



MEET THE INNOVATIVE RESEARCH GRANT RECIPIENTS

SU2C

Last May you helped launch Stand Up To Cancer, a groundbreaking initiative funding translational cancer research with the aim of getting promising new therapies from the bench to the bedside – and doing it *fast*. (You can read more about translational research here.) Thanks to your incredible generosity and support, SU2C has raised over \$100 million in the short twelve months since its launch. But this is only the beginning. We’re thrilled to announce that our Scientific Advisory Committee has selected its first round of [Innovative Research Grant recipients](#) and we think you’ll find the science behind their projects as exciting and inspiring as we do.

An Emerging Tumor Suppressor Pathway to Human Cancer

Fernando D. Camargo, Ph.D., Children’s Hospital Boston

Hippo is a biochemical pathway that is thought to regulate organ growth. It works by preventing further cell division once organs have reached their proper size. Camargo and his group believe that Hippo signals are part of a powerful checkpoint that restricts increases in cell numbers and activates cell death. This checkpoint would allow an organ to “know its size” and stop growing at the appropriate time, and may also suppress the unchecked increases in the numbers of cells that characterize tumor growth.

Camargo’s studies will determine the existence of this checkpoint and its role in suppressing tumor growth by using a model system in which the Hippo signal can be turned off and on. They will also identify novel proteins and small molecules that regulate Hippo signaling and could be used to develop new therapies for cancer. Insight into the relatively unexplored relationship between Hippo signaling, organ growth and tumor suppression holds the promise of yielding an entirely novel set of therapeutic targets for the treatment of human cancer, particularly for pediatric tumors.

“How does your body know that the liver needs to be a certain size?” Camargo said. “What we want to do is understand this powerful intrinsic mechanism that regulates symmetry and tissue size and test whether those same mechanisms also act naturally to prevent cancer growth.”

Modeling Ewing Tumor Initiation in Human Neural Crest Stem Cells

Elizabeth R. Lawlor, M.D., Ph.D., Children's Hospital Los Angeles

Ewing sarcomas are highly aggressive tumors that primarily affect children and young adults. They are believed to arise from neural crest stem cells — rare cells that contribute to the formation of multiple tissues throughout the body. Ewing sarcomas contain an abnormal gene called EWS-FLI1. The precise way in which expression of EWS-FLI1 causes Ewing sarcoma remains to be determined, but it is known to involve disruption of normal gene expression. Lawlor believes that this disruption is due, at least in part, to changes in some of the epigenetic marks on the DNA (DNA methylation) that result in turning on the expression of genes that should be off and turning off the expression of genes that should be on.

This project will use an innovative model to generate neural crest stem cells in the laboratory. Lawlor will study the ways in which expression of EWS-FLI1 affects the epigenetic marks in these neural crest stem cells and how EWS-FLI1 initiates tumor formation. She will also determine whether the epigenetic alterations in Ewing sarcoma cells can be corrected by treatment with a new targeted drug that prevents DNA methylation. These studies will provide novel insights into normal neural crest cell biology and could facilitate the development of more effective, less toxic therapies, such as DNA methylation inhibitors, to specifically target this pediatric malignancy.

“We need to develop drugs that are going to be selective, killing the cancer cells and sparing the normal developing tissue,” Lawlor said. “That way, when children are finished treatment, they're not only free of cancer, but they can go back to school and know they're going to live a normal, healthy life and not be affected in the long term by these terrible side effects.”

Cancer Cell Specific, Self-Delivering Pro-Drugs

Matthew Levy, Ph.D., Albert Einstein College of Medicine of Yeshiva University

Most drugs that kill rapidly dividing cancer cells also kill normal healthy cells. The ability to direct drugs specifically to cancer cells would avoid some of the undesirable side effects of cancer treatment. Levy proposes to tackle this challenge by developing a new type of all-in-one drug that will only be taken up by cancer cells — a drug capable of both finding and killing cancer cells. To do this, he will start with a type of molecule known as an aptamer, which can specifically bind to particular proteins found on cancer cells. These aptamers will be adapted for delivery of anti-cancer drugs resulting in “aptamer-guided pro-drugs” that specifically bind to cancer cells and kill them. A second part of the project involves identifying new aptamers that can selectively bind to different tumor types, thus, expanding the types of cancers that could be treated with this novel class of self-guided drugs. Both efforts combine the power of cell targeting with drug delivery in one single synergistic molecule.

It would be a great advantage in cancer treatment to have drugs that killed cancer cells and left normal cells undamaged. One approach to this is to re-engineer molecules known to bind specifically to cancer cells into anti-cancer drugs. The added level of specificity would significantly reduce toxic side effects common to many current therapies.

“Our hope is that we will be able to use drugs that are currently being used, but we’ll be able to direct them to the unhealthy tissue, the cancer,” Levy said. “In doing so, we should increase the efficacy of the drugs while minimizing the systemic toxicity.”

Targeted Inhibition of BCL6 for Leukemia Stem Cell Eradication

Markus Müschen, M.D., Children’s Hospital Los Angeles

While a great deal of progress has been made in treating some forms of leukemia, the long-term survival rate for leukemia patients has reached a plateau. This is largely a result of the fact that the current treatments are designed to kill the bulk of the tumor cells that are actively multiplying, but do not affect the small population of cancer stem cells that are dormant or sleeping. These rare stem cells are resistant to these drug treatments and contribute to the cancer’s relapse when they do wake up and begin multiplying.

Recent studies by the Müschen laboratory have shown that these sleeping leukemia cells produce high levels of BCL6, a factor that controls the production of many important genes involved in cell division. Müschen now proposes to use a novel drug, which can stop BCL6 from functioning and also works cooperatively with standard leukemia treatments. These studies will test the importance of BCL6 in initiating leukemia and causing relapse, determine the frequency of BCL6-expressing stem cells in human leukemia samples, and conduct preliminary work with the new BCL6 inhibitory drug necessary for clinical trials. This work will provide important insight into the role of BCL6 in leukemia development, treatment and resistance that could lead to a novel therapeutic strategy using a combination of drugs to target both active and dormant cells, thus reducing the chances of resistance.

“For our group, just finding the BCL6 protein that plays a role in the strength of leukemia cells was totally unexpected,” said Müschen. “It was a total surprise. Other funding mechanisms are not available to support this kind of research, work that would break with the traditional ideas about how genes are regulated.”

Identifying Solid Tumor Kinase Fusions via Exon Capture and 454 Sequencing

William Pao, M.D., Ph.D., Vanderbilt University Medical Center

Cells rely on molecular switches to carry out normal functions. One class of switches called tyrosine kinases (TK) control cell division and can cause cancers if they become altered. One alteration found in some cancers results from the fusion of the normal TK

with a cellular protein. This leads to a molecular switch that no longer functions correctly. These fusions are good targets for drug development. Gleevec, which has been used very successfully to treat a specific form of leukemia and an unusual gastrointestinal tumor, is the most notable example of a successful use of this approach.

Pao seeks to identify novel TK fusions in 100 well characterized lung and breast cancers. He will use cutting-edge genomic technologies to capture, sequence and identify TK fusions in relatively small samples of tumor DNA. If successful, this work will provide new targets for future drug development.

“The best example of this is seen in patients with chronic myelogenous leukemia,” Pao said. “We now know that the drug Gleevec is very effective in killing cancer cells in these patients. We propose to find many new targets for therapy so that we can find a lot more Gleevecs. Gleevec has revolutionized the treatment of patients with this type of leukemia. We hope to do the same in patients with lung cancer and other solid tumors.”

Therapeutically Targeting the Epigenome in Aggressive Pediatric Cancers

Charles M. Roberts, M.D., Ph.D., Dana-Farber Cancer Institute

Malignant rhabdoid tumors and atypical teratoid/rhabdoid tumors (RT) occur primarily in children under 2 years old. Despite intensive treatment, over 80 percent of patients with RT die within about a year of diagnosis. These tumors are unique because unlike most cancers, they have not accumulated alterations in their DNA sequence compared to the patient’s normal cells. Instead, this cancer often results from the loss of a specific gene, SNF5, which affects the physical structure or packaging of the DNA. This alteration to the DNA packaging and other epigenetic changes can affect the expression of many genes that cancer cells use to grow.

This is significant because epigenetic changes are not permanent and can potentially be reversed with the right therapies. Roberts has developed a model system to examine different types of epigenetic pathways and to determine if there are therapies that can reverse the cancer-causing effects of losing the SNF5 gene. This could lead to improved treatment for RT and could also have much broader implications since epigenetic changes play an important role in causing almost every type of cancer.

This work could lead to better treatments for aggressive pediatric cancers that affect mostly children under 2 years old and kills most patients within a year. It would also have broad implications for many kinds of cancer, since it involves a new understanding of the impact of epigenetic changes in causing cancers.

“We want to translate the science into patient care because there are kids that have these very lethal tumors,” Roberts said. “Equally important, however, these changes in the epigenome are present in adult cancers as well as pediatric cancers. We’re hopeful that the breakthroughs we make will be applicable to many types of cancer.”

Endogenous Small Molecules that Regulate Signaling Pathways in Cancer Cells

Rajat Rohatgi, M.D., Ph.D., Stanford University

A major goal in cancer biology is to understand the molecules that drive the growth and spread of cancer cells. This understanding is essential for developing targeted therapies that kill cancer cells while minimizing damage to normal cells. Rohatgi will focus on endogenous small molecules in cells that play a role in the signaling processes that cause cancer. Using an integrative strategy combining tools from cell biology and chemistry, he will identify small molecules that regulate the Hedgehog signaling pathway, which drives the development of a large number of adult and childhood cancers. Drugs that interfere with the function of this pathway hold promise for future cancer treatments.

Understanding the complex signaling pathways that lead to cancer is important to developing new approaches to cancer treatment. This proposal focuses on understanding the interaction of small molecules with a pathway that has been shown to be very important in many cancers and using that knowledge to develop new targeted treatments.

Genetic Approaches for Next Generation of Breast Cancer Tailored Programs

José M. Silva, Ph.D., Columbia University Medical Center

Cancer cells accumulate genetic alterations that promote tumor growth and tumor progression. These alterations make the tumor cells different from normal cells, and these differences can be exploited to kill only the cancerous cells. The goal of this proposal is to identify specific gene functions that cancer cells require to live, but that healthy cells do not require.

Systematic inhibition of every single gene in the genome represents the best strategy to identify these differences between normal cells and tumor cells; however, the lack of proper genetic tools has historically prevented these studies. Silva and colleagues pioneered the development of RNAi-based genetic tools that allow them to perform these studies. He proposes to use these cutting-edge tools to systematically turn off every gene in the genome of breast cancer cells to identify those genes that, when absent, compromise the ability of cancer cells to survive, but do not affect normal cells. The ability to screen the entire genome in a high-throughput approach will accelerate the identification of important players in cancer cell biology and could provide new targets for more efficient and less harmful breast cancer therapies.

“Basically, we are using the state-of-the-art genetic technology to try to solve an old problem,” Silva said. “We want to identify the Achilles’ heel of breast cancer cells. Our strategy allows us to do something that was not possible before, which is to functionally examine every single gene in the genome to find the ones that are essential for the

viability of tumor cells but not normal cells. This will allow us to identify the targets to direct our therapeutic arsenal.”

Modulating Transcription Factor Abnormalities in Pediatric Cancer

Kimberly Stegmaier, M.D., Dana-Farber Cancer Institute

Many cancer-promoting proteins are considered difficult to target or “undruggable” by standard pharmacological approaches. This is a significant problem in pediatric cancers where the tumors are often initiated by these intractable proteins. One example is Ewing sarcoma, the second most common bone tumor in children, in which the critical cancer-promoting protein, EWS-FLI, has been considered “undruggable.” For children with metastatic Ewing sarcoma or those who relapse after initial treatment, the prognosis is dismal.

To address this challenge, Stegmaier proposes a new drug discovery approach integrating multiple platforms and disciplines — genomic technologies, chemical biology, computational biology, proteomics, and molecular genetics. She will apply this integrative approach to target the EWS-FLI protein. Her laboratory will first determine the fingerprint of the genes that are turned on or off in the presence of EWS-FLI in Ewing tumors. Then, they will screen a library of chemicals for those that induce the gene fingerprint of the inactive EWS-FLI protein to identify potential anti-cancer drugs. They will pay particular attention to drugs that are already FDA-approved for other indications and, thus, can be rapidly brought into clinical trials for pediatric or adult patients with cancer.

“I don’t think there is going to be a single discovery that will transform cancer research or cancer treatment,” Stegmaier said. “The ultimate dream is one of personalized cancer care — to identify the genes that have gone awry in an individual patient’s disease and then build a toolbox of molecules that will target the proteins encoded by these genes.”

Noninvasive Molecular Profiling of Cancer via Tumor-Derived Microparticles

Muneesh Tewari, M.D., Ph.D., Fred Hutchinson Cancer Research Center

The great promise of personalized medicine is the potential to tailor treatments to a patient’s individual tumor while sparing the healthy tissue. This requires obtaining the molecular profile of the tumor to identify the changes or abnormalities that have occurred. Currently, the only way to do this is by biopsy of the tumor itself. This is often not practical, due to the location or size of metastatic tumor masses, for example, that makes them difficult and/or dangerous to routinely biopsy.

Tewari’s work will develop a new approach to profiling tumors by capturing and examining “microparticles,” tiny genetic material-containing packets that are emitted by cells in the tumor tissue and circulate in the blood. If successful, this would provide a convenient, safe and reliable means of obtaining molecular profiles of tumors. Capturing

and profiling tumor microparticles could facilitate the use of personalized therapeutics by providing data about molecular changes occurring during the disease course following initial surgical therapy and in response to treatment.

A Transformative Technology to Capture and Drug New Cancer Targets

Loren D. Walensky M.D., Ph.D., Dana-Farber Cancer Institute

To develop new treatments for cancer, cancer-causing proteins within the cell must be identified and then neutralized with targeted drugs. Cancer-causing proteins interact with other proteins through a “molecular handshake” between contact points embedded in the proteins’ complex architecture.

Walensky will bring together multiple fields — chemistry, biology and cancer drug development — to deploy a technology that can rapidly and precisely identify cancer-causing proteins and their malignant interaction sites. Modified natural peptides will be used to bind to and capture the target proteins, with the goal of cataloging the full-range of cancer-causing interactions. Information about the critical molecular contact points identified through this method can be used to develop new drugs that interfere with the molecular handshake, thus providing a critical link between cancer protein discovery and cancer drug development.

“When you look back on any scientific breakthrough, whether it be designing the first vaccine or going to the moon, there had to be a new way of thinking and doing,” Walensky said. “It’s really about fresh ideas, passionate commitment and integrating insights and approaches from different fields, even from unanticipated places, in order to put the pieces together and come up with something new.”

Functional Oncogene Identification

David M. Weinstock, M.D., Dana-Farber Cancer Institute

Certain molecular changes or abnormalities are essential in order for cancer to develop and for tumors to survive. If those alterations can be identified through a process called molecular profiling, it may be possible to use existing drugs or develop new therapies that would target these changes and cause the tumor to die. Currently, not enough of these abnormalities are known or targeted correctly in the right cancer types.

Weinstock uses a novel system that identifies molecular abnormalities that drive cancer causation and growth directly from patient tumors. This system will make the molecular profiling process faster, more efficient and more precise. His group has already identified an abnormality that is important in some cases of acute lymphocytic leukemia, a finding that could lead to changes in treatment within the next two years.

Probing EBV-LMP-1’s Transmembrane Activation Domain with Synthetic Peptide

Hang (Hubert) Yin, Ph.D., University of Colorado at Boulder

The human Epstein-Barr virus (EBV) is a type of herpes virus that infects 90 percent of the world population. EBV can trigger unregulated cell proliferation and survival, and is associated with many human cancers including Burkitt's lymphoma. Dr. Yin will study how EBV contributes to cell survival and cell division. He will incorporate knowledge of protein engineering, chemistry and viral biology and use a unique computational algorithm to design a new therapy specific to an EBV protein that is difficult to target with conventional therapies due to its location in the cell. If successful, this study will establish a new technique for targeting transmembrane proteins involved in important signaling pathways in cancer cells that could translate into a broad range of novel anti-cancer therapeutics.

"This virus will hijack your B cells and make them immortal, become cancer in other words," said Yin. "We're trying to use our state-of-the-art computer-based technology to study why this virus can induce cancer. This is important because 90 percent of the population is infected with EBV and some of them develop lymphoma as a result."