Accelerating Therapeutic Somatic Cell Gene Editing Approaches

Mary Ellen Perry, Ph.D.
Office of Strategic Coordination
Division of Program Coordination, Planning, and Strategic Initiatives
Council of Councils Concept Clearance
September 1, 2017
Thousands of incurable genetic diseases are now theoretically treatable by gene editing approaches.

Simple and versatile genome editing methods are democratizing therapeutic development.

For some indications, a single treatment could be a cure.

Therapeutic development is still inefficient.

Development costs for ultra-rare diseases are prohibitive for industry.
What is Gene Editing?

Gene editing is a rapidly developing area of biotechnology in which the nucleotide sequence of the genome of living cells is specifically targeted.
<table>
<thead>
<tr>
<th>Status</th>
<th>Study Title</th>
<th>Conditions</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recruiting</td>
<td>Ascending Dose Study of Genome Editing by the Zinc Finger Nuclease (ZFN) Therapeutic SB-913 in Subjects With MPS II</td>
<td>Mucopolysaccharidosis II</td>
<td>Biological: SB-913</td>
</tr>
<tr>
<td>Recruiting</td>
<td>Ascending Dose Study of Genome Editing by the Zinc Finger Nuclease (ZFN) Therapeutic SB-318 in Subjects With MPS I</td>
<td>MPS I</td>
<td>Biological: SB-318</td>
</tr>
<tr>
<td>Recruiting</td>
<td>Ascending Dose Study of Genome Editing by Zinc Finger Nuclease Therapeutic SB-FIX in Subjects With Severe Hemophilia B</td>
<td>Hemophilia B</td>
<td>Biological: SB-FIX</td>
</tr>
<tr>
<td>Recruiting</td>
<td>Dose-Ranging Study of Recombinant AAV2/6 Human Factor 8 Gene Therapy SB-525 in Subjects With Severe Hemophilia A</td>
<td>Hemophilia A</td>
<td>Biological: SB-525</td>
</tr>
<tr>
<td>Completed</td>
<td>Phase 1 Dose Escalation Study of Autologous T-cells Genetically Modified at the CCR5 Gene by Zinc Finger Nuclease in HIV-Infected Patients</td>
<td>HIV Infection; HIV Infections</td>
<td>Genetic: SB-728-T</td>
</tr>
</tbody>
</table>

www.clinicaltrials.gov
Making the cut
CRISPR genome-editing technology shows its power

By John Travis

CRISPR-based Gene Editing Systems are Simpler and More Efficient than Previously Used Nuclease Systems

**ZFN, TALENs**

Targeting is directed to specific sequence by DNA binding-domains fused to the nuclease

Each new genetic target requires a newly engineered protein

**CRISPR-Cas9**

Targeting is directed to specific sequences by a guide RNA

Each new genetic target requires a new guide RNA; *the same nuclease can target any gene*

[www.addgene.org/genome-engineering/](http://www.addgene.org/genome-engineering/)
CRISPR-Cas9 is Versatile – It Can Be Modified to Make Single Base Edits without Cleaving DNA

Boom in human gene editing as 20 CRISPR trials gear up

A pioneering CRISPR trial in China will be the first to try editing the genomes of cells inside the body, in an effort to eliminate cancer-causing HPV virus.
Limitations

Targeting specificity & efficiency
Off-target effects & unintended consequences

Common Fund Planning Workshop
July 24, 2017

Workshop Participants

Charles Albright, Ph.D., Editas Medicine
Thomas Barnes, Ph.D., Intellia Therapeutics
Ronald Bartek, M.A., Friedreich’s Ataxia Research Alliance
Jennifer Doudna, Ph.D., University of California Berkeley
Cynthia Dunbar, M.D., NHLBI
Lisa Ellerby, Ph.D., Buck Institute for Aging Research
Charles Gersbach, Ph.D., Duke University
Amy Jenkins, Ph.D., DARPA
Keith Joung, M.D., Ph.D., Harvard Medical School/MGH
David Liu, Ph.D., The Broad Institute
Bill Lundberg, M.D., CRISPR Therapeutics
Harry Malech, M.D., NIAID
Samantha Maragh, Ph.D., NIST
Peter Marks, M.D., Ph.D., FDA
Pilar Ossorio, Ph.D., J.D., University of Wisconsin
Matthew Porteus, M.D., Ph.D., Stanford University
Bill Skarnes, Ph.D., Jackson Laboratory
Edward Stadtmauer, M.D., University of Pennsylvania
Sohel Talib, Ph.D., CIRM
John Tisdale, M.D., NHLBI
Fyodor Urnov, Ph.D., Altius Institute
Amy Wagers, Ph.D., Harvard University
Renee Wegrzyn, Ph.D., DARPA
Zhaohui Ye, Ph.D., FDA
Feng Zhang, Ph.D., The Broad Institute
Gaps Identified by Workshop Participants:

1. Relevant human and animal models systems for pre-clinical testing
2. Cell- and tissue-specific delivery systems
3. Standardized assays for measuring genetic off-target effects
4. Improved editing machinery (nuclease alternatives)
5. Long-term cell tracking assays
Program Goals

Facilitate Phase I/II Clinical Trials of New Somatic Gene Editing Therapies by Developing and Providing Broad Access to:

- Animal Models for Gene Editing Research and Preclinical Testing
- New Methods to Assess Intended and Unintended Biological Effects
- Efficient, Effective, and Specifically Targeted *In Vivo* Delivery Systems
- Improved Human Gene Editing Tools
Proposed Initiatives

   - Develop gene editing reporter mice and large animal models
   - Develop non-human primate and other animal models for use in preclinical studies

2. Assessing Biological Effects
   - Test gene editing strategies for detrimental consequences using a variety of assays
   - Develop new technologies to allow for edited cells to be tracked \textit{in vivo} over time

3. Improving \textit{In Vivo} Delivery of Gene Editing Machinery
   - Improve and validate the efficiency, cell- & tissue-specificity, and safety of gene delivery systems
   - Provide QC’d delivery systems to the research community as a service

4. Expanding the Human Genome Engineering Toolkit
   - Support the discovery and optimization of improved genome engineering technologies for therapeutic purposes

5. Coordination and Organizational Center
   - Assemble data from all program components into a coordinated data resource
   - Disseminate knowledge, tools, and methods to the community
   - Manage working groups and committees of the consortium (e.g., the Steering Committee)
   - Coordinate interactions with FDA, DARPA, NIST and industry
The NIH Gene Editing Consortium Will Interact with and Leverage:

**The DARPA Safe Genes Program**

- Control of Gene Editing
  - Enable temporal, spatial, and reversible control of gene editors
- Countermeasures and Prophylaxis
  - Inhibit unwanted gene editing activity
- Genetic Remediation
  - Remove engineered genes from environments to return to baseline

**The NIST Gene Editing Standards Consortium**

**The FDA Office of Tissues and Advanced Therapies, CBER**

Related NIH Efforts, e.g., Immune Tolerance Network, Regenerative Medicine Project
Potential Impact

- Increased access to IND-enabling technologies
- Accelerated filings of new INDs for gene editing therapies
- Faster approval of gene editing therapies
- New therapeutic approaches for both rare and common diseases
- Cures for monogenic diseases