Development of AGN 151587 (EDIT-101), a gene editing approach to restore vision in Leber Congenital Amaurosis Type 10

Vic Myer, Ph.D.
Chief Technology Officer
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EDITING INSIDE THE BODY
IN VIVO CRISPR MEDICINES

OCULAR DISEASES

Leber congenital amaurosis 10*
Usher syndrome 2A
Retinitis pigmentosa
Ocular HSV

CANCER

Autologous T cell medicines**
Allogeneic cell medicines

BLOOD DISEASES

Sickle cell disease
Beta-thalassemia

EDITING OUTSIDE THE BODY
ENGINEERED CELL MEDICINES

EARLY DISCOVERY

Liver – AATD
Muscle – DMD
Lung – CF

*EDIT-101 (AGN-151587) partnered with Allergan; **Partnered with Celgene; LCA10: Leber congenital amaurosis 10; HSV: herpes simplex virus; CF: cystic fibrosis; DMD: Duchenne muscular dystrophy; AATD: alpha-1 antitrypsin deficiency; AAV: adeno-associated virus

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## Considerations for an in vivo Editing Experimental Medicine

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Leber Congenital Amaurosis 10

WT Photoreceptor

LCA10 Photoreceptor

Cone cell
Rod cell

Retina
Fovea
Blind spot

Outer segment
Inner segment

Discs
Connecting cilium

Protein trafficking

CEP290

Degenerated discs
No protein trafficking
Gene Editing to Repair *CEP290* Splicing Defect

**DNA**

- *CEP290* with IVS26 mutation
- *CEP290* corrected with EDIT-101

**mRNA**

- Exon 26
- Exon 27

**Protein**

- p.Cys998X
- Prematurely truncated and non-functional
- Full length, functional *CEP290*
Editing Corrects CEP290 Splicing Thereby Restoring mRNA and Protein Expression

CEP290 mRNA Expression

CEP290 Protein Expression

From LCA10 patient fibroblasts
Challenges with PCR-NGS Assays When Making Multiple Edits

3 PCR assays needed to measure editing at CEP290 intron 26 locus

Even with rigorous standards it is difficult to cross compare 3 assays
Editing Causes Inversions, Deletions, and Indels

Targeted Deletions and Inversions Correct Splicing

Correct Splicing as Determined by GFP Expression

AGN-151587: gRNAs Plus SaCas9 in AAV5

AAV5

U6 323 U6 64 hGRK1

Kozak-ATG SV40 SD/SA Sa Cas9

NLS

pA

Cornea Retina Vitreous

Lens Optic Nerve

Subretinal Injection
Comprehensive Specificity Assessment

**Discovery**
- Predict where an enzyme can cut
  *In silico modeling*
- Find where an enzyme cuts naked DNA
  *Digenome-Seq*
- Find where an enzyme cuts DNA in context of a cell
  *GUIDE-Seq*

**Verification**
- Measures effect of enzyme activity on “discovered” sites
  *Targeted Sequencing in relevant cells*

**Off-Target**
- *Risk assessment and mitigation as needed*
Digencode-Seq Assay

CAS9 + Guide + genomic DNA → 16 hours → WGS Align & analyze 
Identify overabundant start sites

Count of unique cut sites
Includes on-target site

EMX1 (SpCAS9) | g64 (SaCAS9) | g323 (SaCAS9) | no RNP
---|---|---|---
10 nM | 100 nM | 1,000 nM | 10 nM | 100 nM | 1,000 nM | 10 nM | 100 nM | 1,000 nM | -
3 | 21 | 272 | 1 | 1 | 1 | 1 | 1 | 2 | 0

CEP290 Guide 323 on-target example

on:off >100x window
on:off ~100x window
Comprehensive Specificity Assessment

**Discovery**

- Predict where an enzyme can cut *In silico modeling*
- Find where an enzyme cuts naked DNA *Digenome-Seq*
- Find where an enzyme cuts DNA in context of a cell *GUIDE-Seq*

**Verification**

- Measures effect of enzyme activity on “discovered” sites
  - *Targeted Sequencing in relevant cells*
- 1 sites
- 0 sites
- 144 sites

**Off-Target**

- Risk assessment and mitigation as needed
Human Retinal Explant Model

1. **Human Eyes 3-5 hrs Post-Mortem**
   - Remove Neural Retina
   - 3 mm punches

   - Plate 3 mm punches with photoreceptor side down

2. **24-well format**
   - Harvest 28 days post-transduction

   - Histology
   - UDiTaS to measure Editing
   - Specificity verification panel

Human retinal explant model [2]

AAV5-GRK1-GFP (5e11 vg)

28 Day Post Transduction

EDIT-101 (5e11 vg)

28 Day Post Transduction

% Editing

Untreated

EDIT-101

INL

ONL

Inversions

Deletions

AAV insertions

Indels

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Specificity assessment, verification phase using targeted PCR with NGS readout

<table>
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<tr>
<th>Retinal Explant #1</th>
<th>Retinal Explant #2</th>
<th>ARPE-19</th>
<th>U-2 OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>147: 2 On-target, 144 In Silico, 1 Digenome</td>
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Candidate off-target sites
Assay Design (3 sites in repetitive regions)
Assay QC (142 in at least 2 samples)
Below LLoD <0.1% (no editing)
Above LLoD, no difference vs. to control
Verified editing at sites

Both on-target sites identified and **no** off-target candidate sites verified
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Initiated LCA10 Phase 1/2 Clinical Trial

**LCA10 PHASE 1/2 TRIAL**

**DESIGN**
Open-label, dose escalation study to evaluate safety, tolerability, and efficacy

**PATIENTS**
~18 patients with IVS26 mutation*

**COMPARATOR**
Patient’s own baseline value for each efficacy measure

**FOLLOW-UP**
Core measurements every 3 months for 1st year

*Intervening sequence 26 in CEP290 gene containing the c.2991+1655A>G mutation
Somatic cell gene editing has the potential to transform the lives of patients living with serious disease; Editas Medicine is only working on somatic cell gene editing.

Germline gene editing in human clinical settings is currently prohibited across much of the world.

In addition to scientific concerns, robust ethical and legal frameworks are not yet developed for germline gene editing in human settings.

As this topic concerns all of humanity, it is important that we all engage and listen to diverse stakeholders, including members of the patient, caregiver, regulatory, biotechnology, legal, academic, ethical, and faith communities to determine if, and under which conditions, the status quo should change.

To allow this process to develop in the years ahead, we support a global moratorium on clinical applications of human germline editing.
Acknowledgements

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