DYNAMIC MECHANISTIC MODELLING AND CONTROLLED GROWTH FACTOR DELIVERY FOR OPTIMISATION OF SCALABLE HAEMATOPOIETIC CELL PROCESSING

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Cell culture is a complex and dynamic process. Efficient optimisation of economic production, process risk and product quality requires an integrated approach comprising both experimentation and modelling; dynamic mechanistic models offer the benefits of a mechanistic understanding of processes and can potentially predict counter-intuitive outcomes over extended time periods. Further, cost and control optimisation also requires appropriately scaleable production systems with discrete control of potent and costly signalling factors. Haematopoietic cultures are ideal systems to develop such approaches; suspension culture ensures compatibility with scaleable well controlled platforms and high frequency cell sampling for high resolution time series. Haematopoietic cultures also have high clinical potential from haematopoietic stem cell transplants to manufactured red cells, platelets or immunotherapies.

Dynamic mechanistic models are underutilised in the bioprocess community partly due to the skills barrier to entry. A multidisciplinary collaboration has designed a software interface for the description, testing and manipulation of hypothetical mechanistic dynamic models. The approach aims for parsimonious, and hence testable, models built on the dominant phenomena involved in cell culture (e.g. substrate-dependent growth, cell death). We have demonstrated the application of the software in the context of a hypothesis-driven programme of research to determine the productivity limits of human erythroblast culture from cord blood CD34+ cells; the software enabled a team of biologists to develop a low parameter predictive deterministic model of the effects of medium supply and cell density control strategies on erythroblast growth that could optimise cells/$ production for any given facility time and medium volume cost. Relatively small shifts in strategy had greater than 3-fold impact on cost and substantially changed the impact of imprecision in timing of process operations. We have further demonstrated how the software and models are complementary to a novel immobilised growth factor technology for scaleable haematopoietic expansion. Immobilisation of multiple haematopoietic factors on magnetic beads increases the dimensions of control in the culture system and decouples growth factor dynamics from basic medium supply. Further, immobilised factors are shown to be orders of magnitude more potent than their soluble counterparts and remain functional under mechanically mixed, and hence scalable, conditions. Such increased control opportunities and system intensification will increase the potential benefit and power of mechanistic modelling approaches in manufacturing of cell based therapies.