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Development and Optimization of a Novel Centrifugal Bioreactor with a Real-Time Monitoring Sensor for T Cell Exhaustion with Applications in Cancer Immunotherapy

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Cancer has been one of the most significant and critical challenges in the field of medicine. It is a leading cause of death both in the United States and worldwide. Common cancer treatments such as radiation and chemotherapy can be effective in destroying cancerous tissue but cause many detrimental side effects. Thus, recent years have seen new treatment methods that do not harm healthy tissue, including immunotherapy. Adoptive cell therapy (ACT) is one form of immunotherapy in which patients' immune cells are modified to target cancer cells and then reintroduced into the body. ACT is promising, but most current treatments are inefficient and costly. Widespread implementation of ACT has been a difficult task due to the high treatment cost and inefficient methods currently used to expand the cells. Additionally, if the manufacturing process is not carefully controlled, it can result in the cells losing their cancer-killing ability after expansion. To address the need for an economically feasible culture process to expand immune cells for immunotherapy, our laboratory has designed a centrifugal bioreactor (CBR) expansion system. The CBR uses a balance of centrifugal forces and fluid forces, as shown in Figure 1, to quickly expand infected CD8+ T-cells from a bovine model up to high population densities. With other applications, the CBR has achieved cell densities as high as 1.8×10^8 cells/mL over 7 days in an 11.4-mL chamber. For this study, our goal is to begin validating the CBR by optimizing the growth of CEM (human lymphoblastic leukemia) cells, which are similar cell to cytotoxic T lymphocytes (CTLs). This can be accomplished by measuring kinetic growth parameters based on the concentrations of glucose and inhibitory metabolites in the culture. We hypothesize that by designing a kinetic model from static culture experiments, we can predict the parameters necessary to achieve peak CEM and eventually CTL growth in the CBR. We will report on kinetic growth studies in which different glucose concentrations are tested, and a maximum specific growth rate and Monod constant determined, as well as studies where varying levels of the inhibitory growth byproducts, lactate and ammonium, are added to the culture and critical inhibitor concentrations are determined. Another recent conceptual development for the design of the CBR is a real-time monitoring and feedback control system to regulate the cellular environment, based on levels of surface co-receptors and mRNA signaling within the culture. Prior studies have pinpointed T cell exhaustion as a significant issue in achieving successful immunotherapy, particularly in treatments for solid tumors; T cell exhaustion occurs during a period of chronic antigen stimulation when the cells lose their ability to target and kill cancer cells, currently theorized to be associated with particular inhibitory receptors and cytokines in the immune system. Designing a system with a fiber optic sensor that can monitor the cell state and use feedback control to regulate the pathways involved in producing these receptors will ensure the cells maintain cytotoxic properties during the expansion process within a Centrifugal Fluidized Expansion we call the CentriFLEX. In this presentation, we will also report on early results from development of this exhaustion monitoring system. In brief, achieving optimal kinetic models for the CBR system and methods to prevent T cell exhaustion has the potential to significantly enhance culture efficiency and availability of immunotherapy treatments.

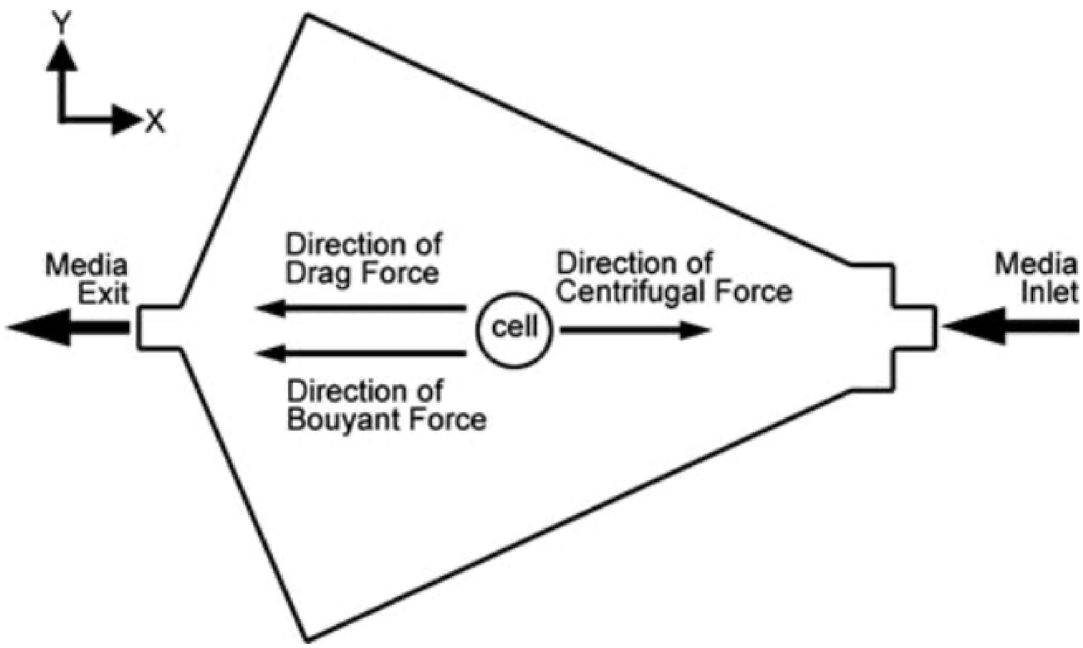

Figure 1: Balance of forces in the CBR’s cell chamber.