Gene Editing of Monogenic disorders in Human Hematopoietic Stem Cells (XLA)

Case: 2018-372
Donald B. Kohn

Distinguished Professor, Microbiology, Immunology and Molecular Genetics; Pediatrics (Hematology/Oncology); Molecular and Medical Pharmacology

Kohn began working on gene therapy as a fellow at the National Institutes of Health in 1985. After, while practicing at Children’s Hospital Los Angeles, he started his own lab focused on stem cell research and has continued this work, advancing new therapies from the lab to the clinic.

More recently, Donald B. Kohn, M.D., studies the biology of blood stem cells. Over the course of 30 years of research, Kohn has developed new clinical methods to treat genetic blood diseases using blood stem cells that have been modified to remove genetic mutation, focusing especially on gene therapy methods.
Executive Summary
X-Linked Agammaglobulinemia is a Genetic Immunological Disorder

- X-Linked Agammaglobulinemia (XLA) is a genetic disorder that affects 1/200,000 people worldwide.
- Patients with XLA require lifelong treatment and have reduced life expectancy.\(^1\)
X-Linked Agammaglobulinemia is a Genetic Immunological Disorder

The cause of XLA is a well characterized recessive mutation in the gene encoding Bruton’s Tyrosine Kinase (BTK) found on the X-chromosome.

Mutant/dysfunctional BTK results in a diminished ability to fight off infections.¹

Normal BTK allows proper function of B cells and production of antibodies.

X-Linked Agammaglobulinemia is a Genetic Immunological Disorder

• Mutant BTK blocks the maturation of B cells to their functional mature state.
• Without a cure, XLA causes patients to have impaired immune function throughout their lives.
Treatments for XLA are Expensive and Ineffective

- **Current standard of care for XLA is immunoglobulin replacement therapy and frequent antibiotic administration.**

- **There remains no curative treatment for individuals afflicted with XLA.**

[1] National Organization of Rare Diseases, X-linked agammaglobulinemia; https://rarediseases.org/rare-diseases/agammaglobulinemia/
Treatments for XLA are Expensive and Ineffective

- There is an urgent need for cost effective, curative treatment for XLA with limited off target effects.

**IgG Replacement Therapy**

- IgG therapy is expensive and needs to be repeated throughout patients’ lives.

**Antibiotic Therapy**

- Antibiotics are not preventative and can have side-effects when relied upon.
XLA Inhibits Maturation of Immune B Cells

- Restoring functional sequence of BTX protein could produce a cure for XLA.
- Gene therapy methods provides the potential to provide this cure.
Gene Therapy Intervention Could Cure XLA

- Restoring functional sequence of BTX protein could produce a cure for XLA.
- Gene therapy methods provide the potential to provide this cure.
Advantages Over Other Gene Therapy Methods

- Existing gene therapy protocols suffer from poor gene editing efficiency, and low expression of inserted gene.

- Novel UCLA-developed method yield high editing efficiency and good expression of inserted transgene.

Current available treatments struggle with efficiency and specificity.

Complications of Gene Therapy

1. Adverse host immune responses
   - Innate Immunity
     - Fever, thrombocytopenia, cytokine storm
   - Adaptive Immunity
     - Humoral response
       - e.g. Anti-AAV capsid Abs
     - Cell-mediated response
       - e.g. Anti-AAV capsid cytotoxic T cells

2. Insertional Mutagenesis

3. Failure of Transgene Expression
   - Too little
   - Not persistent

Applications of Invention

• UCLA Researchers developed a novel gene therapy method that can efficiently and precisely revert disease causing mutations associated with XLA.

• Unlike other gene therapy methods, novel UCLA method does not suffer from low expression or editing efficiency.

• Novel XLA-treating gene therapy method can be used to modify stem cells ex vivo for reintroduction into patient’s body.

Developmental Timeline of Technology

July 2015: Initial Conception.

- Development of novel gene editing platform
- Demonstration of effectiveness at editing gene linked to other X-linked disorders
- Development of BTK-targeting gene therapy

Demonstrated technology efficiently edits BTK gene

Target 1

Target 2

Experimental Groups

Negative Controls

Mock

Experimental

Negative Controls

Experimental

Projected 

Technology
Market Opportunity
# Market Overview: Generalized Market

Global Marker for Genetic Modification Therapies in Rare Diseases, by Indication, Through 2023 ($ Millions)

<table>
<thead>
<tr>
<th>Indication</th>
<th>2017</th>
<th>2018</th>
<th>2023</th>
<th>CAGR% 2018-2023</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPS III (Sanfilippo syndrome)</td>
<td>—</td>
<td>—</td>
<td>1,078.7</td>
<td>—</td>
</tr>
<tr>
<td>ATTR</td>
<td>—</td>
<td>47.1</td>
<td>776.2</td>
<td>75.1</td>
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<tr>
<td>HofH</td>
<td>3.8</td>
<td>4.7</td>
<td>366.6</td>
<td>139.0</td>
</tr>
<tr>
<td>XLMTM</td>
<td>—</td>
<td>—</td>
<td>135.7</td>
<td>—</td>
</tr>
<tr>
<td>MPS I</td>
<td>—</td>
<td>—</td>
<td>82.8</td>
<td>—</td>
</tr>
<tr>
<td>ADA-SCID</td>
<td>—</td>
<td>—</td>
<td>73.2</td>
<td>—</td>
</tr>
<tr>
<td>MPS II</td>
<td>—</td>
<td>—</td>
<td>33.4</td>
<td>—</td>
</tr>
<tr>
<td>Pompe disease</td>
<td>—</td>
<td>—</td>
<td>31.7</td>
<td>—</td>
</tr>
<tr>
<td>ADPKD</td>
<td>—</td>
<td>—</td>
<td>25.8</td>
<td>—</td>
</tr>
<tr>
<td>CASQ2-CPVT</td>
<td>—</td>
<td>—</td>
<td>23.7</td>
<td>—</td>
</tr>
<tr>
<td>Alport syndrome</td>
<td>—</td>
<td>—</td>
<td>19.4</td>
<td>—</td>
</tr>
<tr>
<td>Total</td>
<td>3.8</td>
<td>51.8</td>
<td>2,647.2</td>
<td>119.6</td>
</tr>
</tbody>
</table>

- The global market for gene therapy targeting rare diseases:
  - Global Market - $51.8 million in 2018
  - Projected Growth to $2.65 billion by 2023
  - CAGR of 119.6%, by 2023
  - Some of the fastest predicted growth rates of any therapeutic market.
Market Overview (By Region)

Global Market for Genetic Modification Therapies, by Region, Through 2023

<table>
<thead>
<tr>
<th>Region</th>
<th>2017</th>
<th>2018</th>
<th>2023</th>
<th>CAGR% 2017-2023</th>
</tr>
</thead>
<tbody>
<tr>
<td>North America</td>
<td>908.2</td>
<td>1,609.0</td>
<td>9,330.3</td>
<td>42.1</td>
</tr>
<tr>
<td>Europe</td>
<td>15.1</td>
<td>378.8</td>
<td>6,405.8</td>
<td>76.0</td>
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<tr>
<td>Asia-Pacific</td>
<td>47.2</td>
<td>240.1</td>
<td>1,461.1</td>
<td>43.5</td>
</tr>
<tr>
<td>ROW</td>
<td>—</td>
<td>72.8</td>
<td>233.3</td>
<td>26.2</td>
</tr>
<tr>
<td>Total</td>
<td>970.5</td>
<td>2,300.7</td>
<td>17,430.5</td>
<td>49.9</td>
</tr>
</tbody>
</table>

Relevant Companies:
Comparisons with Existing Innovations in Cancer Therapeutics

- **Short Term XLA Treatment (Non-Curative)**
  - Widespread Toxicity
  - Limited off-target Effects

- **Long Term XLA Treatment (Curative)**
  - Novel UCLA-developed gene therapy Method provides long term cure with high specificity

- Antibiotics
- IgG Replacement Therapy
- Other Gene Therapies
- Novel STING Nanoparticle
Commercialization Potential
Novel UCLA Gene Therapy Treatment will Revolutionize Clinical Intervention for XLA

There is a dire need for a drug that cures XLA with high efficiency and low toxicity.

Table 38
Global Market for Genetic Modification Therapies, by Platform Technology, Through 2023 ($ Millions)

<table>
<thead>
<tr>
<th>Platform Technology</th>
<th>2017</th>
<th>2018</th>
<th>2023</th>
<th>CAGR% 2018-2023</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene therapy</td>
<td>151.7</td>
<td>374.7</td>
<td>9,438.1</td>
<td>90.7</td>
</tr>
<tr>
<td>RNA therapy</td>
<td>797.8</td>
<td>1,763.8</td>
<td>4,692.0</td>
<td>21.6</td>
</tr>
<tr>
<td>Genetically modified cell therapy</td>
<td>21.0</td>
<td>162.2</td>
<td>3,118.9</td>
<td>80.6</td>
</tr>
<tr>
<td>Gene editing</td>
<td>—</td>
<td>—</td>
<td>181.5</td>
<td>—</td>
</tr>
<tr>
<td>Total</td>
<td>970.5</td>
<td>2,300.7</td>
<td>17,430.5</td>
<td>49.9</td>
</tr>
</tbody>
</table>

Source: BCC Research

Novel XLA gene therapy efficiently targets BTK gene; Marketing as a cure for XLA and a platform for treatment of other X-linked genetic disorders.
Thank You