2023 Buck Summer Scholar: Anna Girtle

My name is Anna Girtle, and I am entering my final year at University College London where I am studying cell biology. I am interested in pursuing a career focused on improving our understanding of human diseases so that we can better treat them. Last year I worked in the Gems Lab at University College London's Institute of Healthy Ageing. The Gems Lab works with the model system *C. elegans* to understand the underlying processes that cause age-related pathologies, and how these pathologies lead to death. During my time there, I explored liposomes as a delivery system for potential life-extending drugs and researched the role of autophagy genes in lifespan. This summer at the Buck Institute, I had the opportunity to join the Ellerby Lab, which focuses on understanding the processes underlying neurodegenerative disorders with hopes of identifying novel therapeutic targets.

During my 12 weeks at the Buck Institute for Research on Aging, I worked on two projects involving the role of the retromer complex in disease. The retromer is a sort of "machine" in our cells composed of discrete components which come together to mediate protein sorting. A functional retromer complex ensures toxic proteins are degraded and essential proteins are returned to their appropriate cellular compartments. When the retromer components fail to come together correctly, protein sorting is disrupted and can contribute to disease.

Of particular interest to my research is the gene *OXR1*, which encodes a protein that stabilizes the retromer components. I worked with fibroblasts derived from patients with a loss-of-function *OXR1* mutation. We are interested in examining how age-associated molecular changes are altered with the loss of *OXR1*, and whether the phenotypes can be rescued by the compound R55, which pharmacologically stabilizes the retromer.

The second project I worked on involved human iPSC-derived neurons expressing a form a mutant tau, a protein involved in many neurological disorders. Mutant tau has been shown to interfere with retromer function, which is thought to be involved in synaptic transmission. We therefore monitored electrophysiology metrics in diseased and healthy neurons, with and without R55 treatment, to determine whether retromer stabilization improves disease phenotypes.

Ultimately, the goal of these projects was to better understand the role of the retromer complex in aging and disease, with the hopes that it may be an important therapeutic target to pursue in the clinic.

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