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2023 SEBASTIANSTRONG DISCOVERY SCIENCE AWARD

Determining the Safety of Clinical Grade CAR-iNKTs for the Treatment of Osteosarcoma in Pediatrics

Institution: University of Pennsylvania School of Veterinary Medicine
Primary Investigators: Nicola Mason, BVetMed, Ph.D., Professor of Medicine and Pathobiology, Antonia Rotolo, M.D., Ph.D., Research Assistant Professor of Immunobiology
Co-Investigators: Eoin Whelan (Penn Vet), Troy McEachron (NIH), Enrico Radaelli (Penn Vet), Charles-Antoine Assenmacher (Penn Vet)
Type of Childhood Cancer: Osteosarcoma
Amount Funded: $500,000

Each year, The SebastianStrong Foundation commits to driving pivotal advancements in childhood cancer research through our Discovery Science Award. This initiative showcases our investment in groundbreaking research that promises to significantly reshape the pediatric cancer treatment landscape. This year, we're excited to feature two remarkable projects that together have been awarded $1M in funding, reflecting our ambition for innovation and progress. Through a rigorous selection process led by our esteemed Medical Advisory Board, composed of some of the nation's leading pediatric oncologists, we have identified research endeavors that promise to redefine our approach to cancer treatment. Dr. Nicola Mason and Dr. Antonia Rotolo lead one such project at the University of Pennsylvania, aiming to pioneer a novel osteosarcoma treatment using comparative oncology and Chimeric Antigen Receptor invariant Natural Killer T (CAR iNKT) cell therapy.

Project Description:
Osteosarcoma is a highly aggressive, malignant primary bone tumor that is diagnosed in approximately 400-600 children and adolescents in the United States each year. It is the most common primary bone cancer in children and young adults. Despite aggressive

surgery and chemotherapy, a considerable number of the patients still succumb to tumor progression, underscoring the critical need for more effective and less toxic therapies for this disease. Dr. Mason's project, showcased on “60 Minutes” for its innovative approach, focuses on comparative oncology. It contrasts traditional research, where cancer is typically artificially introduced, by studying osteosarcoma as it naturally develops in dogs. This approach could quickly advance more effective and less toxic treatments, thanks to the notable genetic similarities between dogs and humans.

Dr. Rotolo brings her extensive expertise in iNKT cells, a subset of killer T cells known for their aggressive response to tumors. Invariant natural killer T cells (iNKTs) from healthy donors have emerged as a promising cellular therapy against treatment-resistant cancers. Unlike other conventional T cells, iNKTs can be naturally transferred from one person to another without life-threatening complications such as graft-versus-host disease, and have the potential to coordinate durable anti-tumor responses in conjunction with other blood cells. Furthermore, iNKTs can be genetically modified, allowing for the introduction of a synthetic protein called Chimeric Antigen Receptor (CAR) that enhances their ability to identify and eliminate tumor cells with greater precision and more effectively. The resulting CAR iNKT cells can be easily grown in laboratory settings to generate large quantities of CAR iNKT, providing a viable treatment option for patients unresponsive to standard therapies and lacking therapeutic alternatives. The research led by Dr. Mason and Dr. Rotolo is pioneering not only for its methodological innovation—utilizing live dogs as research models—but also for its collaborative nature, working closely with their peers at Children’s Hospital of Pennsylvania (CHOP). This approach aims to improve treatments for our canine companions and young osteosarcoma patients, potentially avoiding aggressive initial therapies like radiation and amputation.

With the support of the Sebastian Strong Foundation, they will investigate the therapeutic efficacy and safety of donor CAR iNKT targeting B7H3, a molecule found in osteosarcoma cells that correlates with aggressiveness and poor prognosis. To comprehensively assess these CAR-B7H3 iNKTs, they will conduct classical laboratory experiments both in vitro and in murine models. Additionally, they plan to perform a pilot study treating companion dogs diagnosed with spontaneous osteosarcoma, a patient population faithfully reflecting key genetic and immunological features of the human disease. They anticipate that the outcomes of this study will be pivotal for the design of a clinical trial to treat children and young adults with osteosarcoma. The insights gained from the canine

population will not only contribute to refining the therapeutic approach for human patients, but also enhance our understanding of the potential benefits and challenges associated with CAR-iNKT immunotherapy, bringing us closer to more effective and targeted treatments for osteosarcoma patients.

Impact & Promise:

Situated at the forefront of pediatric cancer research, this project signifies a pivotal shift towards more compassionate and targeted treatments. By linking veterinary and human medicine, the project accelerates the path of CAR iNKT cell therapies toward clinical trials, offering new hope to those with osteosarcoma. The outcomes could revolutionize treatment for a variety of cancers, showcasing the vast potential of comparative oncology. The project is expected to be instrumental in developing future clinical trials for treating children and young adults with osteosarcoma, a significant stride towards achieving our goal of developing less toxic, more targeted pediatric cancer treatments.