Cellular and Gene Therapies for Retinal Disorders

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Cellular, Tissue, and Gene Therapy
Advisory Committee Meeting
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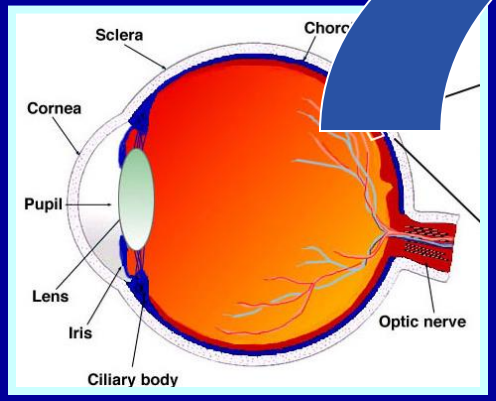
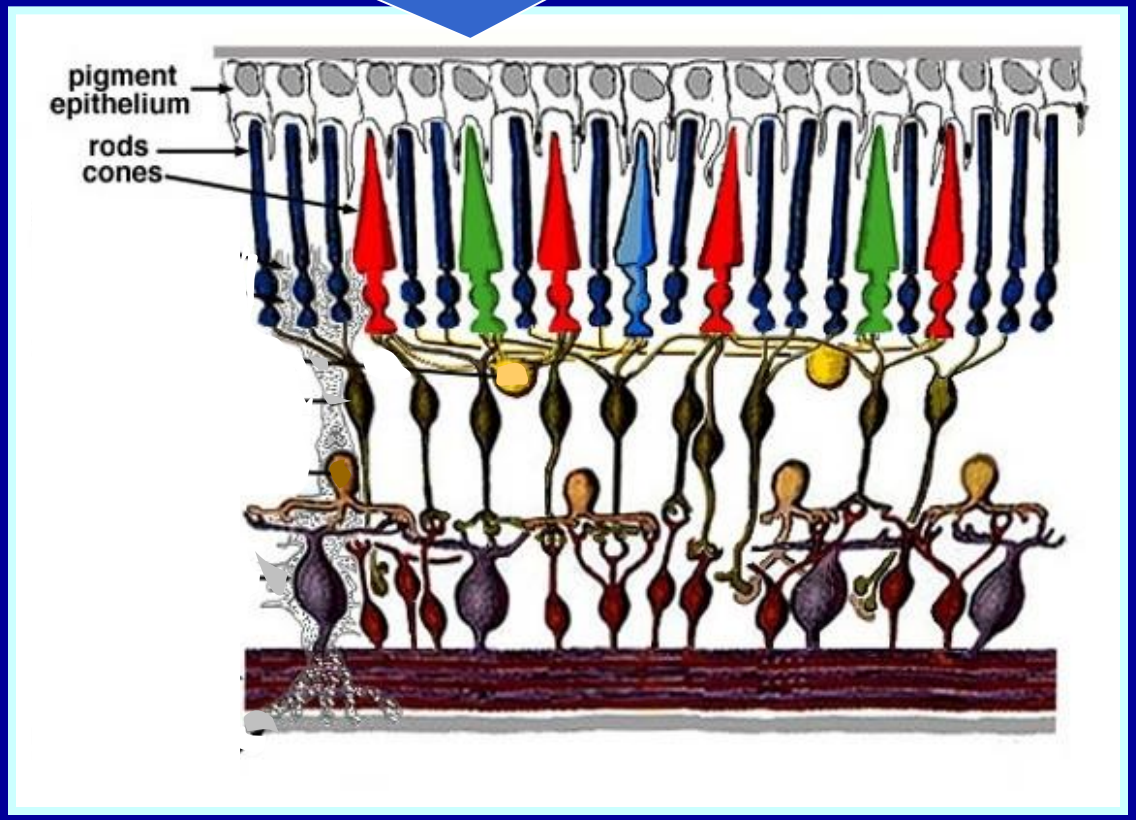
Products in the Office of Cellular, Tissue, and Gene Therapies (OCTGT)

- Cellular therapies
- Gene therapies
- Tumor vaccines and immunotherapy
- Devices used for cells and tissues
- Human cells and tissues for transplant
- Combination products

Retina





Kolb H, *Simple Anatomy of the Retina,* 2005. http://www.ncbi.nlm.nih.gov/books/NBK11533/

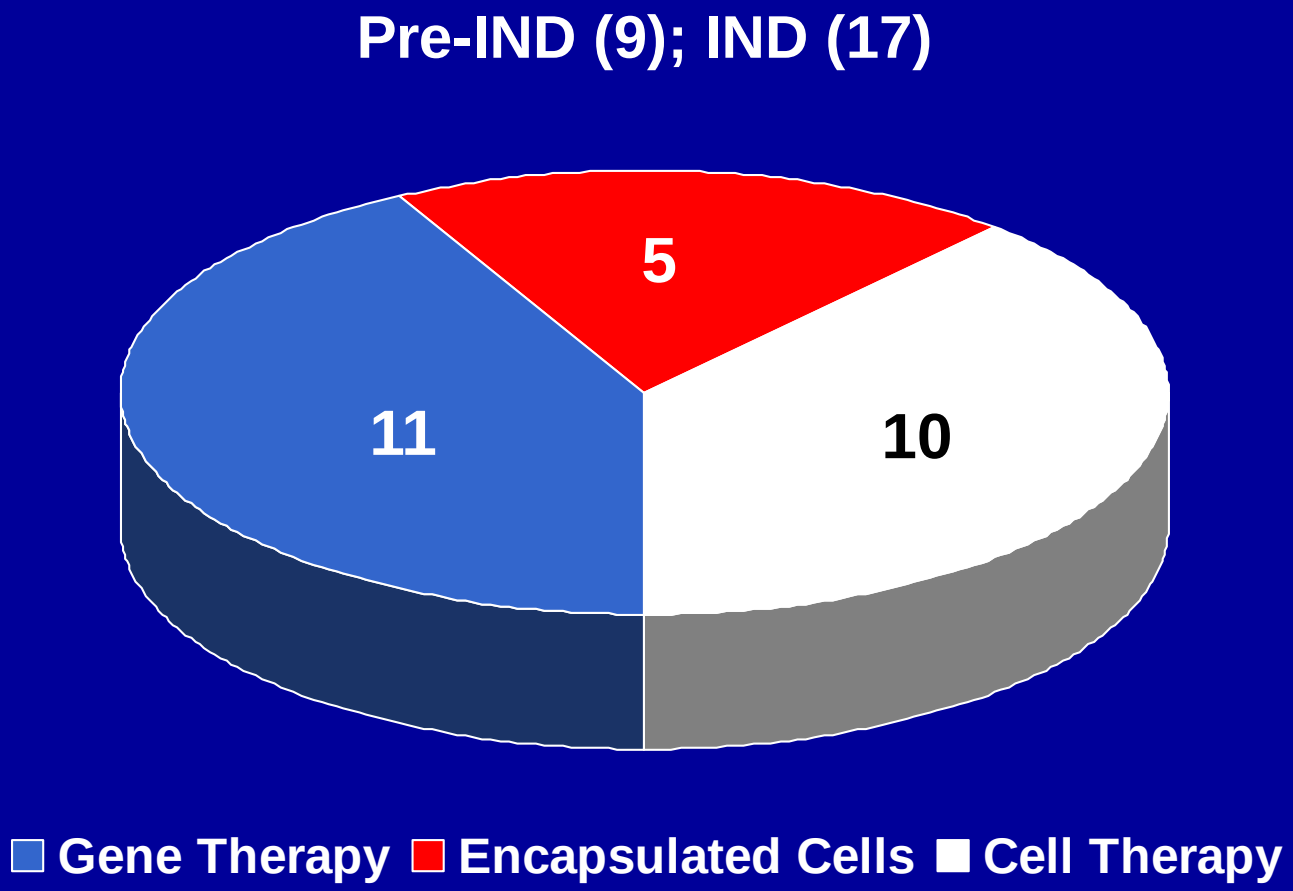
Clinical Indications

- Inherited Retinal Disorders
  - Retinitis pigmentosa
    - 100,000 affected in US Pagon, et al, *Gene Reviews 2000*, 2005.
  - Stargardt disease
    - 30,000 affected in US Riveiro-Alvarez *et al.*, *BJO*, 2009; 93(10):1359.
  - Leber congenital amaurosis
    - 4,000 affected in US Stone, *AJO,* 2007; 144(6):791.

Clinical Indications (cont.)

- Acquired Retinal Disorders
  - Age-related macular degeneration
    - 7.3 million affected in US Friedman, *Arch Ophthalmol,* 2004; 122(4):564.
      - 1.75 million in US with advanced disease
  - Diabetic retinopathy
    - 4.1 million affected in US Kempen, *Arch Ophthalmol*, 2004; 122(4):552.
      - 900,000 in US with advanced disease

OCTGT Ophthalmic Product Submissions (26)



Development Considerations

- Selection of appropriate endpoints for retinal disorders
- Assessment of potential risks with novel therapeutic agents, particularly in regard to contralateral eye or repeat administration
- Evaluation of delivery of the therapeutic agent to target tissues in back of eye

Efficacy Endpoints for Retinal Disorders

Accepted Efficacy Endpoints

- Visual Acuity: a 3-line (15-letter) change
  - clinically meaningful benefit in comparison between treatment arms
- Visual Field
- Color Vision
- Area of Non-Seeing Retina

Efficacy Endpoints

- Challenges in clinical trials for cellular and gene therapy products:
  - Rare diseases with smaller sample size
    - Difficult to power studies to capture efficacy
  - Measuring endpoints in pediatric population
    - Current endpoints may not be feasible
  - Assessing benefit in patients with low vision
    - May be beyond limits of current testing methods (i.e., floor effect or ceiling effect)

Developing Efficacy Endpoints

- Measures of Visual Function
  - limited utility in some populations
- Anatomic Measures
  - clinical meaningfulness may not be well established
- Measures of Functional Vision
  - ability to reflect real-world function is uncertain
- Patient-Reported Outcome Instruments
  - may not be well characterized for use in all retinal disorders

Example: Maguire, High, *et al.*

- Measured improvement in retinal function:
  - Dark adaptometry
  - Pupillometry
  - Electroretinography
  - Nystagmus/eye movement measurements
  - Ambulatory behavior

Lancet, 2009; 374(9701): 1597-605.

Discussion: Efficacy Endpoints

- Ability of existing and novel outcome measures to assess product efficacy in both adult and pediatric populations and their roles in clinical trials

- Methods to assess the clinical meaningfulness of these measures

Safety Concerns with Contralateral Eye or Repeat Administration

Surgical Considerations

- Attempt to maximize vision in both eyes to improve binocular function
- Time interval to surgery on the second eye
  - Avoids simultaneous impairment
    - During normal post-operative course
    - In event of complications
      (e.g. infection, sympathetic ophthalmia)
  - Facilitates surgical plan for second operation

Preclinical Assessment of Immune Response

- Immune response varies with:
  - Animal species
  - Specific product
  - Site of injection (intravitreal vs. subretinal)
  - Injection technique and instrumentation
  - Host immune response to the product prior to or after first eye administration
  - Timing of readministration
  - Disease state of the eye (i.e., local environment of cell administration)
  - Use of immunosuppressive agents

Mitigating Immune Risks

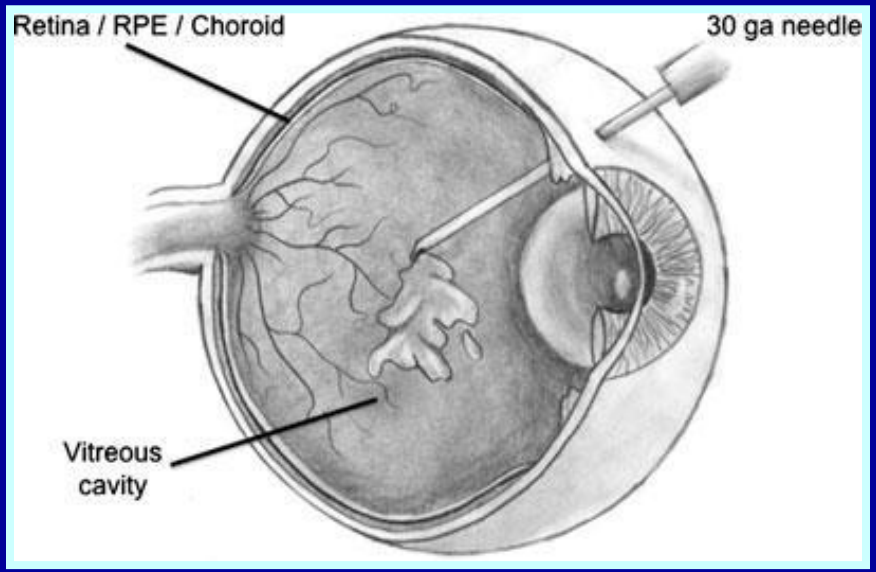
- General safety/adverse reaction surveillance
- Specific monitoring for immune response
- Limited or staggered patient enrollment
- Single, low-dose administration
- Adjusted administration intervals
- Immunosuppressive therapy

Discussion: Safety Concerns with Repeat Administration

- Factors that may influence the recommended timing of administration, particularly considering any safety concerns
- Clinical or laboratory tests to guide the timing of the second eye or repeat administration
- Merits and limitations of preclinical studies to model relevant immunological responses

Ophthalmic Administration Procedures

Intravitreal Administration

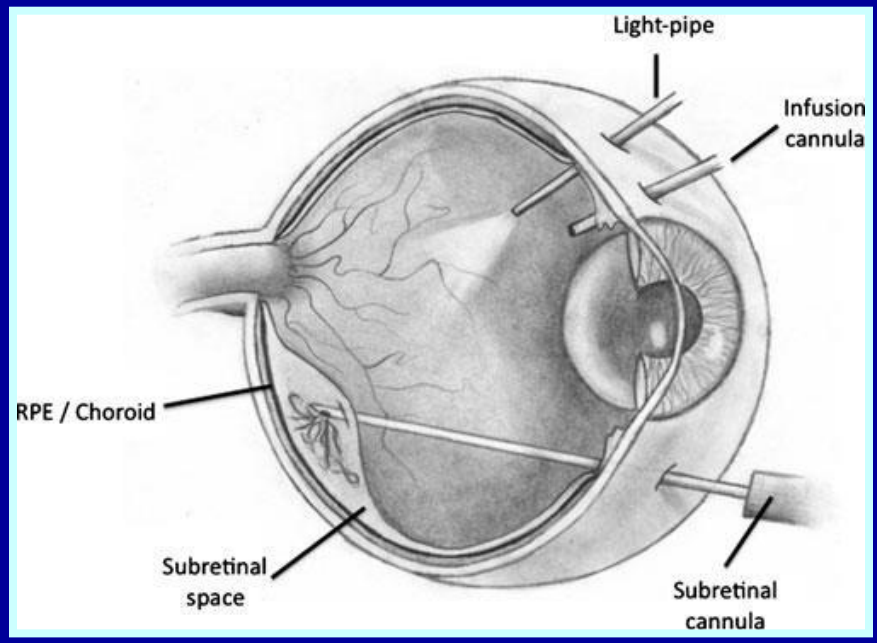


Stout *et al.*, *Hum Gene Ther*, 2011; 22(5):531.

- Routine clinical procedure
- Low complication rate
- Rapid elimination of drugs
- Limited transduction of viral vectors into target tissue

Subretinal Administration

- Efficient transduction of photoreceptors and RPE
- Technically more challenging
- Higher complication rates



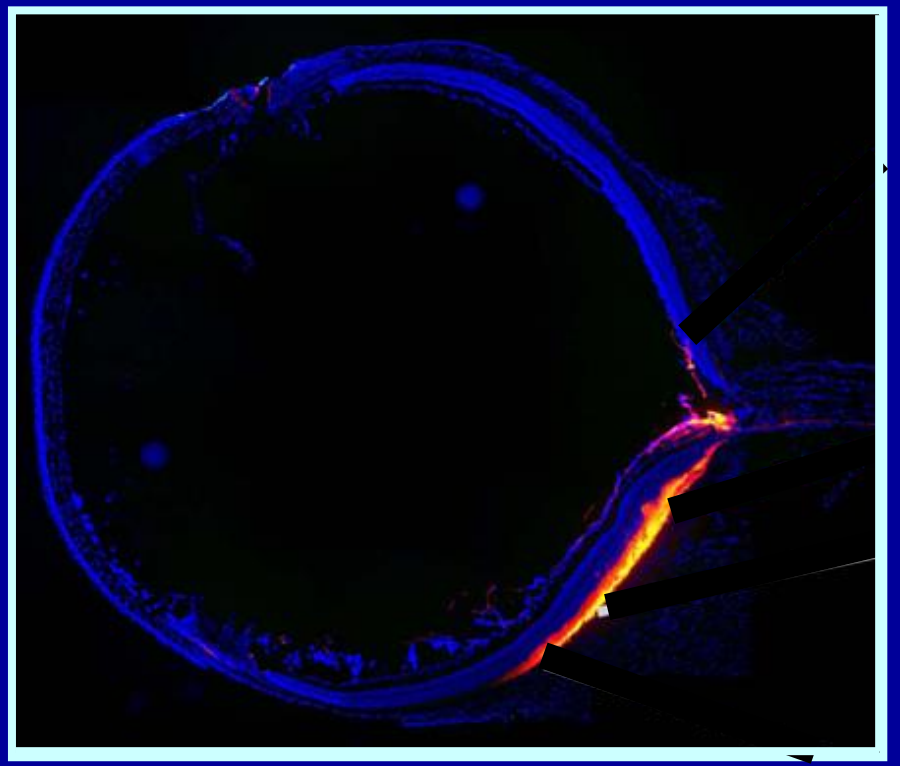
Stout *et al.*, *Hum Gene Ther*, 2011; 22(5):531.

Preclinical Data

- Spectrum of animal species / models for assessing product administration
  - Different delivery devices and techniques
  - Range of eye sizes
  - Comparative ocular anatomy
    (e.g., fovea exists only in some non-human primates)
  - Ethical considerations

Preclinical Data (cont.)

- Determining successful delivery to target
  - Quantitative real-time polymerase chain reaction (qPCR)
  - Immunohisto-chemistry (IHC)
  - Exam and imaging
  - Genetically expressed markers



Johnson *et al., Molecular Vision,* 2008; 14: 2211–2226.

Discussion: Ophthalmic Administration Procedure

- Methods to optimize the product delivery procedure and assess the accuracy of product delivery

- Utility of available animal species to assist in addressing concerns

Invited Speakers

- Albert Maguire, M.D.
  University of Pennsylvania
- Tim Stout, M.D., Ph.D., M.B.A.
  Oregon Health and Science University
- Peter Campochiaro, M.D.
  Johns Hopkins University
- Pete Coffey, BSc., DPhil.
  University College London

Planning Committee

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