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Development of a perfusion bioreactor for the 3D physiological culture and targeted differentiation of embryonic stem cells

Wednesday, November 13, 2013
2:15 p.m.
101 Goergen Hall

Over the last quarter of a century there has been an emergence of a tissue engineering industry, one that has now evolved into the broader area of regenerative medicine and includes the culture of stem cells. Alas, stem cell bioprocessing lags behind the established bioprocess industries and practices of microbial and mammalian cell cultures in terms of control, standardisation, optimisation, and cost-effectiveness (productivity). Even though product quality (cells) is well-established, process parameters and requirements remain fundamentally empirical and their control rudimentary. Furthermore, "functionalization" of the cellular product is currently missing and critical mechanical, electrical, and structural signals are excluded. The pitfalls of stem cell culture will be discussed by evaluating "natural" versus "engineered" culture methodologies. Specifically, a novel, automatable and scalable, perfusion bioreactor will be presented, which features continuous supply of nutrients and removal of metabolic wastes alongside high gas exchange and enhanced mass transport. Perfusion overcomes the metabolic stress experienced by ESCs cultured under fed-batch conditions resulting in enhanced cell expansion of "high stemness" ESCs as determined by 2-fold increase in Dppa3 (pluripotency gene) and a 3-fold down-regulation of Fgf5 (indicative of spontaneous differentiation). 3D mineralized cellular constructs were successfully produced that were superior to those generated in fed-batch systems in terms of osteogenic gene expression, mineralization, hydroxyapatite deposition, and mechanical strength of the cellular constructs. A pilot rabbit animal study confirmed the de novo synthesis of bone at the centre of a critical size cranial defect and demonstrated neovascularisation. Finally, the recent development of the bioreactor to deliver mechanical stimulation using ultrasound, which resulted in enhanced osteogenic differentiation via the bmp-2 pathway will be presented.