Determining Kinetic Parameters for a Mathematical Model to Optimize Growth of Cancer-Fighting T Cells in a Novel Bioreactor

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T cell transfer immunotherapy is a highly effective cancer treatment in which the immune system's inherent ability to fight cancer is amplified by increasing the amount of T cells that are deemed most active within a patient. T cells are a lymphocyte produced as an immune response to cancerous cells. Despite this advanced form of biological therapy, current T cell expansion methods are inefficient, resulting in high manufacturing costs, which brings question to the efficacy of T cell therapies. To address this issue, the recent development of a centrifugal bioreactor aims to rapidly expand T cells for cancer immunotherapy treatments at higher cell densities and in a shorter amount of time compared to current systems on the market. We hypothesize that by producing a mathematical model of a proof-of-concept T cell line to determine substrate consumption and metabolite production over time, we will be able to optimize growth of the cell line in the bioreactor. A series of three studies were performed to produce the growth model: (1) measuring yield coefficients of lactate, ammonium ion, and glucose, (2) determining the Monod constant and maximum specific growth rate, and (3) finding critical metabolite concentrations. To measure yield coefficients, T cells were grown in a 6-well plate at 1×10^5 cells/mL in 4 mL of medium with 100 uL samples taken and frozen each day over a 5-day period. At the end of the study, samples are thawed and used with lactate and ammonium assay kits for microplate reading to determine metabolite levels over time. To determine the Monod constant and maximum specific growth rate, T cells were grown in 12-well plates at pre-calculated varying glucose concentrations in 4 mL of medium in triplicates. Cells were counted for a minimum of six days to determine expansion over time to develop a linearized growth plot. To find critical metabolite concentrations, ammonium and lactate were added to glucose-free T cell medium at four different concentrations in triplicates utilizing a 12-well plate with a seeding density of 1×10^5 cells/mL in 4 mL of medium. The T cells then remained undisturbed in culture and were counted on day three. Once all parameters are determined, we can apply them to the growth model to determine levels of glucose, lactate, and ammonium as the T cells grow to high densities in the bioreactor and, as a result, optimize the manufacturing process for cancer immunotherapy treatments.

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