THE HARTWELL FOUNDATION

2020 Individual Biomedical Research Award

Jeffrey D. "Jeff" Martell, Ph.D.

Assistant Professor
Department of Chemistry

University of Wisconsin-Madison

Safer Cancer Therapies Using Switchable Immune Cells

Pediatric cancers such as leukemia and neuroblastoma are the second leading cause of death in children. With more than 1500 children dying each year in the U.S., existing cancer therapy often causes side effects that permanently reduce the quality of life in a growing child. Withstanding surgical resection, radiation and chemotherapy in children can lead to lifelong complications including neurodevelopmental issues, heart damage, poor growth, infertility and the appearance of new cancers. A promising alternative and rapidly advancing area in anti-cancer treatment is the stimulation of a patient's own immune system to attack and eradicate cancer cells (Chimeric Antigen Receptor T cell or CAR-T cell therapy). This promising approach has been used successfully in treating both acute lymphoblastic leukemia and neuroblastoma. Essentially, the patient's immune T cells are extracted from the blood, genetically *re-programmed* to target cancer cell protein antigens in a way that expresses a specific CAR on their surface, then grown and propagated *ex vivo* before returning them back to the patient where they continue to propagate and eradicate cancer cells. The therapy is remarkably successful for some individuals; but for others, it leads to the immune system attacking healthy tissues. Because few antigens are known to be exclusive for cancer, the side effects of life-threatening cytokine release syndrome caused by on-target off-tumor CAR-T cell activity are especially concerning in young patients, with severity ranging from a mild fever to life-threatening organ failure and neurotoxicity. To avoid permanent complications and to halt these dangerous side effects, a biochemical switching mechanism has been incorporated into the re-programmed immune cells to turn off therapy; but unfortunately, such reversibility also precludes the CAR-T cells from attacking the cancer. To address this control problem in immunotherapy, Jeff proposes to increase CAR-T cell specificity for cancer cells by coating them with a segment of non-coding DNA, which under certain conditions will function as a novel switchable catalyst that causes release of a systemically administered prodrug to regulate CAR-T cell activity. He hypothesizes that when the coated cells (*ProSwitch* cells) recognize and bind specific antigens present on cancer cells, the DNA nanocatalyst will become active, converting the prodrug and triggering gene transcription in the ProSwitch cells that culminates in cancer cell death (or for encounter with antigens present on healthy cells the death of the ProSwitch cell). Validation and optimization of ProSwitch technology in cultured cells followed by demonstration in a mouse model will be used to assess comparative effectiveness with state-of-the-art CAR-T cell approaches. If Jeff is successful, the creation of a "switchable catalyst" that enhances the ability of immune cells to recognize the difference between cancer and healthy cells will not only improve the safety of anti-cancer immune cell therapies for children, but extend effective, personalized precision medicine for treatment of diverse pediatric cancers.