Dear Swim Across America Team, Supporters, and Fundraisers,

As the Beyaz and Moses Laboratories at Cold Spring Harbor Laboratory (CSHL), we are writing to express our sincere gratitude for your generous gift to support our research for the development of small molecule therapeutics that boost the metabolic fitness of immune cells for cancer therapy.

Your support is not merely financial; it represents an investment in a hopeful future where cancer treatment is more effective, less toxic, and accessible to a broader patient community. With your contributions, we are now empowered to explore a truly innovative approach for cancer therapy. By utilizing click chemistry, we aim to develop selective molecules that enhance the metabolic fitness of immune cells, paving the way for eliminating cancer cells without harming healthy cells.

The results of our initial experiments, thanks to your support, have been promising. We have identified several new molecules that robustly improve immune cell fitness, an encouraging step towards developing effective cancer immunotherapies. Your funding is allowing us to continue to:

1. Utilize click chemistry for developing selective molecules that boost the metabolic fitness of immune cells
2. Characterize the therapeutic potential of the lead molecules using clinically relevant cancer models

We are confident that these studies have significant potential to create new, effective, and safe therapeutic options for cancer treatment and prevention.

Project Update:

Hypothesis: The selective targeting of peroxisome proliferator activated receptor δ (PPARδ) agonists towards immune cells would activate PPARδ signaling and significantly boost anti-tumor immunity.

Chemistry: The Moses laboratory envisaged a new approach towards synthesizing novel small molecule agonists of PPARδ using click chemistry. So far, the team has synthesized 11 promising PPARδ agonist derivatives. Biological evaluation of these molecules is currently ongoing. Furthermore, we are currently generating an innovative immunotherapy utilizing the antibody drug conjugate (ADC) approach. Traditionally, ADCs are utilized to deliver cytotoxic drugs to cancer cells, while sparing healthy cells. In our project, we aim to deliver PPARδ agonists specifically to immune cells using immune-targeted ADCs. With this approach, we aim to enhance the metabolic fitness and anti-tumor properties of immune cells *in vivo.*

Biology: The Beyaz laboratory has tested the effects of the newly synthesized PPARδ agonists on immune cell function. Gene expression changes in immune cells after administration of PPARδ agonists were assessed using RNA sequencing. Upon identification of the lead PPARδ agonist derivative, its specificity towards PPARδ over other PPAR family members was confirmed. Moreover, we found significantly enhanced T-cell medicated cancer cell killing upon PPARδ agonist treatment of immune cells. In addition, we showed successful internalization of an immune-cell specific antibody, demonstrating its promise for generating an immune-specific ADC, in order to deliver PPARδ agonists to immune cells *in vivo.*

We recognize that our mission is shared and strengthened by the community of supporters and fundraisers at SAA, who believe in a better future for cancer patients. We are looking forward to share our progress with you soon.

Once again, thank you for your trust, commitment, and contribution to our research.

With warmest regards,

John Moses, Ph.D.
Professor

Semir Beyaz, Ph.D.
Assistant Professor

Update from Dr. Mikala Egeblad:

Dear Swim Across America Friends,

My laboratory is very appreciative of the support we have received during the past several years as a beneficiary of Swim Across America. Thank you for raising awareness and funds to support cancer research.

One of the major problems in cancer treatment is that once the cancer has spread to other organs, most types of cancer can no longer be cured. With your support, we have been working on developing a new strategy to improve patient outcomes after the cancer has metastasized. Apart from cancer cells, tumors are composed of many other cell types, including immune cells such as macrophages and neutrophils. These immune cells are critical for protecting the body from infections, but tumors can hijack their functions to support metastasis. The support from Swim Across America has enabled us to develop a method to target and reprogram macrophages: when mice with breast or ovarian cancer were treated with a cocktail of two agents (monophosphoryl lipid A and interferon gamma), macrophages were reprogrammed to kill the cancer cells instead of helping the cancer cells spread. As a result, the mice lived much longer. Interestingly, the reprogrammed mouse macrophages also activated T cells. During the past year, we have confirmed our results using cells derived from ovarian cancer patients. Our results therefore suggest that the cocktail treatment could be effective when combined with checkpoint blockade immunotherapy.

The support from Swim Across America has also helped us investigate how neutrophils' ability to kill microorganisms can be hijacked by tumors. We discovered that exposing mice to chronic stress releases stress hormones that in turn change the function of neutrophils. In mice, stress exposure caused a four-fold increase in metastasis. This may in part explain why chronic stress, depression, and social isolation are associated with a higher risk of cancer recurrence in people. Importantly, by inhibiting the neutrophils, we could overcome the effect of stress on cancer metastasis in mice.

There is an urgent need to develop new strategies to treat metastatic cancer. We greatly appreciate the support from Swim Across America that have enabled us to develop strategies that change immune cell function to prevent cancer from spreading.

Best regards,

Mikala Egeblad, Ph.D.
Professor