EFFECTS OF CULTURE MEDIA AND SUSPENSION EXPANSION TECHNOLOGIES IN MESENCHYMAL STEM CELL MANUFACTURING – A COMPUTATIONAL BIOPROCESS AND BIOECONOMICS STUDY

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Mesenchymal stem cell (MSC) based therapies are promising for a large spectrum of unmet medical needs. Despite this promise, the scaling-up of production of clinical grade MSCs is hindered by the use of planar technologies that require intensive labor and are not enough to meet market demands, as well as due to high product and process variability introduced by the use of xenogeneic materials. This work presents a new bioprocess and bioeconomics model of stem cell expansion to support informed decisions for stem cells process scaling up at reduced annual costs. The intrinsic equations and parameters that capture the cell biological features, according with their source and media used, are embedded in the model. A target number of cells per dose of 140 million and a GMP facility of 400 sq mt with 4 BSCs and 8 incubators will be used as the baseline for expansion of both bone marrow MSCs (BM-MSCs) and adipose stem cells (ASCs) using planar expansion technologies. The current standard medium for MSC culture containing fetal bovine serum (FBS) will be compared with the xeno-free alternative of human platelet lysate (hPL). The use of hPL for both cell sources results in an increase of the number of doses produced and a decrease of the cost of goods (CoG) per dose (Table 1). In order to improve the production capacity, 8 bioreactors with capacity up to 50L were input in the model, using xeno-free plastic microcarriers for cell adhesion and hPL as the culture medium. The model results indicate that the investment in the use of suspension cultures is valuable due to a considerable increase in the production and a decrease of CoG/dose. As the number of doses produced per year increases, the reagent costs dominate relatively to the facility costs (Fig. 1). Sensitivity analysis was performed by varying 11 model variables by +/- 33%. The main factors that influence annual capacity and CoGs are related to harvesting density and yield, growth rates and microcarrier area and concentration (Table 2). These findings may be used to improve the design of expansion methods with fully xeno-free materials and highlight the relevance of the optimization of harvesting and downstream processing protocols.

Table 2 – Top 3 most influential factors on the model outputs by factor value variation by +/- 33% of the nominal value

Planar		Suspension	
Doses/year (%)	**CoG/dose (%)**	**Doses/year (%)**	**CoG/dose (%)**
Growth rate (57%)	Harvest yield (47%)	Harvest yield (33%)	Harvest yield (42%)
Harvest density (38%)	Growth rate (41%)	Microcarrier area (30%)	Microcarrier area (38%)
Harvest yield (35%)	Harvest density (40%)	Microcarrier concentration (30%)	Microcarrier concentration (38%)

Table 1 – Number of doses produced annually and cost of goods per dose for the three expansion protocols and two cell sources

	BM-MSCs		ASCs	
	Doses/year	CoG/dose ($)	Doses/year	CoG/dose ($)
FBS (P)	240	4023.49	200	5693.06
hPL (P)	400	3693.38	768	2412.08
hPL (S)	1520	1784.26	5280	890.76

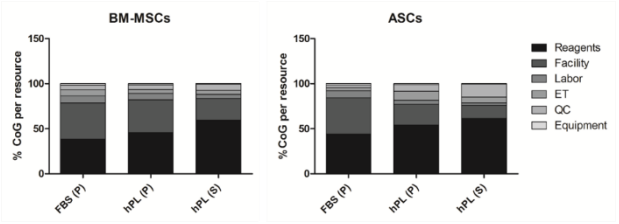

Fig 1 – Cost structure breakdown per resource

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