T-STM : Spatio Temporal Modeling of the Tumor-Microenvironment for in silico Testing of Immunomodulatory Drug Combinations for Enhanced Triple Negative Breast Cancer Immunotherapy

Venkatesh, Ajeet (School: Nikola Tesla STEM High School)

Breast cancer affects 2.3 million women annually with the five-year survival rate for Triple-negative-breast-cancer (TNBC) being 12%. Current immunotherapy treatments are effective only in 25% patients as the multiple immunosuppressive mechanisms of the Tumor-microenvironment (TME) are not understood. T-STM is the first of its kind multi-agent, Spatial-temporal-modeling based simulation of the TNBC TME. T-STM uses a novel hybrid approach with discrete models to characterize tumor, stromal and immune interactions; driven by tumor and patient-specific metabolic profiles, signaling and immune infiltration patterns derived from TCGA(The-Cancer-Genome-Atlas) data along with partial-differential-equations for modeling nutrient diffusion and the multiple immunosuppressive pathways in the TME. Simulation results were successfully validated with TCGA histopathological immunophenotypes matching and cell fraction histograms showing high correlation with r values between 0.785 and 0.91. Simulations run on 100 TNBC datasets for 150 days, testing for optimal combinations of immunomodulatory drugs showed best tumor reduction for the combination of TLR9 agonist with P13k, mTOR and IDO inhibitors combined with LAG3 and PDL1 blockade with an average of 80% reduction in tumor cells across 40 datasets. T-STM shows best immune-efficacy with low stroma and high tumor-infiltrating-lymphocytes scenario validated by Kaplan–Meier survival curves (hazard ratio 0.308 , P = 0.0219) with stromal permeability boost increasing immune response. T-STM can potentially shorten the drug development cycles through identification of combination inhibitor therapies based on simulated remission rates to create customized therapeutics for enhanced cancer immunotherapy with reduced costs.

Awards Won:
Fourth Award of $500