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Inducing cytosolic chromatin fragments in cancer cells to turn cold tumors hot

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Scientific Abstract:

Immune therapy of cancer has revolutionized cancer therapy and has lead to durable remissions across a broad range of cancer types. Unfortunately, immune therapy does not work for patients whose tumors exhibit low levels of immune cell infiltrate. These tumors, also known as "cold" tumors, respond poorly to all forms of immune therapy, including checkpoint blockade, adoptive transfer of anti-tumor lymphocytes, and vaccination. In contrast "hot" tumors, which contain robust immune cell infiltrates, often respond to immune therapy. The co-PIs of this grant have independently made observations that through synergy can convert cold tumors into hat tumors. In a recent Nature publication, Dr. Adams showed that senescent cells and tumor cell lines possess an endogenous pathway to detect cytoplasmic chromatin fragments (CCF) and secrete inflammatory cytokines. In a recent Current Opinion Review, Dr. Bui postulated that cancer cells can act like innate immune cells by secreting inflammatory cytokines. These independent observations support the hypothesis and paradigm that purposeful activation of the CCF pathway in cold tumors could cause cancer cells to secrete inflammatory cytokines that could then recruit immune cells. In this grant, we will use the Conrad Prebys Center for Chemical Genornics at SBP to identify agonists that can activate the CCF-sensing pathway and cause tumor cells to make cytokines. In collaboration, we will validate the potential therapeutic value of CCF formation in animal models of cancer. We envision that small molecule agonists that activate the immune-activating CCF-sensing pathway could find therapeutic benefit, especially in patients with cold tumors.

Lay Abstract:

Immune therapy is a method to treat cancer using the body's own immune system. This method works because immune cells such as T cells can infiltrate a tumor mass and specifically destroy cancer cells. For some patients, the T cells can also seek out and destroy cancer cells that have metastasized throughout the body. Additionally, the T cells survive even when the cancer cells have been destroyed and thus can prevent recurrence of cancer. Thus, immune therapy has the potential to produce durable, long- lasting cures for cancer. Unfortunately, not all patients respond to immune therapy. In particular, some patients have "cold" tumors that do not contain many immune cells. These tumors resist immune therapy by preventing the infiltration and/or accumulation of T cells in the tumor mass. This grant seeks to discover new ways to make a cold tumor "hot". Specifically, we wish to manipulate the cancer cell to force it to make proteins such as cytokines that recruit immune cells. In essence, our research will turn cancer cells into "suicide cells" that act as beacons for anti-tumor immune cells. We envision that our therapy will amplify and broaden the efficacy of current immune therapies and provide longlasting remissions for a large swath of cancer patients.