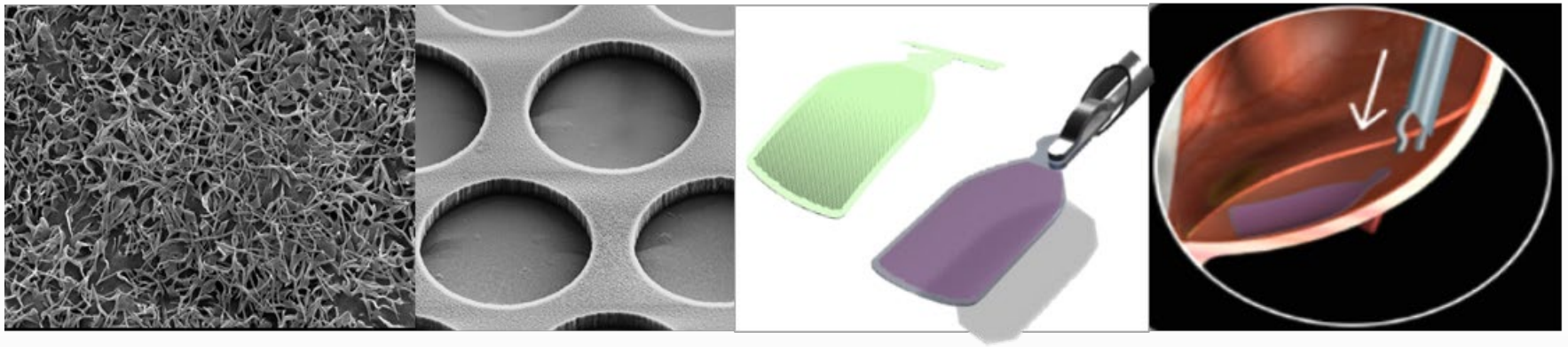


Case Study: The Path to Automation of Manufacturing of a RPE Cell Based Implant for the Treatment of Geographic Atrophy

Emerging Technologies and Innovation in Manufacturing Regenerative Medicine Therapies: A National Academies Workshop

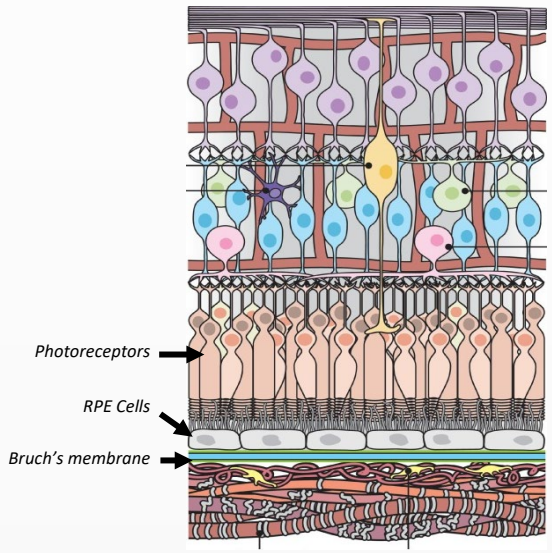
Jane S Lebkowski Ph.D
President, Regenerative Patch Technologies LLC

October 17, 2023

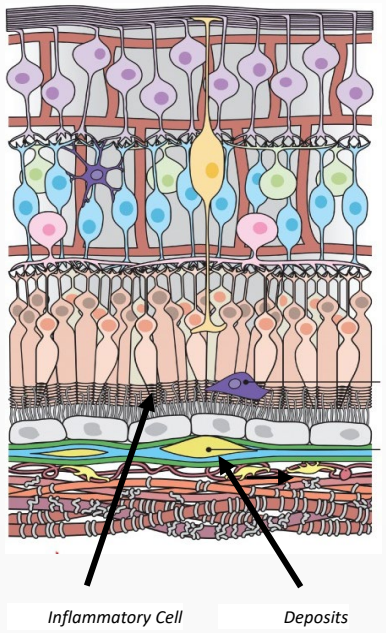
Case Report: The CPCB-RPE1 Implant Addresses the Disease Pathology in Geographic Atrophy

As RPE cells degenerate in Advanced Dry AMD, so does the rest of the retina

Normal Retina

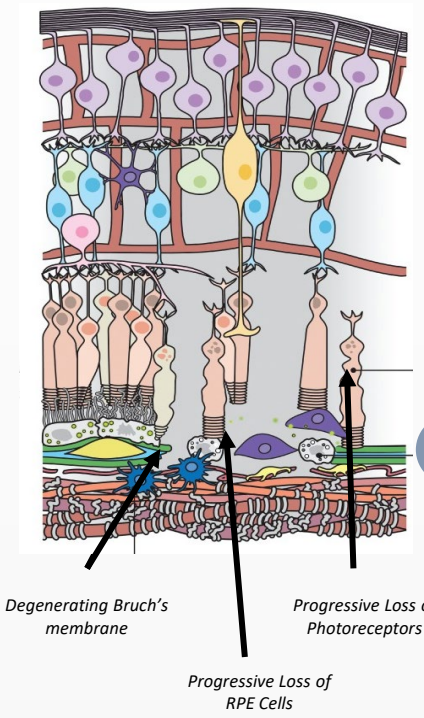


Early Dry AMD

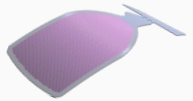


Problem: There are no native mechanisms in the eye to replace degenerating RPE cells.

Advanced Dry AMD



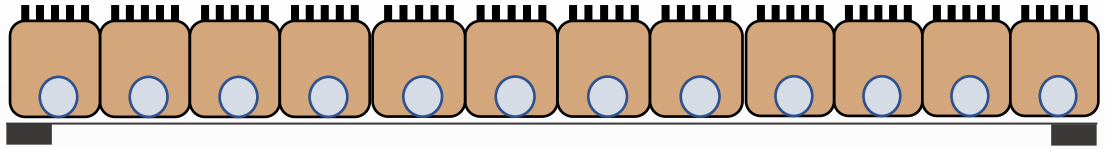
CPCB-RPE1 Implant



The Approach: Insert implant of RPE cells on a synthetic Bruch's Membrane to provide support for retina

The CPCB-RPE1 Implant: A Composite RPE Cell-Parylene Membrane Implant

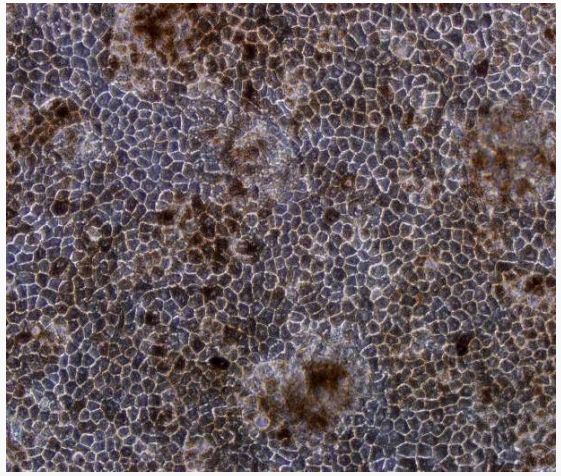
Implant Called CPCB-RPE1



Polarized Healthy RPE Cells:
Replace Dysfunctional RPE Layer in AMD Retina

Ultrathin Diffusible Parylene Membrane:
Replace Degenerating Bruch's Membrane

RPE Cells Produced from Pluripotent Stem Cells



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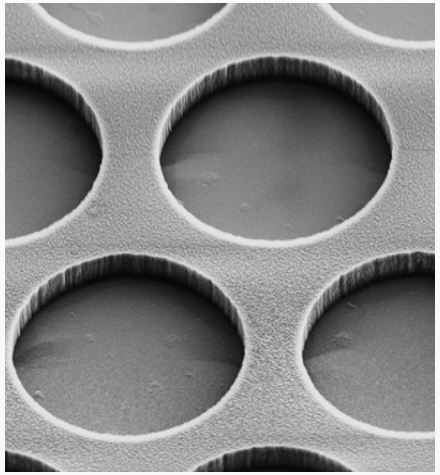
Ultrathin Parylene Membrane



CPCB-RPE1 Implant

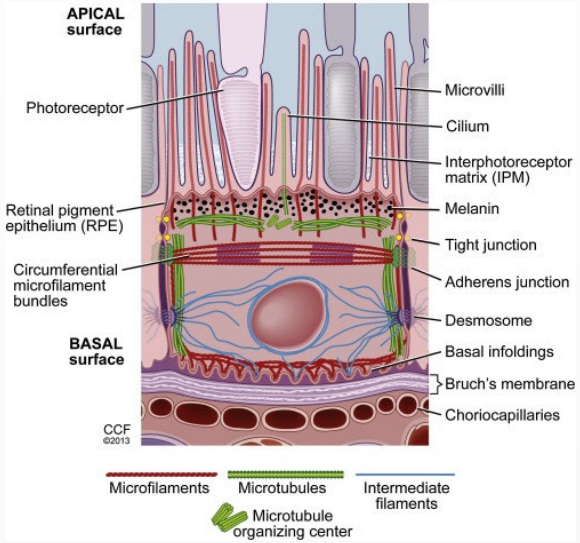
Implant Body

The Unmet Medical Need and the Challenge: Huge Potential Target Population in Geographic Atrophy

- Over 1.7 Million Have Geographic Atrophy in the US with an Annual Incidence of ~200,000
- Similar Numbers in Europe
- Present Throughout Asia Although at Lower Frequency

Prerequisite for Process Development: Identify Critical Attributes of the RPE Cells and Implant

Retinal Pigment Epithelial Cells

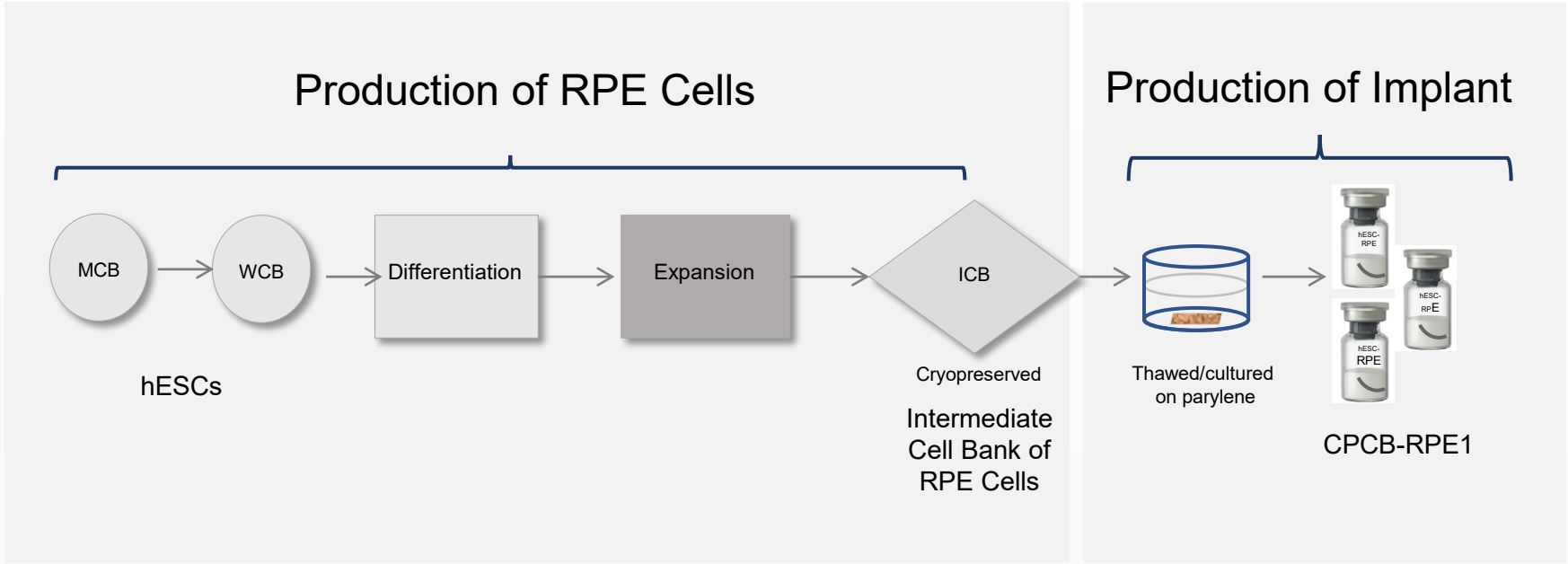


Essential to Develop Assays to Monitor the Critical Quality Attributes of the Cell Therapy Product Throughout Development Including Production, Formulation, Scale-up and Delivery

Evaluate RPE Cells from Scaled Production for Critical Quality Attributes

- Have Phenotypic Markers of RPE Cells Such as Visual Cycle Proteins
- Produce Pigment
- Polarize on Parylene Membrane
- Produce Visual Cycle Proteins
- Form Tight Junctions
- Do Not Migrate
- Secrete PEDF from the Apical Surface to Promote Photoreceptor Survival
- Secrete VEGF from the Basal Surface to Promote Choriocapillaris Survival
- Integrate with PR Outer Segments to Promote Efficient Phagocytosis of ROS

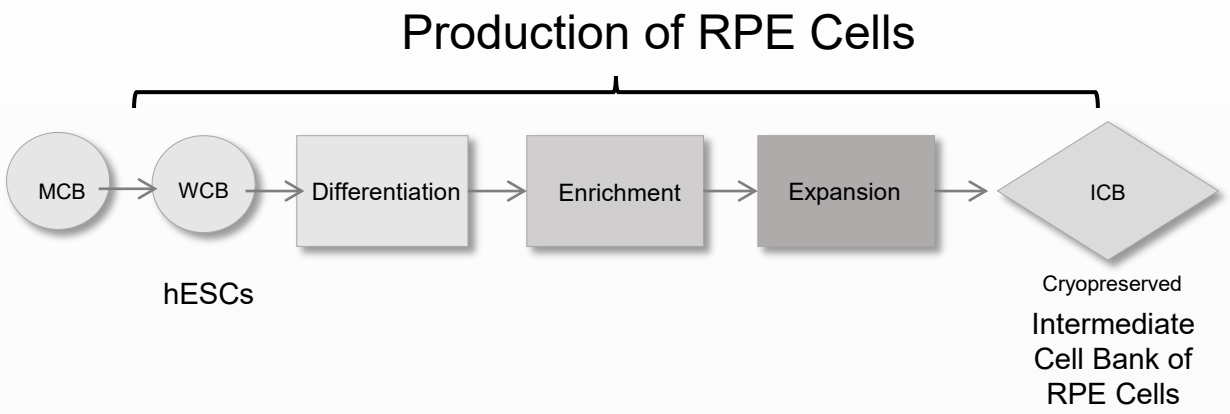
Scale-up and Scale-out is Required for Production of the CPCB-RPE1 Implant



Scale-up

Scale-out

Target Scaled Production of RPE Cells is 5 x 10^{10} Cells Per Year: Implications for Automation.



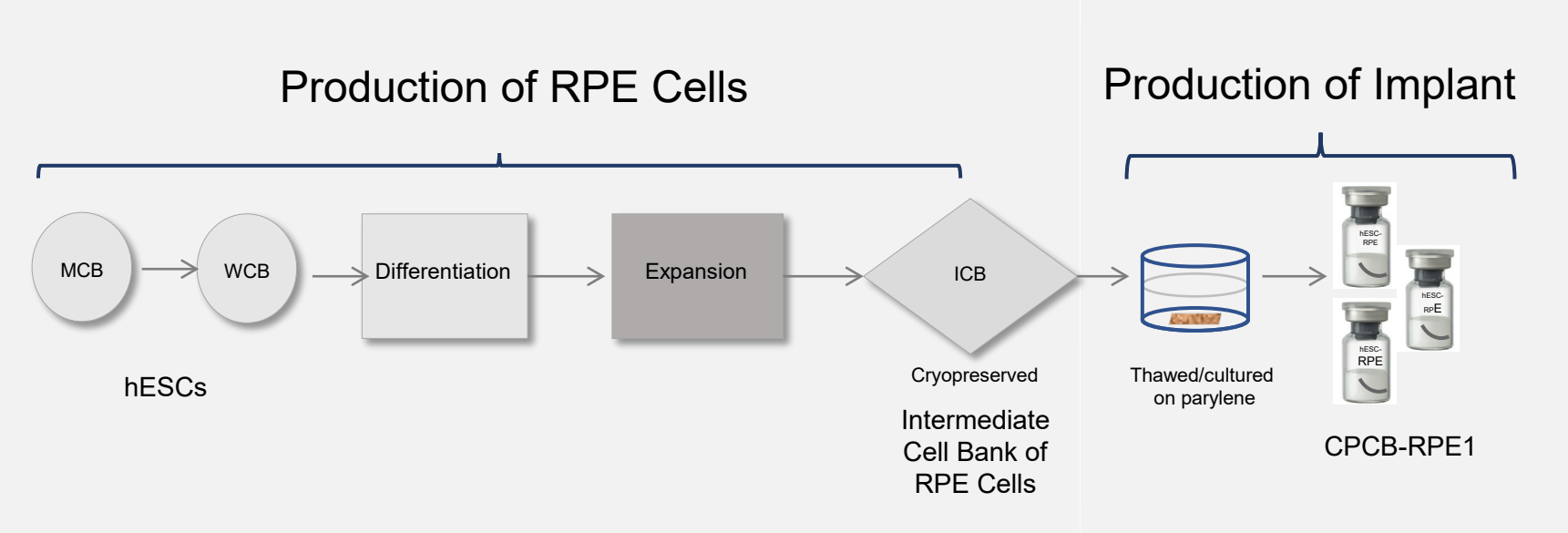
For CPCB-RPE1 Implant

- Only ~120,000 per Implant
- 5 x10^{10} ICB Cells Could Supply Over a Year of Implants
- 10-50 fold Scale-up over Current Production Scale
- Needs Within Current Technology Capabilities

Automation of RPE Production: Consideration of Critical Process Parameters and Scale Required

- Cell Numbers Required Over What Time Period?
- Required Size of Master and Working Cell Banks?
- Variability in Yields/Purity/Function from the Different Banks?
- Scale-Up Vessel?
- Do Cells Need to Be Adherent for Growth or Maturation?
- Do Cells Aggregate? Is Dissociation Required?
- What Frequency of Media Exchanges is Required
- Harvest Procedures?
- Representative Scaled Down Model? DOE Principles
- Define Process Steps and Parameters Before Automation
- In Process Controls and Specifications??
- Use AI and Machine Learning to Characterize Phenotype, Composition, Function, Viability and Uniformity of Cells

Scale-out Production of the CPCB-RPE1 Implants

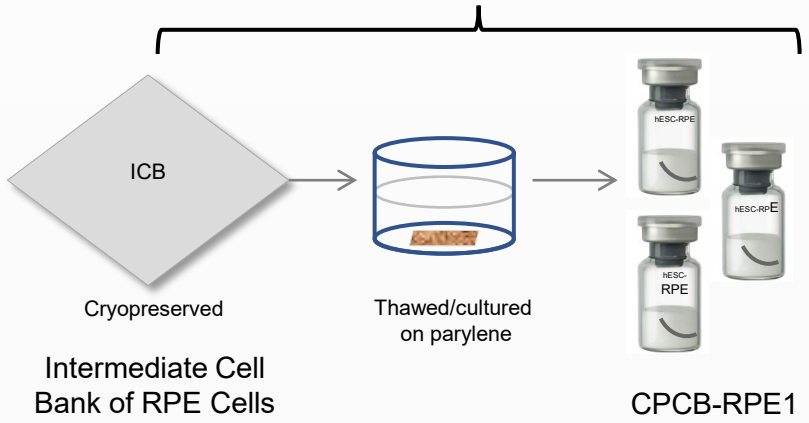


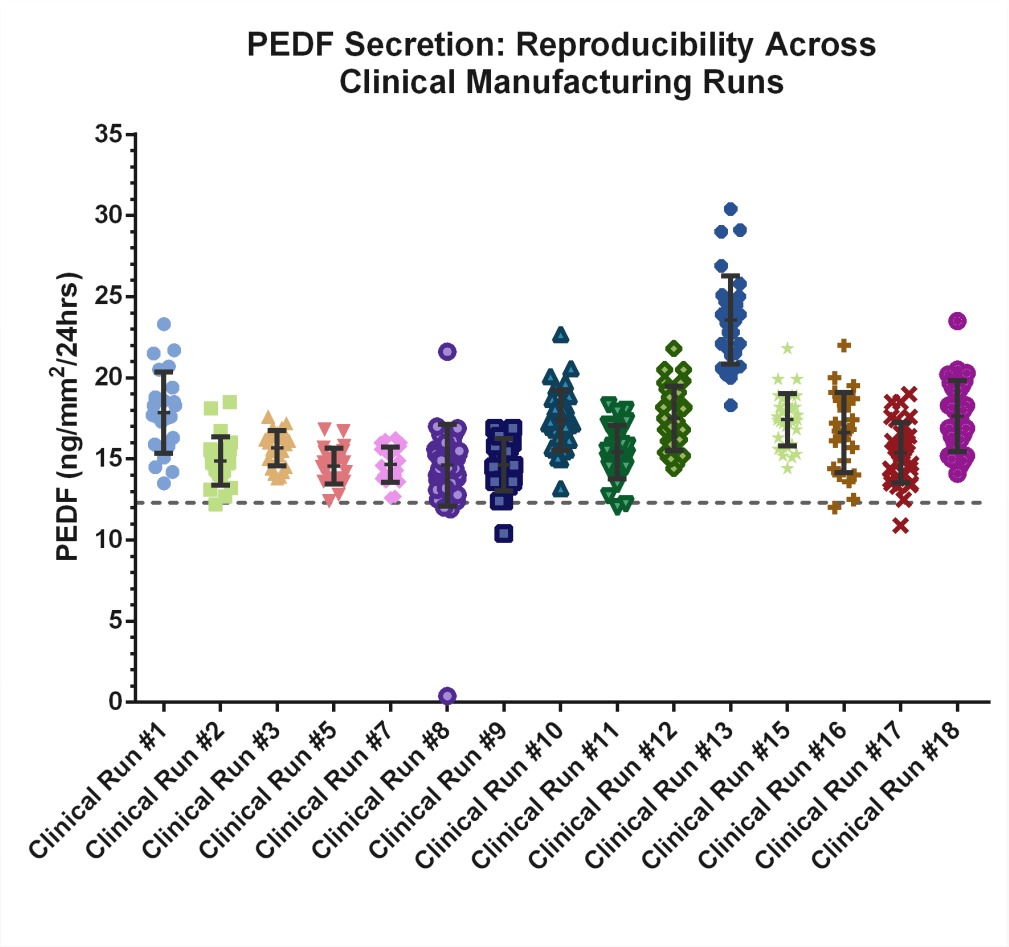
Scale-out

- Eventually Scale to 100,000 to 300,000/ year
- Manual Process Repeatedly Applied to Each Implant

Important to Determine Reproducibility Within and Across cGMP Manufacturing Lots of CPCB-RPE1

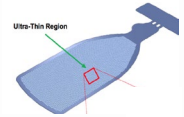
Production of the CPCB-RPE1 Implant



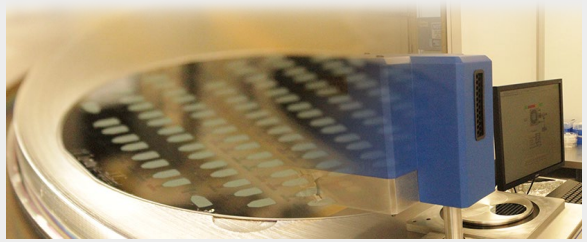


Scale-Out of the CPCB-RPE1 Manufacturing Process: Critical Technology Developments

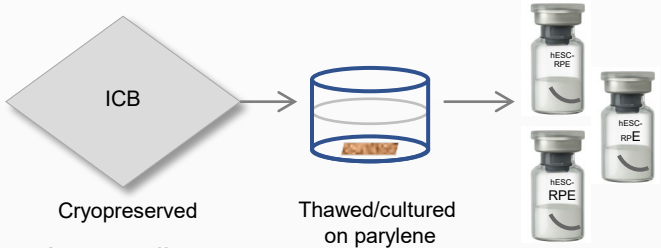
Scale-out of Production of Parylene Membranes



MEMS Manufacturing



Production of Implant



Cryopreserved Intermediate Cell Bank of RPE Cells

Thawed/cultured on parylene membranes

CPCB-RPE1

Long-term Storage Conditions

Release for Patient Implantation

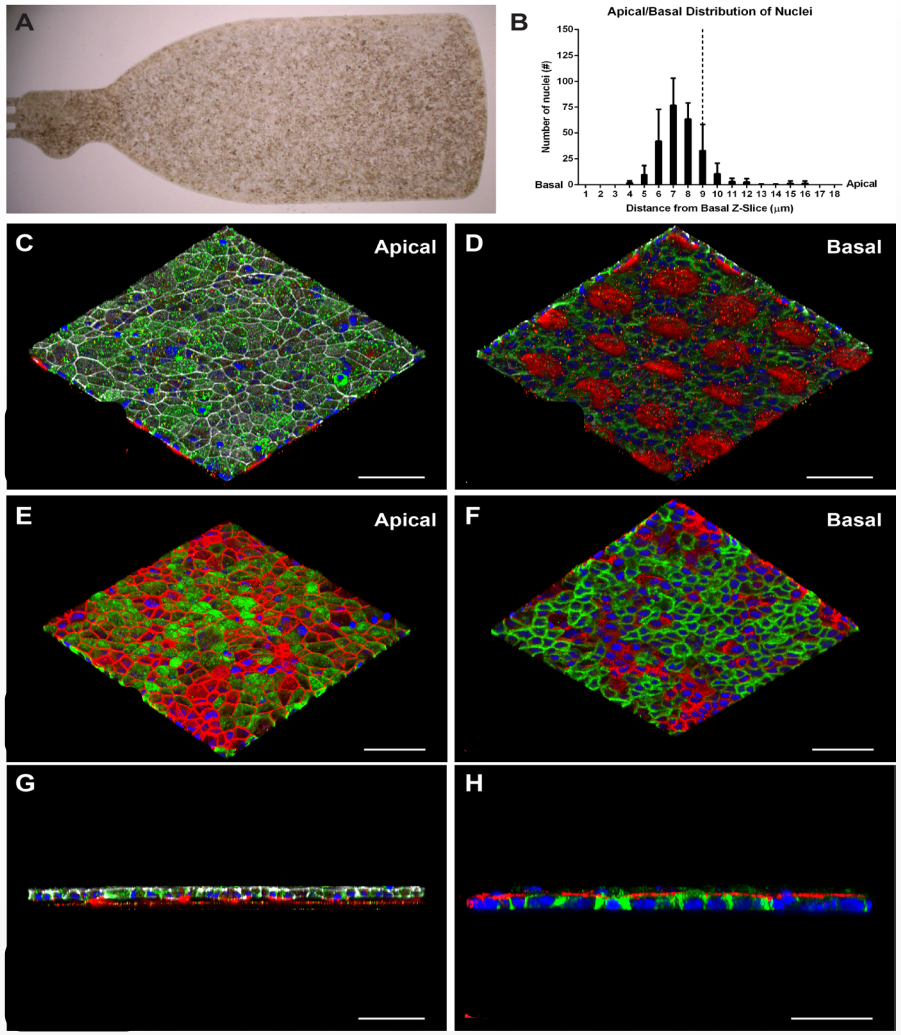
Cryopreservation

Confocal Imaging of Cryopreserved CPCB-RPE1 RPE Cell Polarity Post-Thaw as Assessed for Apical and Basal Markers.

Apical Marker
Basal Marker

Apical Marker
Basal Marker

Apical Marker
Basal Marker

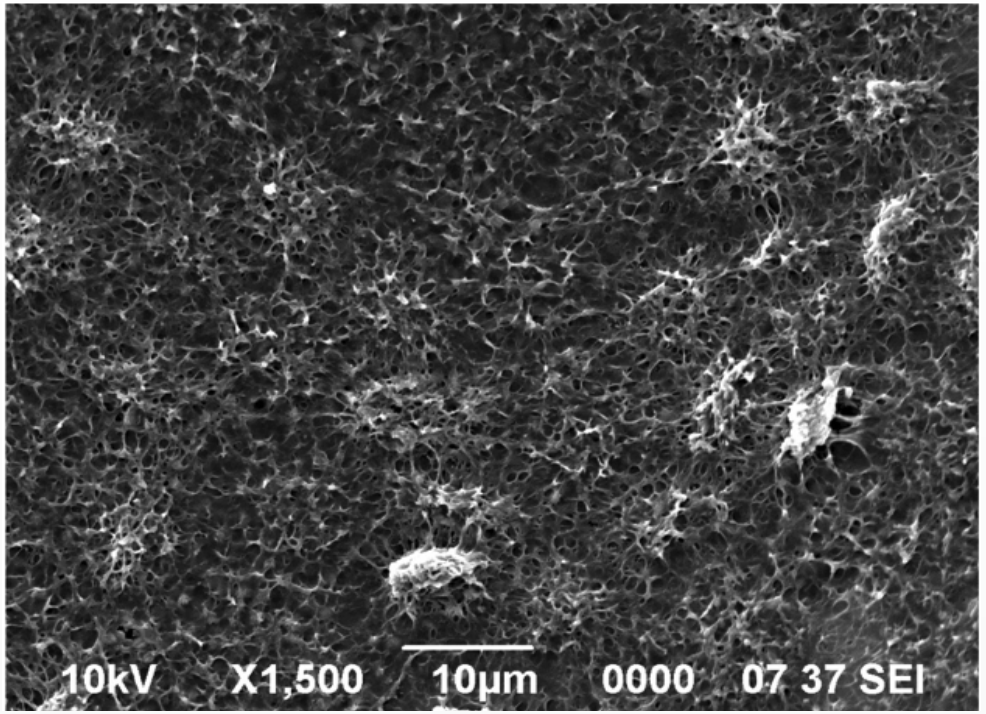


Apical Marker
Basal Marker

Apical Marker
Basal Marker

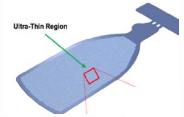
Apical Marker
Basal Marker

Apical Villi Development

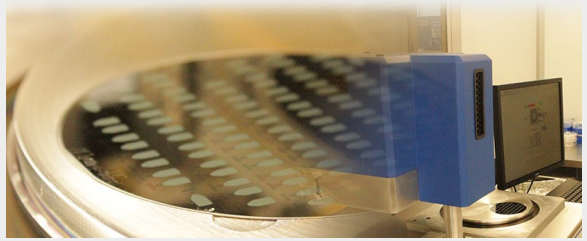


Scale-Out of the CPCB-RPE1 Manufacturing Process: Potential for Use of Imaging, AI and Machine Learning

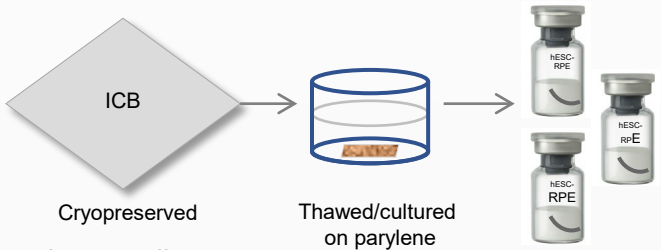
Scale-out of Production of Parylene Membranes



MEMS Manufacturing



Production of Implant



Cryopreserved

Intermediate Cell Bank of RPE Cells

Thawed/cultured on parylene membranes

CPCB-RPE1

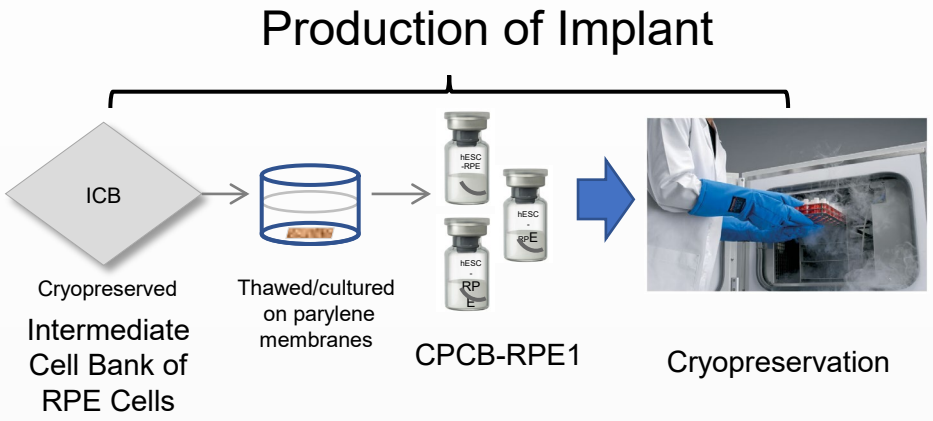
Long-term Storage Conditions

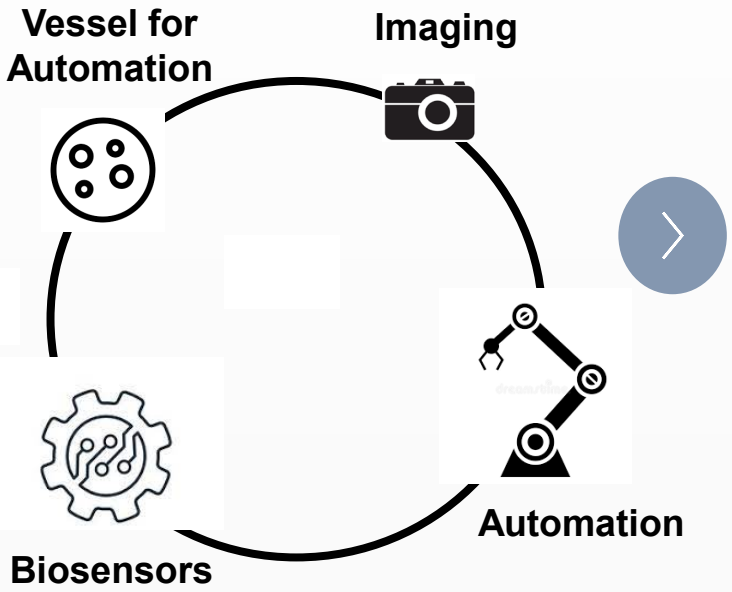
Release for Patient Implantation

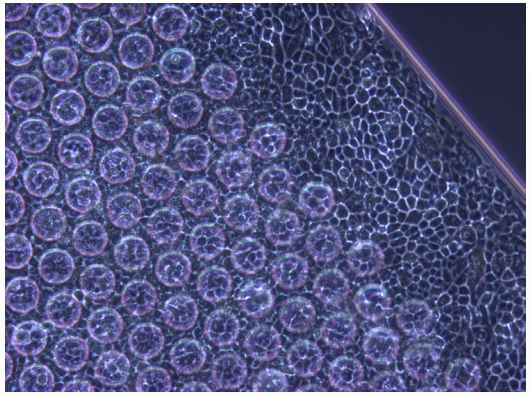
Cryopreservation

Tremendous Potential for Imaging, AI, and Machine Learning to AID in Inspection, In- Process Testing, and Release Testing of the Implants

Automation of the CPCB-RPE1 Implant Manufacturing Process







CPCB-RPE1 Implant

Key Considerations for Automation

- Maintaining a Sterile, Closed System
- Compatibility of Materials with Cell Viability and Growth
- Growth and Maturation of the Cells on the Implant
- Process Times
- Harvesting of the Implants
- Imaging During Production and In-Process Specifications
- Processing Time for In-Process Assays
- Use of AI to Develop Structural and Functional Specifications
- Use of AI to Develop Predictive Algorithms

Collaboration with ARMI

Key Considerations

Knowing the Critical Process Parameters to Produce Cells Is Key Information to Begin Successfully Develop Automated Manufacturing Procedures for Cells

Imaging, AI, and Machine Learning, and Could Be Important Tools to Discover New Automated Ways to Assess the Structure, Composition and Functionality of Cell Products.