



UNIVERSITY OF CHICAGO:

**TED MULLIN FUND *for***  
**PEDIATRIC SARCOMA RESEARCH**



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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 the work done in memory of Ted Mullin, the University of Chicago has been able to enhance its team of experts and now has the opportunity to make a dramatic difference in the research and treatment of this devastating disease.

As you know, philanthropy, in the form of private donations for basic science research, is essential in ultimately finding a cure for sarcoma. Unlike research in other more common types of cancer, where large-scale clinical trials involving thousands of patients have enabled investigators to gain insights into risk factors and effective treatments, breakthroughs for sarcoma patients will come from basic and translational research, like the kind taking place at the University of Chicago.

## IMPACT OF THE TED MULLIN FUND

### **Promoting Skeletal Muscle Differentiation in Rhabdomyosarcoma as a Novel Therapy**

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 biology. In the first phase of this work, Dr. Skapek is focusing on rhabdomyosarcoma, a type of sarcoma that is particularly common in children and young adults. 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, and following is a summary of Dr. Skapek's research, made possible through support from the Ted Mullin Fund for Pediatric Sarcoma Research:

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 aspires to develop new strategies to surmount these fatal obstacles.

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. This strategy avoids the pitfalls limiting our current approaches. During normal development, skeletal myoblasts grow (proliferate)—just like rhabdomyosarcoma cells—until a certain point, after which they begin to differentiate into a mature skeletal muscle cell. Importantly, as a skeletal muscle differentiates, it irreversibly ceases to proliferate. The retinoblastoma tumor suppressor gene, RB, is absolutely essential for the muscle cells to differentiate and cease to proliferate. Dr. Skapek’s recent work has shown that RB protein function is compromised by excess activity of a particular enzyme—a kinase—in rhabdomyosarcoma and that this may block their ability to differentiate and cease proliferation.

Importantly, the molecular machinery needed for a myoblast to differentiate is very different from that required for DNA damage repair or apoptosis. As such, a therapeutic strategy aimed at promoting the differentiation of rhabdomyosarcoma cells into mature skeletal muscle cells will foster permanent cell proliferation arrest in situations where intensive chemotherapy and radiation fail.

Over the last several years, Dr. Skapek and his research team have begun to develop pharmacological strategies to induce differentiation in rhabdomyosarcoma cells and to begin to test this approach in experimental models. He recently showed that a drug that blocks the aforementioned kinase has the

capacity to arrest the proliferation of rhabdomyosarcoma cells and to promote some degree of skeletal muscle differentiation by re-activating the RB tumor suppressor protein.

### **Progress and Future Direction**

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 my laboratory. He has accomplished this by engineering the muscle cells to express a “reporter” protein only when he has induced them to mature. With this assay, 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, by examining a native protein (instead of a reporter) that can be quantified. To do this, he performed immunostaining for a native muscle protein that is only expressed in mature muscle cells and measured its expression using digital photomicrograph images of cultured muscle cells.

The next steps are clear: Having completed the validation of the compounds that promote differentiation and accompanying cell proliferation arrest, Dr. Skapek will apply a “chemical library” of ~1,000 drug-like compounds to the screening test he has developed to identify additional compounds promoting muscle differentiation. 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.

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 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 Cancer Research Center, they are fully committed to incorporating their findings into clinical research trials within three years.

We anticipate that the continued 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 these projects. It will be our pleasure to update you on the federal and other support achieved as result of this important seed funding. 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 should take enormous pride in all that we have already accomplished together in enhancing the pediatric sarcoma research at 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 both your personal support and your tireless enthusiasm for fundraising around our pediatric sarcoma research vision to improve outcomes for pediatric sarcoma patients. We also thank all of those who have contributed time, effort and money to help build the Fund.