DEFINING CELL CULTURE DYNAMICS IN RESPONSE TO GROWTH FACTOR PROVISION FOR EFFICIENT OPTIMIZATION OF CELL BASED THERAPIES

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The design of processes to manufacture Cell Based Therapies (CBTs) is particularly challenging due to the dynamic cell culture environment and the complex response of the cell product. An approach to process design needs to achieve a balance between resource spent and process knowledge gained to meet manufacturing goals around cost, quality and risk. In order to address this, we developed a parsimonious mathematical modelling framework designed to allow representation of common mechanisms in cell culture, and associated process operations, that drive cell culture outcomes[(1)]. We propose that this framework can be applied to generate widely applicable 'template models' and experimental strategies for process optimization. In this case we have demonstrated the application to define provision rates of elements that support cell growth in a hematopoietic culture system (erythroblasts). Building on a model that defined the influence of environmental change (incorporated as a single non-specific variable linked to cell growth and density) on population growth[(2)], we have defined the cell culture dynamics in response to specific elements such as growth factor provision. We have shown how achieving the correct combination of delivery rates of growth factors with other factors (e.g. metabolic) can ensure that each is used with maximal efficiency, significantly driving down volume use (more than 3-fold) and process supplementation costs. The models also define the corollary of such intensification in terms of increasingly demanding process control with respect to volume handling and process timing; however, an advantage of the level of intensification achieved is that the system oxygen demand increases to a level that oxygen input rates can be used to identify cell growth-inhibition in advance of reduced viability. This work demonstrates that models that appropriately represent common process dynamics will be a key tool to achieve the risk and cost reduction required for CBT manufacture.

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