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Cytometry and Atomic Mass Spectrometry Converge in Single Cell Deep Profiling of the Human Immune System

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Mass cytometry addresses the challenges of polychromatic flow cytometry by capitalizing on the analytical benefits of atomic mass spectrometry. Fluorescence flow cytometry has helped to define the cell subsets of the immune system. The addition of intracellular staining facilitated examination of signaling networks and, recently stratification of patients correlated with clinical outcome. However, the potential for further advances has been stymied by the physical and spectral limitations of fluorophores. This technical barrier has been broached by replacing fluorophores with heavy metal isotopes, and optical detection with atomic mass spectrometry. Antibodies raised against phenotypic and functional proteins are tagged with polymers that are labeled with the transition metal isotopes. More than 30 lanthanide isotopes, complemented by noble metals, permit the immunological recognition of more than 40 (and conceptually up to 100) proteins in single cells simultaneously. Individual cells are injected at nearly 1 kHz into an Inductively Coupled Plasma where the cells are vaporized, atomized and ionized. The reporting ions within the vaporization cloud of each cell are extracted, separated and counted by a time-of-flight mass spectrometer. The data output is a massively multivariate signature of each cell. Already the technology has offered dramatic new insights into the operation and function of the human hematopoietic hierarchy, shown novel application for the screening and mechanistic understanding of drug candidates, and foresees improved prognostic and diagnostic application in the clinic. We will report on our work, and the work of others, in profiling the signaling and functional responses of the suite of cell populations in human bone marrow, the revealing of unappreciated levels of organization in virus-specific memory T cell compartments, and massively multiplexed single-cell kinase inhibitor profiling.