Relating single cell function to tissue structure in human tumors using MIBI-TOF

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Understanding the role of distinct cellular phenotypes in tissue function, development, and pathogenesis requires tools that can rapidly and consistently quantify the expression of multiple proteins while preserving spatial information. To meet this need, we have developed Multiplexed Ion Beam Imaging by Time-Of-Flight (MIBI-TOF). MIBI-TOF uses secondary ion mass spectrometry to visualize up to 50 metal labeled antibodies at subcellular resolution simultaneously with histochemical stains and native biological elements. We have used this capability to study how single cell function and tissue structure interact at the tumor immune microenvironment, the human maternal-fetal interface, and in infectious disease. These studies have led us to develop scalable, automated, and extensible tools for image thresholding, single cell segmentation, cell clustering, and cell neighborhood analyses that can be deployed on any tissue. Through NIH HuBMAP and CIMAC initiatives, we are currently working to deploy this computational pipeline as well as preformulated antibody staining master mixes as a streamlined, end-to-end workflow for routine high dimensional tissue analysis in basic and translational research. Lastly, we are currently working to develop brighter primary ion sources and new metal reporter constructs that will permit full tissue section scanning while extending multiplexed detection to include RNA and DNA.