

## Discoveries of Genetic Changes to Fuel New Therapies

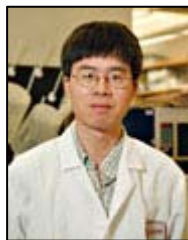
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### **Kwok-Kin Wong, MD, PhD: *Mouse Models as Platforms for Genetic Discovery***



Kwok-Kin Wong, MD, PhD, develops mouse models of lung cancer so DFCI scientists can gain a better understanding of the disease's origins. In addition, these models help validate mutated genes found in human lung cancers, thereby illuminating new genetic relationships and potentially “druggable” targets. The models are also extremely useful in fine-tuning new treatments, which can then be translated back to patients in clinical trials. Dr. Wong's team has generated a mouse lung cancer model to uncover the molecular processes that govern cancer metastasis, the principal cause of death in patients with solid tumors. This unique mouse model will enable Dr. Wong's team to study the genes and pathways that are utilized in the various stages of metastasis – tumor cell invasion, migration, circulation, scattering to distant tissues, migration out of blood vessels, and colonization of distant organs. A better understanding of the genetic events involved in metastatic growth will help guide the development of novel therapeutics to interfere with this deadly process.

### **Qiufu Ma, PhD: *Targeting the Genetics of Physical Pain to Improve Outcome***



Cancer causes physical pain in many ways, from tumor invasion into bone marrow, to the growth of lesions on nerves as a side effect of chemotherapy. Tumor cells and associated immune cells can also release various proteins and chemicals that alter the molecular underpinnings of pain sensation, causing even stronger discomfort. Few effective medicines are available for neuropathic pain that is commonly associated with cancer patients. Accordingly, over 45% of cancer patients in the United States suffer untreatable pain. Qiufu Ma, PhD, is investigating the underlying genes expressed in neurons critical for pain perception, to eventually develop novel therapeutic targets for pain treatment. Improved pain management will improve the quality of life for cancer patients, and also help in treating their disease, as painful side effects from therapies can prevent patients from continuing particular treatments.

### **Loren D. Walensky, MD, PhD: *Unlocking the Therapeutic Potential of an “Executioner Protein”***



At the very core of the cell's circuitry that dictates life and death resides an “executioner protein”, named BAX, which initiates a cellular suicide termed “apoptosis” when a cell has become severely damaged. To avoid unwarranted cell death, systems exist within the cell to prevent the renegade activation of BAX. The specific mechanisms that regulate BAX activation have not been fully determined, and Loren Walensky, MD, PhD, aims to unravel the mysteries of BAX repression and activation. Dr. Walensky's findings will impact the development of therapeutics to thwart unwanted cell death of healthy cells and reactivate cell death in cancerous cells. His laboratory has generated novel compounds that directly bind to and activate BAX, which will be used to uncover the protein interactions that maintain the critical balance between cell life and death. Bringing

together chemistry, apoptosis biology, and cancer medicine, Dr. Walensky's laboratory is uniquely positioned to break new ground in understanding cell death, and potentially manipulate these processes to develop new therapies for cancer patients.

**Rani George, MD, PhD: *New Genetic Target for the Treatment of Neuroblastoma***



Neuroblastoma is a solid tumor in the nervous system that affects one child per 7,000 births, one of the most common solid tumors in children. While lower stage neuroblastomas in infants and toddlers are very responsive to therapy, higher stage tumors in older children carry a poor prognosis. High dose chemotherapy and stem cell treatments have led to improvements in survival, though relapse is common and nearly always fatal. Rani George, MD, PhD, is developing more effective, less toxic agents to combat relapsed neuroblastoma. Utilizing breakthrough technology, Dr. George and her team analyzed the DNA of 100 neuroblastoma tumors, and discovered that a significant proportion contained multiple copies (amplification) as well as mutations of the gene ALK. This gene is essential for nervous system development and belongs to a class of enzymes that regulate cellular processes such as growth. Consequently, its amplification and mutation would likely cause uncontrolled growth of cancerous cells in the nervous system and contribute to neuroblastoma. Dr. Rani's team is currently testing drugs that inhibit ALK amplification and mutation, and seek to translate these new therapies into the clinic for children with the disease.

**Ruben Carrasco, MD, PhD: *Genetic Drug Targets Against Multiple Myeloma***



Dr. Carrasco aims to identify the genetic alterations that lead to multiple myeloma (MM), a cancer of the plasma cells (white blood cells that produce antibodies), with the intent of uncovering new drug targets and developing novel therapies against these genetic alterations. Dr. Carrasco and his colleagues have identified one such alteration in a majority of patients with MM that leads to an aberrant Wnt signaling pathway (a cellular signaling pathway found to be dysregulated in a broad spectrum of cancer types). Dr. Carrasco's team also found evidence suggesting the potential role of this alteration in tumor growth and metastasis. They will initially target this pathway with drugs in mice models, and eventually develop therapies for use in patients with MM and other cancers.

**Martin Sattler, PhD: *DNA Pathways and Drug Resistance in Chronic Myeloid Leukemia***



Chronic myeloid leukemia (CML) is a slowly progressing form of leukemia in which too many white blood cells are made in the bone marrow and accumulate in the blood. Although bone marrow transplant is the only known curative therapy for CML, the revolutionary drug Gleevec<sup>®</sup>, developed in collaboration with DFCI investigators, has shown remarkable results in some patients. However, those who do respond to Gleevec often develop resistance to the drug, which leads to disease progression. Thus, there is a need to develop new, targeted therapies against CML to combat resistance. Martin Sattler, PhD, and his team will study the underlying DNA damage and DNA repair mechanisms in CML cells.

This basic science is essential to understand these altered DNA repair pathways and their role in drug-resistance. Dr. Sattler's findings will potentially fuel the development of drugs that inhibit these processes and prevent or delay drug resistance. Additionally, this research is likely to be relevant to other cancers that are driven by similar genomic instability.

**Ellen Weisberg, PhD: *New Drugs to Combat Therapeutic Resistance in CML***



Ellen Weisberg, PhD, aims to develop new drugs to combat therapeutic resistance in CML patients. A detailed investigation of the underlying genetic mutation in CML – the protein BCR-ABL – revealed the specific structure that causes resistance to Gleevec and similar drugs. This structure is referred to as the “gatekeeper” amino acid (one of the several building blocks that join together to form the BCR-ABL protein). Starting with this discovery, Dr. Weisberg and her colleagues will deploy new drugs that selectively target the mutations within BCR-ABL that harbor the “gatekeeper” amino acid, in order to overcome the molecular underpinnings of therapeutic resistance. Her team will test these drugs in both cell-based and animal-based models, and eventually translate these findings into therapies for patients.

**Dana H. Gabuzda, MD: *The Role of miRNAs in the Aging of the Immune System***



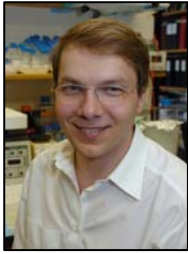
Newly discovered molecules, termed micro RNAs (miRNAs), regulate gene expression and have been implicated in contributing to certain types of cancer. miRNAs regulate a variety of biological processes, including development, cell proliferation, cell differentiation, and cell death. In addition, the genes that produce miRNAs are frequently found in regions of the genome that are either lost or amplified in cancer cells. Dana Gabuzda, MD, aims to uncover the miRNA mechanisms that underlie the decline of immune system function during aging and contribute to an increased susceptibility to infections and certain cancers in elderly individuals. A better understanding of these mechanisms will potentially fuel the development of more effective treatments and vaccines for certain infections, immune disorders, and cancers in older adults.

**Dipanjan Chowdhury: *The Role of miRNAs in DNA repair***



As mentioned above, the study of miRNAs in biology and disease is a rapidly expanding new area of research with important therapeutic implications. Dipanjan Chowdhury will study the role of miRNAs in DNA repair – a fundamental process which, when disrupted, leads to the genomic instability and unrestricted cell growth that characterize cancer. Chowdhury and his team will specifically investigate how miRNAs regulate the expression of different DNA repair proteins. These findings will be of great importance in the field of cancer research, and may open up new avenues to better understand additional cellular processes involving DNA replication.

**Kai W. Wucherpennig, MD, PhD: *miRNAs in the Immune System and Leukemia***



Kai W. Wucherpennig, MD, PhD, aims to create new approaches for the study of miRNAs in cells of the immune system and human leukemias. Dr. Wucherpennig and his team will develop ways to deliver drugs that inhibit miRNAs into certain cell populations. By inhibiting these RNAs, scientists can investigate how their absence impacts the entire cell population, thereby revealing each RNA's function. The application of these inhibitors may also have therapeutic potential should the specific miRNAs be

discovered to play a significant role in the development of cancer.

**Investigating “Cancer Stem Cells” and the Cell Cycle**

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**Ina Rhee, MD, PhD: *Exploring Stem Cells and the Origins of Breast Cancer***



In normal organs, most cells are committed to a specific function, and cannot give rise to the other cell types present in the same tissue. These specialized, “differentiated” cells have a limited lifespan. In contrast, stem cells are long-lived, unspecialized cells that produce each of the cell types needed to carry out the various functions of an organ. Ina Rhee, MD, PhD, seeks to determine whether cancers originate from stem cells, or, as

suggested by her preliminary data, whether non-stem cells can also give rise to tumors. Specifically, Dr. Rhee will compare the key characteristics of tumors arising from different types of mammary cells, thereby yielding insight into whether the range of human breast cancer subtypes can be explained by their origins within the mammary gland. Knowledge of the differences between these mammary cell types might contribute to the development of new, effective therapies custom-tailored for specific types of breast cancer.

**Shengjun Ren, PhD: *Examining the Cell Cycle to Combat “Cancer Stem Cells”***



Recent studies suggest that chemotherapies are at times ineffective due to their failure to eradicate so-called “cancer stem cells”. These are cells that exist in a state of quiescence (they are removed from the normal cell cycle and do not replicate, but eventually re-enter the cell cycle and become cancer cells). This state of quiescence prevents them from being targeted by many conventional therapies. Shengjun Ren, PhD, is examining cell cycle

control with particular focus on a cell cycle regulator called cyclin C. Dr. Ren's team discovered that inhibiting cyclin C completely prevented normal primary cells isolated from mouse embryos from re-entering the cell cycle. However, when they inhibited cyclin C in quiescent transformed cancer cells, it merely delayed their eventual reentry into the cell cycle. Based on these findings, Dr. Ren and his colleagues will further elucidate, on a molecular level, the mechanism that allows a cell to re-enter the cell cycle from quiescence, and will evaluate the role of cyclin C in breast cancer stem cells. These studies will provide a foundation to develop novel therapeutics by targeting quiescent cancer stem cells.

**Ji-Hye Paik, PhD: *Molecules Offer Insight Into Degradation of Brain Cells***



Ji-Hye Paik, PhD, and a team of Dana-Farber researchers discovered that a group of molecules, called FoxOs, are critical in preventing some cancers. Utilizing mouse models, Dr. Paik and her colleagues found that three FoxO molecules normally function as tumor suppressors, which prevent normal cells from becoming cancerous. Thus, the elimination of these FoxOs may allow cancer to develop. Dr. Paik also revealed that FoxOs are robustly expressed in the brain, and seeks to determine their function in aging-related depletion of brain stem cells. Her findings will expand our understanding of cancer pathogenesis and the degenerative conditions brought on by current anti-cancer treatments, while revealing new targets for drug discovery.

**Charles Roberts, MD, PhD: *Regulator of Stem Cells Holds Key to Novel Therapies***



A protein complex called Swi/Snf has a potent role in tumor suppression, while its mutation drives a variety of aggressive cancers. In investigating this complex, Charles Roberts, MD, PhD, found that the Swi/Snf complex also plays a key role in regulating embryonic stem cells, and in controlling cell growth during fetal development. When mutated, however, the Swi/Snf complex mistakenly turns on cell growth programs in mature cells, which leads to the development of cancer. Dr. Roberts and his team will define the specific genetic pathways regulated by this complex in stem cells and during fetal development. This information will enable scientists to eventually manipulate these genetic pathways and stem cells with new therapies to help patients with cancers driven by this mutation.

**Keith L. Ligon, MD, PhD: *Factors that Control Normal Stem Cells vs. Glioblastoma Cancer Stem Cells***



Glioblastoma (GBM) is the most common primary brain tumor in adults and is an increasingly significant cause of cancer-related deaths. Recent studies suggest that GBMs may contain a mixture of cancer stem cells and more mature non-dividing cells. The stem cells are thought to be particularly important for the growth of the tumor and its resistance to treatment. In normal stem cells, growth and differentiation are tightly controlled by transcription factors (TFs), proteins that regulate the activity of networks of other genes. While TFs have been found to be the cause of many types of cancer, their role in GBM is poorly understood. Keith L. Ligon, MD, PhD, and his team within the DFCI/BWH Center for Molecular Oncologic Pathology will comprehensively define the TFs that are expressed in GBM, and identify TFs that control the growth of both normal stem cells and GBM cancer stem cells. By gaining a basic understanding of the TFs that control stem cell growth, Dr. Ligon and his colleagues will be able to potentially uncover new diagnostic pathology markers and identify powerful new drug targets in patients with GBM.

### **Pere Puigserver, PhD: *Understanding Cellular Metabolism to Fight Cancer***



A drug called rapamycin inhibits mTOR, a protein that controls cell growth and metabolism, both of which are required for tumor formation. Drugs that inhibit mTOR are currently administered in clinical trials at DFCI against a variety of tumors and have achieved limited success. Pere Puigserver, PhD, aims to improve the efficacy of these drugs by discovering how mTOR affects the development and maintenance of tumorigenesis.

An important aspect of his research will focus on mTOR control of nutrient metabolism, since maintenance and progression of tumorigenesis and metastasis depend on the ability of tumor cells to metabolize nutrients. Dr. Puigserver's findings will help yield biomarkers to predict patient response to mTOR inhibitors, which may also be used as molecular targets to combat cancer.

### **Jia-huai Wang, PhD: *Delving Into the Life Cycle of the Avian Flu Virus***



The avian influenza virus (H5N1) pandemic has become a global concern. Cancer patients as well as others with immunodeficiency are particularly vulnerable to this threatening virus. Jia-huai Wang, PhD, aims to analyze, at an atomic level, the specific viral and molecular interactions and structural changes that occur in the host's cell throughout the life cycle of the flu virus. Dr. Wang's analysis will provide a clear guide of how to effectively interfere with these interactions, which will form the basis for designing novel

therapeutic and preventative agents against the avian flu virus.

## **Development of New and Powerful Technologies**

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### **John Quackenbush, PhD: *Computer Model to Predict Drug-Resistance in Patients with Ovarian Cancer***



Although ovarian cancer is notable for its initial response to chemotherapy, the vast majority of patients eventually develop progressively deadly drug-resistant tumors. In order to combat chemotherapy resistance, John Quackenbush, PhD, Professor of Computational Biology and Bioinformatics, initiated a project to create the world's largest database containing gene expression profiles of ovarian tumors. By examining the way in which genes turn off and on as tumors

become chemo-resistant, Dr. Quackenbush and his team hope to develop a better understanding of the mechanisms associated with this deadly transition. Using a variety of advanced computational methods, Dr. Quackenbush's team will develop software tools to help 1) identify women likely to become chemo-resistant, 2) discover the mechanisms that lead to chemo-resistance, and 3) identify potential drug targets which, if disrupted, can improve chemo-sensitivity, leading to greater overall survival. In addition, because the computational methods that Dr. Quackenbush is developing can be applied to a wide range of cancers and other diseases, he and his team will create user-friendly software tools that will enable other researchers to perform similar analysis. This interdisciplinary approach –

combining basic and clinical science with groundbreaking computational methods – represents the future of cancer research and care.

**Guo-Cheng Yuan, PhD: Computational Analysis of the Human “Epigenome”**



Epigenetics refers to the mechanisms that regulate the human genome, namely, the processes that turn a gene on or off in an individual. For example, a person’s eye and hair color is in part inherited (genetic), while the propensity or sensitivity with which that person develops a specific condition related to the eye is epigenetic, involving the expression (or lack of expression) of genes. Distinct epigenetic signatures have been identified in human cancers and associated with oncogene activities. Guo-Cheng

Yuan, PhD, and his colleagues will develop new computational approaches that integrate recent epigenetic data together with gene expression and DNA sequence data. This information will provide an understanding of epigenetic regulation and its role in cancer pathology, and has the potential to vastly enhance our understanding of cancer, improve diagnostics, and contribute to the development of new therapeutics.

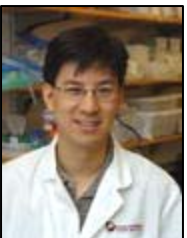
**Pallab Banerjee, PhD: Novel Imaging Methods to Study Apoptosis**



Apoptosis is a form of programmed cell death in which a cell self-destructs. Some cells undergo apoptosis spontaneously, while others do so in response to a particular situation, such as DNA damage. Cancer cells are able to evade apoptosis to proliferate, and, accordingly, many chemotherapies induce apoptosis in an effort to kill these mutated cells. Therefore, apoptosis is a basic process that is vital in understanding and combating cancer. Pallab Banerjee, PhD, aims to develop non-invasive *in*

*vivo* (withn a living organism) imaging methods that would allow scientists to view apoptosis in mouse models. Dr. Banerjee will integrate existing biology with newly emerging imaging technologies to create these tools, which will greatly enhance scientists’ ability to study cancer biology and evaluate drug efficacy.

**William M. Shih, PhD: Using Nanotechnology to View Proteins in Cancer**



Proteins called “G-Protein Coupled Receptors” (GPCRs) transmit signals from outside the cell to the inside of the cell, and are key players in the cellular progression of cancer. Activation of GPCRs can trigger behaviors that cancer cells find useful to hijack for their proliferation and metastasis – cellular growth, recruitment of nutrients and oxygen, invasion of nearby tissues, and dispersion to other parts of the body. For cancer treatment, it would be useful to design drugs that shut down the activity of aberrantly

activated GPCRs, or target cancer cells that over-express such GPCRs. To design such drugs, it is necessary to know the precise 3-dimensional structure of the target GPCR. Thankfully, William Shih, PhD, and his colleagues developed DNA nanotubes—a nanotechnology-based tool that enables scientists to accurately view the structure of proteins—and will apply this technology to characterize the structure of a specific GPCR involved in cancer growth. Dr. Shih’s study will pave the way for the future development of powerful anticancer drugs targeting specific proteins that fuel cancer.

### **Jean J. Zhao, PhD: Kinase “Library” to Uncover Cancer-Causing Molecules**



Kinases are a class of enzymes that make particularly attractive drug targets, because the aberrant activities of kinases are the most common cause of cancer. Examples of commonly used kinase-inhibitors include Gleevec, Iressa<sup>®</sup>, and Herceptin, which are all successful anticancer drugs. There are more than 500 kinases in the human genome, and many have yet to be explored for their cancer-causing potential. In the past, scientists have only been able to study kinases one at a time. Remarkably, Jean Zhao, PhD, and her colleagues developed a new technology to systemically interrogate kinases for their role in cancer. This breakthrough technology involves making “libraries” that contain individual kinases in a form that activates any hidden potential they may possess to cause cancer. Dr. Zhao’s team has already used a preliminary version to successfully find the hidden cancer-causing potential in one kinase, and will further develop the library to identify new targets of kinases in cancer. Dr. Zhao’s team will initially apply this technology to kinases in the human genome that may cause human breast epithelial cells to grow in a tumor-like manner, and then test how these cancer-causing kinases interact with other proteins expressed in cells. This novel project represents the first attempt to systematically reveal kinases with cancer-causing potential in human epithelial cells, and will yield discoveries that will fuel the development of more targeted, less toxic drugs for cancer patients.

### **Harnessing the Immune System to Fight Cancer**

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#### **W. Nicholas Haining, BM, BCh: Making T cells Work Better**



Basic immunology studies show that protective immune responses, such as those that fend off viral infections, involve a process in which normal lymphocytes become “memory lymphocytes”. These memory cells remember each specific pathogen encountered, and are able to mount a stronger response should the pathogen be detected again. However, we know little about what controls the development of memory cells. W. Nicholas Haining, BM, BCh, has identified a gene-expression signature that reflects when normal lymphocytes become memory cells. Using this knowledge, Dr. Haining and his team will probe the specific mechanisms of memory formation to make better tests to predict how well the immune system works, and to develop drugs that induce immune memory. These drugs would strengthen vaccines and have significant clinical impact in patients with an array of cancers.

#### **Harvey Cantor, MD: Immunological Memory to Strengthen Anti-tumor Response**



Harvey Cantor, MD, chairman of the Department of Cancer Immunology and AIDS at Dana-Farber, and Baruj Benacerraf Professor of Pathology at HMS, aims to generate large numbers of T cells capable of persisting in the host, and to develop robust and prolonged immunological memory to conventional and tumor-associated antigens. An essential step in generating durable immunological memory requires the formation of a

stable immunological synapse (an interaction between T cells and antigen presenting cells). Approaches that reliably enhance the formation of stable synapses have yet not been defined; however, an unexpected finding in the Cantor laboratory has revealed a potential key player in this process, the AP-1 adaptor molecule. Dr. Cantor and his team will further study the role of the AP-1 adaptor molecule in memory development in adoptive hosts. The long-term goal of these AP-1 studies is to provide a new framework for novel methods to generate tumor-specific T cells *in vitro* (in a controlled environment, e.g. test tube) that will mediate effective adoptive immunotherapy in patients with an array of cancer types.

**Roberto Bellucci, PhD: *Identifying Genes that Help Cancer Evade Immune Cells***



The primary cells of the immune system include three types of lymphocytes—T cells, B cells, and natural killer (NK) cells—used to fight disease and prevent infections. While it is possible for these cells to induce coordinated responses against cancer, most patients do not develop a response robust enough to impact their disease clinically. In addition, certain genetic events enable tumors to evade the immune system. Roberto

Bellucci, PhD, is studying the impact of thousands of genes on NK and T cells to identify those that hinder a patient's immune response against cancer. These findings will fuel the development of therapeutics targeting these genes in order to strengthen a patient's immune response. These therapies would also greatly enhance the efficacy and safety of existing treatments for a wide array of cancers.

**Koichi Akashi, MD, PhD: *Generating Immune Cells to Overcome Deficiency***



Anti-cancer treatments often deplete a patient's lymphocytes, and Koichi Akashi, MD, PhD, aims to develop new methods to enhance the body's ability to generate these critical blood cells. Such methods would better protect the body during treatment and improve outcomes in patients with a variety of cancers. Dr. Akashi and his colleagues have already discovered several stem cell populations that lead to the production of lymphocytes in mouse bone marrow, and identified the molecular process that makes stem

cells become lymphocytes. Dr. Akashi's team will use this knowledge to generate lymphocytes from human blood stem cells, eventually administering this process for patients in the clinic.