

Research Statement

Tissue stem cells maintain homeostasis by balancing self-renewal and differentiation. Oncogenic mutations can disrupt this homeostasis by predisposing stem cells to undergo aberrant self-renewal, ultimately leading to tumor initiation. Accordingly, activation of cellular differentiation programs represents a powerful mechanism of tumor suppression. Identifying factors that control the balance between self-renewal and differentiation will thus provide fundamental insight into processes controlling tumor initiation and may provide novel avenues to halt tumor growth. Recently, intracellular metabolites have emerged as critical regulators of gene expression programs that control cell fate. In particular, metabolism of specific amino acids has been shown to affect stem cell self-renewal, raising the possibility that local amino acid availability controls stem cell fate and tumor initiation. However, how cells take up critical amino acids is still largely unknown. Through the Paglia Fellowship, I therefore aim to help uncover the specific amino acid transporters that control nutrient uptake in tissue stem cells. This work will provide fundamental insight into how cells couple nutrient uptake with regulation of cell identity in both normal and diseased states.

Dr. Lydia Finley's research group at the Sloan Kettering Institute is on the forefront of elucidating the metabolic pathways controlling cell fate decisions. The Finley Group has identified the crucial role of extracellular serine for tumor initiation in squamous cell carcinoma, one of the most common forms of cancer worldwide. In recent work, the Finley Lab discovered that dietary serine restriction induced epidermal stem cells to undergo metabolic rewiring that triggered differentiation. Oncogenic mutations prevented this metabolic rewiring and rendered cells obligate serine auxotrophs, meaning they must acquire serine from their environment to grow and proliferate. However, how stem cells acquire serine remains unknown. Identifying the routes by which cells acquire serine will reveal fundamental networks that enable cell growth and provide novel strategies to target growth of cancer cells.

In the Finley Lab, I will work closely with senior grad students and postdoctoral fellows to help me identify mechanisms controlling serine transport in epidermal stem cells and squamous cell carcinoma cell lines. The goals of this project are to gain an understanding of the mechanisms by which serine is acquired by cells and to determine how changes in cell state control the pathways involved in serine uptake and metabolism. Working alongside the members of the Finley lab on these projects will expose me to a wide variety of research techniques, including *in vivo* work with mouse models of cancer, *in vitro* work with tumor organoids and cell lines, and a variety of other methods including metabolite quantification, immunofluorescence and CRISPR-Cas9-mediated genome editing. Through lab meetings, working groups and seminars, I will be exposed to a wide variety of cutting-edge research in both basic biology and more translational research labs. Thus, this fellowship will provide a unique chance to prepare me for competitive MD-PhD programs by giving me ample opportunities to engage in the forefront of metabolic oncology research while engaging with and receiving mentorship from a tight-knit and supportive lab group.