UNIVERSITY OF CHICAGO:

TED MULLIN FUND *for* PEDIATRIC SARCOMA RESEARCH

THE UNIVERSITY OF CHICAGO MEDICAL CENTER

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A decade ago, external funding was not a possibility for sarcomas—neither industry nor government would provide significant support for research into these diseases that, while life-threatening, impact a relatively small population. Thanks to the partnership of the Mullin family and Hour of Power swimming event in memory of Ted Mullin, the University of Chicago has been able to enhance its team of experts and is now poised to make a dramatic difference in the research and treatment of this disease.

Philanthropy in support of basic and translational research is essential in our work to ultimately find a cure for sarcoma. Unlike research in other more common types of cancer, breakthroughs in this "orphan disease" will come from the kind of cutting-edge, collaborative research taking place at the University of Chicago Medical Center.

Impact of the Ted Mullin Fund

The Ted Mullin Fund has allowed the University of Chicago to allocate essential seed funding to Dr. Stephen Skapek's study of tumor suppressor genes and how their abnormality contributes to sarcoma, specifically rhabdomyosarcoma, biology. Dr. Skapek is focusing on this type of sarcoma, which is particularly common in children and young adults because of its potential implications on the treatment of other sarcomas. Although currently, we can cure many patients with rhabdomyosarcoma—especially those with tumors that have not spread to other areas of the body—current treatments incorporating surgery, high doses of chemotherapy and radiation therapy can be associated with severe, and in some cases, life-threatening side effects. In situations where tumors cannot be removed surgically, only about 20% of the children are cured—and this number has not significantly improved despite nearly 30 years of research conducted by national collaborative clinical research groups. Innovative approaches are essential to cure more children with rhabdomyosarcoma and other types of sarcoma.

Historically, treatment for rhabdomyosarcoma has focused on trying to kill cancer cells by using radiation or chemotherapy, which causes damage to the genetic material (DNA) in the nucleus of the cells. When the cancer cell "recognizes" that its genetic material has been damaged, it has two choices—either to try to repair the damage using molecular machinery that is present in all cells or, if the damage is too severe, to activate a program in which the cell commits "suicide" in a program called apoptosis. Unfortunately, in children with advanced stages of rhabdomyosarcoma, chemotherapy and radiation usually fail to work because the cancer cells evolve and either more effectively repair the DNA damage or fail to activate the program to induce apoptosis. In either case, the cancer cells survive and continue to grow, and Dr. Skapek has developed the following four new strategies to surmount these fatal obstacles:

Can we induce skeletal muscle differentiation in rhabdomyosarcoma cells?

Rhabdomyosarcoma cells bear striking resemblance to immature skeletal muscle cells, known as myoblasts. One of Dr. Skapek's major goals is to take advantage of insight into fundamental aspects of skeletal muscle biology to develop a novel therapeutic approach for skeletal muscle-derived rhabdomyosarcoma. He is now using high throughput screening to identify new drug compounds or genetic manipulations that can promote muscle differentiation in these myoblasts, which would essentially foster permanent cell proliferation arrest in situations where intensive chemotherapy and radiation fail.

With the support of the Ted Mullin Fund, Dr. Skapek has developed the primary screen assay that allows him to measure muscle maturation in cells grown in his laboratory. He has accomplished this by engineering two complimentary assays to measure the degree of muscle differentiation and also cell accumulation by using an automated, fluorescent microscope. With these assays, Dr. Skapek can now rapidly screen many drug or drug-like compounds to identify those that promote muscle differentiation. He has also developed a secondary screen to objectively confirm any "hits" in the primary screen, and has teamed up with other scientists at the University of Chicago to finalize experimental plans to carry out the screen using roughly 2,000 drug compounds. Much is already known about these drugs—such as how to administer them safely in children and young adults—but they have never been used to try to promote muscle differentiation. In parallel to a chemical biology approach to identify drug-like compounds that promote differentiation and accompanying cell proliferation arrest, Dr. Skapek will also carry out a genetic screen to identify those genes that can block muscle differentiation.

After carrying out these initial screens, Dr. Skapek plans to use the results as the basis of a 5-year research proposal from the National Institutes of Health (NIH), or similar organizations, with plans to conduct secondary functional studies of the chemical compounds or genes that impede muscle differentiation.

Can we uncover mechanisms by which rhabdomyosarcoma cells become resistant to chemotherapy?

Additionally, Dr. Skapek has partnered with Dr. Susan Cohn, an expert in the research and care of neuroblastoma (the most common form cancer among children under the age of three) and together, they are leveraging emerging technological and computational tools to understand exactly why cancer cells become resistant to chemotherapy even though these drugs initially seem to work well. Drs. Skapek and Cohn are focusing their initial work on two of the most devastating forms of cancer that primarily affect children and young adults: neuroblastoma and rhabdomyosarcoma, and hope that their findings will apply to pediatric and adult cancers broadly. By understanding the mechanisms by which these cancer cells evade chemotherapy, they will be able to modify existing treatments to directly "target" those drug resistance mechanisms. By collaborating with a team of laboratory and clinical scientists who are international leaders in the relevant clinical, translational, and basic science and using the physical and academic resources at the University of Chicago and its Comprehensive Cancer Center, they are fully committed to incorporating their findings into clinical research trials within three years.

Over this past year, Dr. Skapek has made substantial progress with Dr. Cohn. Their initial analyses of the data did not reveal clear-cut genetic changes that correlate with resistance to vincristine, a drug commonly used in rhabdomyosarcoma therapy. This indicates that rhabdomyosarcoma cells likely escape the effects of vincristine because a subset of rhabdomyosarcoma cells are capable of surviving vincristine chemotherapy without relying on new mutations. The next step is to analyze data from cyclophosphamide, another chemotherapeutic agent, that is more likely to induce new mutations. Depending on the result of this study in neuroblastoma, Dr. Skapek may replicate the analysis of cyclophosphamide in rhabdomyosarcoma to identify and develop ways to "target" genes that are expressed in recurrent tumors.

Can we identify a "signature" of proteins or genes that are expressed in rhabdomyosarcoma and that correlate with prognosis?

Dr. Skapek has two, complementary approaches to answer this scientific question. First, as a member of the Children's Oncology Group (COG) and vice-chair for biology studies in the Soft Tissue Sarcoma Committee of the COG, he has obtained a "catalog" of all of the genes that are expressed in approximately 100 individual rhabdomyosarcoma tumors. With a University of Chicago collaborator, Dr. Samuel Volchenboum, he is using a computational approach to correlate the complex pattern of gene expression with different sarcoma subtypes and clinical outcome. Importantly, they are applying sophisticated geometric and topological models to essentially describe the "shape" of a tumor based on the expression of many thousands of genes. There is general agreement among oncologists and cancer biologists that more precisely identifying those tumors that are not likely to be cured (by using these molecular, genetic and computational tools), physicians will be better able to apply novel therapies to personalize care and improve outcomes for patients.

In a parallel approach, Dr. Skapek has partnered with investigators in the University of Chicago's Institute for Genomics and Systems Biology (IGSB) to determine the sequence of all of the genes that are expressed in a panel of 20 different rhabdomyosarcoma tumors. This approach has the potential to reveal genes that have undergone a mutation as the sarcoma develops. In many cases of more common types of cancers, these mutated genes have been used to develop new drugs that specifically "target" the abnormal protein generated by the mutant genes. Dr. Skapek anticipates using this preliminary data on gene expression or on gene mutations to perform additional functional studies that will prove the importance of the candidate genes.

Can we use "functional imaging" of a sarcoma to determine how well chemotherapy is working—after just the first dose of chemotherapy?

Emerging evidence from clinical trials of several types of sarcoma supports the concept that typical measurements of tumor size do not accurately predict who will ultimately be cured of the disease. This has been shown to be true for rhabdomyosarcoma and also for sarcomas of the bone. In the latter, tumors rarely actually get smaller during chemotherapy; the first real evidence as to how well the

chemotherapy is working comes from microscopic studies of the tumor obtained nearly three months after therapy was initiated. At that stage, if there is a "poor response" to therapy, it may be too late because changes in treatment at that point do not seem to alter the poor outcome.

In collaboration with other University of Chicago physicians, Dr. Skapek has written a new clinical trial in which they treat children and young adults with osteosarcoma using a chemotherapy regimen that was developed at the University of Chicago. Three weeks following the initial dose of chemotherapy, they obtain a PET scan, which measures how much glucose (sugar) is being used by the tumor cells. Decreased glucose use correlates with the viability (or health) of the tumor cells; but PET scans have not been used as an early marker of chemotherapy effects for sarcoma patients. Dr. Skapek and his collaborators predict that early PET scans will reveal which tumors are likely to be eradicated with chemotherapy. This will allow physicians to intervene with alternative treatment at an earlier point.

This clinical trial is being supported using institutional funds. Dr. Skapek's immediate plan is to obtain "pilot data" on a small number of patients to support the overlying hypothesis and with these data; he will seek additional, federal funds to support a larger, multi-center study center at the University of Chicago.

As is the case with all of these projects, the initial seed funding provided by the Ted Mullin Fund will allow Dr. Skapek and his team to produce sufficient data to leverage significant support for the continued study of sarcoma. As both a basic science researcher and a clinical authority in the treatment of sarcomas, Dr. Skapek will be able to utilize infrastructure at the University of Chicago to translate new scientific discovery into improved outcomes for pediatric sarcoma patients, the primary goal of the Ted Mullin Fund for Pediatric Sarcoma Research.

Thank You

The Mullin Family, their friends, family and participants in the Ted Mullin "Leave it in the Pool" Hour of Power Relay for Cancer Research should take enormous pride in all that we have already accomplished together in advancing pediatric sarcoma research at the University of Chicago. We cannot think of a better way to honor Ted than knowing that the Fund in his memory will help so many others and will pave the way for advances in the field for many years to come. Thank you for your support and your tireless enthusiasm for fundraising around our pediatric sarcoma research vision to improve outcomes for pediatric sarcoma patients.