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

National Institutes of Health
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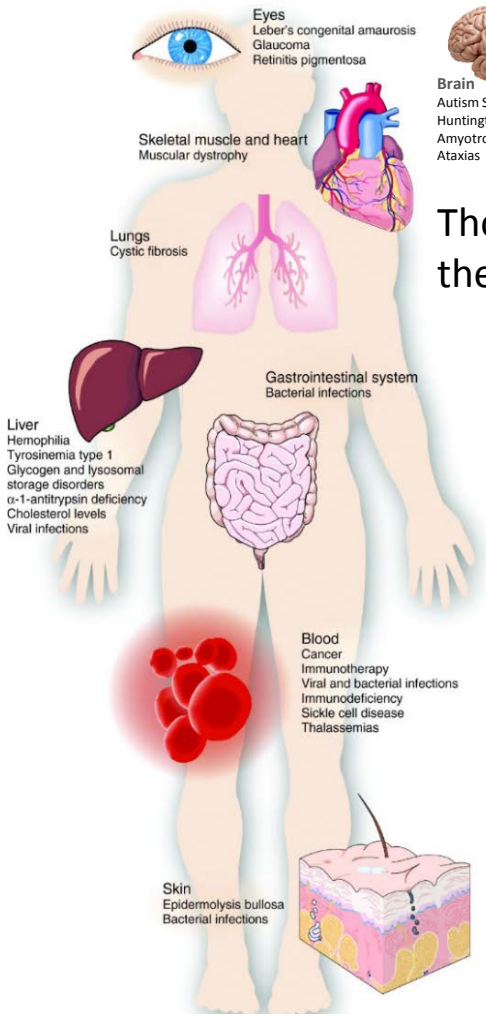
Challenge/Opportunity



Thousands of incurable genetic diseases are now theoretically treatable by gene editing approaches.

Simple and versatile genome editing methods are democratizing therapeutic development.

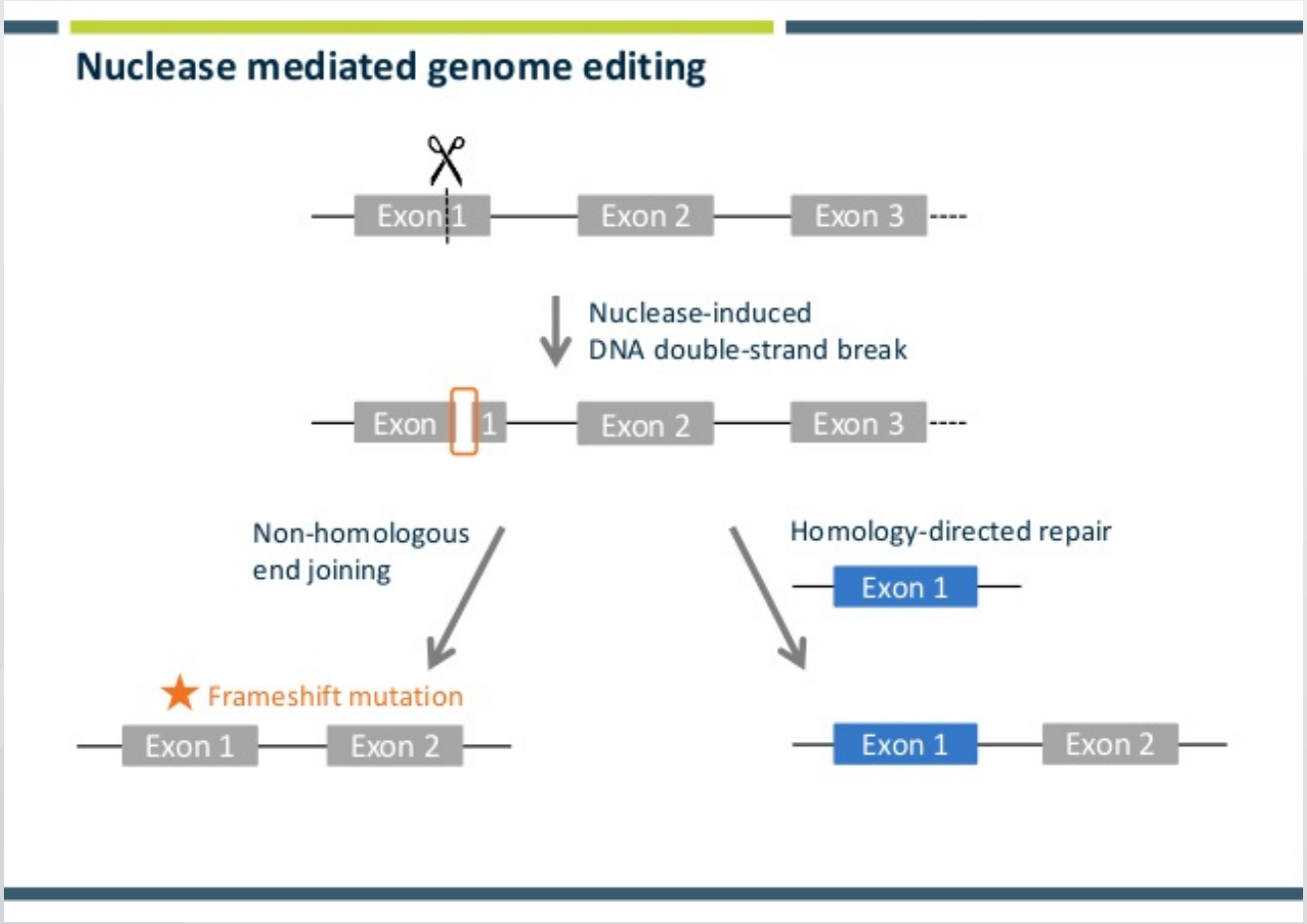
For some indications, a single treatment could be a cure.

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.



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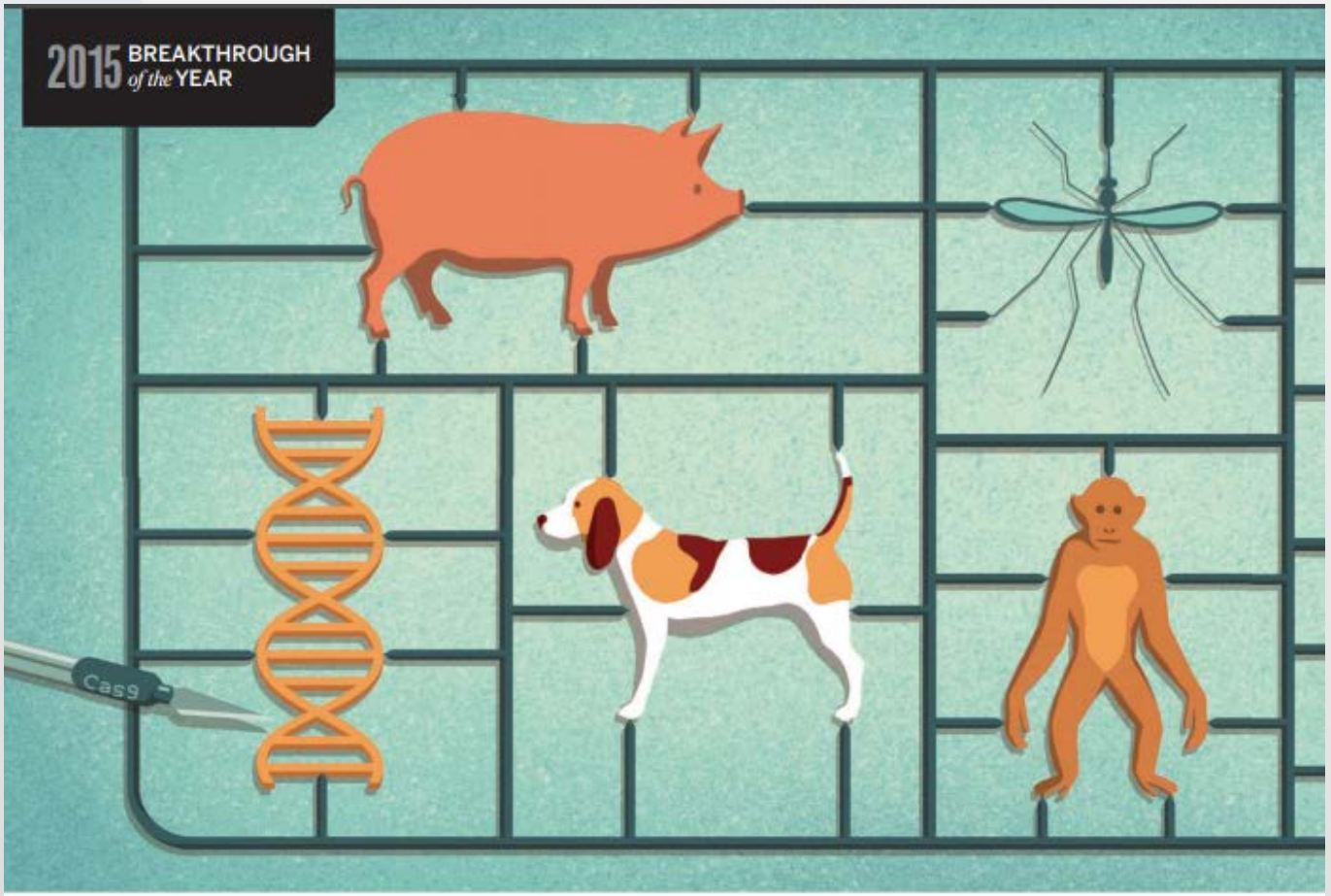
www.slideshare.net/ChrisThorne1/an-introduction-to-crispr-genome-editing-52663021

Nuclease-based Gene Editing Therapies are in Clinical Trials

Status	Study Title	Conditions	Interventions
Recruiting	Ascending Dose Study of Genome Editing by the Zinc Finger Nuclease (ZFN) Therapeutic SB-913 in Subjects With MPS II	Mucopolysaccharidosis II	Biological: SB-913
Recruiting	Ascending Dose Study of Genome Editing by the Zinc Finger Nuclease (ZFN) Therapeutic SB-318 in Subjects With MPS I	MPS I	Biological: SB-318
Recruiting	Ascending Dose Study of Genome Editing by Zinc Finger Nuclease Therapeutic SB-FIX in Subjects With Severe Hemophilia B	Hemophilia B	Biological: SB-FIX
Recruiting	Dose-Ranging Study of Recombinant AAV2/6 Human Factor 8 Gene Therapy SB-525 in Subjects With Severe Hemophilia A	Hemophilia A	Biological: SB-525
Completed	Phase 1 Dose Escalation Study of Autologous T-cells Genetically Modified at the CCR5 Gene by Zinc Finger Nucleases in HIV-Infected Patients	HIV Infection; HIV Infections	Genetic: SB-728-T

www.clinicaltrials.gov



Making the cut

CRISPR genome-editing technology shows its power

By **John Travis**

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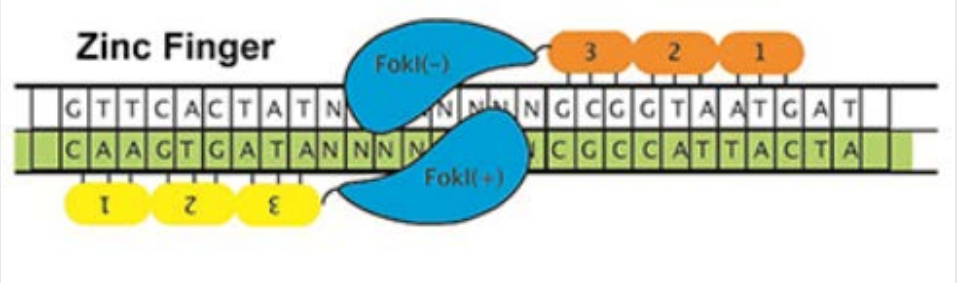
www.sciencemag.org/news/2015/12/and-science-s-2015-breakthrough-year

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

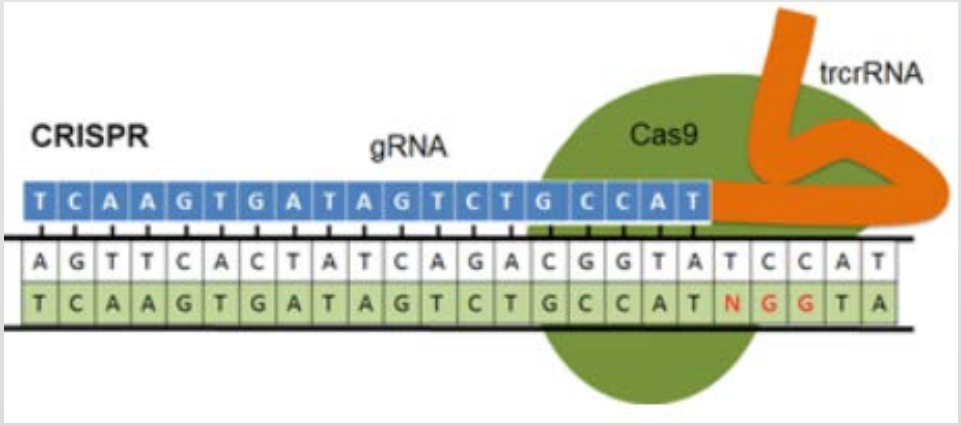
Each new genetic target requires a newly engineered protein



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*



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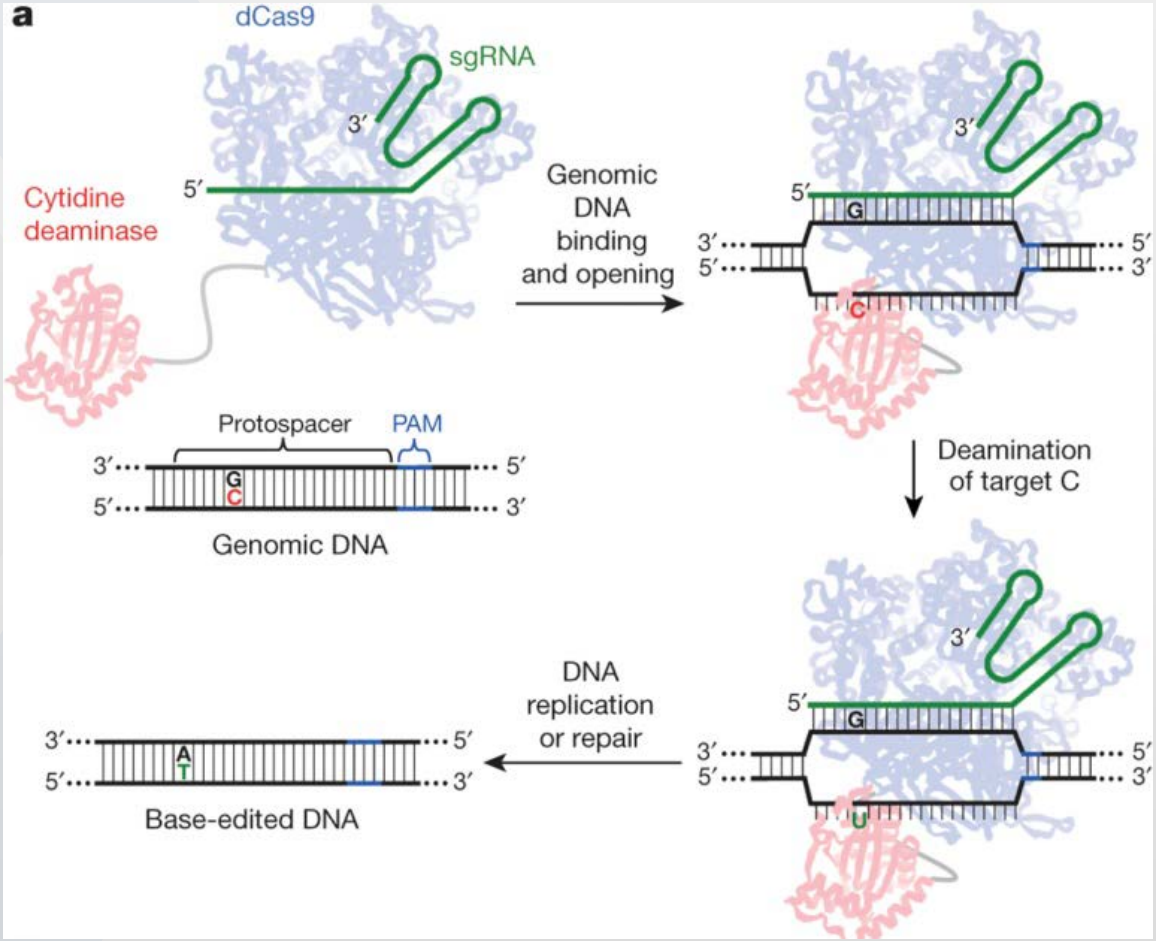
www.addgene.org/genome-engineering/

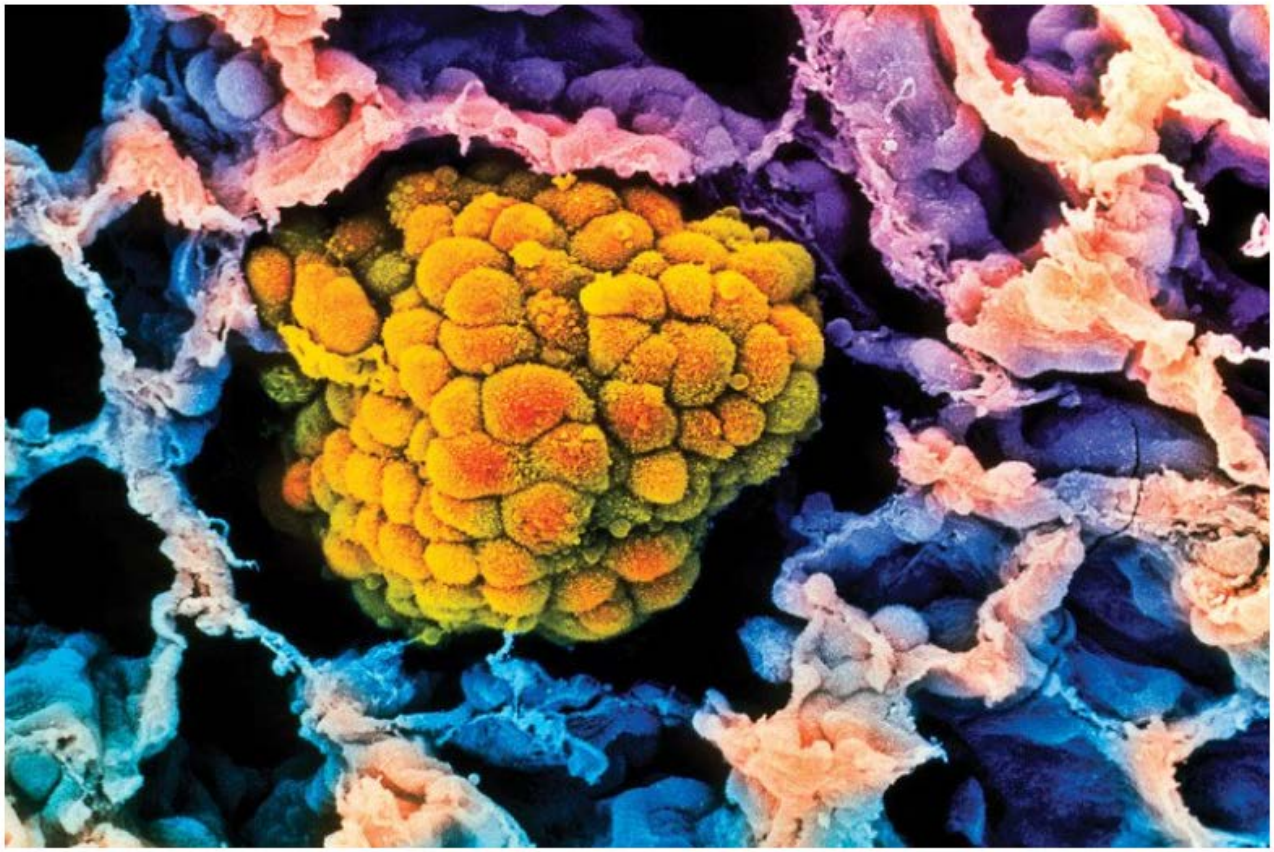
CRISPR-Cas9 is Versatile – It Can Be Modified to Make Single Base Edits without Cleaving DNA



A C Komor *et al.* (2016) *Nature* 533: 420-424. doi:10.1038/nature17946

Boom in human gene editing as 20 CRISPR trials gear up

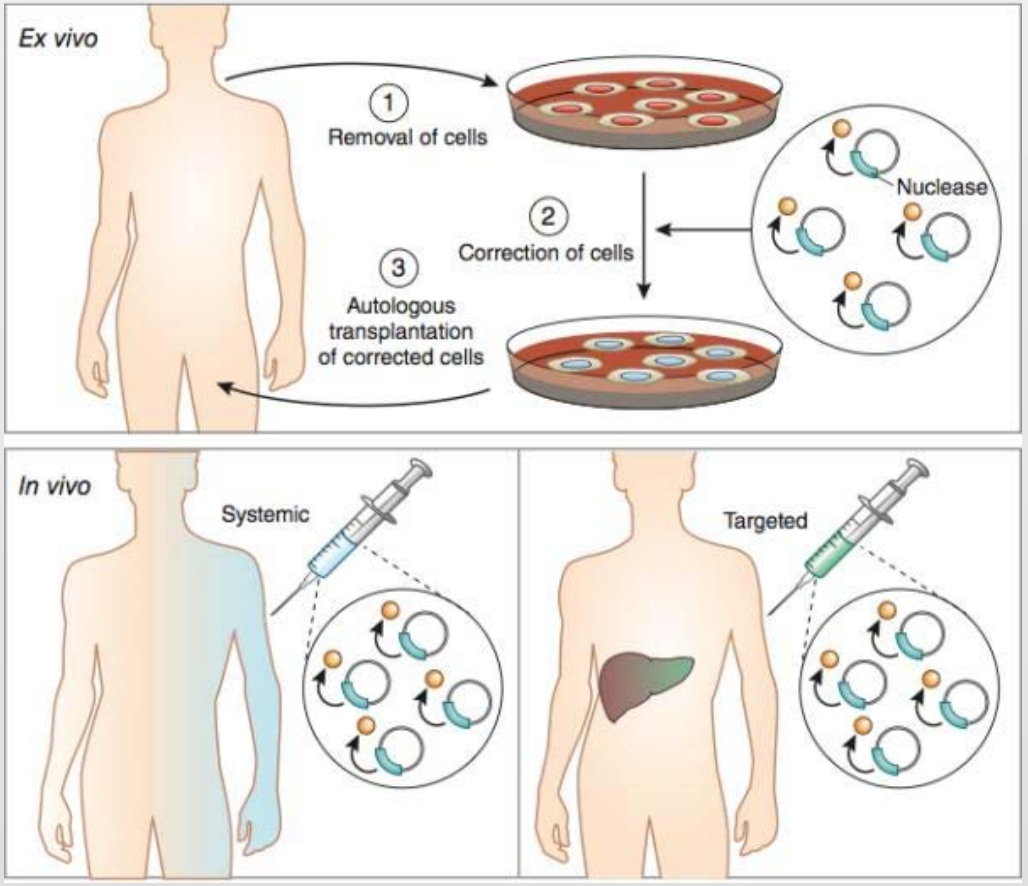
A pioneering CRISPR trial in China will be the first to try editing the genomes of cells inside the body, in an effort to eliminate cancer-causing HPV virus



CRISPR keeps cancer in check

M Le Page (2017) *New Scientist 3128*

Limitations



Targeting specificity & efficiency
Off-target effects & unintended consequences

D B Turitz Cox *et al.* (2015) *Nature Medicine* 21: 121-131. doi:10.1038/nm.3793

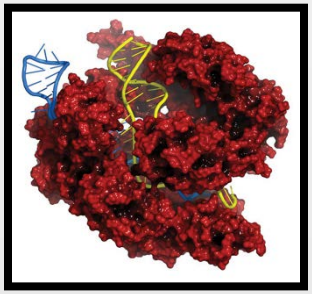
Common Fund Planning Workshop

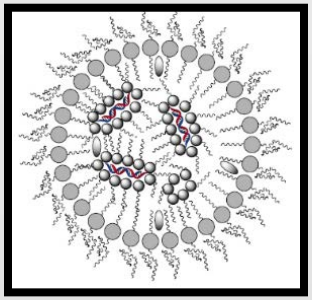
July 24, 2017

Workshop Participants

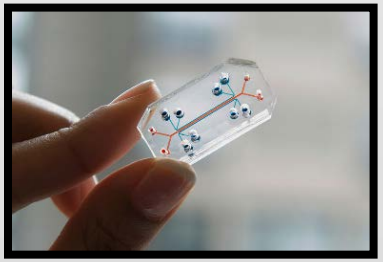
Charles Albright, Ph.D., Editas Medicine
Thomas Barnes, Ph.D., Intellia Therapeutics
Ronald Bartek, M.A., Friedreich's Ataxia Research Alliance
Jennifer Doudna, Ph.D., University of California Berkeley
Cynthia Dunbar, M.D., NHLBI
Lisa Ellerby, Ph.D., Buck Institute for Aging Research
Charles Gersbach, 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

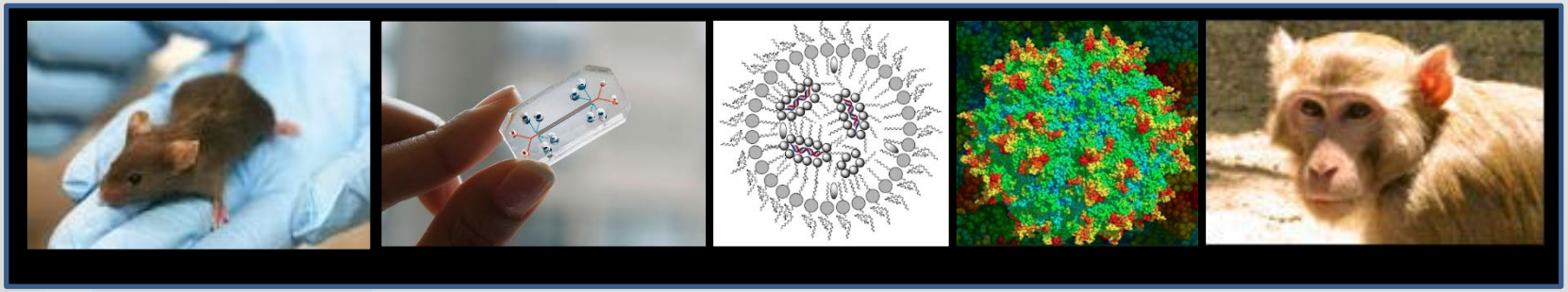
Facilitate Phase I/II Clinical Trials of New Somatic Gene Editing Therapies by Developing and Providing Broad Access to:

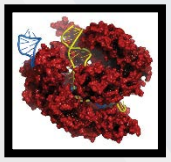
Animal Models for Gene Editing Research and Preclinical Testing

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

1. Better Animal Models for Testing Gene Editing Reagents and Delivery Systems

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 *in vivo* over time

3. Improving *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

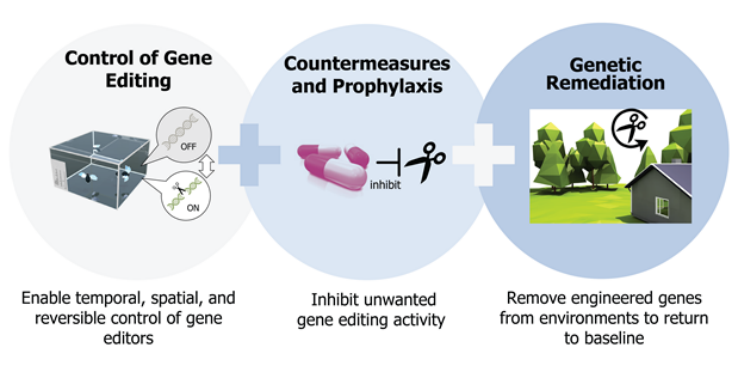
Disseminate knowledge, tools, and methods to the community

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



The NIST Gene Editing Standards Consortium

NIST
National Institute of Standards and Technology
U.S. Department of Commerce

The FDA Office of Tissues and Advanced Therapies, CBER

FDA U.S. FOOD & DRUG ADMINISTRATION

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

U.S. Department of Health and Human Services

FDA U.S. FOOD & DRUG ADMINISTRATION

RARE DISEASE DAY®

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NIH Somatic Cell Gene Editing Working Group Members

Olivier Blondel, NIDDK
PJ Brooks, NCATS
Chamelli Jhappan, NCI
Tom Cheever, NIAMS
Stephanie Courchesne, OSC/OD
Colin Fletcher, NHGRI
Maria Giovanni, NIAID
Linda M. Griffith, NIAID
Tim LaVaute, NINDS

Jerry Li, NCI
Nicole Lockhart, NHGRI
Aron Marquitz, OSC/OD
Oleg Mirochnitchenko, ORIP/OD
Nasrin Nabavi, NIAID
David Panchision, NIMH
Mary Perry, OSC/OD
Betty Poon, NIAID
Jeff Struewing, NHGRI