



SU2C-Lustgarten Foundation Convergence Research Team:

“Computational Deconstruction of Neoantigen-TCR Degeneracy for Cancer Immunotherapy”



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

Checkpoint blockade immunotherapies kill tumors cells by boosting an anti-tumor immune response and have revolutionized modern cancer treatment. Their efficacy is linked to its ability to amplify endogenous T cell recognition of mutational neoantigens in the cancer genome, with enhanced responses observed in heavily mutated tumors. Advances in next generation sequencing now allow rapid neoantigen identification, and have enabled the application of neoantigens as biomarkers of response to immunotherapy, as critical backbones in cancer vaccines, and as cell-based therapies. However, as human tumors can generate several hundreds of putative neoantigens, a central question in the field has remained whether anti-tumor T cell activity is preferentially directed towards specific dominant neoantigens, and if so, could these dominant targets be identified *a priori*.

As such, recent work by our groups and others has demonstrated that T cell activity against neoantigens is: a) preferentially directed towards dominant neoantigens; b) skewed to recognize neoantigens with specific microbial motifs, and c) modulated by the host microbiome. Furthermore, recent groups have used analytical tools to uncover that epitope specific TCR repertoires share core sequence similarities, highlighting both the conserved essential elements of TCR antigen recognition and the ability to computationally identify them.

However, fundamental questions remain: 1) Is TCR recognition of neoantigens governed by conserved principles? 2) Can we define these principles to computationally predict reactive TCR and neoantigen sequences?

Pancreatic cancer and neoantigens: Unlike checkpoint blockade responsive tumors such as melanoma and lung cancer in which robust spontaneous antitumor T cell infiltrates and multiple oncogenic drivers determine patient outcome, PDAC is the prototypical checkpoint blockade-refractory tumor with response rates of <5% and <7% of patients surviving past 5 years. However, although PDAC is characterized by a more modest neoantigen load (mean 38 neoantigens/tumor), it concurrently exhibits a wide spectrum of neoantigen-specific T cell responses associated with survival. Hence, the modest neoantigen and T cell burden limiting computational dimensionality, and the extremes of patient survival driven by neoantigen-specific immunity, make human PDAC an ideal model to dissect T cell-neoantigen recognition dynamics.

