TUMORMAP: Mapping tumor subclones and their immune microenvironment in ultra-high spatial and molecular resolution

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Solving the puzzle of interactions between the tumor and its microenvironment promises to break the current barriers of the understanding and treatment of cancer. Cancer progresses by accumulation of somatic alterations and by forming genetically distinct subclones in the tumor cell population. Depending on their spatial arrangement, distinct tumor subclones adapt to escape different cues from the immune system. High-resolution methods for exploration of the interplay between tumor subclones and their immune environment in space are lacking.

In this proposal, we ask questions about the basic properties of tumor subclone microenvironments: *1) Which immune cells types tend to co-occur with which mutations in the tumor cells and why? 2) What repeatable types of spatial configurations of tumor mutations, immune cells and their states can be categorized?* To this end, we put forward a computational methodology for integrating data from bulk DNA sequencing with spatial transcriptomics, single cell RNA-sequencing and histopathological imaging. A preliminary probabilistic model for localizing the subclones, their genotypes and gene expression profiles in the tumor tissue has already been formulated. In this project this model will be further largely extended to gain power from integrative data modeling. Next, we will construct a model for localizing different immune cell types and inferring their level of gene expression. Finally, we will combine the results of these two methods to localize the tumor subclone-immune microenvironment interactions. The proposed methods will be benchmarked on published prostate cancer data and applied to newly generated breast cancer data to gain such insights that were never possible before.

In summary TUMORMAP will deliver the tools to draw the first ever maps of tumor subclones, their immune microenvironment and their interactions in the tumor tissue in ultra-high spatial (2 -100 micron) and molecular resolution. The project will open new research avenues, providing innovative tools for investigating the possible mechanisms behind the emergence of different microenvironments in the tumor tissue.