



2022 Jawsome Shark Tank – Multidisciplinary Pilot Project Program

Dual targeted therapy to treat aggressive multiple myeloma

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Scientific Abstract:

Despite significant therapeutic advances in the last 20 years, multiple myeloma, the second most common blood cancer, remains incurable. Myeloma is a cancer type with unusually no FDA-approved “targeted” therapies. Despite a flurry of FDA approvals in the last few years, none of the approved agents specifically targets aberrant pathways that drive myeloma cell growth. RAS mutations are found in over 50% of patients at diagnosis and over 75% in relapsed/refractory disease. PI3K/AKT pathway is also activated in human myeloma, Hence, there is an unmet need to identify a novel drug that can concomitantly hit multiple signaling pathways in the tumor compartment to reduce tumor burden. Published studies from the Joshi lab have shown that SF2523 is a dual PI3K/BRD4 inhibitor that hits both targets, BRD4 and PI3K, with nM potency compared to JQ1 which only hits BRD4. Furthermore, SF2523 blocks MYC expression and activation promotes Myc degradation and effectively reduces tumor growth and metastasis in various preclinical mouse models with better efficacy and less toxicity. The Asimakopoulos lab has developed a toolset of genetically-engineered myeloma models, driven by Ras mutation, that reflect distinct molecular profiles of myeloma tumors in humans (1, 2). These models are also driven by MYC (therefore responsive to BRD4 inhibition) and display AKT pathway activity. Hence, the overarching goal of this proposal is to determine the activity of SF2523 in myeloma cell lines *in vitro* and to study the impact of this intervention on the immune microenvironment of our novel immunocompetent myeloma model *in vivo*. We propose to test the central hypothesis that SF2523 will inhibit PI3K and BRD4 signaling in the murine and human myeloma cells *in vitro* and will enhance the anti-tumor immune responses in our novel immunocompetent myeloma model *in vivo*. This collaborative proposal by Dr. Asimakopoulos and Dr. Joshi aims to develop a novel therapeutic option to treat patients with myeloma.

Lay Abstract:

Myeloma is a growing problem in the elderly population, in African-Americans and in veterans exposed to Agent Orange. Despite advances in immunotherapy of myeloma with CAR-T and more recently, bi-specific T cell engagers, our patients relapse and myeloma remains incurable. We need additional therapies for these patients whose myeloma cells have escaped T-cell attack and seem to be invincible. Given the prevalence of MYC and AKT activation in advanced myeloma, dual inhibitors of these pathways may offer new hope for these unfortunate patients. SF2523 is a safe and efficacious dual PI3K/BRD4 inhibitor that hits both MYC and AKT pathways with great potency.