Aging is the single biggest risk factor for developing cancer. This puts a tremendous economic and social burden on society given a steadily growing world population of elderly people and the cost and time associated with cancer diagnosis and treatment. Many cancer therapies fall short of curing patients with aggressive forms of cancer, therefore, there is a huge demand for novel therapies to combat cancers with metastatic potential. Invasion and metastasis of aggressive cancer cells is the final and fatal step during cancer progression, and is the least understood epigenetically. The development of novel therapies for cancer can be further advanced by understanding the basic principles of the aging process and its impact on cancer development. In particular, the understanding of how age-associated changes in chromatin structure, function, and regulation affect cancer cell phenotype.

Our proposal is to study the function of a protein called JMJD3 in cancer. Our reason for studying JMJD3 is that it acts like a molecular switch, modulating chromatin and gene expression, causing key genes to turn 'ON' or 'OFF'. These genes are normally involved in immune activation, injury repair, and cellular aging. Tumors have been described as 'wounds that do not heal' since there are many overlapping similarities between wound healing and cancer. Normally, JMJD3 is turned 'OFF' after completion of tissue repair, but this does not seem to be the case in cancer. Tumor cells overexpress JMJD3 protein, resulting in elevated levels of molecules involved in inflammation and recruitment of immune and stem cells.

JMJD3 also modulates cell proliferation and cancer cell phenotype, including secretion of cytokines, proteases, and growth factors that are collectively known as the senescence-associated secretory phenotype (SASP) which is known to contribute to 'inflammaging' (increased inflammation with aging). Normally, the SASP as part of cellular senescence helps to prevent cancer by blocking damaged cells from multiplying, but ironically this promotes inflammation that drives the progression of cancer over time. Our preliminary data indicates that cancer cells that overexpress JMJD3 display multiple biomarkers of cellular senescence, including the SASP, but do not exhibit a complete G_1 growth arrest which is defined in cellular senescence. In this scenario, JMJD3 overexpression in cancer cells leads to dangerous senescent-like cells that continue to proliferate, thus uncoupling the phenotype of cellular senescence from growth arrest. To describe this type of dysfunctional senescence in cancer cells, we coined the term 'cancer-associated pseudosenescence' (CAPS). We speculate that CAPS is likely a case of cancer cells responding to senescence stimuli, but in a dysfunctional manner due to loss of senescence effectors that are responsible for growth arrest. Moreover, cancer cells that display the CAPS phenotype may be a self-renewing and sustaining source of cytokines, proteases, and growth factors that contribute inflammaging in cancer. As a result, this may help tumors develop and progress, but from a positive outlook may attract therapeutic cells for disease intervention.

The impact of JMJD3 as a key regulator of the CAPS in cancer is two-fold. First, JMJD3 may serve as a novel target for inhibiting inflammatory cytokine production in cancer. Our strategy is to inhibit JMJD3 expression/function using RNA-interference and a small molecule inhibitor of JMJD3 called GSK-J4. Second, previous work has shown that therapeutic immune and stem cells are able to migrate to invasive tumors. This ability has been harnessed in a clinical setting to deliver and localize cancer drugs to target invasive tumor cells. Because tumor-tropism of therapeutic immune and stem cells is dependent upon release of cytokines by cancer cells, the development of effective cell-mediated cancer therapies may hinge on our understanding of the molecular mechanisms of cytokine production by tumors. This knowledge concerning JMJD3 in cancer can be used to develop new targeted therapies and optimize existing ones.