Designing Stem Cell Therapies: A New(t) Approach

Blood Centers of California 9-29-14

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Department of Molecular, Cellular and Developmental Biology
University of California, Santa Barbara


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Regenerative Medicine

Midterm.

What is a Stem Cell?

a) A cell from the stem of a leaf.

b) The latest cell phone from Apple.

c) A self-renewing cell capable of differentiating into a specialized cell.

Midterm Answer Key

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c) A self-renewing cell capable of differentiating into a specialized cell.

Types of Stem Cells

1. **Pluripotent** – Can give rise to most cell types in the body.

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Types of Stem Cells

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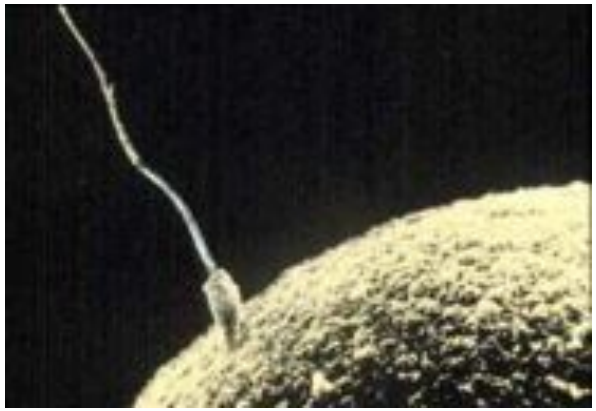
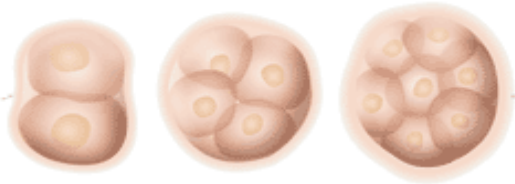
   (Embryonic Stem Cells, Induced Pluripotent Stem Cells)
2. **Multipotent** – Can give rise to a few cell types.
   (Adult Stem Cells)

Where do embryonic stem cells come from?

Early Embryonic Development



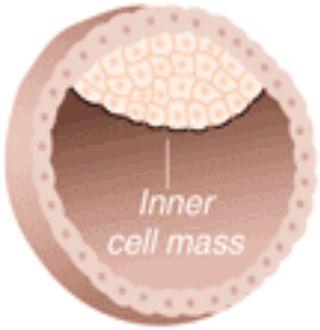
Day 1 – Sperm meets egg



Day 2-3 – Cells proliferate to form **blastula.**

~32 cells

Day 4 – Formation of **blastocyst.**



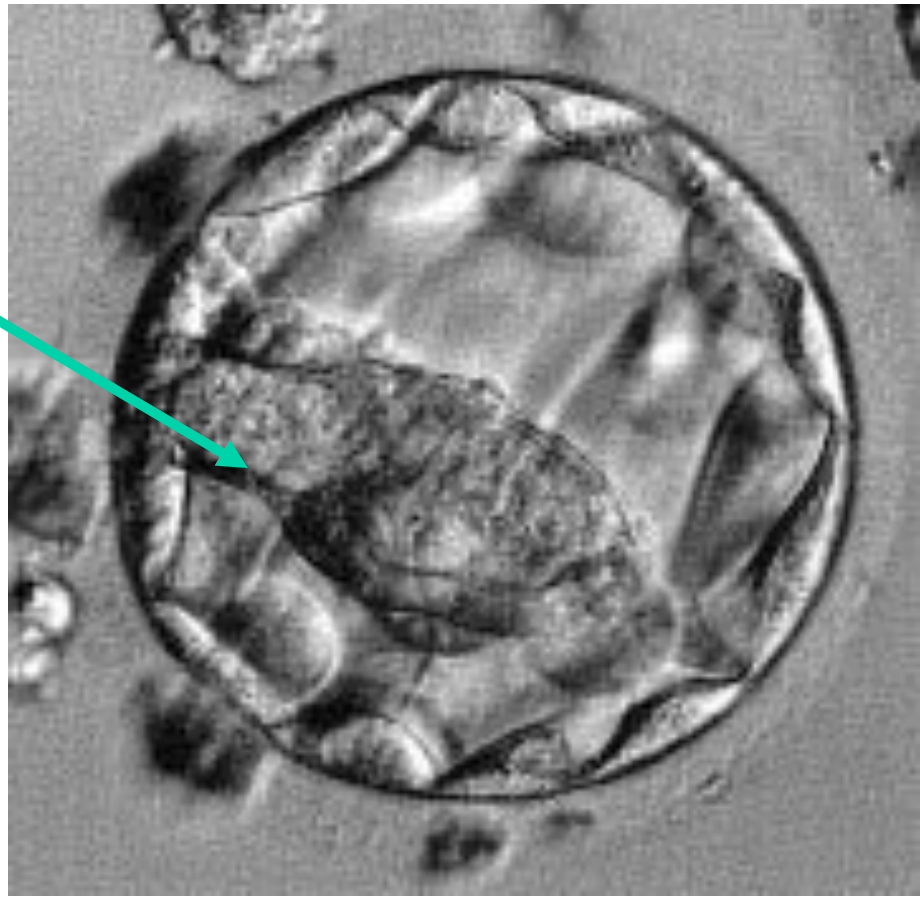
~128 cells

Day 5 – **Inner Cell Mass** appears.

Day 6-9 – **Implantation occurs.**

Embryonic Stem Cells come from the inner cell mass of a 5 day old blastocyst

Inner Cell Mass



~128 cells

Excess blastocysts are generated during in vitro fertilization

Nobel Laureate Robert Edwards (2010) with three generations of Browns

* First baby (Louise Brown) born 1978.

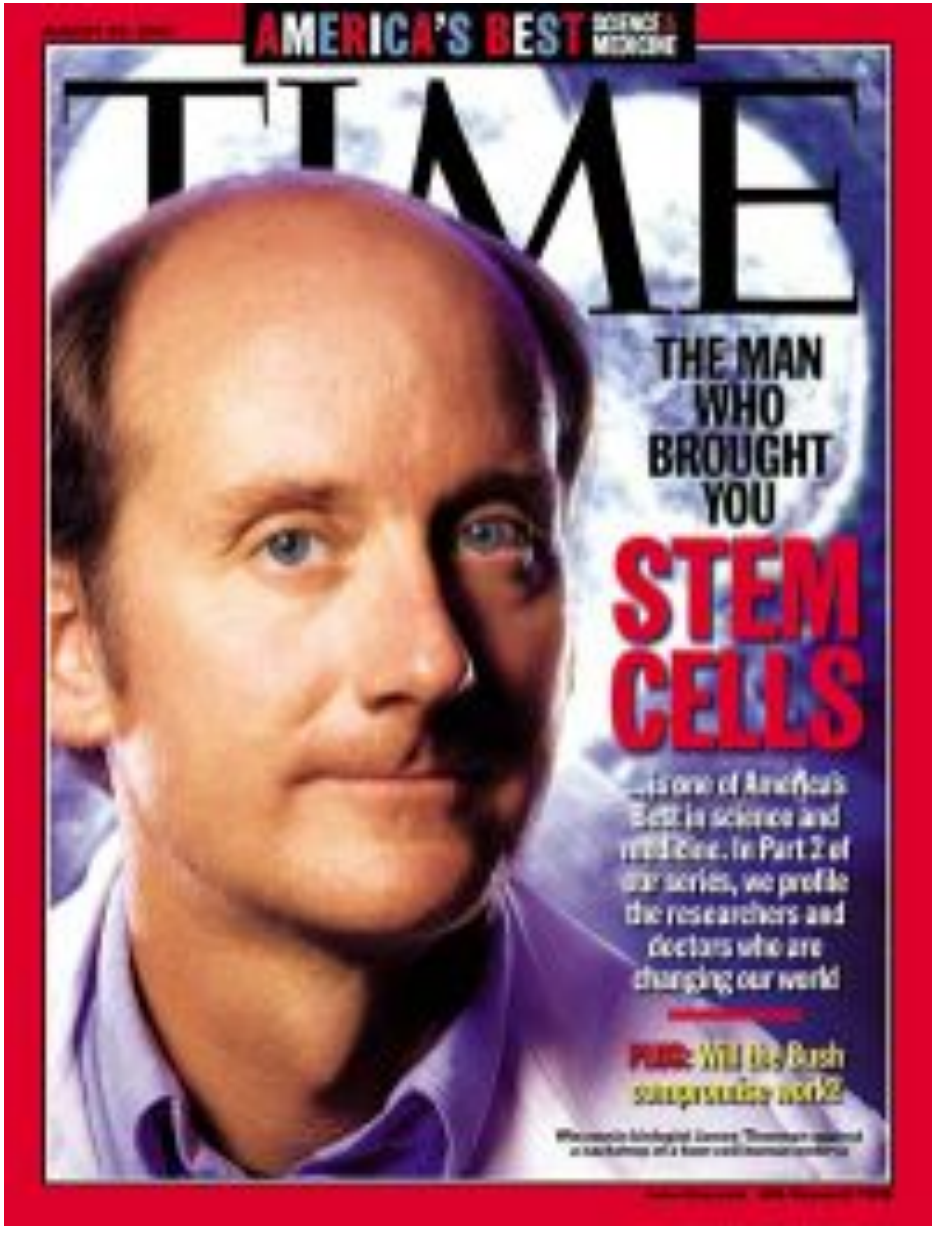
* Over 3,000,000 babies worldwide born to date.

* ~400,000 frozen embryos in the US.

* Most will be discarded.

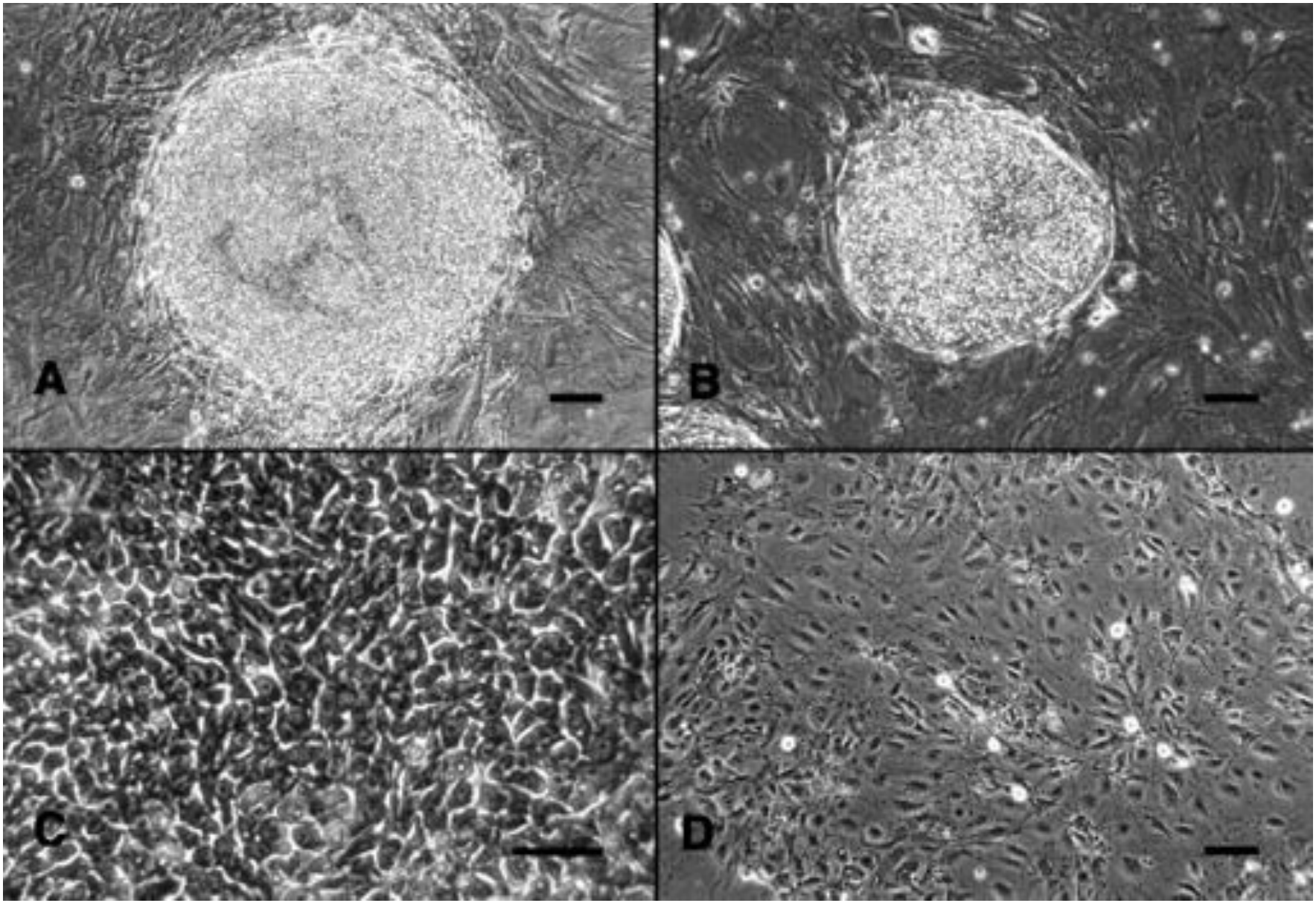
http://www.rand.org/pubs/research_briefs/RB9038/index1.html
http://apps.nccd.cdc.gov/ART/NSR.aspx?SelectedYear=2007

James Thomson, University of Wisconsin, Time Magazine, 8/20/2001

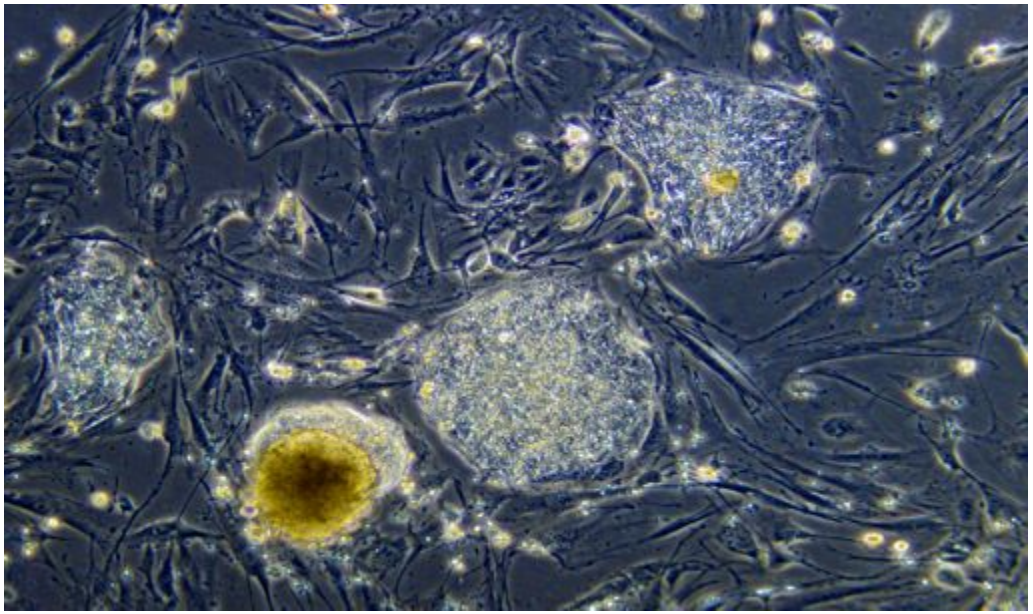


Co-Director, Center for Stem Cell Biology and Engineering, UC Santa Barbara

Colonies of Human Embryonic Stem Cells grown in culture



From Thomson et al, 1998, Science.

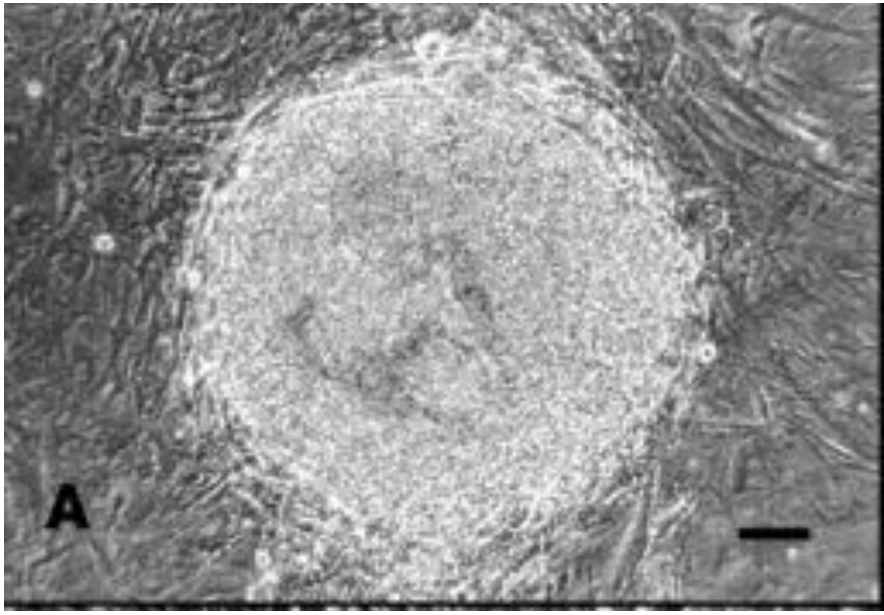


Univ. Wisc.

Human Induced Pluripotent Stem (iPS) cells: skin cells reprogrammed to become stem cells

Oct4
Sox2
Klf4
Myc

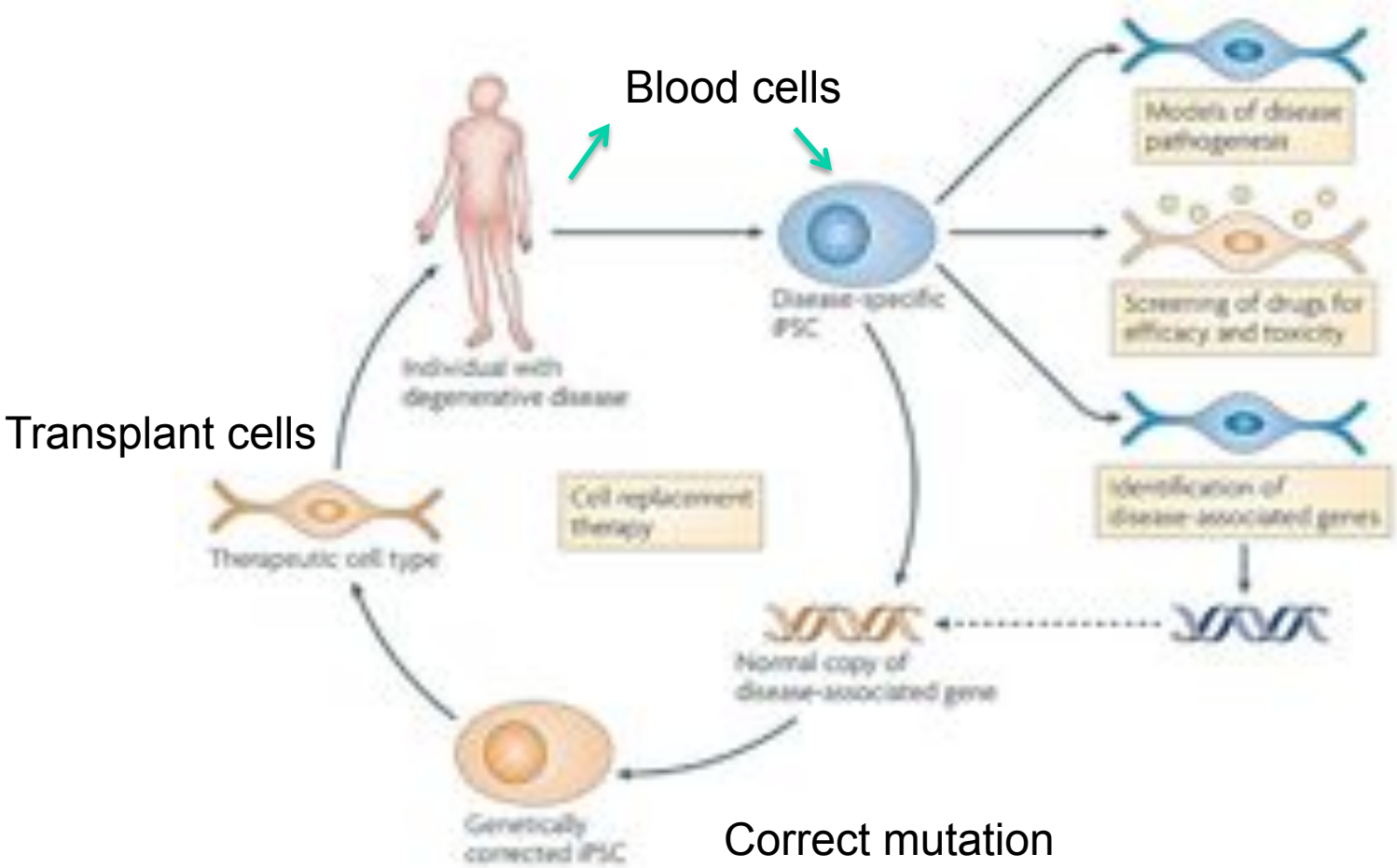
Reported by
Shinya Yamanaka (Kyoto)



Oct4
Sox2
Lin28
Nanog

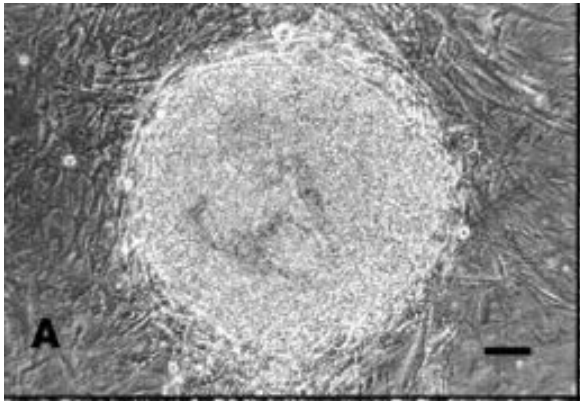
Reported by
James Thomson (UWisc, UCSB)

Reprogram blood cells to make iPS cells

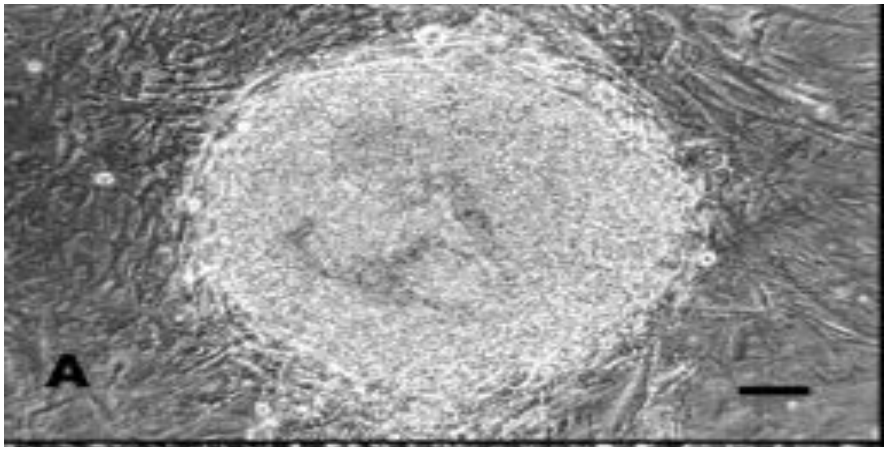


Which stem cell is the best?

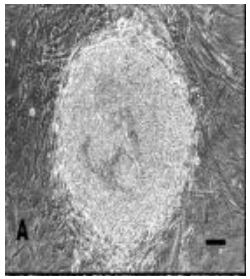
Embryonic Stem Cells?



Induced Pluripotent Stem Cells?

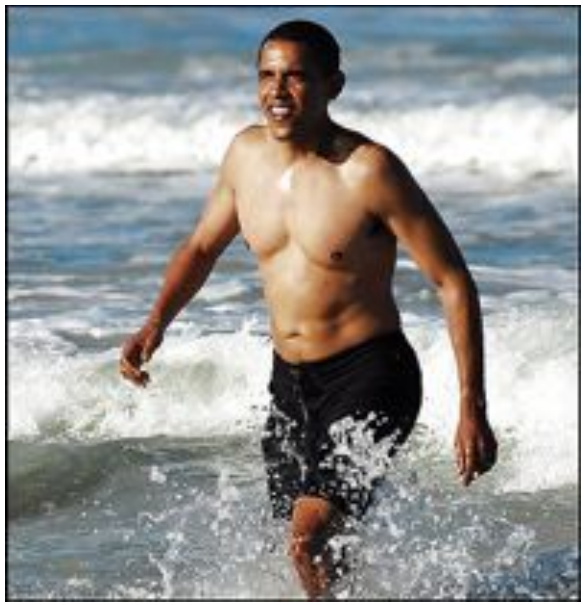


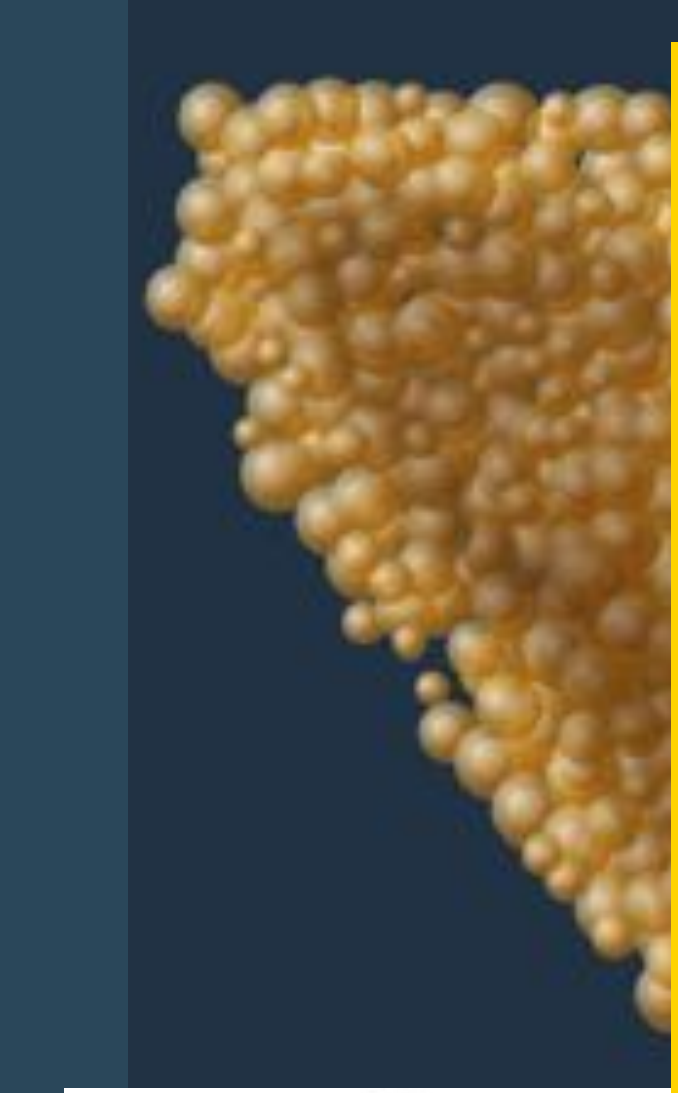
Adult Stem Cells?



More research is needed !

Stem Cell Research: A political football





•California Institute for Regenerative Medicine

- *UCSB Training Program in Stem Cell Biology and Engineering– postdoctoral fellows and graduate students*
- *UCSB Center for Stem Cell Biology and Engineering - renovation of new facilities*
- *UCSB Laboratory for Stem Cell Biology and Engineering – renovation of new lab*
- *UCSB Tools and Technology Grant – research support for bioengineering*
- *Disease Team Grant – macular degeneration*

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

UNIVERSITY OF CALIFORNIA SANTA BARBARA

CENTER FOR STEM CELL BIOLOGY AND ENGINEERING

www.stemcell.ucsb.edu

UCSB Ranked #2 in the world in science and technology!
Leiden University Study, April 2013

UCSB

The Promise of Stem Cell Research

Treatments for:

- Cancer
- Parkinson's Disease
- Alzheimer's Disease
- Diabetes
- Spinal Cord Injury
- Heart Disease
- Macular Degeneration

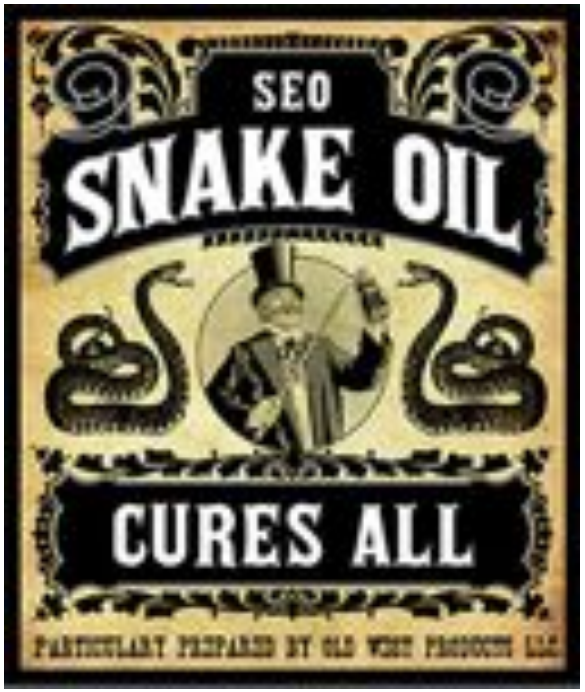
See CIRM website for more

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

Challenges in Cellular Therapy:

1. The cells might not survive after transplantation.
2. The cells might not integrate and function due to damage in the tissue.
3. The cells might be rejected by the immune system.
4. Contaminating cells might form a mass or tumor.

Beware of Snake Oil !!!



Unregulated, unproven foreign stem cell companies prey on desperate patients !

See Stem Cell Links on CIRM web site

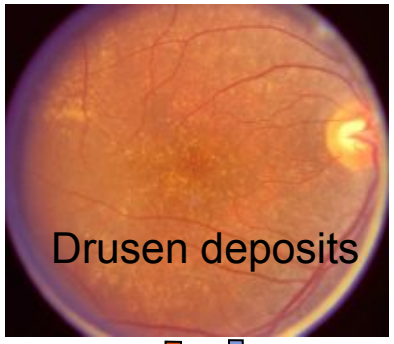
Cellular Therapy:
The eye may be a good place to start

Advanced surgical methods, non-invasive imaging, good endpoint parameters, and small numbers of cells needed make the eye an excellent candidate for cellular therapy.

Age-Related Macular Degeneration (AMD)

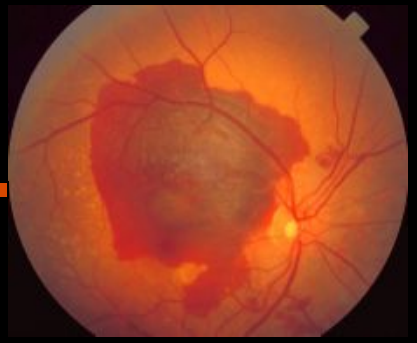
Normal

Early AMD



Disciform Scar

Exudative/CNV



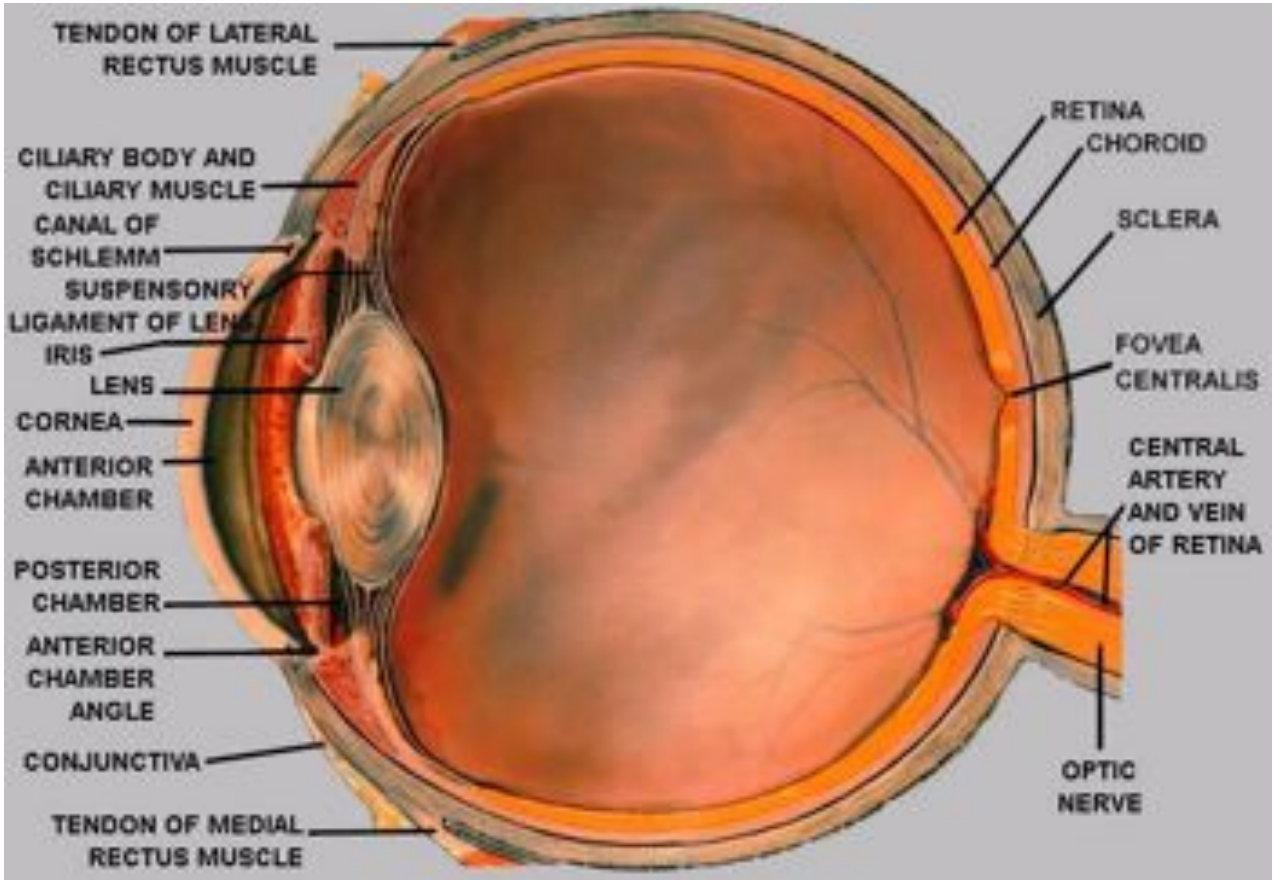
Geographic Atrophy

"Wet" or Exudative AMD ~ 10-20%

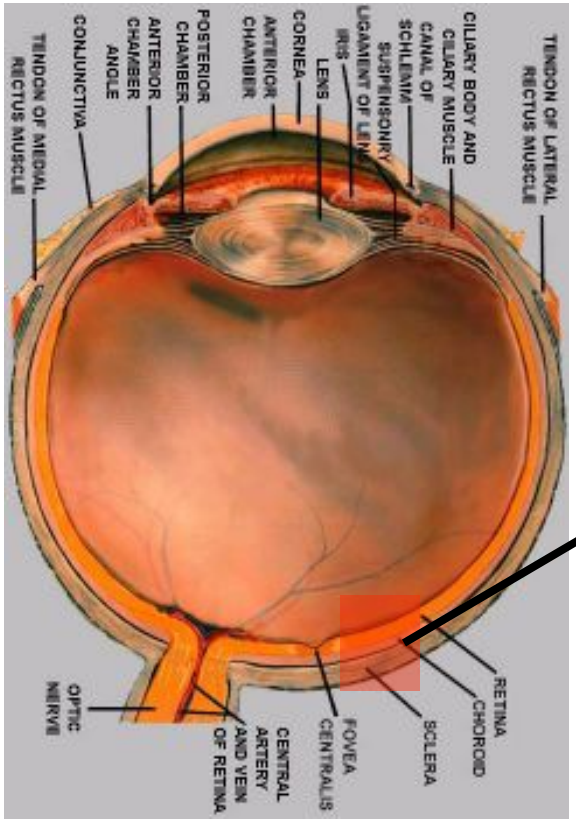
"Dry" or Atrophic AMD ~ 80-90%

Dysfunction / death of RPE leads to AMD

Eye anatomy and microanatomy



Eye anatomy and microanatomy



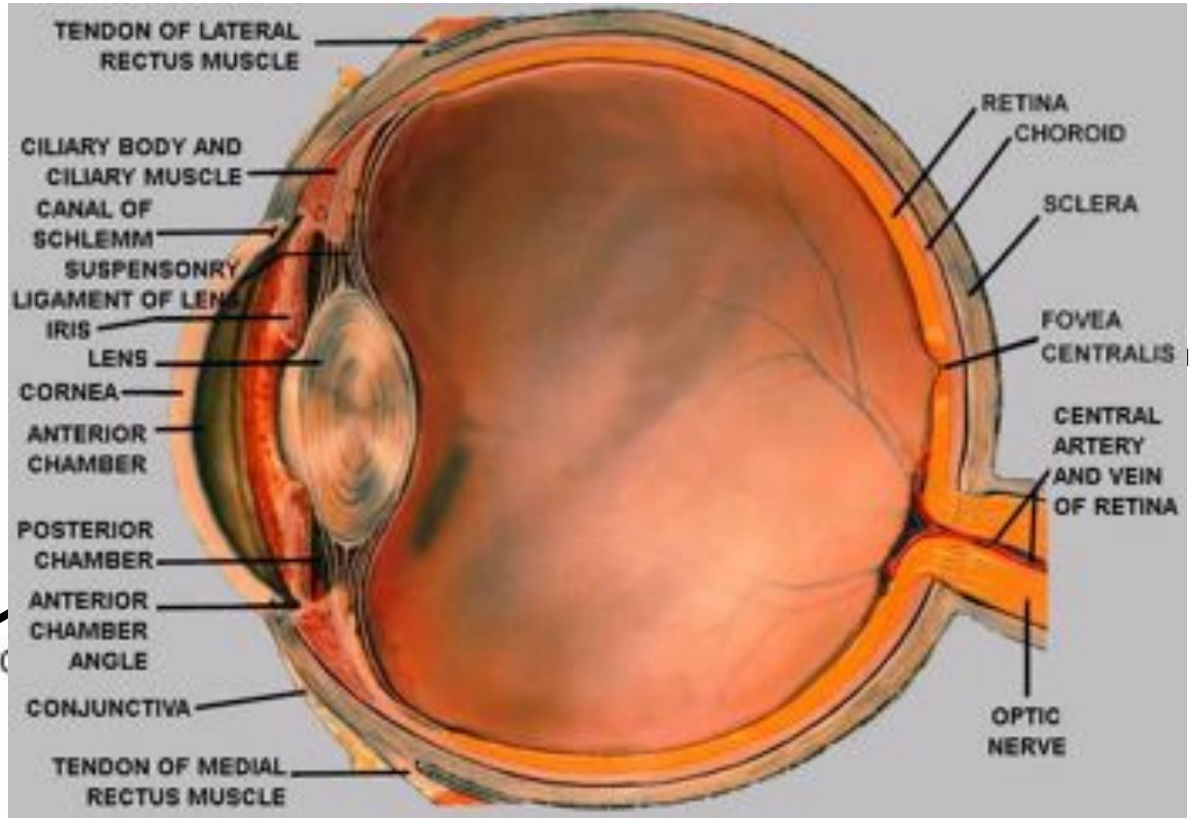


Figure Adapted from Dr. Wendy Gilmore; Microanatomy of the Eye; Class Notes, Keck School of Medicine Neuroscience System; 4/7/03

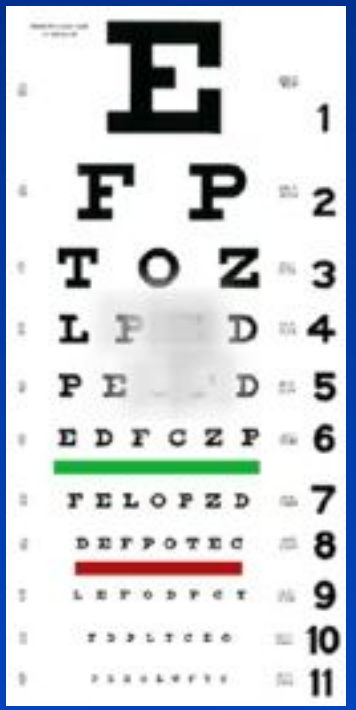
Cells in The Retina

RPE

Retinal Pigmented Epithelium (RPE) – support cells for the photoreceptors

RPE cell death causes Macular Degeneration

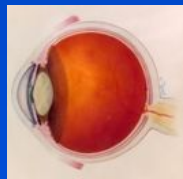
Could Stem Cell Research Lead to a Treatment for Age-Related Macular Degeneration?



1. RPE cell death causes AMD.

2. Human embryonic stem cells and induced pluripotent stem cells can differentiate into RPE cells.

1. These cells could replace damaged RPE and prevent loss of vision.



Development of therapies using hES Cells

The California Project to Cure Blindness

Funded by The California Institute for Regenerative Medicine

Collaboration: UCSB, USC, Cal Tech, Univ. College London, City of Hope, RPT Inc

Goal: Application to FDA for stem cell-based therapy for Macular Degeneration by 2014

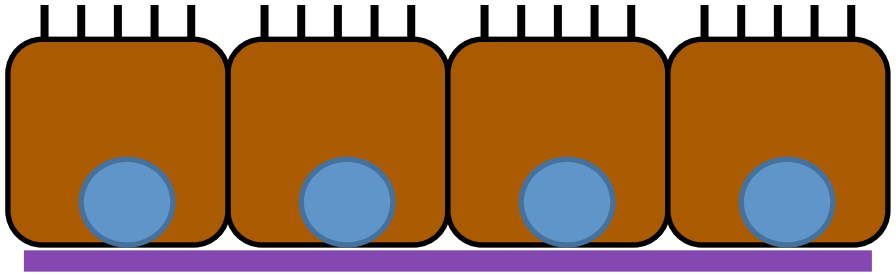
The California Project to Cure Blindness

CIRM Macular Degeneration Disease Team

- USC Doheny Eye Institute (Mark Humayun, PI; David Hinton Co-PI; Gerald Chader (Exec Director), Vas Sadda, Biju Thomas)
- UCSB Macular Degeneration and Stem Cell Centers (Dennis Clegg, Co-PI; Lincoln Johnson, Sherry Hikita)
- UCL London Project to Cure Blindness (Pete Coffey, Partner PI funded by MRC)
- Caltech Biology and Chemistry (Scott Fraser, Bob Grubbs, Yu-Chong Tai)
- City of Hope Center for Biomedicine and Genetics GMP Facility (Larry Couture)
- Regenerative Patch Technologies Inc. (Jane Lebkowski, Katy Spink)

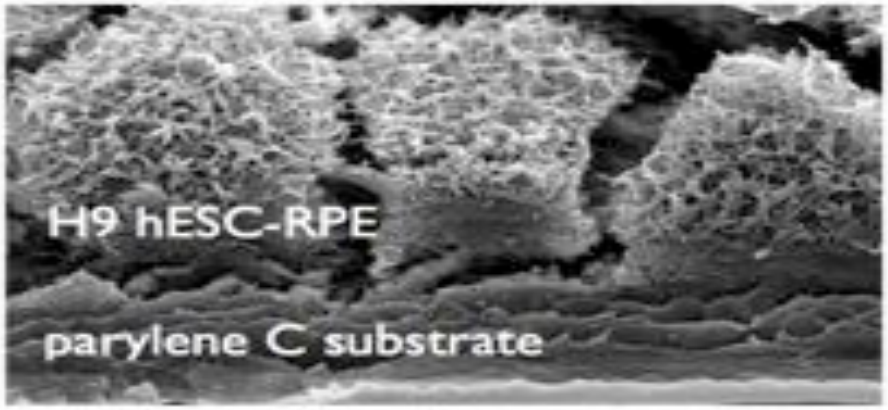
Our Approach:

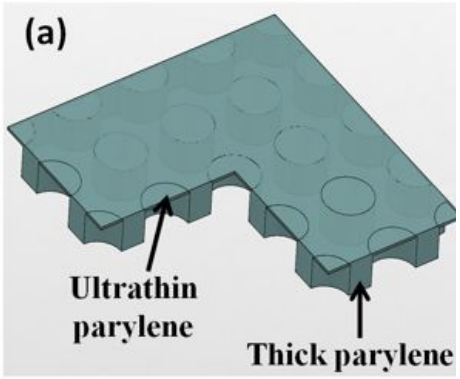
hESC-RPE monolayer on synthetic substrate



hESC-RPE

parylene substrate

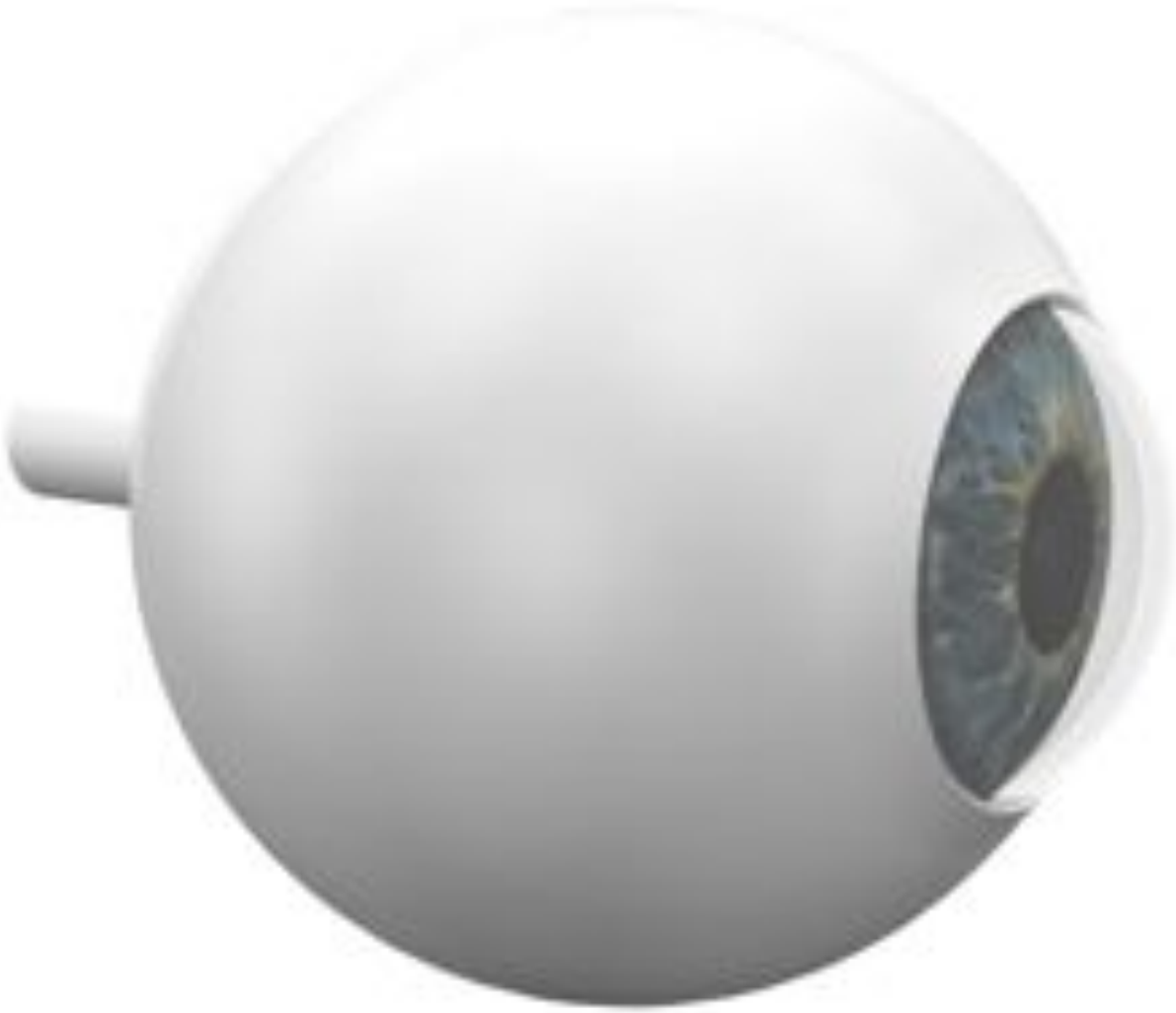




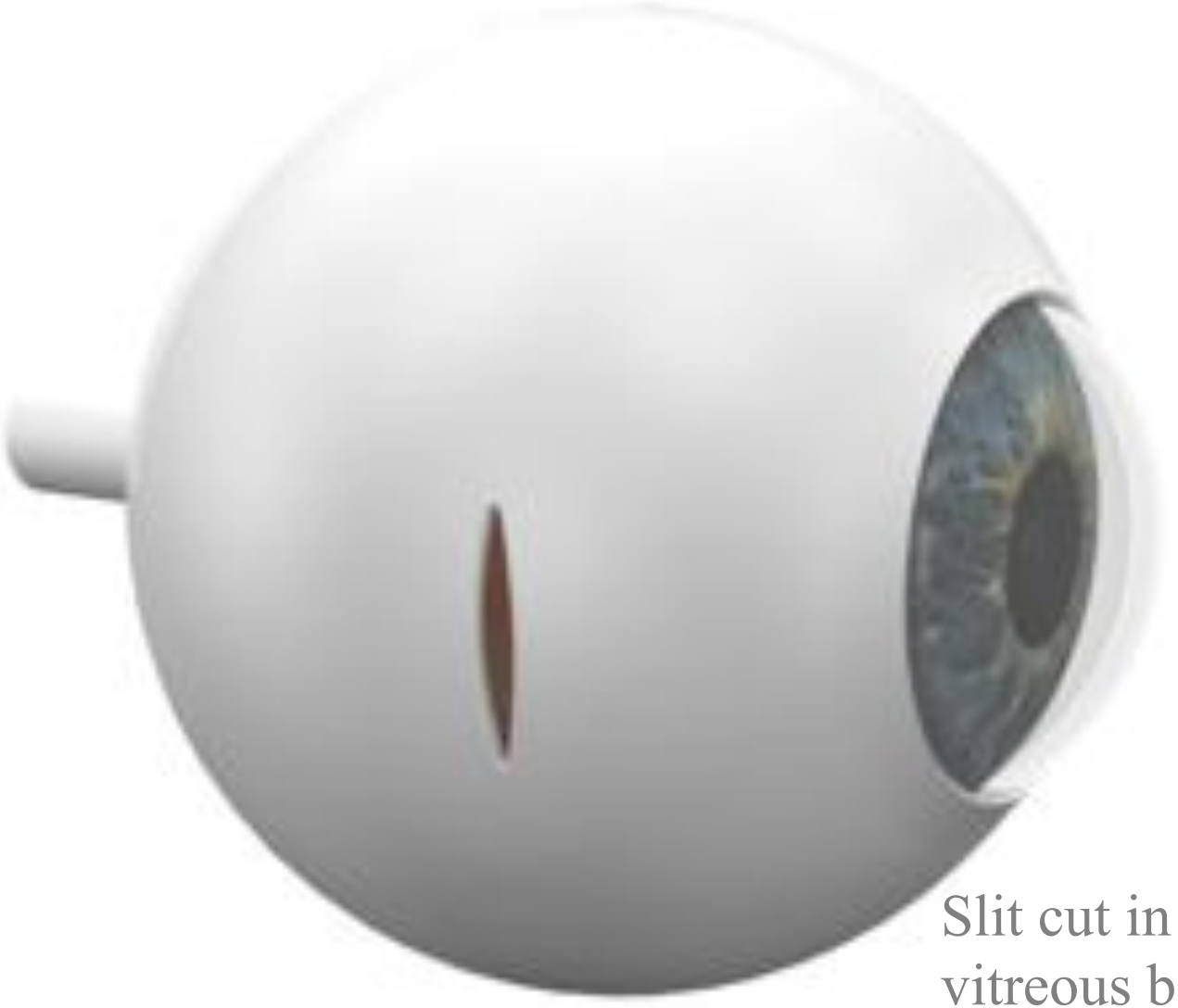
Matrix-coated parylene provides a biocompatible replacement for Bruch's membrane

Proof of Concept: Rescue of Photoreceptors in the RCS Rat Model of Retinal Dystrophy

Strategy for transplantation of RPE grown on a synthetic sheet

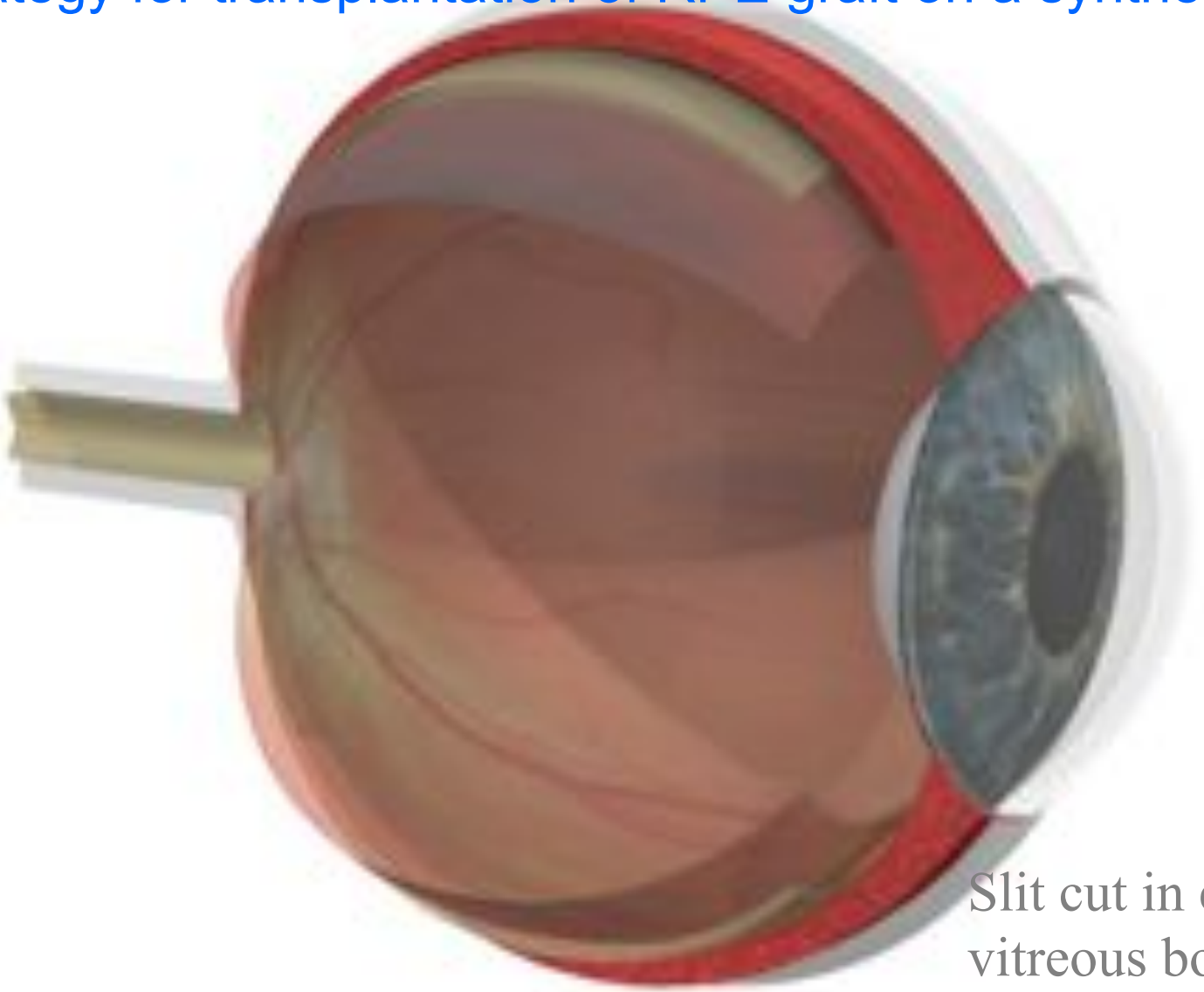


Strategy for transplantation of RPE graft on a synthetic sheet



Slit cut in eye, vitreous body flushed and irrigated

Strategy for transplantation of RPE graft on a synthetic sheet



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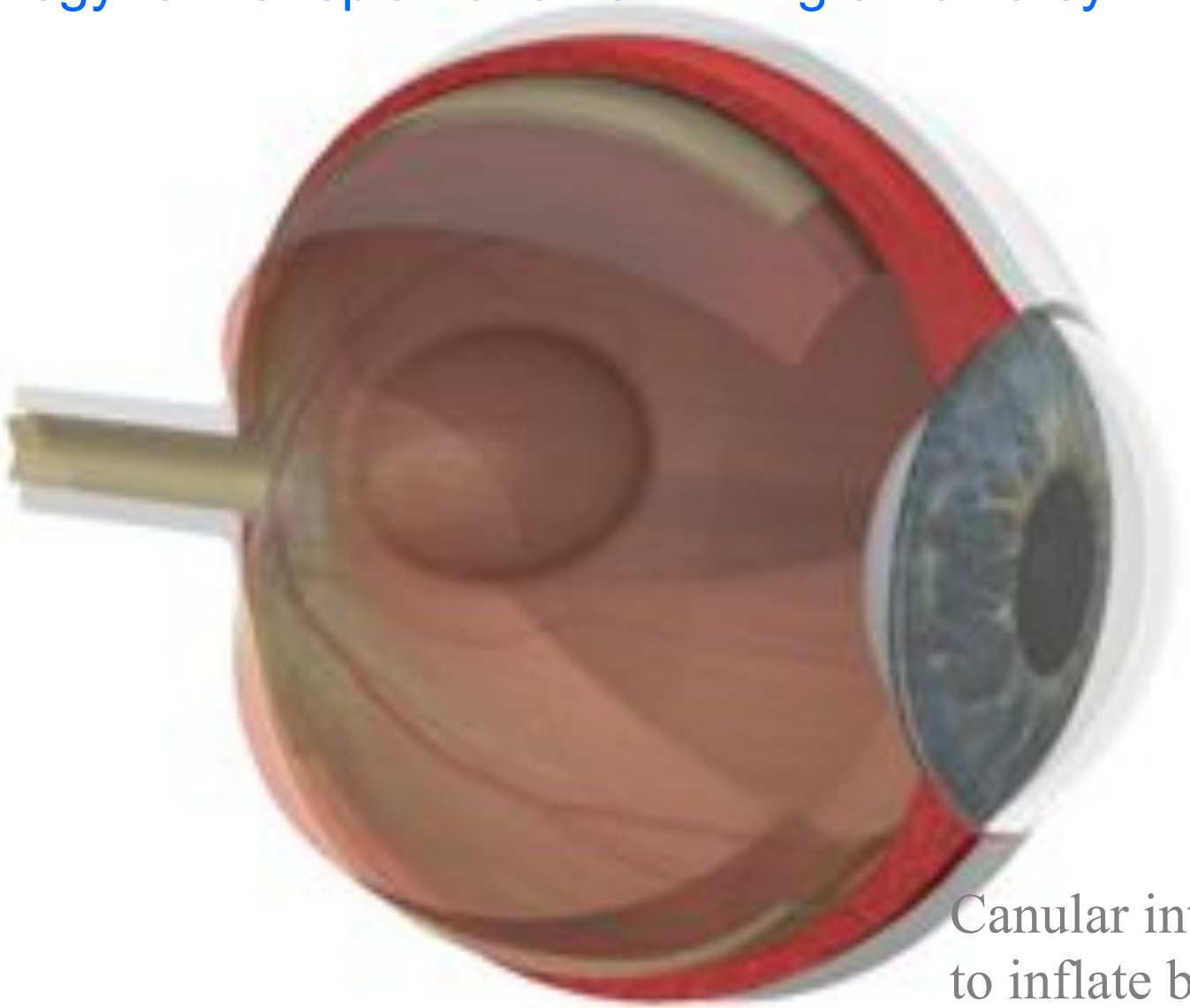
Strategy for transplantation of RPE graft on a synthetic sheet

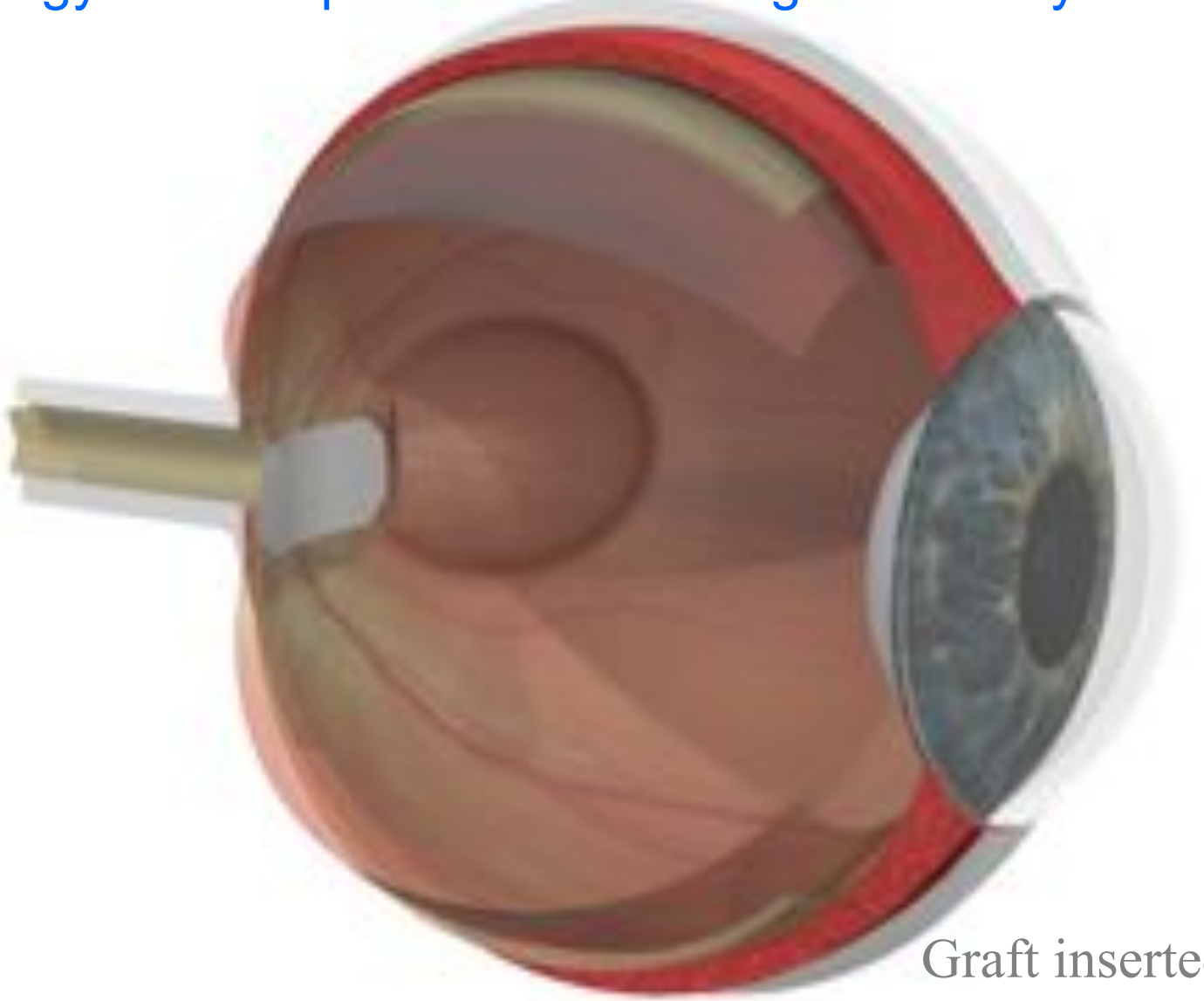


Canular introduced to inflate blister between retina and choroid

Strategy for transplantation of RPE graft on a synthetic sheet

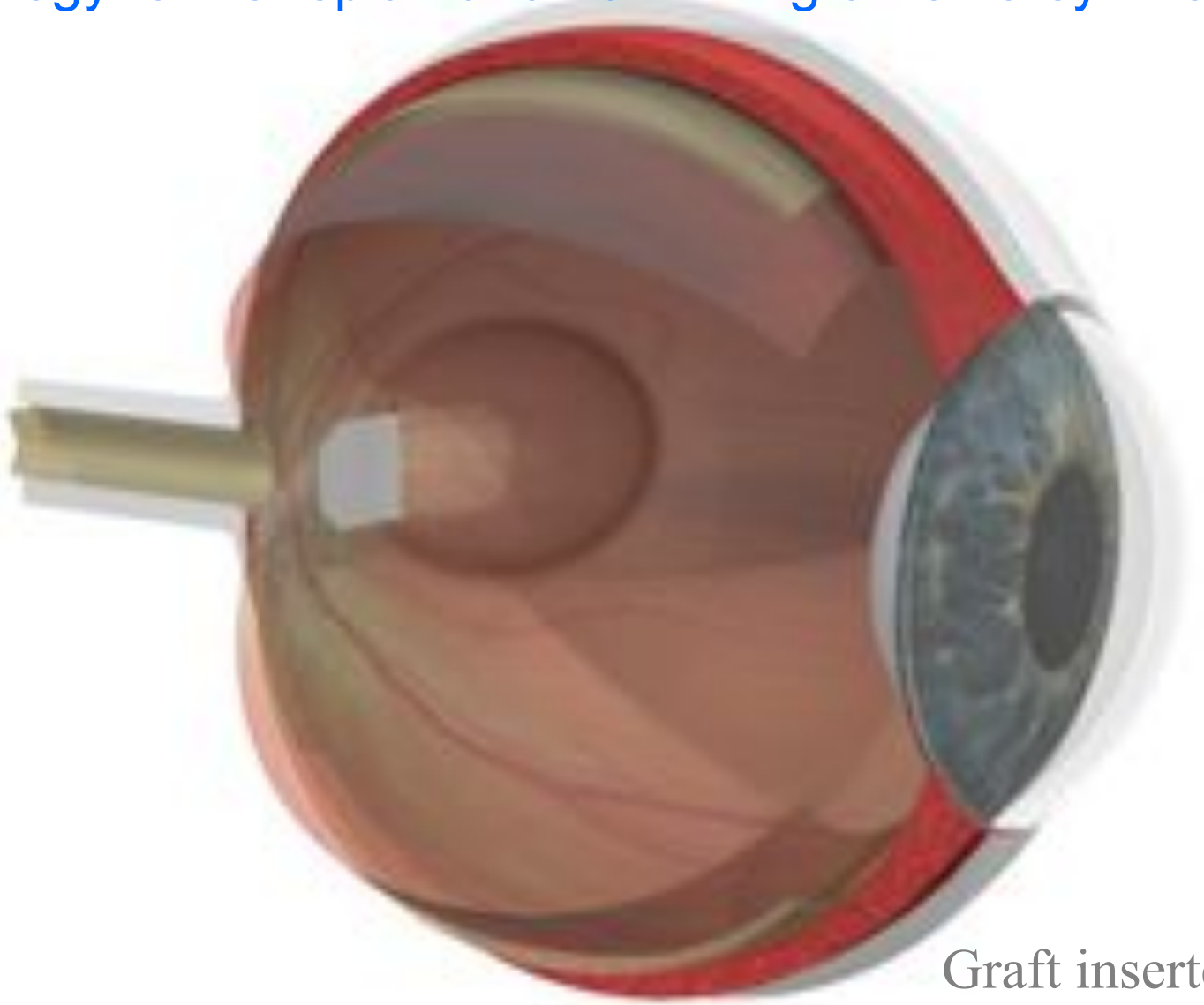
Slit cut in retina
(blister)

Strategy for transplantation of RPE graft on a synthetic sheet



Graft inserted through slit and positioned in blister

Strategy for transplantation of RPE graft on a synthetic sheet



Graft inserted through slit and positioned in blister

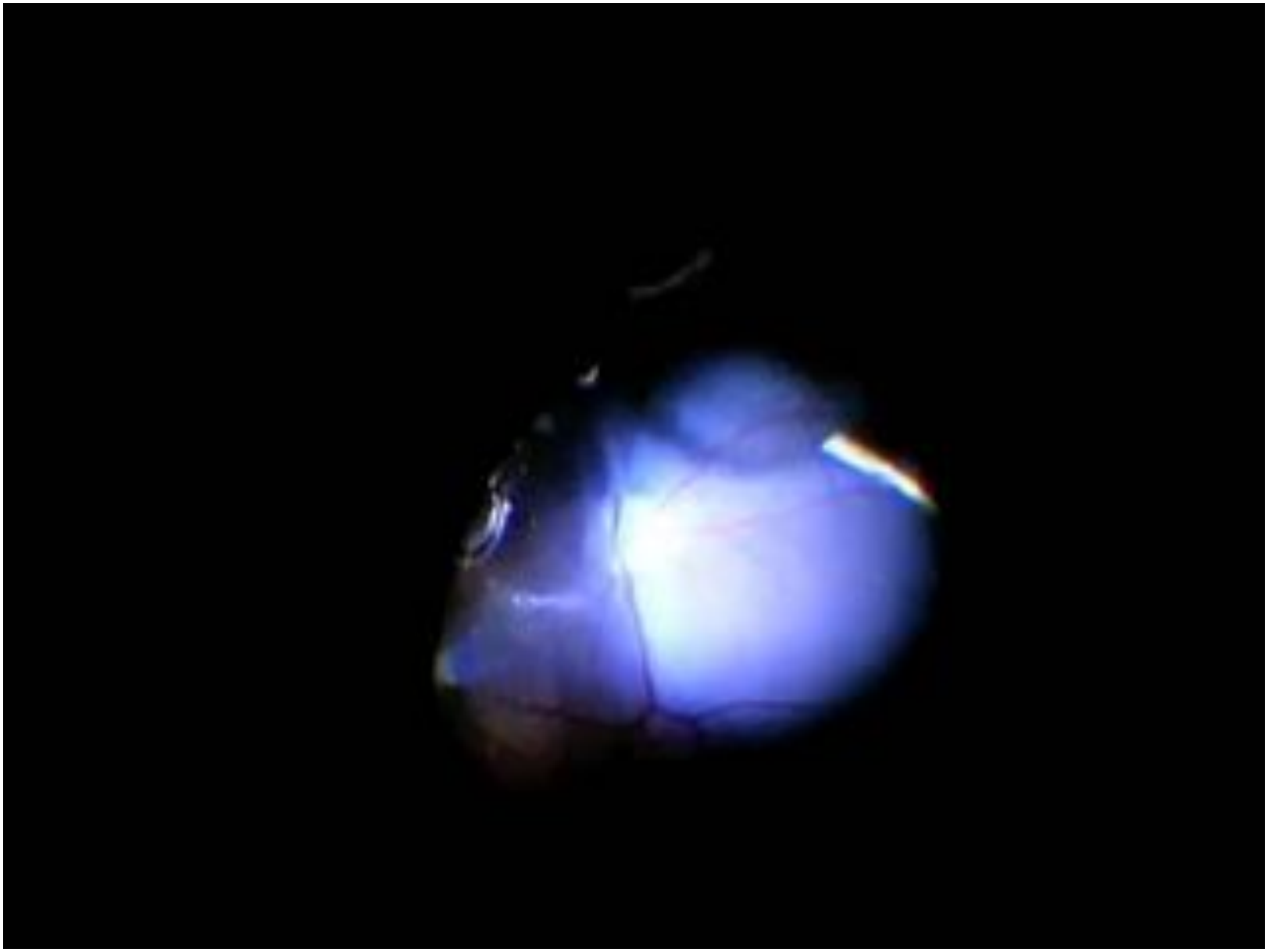
Strategy for transplantation of RPE graft on a synthetic sheet

Graft inserted through slit and positioned in blister

Strategy for transplantation of RPE graft on a synthetic sheet

Blister evacuated and holds graft in place

Transplant of RPE patch into pig eye



Rodrigo Brandt, Mark Humayun, University of Southern California

On to Clinical Trials

City of Hope

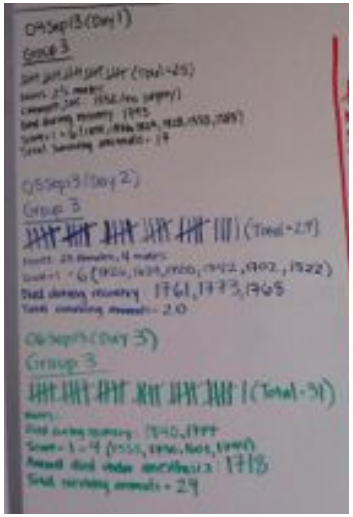
Center for Applied Technology Development

cGMP Compliant Production of Cells, Vectors and Protein for Academia and Industry

- Manufacturing Protocols Transferred from UCSB to City of Hope
- Production of cells for Phase I clinical trial completed
- Meetings with FDA to identify requirements for trial completed
- On track for 2015 phase one clinical trial

THE CALIFORNIA PROJECT to cure blindness

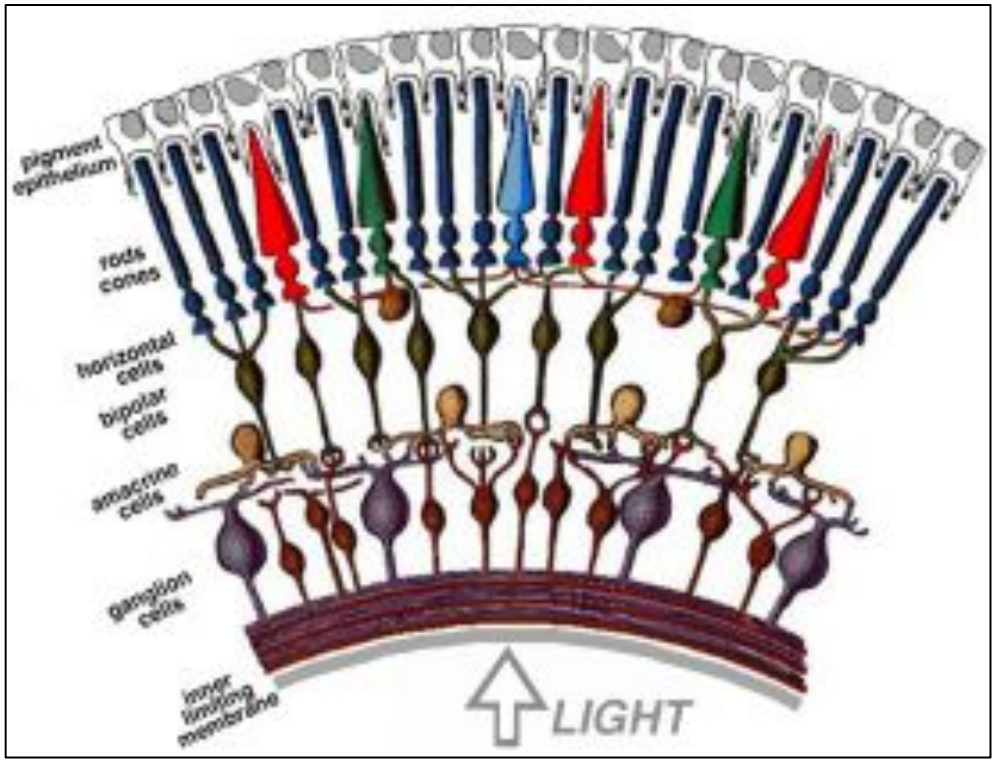
IND-Enabling Studies of Toxicity, Tumorigenicity, Biodistribution, and Efficacy



Looking Forward …..

Development of therapies using iPS Cells

Lily Wash
Retinitis Pigmentosa



Meghan Downing
Stargardt's Disease

Can we make photoreceptors and combine with RPE to treat retinal disease?

iPS RPE + photoreceptors for retinal degeneration

Foundation Fighting Blindness

Wynn Gund Translational Grant

University of Wisconsin
David Gamm, Jamie Thomson, Derek Hei

UC Santa Barbara
Dennis Clegg

Goal: Generate RPE and Photoreceptors from iPS cells made from blood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THE CALIFORNIA PROJECT to cure blindness

UCL

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- Nico Kahl
- William Thi

- Linc Johnson
- Monte Radeke
- Ken Kosik
- Craig Hawker
- Erkki Ruoslahti
- Pete Coffey

Collaborators

Mark Humayan, David Hinton, Doheny Eye Institute, USC

James Thomson, Morgridge Institute, University of Wisconsin and UCSB

David Gamm, Waisman Institute, University of Wisconsin

Funding: California Institute for Regenerative Medicine, Army Research Office, Institute for Collaborative Biotechnologies, Fight for Sight, Foundation Fighting Blindness, Wiiliam K. Bowes Foundation and Other Important Private Donors

www.stemcell.ucsb.edu


The End