Research Summary – Neelam Sinha

My research is focused on developing computational approaches for analyzing cancer omics data from pre-clinical and clinical data to advance immunotherapy. Below is a brief review of my efforts during my time (eight months) at the Cancer Data Science Lab, NCI.

My first project is motivated by the recent studies indicating that high-Tumor mutation burden levels, a recently approved biomarker for the treatment of any solid tumor with Immune checkpoint inhibitor (ICI), are only able to stratify ICI responders in a subset of cancer types. The mechanisms underlying this observation have remained unknown. We hypothesized that the tumor immune microenvironment (TME) may modulate the stratification power of TMB (*TMB power*), leading to this observation and built a framework that leverages existing publicly available large-scale omics data to identify the key immune factors that can determine this *TMB power* across different cancer types. Briefly, we find that high levels of M1 macrophages and low levels of resting dendritic cells in the TME characterize cancer types with high *TMB power*. We also predicted TMB power in additional 9 cancer types, including rare cancers, for which TMB and ICI response data are not yet publicly available on a large scale. This could potentially help in prioritizing cancer types for clinical trials with this ICI biomarker. This project is currently in review in *Nature Genetics* where the preprint link is provided below [1].

Our second project is motivated by recent studies suggesting that TMB levels and response to ICI treatment may differ between male and female melanoma patients. Thus, we investigated whether using this absolute threshold (>10 mut/MB) based high-TMB biomarker for selecting patients for ICI treatment can induce a sex-dependent bias. From our analysis, we find that the usage of this biomarker in clinics can introduce an unwarranted sex bias in Melanoma patients, stratifying responders in females, but not in male patients. Our finding also suggests that such sex bias may extend to other cancer types, including Glioblastoma and Cancer of Unknown origin, however insignificant. This study is *in press* in the Journal of Clinical Oncology, Precision Oncology where the print link is provided below [2]. This work has been presented at AACR 2021 as a highlight talk and has gathered considerable interest (Articles via Hem Oncology, Cancer Network).

Aside from leading these projects, I have contributed to the computational analysis of two collaborative projects of our lab with a close experimental collaborator, Brid Ryan at the National Cancer Institute. These projects have provided me wonderful opportunities to further contribute to therapy development in the context of very focused biological questions, and it is an exceptional experience for me to be exposed to such a wide range of experimental approaches for tackling important research questions across multiple cancer types. These collaborative efforts are published at Nature Cancer and *in press* at Nature Communication and can be found below [3, 4].

The current project I am leading is motivated by the observation that even though there are numerous gene expression signatures of ICI response, there is limited success in their clinical adoption due to poor robustness in independent patient cohorts. Previous works have shown that transcriptomic-based biomarkers are confounded by the intratumor heterogeneity of the expression and is a key contributor to this poor robustness. To overcome this problem, we first identify the subset of genes that are not affected by this confounding factor (low intra-tumor heterogeneity) and have high prediction power (high inter-tumor heterogeneity) by leveraging publicly available bulk and single-cell-expression profiles from patient tumors and are currently building biomarkers based on this geneset.

As described above, my research has focused on the use of computational methods that leverages large-scale publicly available datasets to answer important clinical questions. I am hopeful that some of those may have translational contributions and may help better the treatment of cancer patients.

References

1. Sinha N., Sinha S., ... & Ruppin E., Immune determinants of the association between tumor mutational burden and immunotherapy response across cancer types, *In review at Nature Cancer*, BioRxiv [Link]
2. Sinha N., Sinha S., Cheng K., … & Ruppin E., Using a recently approved tumor mutational burden biomarker to stratify patients for immunotherapy may introduce a sex bias, *JCO Precision Oncology (2021)* [Link]

3. Sinha S, Mitchell KA, Zingone A, Bowman E, Sinha N, ... & Ryan BM., Higher prevalence of homologous recombination-deficiency in lung squamous carcinoma from African Americans. *Nature Cancer (2020).* [Link]
4. Zingone A., ..., Sinha N., … & Brid Ryan., A comprehensive map of alternative polyadenylation in African American and European American lung cancer patients. *In press at Nature Communication*.