A SCALE-DOWN MODEL TO INVESTIGATE CELL RETENTION FOR CONTINUOUS MONOCLONAL ANTIBODY MANUFACTURE

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The use of monoclonal antibodies (mAbs) as therapeutic agents is expanding rapidly. A shift towards continuous processes, with the use of perfusion systems, is taking place for more efficient and lean manufacturing. Scale-down tools to inform bioprocess discovery, optimise scale-up operation and evaluate the impact of perfusion on the subsequent downstream is required. While quasi-perfusion (i.e., repetitive media exchange in batch mode overall several days of harvest) has scale-down models established in well-plates, tubes and flasks, most of these studies focus on cell line development, media screening and mAbs production rates. Little attention has been placed on the impact of cell retention devices on perfusion processes. Alternating tangential flow filtration (ATF) and tangential flow filtration (TFF) are the most commonly used cell retention systems. The main components of these systems which may affect cell retention performance are the membrane filter and recirculating pump for the transfer of material between bioreactor to filter. However, the study of these components using current scale-down methods is difficult because typical scale-down quasi-perfusion perform the media exchange through cell centrifugation and resuspension. These do not capture the elements of cell retention devices at larger scale operation that uses ATF or TFF. Previous studies have highlighted that process shear is a major source of the difference in fouling between TFF systems. Thus, characterization of the cell retention device and optimisation of filtration operation is required in terms of recirculation rates, and their corresponding shear stresses, and the selection of membrane filters which are frequently described as process limiting factors. To this end, this presentation will showcase results of a proposed perfusion scale-down method with cell retention characterisation. Quasi-perfusion in shake-flasks was established up to 12 days with varied upstream conditions (e.g., daily bleed rate, media). The viable cell densities achieved were greater than 40 million cells per mL, which are similar to the published cell densities obtained in some perfusion bioreactors. Filterability studies were performed over the course of quasi-perfusion cell culture on cell culture samples and the harvested supernatant (before media exchange). The aim was to determine the impact of these materials on filter fouling as the perfusion process progresses. Figure 1 shows an example filtration profile over 10 days using 0.22-micron filter. The effect of shear on the filterability of the daily supernatant harvest demonstrates how cell retention devices may be affected by the changes in the cell's sensitivity to shear during perfusion. For example, the filterability of the supernatant harvest in Day 7 has reduced by 26% due to shear and this reduction has increased to 61% by Day 10 (Figure 2).

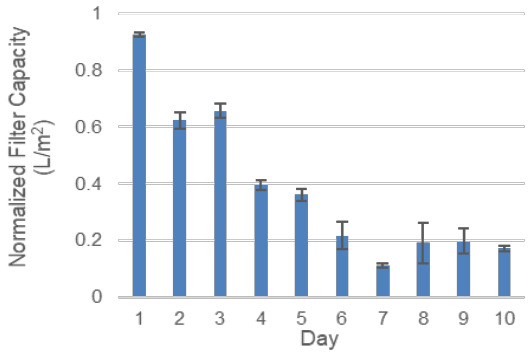

Figure 1- Supernatant filtration profile from ultra scale-down experiments over the course of a quasi-perfusion in flask. n=4. Error bars are ± 1 SD.

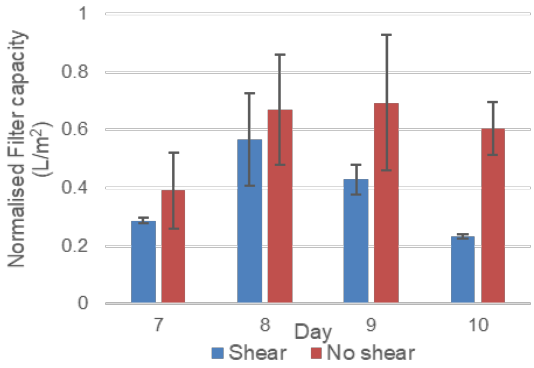

Figure 2- Impact of shear on filterability of clarified cell culture. Data in red (no-shear) are the same data in Figure 1 days 7 to 10. For the blue columns, n=2; error bars are ± 1 SD.