The Impact of Gene Editing on Innovation in Human, Plant, and Animal Science

Carrie Wolinetz, Ph.D.
Acting Chief of Staff and Associate Director for Science Policy, NIH

NIH
National Institutes of Health
Office of Science Policy
Overarching Policy Questions

- How do you anticipate an emerging biotechnology that will create policy/safety/ethical/security challenges?
- How do you develop a flexible/dynamic oversight framework that evolves with the technology?
- When has an emerging technology emerged?
- How do you keep the focus on the applications of the technology, vs. technology itself?
- And... how do you do this in the real world?
Gene Editing: The Promise...

A human has been injected with gene-editing tools to cure his disabling disease. Here's what you need to know.

CRISPR treatment for rare genetic eye disorder gains FDA study approval

CRISPR and other gene editing tools hold great promise for curing a wide range of devastating conditions caused by misfolding in RNA. Among the many looking to gene editing with hope are kids with Duchenne muscular dystrophy (DMD), an uncommon and tragically fatal genetic disorder in which their muscles—including skeletal muscles, the heart, and the main muscle used for breathing—gradually become too weak to function. Such hopes were recently buoyed by a new study that showed infusion of the CRISPR-Cas9 gene editing system could halt disease progression in a dog model of DMD.

Days after a Chinese researcher roused the world of science with claims of editing the genomes of twin girls, an American company is plotting a CRISPR trial of its own. But in place of the secrecy and stargazing that marked the Chinese experiment, Editas Medicine went the old-fashioned way: waiting for approval from the Food and Drug Administration.
Gene Editing: The Peril...
Gene Editing: Advances in the Science

- Powerful tools rapidly becoming ubiquitous
- Ease, precision of technology makes feasible experiments too difficult to conduct using older techniques
- Multiple Applications:
  - Basic Science
  - Gene Drives – the end of malaria?
  - Somatic Cell Gene Therapy
  - Human Germline Modification
CRISPR: One tool to rule them all?

Meganucleases

ZFNs

TALENs

CRISPR-Cas9

Gene editing technologies

Research tool

Somatic gene therapy

Germline modification

Gene drives

Organism creation/modification (plants, insects, animal models of disease)

Anti-microbials

Gene editing ≠ CRISPR ≠ Germline modification

Different applications present different risks... How do you appropriately balance oversight?
Animal, Agricultural, and Environmental Applications
Animal Models

- Challenging to use traditional techniques to establish large animal models
- CRISPR/Cas9 being used successfully to modify the genomes of various species
- CRISPR/Cas9 can be used to generate large animal models of diseases (e.g., non-human primate models of neurodegenerative disease)
Agricultural and Environmental Applications

- Crop improvements such as pest, drought, or spoilage resistance, and increased yields or nutrient levels
- Livestock resistance to disease or modification to produce therapeutic proteins
- Organisms modified to produce biofuels or plastics
Gene Drives

- Technology for spreading engineered traits through populations of sexually reproducing organisms

- Potential applications:
  - Public health
    - Control spread of vector-borne infectious diseases
  - Agriculture
    - Engineer weeds without herbicide resistance
    - Improvements in crops
  - Ecology
    - Control invasive species
    - Protect vulnerable species

**A CRISPR-Cas9 gene drive system targeting female reproduction in the malaria mosquito vector Anopheles gambiae**

Andrew Hammond¹, Roberto Galizi¹, Kyros Kyrou¹, Alekos Simoni², Carla Siniscalchi², Dimitris Katsanos¹, Matthew Gribble¹, Dean Baker³, Eric Marois⁴, Steven Russell⁵, Austin Burt¹, Nikolai Windbichler¹, Andrea Crisanti² & Tony Nolan⁵
Gene Drive Concerns

- **Biosafety**
  - Unknown risks to entire ecosystems
    - Spread into related species
    - Effect of alteration of targeted species on other species and environment

- **Biosecurity**
  - Potential for dual use

- **Ethics**
  - Selection of release sites
  - Need for engagement at community and international levels

- **Governance**
  - Adequacy of existing oversight mechanisms?
  - Lack of containment leading to international impacts
“There is insufficient evidence available at this time to support the release of gene-drive modified organisms into the environment. However, the potential benefits of gene drives for basic and applied research are significant and justify proceeding with laboratory research and highly-controlled field trials.”
Somatic Gene Therapy
Clinical Applications
Gene Editing in Human Somatic Cells

- ZFNs- make human cells resistant to HIV-1, correct Hunter syndrome
- TALENs- create “off-the-shelf,” universal, chimeric antigen receptor T cells for cancer patients
- CRISPR/Cas9- approaches targeting sickle cell disease, retinal disorders, cancer
NIH Gene Editing Initiatives

Somatic Cell Genome Editing

- Speed development of safe, effective editing tools for human patients
- Make tools widely available to researchers
- Reduce time, cost to develop new therapies

Cure Sickle Cell

- Accelerate the development of treatments aimed at a genetic-based cure for sickle cell disease
Other Clinical Applications

- Antibacterials targeting specific pathogens to help combat the development of antimicrobial-resistant bacteria

- Diagnostic systems to detect very low levels of nucleic acids from Zika virus and pathogenic bacteria

- Potential human replacement organs from pigs with viruses eliminated
What’s Past Is Prologue:
Advent of Recombinant DNA Technology

- Concerns about biohazards and the regulation of biotechnology
- Call for a moratorium on rDNA research until safety issues were assessed and recommendations made
- Asilomar conference

Lessons from the past... Asilomar

The NIH Guidelines

The Recombinant DNA Advisory Committee (RAC)
We’ve come a long way...
Current State of Human Gene Therapy (HGT) Oversight
From “Emerging” to “Emerged”: The Next Phase of HGT Oversight

The Next Phase of Human Gene-Therapy Oversight

The National Institutes of Health (NIH) and the Food and Drug Administration (FDA) have played key roles in the emergence and effective human gene therapies. Now, we are preparing for new efforts to encourage further advances in this rapidly evolving field.

The potential to alter human genes directly was first recognized nearly 50 years ago, around the same time as initial groundbreaking advances were being made in recombinant DNA technology. After intense discussions regarding the ethical, legal, and social implications of this technology, conventions were initiated at the NIH that led to the establishment of the Recombinant DNA Advisory Committee (RAC) in 1974. The RAC’s mission was to advise the NIH director on research that used emerging technologies involving manipulation of genetic material — a mission that was expanded to encompass the evaluation and discussion of questions related to gene therapy in humans. In 1990, the FDA oversaw the first U.S. human gene-therapy trial, which involved patients with adenosine deaminase deficiency. The 1990s saw an explosion of trials, with the first RAC approval for a gene therapy trial in 1992.

These efforts have increased understanding of the basic biology of the diseases being treated, the development of safe and effective gene therapy products, and the potential for using these technologies to treat diseases. However, the development of gene-therapy products has been slow, with only a small number of products approved for clinical use.

It is increasingly clear that combining gene therapy with other approaches, such as stem-cell therapies, may be necessary to achieve consistent success. The RAC has been instrumental in ensuring that gene therapy products are rigorously tested and approved for use, and that they are delivered in a safe and effective manner.

We are entering a new era of gene therapy, one in which years of painstaking research have begun to yield products that are delivering a meaningful benefit to human health. In the past year, three new gene therapy products have been approved by the FDA for the treatment of severe combined immunodeficiency, Wiskott-Aldrich syndrome, and adenosine deaminase deficiency.

In this emerging era of gene therapy, we must continue to be vigilant in our oversight and evaluation of these products. We must ensure that they are delivered in a safe and effective manner, and that they are used in a manner that is consistent with the needs of the patients being treated.

I applaud the progress that has been made in the field of gene therapy, and I am confident that we will see continued advances in the years to come. However, we must remain vigilant in our oversight and evaluation of these products, and we must continue to be mindful of the ethical and social implications of this technology.

Sincerely,

Francis S. Collins, M.D., Ph.D., and Scott Gottlieb, M.D.
NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules

- Evolving, scientifically-responsive document
  - Multiple revisions since 1976
    - rDNA → HGT
  - Latest version – April 2019
  - Updated to streamline gene therapy oversight

https://osp.od.nih.gov/biotechnology/nih-guidelines/
Flexible, dynamic oversight framework? 21st Century NIH Guidelines

- Ensure oversight system retains currency for assessing/managing biosafety risks

- 2017 Workshop: NIH Guidelines: Honoring the Past, Charting the Future
  - Need transparent forum for discussion
  - Is recombinant/synthetic nucleic acid molecule research the right focus?
  - Re-calibration needed for risks and benefits of today?
Introducing the NExTRAC
Novel and Exceptional Technology and Research Advisory Committee

- Focus on scientific, safety, and ethical issues associated with emerging biotechnologies
  - E.g., gene editing, gene drives, synthetic biology, neurotechnology
  - Cutting edge clinical applications?
- Continue roles as
  - Public forum for transparent discourse on challenging issues
  - Source of advice to NIH Director, and resource for scientific community and public
Human Germline Modification
What do you do in the face of systems failure...?
NIH does not fund any use of gene editing technology in human embryos

Director’s statement, March 2019-
Support for international moratorium on human germline editing

“Human gene editing for reproductive purposes carries very serious consequences — social, ethical, philosophical and theological. Such great consequences deserve deep reflection.”
Questions?