The Impact of the Ted Mullin Fund

At the University of Chicago Medicine Comer Children’s Hospital

April 2016
The University of Chicago Medicine Comer Children’s Hospital, opened in 2005

Philanthropic investments from the Ted Mullin Fund have helped to leverage the University of Chicago’s institutional strengths in big data, cancer immunotherapy, basic biology, and clinical research—to ask the biggest questions and advance discoveries that help our smallest patients. As a result, our patients and families have access to some of the latest treatments and play a role in improving treatment options for future generations. The Ted Mullin Fund continues to advance groundbreaking research while training the next generation of physician-scientists in pediatric cancer, the Ted Mullin Fund Scholars. We are pleased to share just a few highlights demonstrating the broad reach and impact of your long-time generosity and support.
Support for the Chicago Center for Childhood Cancer and Blood Diseases

Each year the Ted Mullin Fund provides critical support for groundbreaking research efforts conducted by physicians and scientists at Comer Children’s Hospital. In 2015, funds supported the efforts of Joanna Gemel, PhD, Assistant Professor of Hematology/Oncology. Dr. Gemel has been a valued research partner to Eric C. Beyer, MD, PhD, and his laboratory for many years. Together, they have been investigating the process of intercellular communication, specifically the direct exchange of ions and small molecules between gap junction proteins called connexins. Their studies may lead to new pharmacologic or molecular approaches to cancer therapy by manipulating the exchange of drugs and drug metabolites between cells and the growth and viability of blood vessels. They also have major implications for other clinical areas including cardiac arrhythmias and cataracts.

With the philanthropic support of the Ted Mullin Fund, Dr. Gemel has continued her work studying connexins expressed in the heart (Cx40 and Cx43), and their role in the most common cardiac arrhythmia, atrial fibrillation (AF). The goal of Dr. Gemel’s study is to better understand the pathogenesis of AF in order to contribute to novel approaches to therapy. 2014 Ted Mullin Fund Scholar, Katie Bennett, worked with Dr. Gemel to research ways that cancer cells communicate with other cells.

Ted Mullin Fund Scholars

The University of Chicago Medicine Comer Children’s Hospital welcomed four new Ted Mullin Fund Scholars in 2015 to train alongside some of the best and brightest minds in pediatric cancer research and patient care. The selected scholars study for a full summer in a pediatric cancer laboratory under the direction of an expert faculty member, gaining invaluable experience and making meaningful and long-lasting relationships. The scholars’ work contributes to the groundbreaking pediatric and adult cancer research underway across the medical center.

Samuel Kim, a current student at Illinois Wesleyan University, partnered with Jill de Jong, MD, PhD, whose current research focuses on hematopoietic stem cells and understanding the genes which can cause leukemia. With Dr. de Jong, Samuel studied the mechanism of leukemia development by working with CRISPR/Cas9 complexes to make a CG2 Casper fish. His experience solidified his choice to pursue a future career in medicine and provided the framework to better understand both clinical and basic research.
Milee Nelson, a student at Vassar College, worked with Mark Applebaum, MD, and Susan Cohn, MD, one of the nation’s leading authorities on the study and treatment of neuroblastoma. Under their guidance, Milee investigated the phenotypic effects of hypoxia on various neuroblastoma cell lines, specifically regarding apoptosis and proliferation. She also studied neuroblastoma cell lines transfected with siRNA, a continuation of genomic analysis work conducted by Dr. Applebaum. Beyond these basic tissue culture skills, Milee became proficient in a variety of laboratory techniques, including flow cytometry for cell cycle and side population analysis, MTT and Caspase assay analysis, RNA and cDNA purification, TUNEL staining, and transductions and plasmid preps.

“I greatly benefited from the Ted Mullin Fund in every way possible.” - Samuel Kim

Zihan Su, a student at Williams College, trained with Eric Beyer, MD, PhD, an expert in the care and treatment of children with all forms of cancer and blood diseases. Zihan studied gap junctions and their role in arrhythmias induced by sleep apnea, in a model where mice were subjected to intermittent hypoxia. His experience greatly improved his laboratory skills, and it allowed him to develop the organizational and planning expertise critical to the design and execution of an experiment. Through it all, Zihan reaffirmed his commitment to the field of science and medicine.

“I was able to observe the first-hand intellect and passion of everyone in the lab. They were not only amazing teachers, but also wonderful people to work with… I cannot say enough about the wonderful relationships I made.” - Zihan Su

Amanda Wu, a student at MIT, shadowed Kenan Onel, MD, PhD, who is an expert in pediatric and other familial genetic cancer syndromes. Through her work with Dr. Onel, Amanda was introduced to the complex world of cancer research, participating in inpatient rounds and discovering the ins-and-outs of the medical center. The University of Chicago Medicine's rich academic and collaborative environment offered her an excellent paradigm of how teaching, research, and treatment all team up together to be at the forefront of medicine and patient care.

“The Ted Mullin Fund Scholarship...made me feel even more passionate about cancer research and has inspired me to continue it at MIT.” - Amanda Wu
Scholars Past: Where Are They Now?

Four years following the inception of the program, Ted Mullin Fund Scholars continue to contribute to the field of science and medicine and make significant achievements and advancements in their scientific careers.

By the Numbers

8 of the previous 13 Scholars graduated from college, and of these individuals, 6 are now pursuing postgraduate education by way of medical school, joint MD/PhD programs, or postgraduate research. The remaining 2 students are studying for the MCAT and looking forward to applying to medical school soon. 5 previous scholars still pursuing their undergraduate degrees have secured excellent scientific research opportunities to further their education and training in the field.

Updates from the Section of Pediatric Hematology/Oncology

The Ted Mullin Fund has generously supported various research projects and endeavors in the Section of Pediatric Hematology/Oncology. We are pleased to share a snapshot of the exciting efforts underway this year.

Adolescent and Young Adult (AYA) Oncology Program

Adolescent and young cancer patients often confront different personal, psychosocial, and medical challenges than younger children and older adults with the same diagnosis. Therefore, in 2012, with assistance from the Ted Mullin Fund, the University of Chicago Medicine created the Adolescent and Young Adult (AYA) Oncology Program, a collaborative program offering coordinated care for young adults ages 15 to 30 with leukemia or lymphoma. The AYA medical team includes nationally-recognized pediatric and adult hematologists/oncologists, dedicated nurse practitioners, and social workers. Recently the program included sarcoma patients on a research study evaluating physical and mental health using a standardized patient-reported outcomes measurement tool. The AYA Program is hoping to expand to include sarcoma patients in regular treatment in the near future following the recruitment of an additional hematology/oncology faculty member.
Developments in Sarcoma Research and Hypoxic Response

Mark Applebaum, MD, is researching a project on Ewing’s Sarcoma in collaboration with the Dana-Farber Cancer Institute and UCSF. The study follows several hundred patients with Ewing’s Sarcoma, using patient DNA to determine how patients develop second cancers. Dr. Applebaum recently received permission from the Children’s Oncology Group (COG) to use this clinical data and garnered the regulatory approvals from the Clinical Trials Review Committee (CTRC) and the Institutional Review Board (IRB) at the University of Chicago, which are necessary to move forward with this research. Dr. Applebaum hopes to obtain the patients’ genotype and clinical information in the next few weeks. The genotype information will come from University of Utah and Harvard University, collaborators who are helping Dr. Applebaum to obtain the clinical data.

Dr. Applebaum also seeks to understand hypoxic response. Similar to other cancers, neuroblastoma tumors have decreased access to oxygen compared to normal cells, causing changes leading to aggressive growth and therapy resistance. Two proteins primarily mediate this process, hypoxia inducible factors 1 and 2, with both exerting unique effects. Dr. Applebaum hypothesizes that identifying the mechanisms responsible for disparities in neuroblastoma growth in hypoxia will lead to the identification of different hypoxia inducible factor protein activity patterns that cause aggressive tumor growth. His goal is to identify patients who may benefit from drugs blocking specific hypoxia response mechanisms, thus improving the prognosis of fatal childhood cancers.

Milee Nelson, a 2015 Ted Mullin Scholar, was instrumental in generating the preliminary data that will be used in Dr. Applebaum’s next round of grant applications.

The Interactive International Neuroblastoma Risk Group Database

In 2005, Dr. Susan Cohn and a colleague from the UK established the International Neuroblastoma Risk Group (INRG) Task Force to analyze information on children diagnosed with neuroblastoma around the world. This was the first step towards forming a network that connects this international clinical and biological information on neuroblastoma patients, with the hope of eventually conducting investigations using data from thousands of patients, greatly accelerating our research and ability to improve treatment for children with high-risk neuroblastoma. To date, the INRG Task Force has collected data from approximately 16,500 patients and created a process to make these data available to researchers around the world.
The next step in this important work is to link genomic data with clinical information from multiple databases. By working closely with Sam Volchenboum, MD, PhD, MS, and the Center for Research Informatics, and by leveraging current resources available at the University of Chicago, we established links between the iINRGdb and the COG Biobank and the COG Nucleic Acids Neuroblastoma Tumor Bank. With Dr. Robert Grossman’s team, they successfully connected neuroblastoma tumor genomic data from several hundred children treated in Europe with patient information in the Bionimbus Protected Data Cloud he developed. They are also linking genomic data generated from more than 3,000 patients diagnosed with neuroblastoma in North America to clinical information. This database is poised to serve as a model for storing, computing, and analyzing patient information and samples in other pediatric and adult cancers, including sarcoma, for accelerated research and discoveries.

**Genomics of Risk Evaluation and Anticancer Treatment in Children (GREAT KIDS)**

Kenan Onel, MD, PhD, has advanced his study of genetics in the context of family and family history in order to better understand rare pediatric diseases and cancers, which continue to be major cause of non-traumatic childhood mortality. The University of Chicago Program in Childhood and Young Adult Cancer developed a repository of tumor samples derived from patients with such cancers, selected for their difficulty of diagnosis, lack of response to therapy, and ability to reveal insights into both childhood and common adult cancers. Dr. Onel and his team are sequencing these tumors, as well as normal DNA from each child and his or her family, in order to learn how DNA transitions from normal to cancer. The results of this study will inform not only rare familial cancers, but also the etiology of all cancers.

In collaboration with the Dana-Farber Cancer Institute and the McDonnell Genome Institute at Washington University, Dr. Onel is currently leading a study of patients with low-risk acute lymphoblastic leukemia (ALL), all of whom were given a 95 percent cure rate following treatment, but who sadly relapsed. Dr. Onel and his team are analyzing the genomes of the ALL cells from these children in order to identify how they change over time in response to chemotherapy. They expect that these studies will reveal clues to explain how cancers evolve mechanisms of drug resistance that lead to treatment failure. They hope their results will be broadly applicable across all cancers and may lead to new treatments targeting resistant cancer cells. Large-scale sequencing
studies like this rely upon having already collected and properly stored well-characterized clinical samples. They are also expensive and difficult to perform. Nonetheless, only by taking on projects such as these, in which cancers from individual patients are sampled and sequenced serially over time, will physicians and scientists actually be able to beat cancer by allowing cancer to reveal its innermost self.

Dr. Onel and his team were also recently awarded a grant from the NIH for GREAT KIDS to sequence tumors from 200 patients with osteosarcoma. This sequencing is done in tumors before and after chemotherapy to demonstrate the potential genetic changes that may play a factor in instances of relapsed disease, or when a tumor survives chemotherapy, allowing for relapsed disease and metastasis. Dr. Onel and his team have analyzed patient tumors from Comer Children’s Hospital, a number of other institutions, and in collaboration with the COG.

**Cell Death Protein Family Profiling and Therapeutic Targeting of Regulatory T Cells**

James LaBelle, MD, PhD, is working to identify innovative therapies for rare cancers by manipulating the immune system and its response to solid tumors such as Ewing’s sarcoma, rhabdomyosarcoma, neuroblastoma, and lymphoma. A paramount obstacle in the progression of personalized forms of cancer treatment is identifying ways to promote the patient’s immune response to attack cancerous cells. To address this, Dr. LaBelle and his team are working on developing a new therapeutic strategy that stimulates immune cells to work against tumors that have gone undetected by the immune system and are otherwise refractory to conventional therapies. This immune unresponsiveness is in large part secondary to an otherwise normal immune cell called a regulatory T cell (Treg). Therefore, if Tregs are removed either in culture or in cancer patients, the suppressive “veil,” which inhibits the immune response to attack the tumor, can be lifted. Unlike other immune cells, Tregs are exquisitely dependent upon a specific protein, called MCL-1, to direct their response. The challenge in traditional cancer therapies is that Tregs are difficult to target in patients without affecting other immune cells. Using novel MCL-1 small molecule and peptide mimetics, or laboratory-derived compounds, Dr. LaBelle aims to develop an innovative therapy specifically directed towards inhibition of Tregs by using a multidisciplinary approach spanning chemical engineering, immunology, immunotherapy, and molecular biology. The inclusion of both animal and human samples in preclinical testing greatly enhances the translational power of this approach that has the potential to affect a large number of cancer treatment strategies.