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Neoantigen driven eradication of immune-reprogrammed ovarian cancer

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Scientific Abstract:

This proposal will leverage neoantigen-identification technology and adoptive cell therapy expertise from LJIA with tumor-microenvironment modulating approaches pioneered at UC San Diego to tackle a highly aggressive subtype of ovarian cancer. High grade serous ovarian cancer (HGSOC) is highly resistant to immunotherapy. The Stupack/Schlaepfer labs showed that immunosuppression can be relieved via the genetic or pharmacologic inhibition of focal adhesion kinase. FAK inhibition relieves a wide range of immunosuppressive factors, yet does not eliminate the expression of CD155, a coreceptor for the checkpoint inhibitory protein TIGIT highly expressed in HGSOC patients. Targeting TIGIT and FAK promotes an activated T cell signature and the formation of tertiary lymphoid structures, creating an environment that we hypothesize would optimize adoptive cell therapies and/or vaccination strategies. The proposal builds on recently published data from the Schlaepfer/Stupack labs and on preliminary evidence generated by the Schoenberger lab which ranked 84 of >1200 genetic lesions neoantigens. The first AIM will assess T cell activation by each of these epitopes in vitro, and rank them functionally. The second AIM will use two arms, The first tests adoptive cell therapy of tumor-specific T cells with a supportive FAKi-preconditioned TME to eradicate tumor as front line therapy. The second arm is a maintenance study after standard of care chemotherapy with FAK inhibition/Anti TIGIT and neoantigen vaccination. It focuses on eradication of residual disease and is translated rapidly to the clinic. All platforms are in place, studies can be rapidly executed, and will absolutely provide a roadmap for future clinical trials and extended collaborative proposals.

Lay Abstract:

One approach to treating tumors uses intravenous therapies that help the immune system. This works in many cancers, however, this approach does not always work, and can fail with time as tumors find ways to avoid the immune system – even shutting off its ability to attack tumors. Our ability to avoid a "shut down" of the immune system in ovarian cancer was strengthened by studies showing that an oral drug called a FAK inhibitor, which targets a gene that is altered in 3 of 4 ovarian cancer patients. The drug has broad benefits to the immune system. Importantly, FAK can be combined with other immunotherapies. A second type of immunotherapy in development is a cell-based therapy that uses vaccination against unique features of the tumor. While very precise, and potentially very potent, this approach is highly vulnerable to the ability of tumors to shut off the tumor-attack part of the immune system.
This proposal will test a new idea; treat tumors to block their ability to shut off the immune response with the FAK drug first, then expose them to a vaccine engineered directly against them. The studies here will use a mouse model that recapitulates HGSOC determine [1]- which features are best to target, [2a] Can we use vaccination in a test tube and deliver the immune response to a more immune-active mouse conditioned by FAK, and [2b] For tumors treated with chemotherapy and surgery, can we then treat them with FAK drugs together with vaccination to allow the immune system to get rid of residual

disease. A lot of groundwork has gone in to reach this point, and we are now set to finish the studies within a year.