Potency Considerations for a hUTC-derived Therapy

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Agenda

- Review of disease target and pathogenesis: AMD
- hUTC characteristics
- Mechanism of action
- Potency assay approach
Age-related Macular Degeneration (AMD) is the Leading Cause of Irreversible Vision Loss in the World

Advanced AMD has well-validated, unmet needs

- **Wet AMD**
  - Increased Efficacy in Initial Recovery of Decreased BCVA
  - Maintain Gained Vision Over Time
  - Prevent Initial Loss of Vision

- **Geographic Atrophy**
  - Prevent/Reduce Progression of Vision Loss (VA and/or lesion size)
  - Recovery of Decreased VA
  - Prevent Initial Loss of Vision (VA and/or lesion size)

BCVA = best corrected visual acuity
VA = visual acuity
Geographic atrophy (GA) is an advanced form of age-related macular degeneration (AMD) that affects the macula, the part of the retina responsible for sharp, central vision.

Loss of vision in patients with GA is associated with:
- Severe emotional distress
- Depression
- Loss of independence
- Inability to conduct daily activities, such as:
  - Reading
  - Recognizing faces
  - Watching television
  - Driving

AMD is the leading cause of irreversible blindness globally among adults over 65.

6% of the 15 million people in the U.S. with AMD are at risk for developing GA.

AMD incidence is expected to increase nearly 50% by 2040.

More than 900,000 individuals in the U.S. are estimated to suffer from GA.
Progression of Vision Loss due to AMD

Normal Vision

Progressive Vision Loss With AMD
Role of Retinal Pigment Epithelium (RPE)

- Retinal pigment epithelium (RPE)
  - Essential for photoreceptor health
  - Selectively exchanges material between the avascular outer retina and the choriocapillaries

- Photoreceptors
  - Light-sensitive cells
  - Cones and rods

- Bipolar cells

- Ganglion cells

- Nutrients

- Waste

- Subretinal space

- Bruch’s Membrane

- Choriocapillaris
  - Provides O₂ and nutrients to retina

- RPE
  - Damage progresses to GA
**AMD Progression Can Result in Vision Loss**

**Effects 15M patients in the US**

- **Early AMD**
  - ~1.5 M patients
  - Small Drusen (>63 and <125 μm)
  - Minimal effect on vision

- **Intermediate AMD**
  - ~7M patients
  - Drusen (>125 μm)
  - Patient may notice dim or “wavy” regions in central vision

- **Dry AMD (~90%)**

- **Wet AMD (~10%)**

**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

- **Available treatments: None**

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

- **Available treatments: Lucentis, Avastin, Eylea**
The macula comprises only ~4% of the retina, but provides 50% of visual information reaching the brain.

**Macula**
- 6 mm diameter
- 6,000 cones/mm²

**Fovea**
- 1.5 mm diameter
- 165,000 cones/mm²
- Origin of ½ of optic nerve fibers

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

Rod density ranges from ~35,000 rods/mm² at the periphery to ~150,000 rods/mm at about 3-5 mm from the foveola.

Surgical procedure and device has been developed

Transvitreal -> Suprachoroidal
Model of AMD pathogenesis

Risk Factors for AMD

- Age
- Oxidative Stress
- Smoking

Genetic Factors
- Angiogenesis
- Lipid metabolism
- Complement
- ECM remodeling
- Other

Phagocytic impairment

Build up of visual cycle waste

Drusen formation (C5, C5b-9, Aβ, lipids, apoE, Ig)

Anti-retina autoantibodies

Blood-retina barrier breakdown

Pathological angiogenesis

Inflammasome activation

Complement activation

Classical

Alternative

RPE Damage

RPE Atrophy

Retinal Neural Atrophy

Wet AMD

Gelatinous atrophy (GA)

Modified from: Ambati et al., 2013; Fritsche et al., 2014
hUTC (PaluCorcel) Characteristics
Palu-corcel

- **Is:**
  - Allogeneic cell therapy
  - Human umbilical tissue-derived cells (hUTC)

- **Is not:**
  - A retinal pigment epithelial (RPE) cell
    - Not replenishing or recolonizing
  - A stem cell
    - Cannot spontaneously differentiate into different functional cell types
Palucorcel (hUTC) has Unique Properties

Cell Growth

- Umbilical cord cells are not immortal
- Product can be made from the same donor
- Properties differ from fibroblast or mesenchymal stem cells (MSC)
- Umbilical cells can be expanded more than MSC
Differential Gene Expression in UTCs

Primary Component Analysis of Gene Microarrays

PCR for Differentially expressed genes

Fibroblast
Ileac Crest derived bone marrow
Mesenchymal stem cells
Placenta
Umbilical cord derived cells

reticulon
rennin
oxidized LDL receptor
GAPDH
hUTCs secrete sVEGFR1 and other cells do not

- May prevent GA patients from converting to wet AMD

Notebook #13650 p87, p130-131
Single injection of 20K Palucorcel preserves retinal architecture in RCS rat

Almost complete absence of photoreceptors at post-natal day 90 (P90)

Significant preservation at P90 (69 days post hUTC injection)

Area of Photoreceptor Preservation in the RCS rat

Superior

Area preserved >30% rat retina

Inferior

Injection site

Outer nuclear layer

Photoreceptors are preserved beyond where PaluCorcel is injected
From preclinical proof of concept to potency assay
*hUTC rescue phagocytosis in dystrophic RPE*

(RCS phagocytosis studies performed in collaboration with Dr. George Inana, Bascom Palmer Eye Institute)
Optomoter does not show a dose response

P21 Injection

Wild Type
4,000 hUTC
20,000 hUTC
100,000 hUTC

Sham Untreated

threshold (c/d)
Mechanism of Action
Hypothesis: Palucorcel rescues phagocytosis in RCS RPE through the secretion of Receptor Tyrosine Kinase (RTK) Ligands
Mechanism of Action

Human umbilical tissue-derived cells (hUTC) secrete:
• receptor tyrosine kinase (RTK) ligands
  • can rescue phagocytic activity
• opsonizing bridge molecules
  • target/facilitate ingestion by RPE
RTK ligands can compensate for loss of Mertk function

RTK ligands secreted by hUTCs are required for bioactivity

Potency Assay Approach
Potency Measurement

- What should be measured for potency?
  - Product attributes related to biological activity
  - Potency measurements related to the mechanism of action that reflect the product’s relevant biological properties

- More than one potency assay may be needed if the product has:
  - A complex or partially characterized mechanism of action
  - Multiple active ingredients
  - Multiple biological activities
  - Limited product stability
  - A non-quantitative, imprecise or non-robust assay
Potency Assay

**Characteristics**

- Quantitative
- Predictive of efficacy or bioactivity
- Able to detect changes in inactive or degraded material
- Related to mechanism of action
- May be more than one assay (matrix)

**Challenges**

- Wide variability in assays may limit quantitation and link to efficacy
- MoA can be complex and involve many factors
- Limited history (limited material, batches, quantities for analysis)
Assay Acceptance Criteria throughout Development

Progressive Assay Implementation (or Phase-Appropriate Assay Development)

- **Phase 1/2**
  - Wide range adjusted as development progresses
  - Should be meaningful to allow comparability
  - Based on manufacturing and clinical experience

- **Phase 3**
  - Establish appropriate limits to assure that product lots are well-defined and biologically active
  - Ensure manufacturing consistency

- **License Application**
  - Based on product, process and clinical information collected throughout development
# Challenges for Potency Assay Development

*Applicability to hUTCs (✓)*

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<tr>
<th>Challenges*</th>
<th>Examples</th>
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| Inherent variability of starting materials | • Autologous and allogeneic donor variability  
• Cell line heterogeneity |
| Limited lot size and limited material for testing | • Single dose therapy using autologous cells suspended in a small volume |
| Limited stability | • Viability of cellular products |
| Lack of appropriate reference standards | • Autologous cellular material |
| Multiple active ingredients | • Multiple cell lines combined in final product  
• Heterogeneous mixtures immune-modulatory cells |
| The potential for interference or synergy between active ingredients | • Multiple cell types in preparation |
| Complex mechanism of action(s) | • Multiple potential effector functions of cells |
| In vivo fate of product | • Migration from site of administration  
• Cellular differentiation into the desired cell type |

* FDA Guidance for Industry
Types of Potency Assays

- Direct biological activity (bioassay)
- Indirect biological activity
  - Non-bioassay correlated to activity
  - Compare to *in vivo* or *in vitro* bioassays
- Matrix
  - Other assays based on product attributes
Potency Assay Considerations

• Potency testing of cell therapies must:
  • Indicate product-specific biologic activity
  • Link to MoA when possible
  • Provide quantitative release data using a validated method
• Potency assay required for batch release, stability, comparability for process and site changes, and biological characterization.
• Inherent variability complicates specification setting
• Limited Release Testing Panel
  • Orthogonal methods may not be difficult to establish
• Stability testing limited to real-time data
  • Accelerated stability approaches may not apply to cell therapies
Going forward

- Potency development is an ongoing effort throughout development
- Continue to establish correlations between assays
- Continue to evaluate orthogonal assays
Thank you