Defining the gene regulatory response and pathways for acquired resistance to CDK inhibitor treatment in hormone receptor positive breast cancer

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Abstract**:** Pharmacological inhibition of the CDK4/6 kinases that regulate the G1 cell cycle checkpoint have improved outcomes in patients with estrogen receptor positive (ER+) breast cancer. Nevertheless, after a limited time of control, resistance develops in a majority of individuals. Evidence from multiple cancer types indicates that CDK4/6 inhibitors (CDK4/6i) drive not only cell cycle arrest, but also promote geroconversion, a dynamic transition in which quiescent cells evolve into a permanently arrested senescence-like state. We hypothesize that acquired resistance can arise from cells that fail to complete geroconversion.

We have identified a novel regulator necessary for geroconversion in ER+ breast cancer cells and established that its loss can affect patient outcome. In this application, we propose to combine our expertise in cancer genetics, senescence, and quantitative sequencing-based chromatin assays to investigate this regulator's mechanism of action and to define the dynamics of geroconversion, ultimately identifying other regulators and pathways that drive transitions between the stages of geroconversion. Our approach combines genetically defined and patient-derived HR+ breast cancer models, senescence and cell cycle assays, single-cell and bulk ATAC-seq and RNA-seq, integration with clinical trial data, as well as piloting of a cell barcoding approach that will set the stage for further investigations of the relationship between transcriptional and clonal heterogeneity during geroconversion. Collectively, we anticipate this will advance our understanding of geroconversion in breast cancer and reveal new opportunities for precision therapies targeting those patients who initially respond to standard CDK4/6i therapy for several months before developing resistance.