



# Preclinical proof of concept and other preclinical issues

**International Regulatory Forum of Human Cell Therapy and Gene Therapy Products**

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# Proof of concept (POC)

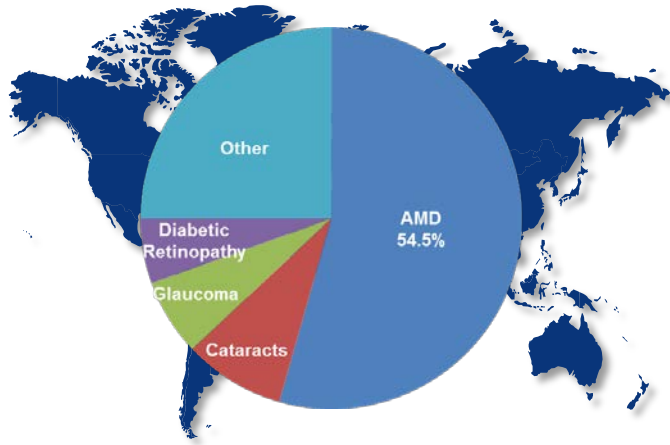
## Scientific Rational for clinical

- Biologically active dose levels
- Dosing regimens (single, repeated)
- Appropriate route of administration
- Duration of response
- Mechanism of action
  - Protection/prevention
  - Regeneration
- Timing of administration relative to disease/injury
- Potential patient population
- Monitoring efficacy and safety

# Umbilical Tissue Derived Cells (palucorcel, CNTO 2476, hUTC) for the treatment of Geographic Atrophy

- Why Geographic Atrophy?
- Why Umbilical Tissue Derived Cells (palucorcel) ?

# Age-Related Macular Degeneration (AMD) is the leading cause of irreversible vision loss in the world



AMD affects 1 in 2000 people in the U.S. and other developed countries\*

The macula is required for reading, driving and recognizing faces



**Normal Vision**



**Vision with AMD**

# The macula comprises only ~4% of the retina, but provides 50% of visual information reaching the brain

## Macula

- o 6 mm diameter
- o 6,000 cones/mm<sup>2</sup>

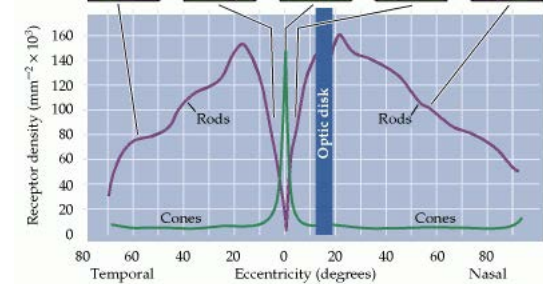
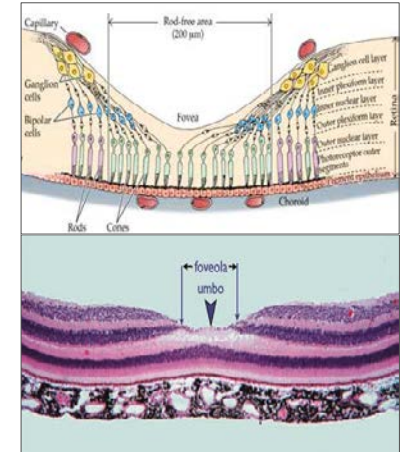
## Fovea

- o 1.5 mm diameter
- o 165,000 cones/mm<sup>2</sup>
- o Origin of ½ of optic nerve fibers

## Foveola

- o 0.35 mm diameter at center of fovea
- o Only cones and Mueller cells

Rod density ranges from ~35,000 rods/mm<sup>2</sup> at the periphery to ~150,000 rods/mm at about 3-5 mm from the foveola



Neuroscience, 2nd ed., Purves D, Augustine GJ, Fitzpatrick D, et al., eds., Sunderland (MA): Sinauer Associates; 2001

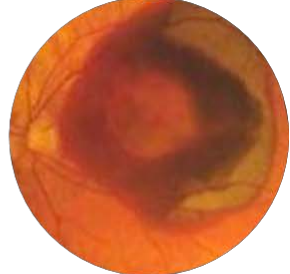
# Approximately 15% of the 15 M AMD patients in the US progress to an advanced form and lose central vision



## Advanced AMD Presentations

### Geographic Atrophy (GA)

- 5-7% of AMD patients
- Death of RPE and PRs they support
- Depigmented area due to RPE "dropout"
- Significant vision loss



- ### Early AMD
- ~1.5 M patients
  - Small Drusen (>63 and <125  $\mu\text{m}$ )
  - Minimal effect on vision

- ### Intermediate AMD
- ~7M patients
  - Drusen (>125  $\mu\text{m}$ )
  - Patient may notice dim or "wavy" regions in central vision

- ### Wet/Exudative AMD
- ~10% of AMD patients
  - Abnormal, leaky vessels
  - Edema causes retinal separation & PR death
  - Significant vision loss

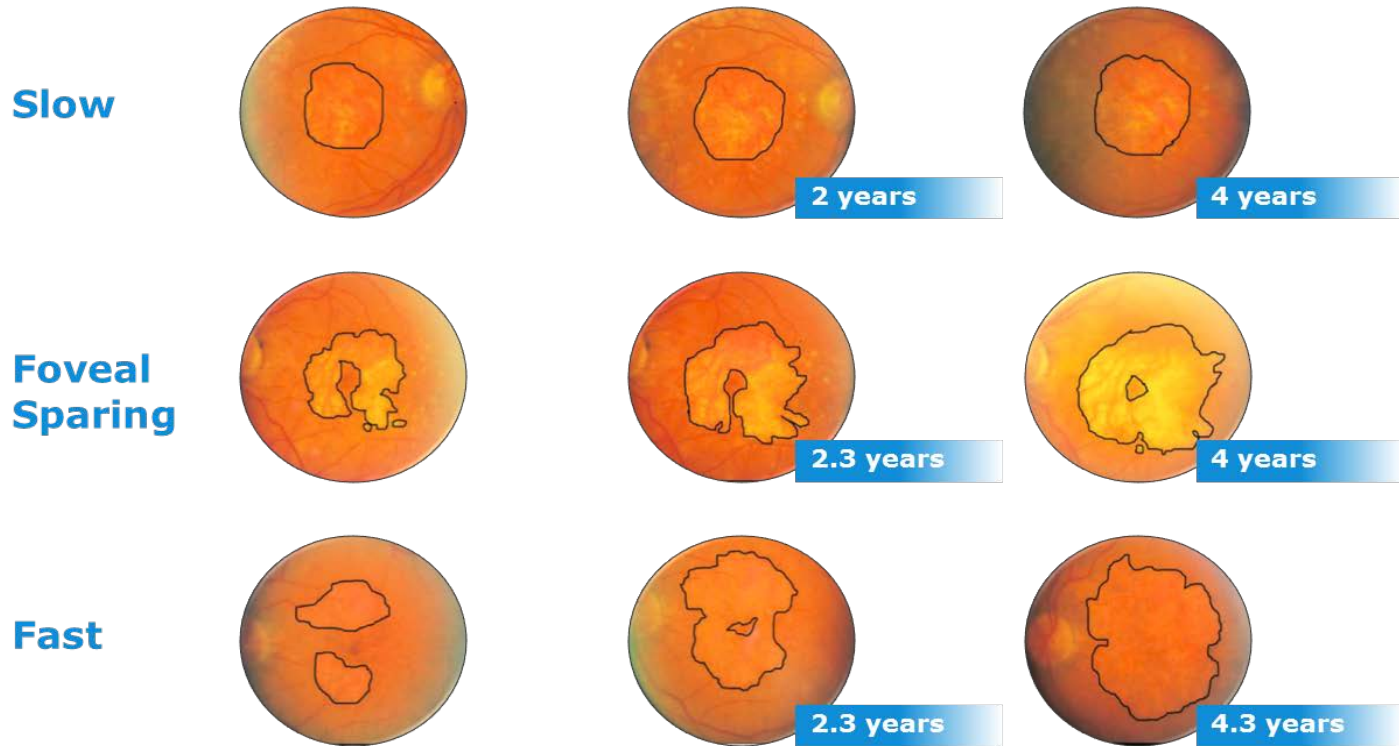


 Dry AMD (~90%)

 Wet AMD (~10%)

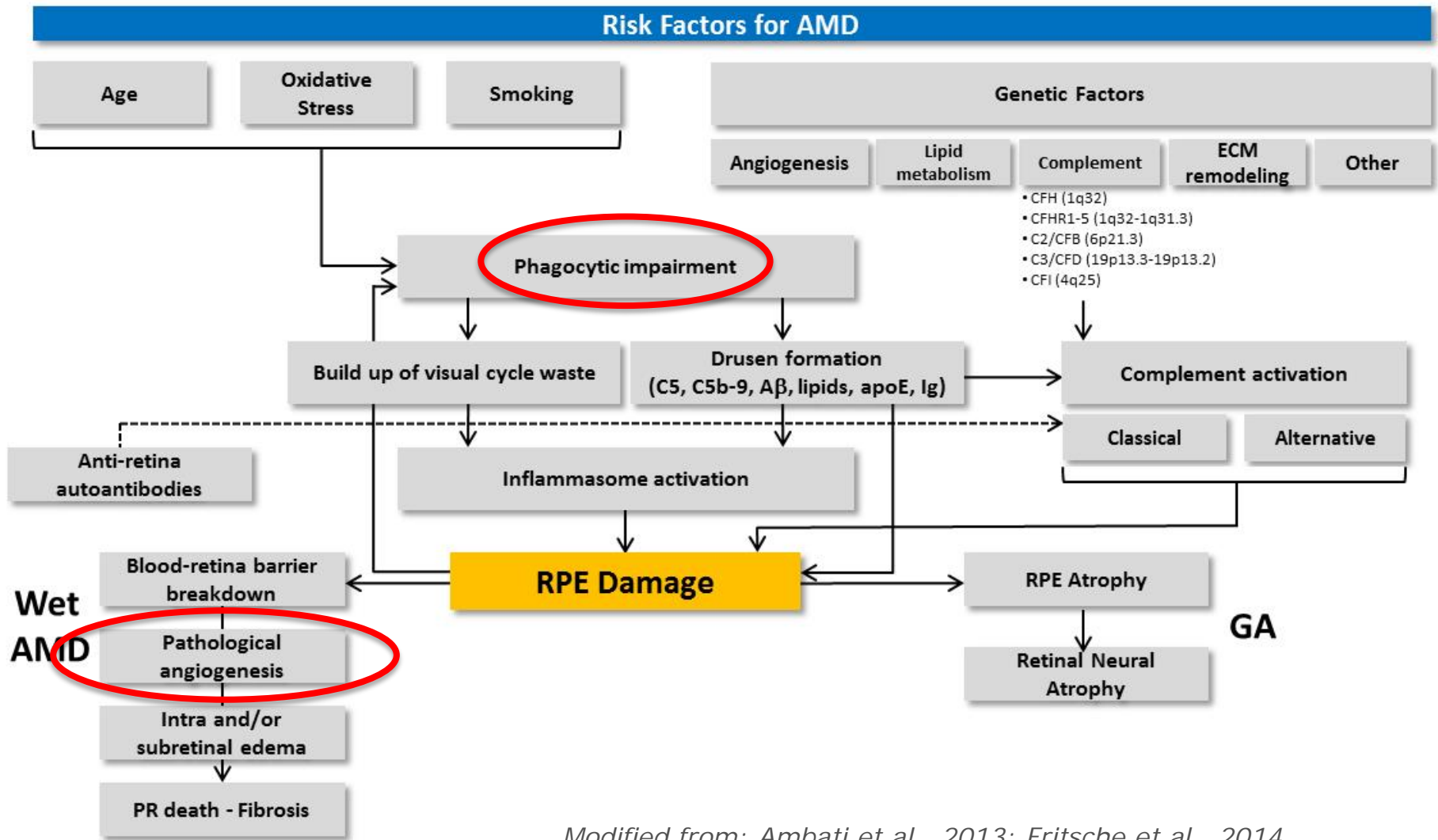
# Lesion progression rates vary significantly in GA, as does position relative to the fovea

## Rates of Progression



- Differences in progression rate do not correlate with visual acuity decline
- Foveal sparing enables a patient to see 20/20 while a smaller lesion encompassing the fovea impairs visual acuity significantly (<20/400)
- Diagnosis and onset of symptoms is associated with loss of autonomy, depression, and overall reduced quality of life

# A model of AMD pathogenesis

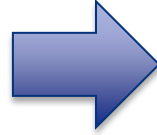


Modified from: Ambati et al., 2013; Fritsche et al., 2014



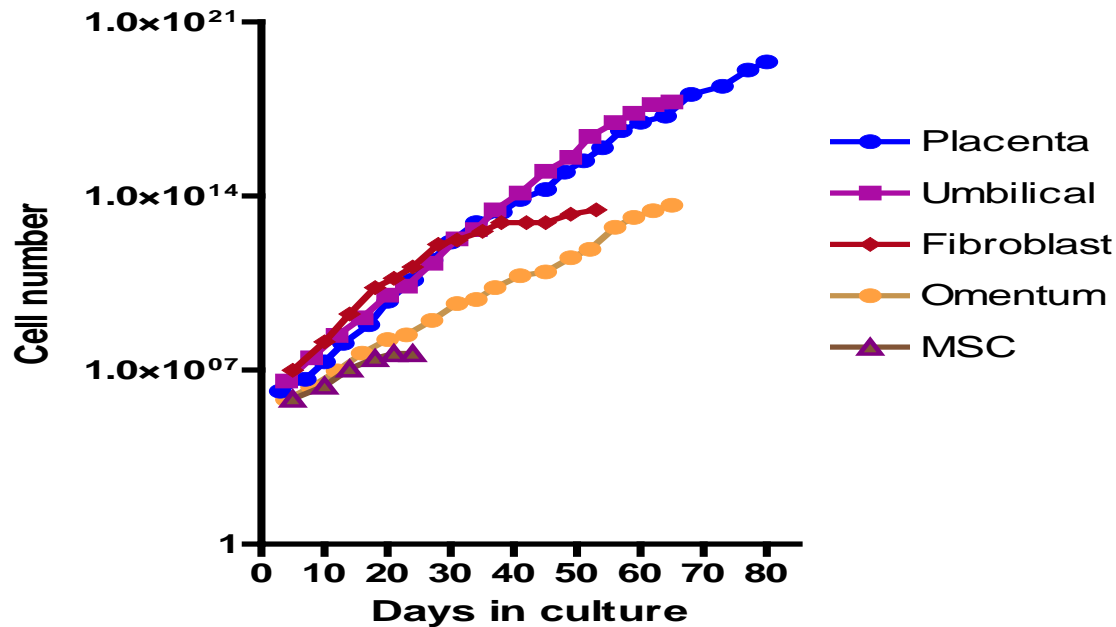
# Why Human Umbilical Tissue Derived Cells?

- Microarrays
- RNA Seq
- Secretome analysis



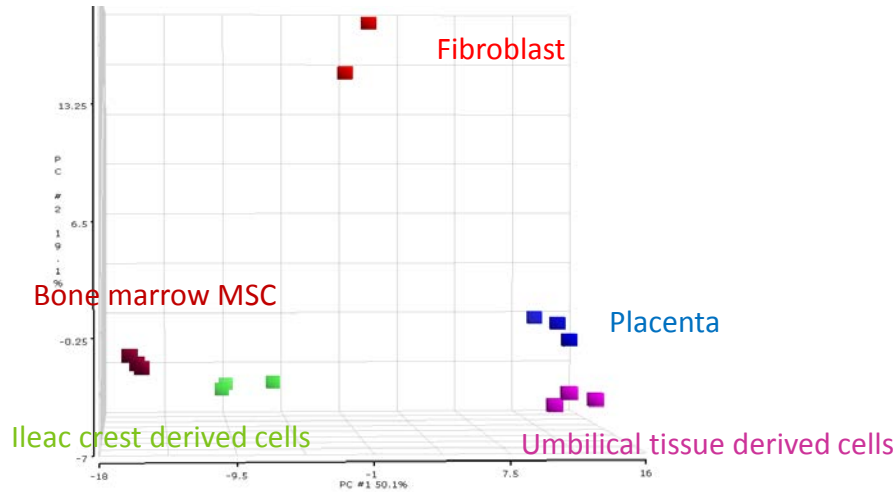
Neurotrophic factors

TSP1, TSP2, TSP4, SPARC, Hevin, BDNF, GDNF, LIF, IL-6, Neurotrophin 3, LEDGF, PDGF-DD, HGF

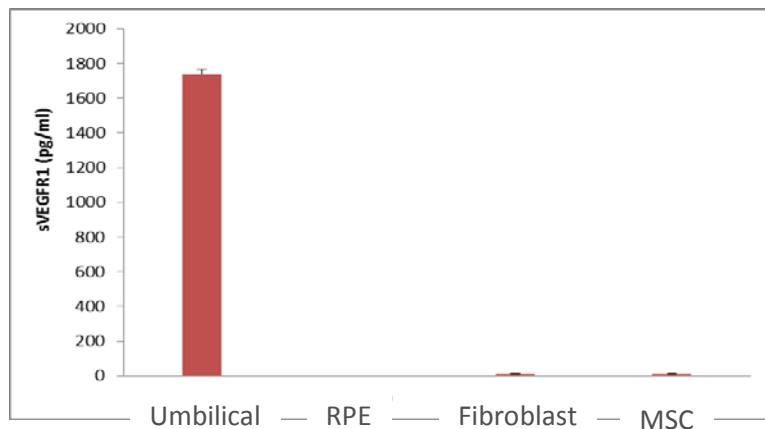
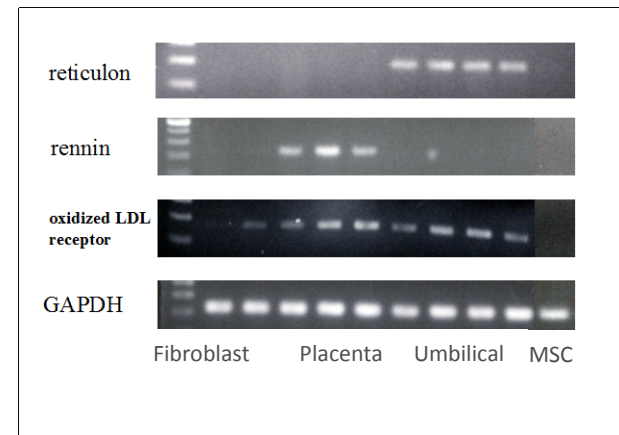


# Palucorcel (Umbilical tissue derived cells) are not comparable to mesenchymal stem cells (MSC)

## Primary Component Analysis of Gene Microarrays



## PCR for Differentially Expressed Genes



- sVEGFR1 may be important to prevent GA patients from converting to wet AMD

# Selection of animal model

## Scientific rational

- Appropriate species
  - To characterize physical, mechanical, biological properties
- Relevant to demonstrate proof of concept
- Immune tolerated and biologically active
- Genetic background
  
- Number of animals for statistical and scientific interpretation
  - Animal model, test species, delivery system

# Other preclinical studies

Identify potential risks and guide clinical monitoring

- Local & Systemic toxicity
  - Ectopic tissue or transformation
- Biodistribution/ retention
  - Distribution, persistence, clearance
- Tumorigenicity
- Immunogenicity
- Safety of delivery

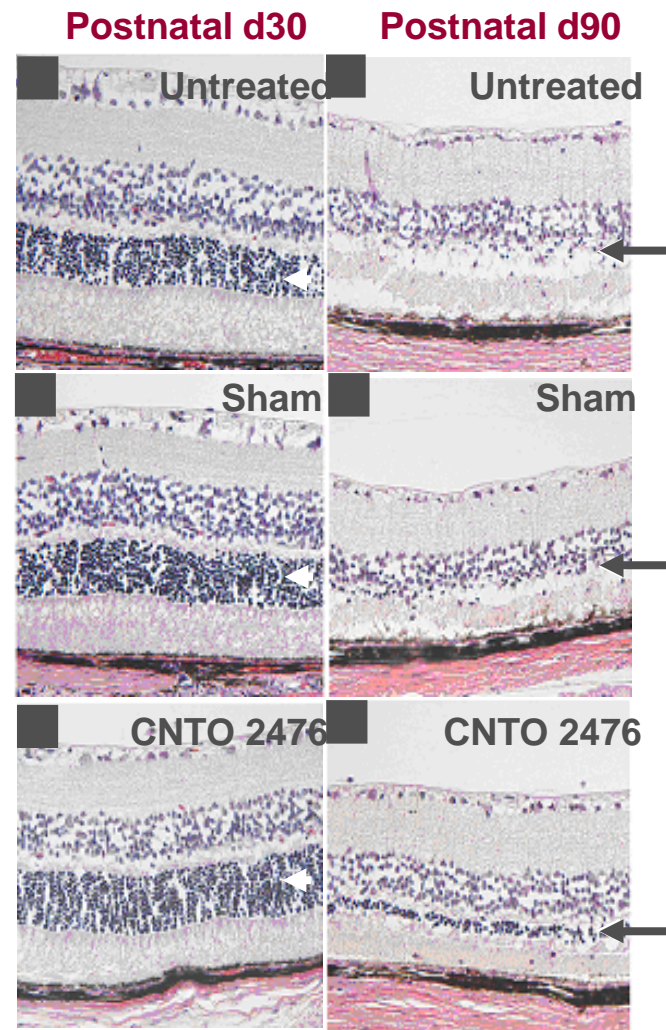
ICH S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals  
FDA Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products (November 2013)

# Royal College of Surgeons (RCS) rat

- The RCS rat is a widely studied animal model of retinal degeneration due to a genetic defect in the retinal pigmented epithelium (RPE), i.e., a null mutation of the gene encoding Mertk.
- Cell culture studies demonstrate that Mertk-deficient primary RCS RPE cells have normal levels of outer segments binding, but are defective in the ingestion phase of phagocytosis.
- Delivery of a recombinant Mertk to RCS RPE completely corrected the phagocytic defect of the cells, resulting in photoreceptor rescue.

# Palucorcel (hUTC) preserves retinal architecture

- Single injection of 20,000 human cells at Postnatal day 21 in RCS rat preserves photoreceptors to postnatal day 90



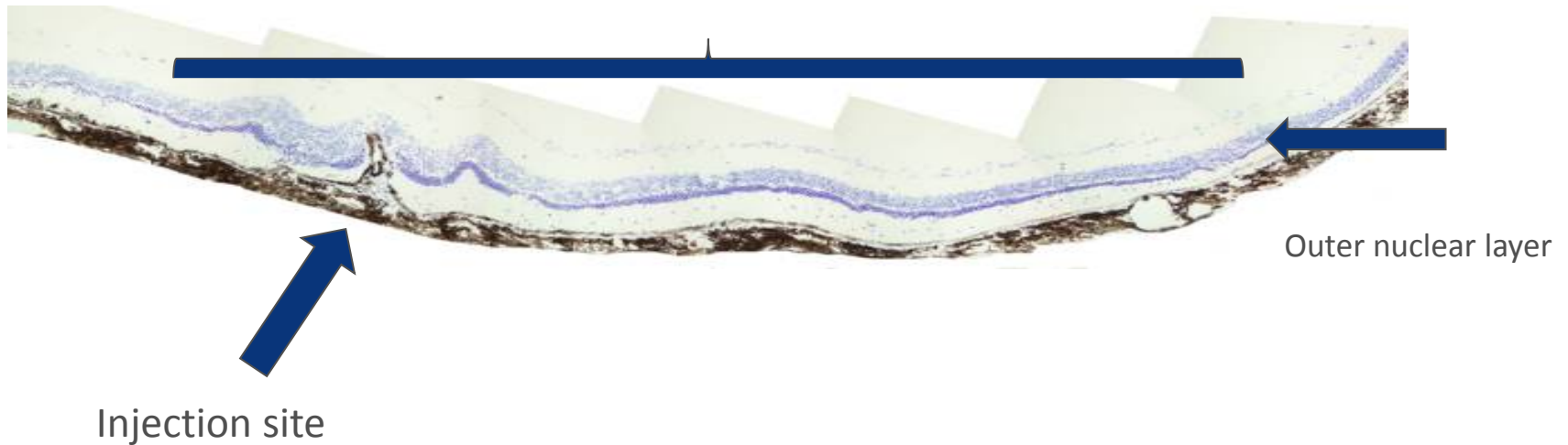
Lund RD, et al., Cells isolated from umbilical cord tissue rescue photoreceptors and visual functions in a rodent model of retinal disease. *Stem Cells*. 2007 Mar; 25(3):602-11.

# Area of Photoreceptor Preservation in the RCS rat

Superior

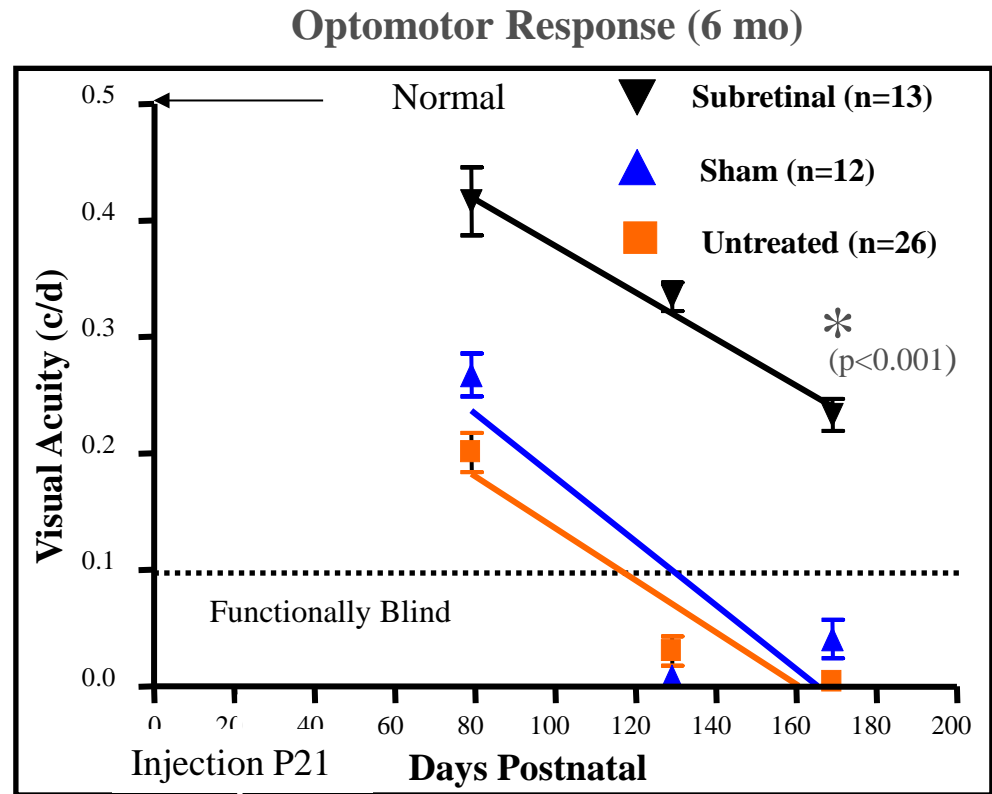
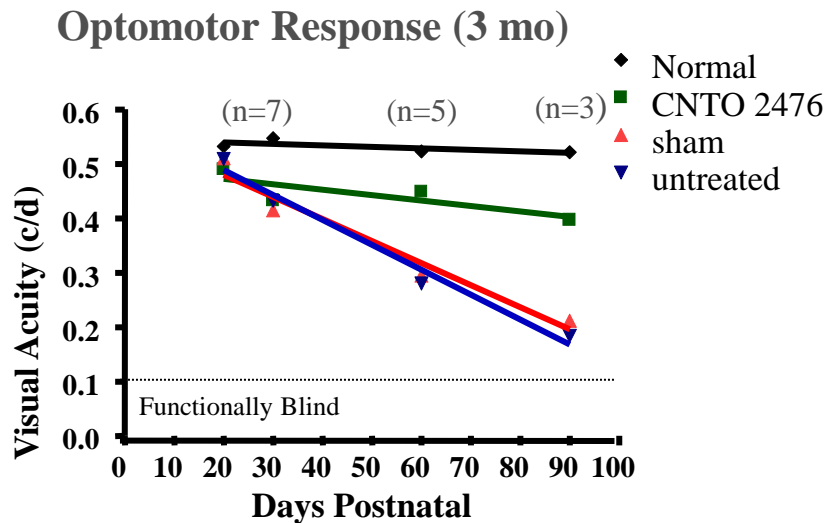
Area preserved >30% rat retina

Inferior



Photoreceptors are preserved beyond where CNTO 2476 is injected

# Palucorcel (hUTC) Improves Optomotor Response over 180 d

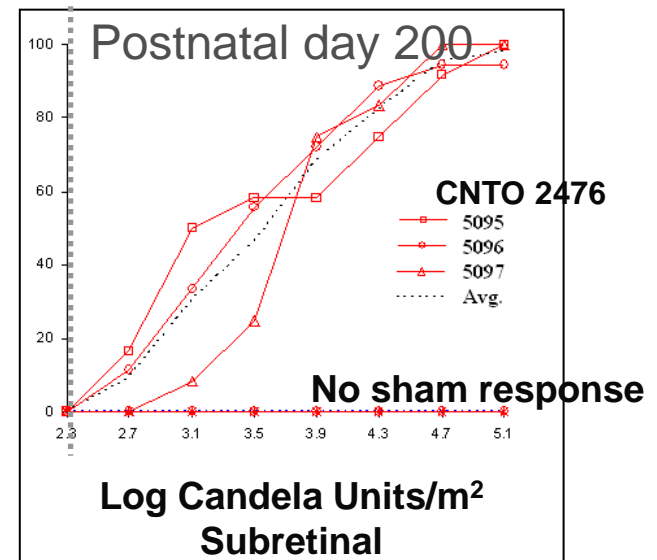
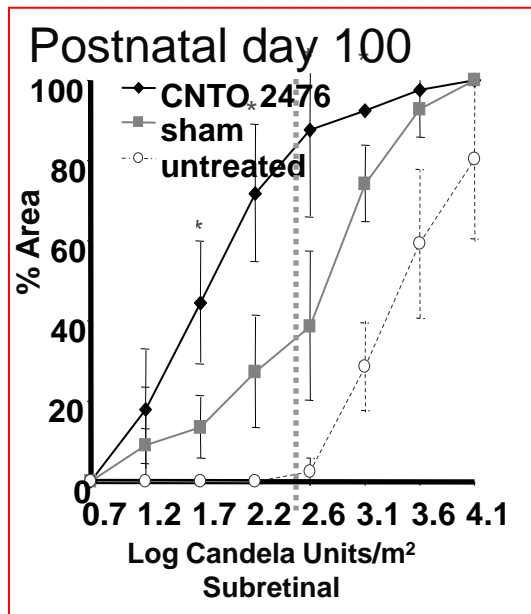


**Optomotor** response (*head tracking*) is used to measure the elicitation of a consecutive motor response, enabling assessment of all components of visual integration. Animals placed in a rotating drum covered with vertical black and white stripes at various spatial frequencies follow the movement of the drum by moving the eye/head whereas animals with altered vision cannot track the stripes



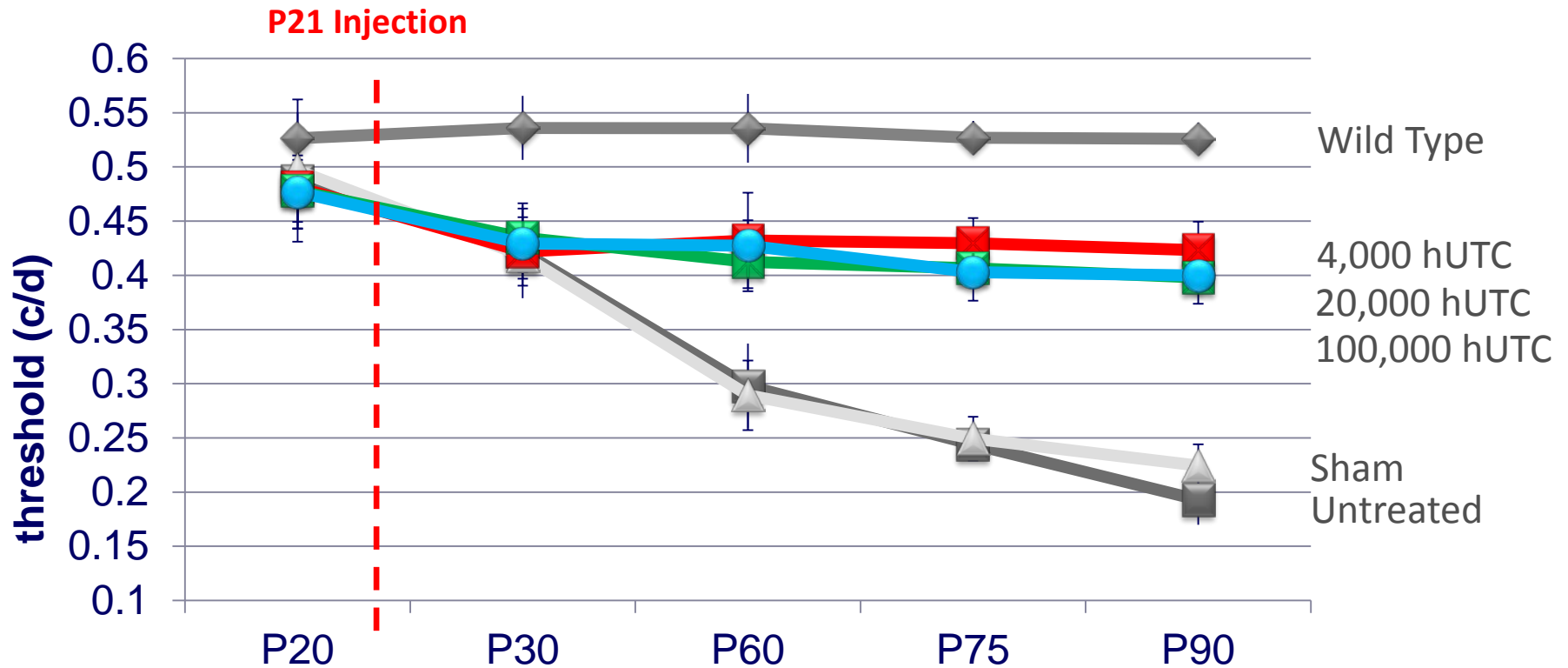
# Correlation of luminescence with anatomical preservation

**Luminance threshold** is used to measure spatial vision as single and multiunit activity in the superficial layers of the superior colliculus



Larger area of retina is sensitive to lower levels of light with treatment

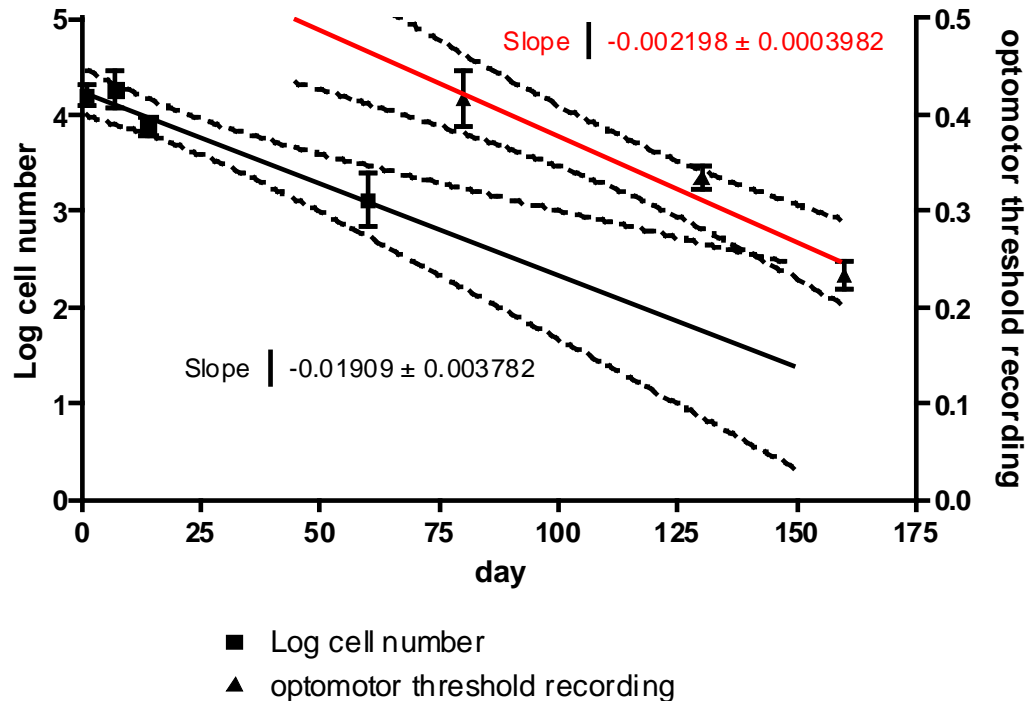
# Optomoter does not show a dose response



# hUTC was detected in the RCS rat eyes 60 days post subretinal injection

- In order to understand cell fate after subretinal injection, biodistribution studies were performed based on an indirect measurement of human gene expression in animal tissue using Q-RT-PCR
- Biodistribution studies demonstrated long-term cell retention of hUTC in eyes
- hUTC were detected in nontarget organs (peripheral blood, kidney and liver) in nude rats 2 weeks following subretinal delivery, but there was no evidence for long term survival of cells in non-target organs

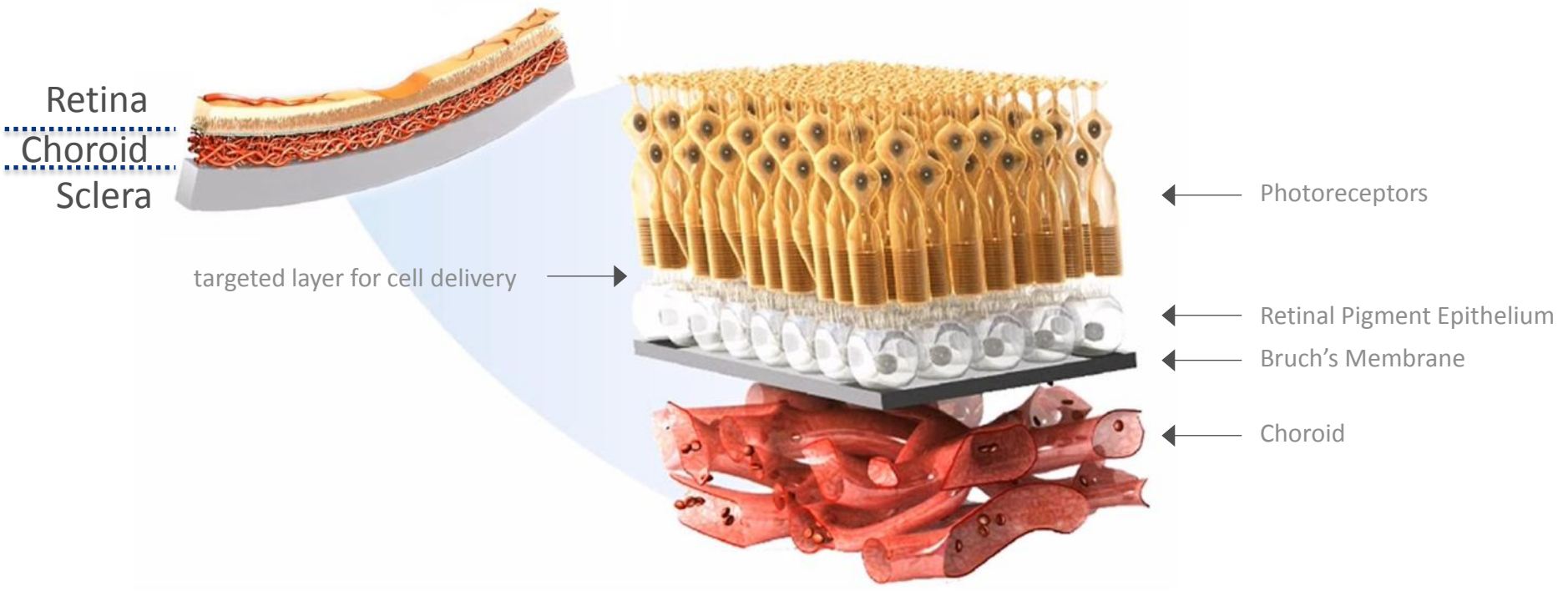
# Human cell retention in the rat eye and visual function



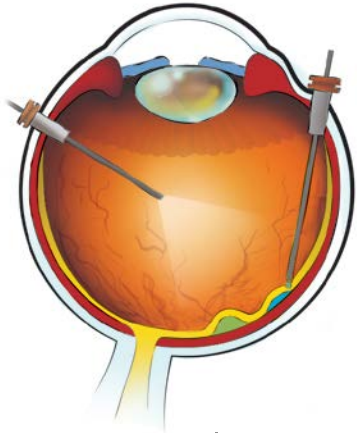
- Similar rate of change are observed in cell number and Optomoter
- Optomoter response starts to decline when estimated ~500 cells remain

# Administration

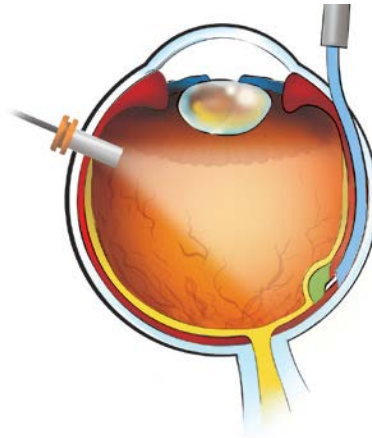
- Intravitreal
- Choroid
- Subretinal



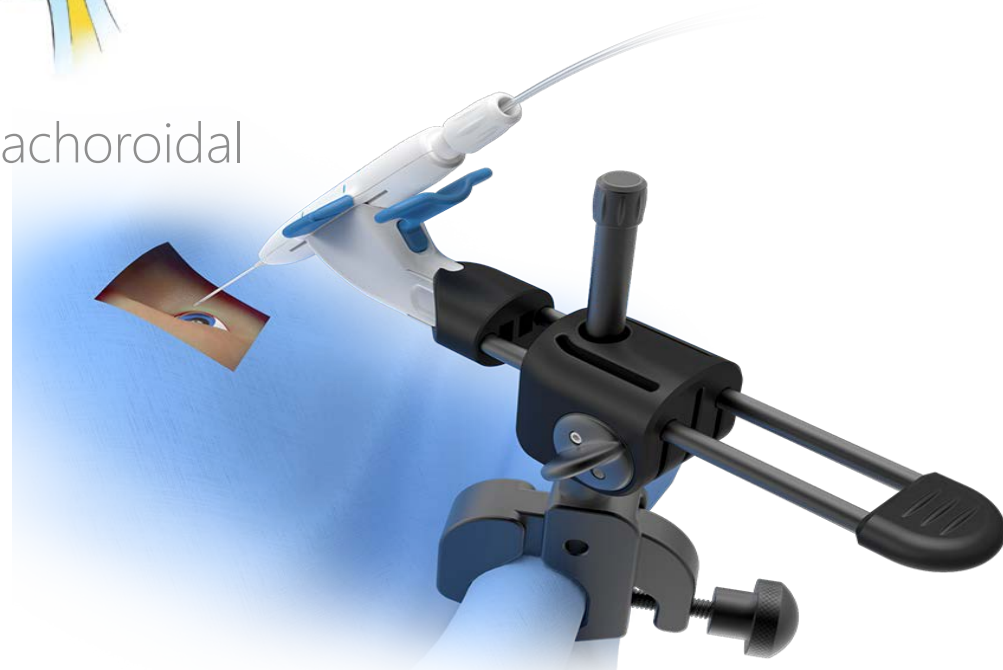
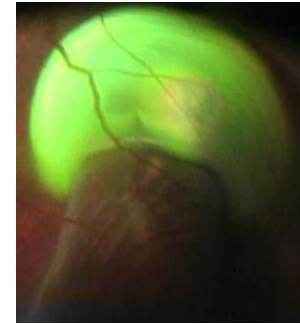
# Development of surgical procedure & devices



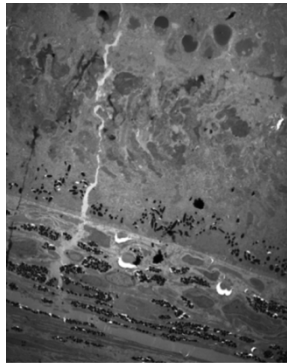
Transvitreal



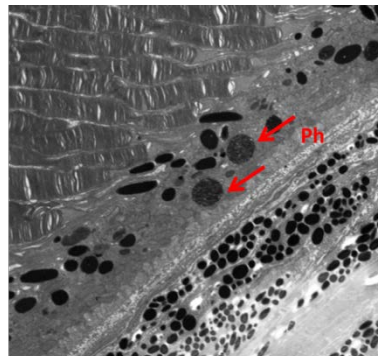
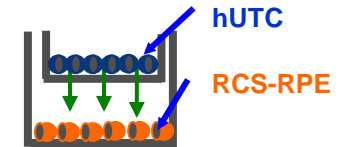
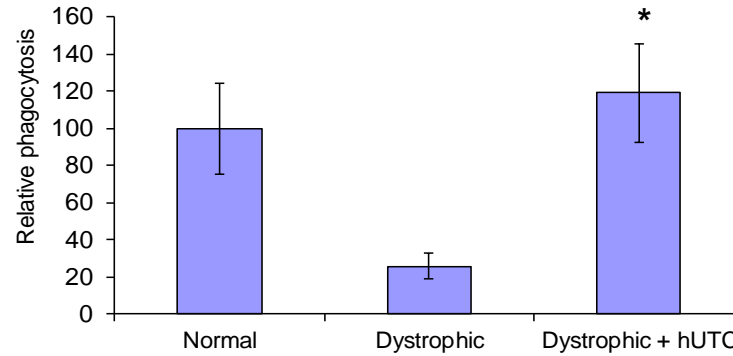
Suprachoroidal



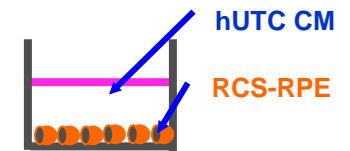
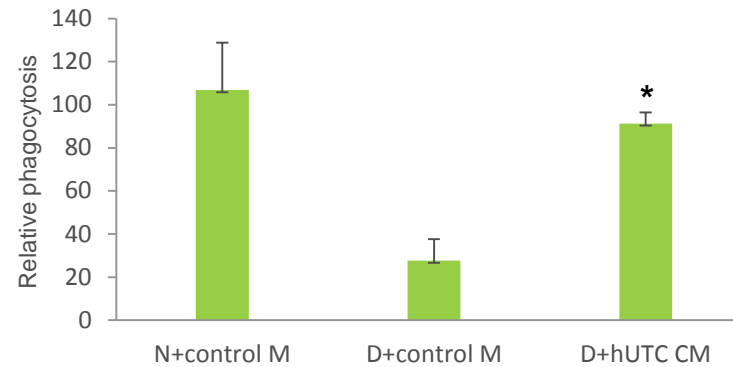
# From preclinical proof of concept to potency assay



RCS No Treatment (P60)

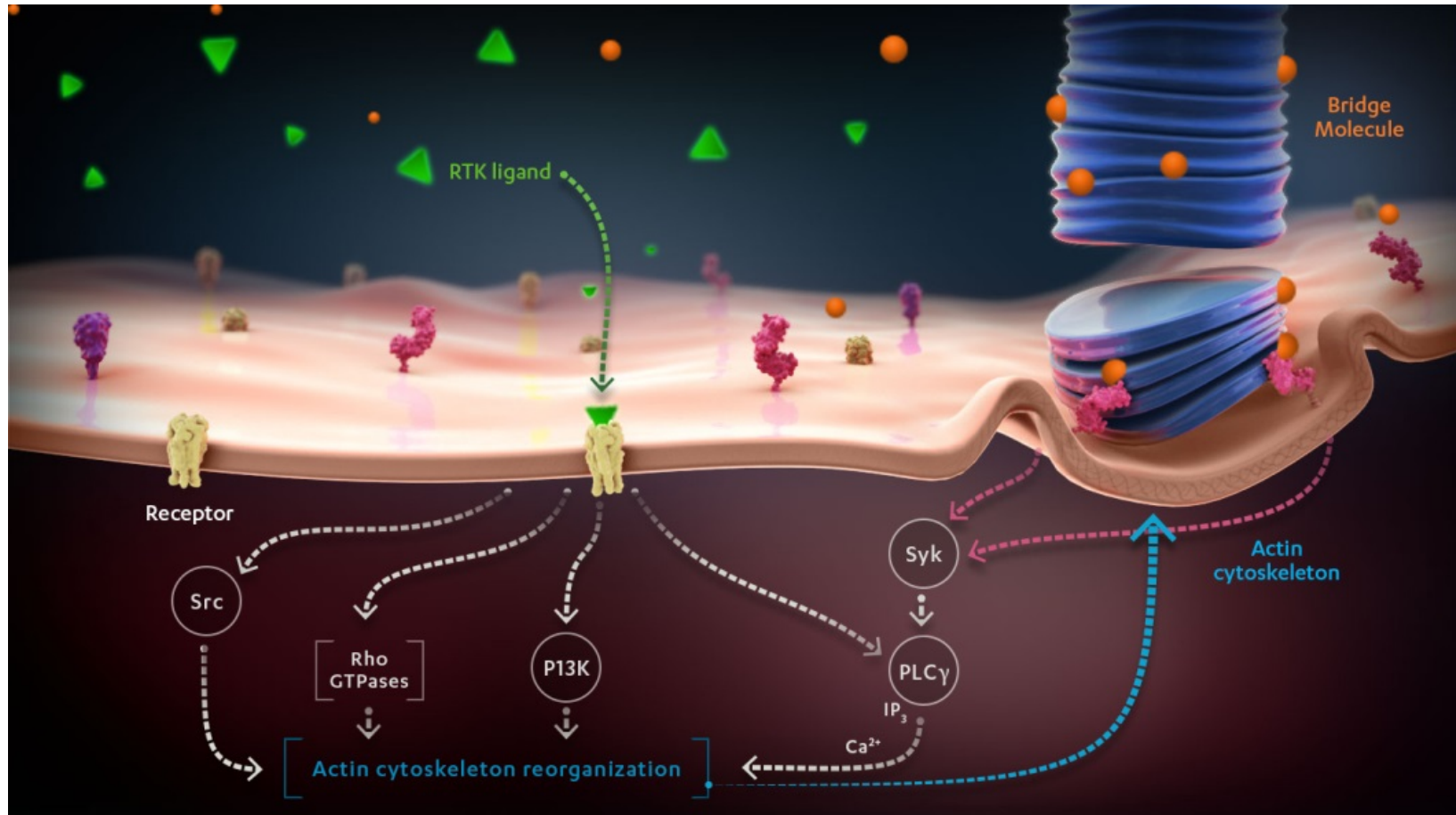


RCS + hUTC(P60)



(RCS phagocytosis studies performed in collaboration with Dr. George Inana, Bascom Palmer Eye Institute)

# Hypothesis: Palucorcel rescues phagocytosis in RCS RPE through the secretion of Receptor tyrosine kinase (RTK) ligands





# Receptor tyrosine kinase ligands can compensate for loss of Mertk function

BDNF

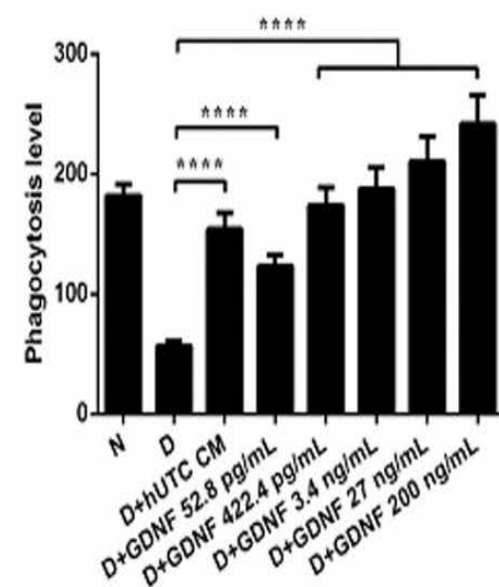
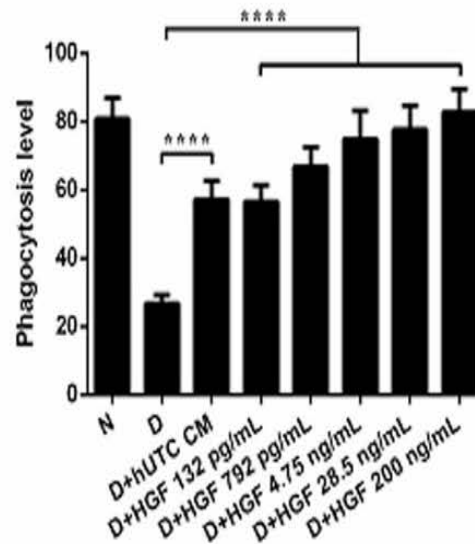
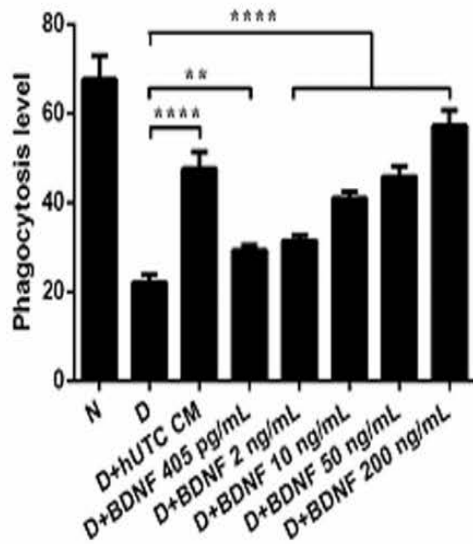
HGF

GDNF

A

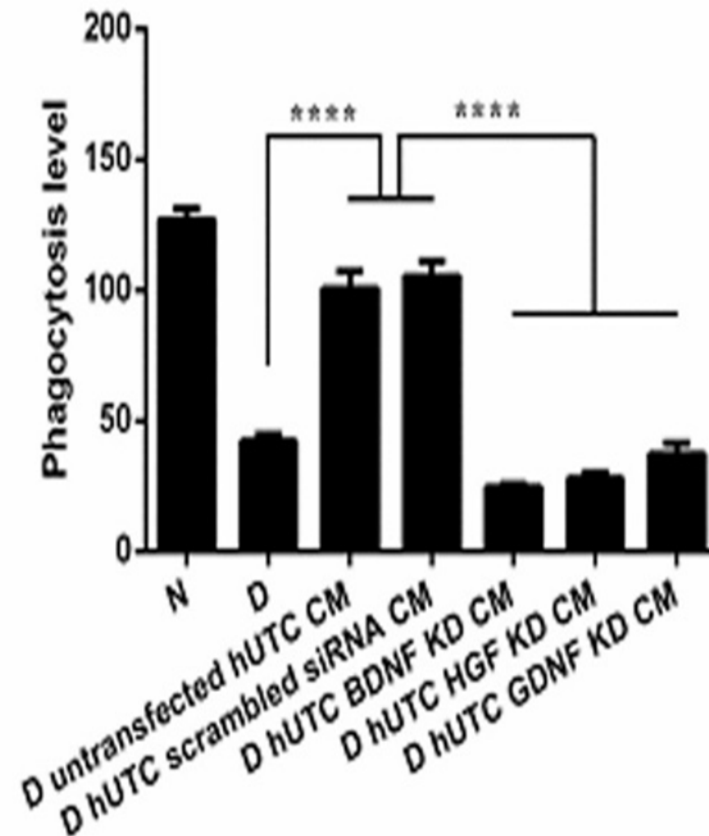
B

C



Cao, Jet al., (2015) Human umbilical tissue-derived cells rescue retinal pigment epithelium dysfunction in retinal degeneration Stem Cells. doi: 10.1002/stem.2239. [Epub ahead of print]

# Receptor kinase ligands secreted by umbilical tissue derived cells are required for bioactivity



Cao, Jet al., (2015) Human umbilical tissue-derived cells rescue retinal pigment epithelium dysfunction in retinal degeneration Stem Cells. doi: 10.1002/stem.2239. [Epub ahead of print]

Thank you