advances in cancer genomics

how researchers are transforming cancer treatment with focused genomics
Cancer Genomics
How Researchers are Transforming Cancer Treatment with Focused Genomics

Promising Results of CCR5 HIV Drug May Prove Useful in the Treatment of Metastatic Breast Cancer

Melanoma Treatment
JKCC Research Teams Explore Resistance to BRAF Inhibitors in Melanoma Patients

Experimental Therapeutics
How New Treatments Make It Out of the Lab and Into the Hospital and Clinics

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Courage is one of the key values respected at Jefferson’s Kimmel Cancer Center. Courage is one of the greatest of virtues, as without courage, few other virtues can exist. You cannot have courage cautiously. Courage “cannot see around corners, but goes around them anyway.” Every day, caring for patients at the cancer center, courage is everywhere. The courage of our patients inspires us as caregivers and as research scientists. The courage of the caregivers to believe in their patients helps everyday with a patient’s journey. The courage of our scientists who believe in a new idea that will transform the way we treat this disease is truly inspiring. It is for these reasons that we value courage at the Kimmel Cancer Center.

The cancer programs were ranked 20th in the U.S. News & World Report this year. The success of the cancer programs is a result of perseverance, focus, hard work, and shared values amongst the team at the Kimmel Cancer Center. Every member of the team – nurses, clinicians, researchers, students, and administrators – shares a common vision of providing the highest quality of cancer care. Working as a team with a common mission, we continue to strive each day to provide the highest quality experience that any patient can receive. As we look to the future, we look to becoming a top ten cancer center. We aim to provide the safest and most respectful environment that a patient can find.

In this issue of the Kimmel Cancer Center magazine Milestones, you will see some of the recent discoveries of practical value to our patients. Recent studies by Dr. John Pascal provide the basis for completely novel therapies based on a new understanding of the factor PARP (poly (ADP-ribose) polymerase).

Dr. Rani Anne’s work on maximizing the dose of radiation to the tumor while minimizing damage to the surrounding tissue and organs uses the latest technology, the Active Breathing Coordinator in treating breast cancer patients.

Studies by Dr. Marco Velasco-Velázquez demonstrate that the use of HIV drug inhibitors can block cancer metastasis in a dramatic way.

The new phase I program led by Dr. Nancy Lewis will increase the translation of our basic discoveries to treatment for our cancer patients.

The work of Dr. Paolo Fortina and the staff in the Cancer Genomics Shared Facility allows the cancer center to provide the highest quality genomic analysis using Next Generation Sequencing (NGS) technology. This allows us to determine the molecular drivers of an individual patient’s tumor. With NGS, we will provide more specific therapy, targeting the molecular mechanisms driving an individual patient’s tumor. In this way, we will provide the most specific and least toxic therapies for all patients who come to our door. This technology has recently been used by Dr. Andrew Aplin to understand mutant BRAF signaling Melanoma and its implications in treatment.

Highlights we celebrate include new grants, new awards, and new capabilities at the cancer center. Our 20 year anniversary is an exciting year for the Kimmel Cancer Center at Jefferson.
Tribute Dinner Honoring Steve Sabol

On June 5, 2012, the Sidney Kimmel Foundation, Jefferson’s Kimmel Cancer Center and 300 guests honored Steve Sabol, President of NFL Films, with a “Spirit of Courage” award and tribute dinner at the Union League of Philadelphia. The “Spirit of Courage” is awarded to an individual who has demonstrated great personal courage, strength and dignity while battling cancer.

Sadly, in September, Mr. Sabol lost that battle. His fight inspires us all and will no doubt continue to empower others suffering from the disease.

Mr. Sabol and his care team, pictured above. Left to right: Dr. Richard Pestell, Dr. Maria Werner-Wasik, Mr. Steve Sabol, Dr. Lyndon Kim, Dr. Kevin Judy, Alisha Amendt, CRNP

Recognized as among the best.

Jefferson’s Kimmel Cancer Center is a National Cancer Institute (NCI) designated clinical cancer center for excellence in cancer care and research. U.S. News & World Report also recognizes Jefferson in the top 20 best hospitals in the nation for cancer care. Jefferson is also a Blue Distinction Center for Complex and Rare Cancers. Blue Distinction is a nationwide program of the Blue Cross and Blue Shield Association, recognizing specialty centers that offer the best practices and standards of cancer care.

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The HIV drugs known as CCR5 antagonists may also help prevent aggressive breast cancers from metastasizing, researchers from the Kimmel Cancer Center at Jefferson suggest in a preclinical study published in a recent issue of Cancer Research. Such drugs target the HIV receptor CCR5, which the virus uses to enter and infect host cells, and has historically only been associated with expression in inflammatory cells in the immune system.

Researchers have now shown, however, that CCR5 is also expressed in breast cancer cells, and regulates the spread to other tissue. What’s more, blocking the receptor with the CCR5 antagonists Maraviroc and Vicriviroc, two drugs that slow down the spread of the HIV virus by targeting the CCR5 co-receptor of the chemokine CCL5, also prevents migration and spread of breast cancer cells, the researchers found.

“These results are dramatic,” said Richard Pestell, MD, PhD, Director of Jefferson’s Kimmel Cancer Center and Chair of the Department of Cancer Biology at Thomas Jefferson University, and study senior author. “Our team showed that the CCR5/CCL5 axis plays a key role in invasiveness, and that a CCR5 antagonist can slow down the invasion of basal breast cancer cells.” “This suggests it may prove to be a viable adjuvant therapy to reduce the risk of metastasis in the basal breast cancer subtype,” he added.

Basal tumors, which do not express the androgen or estrogen receptors or HER-2, are typically associated with metastasis and often do not respond to hormonal therapies. Current treatments include chemotherapy, radiation, and surgery, but all demonstrate poor outcomes, thus highlighting the urgent need for a specific targeted therapy for the subtype.

For the study, Dr. Pestell and colleagues investigated the CCL5/CCR5 axis expression in human breast cancer cell lines and the effect of CCR5 antagonists in vitro and in vivo. An interrogation was conducted using a microarray dataset to evaluate CCR5 and CCL5 expression in the context of 2,254 patient breast cancer samples. Samples in the dataset were assigned to five breast cancer subtypes, including luminal A, B, normal-like, basal and HER-2 overexpressing disease.

The analysis revealed an increased expression of CCL5 and CCR5 in patients with basal and HER-2 subtypes, with 58 percent indicating a positive CCR5 and CCL5 signature. The team showed that oncogenes turn on the CCR5 receptor in normal breast cells as they became transformed into cancer cells. Spread of those cells is also regulated by CCR5, they found.

To evaluate the functional relevance of CCR5 in cellular migration and invasion, the team tested the drugs in 3-D invasion assays with two different cell lines. Here, too, they discovered that both antagonists inhibited breast cancer cell invasiveness.

Next, to determine its effects in vivo, the team injected mice with the antagonists and tracked invasiveness of the basal breast cancer cells to other tissue, i.e. lung, with bioluminescence imaging. Mice treated with the drug showed a more than 90 percent reduction in both the number and size of pulmonary metastases compared to untreated mice.

“Our preclinical studies provide the rational basis for studying the use of CCR5 antagonists as new treatments to block the dissemination of basal breast cancers,” said Dr. Pestell. These findings may also have implications for other cancers where CCR5 promotes metastasis, such as prostate and gastric.

- Stephen Graff, Science Writer
Among the keys to deciphering normal physiological processes and their derangements in neoplasia is an understanding of the spatial and temporal relationship of different cellular components to each other. Understanding this relationship provides needed information to correlate cellular structure with function. The goal of KCC Bioimaging Shared Resource is to provide powerful, reliable, and readily accessible light microscopic image acquisition and analysis capabilities for KCC investigators. The Facility is operated under the auspices of the Kimmel Cancer Center and is run by a well-trained staff and a faculty supervisor, Dr. James Keen in the Department of Biochemistry. The staff of the shared resource provides training in operation of all instruments as well as consultation in operation, methodology, experimental approach, and interpretation. It is open for scheduled use at any time by trained investigators, or the Facility operator can perform imaging and analysis with laboratory personnel. Through the operation of this Shared Resource, individual KCC investigators are assured of state-of-the-art and reliable facilities operated with a high degree of technical expertise, and are relieved of the obligation for substantial outlay for equipment, maintenance and personnel training. Equipment in the Shared Resource includes: Zeiss LSM 510 Meta Confocal Laser Scanning system with Zeiss Axiovert 200M Microscope; Nikon C1 Plus Confocal Laser Scanning Microscope; Andor/Nikon TIRF (Total Internal Reflection Fluorescence)/Spinning disk confocal/Widefield Microscope with dual EM-CCD cameras and Dualview2; Wide-field System: Zeiss Axiovert 200M inverted fluorescence/CoolSnap HQ CCD/ Sutter Lambda DG4 Fast-wavelength changer; Nikon Eclipse TE-2000-S survey microscope; Metaamorph, Nikon, and Zeiss Image Software.
Melanoma is the deadliest form of skin cancer with a high lifetime risk. There are greater than 60,000 new cases in the U.S. per year and over 8,000 deaths. The incidence of melanoma is rising rapidly, most notably in females between the ages of 15 and 39. Currently, metastatic disease is only preventable through early detection and surgical excision of primary tumor. With few options for treating metastatic disease, there is an immediate need to understand the mechanisms underlying melanoma initiation and progression, which can be exploited in new treatment strategies. Andrew Aplin and his collaborators at the Kimmel Cancer Center are actively engaged in translational melanoma research. His laboratory utilizes molecular and clinical grade inhibitors to alter key signaling transduction pathways in normal melanocytes and human melanomas to better understand this deadly disease.

Like many other cancers, melanoma is not a single disease but consists of genetically defined sub-groups. One main research focus is on the gene BRAF that is mutated to an active form in approximately half of melanomas. Mutation of BRAF typically causes an amino acid substitution, valine (V) to glutamate (E), at position 600 of the BRAF protein. This substitution occurs in the activation loop of BRAF and causes the protein to be hyper-activated and, in turn, promotes signaling through a kinase phospho-relay known as the MEK-ERK1/2 cascade. This pathway is required for melanoma growth and invasion. Dr. Aplin’s laboratory is determining the effectors of the mutant BRAF signaling pathway that elicit malignant traits in melanoma cells. They have identified mechanisms whereby mutant BRAF regulates hallmark features of tumor cells including resistance to apoptosis, enhanced migration and invasion, and proliferation. These studies have implicated mutant BRAF as a driver gene in metastatic melanoma.

The BRAF inhibitor, vemurafenib/ zelboraf, has recently been FDA-approved for the treatment of mutant BRAF melanoma patients. In clinical trials, BRAF inhibitors cause tumor shrinkage and improve the rates of progression-free and overall survival in naive mutant V600E BRAF melanoma patients. However, the initial response to BRAF inhibitors is heterogeneous and many patients who show initial tumor shrinkage are likely to acquire drug resistance within months. These modes of resistance are major obstacles to the prolonged effects of BRAF inhibitor-based therapies.

Dr. Aplin and his laboratory are collaborating with the KCC genomics facility to elucidate mechanisms of resistance to RAF inhibitors. The laboratory has identified a novel mechanism of drug-induced, adaptive response that promotes primary resistance to BRAF inhibitors. This adaptive response activates a compensatory AKT signaling pathway that the laboratory has shown is able to promote tumor cell survival in the presence of BRAF inhibitor. Additionally, the laboratory is investigating mechanisms of acquired resistance to BRAF inhibitors. A particular research focus is on the acquisition of secondary mutations within other genes involved with ERK1/2 pathway signaling. Ultimately, these secondary mutations lead to re-activation of the MEK-ERK1/2 pathway that is refractile to BRAF inhibitor treatment. Overall, these studies are utilizing BRAF inhibitors as the building blocks for possible new combinatorial therapeutic strategies. The laboratory aims to provide the preclinical basis for new treatment options to further improve on the progression-free and overall survival of mutant BRAF melanoma patients.
advances in cancer genomics

how researchers are transforming cancer treatment with focused genomics
The field of Cancer Genetics and Genomics has undergone extraordinary advances over the last decade in understanding the initiation, onset and progression of this debilitating disease. The ability to translate this knowledge for better diagnosis and treatment of cancer is a major goal of the Kimmel Cancer Center. In this approach, the determination of a person’s unique genetic makeup and molecular characteristics are used to select the correct targeted therapy and represents a new paradigm for the practice of medicine. For the patient this enhanced knowledge can translate to improved diagnosis and fine-tuned selection of treatment that increase the chances of a positive outcome and minimizes adverse toxicity. For the healthy individual, personalized medicine can translate to determining one’s susceptibility to disease and provides the opportunity to develop an appropriate plan of action to minimize disease severity or to avoid it altogether.

Cancer is a genetic disease which continues to be a major cause of morbidity and mortality, and one of its distinguishing features is the disruption of critical genes. Overexpression of growth factor receptors such as EGFR or HER2 plays an important role in the oncogenesis of lung, colorectal and breast cancer, for example. Activating mutations in the BRAF gene are common in melanoma and thyroid cancer. Over the past decades, there have been tremendous advances in identifying these genetic abnormalities and understanding their implication in cancer.
As part of this work, new drugs have been developed that specifically target these genes or the pathways they regulate. In addition, it has been established that a particular cancer type such as breast cancer, is not a single disease, but may be distinct diseases with different mutations and other genetic abnormalities being responsible for the disease. In addition, because an individual tumor may carry several mutations, a drug that targets one gene may not be effective in patients that carry other mutations that are downstream of the gene targeted for therapy. For example, drugs such as erlotinib that target the growth factor receptor EGFR are ineffective in patients that carry an activating mutation in kRAS. Determining if a patient carries one of these mutations is only a small part of the story, and the ability to truly understand the complex interactions amongst different genes will require significantly more knowledge which is enabled by emerging technologies.

Many of these discoveries were enabled using chip-based technologies, real-time PCR or Sanger sequencing. However, recent advances in sequencing technologies are transforming the field by providing a deeper understanding of the genomic variability in tumors; and can provide significantly more detailed and quantitative information about the genetics of a particular individual and their cancer. Next-generation sequencing (NGS) instruments have greatly accelerated the pace of discovery in just a few years. As the technology matures, NGS will become increasingly critical in the area of personalized medicine. The technology has helped to determine variant Single Nucleotide Polymorphisms (SNPs) in the genome, which may play a role in patient response to drugs. It has facilitated determination of normal and tumor tissue and helped in the identification of genes that are expressed in normal/malignant cells.

Because each individual's tumor can carry a different collection of genetic abnormalities, there is movement towards personalized medicine which is the selection of therapy based on testing for these mutations in the tumor. Perhaps the most comprehensive approach to identify genomic variants associated with complex diseases such as cancer is to perform massively parallel sequencing or NGS. This approach involves either sequencing the entire or specifically targeted regions of the genome.

Recently, a variety of platforms are available to perform massively parallel sequencing, with each allowing for differences in the scale of the sequence being performed. The Cancer Genomics Shared Resource provides access to NGS platforms including Life Technologies SOLiD and 5500x1 sequencers, and Ion Torrent PGM. Taken together, these machines can produce billions of base pairs of sequence in a relatively short period of time (days to a few weeks) allowing for the sequencing of entire genomes or specifically targeted regions (e.g., whole-exome sequencing). The Ion Torrent PGM Sequencer, which utilizes very short run times for targeted mutation detection, allows for fast turnaround, so the clinician attending to the patient will be able to start treatment in a timely manner. This technology is based on semiconductor chip technology and current assays allow interrogation of the coding region of 409 tumor suppressor genes and oncogenes most frequently cited and most frequently mutated and can detect mutations at a frequency of 5%.

Because of the sheer mass of the data generated and the complexities of its interpretation, one of the bottlenecks to NGS is the bioinformatic analysis of the data. The Computational Medicine Center (CMC) has been developing the infrastructure that it needs to fulfill its own basic research and translational missions. At the same time, the CMC...
has developed several tools that are available through the web for the analysis of NGS data. The CMC has developed a “hands-free” computational infrastructure that seamlessly connects to the Cancer Genomics Shared Facility’s computers and permits the automated transfer of primary raw sequence datasets from a given project to the CMC and the datasets are automatically processed and mapped on the genome of interest, and a preliminary analysis is performed.

DNA sequencing technologies along with advanced analysis tools have given human geneticists new tools to delineate the genetic basis of both rare and common diseases. In addition, we have begun to see that NGS will play an important role in assessing an individual’s genomic sequence which provides information needed to make informed decisions about disease risk, treatment and outcome.

“Cancer genomics provides innovative tools for research.”
- Paolo Fortina, PhD, Director Cancer Genomics Facility at Jefferson’s Kimmel Cancer Center

Computational Medicine Center

Isidore Rigoutsos, PhD
Professor and Director

The Computational Medicine Center at Thomas Jefferson University focuses on the use of computational and experimental techniques to solve problems from genomics, genetics, molecular biology and medicine.

The strengths of the center are in the areas of pattern discovery and non-coding RNAs. The Center’s research emphasis is on organism-specific regulatory motifs, on determining how short as well as longer non-coding RNAs are involved in the onset and progression of disease, and on translating the knowledge of RNA interactions into novel approaches to diagnosis and personalized therapy (“Personalized Medicine”).
The Kimmel Cancer Center (KCC) at Jefferson is one of only 66 National Cancer Institute designated Cancer Centers in the United States. One of the goals of the KCC is to provide our patients with the latest therapeutic agents that are available and to translate the findings of the research laboratories at Thomas Jefferson University to the clinic. The clinical arm of the Cancer Center, Thomas Jefferson University Hospital, consistently ranks in the U.S. News and World Report Top 50 Hospitals survey lists in a variety of specialties, and was ranked #20 in the nation for cancer care in 2012.

To achieve these goals, the KCC has recently developed a Medical Oncology Phase 1 program. The program is structured to provide the needed infrastructure to allow for the deployment of new drugs in a time-efficient and safe manner. In addition, because many of the new therapeutics target specific genes and molecular pathways, there are often corresponding complex molecular assays that are part of the trial and require the ability to process samples for complex testing. There has been tremendous effort made to streamline the protocol review, budgeting and contract process, as well as establishing a Phase I Laboratory, which has attracted many pharmaceutical companies to conduct phase I studies here.

The medical oncology phase I program is led by Nancy Lewis, MD, Associate Professor and Clinical Director of Experimental Therapeutics. Since her recruitment to the Kimmel Cancer Center, Dr. Lewis has made remarkable progress in establishing a robust phase I program here. Early phase trials are performed to determine dosing, scheduling, safety and pharmacokinetics of novel therapeutics, as single agents or in combination.

The Cancer Center and the Department of Medical Oncology has dedicated resources and highly trained personnel for the phase I program. Members of the phase I team include clinical research coordinators, regulatory supervisors and data managers. Our dedicated Phase I Nurse Practitioner, Anne Markham, DNP, CRNP, AOCN was recruited to the program given her unique experiences as both an oncology nurse practitioner, as well as her work in the pharmaceutical industry. The phase I Unit encompasses both inpatient and outpatient services. The team is capable of conducting a wide range of studies that include extensive pharmacokinetic and pharmacodynamic monitoring, surrogate tissue collection and tumor biopsies. The phase I protocol laboratory staff processes all biologic correlative samples. Studies may encompass all oncology disciplines including medical oncology, radiation oncology, and surgery.

With a record-breaking number of new FDA-approved drugs, this continues to be a very exciting time in the field of oncology. There are many highly promising new targets and compounds to develop. Building an active phase I program provides the Jefferson community access to state-of-the-art oncologic therapies.
Newly Opened Therapeutic Trials

BRAIN & NERVOUS SYSTEM
- Phase II Randomized Study of Rituximab, Methotrexate, Procarbazine, Vincristine, and Cytarabine with and without Low-Dose Whole-Brain Radiotherapy for Primary Central Nervous System Lymphoma (RTOG-1114)
- Phase I, Dose Finding Trial of the Combination of Panobinostat and Stereotactic Radiation in the Treatment of Brain Tumors
- A Randomized, Double-Blind, Controlled Phase Ib Study of the Safety and Efficacy of ICT-107 in Newly Diagnosed Patients with Glioblastoma Multiforme Following Resection and Chemoradiation

BREAST CANCER
- Tolerability of the Combination of Lapatinib and Trastuzumab in Adults Age 60 or Older with Her2 Positive Metastatic Breast Cancer
- A Phase III Trial of Accelerated Whole Breast Irradiation with Hypofractionation plus Concurrent Boost Versus Standard Whole Breast Irradiation plus Sequential Boost for Early-Stage Breast Cancer (RTOG-1005)

GASTROINTESTINAL ONCOLOGY
- A Phase Ib Study of Fractionated 90Y-hPAM4 with or without Gemcitabine in Patients with Metastatic Pancreatic Received at Least Two Prior Treatments Cancer Who
- MAVERICC: A Randomized Phase II Study of Bevacizumab/mFOLFOX 6 vs. Bevacizumab/FOLFIRI with Biomarker Stratification in Patients with Previously Untreated Metastatic Colorectal Cancer

GENITOURINARY ONCOLOGY
- EVEREST: Everolimus for Renal Cancer Ensuing Surgical Therapy, A Phase III Study (SWOG-S0931)
- A Randomized Phase 2 Open Label Study Evaluating DN24-02 as Adjuvant Therapy in Subjects with High Risk HER2+ Urothelial Carcinoma
- A Randomized Phase 2 Open Label Study Evaluating DN24-02 as Adjuvant Therapy in Subjects with High Risk HER2+ Urothelial Carcinoma
- A Phase II Study of Cabazitaxel in Patients with Urothelial Carcinoma Who Have Disease Progression Following Platinum-Based Chemotherapy
- A Phase II Study of Cabazitaxel in Patients with Urothelial Carcinoma Who Have Disease Progression Following Platinum-Based Chemotherapy

GYNECOLOGIC ONCOLOGY
- Randomized Phase 2 Study of MLN8237, an Aurora A Kinase Inhibitor, plus Weekly Paclitaxel or Paclitaxel Alone in Patients with Recurrent Ovarian, Fallopian Tube or Primary Peritoneal Cancer, Proceeded by a Phase I Portion in Patients with Ovarian or Breast Cancer
- Chemotherapy Toxicity in Elderly Women with Ovarian, Perimary Peritoneal, or Fallopian Tube Cancer (GOG-0273)
- A Phase II Evaluation of BIBF 1120 (IND #113086) in the Treatment of Recurrent or Persistent Endometrial Carcinoma (GOG-0229K)

HEMATOLOGIC MALIGNANCIES
- A Two Step Approach to Allogeneic Hematopoietic Stem Cell Transplantation for High-Risk Hematologic Malignancies Using Two Related Donors
- An Open-Label, Dose Escalation, Phase 1 Study of MLN9708, A Second Generation Proteasome Inhibitor, in Adult Patients With Lymphoma

MELANOMA & SKIN CANCERS
- Randomized Phase II Trial of Temozolomide (TMZ) Versus Hyd-Sulfate AZD6244 [NSC 748727] in Patients with Metastatic Uveal Melanoma
- A Phase 2 Study of IMC-A12 in Metastatic Uveal Melanoma

THORACIC & AERODIGESTIVE ONCOLOGY
- A Randomized Phase III Study of Sublobar Resection (+/- Brachytherapy) versus Stereotactic Body Radiation Therapy in High Risk Patients with Stage I Non-Small Cell Lung Cancer (NSCLC) (ACOSOG-Z4099/RTOG-1021)

New Research Grants

Toll-like receptor signaling in the generation of B1b cell memory
K. ALUGUPALLI · NCI U56 · $387,500

FOXO3 up-regulation and ERBB3 signaling as an adaptive response to raf inhibitors
A. APLIN · NCI R01 · $321,625

Training program in cellular; biochemical; and molecular sciences
J. BENOVIC · NIH T32 · $89,300

Multisubunit viral ATPases that couple ATP-hydrolysis to genome translocation
G. CINGOLANI · NIH R01 · $294,500

Main Line Health CCOP
P. GILMAN · NCI U10 · $509,325

EGFR therapies for fatty liver surgery
T. KONIARIS · NIH R01 · $337,125

Negative selection of autoreactive antibodies
T. MANER · NIH R56 · $387,500

Regulation of persistent antibody responses by FC receptors
T. MANER · NIH R56 · $387,500

Aberrantly secreted glycoproteins as markers of liver cancer
A. MEHTA · NCI U01 · $293,348

Effects of opiates on neurons and their impact on HIV neuropathology
O. MEUCCI · NIH R01 · $328,313

Progranulin signaling in bladder cancer
A. MOTTINE/R. ROZZO · NCI R01 · $321,625

OPPC targeting to improve pancreatic cancer treatment
G. PRENDERGAST/I. YAYEN · NCI R03 · $82,500

Role of the cytoskeleton in cardiac regeneration
G. RADICE · NIH R01 · $323,500

Manipulating alpha-catenins to stimulate cardiomyocyte proliferation
G. RADICE · AHA Grant · $77,000

Use of closely related inbred strains to identify modifier loci of tumorigenesis
L. SIRACUSA · NCI R01 · $202,275

Mineralization/anti-mineralization networks in the skin
J. UITTO · NIH R21 · $206,080

GUCY2C hormone signaling at the intersection of obesity and colorectal cancer
S. WALDMAN · NCI R01 · $331,625

Impact of ERBB2 and RB pathways on DCIS progression and treatment
A. WITKIEWICZ/C. Z· NCI R01 · $331,162

Tumor microRNA signatures as prognostic biomarkers of colorectal cancer
H. YANG · NCI R03 · $77,500
Benchside Q&A: John M. Pascal, PhD and His Fresh Take on PARP-1

PARP-1 has been identified as a valuable target in cancer therapeutics, but what's really special about it? That's the question John M. Pascal, Ph.D., an assistant professor in the Department of Biochemistry and Molecular Biology at Thomas Jefferson University and Jefferson's Kimmel Cancer Center, is starting to answer. A recent study led by Dr. Pascal and colleagues published in Science revealed new target sites for drugs aiming to stop PARP-1, the DNA damage-detecting enzyme that plays a role in tumor growth. Drugs inhibiting PARP-1 have shown to be effective in fighting the disease, but Dr. Pascal thinks we can do better. Today's approach in the preclinical and clinical setting is limiting, he says, because the catalytic site is similar to those found in other PARP-like proteins that carry out other essential cellular functions, and therefore increases the potential for off target side effects. Dr. Pascal discusses his newly discovered weak points of PARP-1 and what it could mean for more precise cancer therapeutics.

Why is it important to focus on PARP-1, with respect to cancer therapeutics?
PARP-1 contributes to the overall integrity of our genomes, which is essential for the normal and healthy growth of a cell. A signature feature of many cancer cells is genome instability, which often arises from alterations made to the cell's DNA repair mechanisms. Inhibiting PARP-1 activity increases the level of cellular DNA damage to a tipping point that kills cancer cells with pre-existing genome instability. Normal cells can handle this additional level of DNA damage, so in some contexts PARP-1 inhibitors have provided a mechanism for specifically killing cancer cells, and leaving our healthy cells alone. In other contexts, PARP-1 inhibitors have sensitized cells to DNA damaging agents that are already used in chemotherapy.

Barbara Gerratana, Ph.D., of the National Institutes of Health's National Institute of General Medical Sciences, recently called your work in Science “a major breakthrough in understanding an enzyme essential for regulation of cell proliferation and a promising target for cancer therapeutics.” What distinguishes your work from what we already know about PARP-1 inhibitors?
PARP-1 is composed of six functional units, or domains, and several of these domains are essential for the important roles that PARP-1 plays in the cell. Current inhibitors target just one of the domains, the catalytic domain. Although we knew that multiple domains of PARP-1 were required for its function, we did not know why they were important, or how they worked together to help PARP-1 carry out its roles in the cell. We were able to capture the essential domains of PARP-1 in complex with DNA damage, which is an acute activator of PARP-1 function. Our structural and biochemical analysis defines the roles of each of the essential PARP-1 domains. We discovered that multiple domains of PARP-1 engage the DNA damage, and we found that the contacts and "communication" between PARP-1 domains are essential for PARP-1 activity. The "communication" between domains is unique to PARP-1, therefore we have identified potential targets for drug design that could steer clear of the conserved catalytic domain and provide new ways of inhibiting PARP-1.

You use X-ray crystallography as a primary tool to study the structure PARP-1. How does this technology capture the structure and how is it helping researchers better understand PARP-1’s role in tumor growth?
X-ray crystallography provides a wealth of structural information, from the overall architecture and design of a molecule to the detailed arrangement of atoms. There really is no other technique that yields this type of information. To study PARP-1 using x-ray crystallography, we first had to grow crystals of PARP-1, and this required a great deal of effort and innovation. Our biggest technical advance came when we discovered that the isolated domains, or parts of PARP-1, could be mixed together as separate entities and still retain function. The resulting structure provides the intricate details of how the pieces of PARP-1 come together, and how they collectively bind to DNA damage. The level of detail obtained from our structure allows us to think about ways of designing new PARP-1 inhibitors in a rational, knowledgeable way that was not previously possible.

What’s the next step in your research?
One direction is to capitalize on the identification of the domain contacts that are essential for PARP-1 function. We have developed a set of biochemical assays that detect the formation of these contacts, and we are using these assays to identify small molecules that disrupt the domain "communication." The goal is to identify new and specific ways of inhibiting PARP-1 activity in cells with small molecule drugs.
Today, the crux of radiation oncology treatment is sparing healthy tissue, with new technologies emerging regularly that deliver more precise and higher doses of radiation to treat tumors of the breast, prostate and many other cancers while minimizing impact on adjacent organs. But the ability to deliver radiation with precision is only valuable if the target is in an identifiable, repeatable and stationary position. It’s called motion management, and a prime example at Thomas Jefferson University Hospital is the active breathing coordinator (ABC) for use in breast cancer patients. Such a device also helps radiation oncologists spare one of the most important organs in the body from unwanted radiation through the act of breathing: the heart.

Jefferson’s ABC device, one of only a few in the region, lives in the Bodine Center for Radiation Therapy, where Dr. Rani P. Anne, associate professor in the Department of Radiation Oncology and Director of Clinical Operations and Quality Assurance, has been using it on patients for the last decade. More recently, Dr. Anne and her team finished a clinical trial evaluating its use in patients, who come from all over the region for treatment.

Dr. Anne shares details on the device, why women who snorkel may feel more comfortable using it.

**What’s the purpose of the active breathing coordinator, and what benefit does it serve to women receiving radiation therapy?**

Avoiding the heart, as a critical structure, during left breast radiation treatment is a challenge that has gained increased interest.

The ABC is designed to help spare critical organs, like the heart, liver and lung, which are constantly in motion, from adverse effects of radiation therapy in the treatment of cancer in the left breast.

With such a technique, the lung expands, pulling the heart away from the breast/chest wall area to be irradiated. In this way, it is possible to significantly reduce, or even eliminate, the amount of heart included in a tangential field, in an accurate and repeatable way.

In essence, ABC helps the patient hold their breath. And that deep inhalation increases the distance between the area receiving radiation and the heart, meaning there is less risk the heart will receive any incidental radiation during radiation treatment.

The device is approved by the U.S. Food and Drug Administration, but it is not suitable for everyone. Who is the ideal patient?

The best patient for using the ABC device, is one who is able to hold their breath for the 20 second interval, and who can understand and follow the directions. A very anxious patient, a patient who has never tried to hold their breath, or one with a chronic cough may have trouble. For these patients, we have other methods, such as intensity modulated radiation therapy or use of prone (lying on the belly) position to prevent the heart from getting radiation.

Those with more experiences in breathing exercises—for example, women who have snorkeled or scuba dive—are more likely to feel comfortable using the device. Because a mouthpiece is inserted in between the teeth, like a snorkel, and the nose is clamped off, some patients feel restricted and uneasy.
For tickets and information about the 2012 Men’s Event please contact Mika K. Harding at (215) 503-1195.

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Office of the Director
233 South 10th Street
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Special Guest  JAY MOHR

MEN’S EVENT
Benefiting Prostate Cancer Research and Awareness

NOVEMBER 15, 2012