UC San Diego
MOORES CANCER CENTER

2022 Jawsome Shark Tank – Multidisciplinary Pilot Project Program

Combating Cancer with Chemokine-Coated Viral Nanoparticles

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Scientific Abstract:

Head and neck squamous cell carcinoma (HNSCC) remains a significant health problem despite revolutionary advances in cancer treatment with immune checkpoint inhibitors (ICIs). Poor five-year survival rates of only 40- 50% from standard therapy, response rates of <20% to anti-PD1 ICI therapy, and race, gender and socioeconomic status influences on outcomes all emphasize the need for more effective HNSCC treatments. ICI treatment failures result from an array of resistance mechanisms that enable tumors to evade anti-tumor immune responses. In particular, sparse infiltration into the tumor microenvironment (TME) by cytotoxic and other antitumoral immune cells leads to immune suppression and "cold tumors" that are non-responsive to ICIs. To address this problem, the Handel and Gutkind labs have shown that intratumoral delivery of the chemokine CXCL10 substantially reduces tumor growth in mouse models of HNSCC, including complete elimination with durable responses in 30% of the mice. Using an entirely different approach, the Steinmetz lab has developed a variety of plant viral nanoparticles (VNPs), some of which enhance the activity of therapeutic payloads through multivalency effects and prolonging their residence time in the TME, and others that are inherently immunomodulatory and capable of reducing or eliminating tumor growth with remarkable efficiency. The objective of this proposal is to combine CXCL10 with VNPs and explore their antitumoral efficacy and mechanisms of action in HNSCC mouse models. The synergy of the most potent CXCL10/VNP combination with anti-PD1 will also be determined with the ultimate goal of identifying a multimodel combination therapy that achieves durable anti-tumor responses.

Lay Abstract:

Head and neck squamous cell carcinoma (HNSCC) remains a significant health problem despite revolutionary advances in cancer treatment with "immune checkpoint inhibitors". Risk factors include tobacco and alcohol consumption which account for ~75% of the cases, while human papillomavirus (HPV) infection accounts for the rest. Poor five-year survival rates of only 40-50% from standard therapy, response rates of < 20% to immune checkpoint inhibitors therapy, and race, gender and socioeconomic status influences on outcomes all emphasize the need for more effective HNSCC treatments. To address this problem, the Handel and Gutkind labs have shown that a protein called CXCL10 substantially reduces or eliminates tumors in experimental models of HNSCC. The protein works by attracting cancer-killing immune cells to the vicinity of the tumor. Using an entirely different approach, the Steinmetz lab has developed proteins from plant viruses that form "nanoparticles" or VNPs. The VNPs don't infect

humans, but like CXCL10, they attract key immune cells that are important for eliminating cancer cells. In the proposed work the Handel/Gutkind/Steinmetz team will combine CXCL0 with the VNPs to make even more powerful anticancer therapies. These therapies should not only work by themselves, but also improve other therapies like immune checkpoint inhibitors. Moreover, they should be broadly applicable to other solid tumors in addition to HNSCC. The team plans to identify treatment formulations that would lead to clinical trials and ultimately powerful treatments for many types of cancers.