Bringing continuous bioprocessing to the manufacture of therapeutic cells

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Tissue Engineering: cell - tissue - patient

CellulaREvolution

Technology addressing bottleneck to cell scale-up

Miotto et al. ACS Applied Mat. & Int. 2017

Geomechanical Cell Guidance

Providing cues to instruct cells to grow into functional tissues

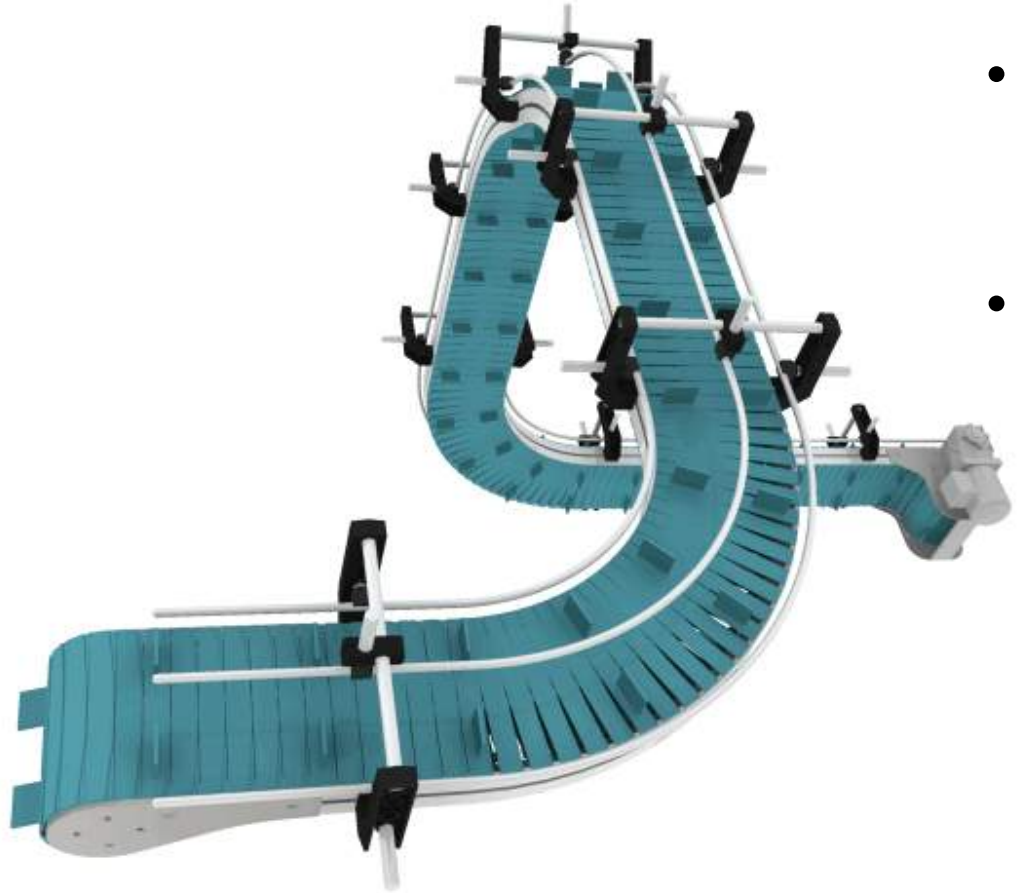
Gouveia et al. Adv. Biosystems 2017

Hypothermic Cell Storage

New Spin-out (Atelerix Ltd) technology for research and clinical applications

Company registered June 2017, first funding round completed Jan 2018

What is a continuous process?



- A production method used to produce materials without interruption.
- The materials that are being processed are continuously in motion e.g. undergoing chemical reactions.

What does it mean for cell manufacturing?

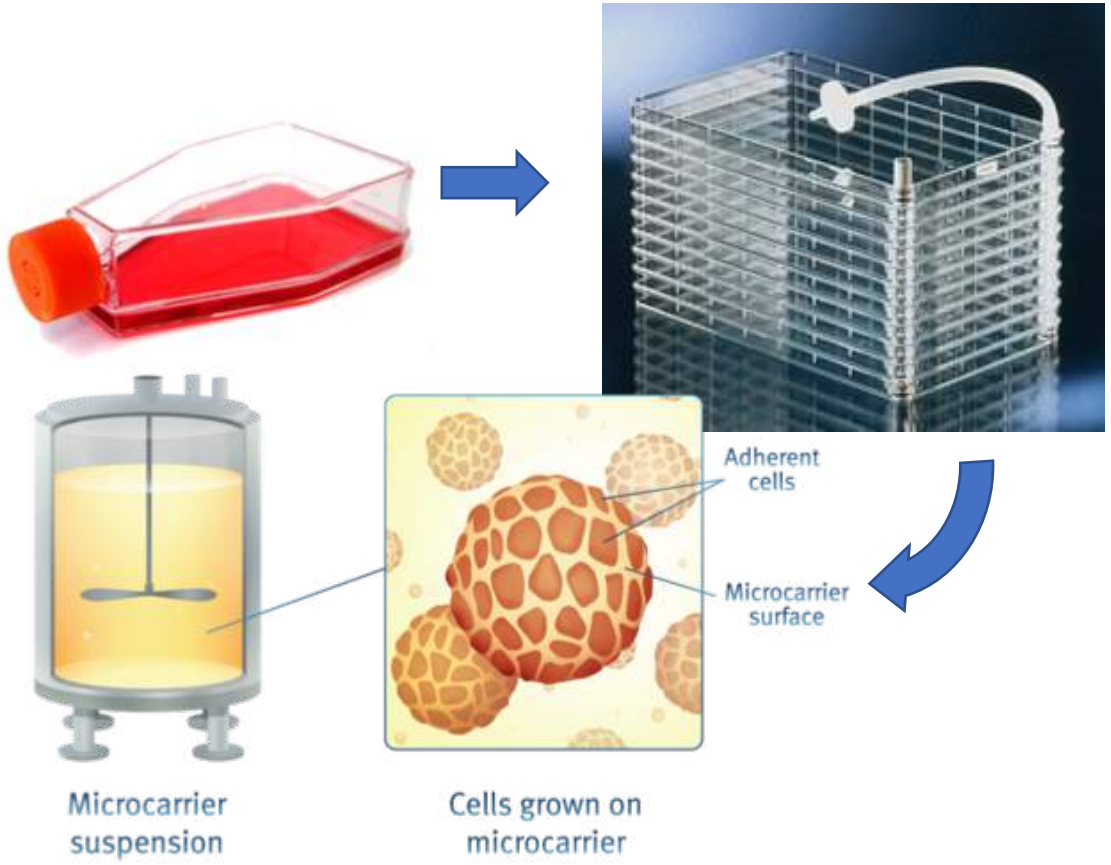
- Currently cells are all produced using Batch Production

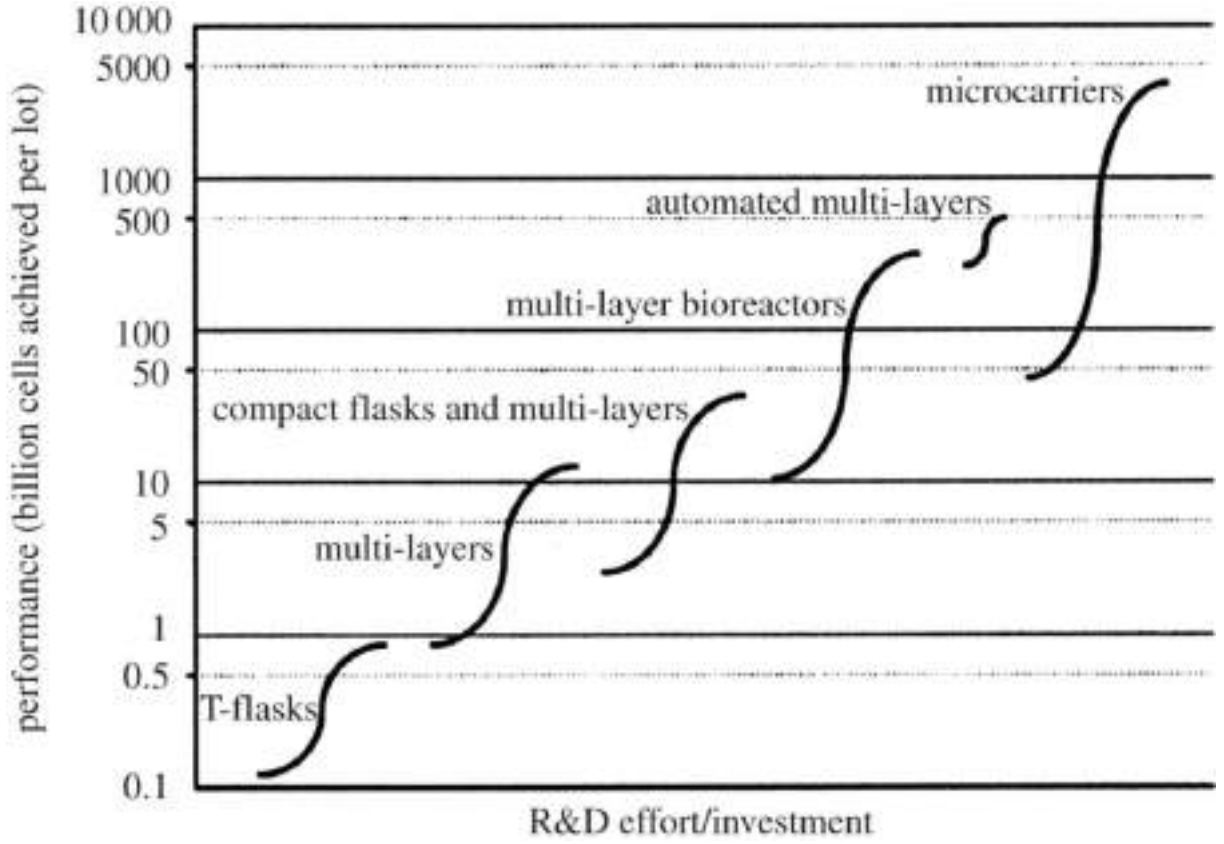
- Pro's
  - Production line can be used for different cell types
  - Production line can be modified at any point

- Con's
  - Inefficient.
  - Equipment must be stopped, prepared and tested again between batches
  - Downtime is costly

Scale up of batch produced adherent cells

- Available surface area is a significant limitation for scale up of adherent cells





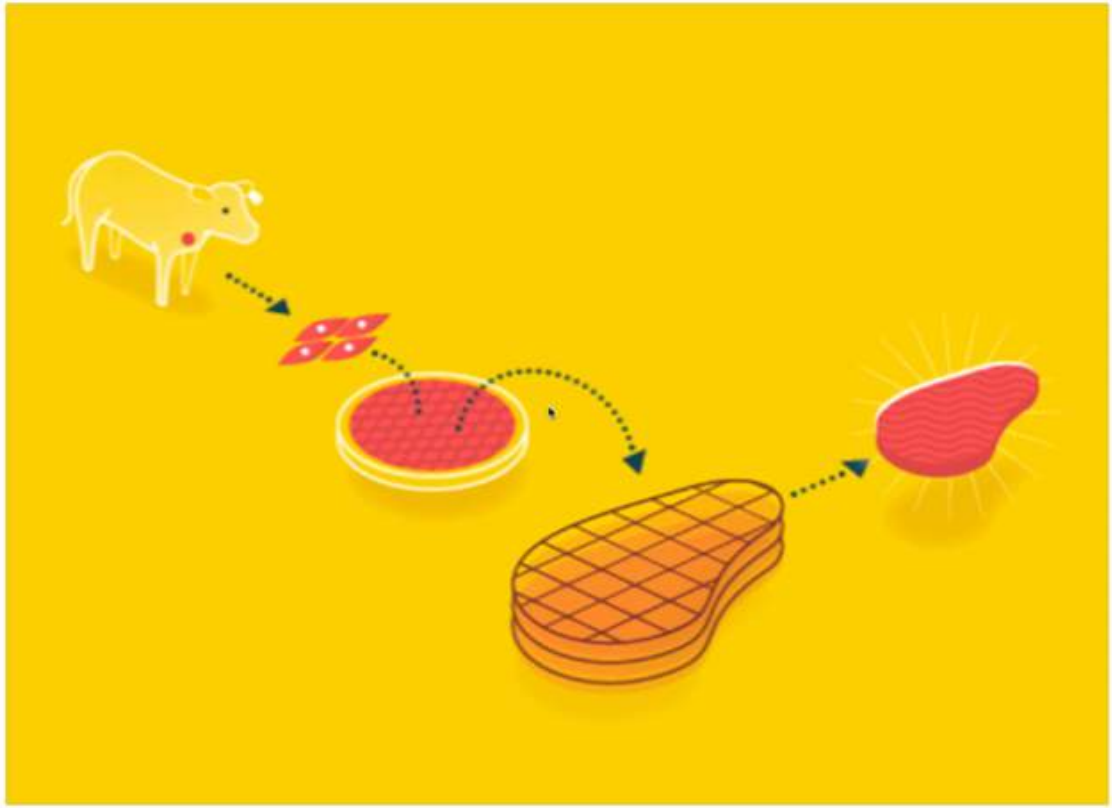
So what's the problem?

- For cell therapy treatments, individual cell doses can range from 10^5–10^9 cells.
- Treatment for heart failure (allogeneic) may require a 10^9 cell-dose in 10^7 patients, thus requiring the manufacture of **10^{16} cells**.
- Current bioreactors can produce 10^{12} cells per lot.
- Factor 10^4 out – just for one indication!

If you thought those numbers were large….

- Cellular agriculture, aka ‘clean meat’ requires even more cells.
- A burger contains 10^9 cells. Annually 50 billion burgers a year are consumed in US.
- Thus 10^{18} cells would be required

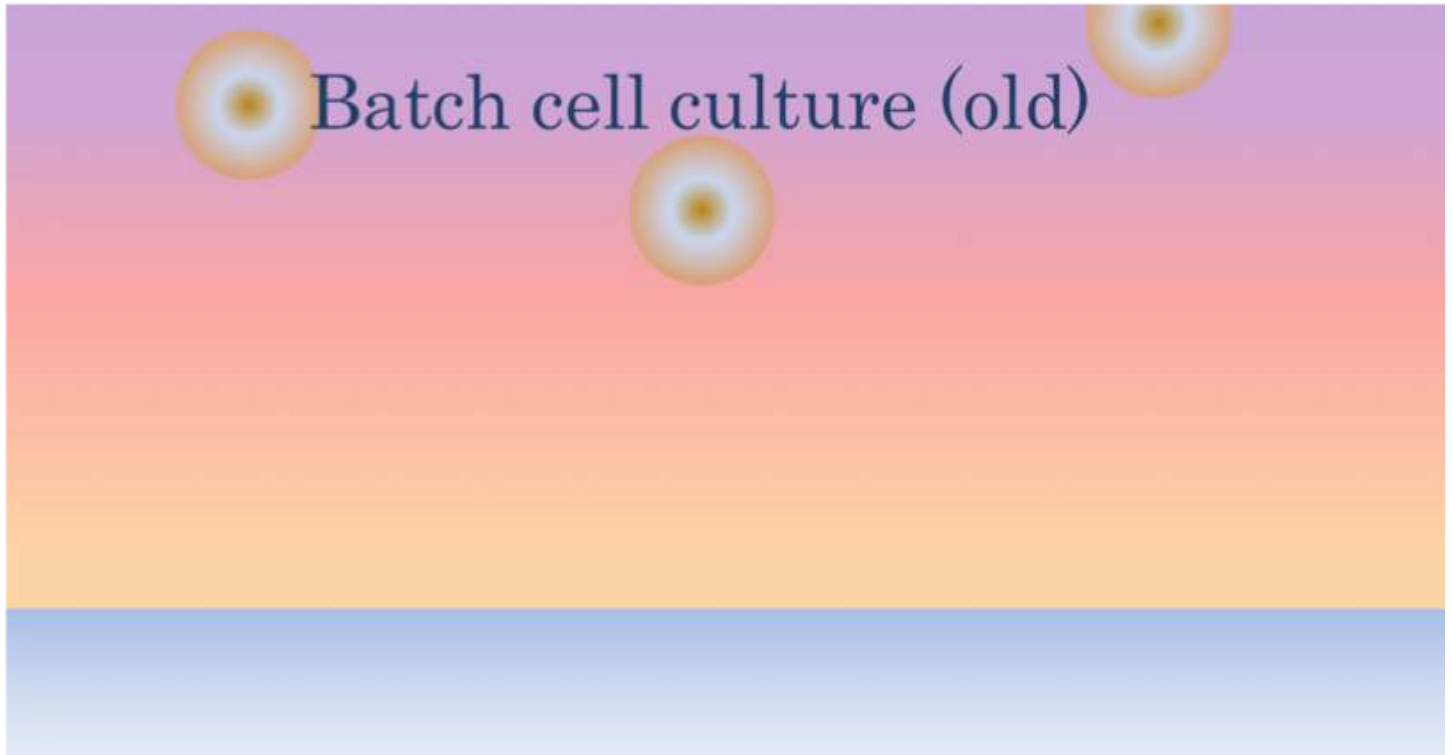
- By including adherent cells used in Biologics (viruses, vaccines etc.) and cell-based assays (monolayers, organoids etc.) then need for adherent cells could rise to 10^{50} per year!



Our Solution

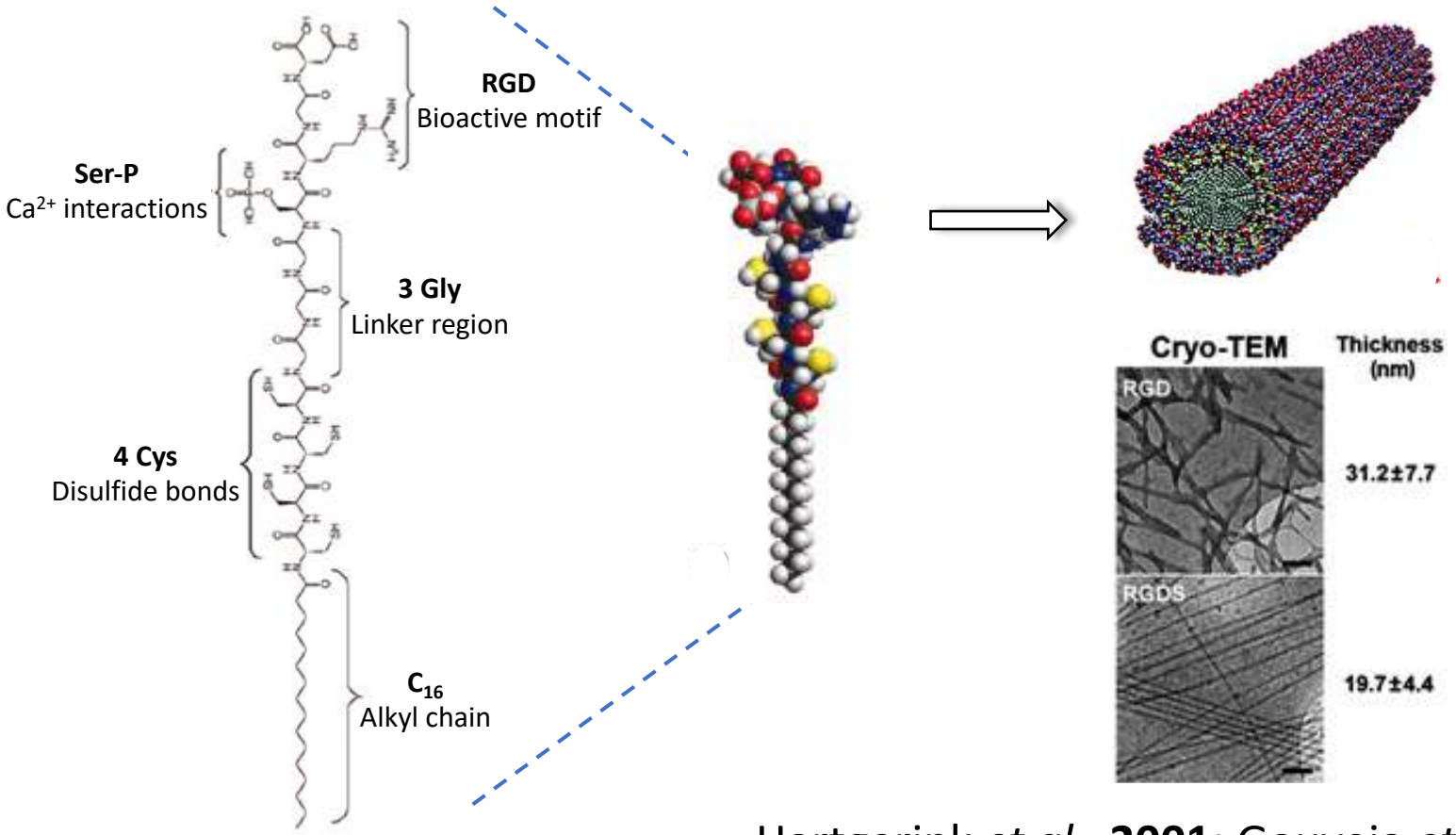
- Rationally design a coating that allows adherent cells to reach a **steady state** (proliferation **=** detachment).

- Thus a single **limited** area could produce an **unlimited** number of cells - continuously.



So what's the coating?

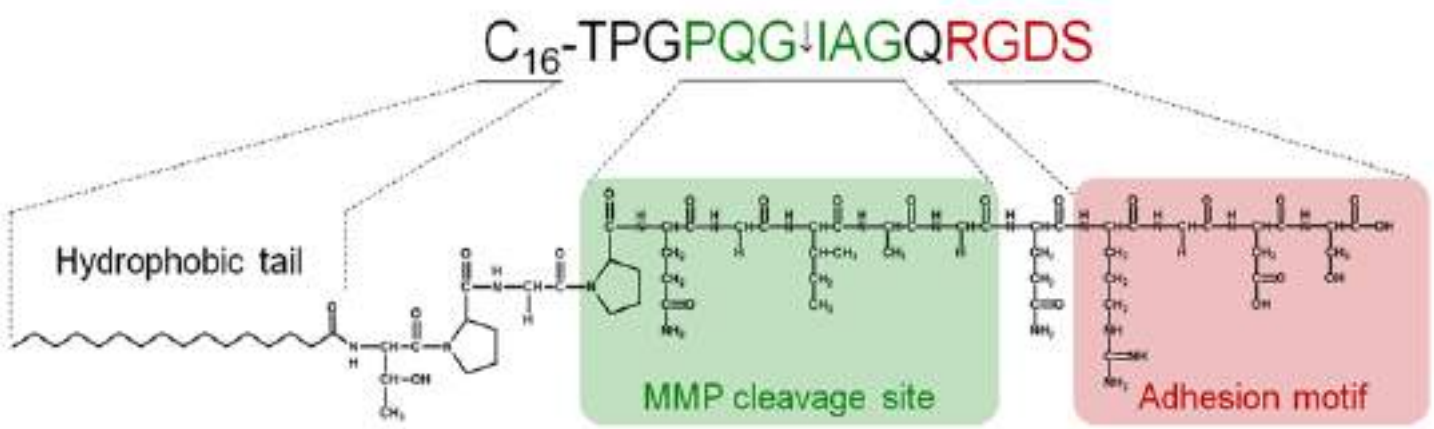
- Self-assembling peptide amphiphiles (hydrophobic tail, hydrophilic head)

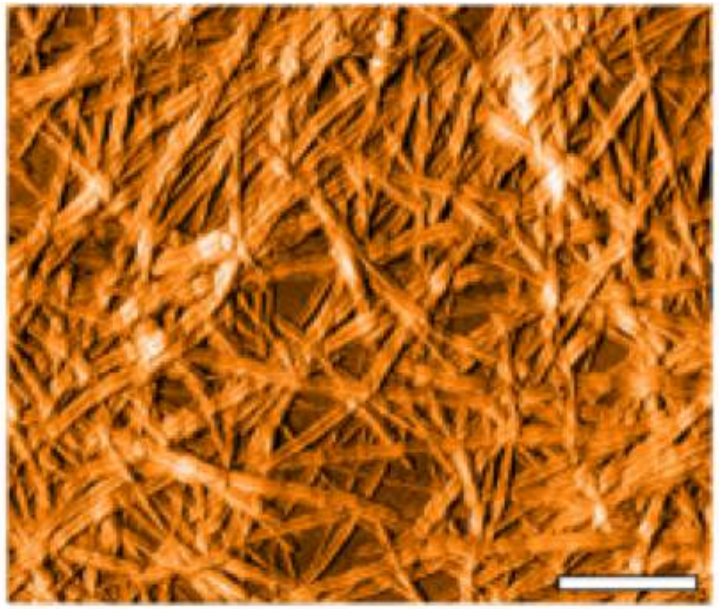


Hartgerink *et al.*, **2001;** Gouveia *et al.*, **2013**

Making the coating ‘smart’

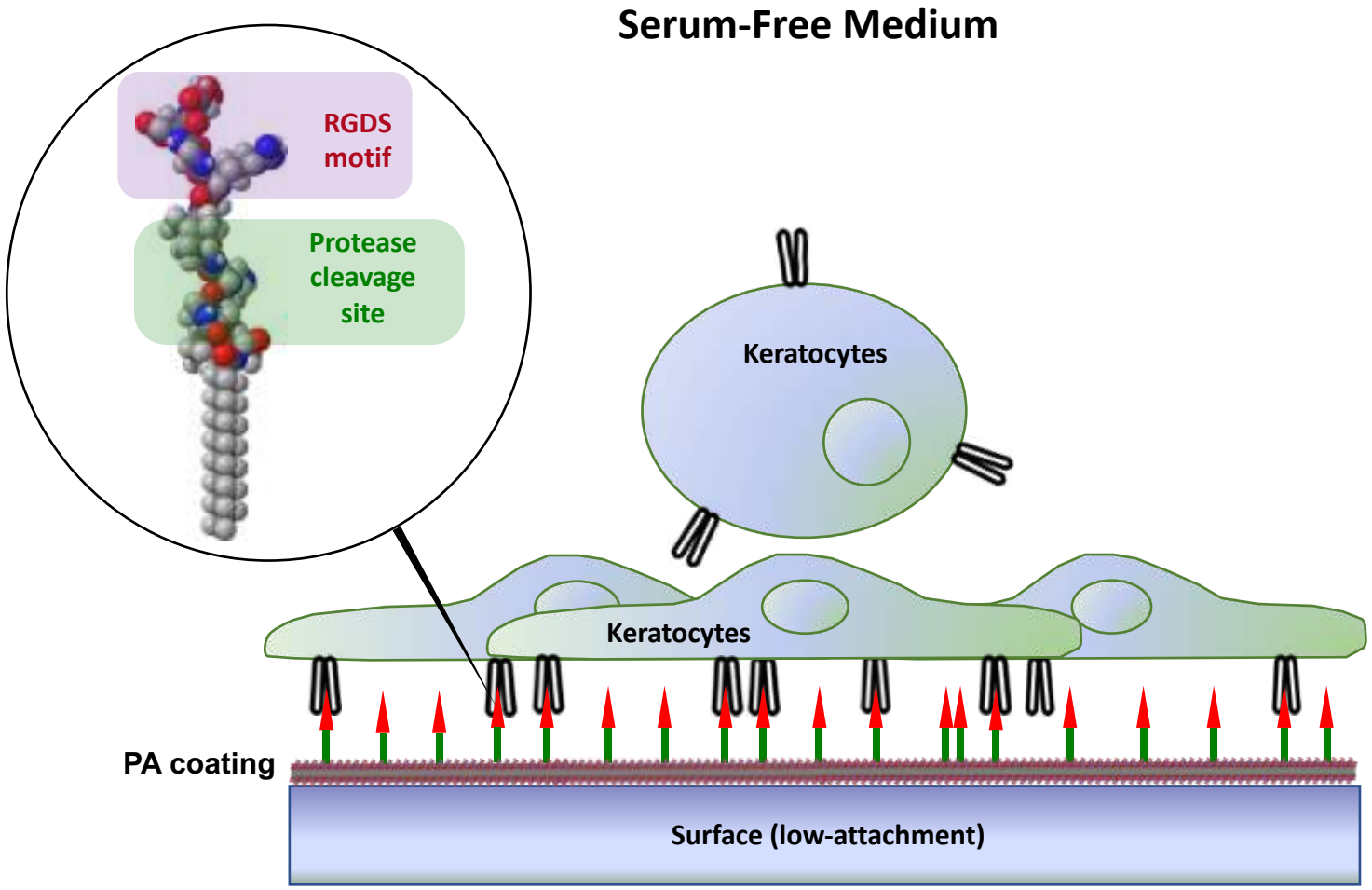
- Enzyme cleavable linker inserted beneath cell adhesion peptide sequence





Gouveia *et al.*, Tissue Eng Pt.A, **2015**

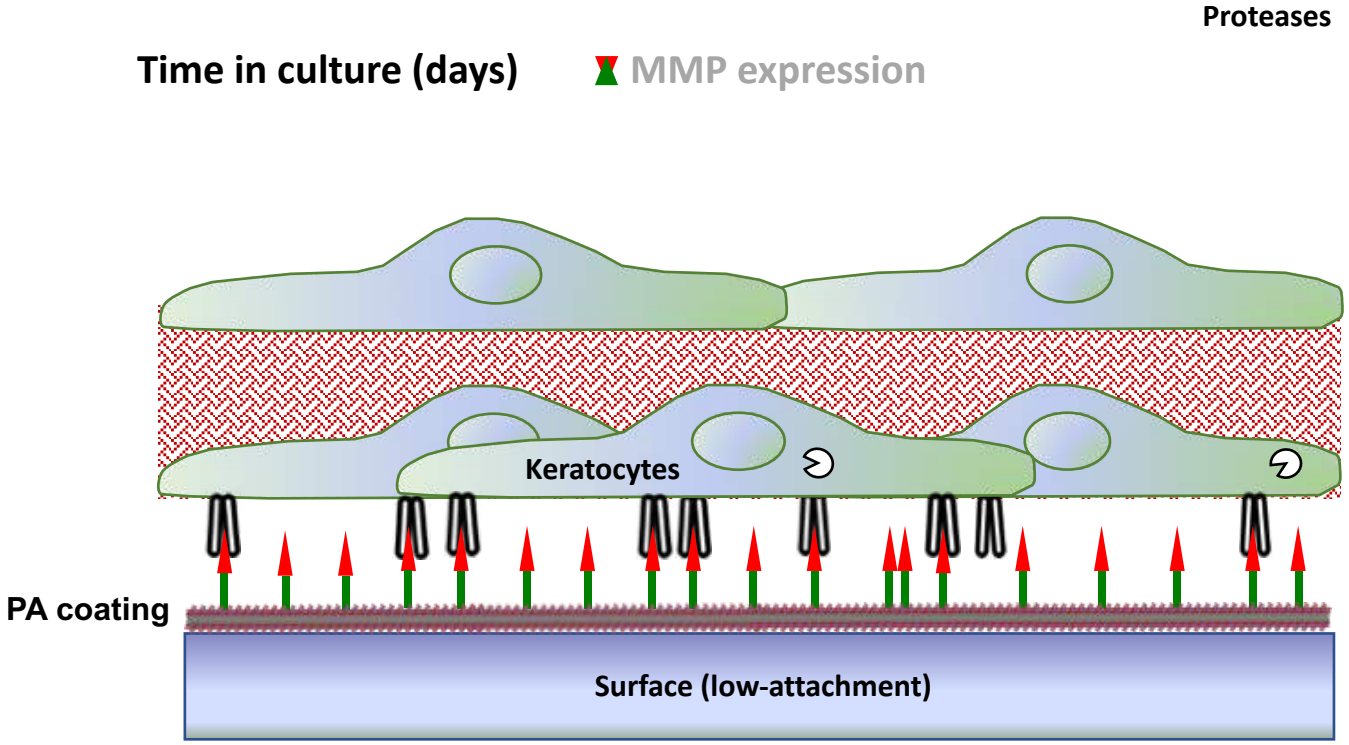
Smart coatings for tissue production

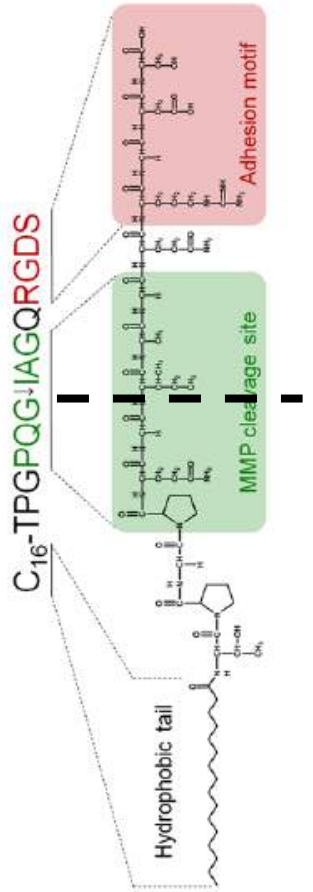


Smart coatings for tissue production

Serum-Free Medium + RA

Gouveia and Connon (2013) *IOVS*

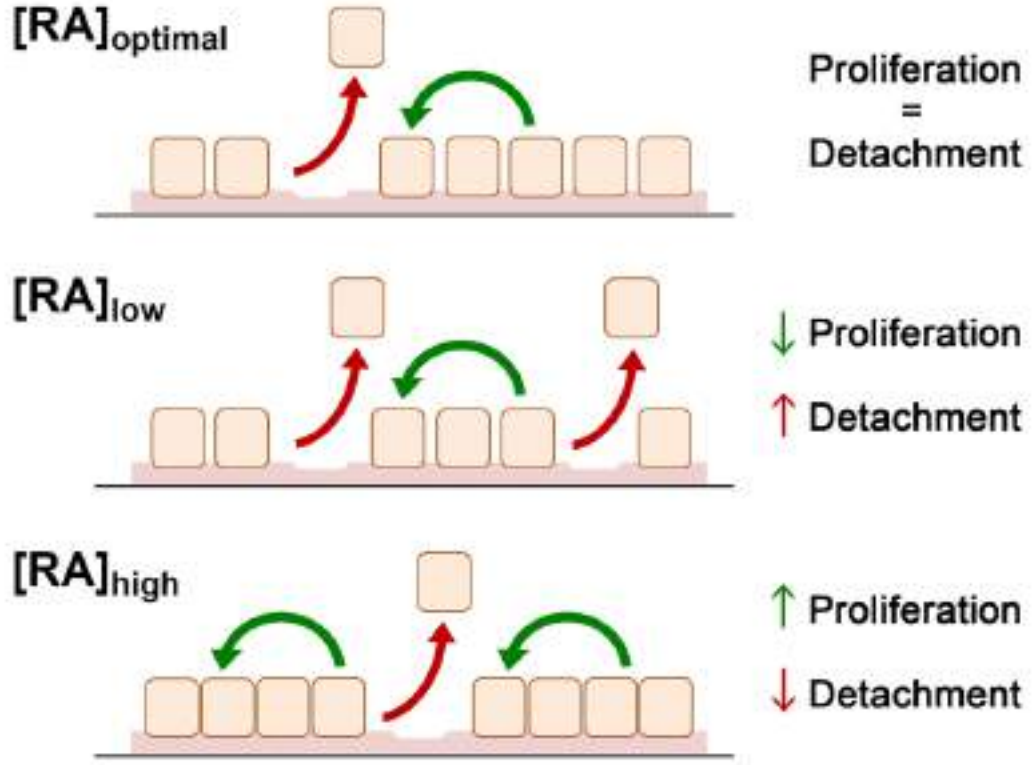




Next step: Use same coating to control individual cell adhesion and release

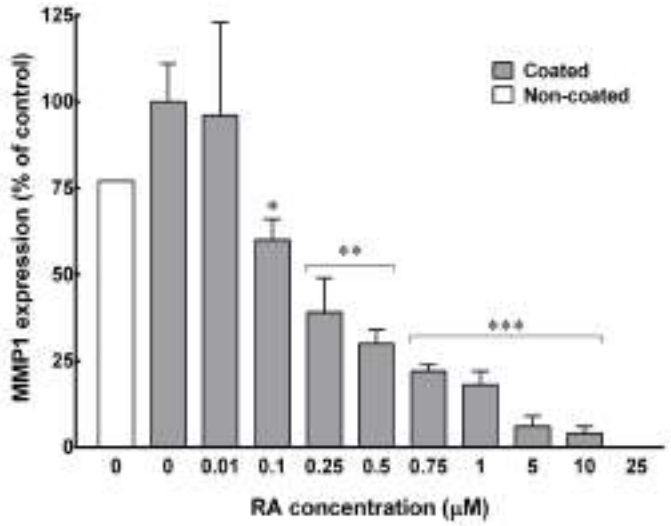
- Is there an accurate correlation between [RA] and [MMP]?

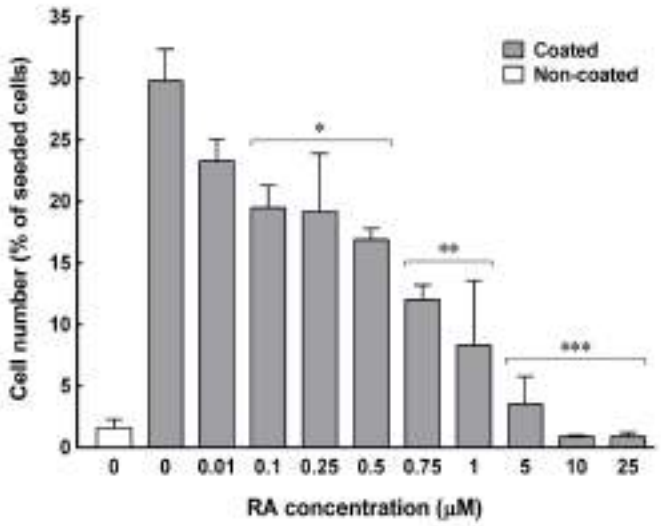
- Test affect of increasing [RA] on cell adhesion with smart coating

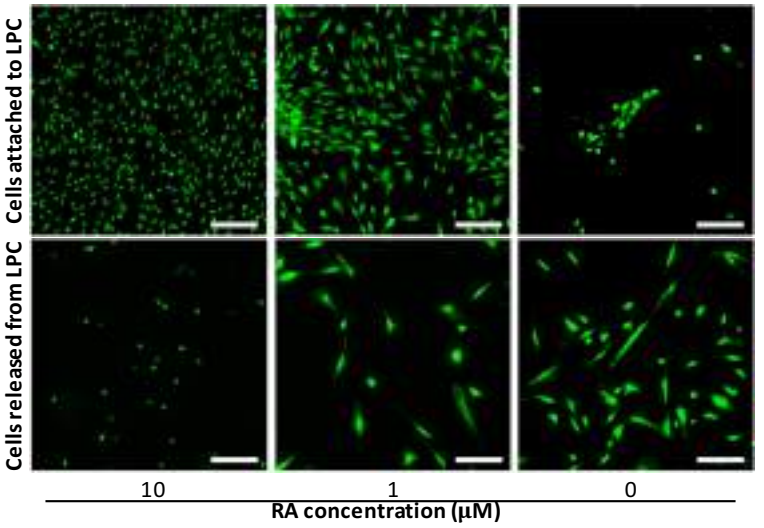


Static culture experiment

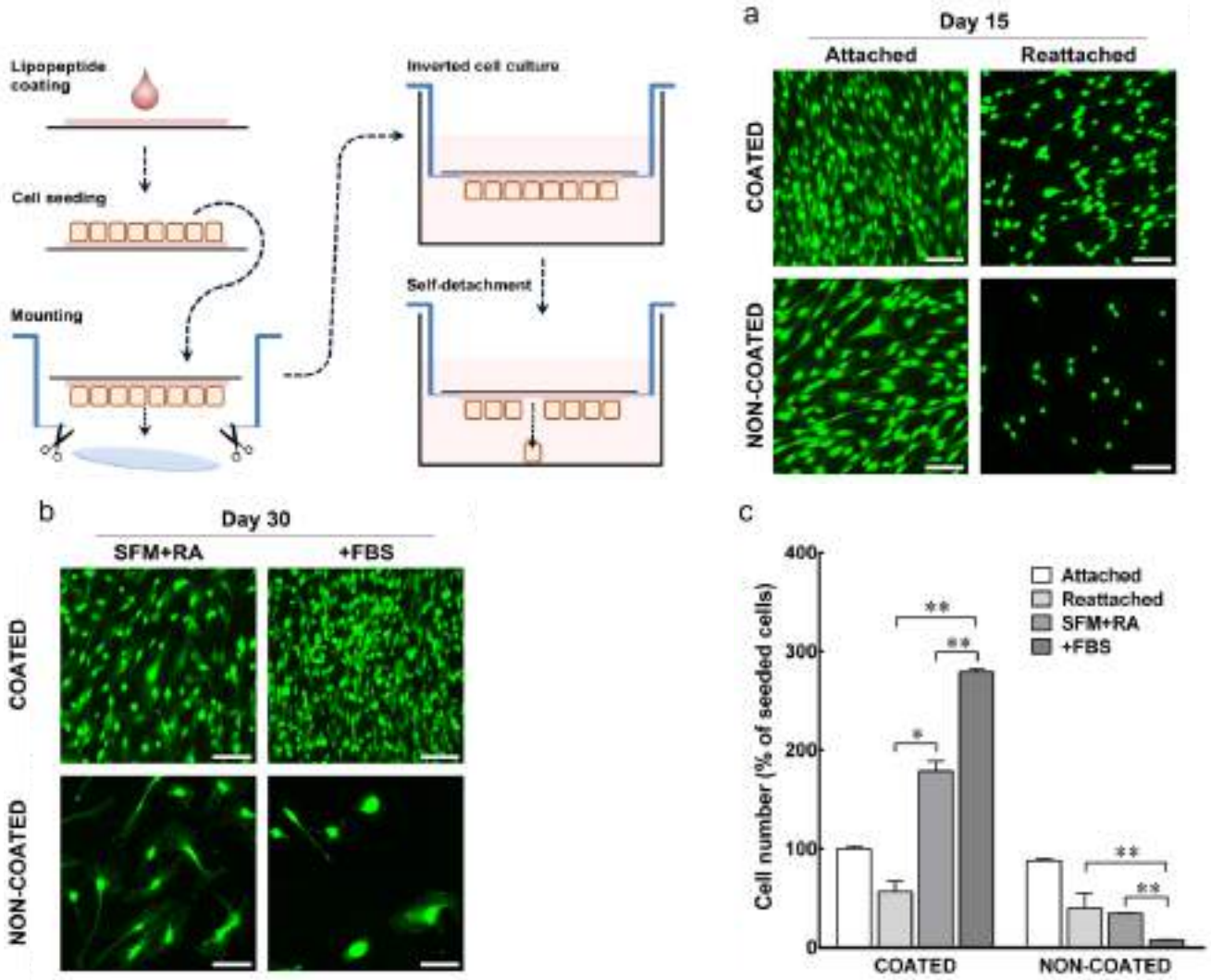
- Effect of [RA] on cell detachment from smart coating







Dynamic culture experiment

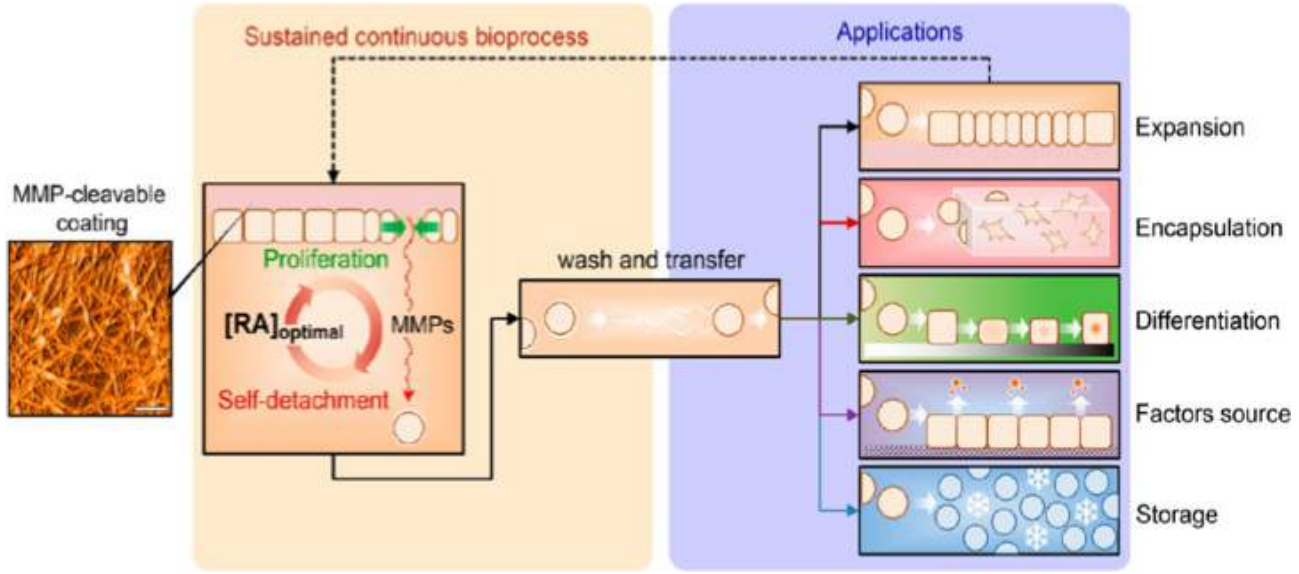


- Maintained for 1 month
- 1% yield per hour
- Serum free culture
- Works with range of stromal cells
- Non-destructive, cells retain functionality

Miotto *et al.*, ACS Appl Mater Inter, **2017**

Summary and future perspectives

- We have developed a special coating that allows adherent cells to reach a **steady state**
- Thus a single **limited** area can produce an **unlimited** number of cells - continuously



- A small tissue culture flask could produce 1 million cells over 1 day or 1 billion cells in 3 months
- Thus 1m^2 could produce enough cells for 4000 patients (this would require an area of a football pitch using traditional methods)
- Technology lends itself to microfluidics i.e. miniaturised cell-factories





Newcastle University

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Mr Thomas Volatier

Miss Olla Al-Jaibaji

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Prof. Andrzej Pacek, Birmingham University, UK

Dr. Ana Maria Ionescu , Granada University, Spain

Prof. Ian Hamley, University of Reading, UK

Dr. Miguel Gonzalez, Harvard Medical School, USA

Prof. Rajiv Mohan, University of Missouri, Columbia, USA

BBSRC bioscience for the future

MRC Medical Research Council

EPSRC Engineering and Physical Sciences Research Council

[dstl]

Thank you

- Any questions?