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MICROFLUIDIC ACCELERATED EVALUATION OF CHO CELL CLONES BY PERFUSION OF FED-BATCH CONDITIONED MEDIA

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The generation of genetically engineered production CHO cell lines is normally the longest step in the race to scale-up protein manufacturing. This labor-intensive screening includes the expansion of hundreds of clonal cultures to sufficient numbers for their growth and productivity to be evaluated. Unfortunately, many clones that perform well when screened at the batch cloning stage display reduced performance under fed-batch conditions. Thus, screening potential clones under conditions more similar to the ultimate production cultures provides an opportunity for more effective clone selection.

We combined the advantages of precise measurements in microfluidic nL volume cultures with our ability to modify the medium during cultures where clones are retained in thousands of isolated chambers. Our bead assay coupled with an automated image analysis pipeline quickly and reproducibly detected as little as 10^6 human IgG molecules in 4 nL chambers after 2 h of incubation. Thus, it is possible to evaluate the production of a single high performance CHO cell at the very start of the microfluidic culture. To further evaluate the performance of CHO-S clones under production conditions, we perfused media from untransfected parental CHO-S fed-batch cultures into the microfluidic device daily. This conditioned medium perfusion technique was developed using an automated robotic 24-well deep well plate culture system to demonstrate that clones in perfused fed-batch medium matched the growth profiles and specific productivities of those in larger scale fed-batches. This was replicated for multiple clonal CHO-S and CHO-K1 cell lines. Analysis of both the growth rate and productivity of the microfluidic cultures enabled the screening of hundreds of cultures in parallel under simulated fed-batch conditions. The dynamic nature of our microfluidic assay coupled with the perfusion of conditioned medium in nanoliter volumes enables more rapid and effective characterization of clonal CHO cell performance, thereby accelerating progress towards the manufacturing of valuable products.