# Campisi Lab

Buck

Our laboratory studies cell fate decisions, with an emphasis on cellular senescence, that drive the phenotypes and pathologies of aging. Cells constantly assess their functional state and tissue microenvironment to repair or overcome molecular and cellular damage. While these responses often benefit young organisms, they can become maladaptive during aging, such as when senescent cells accumulate with age. Many diseases are thought to be driven by senescent cells, which may also cause age-related chronic inflammation, including cancer, arthritis and osteoporosis, dementia and frailty, among others. To study cell fate decisions, we primarily use human and mouse cells and organoids *in culture* as well as mouse models.

**Cellular senescence in the eye:**

Age-related visual impairment affects the physical, psychological, and social function of the elderly. 80% of our sensory impressions are perceived through the eyes. Therefore, it is essential to maintain healthy vision for a good quality of life. The ocular surface protects the cornea, keeping it smooth and wet for proper eyesight, cooperating with structures that include the conjunctiva and lacrimal glands. The retina is at the eye posterior and plays a major role in vision. Aging can change the ocular microenvironment as corneal epithelial stem cells decline. Tear fluid can also change, photoreceptor density can decline, and the retinal microvasculature can promote inflammation through the infiltration of macrophages and microglia.

Our hypothesis is that cellular senescence is a primary cause of age-related eye disease, including dry eye disease (DED), corneal stem cell deficiency, corneal endothelial failure, and macular degeneration. It was recently reported that as cells enter senescence in the eye they acquire an inflammatory phenotype called the senescence-associated secretory phenotype (SASP), which includes many inflammatory cytokines, matrix metalloproteases (MMPs), chemoattractants, and even bioactive lipids. These deleterious molecules that senescent cells secrete can cause tissue degeneration, resulting in pathologies and diseases associated with aging. We are studying the pathology of senescence-related eye diseases and aim to discover novel options for treatment based on interventions that reduce the deleterious effects of senescent cells.

**DNA damage response changes with age and age-related diseases:**

DNA damage is one of the strongest, causal theories of aging, and how cells respond to DNA damage may be indicative of a root cause for dysfunction with age and age-related disease. To study DNA damage response (DDR), we induce DNA double-stranded breaks in primary human cells which can result in a senescent-like phenotype. We are specifically interested in senescence states in neurons, as senescence is poorly described in post-mitotic cell types. To generate primary neurons *in culture*, we use a technique called direct differentiation in which we differentiate fibroblasts directly to neurons, skipping the stem cell state and retaining many age-related signatures. We then profile the senescent state and functional differences in neurons with and without DNA damage using transcriptomics, immunofluorescence, and functional assays, such as synaptic function and Seahorse assays. We hypothesize that senescent neurons are detrimental to their surroundings, which would uncover a causal link between DNA damage and aging through senescence in post-mitotic cell types. We plan to extend this research to neurodegenerative diseases, such as Alzheimer's disease and related dementias, and ultimately, we would like to better

understand how different cell types respond to damage with age and age-related disease to develop specific and universal predictors and therapeutics for aging.

**Desired Skills or Experience:** Cell culture, Western blot, qRT-PCR, and ELISA

To learn more about the Campisi lab, click HERE.
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