Weill Cornell Medicine
Sandra and Edward
Meyer Cancer Center

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To our friends from *Swim Across America*,

The physicians and scientists of the *Swim Across America* team at the Sandra and Edward Meyer Cancer Center at Weill Cornell Medicine are grateful for your support. Your contribution has significantly impacted our team, and we are grateful to the swimmers and volunteers who participate in Swim Across America events. We continue to advance progress by translating the results of our basic research program into new treatments for patients with cancer. Through your kind philanthropic gift, we have been able to establish a collaborative research network that spans diverse fields. This network has not only complemented our work but have also attracted additional funding to further expand the field of immunotherapy.

The immune system is inherently programmed to recognize and combat foreign pathogens, such as bacteria and viruses, while sparing our cells. However, cancer is unique because it arises from our own tissues. As a result, immune cells struggle to recognize and destroy tumor cells. Our investigators are leaders in finding innovative ways to stimulate the immune system and outsmart cancer.

We apply the lessons learned from how the immune system behaves during infectious diseases to manipulate immune cells, empowering them to recognize and combat cancer cells. While we currently utilize melanoma as a model to study the interplay between the immune system and cancer, our goal is to translate our knowledge to treat other types of cancer, including non-small cell lung cancer (NSCL), triple-negative breast cancer, and metastatic bladder cancer.

We aim to answer two key questions—First, why do only some, but not all patients respond to therapy? And second, how can we ensure that patients who do not respond become responders with new therapies?

One of the challenges we face is that tumor cells can evolve to evade immune recognition by losing the expression of proteins that immune cells typically recognize. We call these cells “immune escape variants”. They persist within the tumor even after treatment, which can explain why some patients stop responding to therapy and become resistant. Our group has recently discovered that blocking OX40, a tumor necrosis factor receptor-related protein, activates an immune cell type called neutrophil which can eliminate the “immune escape variants” within the tumor. We have published these results (Hirschhorn et. al., *Cell*, *2023)*, and are currently exploring strategies to mobilize neutrophils to eliminate tumors in different disease contexts. We have also developed an oncolytic virus that infects both cancer cells and immune-suppressive cells expressing OX40 and destroy them. This oncolytic virus therapy has improved immune-based therapies’ efficacy (Yang et. al., J Exp Med., 2023).

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We have recently reported on our work on local cryoablation, a technique that uses extreme cold to destroy abnormal tissues or tumor cells, in combination with immune checkpoint blockade in early-stage breast cancer. Inducing immune recognition of tumors by local tumor destruction, with cryoablation in this case, is one potential approach to induce antitumor immunity in otherwise immune checkpoint resistant tumors. In this small subset of patients, we provide evidence that preoperative cryoablation plus ipilimumab and nivolumab is feasible and induces systemic adaptive immune activation potentially more robust than cryoablation with or without ipilimumab (Comen et al, *iScience.* 2024).

We have also demonstrated that antitumor responses can be improved by treating tumors with a cysteine binding drug, methylene quinuclidinone (MQ), that increases the ability to provoke an immune response of tumor cells directly. The combination of MQ with TLR-4 agonist, monophosphoryl lipid A, and a CD40 agonist further enhanced these immunogenic effects and demonstrated a significant antitumor response in preclinical models (Michels et al, *Life Sci Alliance*. 2023). We are now working on developing similar classed of drugs which we hope to translate for use in patients.

Our *Swim Across America* team has experienced another highly productive year yielding many exciting results. SAA's funding has also helped us support investigators from underserved populations and address health disparities by developing cell therapies to treat cancers prevalent in populations of various descents, ethnic minorities and socioeconomical levels. Every step forward and breakthrough we achieve represents progress and adds to our growing arsenal of options for patients *everywhere* fighting cancer.

We are tremendously grateful for your continued support and confidence in our team's ability to bring forth new and better approaches to treating patients with cancer.

Warmest regards,

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