Using morphological pharmacodynamic markers to analyze drug sensitivity, resistance, and toxicity

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Abstract: Developing therapeutic agents to treat cancer largely focuses on the analysis of cell proliferation as the readout of a compound's efficacy (i.e., ability to kill cancer cells) and toxicity (killing healthy non-cancer cells). In this project, we will test the hypothesis that morphological pharmacodynamic (PD) markers exist that reveal, at earlier timepoints and with more mechanistic detail than cell proliferation analyses, whether a given cell will be sensitive or resistant to a given oncology drug, either prior to treatment or soon thereafter. We will select drugs with diverse targets and systematically examine morphology in cells engineered to have altered drug responses. In particular, we will employ different known direct (e.g. mutations in the target of a given drug) and indirect (e.g. upregulation of signaling pathways) mechanisms of resistance. Using state-of-the-art image analysis algorithms including deep learning, we will extract hundreds of features at single-cell resolution from several microscopy assays to richly characterize cell state before and after drug treatment. If successful, this project will identify single-cell morphological pharmacodynamic (PD) markers associated with specific mechanisms of drug sensitivity and toxicity. The identity of such markers - such as which organelle is involved or what stage of the cell cycle is disrupted - will provide new information on the basis of drug efficacy and toxicity. These data will be valuable for designing agents with maximal therapeutic indices, and will lay the groundwork to take patients' primary tumor cells and image them to quickly reveal their chemical sensitivities and guide specific therapy choices.