ERBI BIOSYSTEMS – CELL THERAPY PROCESS DEVELOPMENT WITH A 2 ML CONTINUOUS PERFUSION BIOREACTOR

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With five chimeric antigen receptor (CAR) T cell immunotherapy products currently approved by the FDA for the treatment of hematological cancers, there are increasing efforts to develop novel and better manufacturing technologies and processes for cell therapies to improve efficacy, reduce variability, and reduce cost. Knowledge in the field about how to optimize cell expansion for consistent and reproducible cell-based treatments is improving, but major challenges still exist in experiment reproducibility and robustness during process development. For autologous processes, donor variability and differences between healthy donor-derived versus patient-derived material can confound experiment results. Materials are also costly, including peripheral blood mononuclear cells (PBMCs), growth factors, viral vectors, and serum or chemically defined media. Therefore, process development experiments in cell therapy are typically done in milliliter sized, often static culture with minimal environmental control. While these systems can generate data quickly, the lack of control and monitoring can result in variabilities that may prove difficult to translate to larger culture systems. To address this gap, Erbi Biosystems has developed the Breez™ True Perfusion™ bioreactor. This fully closed sterile single-use perfusion bioreactor operates at a 2 mL working volume and can operate outside of a biosafety cabinet to replicate bench scale perfusion processes to industrially relevant cell densities in excess of 100e6 cells/mL. The advanced microfluidics, including bubble free mixing, on-line cell density monitoring, and automated dO/pH control allow the Breez™ to achieve excellent cell growth in a 2 mL scale, reducing labor and bench space required. By introducing a milliliter scale perfusion reactor, material from a single patient can be used for many bioreactor experiments, enabling process development under controlled conditions. Using the Erbi Breez™ bioreactor, we have demonstrated equivalent performance to a static 24-well G-rex for expansion of CAR-transduced T cells when supplying the same total volume of media, with similar phenotypes at the end of a 14-day culture. We then explore the advanced capability provided by the Breez™ automated perfusion system to perform in-place activation, transduction, and expansion. We show that with improved media exchange rates, cell expansion performance is improved, achieving nearly patient dose levels with more than 400-fold expansion from 0.6 million cells at the point of transduction to more than 200 million cells at 14 days post-transduction at consistently high cell viability of above 95%. This is in contrast to maximum viable cell density (VCD) in the range of 10e6 cells/mL for the 24-well G-rex, with a similar total media volume consumed to total cell number ratio. Initial transduction efficiency was comparable between the bioreactor (without transduction enhancer) and spinoculation on a retronectin-coated 24-well plate. Additionally, on-line data showing optical density, pH, and dissolved oxygen will be presented, providing insight into the metabolic state of cells during culture. These data show that the Breez™ platform is well suited for cell therapy process development and process characterization studies and having already demonstrated cell doses nearly sufficient for patient infusion, may be a promising future production platform.