



Scientific Abstract

SU2C-Fanconi Anemia Research Fund-Farrah Fawcett Head and Neck Cancer Research Team:

“Precision Therapy for Fanconi Anemia and HPV-related Head and Neck Cancers”

[This abstract was provided by the scientists when their application was accepted.]

Head and neck squamous cell cancers (HNSCC) affect almost 900,000 people annually worldwide with numbers predicted to continue to rise. More than 25% of these cases are related to human papillomavirus. Very modest survival benefits have materialized over the last decades in HNSCC patients and among the 25% of patients with HPV-related disease who fail initial therapy, the majority will not be cured. Even when successful, HNSCC treatments continue to be exceptionally morbid, leading to compromised quality of life.

Thus, novel treatment approaches are necessary to reduce the toxicity of therapy in those patients with a curable disease. More effective, but also more precise treatments are necessary for patients progressing on current therapies.

A particularly challenging treatment circumstance exists for Fanconi anemia patients, who are constitutionally sensitive to DNA damaging therapy due to a germline deficiency of DNA interstrand crosslink repair. For this population, novel preventive, and therapeutic options are critical.

To address these highlighted needs, we propose to gain fundamental knowledge about the HPV-related and FA-associated HNSCCs and a three-pronged approach to develop novel therapies for HPV-related and FA-associated HNSCCs: exploiting synthetic lethal interactions, use of combinatorial therapeutics, and chemoprevention.

In AIM1, we propose to perform proteogenomic and digital histologic analysis of FA-related and HPV-related HNSCCs to identify common and cohort-specific therapies.

In AIM2, to identify and test novel therapeutic approaches in HPV-related HNSCC, we will characterize initiating cancer stem cells, test multimodal precision immunotherapy including the interaction between HER3 and immune checkpoint inhibition, and test TEAD, mTOR and CDK4 inhibition, as well as G2/M blockade as potential therapeutic strategies.

AIM3 will concentrate on the identification of novel therapeutic and preventive strategies in FA-associated HNSCCs. These will include targeting the G2/M transition, and validation of new synthetic lethal interactions with the highly genomically unstable cancers.

For prevention studies, we will screen multiple chemoprevention drugs including metformin, and will perform oral gene therapy using novel mouse models of FA tumorigenesis. Therapy-related toxicity studies will be performed to identify those therapies that would be well tolerated by Fanconi patients. By bringing multipronged approaches we are set to improve outcomes for those with HPV-related HNSCC and with Fanconi anemia.

