regulation of Human Subject Research	2 SCH
CBAN 6341	Functional Genomics and Proteomics	3 SCH
CBAN 6440	Methods in Molecular Biology	4 SCH
MOLB 6200	Advanced Molecular Biology: Transcriptional and Translational Regulation – offered every other fall (even years)	2 SCH
MOLB 6202	Advanced Molecular Biology: Techniques and Principles - offered every other fall (odd years)	2 SCH

**\*\*Journal Club/Current Topics**

MOLB 5160	Current Topics in Cancer Biology	1 SCH
MOLB 5210	Signal Transduction	2 SCH
BMSC 5220	Novel Macromolecules that Regulate the Cell Cycle	2 SCH

### **3. Discipline Policies**

The Graduate Program in Cancer Biology conforms to the general policies outlined in the Graduate School of Biomedical Sciences Catalog. The forms and guidelines are available from the GSBS website. Specific policies of the program are as follows:

#### **3.1. Graduate Student Orientation:**

Students entering the program in Cancer Biology should interview (informal) with the tenure/tenure-track faculty engaged in cancer research within two to three weeks of orientation. The purpose of this exercise is to introduce faculty to students (and *vice versa*) and to provide an opportunity for faculty members to describe research being conducted in the laboratory. The student will make an appointment with each faculty member and the visit should be documented by faculty signature.

#### **3.2. Laboratory Rotations:**

New students (other than those being supported from a faculty member's grant) are encouraged to set up at least 2 laboratory rotations before deciding on a major advisor. These rotations will be approximately 6 weeks long. Laboratory rotations should be completed by the end of the first semester. The student may elect to do more than 2 rotations.

#### **3.3. Selection of Dissertation Committee:**

Students have to select a major advisor, a dissertation committee and file a degree plan with the Graduate Office by the end of the second semester (24 SCH) according to policies published in the graduate school catalog. At least two members of the master's degree committee (a total of 3 or more members) must be graduate faculty of Cancer Biology. For a doctoral dissertation committee, at least 3 members of the five-member committee must be graduate faculty of Cancer Biology.

When the advisory committee is formed, the graduate dean will appoint the University member. The purpose of the university member on student committees is to ensure that the policies and procedures of the Graduate School of Biomedical Sciences and UNT Health Science Center have been upheld. The presence of the university member is essential for the process of approval of thesis proposals and thesis examinations. The university member's signature on appropriate forms indicates that the integrity of the review process has been preserved. It is the responsibility of the university member to report to the graduate dean any inappropriate due process.

#### **3.4. Committee Meeting:**

Each student will meet with his/her advisory committee at least once a year. Often, it is beneficial for the student to meet more frequently. Assurance that this committee met

during the year will be required via a yearly checklist that is to be signed by both student and major advisor. Failure to abide by this policy may result in the withdrawal of any stipend support from the department.

### **3.5. Work-in-Progress Seminar:**

All students, whether enrolled in Master's or Doctoral program will be required to participate in WIPS. WIPS are designed to give students an informal forum for gaining experiences in research presentations and to generate new ideas to help with their projects. Only under exceptional circumstances will students be allowed to miss their turn in the rotation; if absence is unavoidable, the student will be required to work out an arrangement to reschedule with another student or speak to their graduate advisors to get permission to postpone.

### **3.6. Seminar and Grand Round:**

Seminars are important part of our graduate program. Students are expected to attend departmental seminars held alternate Mondays and Cancer Research Grand Round held first Wednesday of each month.

### **3.7. Research Appreciation Day (RAD):**

All students enrollment in the Graduate program are required to present at the RAD. Freshmen students are required to participate although students entering the program in the Spring semester may request exemption during the first year.

### **3.8. Qualifying Examination:**

The qualifying examination is to ensure a doctoral student has sufficient mastery of fundamental principles of cancer biology and biomedical sciences, including biochemistry, molecular biology and cell biology to be successful as a Ph.D. candidate and independent researcher. A list of major topics to be examined will be distributed to the student after the completion of the first two semesters. The student is expected to become knowledgeable in each of these topics through coursework, individual reading, or discussions with faculty members. The qualifying examination will be administered by faculty members of the cancer biology program, and will consist of an oral examination. A student will answer a given set of questions within a given time. The student must demonstrate an ability to discuss and apply concepts of cancer biology. Two attempts to successfully pass the qualifying examination are allowed. Failure of the student to pass the qualifying examination results in dismissal of the student from the doctoral program. In this case, a student may be allowed to complete the requirements for a Master of Science degree.

### **3.9. Grant Writing (Advancement to Candidacy): BMSC 6310**

This stage of the advancement to doctoral candidacy will evaluate a student's aptitude for independent thought and scientific writing. The student is required to (a) prepare an NIH-style research proposal without the assistance of his/her major professor, (b) present the proposal in a public seminar, and (c) address specific questions of an examination committee. The proposal should be based on an original hypothesis that could be related

but should be distinct from the student's dissertation, and should describe specific experimental approaches to address the hypothesis. The student will present this proposal in the form of a public seminar and then privately address specific questions of an examination committee. The examination committee will consist of Cancer Biology faculty (4 members) appointed by the Graduate Advisor. The chairperson of the committee (appointed by the graduate advisor) will serve as coordinator and will meet with the student at the beginning of the semester to review guidelines and answer relevant procedural questions. The grant proposal and the student's oral presentation and defense will be evaluated on the basis of originality and ability to communicate the proposal content. Upon successful completion of this course, the student is advanced to doctoral candidacy. Two attempts to successfully pass the BMSC 6310 Grant Writing are allowed. Failure of the student to pass the BMSC 6310 Grant Writing results in dismissal of the student from the doctoral program. In this case, a student may be allowed to complete the requirements for a Master of Science degree.

### **3.10. Research Proposal:**

All students are required to submit a dissertation research proposal that includes a summary of the project, problem/hypothesis, significance of the project, background, research design and methodology. The research proposal must be approved by the advisory committee prior to registration to doctoral dissertation (BMSC 6950). Research proposal guidelines and the research proposal approval form are available on the GSBS Forms and Guidelines website.

### **3.11. Dissertation:**

The Advisory committee follows the progress of the students. The students are required to submit a copy of the dissertations to the members of advisory committee at least two weeks prior to the defense. A graduating doctoral student must have at least one research article published (or in press) in a peer-reviewed journal at the time of graduation. Students having more than one article are permitted to file a non-traditional dissertation where the published articles constitute individual chapters. A formal public seminar of the dissertation research followed by an oral defense of the thesis to the advisory committee will constitute the final exam.

## **4. Time-line at a glance:**

- i. Year 1, 1<sup>st</sup> semester - Select laboratories for lab rotation.
- ii. Year 1, 2<sup>nd</sup> semester - Select a major professor.
- iii. Year 1, 2<sup>nd</sup> semester - Form an advisory committee. You must have an assigned University member prior to the qualifying exam.
- iv. Prior to the end of the 2<sup>nd</sup> semester - File a degree plan approved by the

advisory

committee.

- v. Year 1, Summer - Oral Qualifying Exam
- vi. Year 2, Spring - 6310 Grant Writing Exam
- vii. Year 3, Fall - Research Proposal
- viii. Final Exam

## **Oral Qualifying Examination Policy**

**Preamble:** This examination is to ensure that a student possesses a fundamental knowledge of the biological sciences to a level commensurate with a doctoral candidate. Students enrolled in the Doctoral program who have completed integrated core courses are required to take this comprehensive examination before they can register for Grant Writing (Advance to Candidacy Qualifying Examination).

### **Specifics:**

1. The comprehensive examination will be scheduled during the summer of the first year of graduate school following completion of the core courses.
2. A four-member committee will be formed, and 3 out of 4 will be needed for approval.
3. The topics of the examination will be based on the core courses and Cancer Biology Advanced course. The students have to answer questions from Principles of Biochemistry and Molecular Cell Biology core courses. Additional core courses may be included based on the student's primary affiliation.
3. The length of the examination will be approximately 2 h. The students will be required to answer 6 out of 12 questions. The students have to select at least one question from different categories, such as Cancer Biology, Cell Biology, Enzyme and Metabolism and Molecular Biology.
4. The student will be given the question set thirty (30) minutes prior to the oral examination, from which he/she will prepare answers for 6 questions. The questions should be answerable in approximately 15 min so that the students can be tested in all of the defined areas.
5. On completion of the examination, the faculty will vote on a pass/fail grade for the student. At least 75% favorable vote will be required for the student to successfully pass. The entire committee should approve for distinction. If a student does not pass, the faculty will inform the student of specific areas of weakness in writing.
6. If necessary, a student will be allowed to retake the oral examination once but this must be completed before the end of the following semester. Failure on the second attempt will result in dismissal from the doctoral program, although the student will be permitted to pursue a Master of Science degree.
7. Following designations could be used to indicate the performance of the student.
  - Qualifying examination passed
  - Qualifying examination passed with distinction
  - Qualifying examination failed
8. It is the responsibility of the student to obtain signatures from the Examination Committee Chair, Graduate Advisor, University Member and Department Chair on

completion of the examination. The appropriate form may be obtained from the graduate school website.

## **Grant Writing (Advancement to Candidacy): BMSC 6310**

**Purpose:** Students must pass Grant Writing to attain status as a doctoral degree candidate. This examination is designed to test the student's aptitude to independent research by assessing his/her ability to develop a research hypothesis and design ways to address this hypothesis. The student is required to prepare an NIH-style (RO1) research grant proposal and to present, discuss and defend this proposal before an examination committee. This examination must be completed within the semester registered.

### **Specifics:**

**(i) Prerequisite:** A student must have passed the discipline qualifying examination to be eligible to enroll in Grant Writing. A student must register for grant writing in the first long semester immediately following successful completion of the oral examination and before the completion of 84 SCH.

**(ii) Examination Committee:** The graduate advisor will serve as the examination coordinator and select an examination committee from eligible faculty. The examination committee will consist of Cancer Biology faculty (4 members) appointed by the Graduate Advisor. The chairperson of the committee (appointed by the graduate advisor) will serve as coordinator and will meet with the student at the beginning of the semester to review guidelines and answer relevant procedural questions. The University member of the student's dissertation committee will oversee the entire examination process. The student's mentor will be excluded from this committee.

**(iii) Topic:** The proposal should be based on an original hypothesis in the area of Cancer Biology. A student may choose an area related to his/her dissertation research but it must be distinct from the major professor's funded research. The proposal should be developed without the assistance of his/her major professor.

**(iv) Preproposal:** The student will first construct a short pre-proposal (5 pages maximum) constituted by a brief background, a stated hypothesis, an outline of the specific aims designed to test the hypothesis and experimental approaches. Following approval by the committee members, the student will make a brief oral presentation (15-20 min) to the examination committee who will assess appropriateness based on originality and scientific soundness. The decision of the examination committee to accept or reject the pre-proposal as suitable for development into a final proposal will be by majority vote of the members. If the pre-proposal is accepted with some reservations, those reservations will be conveyed in writing to the student by the chair of the examination committee.

**(v) Submission of Proposal:** Upon approval of a pre-proposal, the student must submit a completed proposal typed on official NIH forms within 1 month of the pre-proposal meeting. The committee members will review the proposal and will inform the chair if there are any concerns. The members will submit their comments to the chair and the chair should summarize the comments and ask the student to resubmit a revised proposal taking into account committee's critique. The chair will decide the date when to resubmit the revised proposal. The final proposal must be presented to the examination committee at

least one week prior to the date of the examination. Final examination must be held within 2 months of the pre-proposal meeting. The student must also inform the Graduate Secretary of the date and location of the examination.

**(vi) Examination procedures:** At the examination, the student will make an oral presentation (30-45 min) before the examination committee and other interested faculty and students. Immediately following the presentation, questions will be invited from the general audience. Subsequently, non-committee persons will be excused and the student will proceed to defend his/her proposal before the examination committee. The oral examination will focus on the students understanding of the topic presented and knowledge of the strategies and techniques employed. The entire examination process should last 2 to 3 h.

**(vii) Assessment:** The written proposal and oral defense will be evaluated on the basis of originality, the ability to synthesize and communicate information, and competence in biochemical principles involved. Following designations could be used to indicate the performance of the student on the basis of the majority opinion of the committee..

6010 Grant writing examination passed

6010 Grant writing examination passed with distinction

6010 Grant writing examination failed

The examination committee will inform the examination coordinator in writing of the decision and the recommended grade for the student. If the grade is “pass”, the student is advanced to candidacy. If the grade is “no pass,” the student will be given one additional opportunity to rewrite and/or defend orally. A critique of the proposal and defense will be prepared by the examination committee chair and given to the student to aid in the rewrite and/or second defense. The second defense must occur by the end of the next semester. All of the graduate, associate graduate and adjunct faculty of the department will be strongly encouraged to attend the second defense, and all faculty, with the exception of the major professor, will vote on the pass or fail. If the second defense is not successful, a “no pass” will be assigned and the student will be dismissed from the Ph.D. program. Under these conditions, the student will be allowed to complete a Master’s degree.

## **5. Contacts in Situations of Uncertainty or Emergency**

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