INTERROGATING CELL CULTURE POPULATIONS FOR THE SELECTION OF PRODUCTION CELL LINES USING MICROFLUIDIC CULTURING, SINGLE CELL ANALYSIS, AND PREDICTIVE MODELLING

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Cell line development for manufacturing is a lengthy, multi-step, resource intensive, critical path activity. Attempts to perform in silico modelling and prediction of cell culture has been difficult due to complexities around heterogeneous cell culture populations that rapidly shift over generations under changing selective conditions. For example, early populations will often change as response to media and culturing conditions from a static colony culturing in microtiter plates, to small scale suspension culturing, and finally in a controlled bioreactor processes. As a result, it is challenging to make the final cell line selection early, while predicting future bioprocess performance, and ultimately estimate the protein product quality. We address this challenge by drastically increasing the amount of early cell culture population data obtained through use of emerging single cell technologies. Data obtained is combined with modelling approaches to select the best cell lines upfront to reduce timelines and processing steps. To achieve this, we have implemented a platform from Berkeley Lights that effectively digitalizes most aspects of cell culture. Thousands of individual cell lines can be manipulated, cultured and interrogated on a perfusion nanofluidic chip resulting in extensive data on cell behavior on an individual cell level as well as the populations. Through multivariate predictive modeling of this data, we can predict the performance of candidate clonal cell lines in larger scale production runs. Incorporation of additional single cell analysis such as digital droplet RT-PCR and next generation sequencing further predicts product quality, such as heterogeneity of bispecifics and sequence variant detection. Similar approaches can further be used to then study the stability and integrity of a final CHO cell banks. When combined, single cell interrogation of early culture populations allow for the dematerialization of the CLD process, make better predictions of bioprocess performance, and reduce select the final production clone earlier.