Dissertation Defense - Li Jia, PhD Bioinformatics and Computational Biology

November 30, 2021 4:30 AM - 6:00 PM

All are invited to attend the defense. For more information please contact Graduate Coordinator at dstgerma@gmu.edu

Candidate: Li Jia

Program: PhD, Bioinformatics and Computational Biology

Date: Tuesday, November 30, 2021

Time: 4:30 PM

Zoom Link: https://gmu.zoom.us/j/98450653290?pwd=R0c4bDhzSG5TS3J5L0xycUMrWmxodz09

Title: Modeling Impact of Clonal and Driver Events on Tumor Heterogeneity and Evolution

Committee Chair: Dr. Iosif Vaisman

Committee Members: Dr. Saleet Jafri, Dr. Chris Lockhart, Yong-Chen William Lu

ABSTRACT:

Adoptive T cell therapy (ATC) can mediate tumor regressions in patients with metastatic cancers, especially for cancers with high mutation rates. However, clinical responses are rarely observed in patients with common epithelial cancers, likely due to tumor heterogeneity that shows distinct morphological and phenotypic profiles observed in different tumor cells. To examine tumor heterogeneity, exome sequencing data with 220 tumor samples in GI patients and 28 samples in melanoma patients were operated on analyses of the clonal and driver events, including somatic mutations and copy number aberrations, chromosomal instability, and phylogenetic profiling on multiple spatially separated samples mainly obtained from metastatic sites and few from the primary and progressed sites. A critical challenge for predicting clinical outcomes to cancer treatment is the heterogeneity of cell populations within each tumor. The identified reactivity neoantigens in vitro may not functionally facilitate recognizing T cells to kill tumor cells in vivo due to the heterogeneity. To understand the heterogeneity effect, the genome doubling, intra-tumor heterogeneity, and proportion of LOH regions in the tumors were explored and found that they can result in a poor prognosis in the responses to the cancer immunotherapy, especially in GI cancer. Phylogenetic trees were constructed from each patient with multi-region or -lesion samples, and the trees from multiple patients often appear very distinct. To uncover repeated evolutionary trajectories across patients, clonal and driver events were identified to reconstruct the phylogenetic tree on each patient. The driveRF model was constructed by a random forest algorithm and outperformed other feature predictors on testing (AUC >99%) and validation datasets (AUC >93%). KRAS and TP53 driver mutations were significantly enriched in GI cancer, and 27% of KRAS mutants are associated with TP53 mutants in the initial events, which could influence the tumor immunity. Furthermore, understanding the mechanism by which aneuploidy affects responses to T cell therapies may provide an avenue for the therapeutic intervention that could improve the efficacy of the current ACT.