

USING NANOSCALE BIOREACTORS TO CHARACTERIZE SUB-POPULATIONS OF CHO CLONES AND SCREEN TRANSFECTED POOLS

Tanner Nevill, Berkeley Lights, 5858 Horton St #320, Emeryville, CA 94608
tanner.nevill@berkeleylights.com

Hari Chirra, Berkeley Lights, 5858 Horton St #320, Emeryville, CA 94608
Phillip Elms, Berkeley Lights, 5858 Horton St #320, Emeryville, CA 94608
Troy Lionberger, Berkeley Lights, 5858 Horton St #320, Emeryville, CA 94608

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Traditional means to quantify growth and production rates for antibody-expressing CHO lines involve sampling aliquots and supernatants from well plates that have been seeded with single cells. The number of clones studied is often limited by cloning efficiencies (typically 5-50%) and the inability to handle large numbers of well plates. The speed at which each clone can be measured is limited by the growth rates of cells and the number of cells required to perform each assay. Both of these factors lead to a practical throughput of 100s of clones screened over the course of 2-4 weeks. Furthermore, each readout of a clone offers little to no insight into the behavior of sub-populations within each clone since the aliquot or supernatant is just a small sample representing the entire population.

We have developed a platform that enables screening of thousands of clones in less than 5 days. The assays employed allow for a direct measurement of growth and secretion opening a previously unattainable window into the behavior of the entire population. A disposable nanofluidic chip has been developed that can house over 1000 individual nanoscale bioreactors. Individual cells are placed in separate chambers using light-induced dielectrophoresis and continuously perfused under culture conditions that lead to 60-80% cloning efficiency. Due in part to the small volumes of these nanobioreactors, it is possible to assay for production of antibodies directly across all clones simultaneously using a fluorescently-tagged small molecule. A picture of the steady-state concentration being produced by each clone provides for faster relevancy detection, stable clone identification, sub cloning abilities, and can be applied across numerous applications. Additionally, the cells can be imaged with a deep learning algorithm to provide very high-fidelity growth rate characteristics by counting cells at regular intervals.

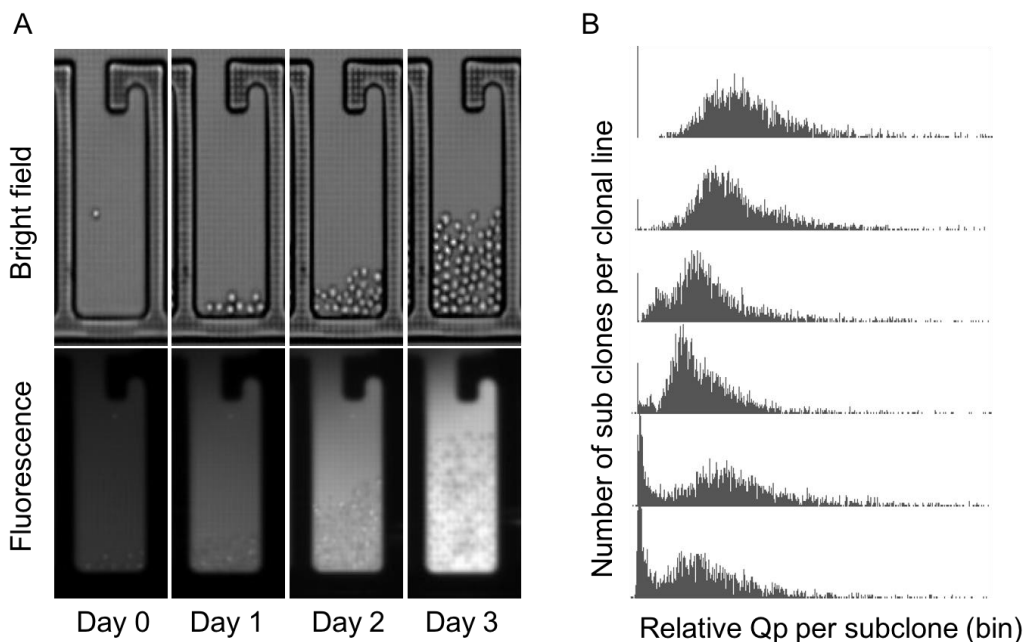


Figure 1. A) Representative image of a clone growing in a single nanobioreactor over the course of 3 days (top). The bottom shows the fluorescent assay used to quantify the steady-state concentration of antibody being produced over time as the clone grows. B) Histograms for six different clonal lines where the relative production was normalized to the size of each clone after 4 days of culture. The result measurements from over 3500 clones studied in less than 5 days is shown here.