Novel Deconvolution Algorithm to Study the Effect of Copy Number Variation on Response of Cancer Cells to Anti-PD1 Therapy with Time

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Copy number variation (CNV) of genes in cancer cells affects the response of cancer cells to cancer immunotherapies, such as anti-PD1 immunotherapy.\(^1,2\) CNVs contribute to the presence of tumor heterogeneity which is defined by the cancer cells with various morphological or molecular features present in the tumor.\(^3\) Since different tumor clones may respond differently to the same treatment, it is important to study tumor heterogeneity and the function and dynamics of diverse tumor cells to understand mechanisms of response or resistance to therapy and, consequently, develop improved therapies for cancer.\(^4\)

The ability to study how CNV impacts tumor cells is limited by the fact that the whole genome sequencing data is bulk data (i.e. averaged across all cells in a sample) and is therefore not informative of intra-tumoral heterogeneity. I aim to develop a deconvolution model that incorporates single-cell resolution RNA sequencing (scRNA-seq) data which would provide the higher resolution required to study how CNV impacts the response of cancer cells to anti-PD1 immunotherapy over time by profiling pre-treatment, on-treatment, and post-treatment biopsies from melanoma patients. My mentor, Joy Fan, has previously identified 4 clones, or groups of tumor cells, defined specifically based on their CNV profiles from the scRNA-seq data of a patient and using this, I determined their proportions in each sample at each timepoint. Utilizing this data and the fact that the sequencing data allows for the identification of genetic alterations\(^5\), I will develop and test a probabilistic graphical model representing the whole genome sequencing data as a weighted sum of the genetic alterations in each clone. This model will truly allow us to identify the genetic profile of each tumor clone, connect its genotype to phenotype, and map its dynamics during response to anti-PD1 immunotherapy.

References: