

Potential Research Opportunities
ABIM Research Pathway

Temple

Carmen Sapienza, Ph.D., Professor of Pathology and Laboratory Medicine, Associate Director, Fels Institute for Cancer Research and Molecular Biology, Temple University School of Medicine

One of the long-awaited promises of the human genome sequencing project is the identification of genes involved in common human disease. Human geneticists have identified genes involved in type 2 diabetes, asthma and many other common diseases. Despite these successes, there has been little translational impact of identifying these “common disease genes” because the relative risk of developing disease for carriers of each defective gene is small. Although this fact is not surprising to geneticists, it begs the question of what type of information could be added to genetic risk data to increase the predictive power of who is at highest or lowest risk for any particular disease. In this vein, there is great interest in the potential for “epigenetic biomarkers” to add predictive value to genetic risk data. There is perhaps no better case for a major role for epigenetic effects in common disease than colon cancer. Colon cancer accounts for more than 10% of all invasive cancer cases in the United States and more than 100,000 new cases are diagnosed each year. It is the third most common cancer in both men and women and the third leading cause of cancer deaths. Epigenetic alterations are associated with both increased risk of disease and tumor progression. Moreover, there is compelling evidence linking environmental influences such as western diets and cigarette smoking with increased risk of colon cancer. We have recently demonstrated the existence of many epigenetic differences the “normal” colon mucosa of cancer patients and the normal colon mucosa of patients without cancer (1-3). We now propose to expand this analysis with the goal of changing the standard of care for colorectal cancer screening from an invasive and subjective test (colonoscopy) to a non-invasive objective test. The long-term interests of the Sapienza laboratory are gene/environment interaction and the laboratory has been successful in identifying DNA methylation differences associated with assisted reproduction (4,5), diabetic nephropathy (6), as well as colon cancer.

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Jean P. Issa, Professor of Medicine, Jeanes Hospital – Bone Marrow Outpatient

The Issa lab studies the role of epigenetics in aging and age-related diseases including cancer. Current projects include a search for biomarkers (cancer risk, cancer outcomes, treatment responses), basic and translational studies of drugs that modify the epigenome (from drug discovery to clinical trials) and mechanistic studies of epigenetic regulation and deregulation (genomic view and the role of specific proteins).

David Essex, MD, Associate Professor of Medicine, Sol Sherry Thrombosis center, Division of Hematology

Current Research Interests: Redox Regulation of Platelet Function. Our research on platelets focuses on a new field involving the dynamic rearrangement of disulfide bonds as a signaling mechanism in stimulus response coupling. We were the first to discover an enzyme on the platelet surface, protein disulfide isomerase (PDI) that catalyzes the rearrangement of disulfide bonds in proteins, modifying protein function. We were the first group to report that platelets secrete an extracellular PDI and that extracellular PDI mediates platelet aggregation. We were the first to show that a novel platelet PDI called ERp57 mediates platelet aggregation hemostasis and thrombosis. We found that PDI and ERp57 regulate activation of the platelet fibrinogen receptor, GPIIb-IIIa. This receptor plays a central role in platelet function in hemostasis and thrombosis and is the target of commonly used anti-platelet drugs.

Koneti Rao, MD, Sol Sherry Professor of Medicine; Co-Director, Sol Sherry Thrombosis Research Center, Division of Hematology

Platelet Function in Health and Disease. In the vast majority of patients with inherited platelet bleeding disorders the molecular mechanisms leading to the platelet dysfunction are unknown. Our studies have focused on platelet mechanisms in these patients and have delineated novel abnormalities in key signaling proteins. This laboratory is one of the leading laboratories for platelet studies in both thrombotic and bleeding disorders. Potential projects provide an opportunity to learn platelet mechanisms and techniques applicable to a wide range of disorders.

Blood Coagulation Mechanisms in Diabetes Mellitus, Obesity and other Disease States. Diabetes mellitus patients have a high incidence of acute cardiovascular events. Ongoing studies focus on the activation of blood coagulation mechanisms induced by hyperglycemia and hyperinsulinemia in healthy subjects and in diabetes mellitus. Our laboratory has extensive experience in studies on blood coagulation mechanisms, focusing on tissue factor, in various diseases, including in stroke, sickle-cell anemia, COPD and obesity. These projects provide an opportunity to study aspects of blood coagulation in various disease states.

Fox Chase Cancer Center

Kerry S Campbell, PhD, Associate Professor

Signal Transduction in Natural Killer Cells

Natural killer (NK) cells constitute about 10-15% of the normal lymphocytes in human peripheral blood. They are important sentinels of the innate immune system that can detect and kill tumor cells and virus-infected cells, and produce cytokines, including interferon- γ and tumor necrosis factor- α . NK cells are regulated by a dynamic balance between positive and negative intracellular signals that are transduced from cell surface activating and inhibitory receptors. This makes them an ideal cellular model system to study signal transduction crosstalk. Our goal is to understand the molecular mechanisms by which NK cells recognize and attack abnormal cells in the body, but are tolerant toward normal cells. This

knowledge should lead to therapeutic strategies that can enhance NK cell responsiveness toward tumors and viruses in patients.

Killer cell immunoglobulin-like receptors (KIRs) are key regulators of human NK cell function. KIRs bind major histocompatibility complex class I (MHC-I) molecules on the surfaces of all healthy normal cells in the body. Upon detecting MHC-I, KIRs transduce a negative intracellular signal that suppresses NK cell killing responses. The inhibitory signal derived when KIR detect MHC-I is important for establishing tolerance toward normal cells. Many abnormal tumor cells and virally infected cells eliminate MHC-I expression, however, which abolishes the KIR negative signals and releases the NK cells to specifically attack only these abnormal cells and eliminate them from the body. We are studying the molecular mechanisms controlling the surface expression of KIRs. Improved understanding of the regulation of KIR surface expression should lead to therapeutic treatments to alter their surface expression and thereby change the NK cell activation threshold to more efficiently attack tumor cells and virus-infected cells.

Alternatively, KIR2DL4 is an activating receptor that stimulates NK cells to secrete cytokines, but uniquely does not stimulate tumor cell killing. Interestingly, KIR2DL4 is only expressed on a small subset of NK cells. Furthermore, receptor expression is upregulated in stimulated NK cells, and some individuals cannot express this receptor at all, due to a common genetic polymorphism. The physiological implications and potential for disease susceptibility resulting from the inability to express KIR2DL4 in some individuals are currently unknown and warrant further detailed study. Our overall goals are to define the molecular mechanisms controlling the unique expression and function of KIR2DL4. The results will allow us to better understand its role in regulating inflammation and fighting cancer.

David Wiest, Ph.D., Vice President, Deputy Chief Scientific Officer, Co-Leader, Immune Cell Development and Host Defense, Co-Leader, Blood Cell Development and Cancer Keystone

Research Overview

T lymphocytes recognize and destroy invading pathogens through an assembly of proteins called the T cell antigen receptor (TCR) complex. The TCR has protein subunits that are highly variable and responsible for target recognition (either α/β or γ/δ) and subunits that are invariant proteins and serve to transmit signals (CD3 $\gamma\delta\epsilon$ and ζ). This critical protein assembly (the TCR) controls not only the behavior of mature T lymphocytes but also their development in the thymus. My laboratory seeks to understand how T cell development is controlled by the TCR and how these developmental processes are corrupted during development of cancer. There are two types of TCR variable proteins, α/β and γ/δ . Utilization of these α/β and γ/δ pairs characterizes two distinct types of T lineages, α/β and γ/δ , respectively. These two T lineages are thought to arise from a single immature precursor in the thymus. We are attempting to identify the cellular factors that are essential for transmitting the signals that direct adoption of these alternate fates (i.e., α/β or γ/δ). We hypothesize that the genes, which are essential for normal cell development, are also likely to regulate development of cancer. Indeed, through these efforts we have identified such a factor, Rpl22, which is a component of the cellular machine responsible for synthesis of all cellular proteins, the ribosome. Rpl22, is not only essential for normal T cell development, but also may regulate the development of human cancers including T acute lymphoblastic leukemia (T-ALL), myelodysplastic syndromes (MDS), and acute myelogenous leukemia (AML).

Sergei Grivennikov, PhD, Member & Assistant Professor

It has become recently clear that Inflammation plays important roles at different stages of tumor development, including initiation, promotion, malignant conversion, invasion, and metastasis. Immune cells that infiltrate tumors engage in an extensive and dynamic crosstalk with cancer cells and some of the molecular events that mediate this dialog have been revealed. Inflammatory microenvironment is an

essential component of all tumors, including some in which a direct causal relationship with inflammation is not yet proven. Importantly, only a minority of all cancers are caused by germline mutations, whereas the vast majority (90%) are linked to somatic mutations or epigenetic changes and environmental factors, including preceding chronic inflammation. Recent studies provided further evidence about the connection between inflammation and cancer, as non-steroid anti-inflammatory drugs such as aspirin, significantly lower the risk of cancer death. Several types of tumor-associated inflammation have been outlined, which either pro- or anti-tumorigenic effect. Given the importance of the functional interaction between immune cells and cancer cells, the outstanding question is what mediates such a cross-talk?

Our research interests are to connect various immune signaling pathways with pathogenesis of inflammation-associated and sporadic cancers, including colon cancer. Research in the lab utilizes various genetic animal models of immunodeficiency and cancer as well as human tissues and follows several major directions:

1. Examine the role of various inflammatory cytokine pathways in tumor growth, invasion and metastasis
2. Explore the mechanisms of how inflammatory response in the tumors is induced, including potential contribution of microbiota and endogenous factors produced by the host.
3. How manipulations with the strength and specificity of the host inflammatory response may aid to the development of better preventive and therapeutic strategies

Siddharth Balachandran, PhD, Assistant Professor

Cytokine Signaling in Host Innate Immune and Anti-Tumor Responses

A key component of mammalian immunity against viruses and cancer is a family of cytokines called the interferons (IFNs, so called because they ‘interfere’ with virus replication). The IFNs are classified into two groups, type I and type II. Type I (α/β) IFNs are produced by most cell types in response to viral infection, whereas type II IFN (called IFN- γ) is made by a select subset of immune system cells and is not virus inducible.

Type I IFNs (e.g. IFN- $\alpha 2$) were approved by the Food & Drug Administration (FDA) in 1986 as the first commercial anticancer biotherapeutic, and are currently employed in the treatment of over twenty human cancers. It is thought that the IFNs exert their antitumor effects by modulation and reactivation of the immune response to the tumor and/or by direct tumoricidal activity, but the underlying mechanisms remain poorly described. In the years preceding their approval by the FDA, the IFNs were touted as a potential ‘silver bullet’ cure for many forms of cancer, even making the cover of Time magazine in 1980. Unfortunately, these cytokines have, in recent years, fallen out of favor with many oncologists because of their very unpleasant side-effects. Nevertheless, IFNs continue to be used in the clinic and provide spectacular cures of several highly malignant cancers (such as AIDS-associated lymphomas and metastatic renal cell carcinoma), highlighting their Janus-faced nature.

The primary problem with IFN therapy is that IFN is, of course, also a potent antiviral cytokine and triggers a powerful innate immune response in the patient, whose body responds to systemic therapeutic IFN as it would to an acute viremia. Efforts are currently underway to target IFN delivery to the tumor site (particularly for solid tumors), but an equally compelling avenue of research is to determine the mechanism(s) by which IFNs selectively mediate their cytotoxic effects, and exploit these mechanisms to make IFN a more potent therapeutic (and thereby reduce its effective dose by, hopefully, at least one order of magnitude). Our laboratory is therefore very interested in the molecular processes by which IFNs specifically exert their anti-proliferative effects. We have recently identified novel pathways by which the IFNs induce cell survival and death and are currently elucidating these mechanisms.

Another area of research in the laboratory is to understand how type I IFNs and other antiviral genes are induced after virus infection. In a current model, virus replication in the cytosol activates at least three classes of transcription factors to induce primary antiviral genes (including type I IFNs). Of these factors, we are particularly interested in NF- κ B, and are currently defining its mechanism of activation and role in antiviral responses.

Igor Astsaturov, MD, PhD, Assistant Professor

Treatment Choices Defined by Molecular Profile

The main focus of my research is to improve targeted therapy for cancer, and to develop new rational strategies for combination of targeted agents. In the clinic, epidermal growth factor receptor (EGFR)-targeting antibodies or small kinase inhibitor molecules are widely used to treat patients with gastrointestinal (GI), breast, head and neck, and lung cancers. Unfortunately, the clinical efficacy of these agents is limited by intrinsic primary and acquired resistance factors. Our lab has initially focused on development of new treatment strategies utilizing a systematic synthetic lethal screening approach to identify new signaling proteins that can be blocked simultaneously with EGFR, to improve the anti-cancer activity of EGFR-targeting drugs. We have identified a number of potential therapeutically exploitable targets have been identified (Astsaturov I. et al., *Science Signaling* (2010)), and ongoing work in the lab assessed their mode of action. Besides testing novel signaling mechanisms in the laboratory, we also are using the research data to generate concepts for testing in the clinical trials. One such clinical trial is ongoing (Vandetanib [a vascular endothelial growth factor receptor (VEGFR) inhibitor] in combination with chemotherapy and radiation for patients with operable esophageal cancer), and several more are in the late stages of preparation.

Erica A. Golemis, PhD, Professor

Identifying and Targeting Signaling Hubs in Cancer

Our laboratory is interested in defining the changes in cell signaling that occur as tumors initiate, progress, and develop resistance to drugs, with the ultimate goal of inhibiting these processes. Part of our research focuses on study of NEDD9, a member of the Cas protein family. NEDD9 acts as a scaffold for signaling proteins that play essential roles in cancer progression and normal organismal development. Part of the laboratory also addresses the biological functions of NEDD9-interacting proteins, including particularly an oncogenic kinase, Aurora-A. Complementary projects use computer-based bioinformatic approaches to look for genes that sensitize cells to therapies targeted against cancer-promoting proteins such as EGFR. We hope through these studies to better define the interactions of signaling pathways in malignant versus normal cells, allowing improvements in cancer diagnosis and treatment.

Yanis Bumber, MD, PhD, Medical Oncology, Attending Physician

Tumor Drivers and New Treatments in Lung Cancer

Non-small cell lung cancer remains the deadliest of cancers, and despite many advances in therapeutic management, the five-year survival rate this disease remains very low. The long-term goal of my laboratory is to establish an expertise in translational research addressing lung cancer biology and the treatment of thoracic malignancies.

Part of our research focuses on the role of Musashi-2 (Msi2) in non-small cell lung cancer. The Musashi family of RNA-binding protein regulates mRNA translation to control numerous cancer-related signaling

processes. Our preliminary studies for the first time identified Msi2 as an oncogene driving lung cancer progression. We are using mouse models, human cell lines, and analysis of primary tumor samples to define to function of Msi2. The goal of this work is to obtain a better understanding of the events contributing to lung cancer progression, with the anticipation that this knowledge will support more effective use of targeted and cytotoxic therapies in the clinical setting.

Another important focus of the laboratory is small cell lung cancer (SCLC). This is an aggressive and deadly disease, with essentially no effective treatments, no new drugs approved in recent decades, and no targeted agents in existence. We are currently evaluating a new class of drugs developed by Synta Pharmaceuticals which use anticancer drugs conjugated to an HSP90-binding moiety as a novel way to deliver anticancer agents directly to tumors. In the lab, we focused on pre-clinical safety and efficacy and mechanistic studies of this new compound in cell lines and in mice. The proposed study could be a step forward to development of future effective treatment strategies for small cell lung cancer patients.

Denise C. Connolly, PhD, Associate Professor

Human Epithelial Ovarian Cancer: Development, Progression and Metastasis

The overall goal of our research is to discover ways to improve the treatment of epithelial ovarian cancer (EOC). Most cases of EOC are diagnosed at advanced stage when disease has spread beyond the ovary. From a clinical standpoint, EOC metastases and ascites production are perhaps the most significant cause of morbidity and mortality in patients because they can affect multiple vital organs in the abdominal cavity. At present, the cellular mechanisms regulating EOC metastasis remain only partially understood. Our laboratory is interested in defining molecular mechanisms that contribute to peritoneal dissemination of ovarian cancer cells to identify targets for therapeutic intervention in patients. Using a combination of in vitro and in vivo approaches, we hope to better understand EOC tumor biology at the cellular level as well as disease development and progression in animals. Several projects in our laboratory are focused on the cellular pathways involved in ovarian cancer cell migration, attachment and invasion with the ultimate goal of identifying therapeutic agents that inhibit the spread of ovarian cancer.

To facilitate our studies, we have developed a variety of mouse models of EOC, including the first transgenic model of spontaneous EOC by expressing the SV40 TAg under transcriptional control of the Müllerian inhibiting substance type II receptor (MISIIR) gene promoter. Female MISIIR-TAg mice develop spontaneous EOC that share pathological and molecular features with human EOC. We also use human ovarian carcinoma cells line xenograft models, and more recently have begun to develop novel xenograft models from patient-derived tumor tissue. These mouse models, as well as tissues and cell lines developed from them are currently being used to study the mechanisms of EOC tumor progression and metastasis.

James S. Duncan, PhD, Assistant Professor

Protein kinases

Protein kinases represent one the most tractable drug targets in the pursuit of new and effective cancer treatments. Although kinase inhibitors have shown great promise for the treatment of cancer, most single agent kinase inhibitor therapies have had limited clinical success due to rapid development of drug resistance. Tumors can evade drug therapy by activating compensatory protein kinase networks that promote cell growth and survival overcoming initial treatment. Therefore, combination therapies blocking these changes in kinase activity will likely be required to prevent tumor resistance in cancer.

To meet this challenge, our laboratory employs a mass spectrometry based technology that identifies protein kinases responsible for drug resistance, providing an innovative approach to rationally design new combination treatments for cancer. Using this technology, we can capture the majority of the human kinome and detect altered kinome patterns in response to kinase inhibitors currently used to treat cancer. Kinases from all major kinome subfamilies are captured including the majority of kinases implicated in cancer development and progression, as well as a significant proportion of the understudied or (un)targeted kinome. Overall, the goals of our research are to utilize this innovative approach to assess global kinome behavior and its response to small molecule inhibitors to identify previously undiscovered kinase targets leading to new and effective combination therapies to treat cancer.

Zeng-jie Yang, MD, PhD, Assistant Professor

Research Summary

Medulloblastoma is the most common malignant brain tumor in children, and also occurs in adults. Despite significant progress in development of treatments for this cancer, the mortality rate of medulloblastoma is still very high. Our research seeks to elucidate the mechanisms of medulloblastoma initiation and progression, with the aim of translating the findings into improved strategies for the treatment of medulloblastoma.

To study the basis of medulloblastoma formation, we first focus on the tumor cell itself, to define what genetic and/or epigenetic events could convert a normal cell into a tumor cell. We are also examining the functions of tumor-supporting cells (the tumor stroma, and other constituents of the tumor microenvironment) in medulloblastoma formation. We hope to find a more effective way to control medulloblastoma growth, through targeting both tumor cells and their supporting stroma.

Jonathan Chernoff, MD, PhD, Professor

Role of Protein Phosphorylation in Neoplastic Transformation

The process of neoplastic transformation can be conceptually divided into two components. The first of these, proliferative transformation, refers to the ability of transformed cells to bypass growth suppression signals, dividing when normal cells would not. The second, morphologic transformation, refers to loss of normal cytoskeletal architecture, often accompanied by decreased adhesion and acquisition of the ability to invade surrounding tissues. These two fundamental properties are intimately linked to one another, although experimentally they can be dissected apart through the use of mutant oncogenes and other abnormal signaling molecules. The overall focus this research is in uncovering the roles of protein phosphorylation in governing these two fundamental aspects of cancer biology.

Hossein Borghaei, DO, Medical Oncology, Associate Professor, Director, Lung Cancer Risk Assessment

Research Interests

My laboratory is interested in immunotherapy for cancer, with particular emphasis on the clinical development and application of monoclonal antibodies. Recent work from my group includes a Phase I trial of naptumomab estafenatox, a recombinant fusion protein consisting of a mutated variant of the superantigen staphylococcal enterotoxin E (SEA/E-120) linked to the antigen binding moiety of a monoclonal antibody recognizing the tumor-associated antigen 5T. In addition to developing new monoclonal antibodies, I am conducting clinical trials exploring the immunological responses that occur as a result of cetuximab therapy-associated antibody-

dependent cellular cytotoxicity (ADCC)ADCC, with the goal of augmenting these immune responses to achieve improved efficacy of antibody therapy. In addition, I am involved in a number of clinical trials with various other monoclonal antibodies such as cetuximab. My latest lung cancer trial explores the relationship between EGFR and Aurora Kinase in lung cancer.