Clinical Development of Stem Cell Therapies for Retinal Disorders: Regulatory Considerations

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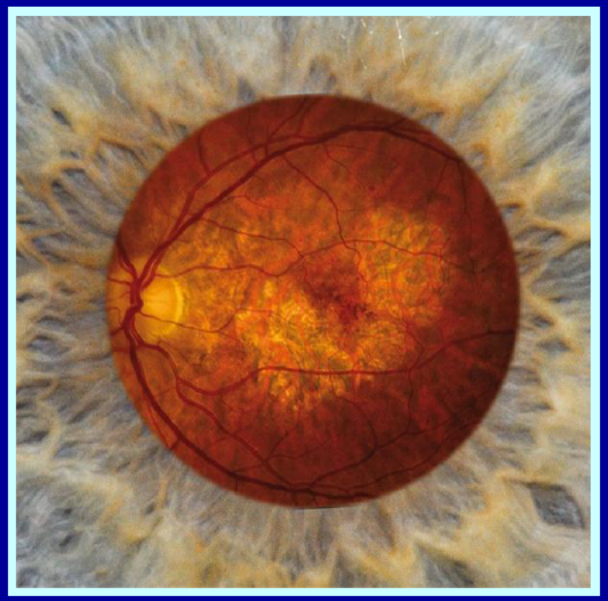
Today's Discussion

- IND Basics
  - Authority
  - Responsibilities
  - Submission process
  - IND elements



- Issues in clinical development of cell and gene therapies for retinal disorders
  - Endpoints
  - Immune response
  - Administration procedures

Meister, *Nature*, 2011; 471: 308-309.

Authority

- 21 U.S.C. 355(a); 42 U.S.C. 262(a)
  - Valid biologics license must be in effect to lawfully market a biological drug product.
  - Licenses are issued only after demonstration of safety and efficacy for the product's intended use.
- 21 U.S.C. 355(i); 21 CFR Part 312
  - While in the development stage, such products may be used in humans only if the sponsor has an investigational new drug (IND) application in effect.

Investigational New Drug Application

- Provides an exemption from restrictions on interstate commerce of shipment of an unapproved new drug
- Defined structure and content as outlined in 21 CFR 312
  - 312.23 IND Content and Format
  - 312.42 Clinical Holds
  - 312.50 – 312.69 Responsibilities of Sponsors / Investigators

Sponsor

- *Sponsor* is the IND applicant
  - Person / Organization who takes responsibility for and initiates a clinical investigation
  - May be a company, institution, or individual
- *Investigator* conducts the clinical study
- *Sponsor - Investigator* both initiates and conducts the clinical investigation
  - Must be an individual

Responsibilities of IND Sponsors

- Select qualified investigators
- Providing investigators with needed information
- Ensure study conducted in accordance with Investigational Plan
- Ensure investigation is properly monitored
- Promptly report adverse events and new risks to FDA and all investigators
- Maintain adequate records

21 CFR 312.50 - 312.59

Responsibilities of Investigators

- Perform investigation consistent with protocol
- Ensure safety and welfare of subjects under care
- Obtain IRB approval for investigation
- Promptly report any adverse events to Sponsor
- Maintain adequate records

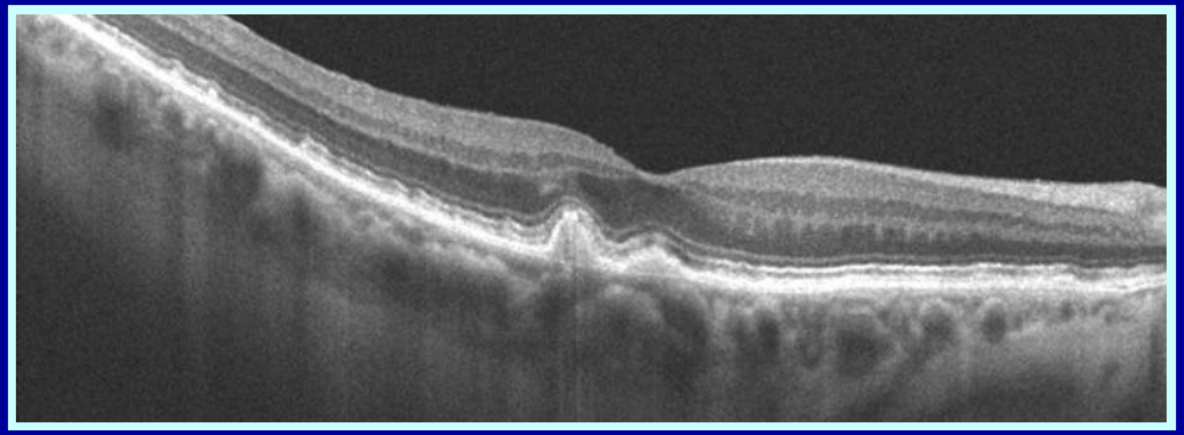
21 CFR 312.60 - 312.69

IND Submission Process

- Step 1: Pre-IND teleconference with OCTGT
  - Highly recommended for new products
- Step 2: Submission of complete IND package
  - All forms, all sections
- Step 3: IND Review
  - Within 30 calendar days of receipt of the IND, the FDA will notify Sponsor whether the study may proceed or is placed on clinical hold
    - Studies may not begin until 30-day review is complete or FDA notifies Sponsor that studies may proceed.

Elements of an IND Application

• Form FDA 1571	21 CFR 312.23(a)(1)
• Table of Contents	21 CFR 312.23(a)(2)
• Introductory statement and general investigational plan	21 CFR 312.23(a)(3)
• Investigator's Brochure	21 CFR 312.23(a)(5)
• Protocols	21 CFR 312.23(a)(6)
• Product/CMC information	21 CFR 312.23(a)(7)
• Pharmacology/Toxicology information	21 CFR 312.23(a)(8)
• Previous human experience	21 CFR 312.23(a)(9)
• Additional Information	21 CFR 312.23(a)(10)



http://www.oct.zeiss.com/articles/179761/application-and-interpretation-of-advanced-retinal/

Clinical Information

- Protocol
  - Starting dose and dose-escalation schemes
  - Route of administration
  - Dosing schedules
  - Definition of patient population
    - Detailed entry and exclusion criteria
  - Safety monitoring plans
    - 21 CFR 312.32
  - Statement of the study objectives and endpoints
  - Statement of the phase of the investigation

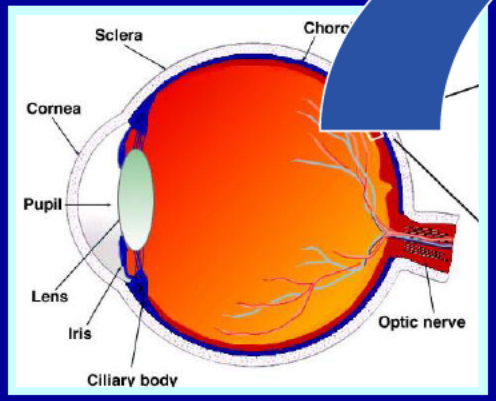
Investigator's Brochure

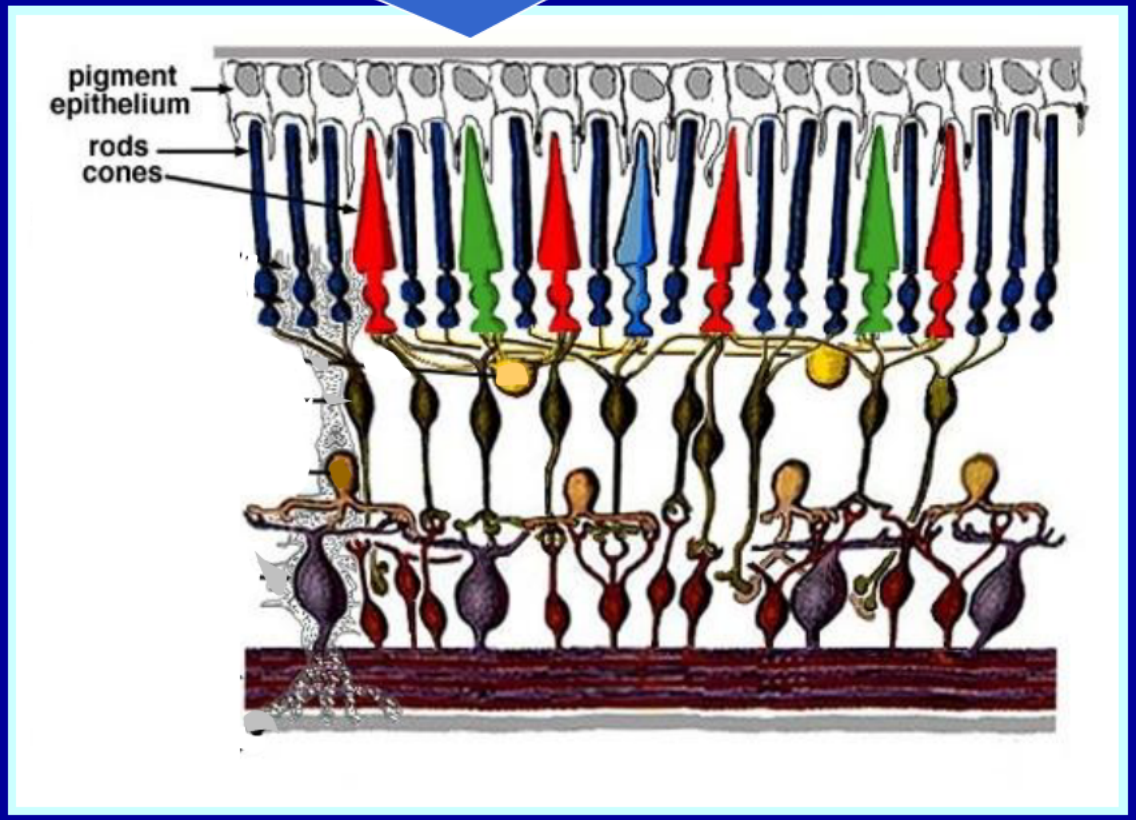
- Not required of Sponsor-Investigators
- Brief description of the product
- Summary of pharmacological and toxicological effects of the product in animals and if known in humans
- Summary of pharmacokinetics, if known
- Summary of any safety information from prior clinical studies
- Description of anticipated risks based on prior human experience with this or related products

Phases of IND Investigation

- Phase 1
  - Designed to predominantly evaluate safety
- Phase 2
  - Preliminary efficacy studies and dose ranging
- Phase 3
  - Confirmatory efficacy studies intended to provided statistical evidence of effectiveness
- Primary concern in all phases is safety

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.
- 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

Development Considerations

- Selection of appropriate endpoints for retinal disorders
- Assessment of potential risks with novel therapeutic agents, particularly in regard to a potential inflammatory response and repeat or contralateral eye 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)

Advisory Committee Discussion: Efficacy Endpoints

- Need for clinically meaningful measurements that indicate the treatment benefits the patient
  - Potential different endpoints for different diseases
    - E.g., macula versus peripheral retina
- Secondary endpoints
  - Could be anatomic, physiologic, and performance-based
- Surrogate endpoints
  - Need studies to correlate with clinical meaningfulness
- Pediatric populations
  - Reasonable to consider trials in younger populations, particularly if the product might also be used in children

Immunologic Safety Concerns

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

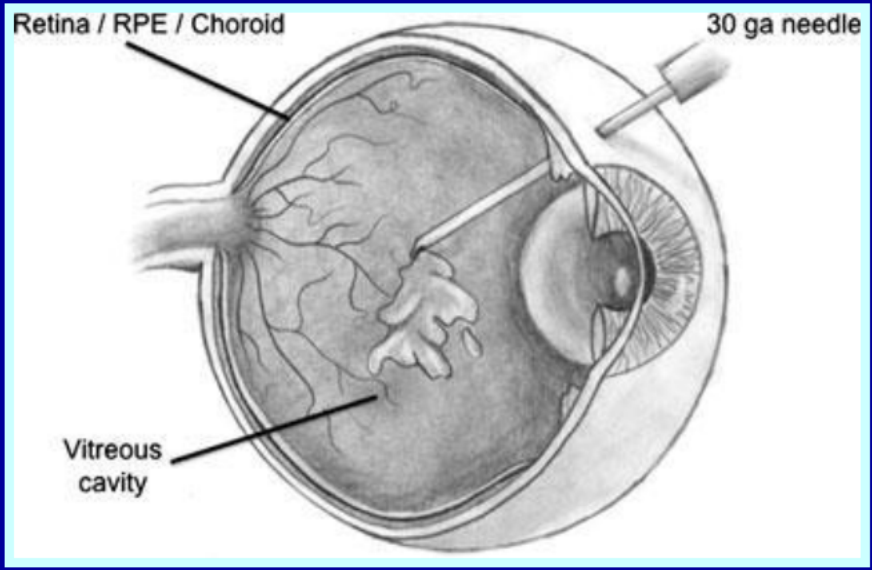
- General safety / adverse reaction surveillance
- Specific monitoring for immune response
- Staggered patient enrollment
- Single, low-dose administration
- Adjusted administration intervals
- Immunosuppressive therapy

Advisory Committee Discussion: Immunologic Safety Concerns

- No specific pre-clinical tests to determine safety
  - Preclinical allograft models probably most useful
  - Concurrent control (vs. before- and after-treatment studies)
- Treating second eye
  - Lack of data correlating initial and subsequent immune response
  - No consensus regarding an appropriate follow-up period before treating the second eye
- Repeat administration into the same eye
  - Potential ways to minimize risks
    - Monitor T cell and antibody responses
    - Allow time for the passing of acute and subacute inflammation

Ophthalmic Administration Procedures

Intravitreal Administration

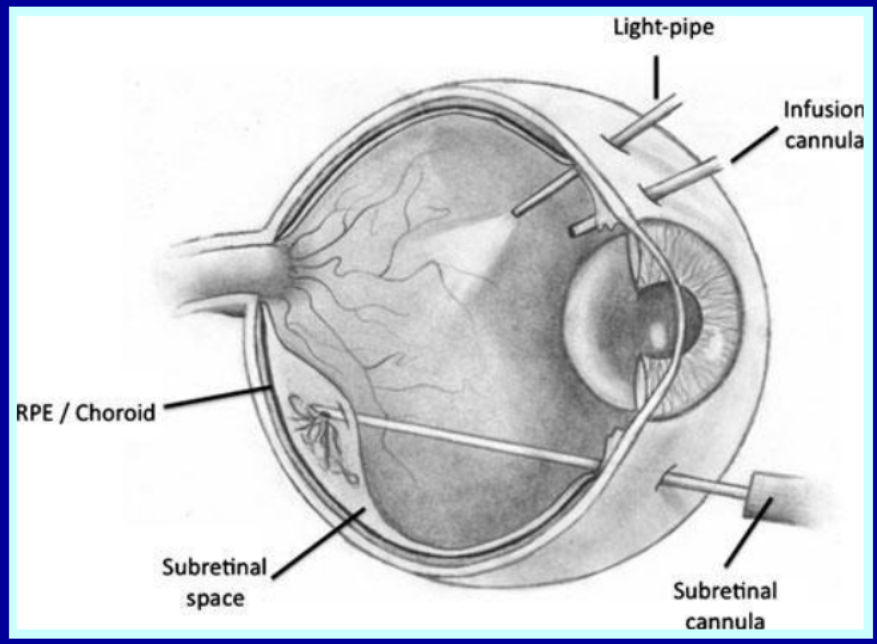


Stout *et al.*, *Hum Gene Ther*, 2011; 22(5):531.

- Routine clinical procedure
- Low complication rate
- Limited engraftment and transduction into target tissue

Subretinal Administration

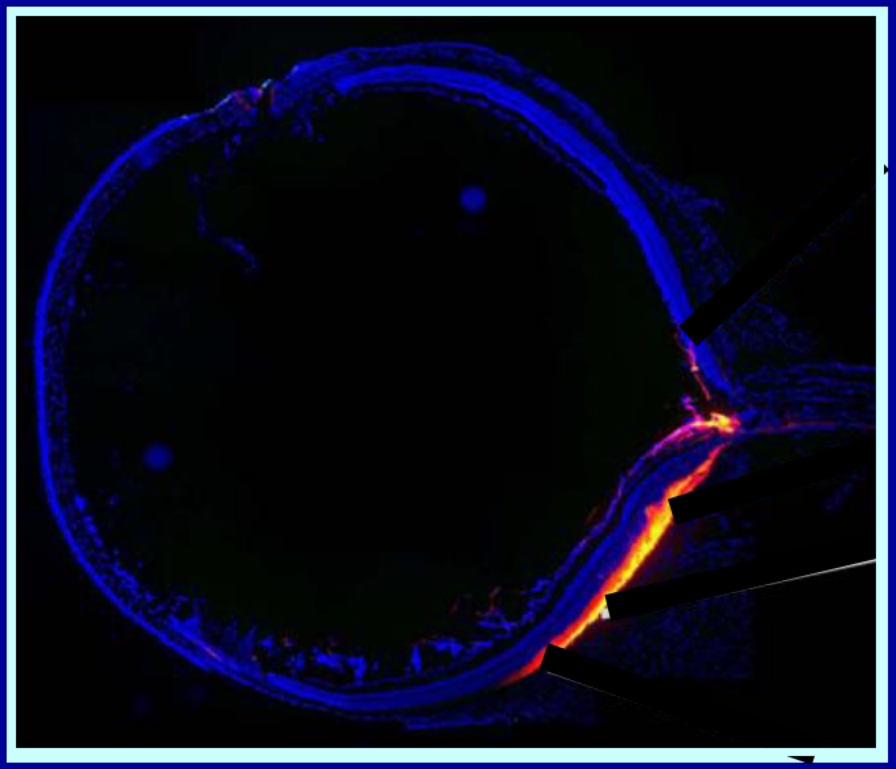
- Improved engraftment and transduction of photoreceptors and RPE
- Technically more challenging
- Higher complication rates



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

Preclinical Data

- Challenges to standardization
  - Spectrum of animal species / models for assessing product administration
  - Determining successful delivery to target



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

Advisory Committee Discussion: Ophthalmic Administration

- Monitoring can be achieved using current direct visualization procedures such as slit lamp biomicroscopy and indirect ophthalmoscopy.
- Administration in the subretinal space may be safe.
- Administration of these novel therapies should only be done by appropriately trained ophthalmologists.

Review

- Regulations exist that define the responsibilities of sponsors and investigators as well as the required elements of IND submissions
- Challenges remain in evaluating the safety and efficacy of cell therapies for retinal disorders

Further Information

OCTGT Learn:

http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm?utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=octgt%20learn&utm_content=1

CTGT Advisory Committee Meeting 6/29/11:

http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/CellularTissueandGeneTherapiesAdvisoryCommittee/ucm249846.htm

OCTGT Submissions

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Thank You