Cell Therapies – Challenges from An Industry Perspective

Ron Fedechko and Tricia Harbinson

PSA/IMD Conference - Making Gene and Cell Therapy Medicines a Reality

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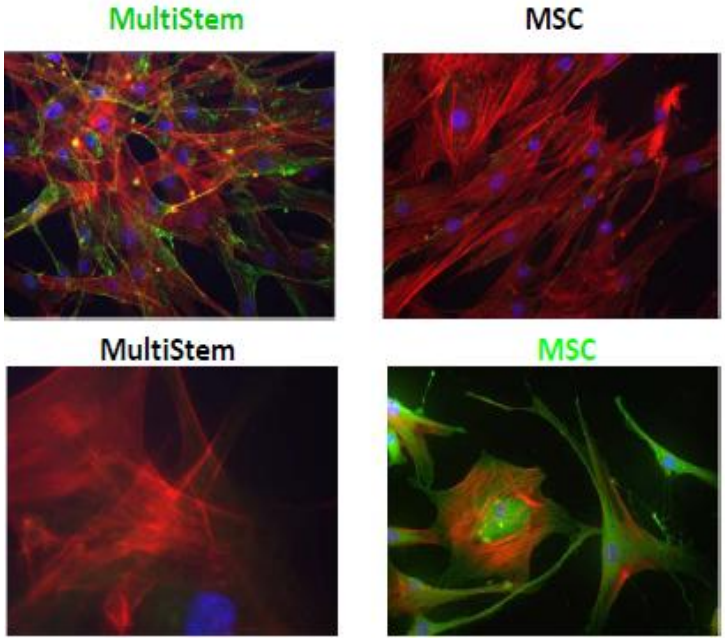
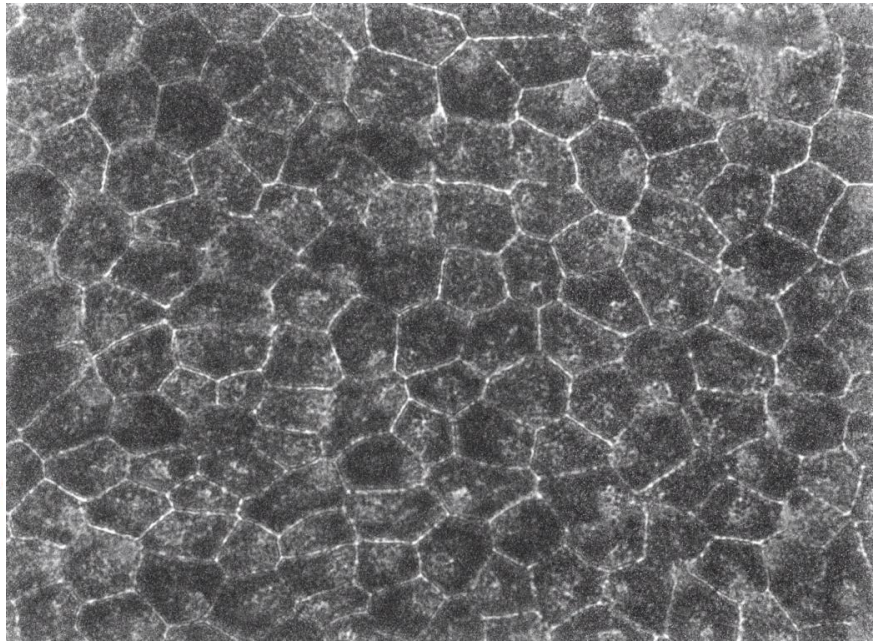
Outline

- Introduction to Cell Therapy Programs
- Challenges Addressed and Solutions
- Summary



Comparison of Stained Multistem Cells Versus Mesenchymal Stem Cells (MSC)

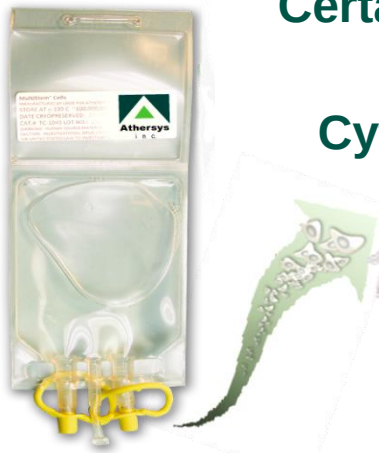


Pigmented Retinal Pigmented Epithelial (RPE) Cells

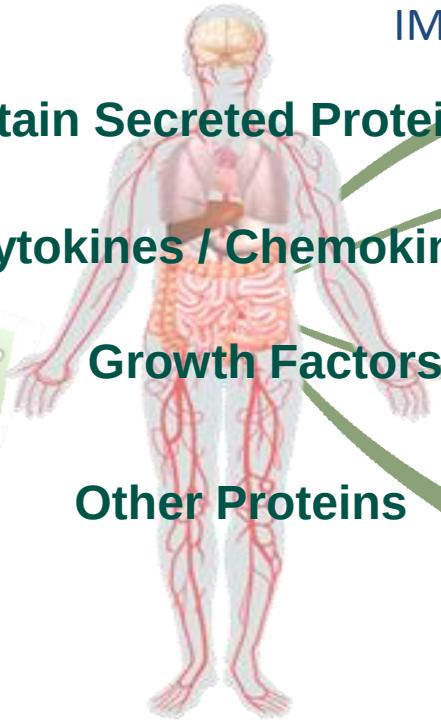
- MultiStem™ Program
Collaboration with Athersys
  - Cleveland OH based (founded 1995)

- MultiStem™
  - Bone marrow-derived multipotent stem cells
  - Pfizer Collaboration is for Ulcerative Colitis
    - Currently in Phase 2 in US, Canada, EU
  - Athersys also has trials ongoing in (Acute Myocardial Infarction (AMI), Stroke, and Graft versus Host Disease (GvHD)

Therapeutic Hypothesis - Immunomodulatory and anti-inflammatory influence of human MultiStem can restore immune homeostasis in the inflamed gut and improve tissue integrity and function



MultiStem® cells express multiple therapeutically-relevant proteins at significant levels



Certain Secreted Proteins

Cytokines / Chemokines

Growth Factors

Other Proteins

IMMUNOMODULATION

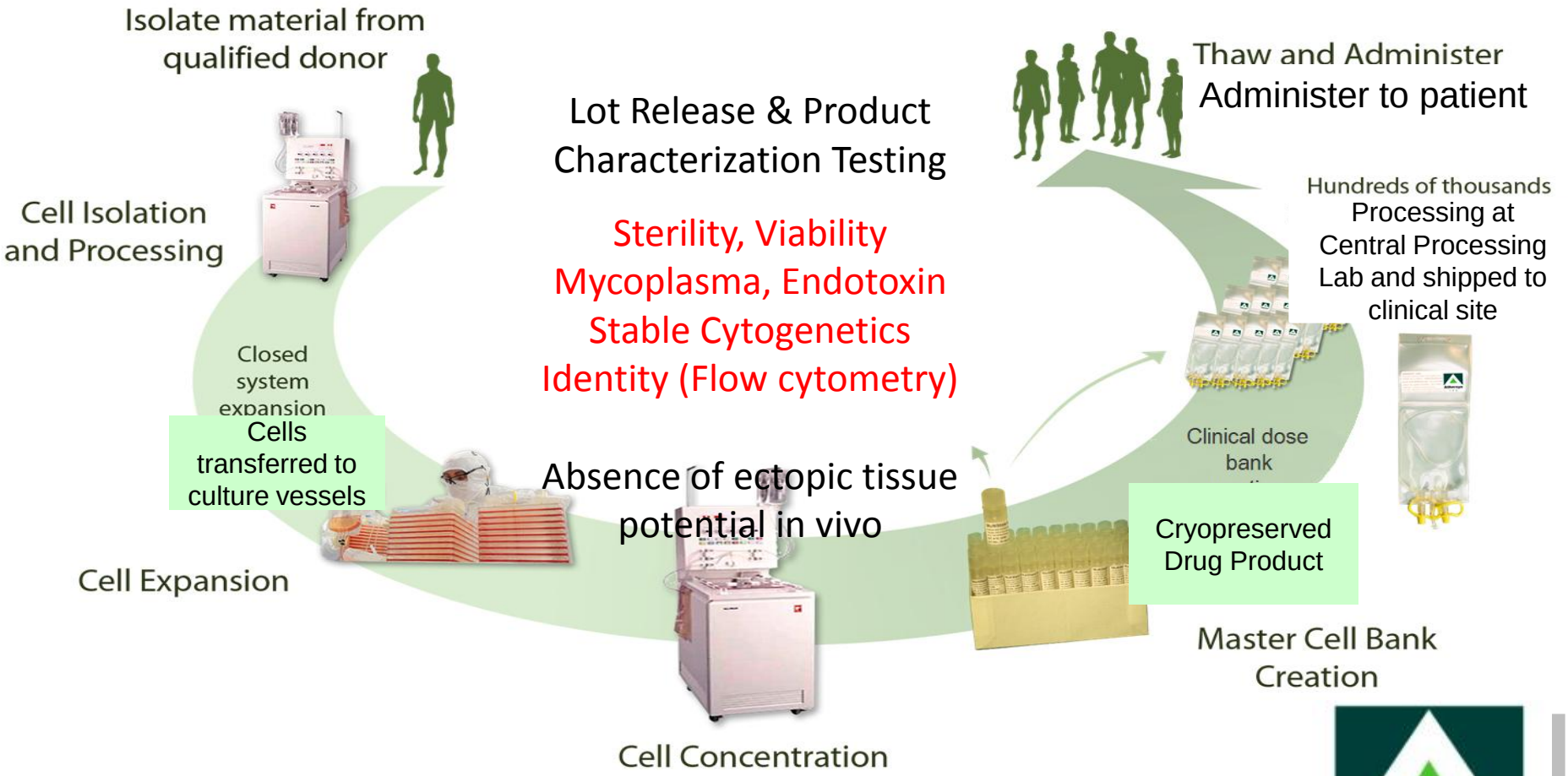
INFLAMMATION REDUCTION

CYTOPROTECTION

ANGIO- / VASCULOGENESIS

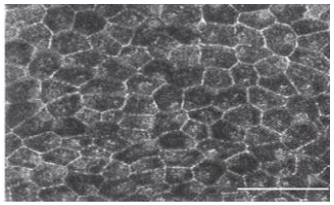
HOST CELLULAR REGENERATION / REPLACEMENT

MultiStem Production Process

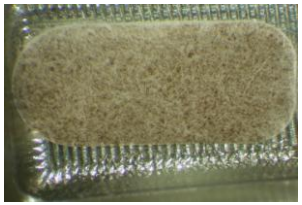


- RPE cells for Age Related Macular Degeneration (AMD)
  Collaboration with University College London
  - Professor Pete Coffey is lead investigator

- RPE cells
  - Embryonic Stem Cell based Product
  - Currently filing regulatory documents

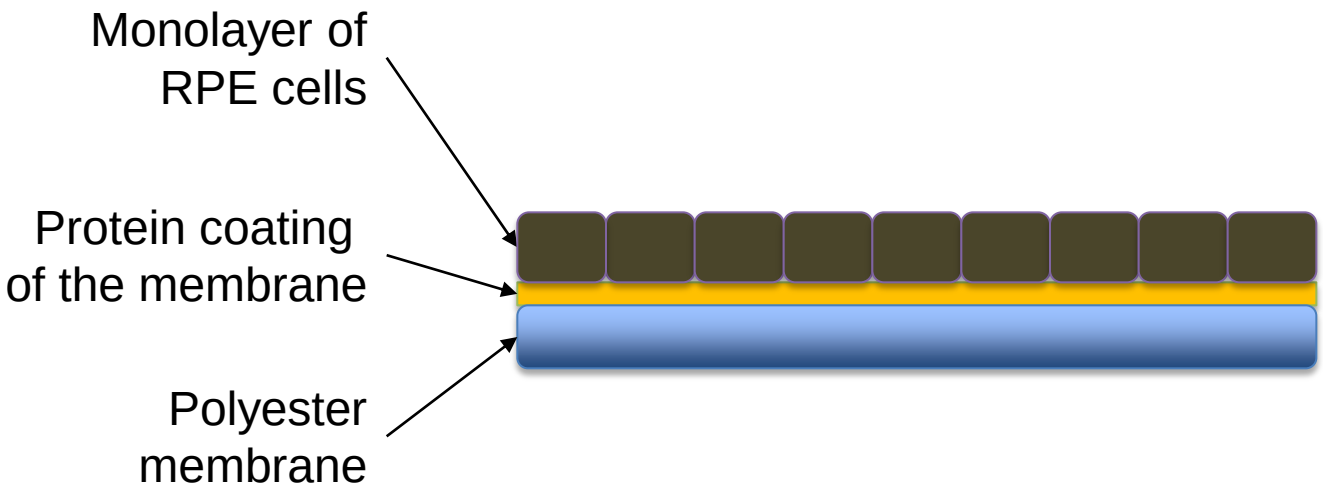


"Cobblestone" morphology of RPE cell monolayer

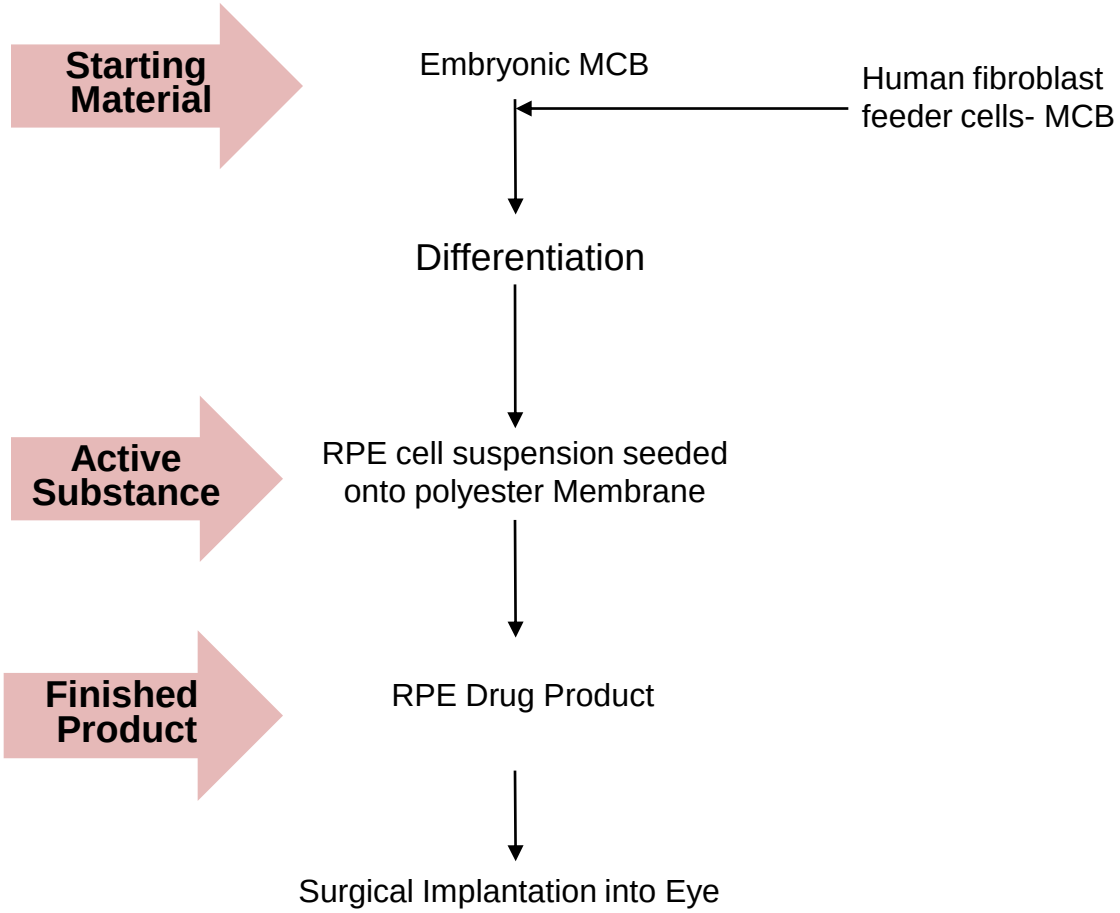


Cut RPE Drug Product

RPE Drug Product Details



Separate administration device
(medical device)



Production Process

Challenges we have addressed getting prepared for the clinic

Challenge – Complex Manufacturing Issues

➢Master/Working Cell Bank (MCB/WCB)

•Must qualify multiple MCBs and WCBs (allogeneic) usage in clinical program (EU)

•Solution - Need suitable comparability program

➢Process Scale up

•Adherent cell growth limits scalability

•Labor intensive due to multiple manual manipulations

•Suspension growth desirable but challenging

•Solution – Extensive development work needed to address this issue

- Stage Process Changes according to stage of development

➢Cellular Harvest

•Methods can be a challenge depending on robustness of cells

- •Centrifugation – not readily scalable
- •Tangential Flow Filtration (TFF)

Must be tested to ensure no affect on cell integrity

➢Different environmental standards EU / US

•EU Grade A hood, Grade B room. US ISO 5 hood in ISO 7 room

•Solution - Manufacture in most conservative environment, but cost more money

Challenge – Comparability of product produced via different production processes

- Multipotent nature of stem cells makes this a challenge
  - Cells as therapeutics in early development stages, so regulators are cautious

- Solution:
  - Comprehensive data package to show that any process or cell bank changes yield a comparable product
  - Bioassay
    - Must clearly demonstrate biologic response that is linked to potency
    - As cells may have different functions, will need indication specific assay
  - Cell surface markers indicative of cell type are also critical

Challenge –Outsourcing

- **Manufacturing Infrastructure not readily available**
- Requires multiple Contract Manufacturing Organizations (manufacture and testing).
- Process oversight can be a challenge
- **Key to Success**
- Develop open relationships so that if there are issues, these are communicated
- Must progress as a partnership
- CLEARLY defined roles and responsibilities (i.e., who releases product)
- Quality agreements between all parties essential (who is responsible for oversight of what)

Challenge – Release Processes

➢Dose vs Batch

•Cell therapies generally use dose release vs batch release as process very different. Must adapt to get product released

➢Short Expiry Period

•This is on the order of hours, not years (standard for Pharma)

➢Testing turn around times

•Release required before results are available.

➢QP resource outsourced

•Need to ensure part of IMPD discussions etc

➢Labels

•Standard approach may not always apply: May need to be applied in Grade A hood or withstand freezing

•Limited room for text but must ensure complies with regulations.

Challenge – Release Processes

➢Adaptation

•QP with ATMP certification involved with all aspects of the process - ensure fully engaged.

•Staged release approach so that on day of clinic dosing minimal review required.

•Consider parametric release approach – Need to demonstrate control during development.

•Work with analytical labs to ensure they are aware of the timelines, part of Quality Agreement.

•Ensure clearly define release criteria and reflect this in the IMPD.

•Innovative solutions – re labels, flagging.

•Need to work with the clinic on when the first dose expected.

Challenge – Stability Studies

➢In Use Stability studies difficult

•Product produced in small lots, so not a lot of material for lengthy studies

•Solution – After process lockdown, use material from engineering runs to establish use period

•Provide additional supportive data from material from early GMP production runs

➢ICH Stability Studies for Phase 3

•Should cell therapies follow ICH?

➢Shipping Stability

•Evaluate shippers using standard ASTM methods

•Carry out trial shipments with product to qualify shipment for proposed use period

•Carry out mock shipments to various sites to ensure material can arrive within use period window

•Use known shipper status to expedite movement within EU

Challenge – Devices

- Cellular therapies may require devices
  - Regulations constantly changing/getting tighter – must follow the Medical Device Directive if required.

- Solution
  - Consult with agencies early regarding requirements (CE marking).
  - Don't over engineer. Design appropriate for stage of development.

Challenge – Regulations Different in EU versus US

➢ Regulatory Agencies expectations can be different

- Different test methods for EU and US (European Pharmacopeia versus United States Pharmacopeia compliance for sterility/mycoplasma)
- Acceptability of Cell Lines may vary by country
  - UK derived cell lines may not be acceptable in US (dependent on date of origin; discuss circumstances with FDA)

➢ Solution

- Utilize Harmonized tests
- Be upfront with concerns
- Engage with agencies early
  - Obtain agency opinion in Scientific Advice Meetings
  - If filing in US and EU, try to have joint scientific advice meetings

Challenge – Supply Chain Logistics

- Manufacture, shipping, and clinical dosing must be perfectly coordinated
- Traceability to the dose level is essential
- Documentation showing dose level traceability is essential
- Solution
  - Ensure all details are worked out and coordinated before dosing initiated

Challenge – Clinical Trial Study Design

➢Need an understanding of the trial design e.g. Blinding.

•Nature of the product automatically rules out producing a placebo that looks exactly the same as with conventional blinding.

➢Solution

•Use shrouds on iv bags to help keep clinical sites blinded.

➢Must ensure appropriate clinical and production staff remain blinded.

•Set up systems to ensure this kept (only certain, very limited, people, know who received active versus placebo

Summary

- **Pfizer recognises this does not fit with conventional drug product development:**
  - Adapted our approach to Quality oversight to allow progression of cellular therapies
  - Further enhancing our Quality Management System to support ATMP supply chain control to dose level instead of the batch.