Allogeneic cell therapy process economics for successful development, manufacture and commercialisation

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Project Partners & Acknowledgements

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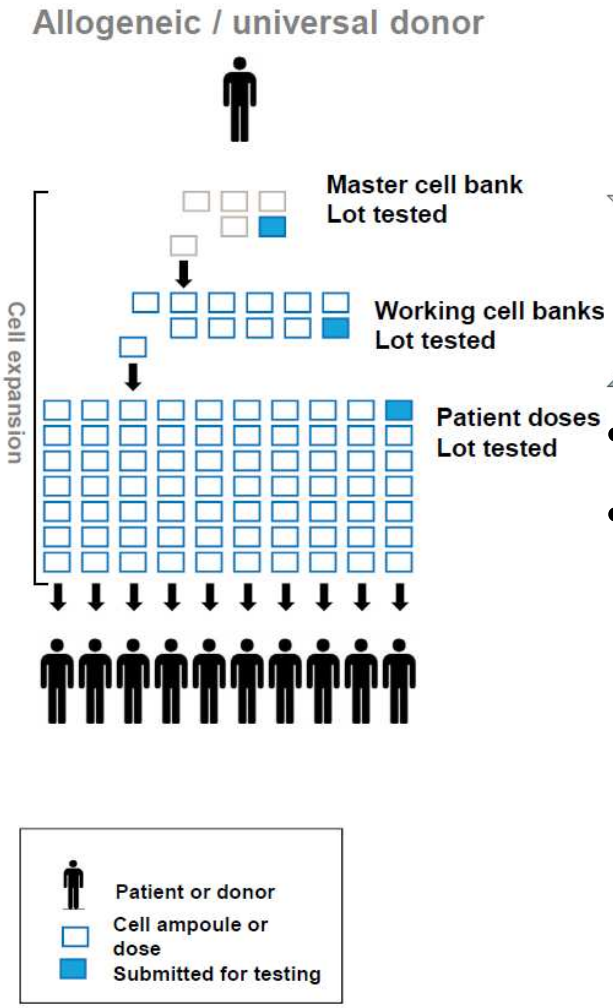
- ❑ Lonza Biologics — Kim Warren, Dave Smith, Behzad Mahdavi, J Zurdo
- ❑ UCL Biochemical Engineering — Suzanne Farid, Chris Mason
- ❑ UCL Mgt Science & Innovation — Simcha Jong, Hsini Huang
- ❑ London Regen Med Network — Emily Culme-Seymour

BRITS Project Funding: Technology Strategy Board, Lonza Biologics

Challenges for *Allo* Cell Therapy (CT) Manufacture



- Several CT failures attributed to manufacturing*:
  - High cost of goods (COG), process variability, loss of clinical efficacy upon scale-up, inadequate characterisation

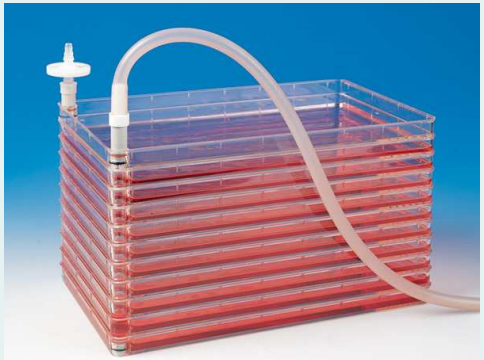
How can cell therapies achieve the manufacturing success of protein biopharmaceuticals?

- 'Allo' CTs: Product-driven business model
- Unique manufacturing & supply chain issues:
  - Limited large-scale bioprocessing options
  - Adherent culture, cells from healthy donors
  - Serum-containing cell culture media
  - Single-use technologies essential
  - Poorly automated, labour-intensive, open
  - Fresh / cryo products
  - Costly cold-chain transportation
  - Point-of-use care

Image source: Lonza

**Source: Brandenberger et al, Bioprocess Intnl, March 2011 Supplement*

USP Challenges for Cell Therapy Manufacture

	mAbs	Cell therapies (MSCs)
Technologies used in clinical / commercial batches	Bioreactors 	10-layer vessels 
Dose per admin	100-2000 mg	100 K – 1 B cells
Annual demand	100-1000 kg	1 B – 100 T cells
Cell culture yield	1-5 g/L	25,000 cells / cm^2
Scale required @ max. demand	**6 x 10,000 L SS 6 x 2,000 L SUB**	**100,000 (!) x 10-layer vessels**
	But can only handle	**50-100 x 10-layer vessels / batch**

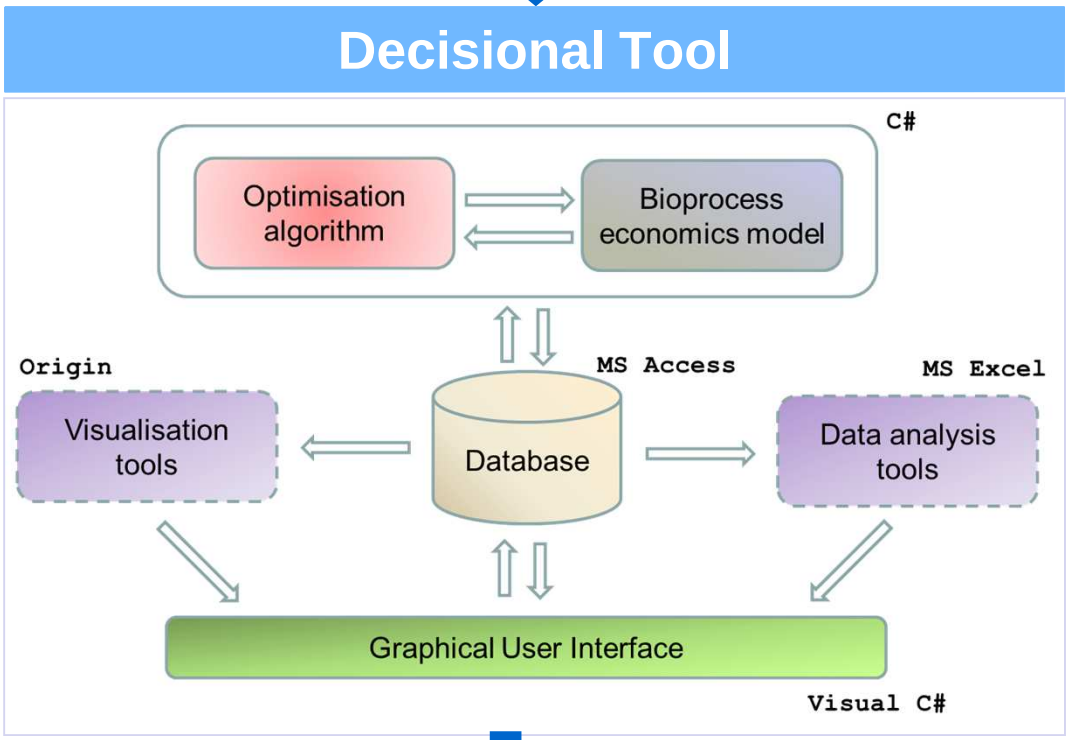
Decisional Tool For Cell Therapy Manufacture

Aim: Create a decisional tool to identify the optimal technologies for commercial cell therapy bioprocesses and the technical innovation required to realize their potential

Cell type **Demand** **Technology options** **Process /Facility/Cost parameters**

Decisional tool integrated:
- Process economics
- Optimisation
- Visualisation

Case study scope:
- Allogeneic manufacture
- Optimal USP & DSP kits
- Current technology gaps
- Performance targets



Optimal USP & DSP strategy for each demand
COG/dose & COG breakdowns

Case Studies: Cell Therapy Bioprocess Economics

Allogeneic single-use cell expansion decisions

(Simaria et al, 2014)

- Scenario: New build for commercial allogeneic cell therapy manufacture
- Impact of dose, demand, lot size on optimal USP technology

Allogeneic single-use volume reduction decisions

(Hassan et al, 2015)

- Scenario: New build for commercial allogeneic cell therapy manufacture
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Process change impact on drug lifecycle costs

(Hassan et al, 2016)

- Scenario: Switching from planar to microcarrier technology
- Impact of timing of switch and drug development costs on ranking of strategies

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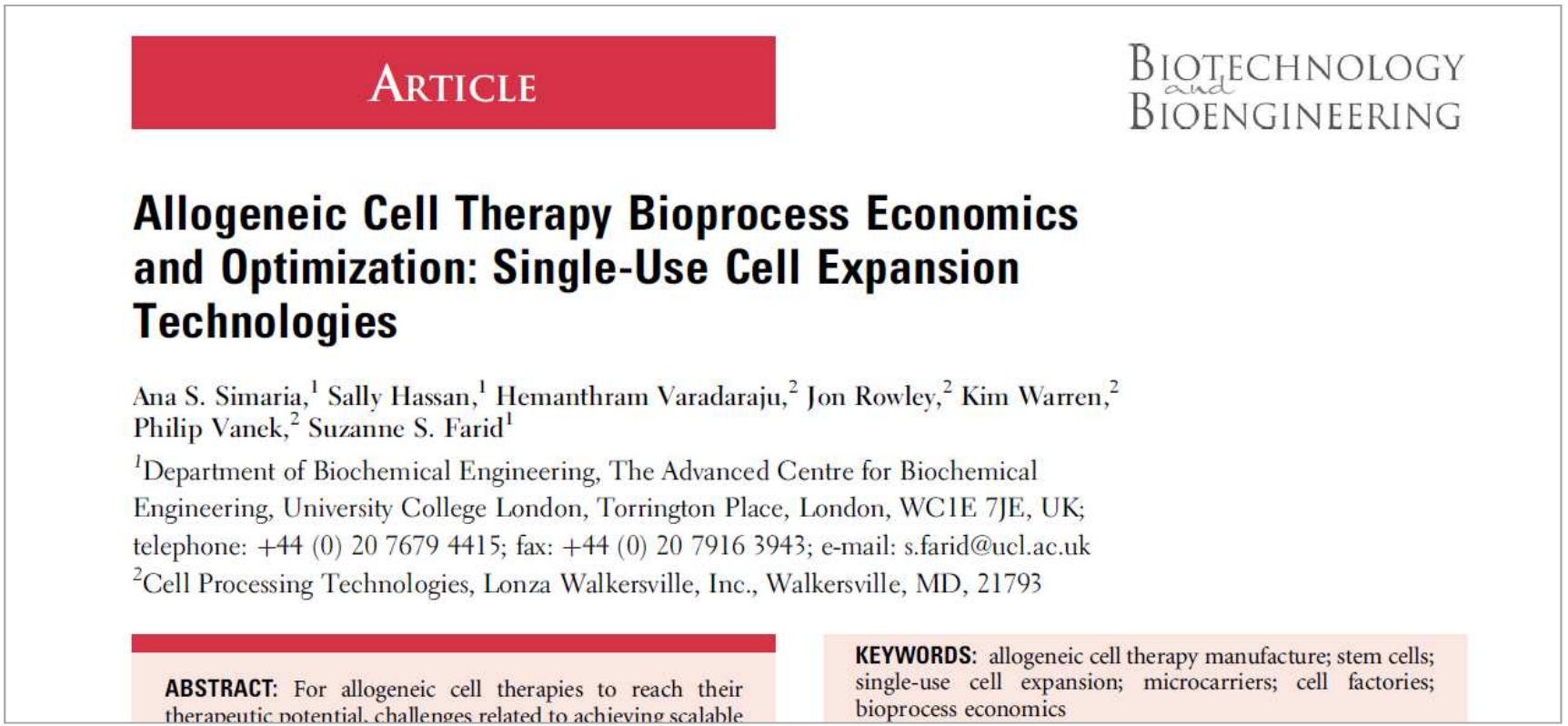

ARTICLE

BIOTECHNOLOGY and BIOENGINEERING

Allogeneic Cell Therapy Bioprocess Economics and Optimization: Single-Use Cell Expansion Technologies

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ABSTRACT: For allogeneic cell therapies to reach their therapeutic potential, challenges related to achieving scalable

KEYWORDS: allogeneic cell therapy manufacture; stem cells; single-use cell expansion; microcarriers; cell factories; bioprocess economics

Case study: Allogeneic cell expansion decisions

Case study setup

Dose: 10^6-10^9 cells

Demand: [1,000-500,000] doses/year

Lot size: [50-10,000] doses/lot

Max nr technology units/lot = 80

Max nr SUBs/lot=8

Lot size (#doses/lot)

Demand (#doses/year) \ Lot size (#doses/lot)	50	100	500	1 000	2 500	10 000
1 000	20	10				
5 000	100	50	10			
10 000	200	100	20	10		
50 000			100	50	20	
100 000			200	100	40	10
500 000					200	50

< 10 lots/year

Nr lots/year

> 200 lots/year

Question:

What is the most cost-effective cell expansion technology for each demand-lot size combination?

- **Candidate cell expansion technologies:**

T-flasks (T)

Multi-layers (L)

Compact multi-layers (cL)

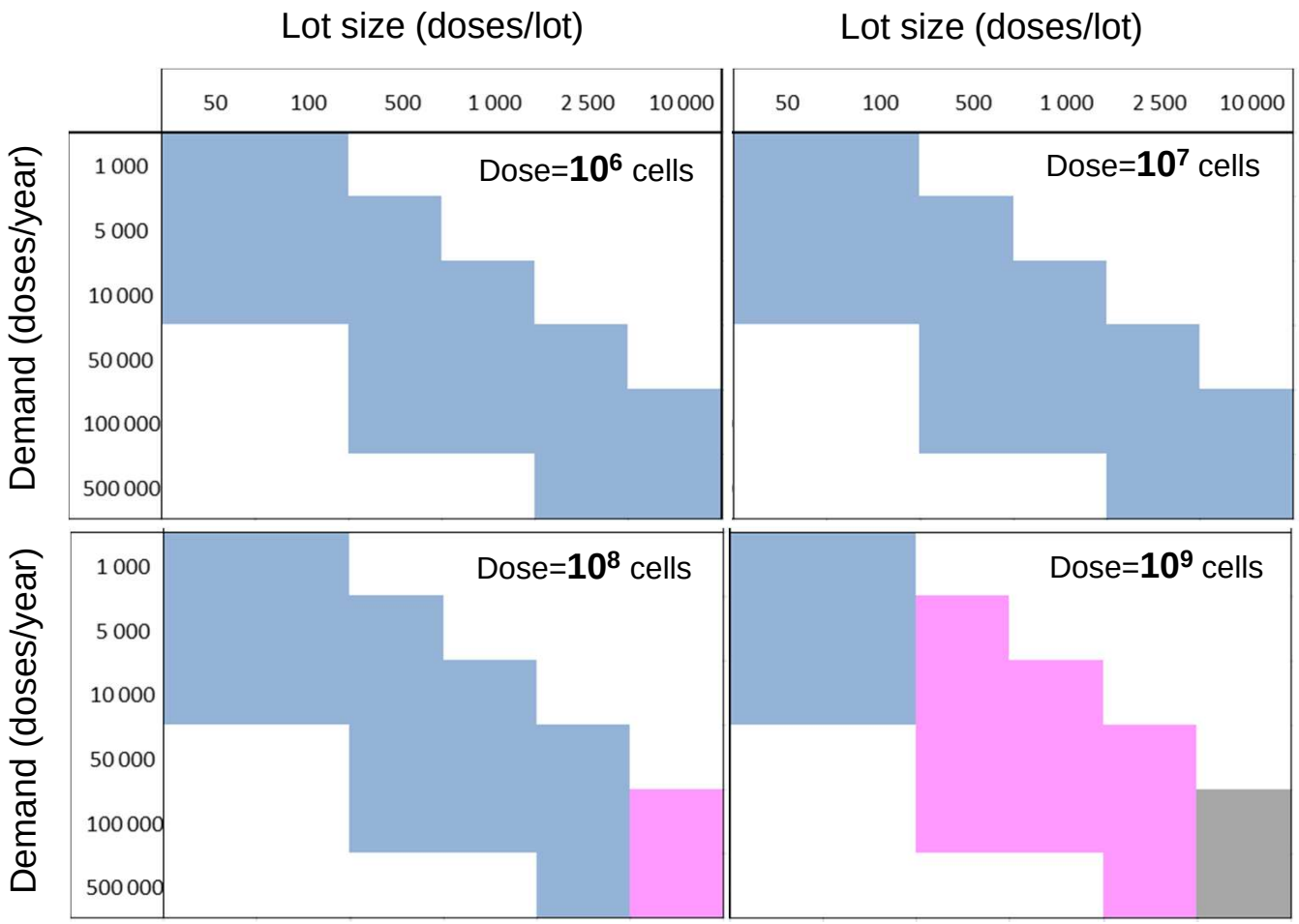
Multi-layer bioreactors (bL)

Hollow fibre bioreactors (HF)

Microcarriers in SUBs (M)

Case study: Allogeneic cell expansion decisions

Results: optimal technologies across demand/lot size matrix and dose



Optimal technologies:

Tool identified where

- planar technologies cease to be feasible
- microcarrier-SUBs become the only option

Gap at higher doses:

Current cells/ml value does not allow making 10^{13} cells/lot

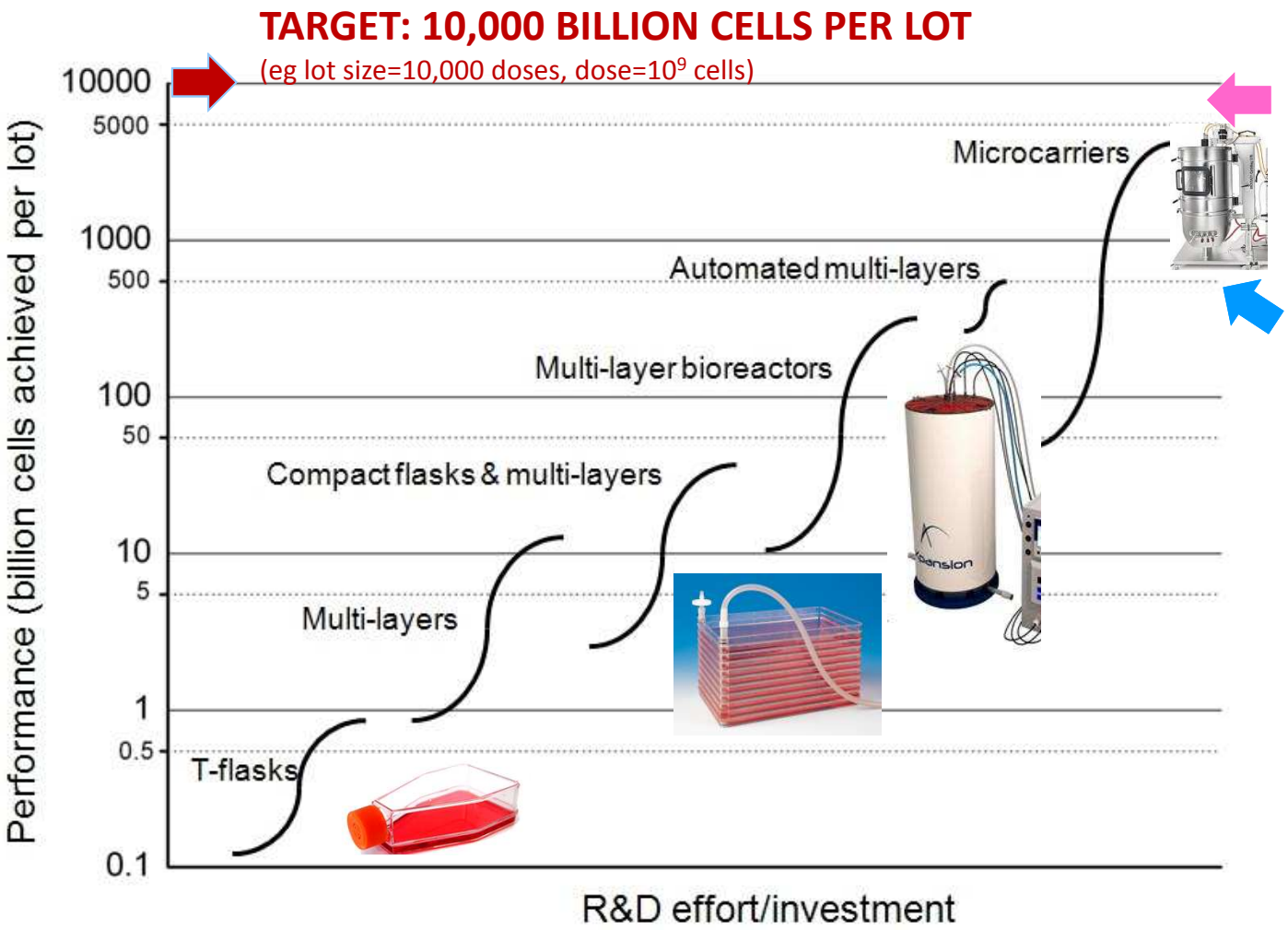
Here, the use of microcarriers was allowed only when the maximum number of units was exceeded for all planar technologies.

Simaria, Hassan, Varadaraju, Rowley, Warren, Vanek, Farid. 2014. *Biotechnol. Bioeng.* 111(1) 69-83

Case study: Allogeneic cell expansion decisions

Technology S-curve for cell therapy manufacture

S-curve illustrates performance limits of each technology



Technology Gap:

Microcarrier-SUBs require x2 increase in performance for high demand scenarios

Planar capacity capped at ~500B cells/lot (MSCs)

Simaria, Hassan, Varadaraju, Rowley, Warren, Vanek, Farid. 2014. *Biotechnol. Bioeng.* 111(1) 69-83

Case Studies: Cell Therapy Bioprocess Economics

Allogeneic single-use volume reduction decisions

(Hassan et al, 2015)

- Scenario: New build for commercial allogeneic cell therapy manufacture
- Impact of dose, demand, lot size on optimal DSP technology

Research Article

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Regenerative Medicine

Allogeneic cell therapy bioprocess economics and optimization: downstream processing decisions

Aim: To develop a decisional tool to identify the most cost-effective process flowsheets for allogeneic cell therapies across a range of production scales. **Materials & methods:** A bioprocess economics and optimization tool was built to assess competing cell expansion and downstream processing (DSP) technologies. **Results:** Tangential flow filtration was generally more cost effective for the lower cells/lot achieved in planar technologies and fluidized bed centrifugation became the only feasible option for handling large bioreactor outputs. DSP bottlenecks were observed at large

Sally Hassan[1], Ana S Simaria[1], Hemanthram Varadaraju[2,3], Siddharth Gupta[2], Kim Warren[2] & Suzanne S Farid*[,1]

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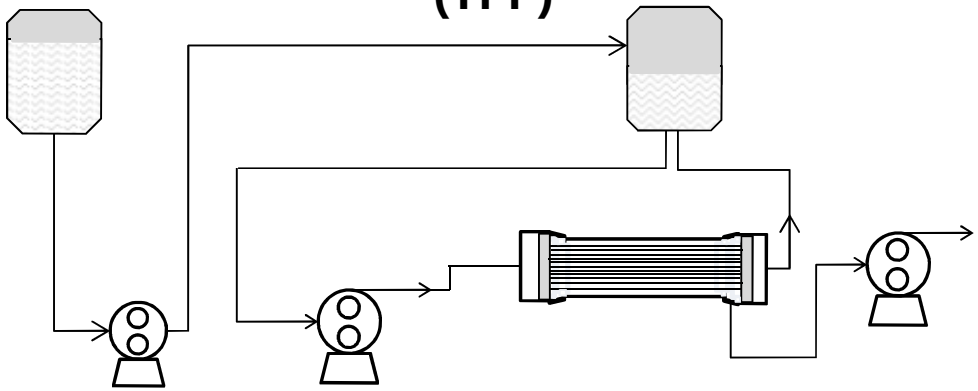
DSP Challenges for Cell Therapy Manufacture

- Current volume reduction processes typically use:
  - Benchtop centrifuges
- Quantities of cells required for commercial products:
  - Doses: 10^5 – 10^9 cells/patient
  - Potential market demands: 10,000 – 500,000 patients /yr
  - Annual cell demand: 10^9 – 10^{14} cells/yr
  - Cells per lot: 10^8 – 10^{13} cells/lot
- **To meet max. demand need 25,000 benchtop centrifuges!**

Case Study: Allogeneic DSP Decisions

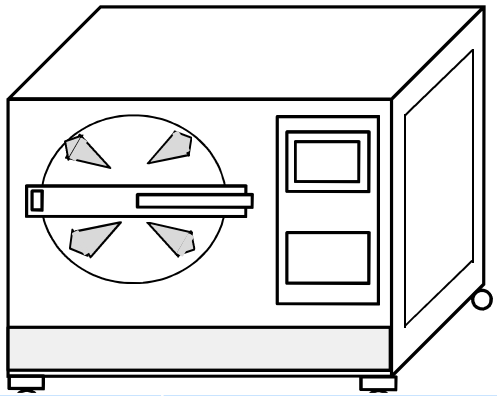
Candidate Volume Reduction Technologies:

Tangential flow filtration (TFF)



TFF membrane area	0.02 - 1.15m^2

Fluidised bed centrifugation (FBC)



FBC chamber volume	1-4 x 100ml chambers 1-6 x 1000ml chambers

Max nr volume reduction units/lot =1
Max volume reduction time = 4 h
Target concentration: 10 M cells/ml

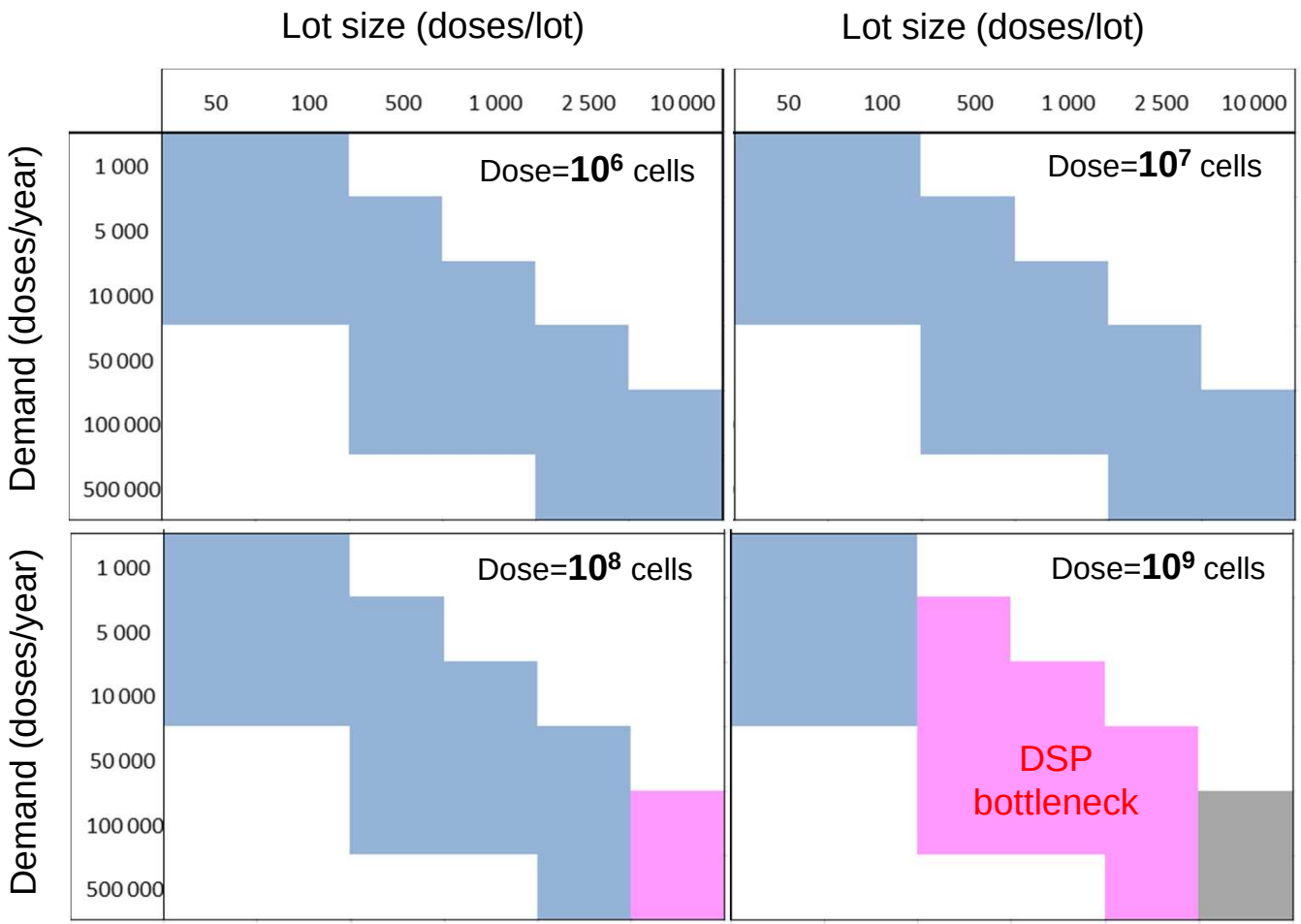
Question:

What is the most cost-effective cell volume reduction technology for each demand-lot size combination?

Hassan, Simaria, Varadaraju, Gupta, Warren, Farid. 2015. *Regen Med* 10 (5), 591-609.

Case study: Allogeneic DSP decisions

Results: optimal technologies across demand/lot size matrix and dose



Gap at higher doses:
For large lot sizes bottleneck hits DSP before USP

For microcarrier-SUBs, no DSP technology meets limit on number of units without debottlenecking efforts

Hassan, Simaria, Varadaraju, Gupta, Warren, Farid. 2015. *Regen Med* 10 (5), 591-609.

Case study: Allogeneic process decisions

Cost of goods as %sales

- Typical biologics COG = 15% sales
- Assumption: cell therapies will have similar gross margins to biologics

*Assumption: reimbursement value of $40K/dose @dose=$10^9$cells, 50 doses/lot, demand = 10,000 doses/y

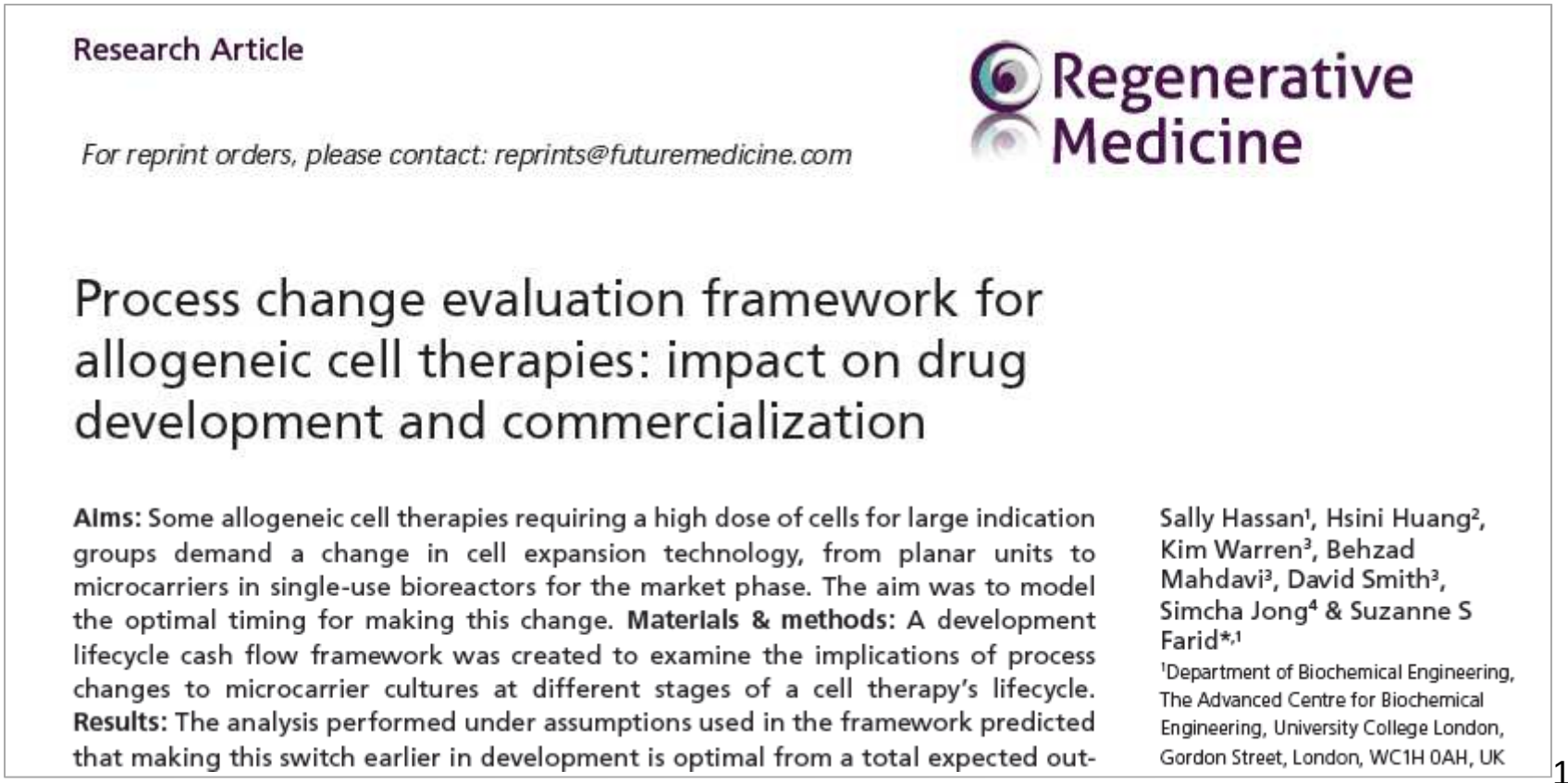
Simaria et al., 2014. *Biotechnol Bioeng*; Hassan et al. 2015. *Regen Med*

Case Studies: Cell Therapy Bioprocess Economics

Process change impact on drug lifecycle costs

(Hassan et al, 2016)

- Scenario: Switching from planar to microcarrier technology
- Impact of timing of switch and drug development costs on ranking of strategies



Research Article

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Regenerative Medicine

Process change evaluation framework for allogeneic cell therapies: impact on drug development and commercialization

Aims: Some allogeneic cell therapies requiring a high dose of cells for large indication groups demand a change in cell expansion technology, from planar units to microcarriers in single-use bioreactors for the market phase. The aim was to model the optimal timing for making this change. **Materials & methods:** A development lifecycle cash flow framework was created to examine the implications of process changes to microcarrier cultures at different stages of a cell therapy's lifecycle. **Results:** The analysis performed under assumptions used in the framework predicted that making this switch earlier in development is optimal from a total expected out-

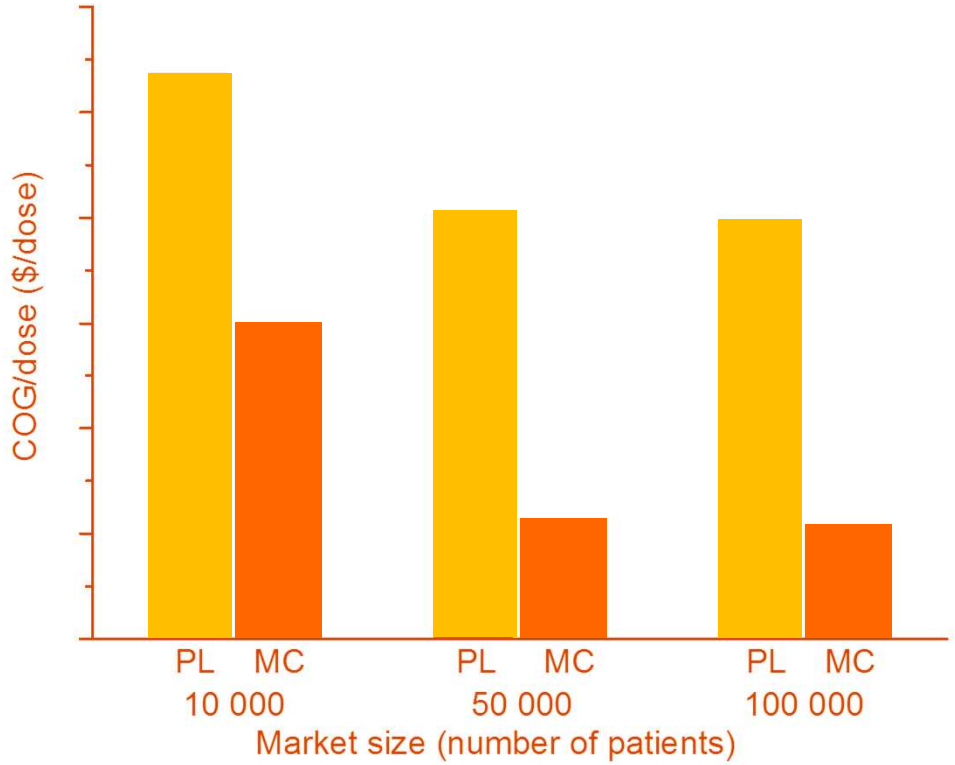
Sally Hassan[1], Hsini Huang[2], Kim Warren[3], Behzad Mahdavi[3], David Smith[3], Simcha Jong[4] & Suzanne S Farid*[,1]

[1]Department of Biochemical Engineering, The Advanced Centre for Biochemical Engineering, University College London, Gordon Street, London, WC1H 0AH, UK

Case study: Process change decisions

Planar v Microcarriers: COST OF DEVT v COG savings

Microcarriers: **45-75% COG savings (Commercial scale)**



Will the COG savings outweigh the COST OF DEVT?

PL = planar technology
MC = microcarriers in SUBs
Cell type: MSCs. Example dose: 2×10^8 cells

Hassan, Huang, Warren, Mahdavi, Smith, Jong, Farid. 2016. *Regen Med* 11(3), 287-305

Case study: Process change decisions

Technologies used in each phase and case

- Scenario: Switching from planar to microcarrier technology
- Impact of timing of switch and drug development costs on ranking of strategies

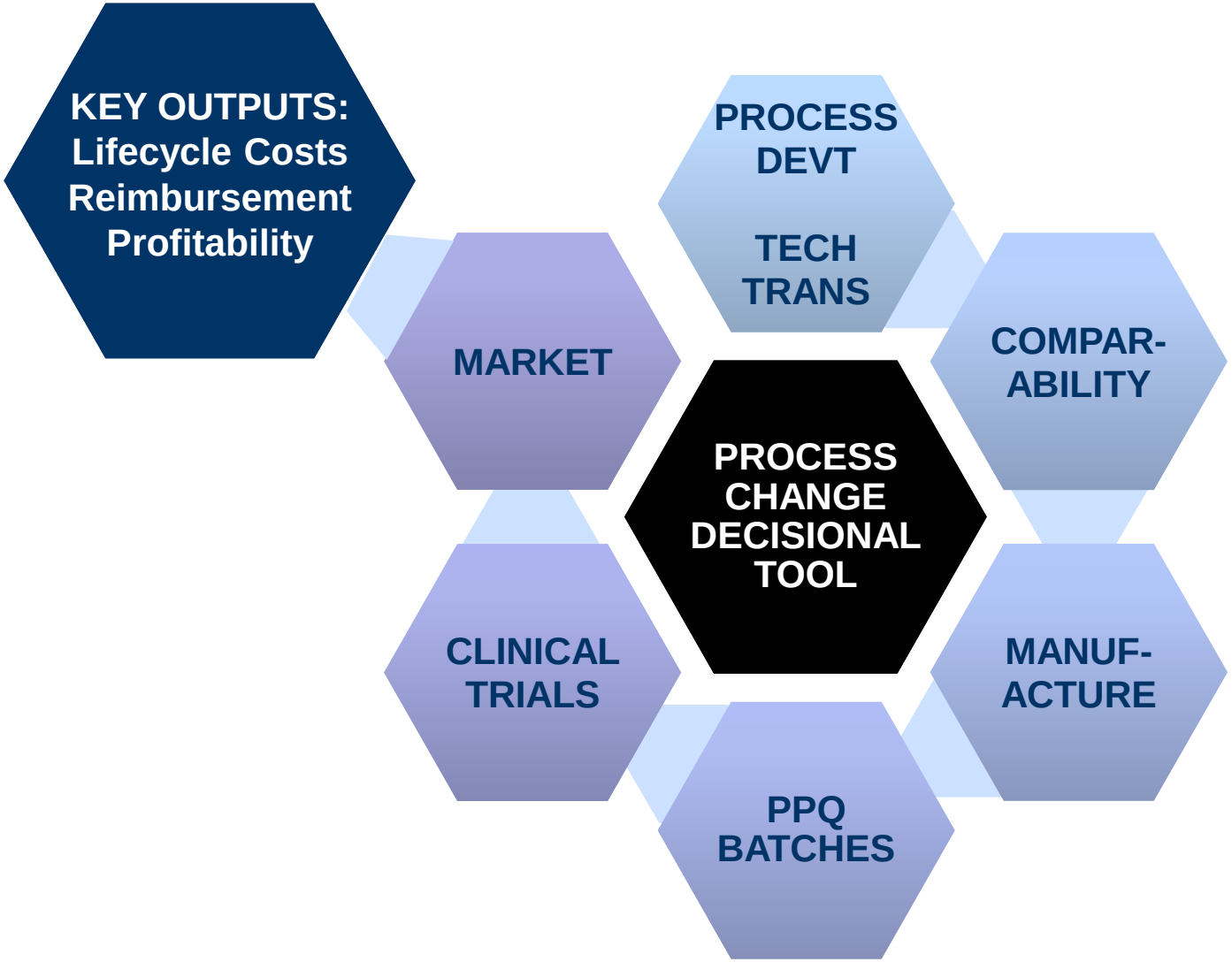
		Phase I	Phase II	Phase III	Market
Planar technologies throughout	PL	CF-10	CF-10	CF-40	CF-40
Change to MC-SUB post-approval	MC-PA	CF-10	CF-10	CF-40	MC-SUB
Change to MC-SUB at Phase III	MC-P3	CF-10	CF-10	MC-SUB	MC-SUB
Change to MC-SUB at Phase II	MC-P2	CF-10	MC-SUB	MC-SUB	MC-SUB
MC-SUB throughout	MC-P1	MC-SUB	MC-SUB	MC-SUB	MC-SUB

- In all cases DSP includes TFF and cryopreservation.
- Each switch to MC-SUB involves parallel arm with cell factory equivalent.
- CF = Cell Factory, MC-SUB = Microcarrier in SUB

Hassan, Huang, Warren, Mahdavi, Smith, Jong, Farid. 2016. *Regen Med* 11(3), 287-305

Case study: Process change decisions

Process Change Lifecycle Cash Flow Model

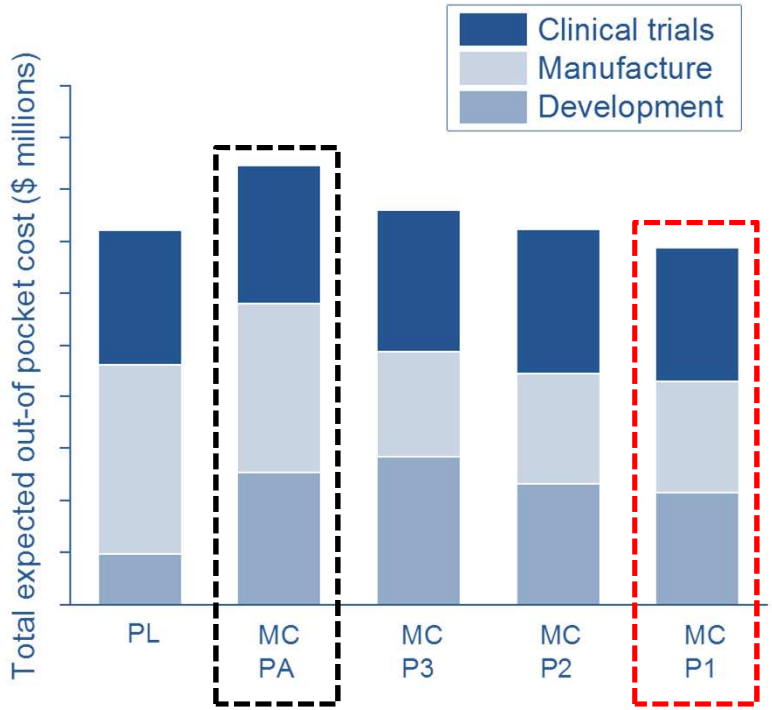


Hassan, Huang, Warren, Mahdavi, Smith, Jong, Farid. 2016. *Regen Med* 11(3), 287-305

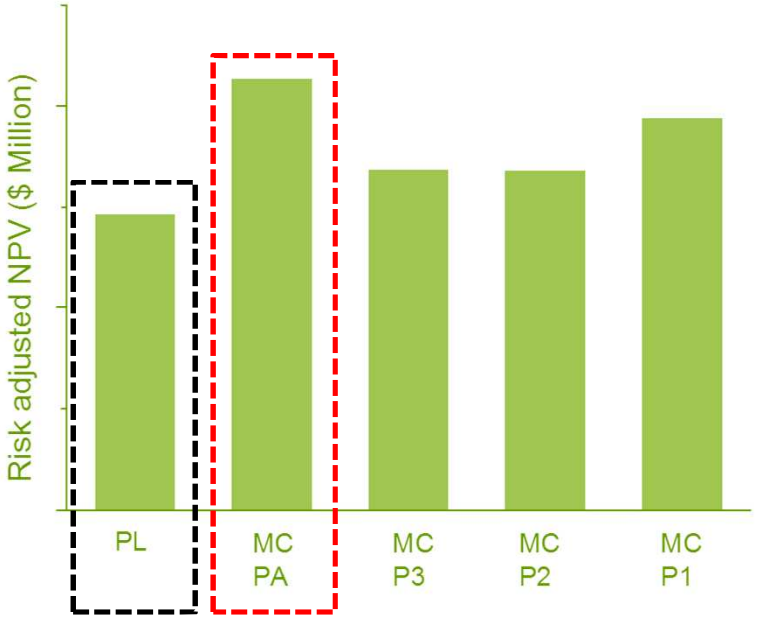
Case study: Process change decisions

Results: Total phase costs and profitability for each process change case

COST OF DEVT



PROFITABILITY



DRUG DEVT PERSPECTIVE:

- Switch to MC-SUB early best
- Switch to MC-SUB post-approval worst

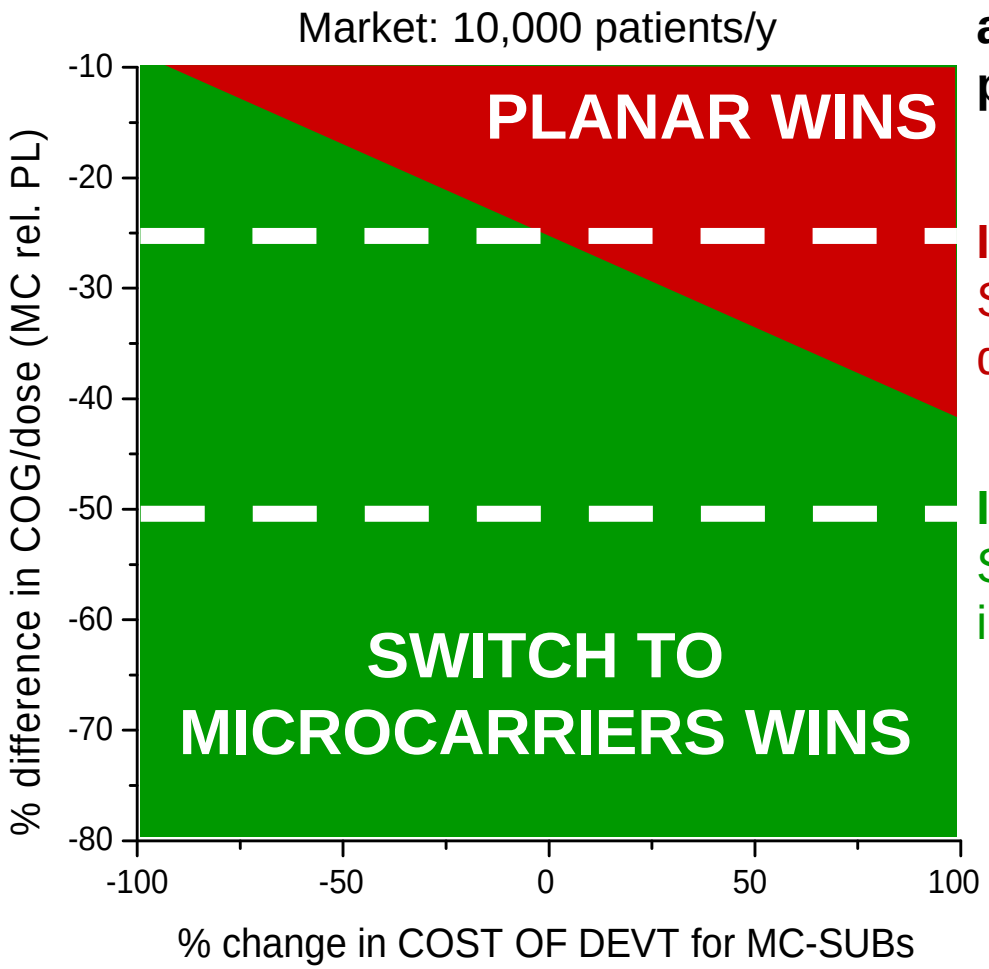
DRUG LIFECYCLE PERSPECTIVE:

- Switch to MC-SUB post approval best
- Sticking to planar worst

Hassan, Huang, Warren, Mahdavi, Smith, Jong, Farid. 2016. *Regen Med* 11(3), 287-305

Case study: Process change decisions

Results: Impact of COST OF DEVT v COG savings on PROFITBAILITY



Will switching to microcarriers post approval always beat sticking to planar?

If COG difference is low (eg -25%)
SWITCH TO MICROCARRIERS depends on COST OF DEVT

If COG difference is high (eg -50%)
SWITCH TO MICROCARRIERS wins irrespective of COST OF DEVT

Hassan, Huang, Warren, Mahdavi, Smith, Jong, Farid. 2016. *Regen Med* 11(3), 287-305

Summary

Cell therapy company

Cell therapy candidate in early phase development with:

- Early clinical data
  - e.g. cell type, dose estimate, patient numbers
- Early process data
  - e.g. yields

UCL Decisional Tools researchers

UCL Decisional Tools outputs can be used to help with decision-making:

- ❑ Compare the cost-effectiveness of alternative manufacturing processes / supply chains
- ❑ Identify the most **cost-effective** and **GMP-ready** process for
  - *current* scale of operation
  - *future* scales for late phase / commercial manufacture
- ❑ Predict and manage the risk of process changes as products proceed through development pathway
- ❑ Identify most promising technologies and targets to reach for future R&D investment

UCL cell therapy process economics publications

Decisional Tools industry collaborators include: Lonza, Pall, Pfizer, GSK

s.farid@ucl.ac.uk

Allogeneic MSCs

Process change evaluation framework for allogeneic cell therapies: impact on drug development and commercialization. Hassan S, Huang H, Warren K, Mahdavi B, Smith D, Jong S, Farid SS. **2016**. Regenerative Medicine, 11(3), 287-305. DOI 10.2217/rme-2015-0034

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iPSCs

Patient-specific hiPSC bioprocessing for drug screening: Bioprocess economics and optimisation. Jenkins, M.J., Bilsland, J., Allsopp, T.A., Ho, S.V., Farid, S.S. **2016.** Biochemical Engineering Journal, 108, 84–97. DOI 10.1016/j.bej.2015.09.024

Human pluripotent stem cell-derived products: Advances towards robust, scalable and cost-effective manufacturing strategies. Jenkins MJ, Farid SS. **2015.** Biotechnology Journal. 10, 83–95. DOI 10.1002/biot.201400348

CAR T-cells and RPE cells

Tania Chilima *et al* & Michael Jenkins *et al* coming soon…

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