What's New at the NIH Office of Science Policy?

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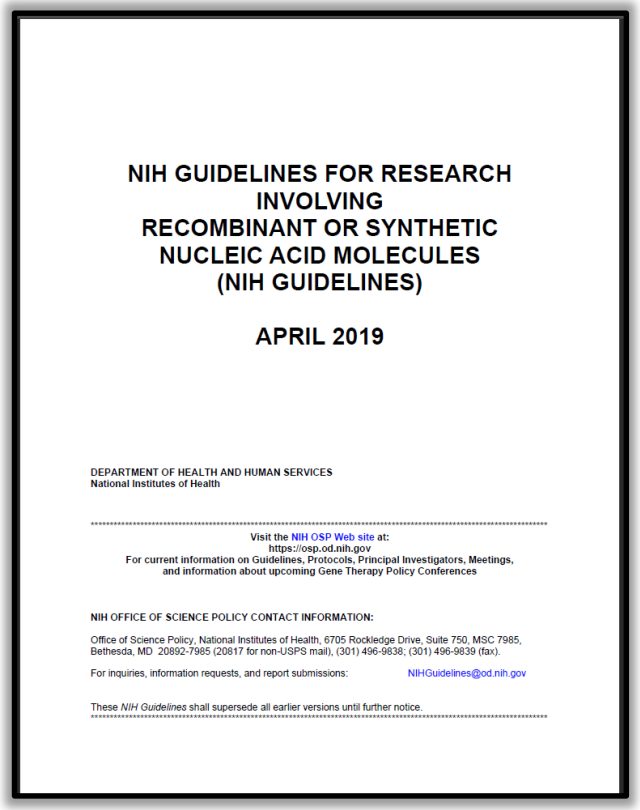
Presentation Overview

- **Oversight of Human Gene Transfer (HGT) Research**
  - **Recent Amendment to the *NIH Guidelines***
- **Oversight of Emerging Technology**
  - **Evolution of the RAC**
  - ***NIH Guidelines* for the 21st Century**

NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules



NIH GUIDELINES FOR RESEARCH INVOLVING RECOMBINANT OR SYNTHETIC NUCLEIC ACID MOLECULES (NIH GUIDELINES)

APRIL 2019

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Visit the NIH OSP Web site at:
https://osp.od.nih.gov
For current information on Guidelines, Protocols, Principal Investigators, Meetings, and information about upcoming Gene Therapy Policy Conferences

NIH OFFICE OF SCIENCE POLICY CONTACT INFORMATION:

Office of Science Policy, National Institutes of Health, 6705 Rockledge Drive, Suite 750, MSC 7985, Bethesda, MD 20892-7985 (20817 for non-USPS mail), (301) 496-9838; (301) 496-9839 (fax).

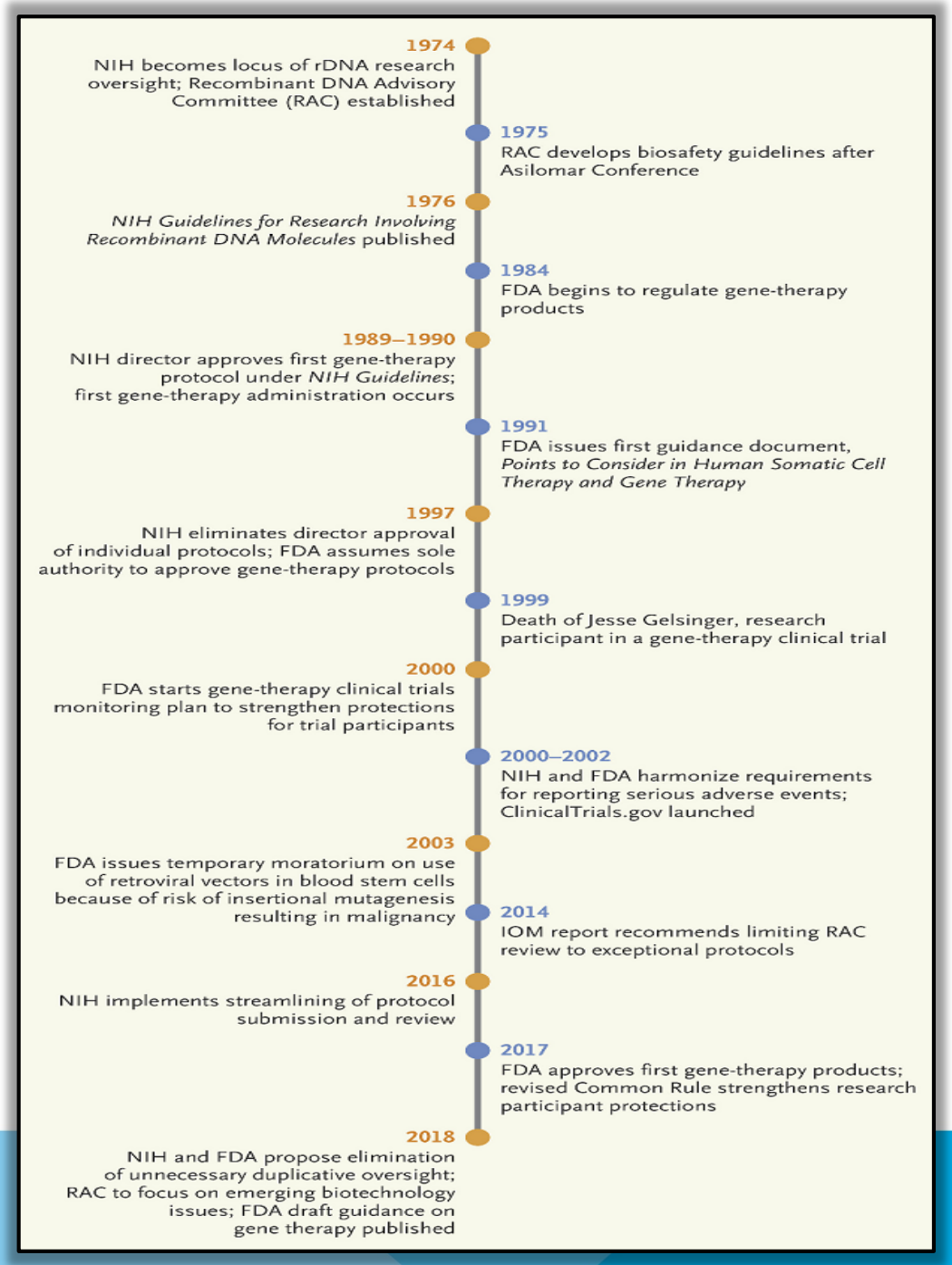
For inquiries, information requests, and report submissions: NIHGuidelines@od.nih.gov

These *NIH Guidelines* shall supersede all earlier versions until further notice.

- **Evolving, scientifically-responsive document**
  - **Multiple revisions since 1976**
  - **Latest version – April 2019**

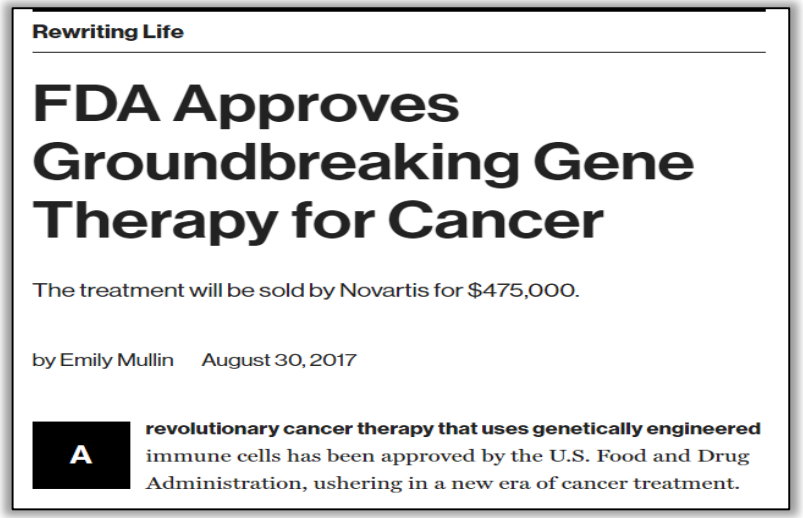
https://osp.od.nih.gov/biotechnology/nih-guidelines/

HGT Timeline



HGT - We've Come A Long Way…

- **Significant progress, several FDA approved products**
  - **As of September 2018, more than 700 active investigational gene therapy products have been submitted to the FDA for review**



Rewriting Life

FDA Approves Groundbreaking Gene Therapy for Cancer

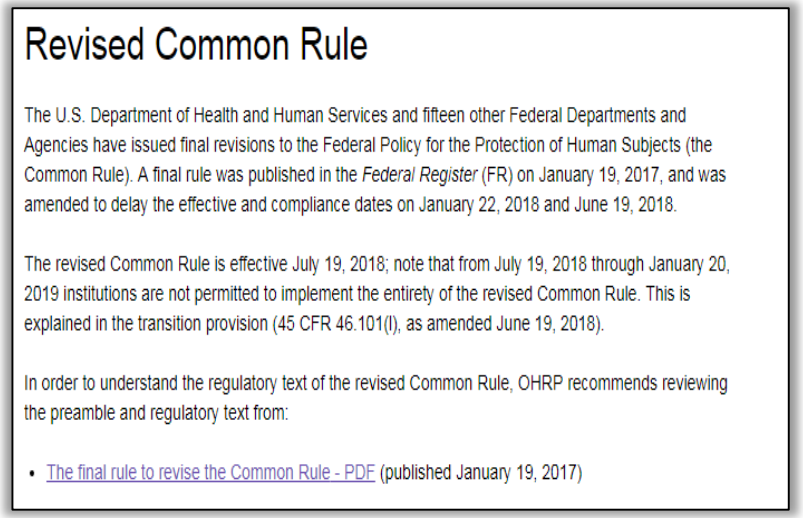
The treatment will be sold by Novartis for $475,000.

by Emily Mullin August 30, 2017

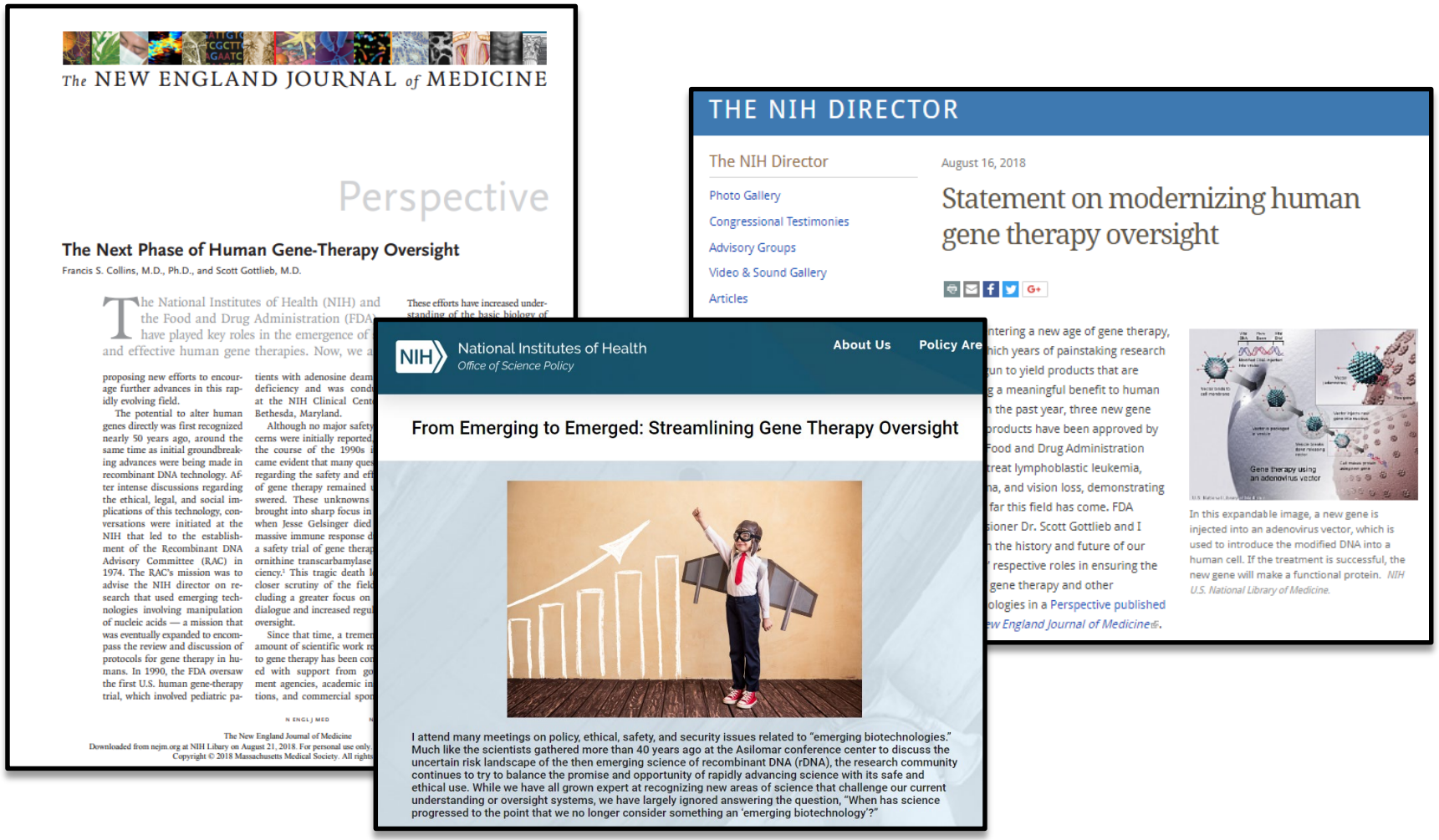
A **revolutionary cancer therapy that uses genetically engineered** immune cells has been approved by the U.S. Food and Drug Administration, ushering in a new era of cancer treatment.

HGT - We've Come A Long Way…

- **Oversight has evolved**
  - **ClinicalTrials.gov provides transparency for all clinical trials;**
  - **Human research participants protections strengthened by changes to Common Rule;**
  - **FDA recent draft guidances (manufacturing, LTFU, clinical development)**
- **Duplication in review and reporting not afforded to other areas of clinical research**



From “Emerging” to “Emerged”: The Next Phase of HGT Oversight



The NEW ENGLAND JOURNAL of MEDICINE

Perspective

The Next Phase of Human Gene-Therapy Oversight

Francis S. Collins, M.D., Ph.D., and Scott Gottlieb, M.D.

The National Institutes of Health (NIH) and the Food and Drug Administration (FDA) have played key roles in the emergence of and effective human gene therapies. Now, we a

proposing 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, conversations 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 nucleic acids — a mission that was eventually expanded to encompass the review and discussion of protocols for gene therapy in humans. In 1990, the FDA oversaw the first U.S. human gene-therapy trial, which involved pediatric pa-

tients with adenosine deam deficiency and was cond at the NIH Clinical Cent Bethesda, Maryland.

Although no major safety cerns were initially reported the course of the 1990s came evident that many que regarding the safety and eff of gene therapy remained swered. These unknowns brought into sharp focus in when Jesse Gelsinger died massive immune response a safety trial of gene therap ornithine transcarbamylase ciency.[1] This tragic death closer scrutiny of the field cluding a greater focus on dialogue and increased regu oversight.

Since that time, a tremen amount of scientific work r to gene therapy has been co ed with support from go ment agencies, academic in tions, and commercial spo

These efforts have increased understanding of the basic biology of

N ENGL J MED

The New England Journal of Medicine

THE NIH DIRECTOR

The NIH Director

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August 16, 2018

Statement on modernizing human gene therapy oversight

ntering a new age of gene therapy, hich years of painstaking research un to yield products that are g a meaningful benefit to human n the past year, three new gene products have been approved by Food and Drug Administration treat lymphoblastic leukemia, a, and vision loss, demonstrating far this field has come. FDA sioner Dr. Scott Gottlieb and I n the history and future of our respective roles in ensuring the gene therapy and other ologies in a Perspective published ew England Journal of Medicine.

In this expandable image, a new gene is injected into an adenovirus vector, which is used to introduce the modified DNA into a human cell. If the treatment is successful, the new gene will make a functional protein. *NIH U.S. National Library of Medicine.*

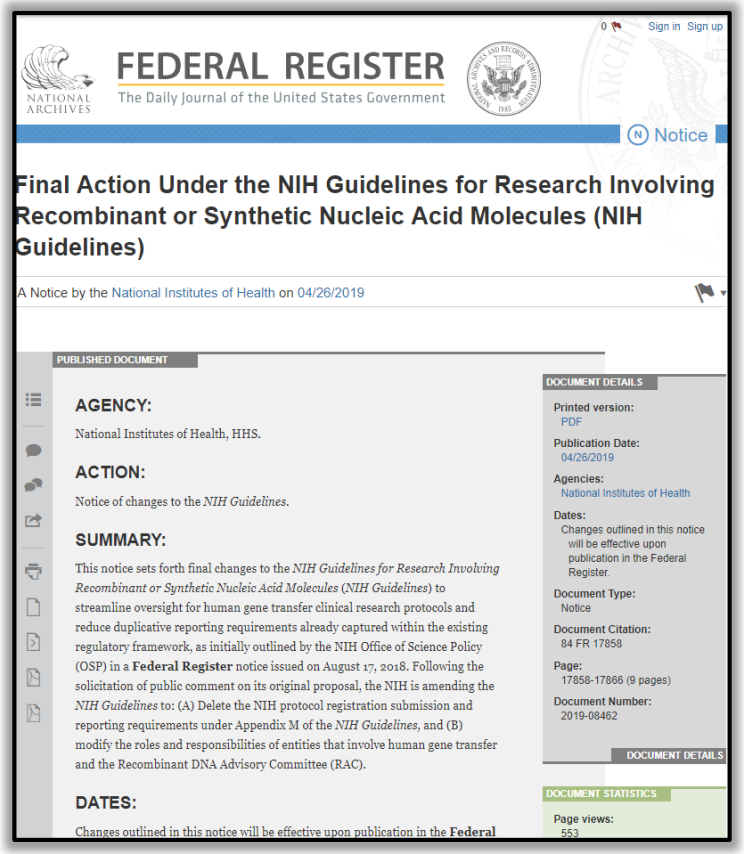
NIH National Institutes of Health
Office of Science Policy

About Us Policy Are

From Emerging to Emerged: Streamlining Gene Therapy Oversight

I attend many meetings on policy, ethical, safety, and security issues related to “emerging biotechnologies.” Much like the scientists gathered more than 40 years ago at the Asilomar conference center to discuss the uncertain risk landscape of the then emerging science of recombinant DNA (rDNA), the research community continues to try to balance the promise and opportunity of rapidly advancing science with its safe and ethical use. While we have all grown expert at recognizing new areas of science that challenge our current understanding or oversight systems, we have largely ignored answering the question, “When has science progressed to the point that we no longer consider something an ‘emerging biotechnology’?”

Notice of Final Action
Federal Register (April 25, 2019)



FEDERAL REGISTER
The Daily Journal of the United States Government

Notice

Final Action Under the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines)

A Notice by the National Institutes of Health on 04/26/2019

PUBLISHED DOCUMENT

AGENCY:

National Institutes of Health, HHS.

ACTION:

Notice of changes to the *NIH Guidelines*.

SUMMARY:

This notice sets forth final changes to the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* (*NIH Guidelines*) to streamline oversight for human gene transfer clinical research protocols and reduce duplicative reporting requirements already captured within the existing regulatory framework, as initially outlined by the NIH Office of Science Policy (OSP) in a **Federal Register** notice issued on August 17, 2018. Following the solicitation of public comment on its original proposal, the NIH is amending the *NIH Guidelines* to: (A) Delete the NIH protocol registration submission and reporting requirements under Appendix M of the *NIH Guidelines*, and (B) modify the roles and responsibilities of entities that involve human gene transfer and the Recombinant DNA Advisory Committee (RAC).

DATES:

Changes outlined in this notice will be effective upon publication in the **Federal**

DOCUMENT DETAILS

Printed version: PDF

Publication Date: 04/26/2019

Agencies: National Institutes of Health

Dates: Changes outlined in this notice will be effective upon publication in the Federal Register.

Document Type: Notice

Document Citation: 84 FR 17858

Page: 17858-17866 (9 pages)

Document Number: 2019-08462

DOCUMENT STATISTICS

Page views: 553

Effective Immediately

Amendment of HGT Oversight Under the *NIH Guidelines*

- **April 2019 – Publication of Federal Register Notice to streamline HGT oversight**
  - **NIH no longer accepting new HGT protocols, annual reports, safety reports, amendments or other documentation required for previously registered protocols under the *NIH Guidelines***
  - **NIH not convening the RAC to review individual protocols**

Amendment of HGT Oversight Under the *NIH Guidelines*

- **Institutional Biosafety Committees (IBCs) and Institutional Review Boards (IRBs) not required to submit documentation to the NIH assessing whether a particular protocol meets the criteria for RAC review**

- **Other roles and responsibilities of IBCs at the local level, including review and approval of HGT research, continue as described in the *NIH Guidelines***

- **Investigator or Sponsor remain responsible for ensuring FDA regulatory requirements and all other relevant requirements are met prior to proceeding with the trial**

Amendments to the *NIH Guidelines*

ENTITY	PREVIOUS RESPONSIBILITIES	CURRENT RESPONSIBILITIES
INSTITUTIONAL BIOSAFETY COMMITTEES (IBCS)	▪ Review and approve individual HGT protocols ▪ Review biosafety, clinical, and human subjects aspects (e.g., Informed Consent Documents) of HGT protocols ▪ Continue oversight of safety reporting after time of administration	▪ Review and approve individual HGT protocols ▪ Review biosafety aspects (e.g. administration, shedding) of HGT protocols ▪ May complete any oversight after time of final administration or end point based on biosafety assessment

Amendments to the *NIH Guidelines*

ENTITY	PREVIOUS RESPONSIBILITIES	CURRENT RESPONSIBILITIES
PRINCIPAL INVESTIGATORS (PI'S)	▪ Ensure all requirements for protocol submission, review and reporting for HGT protocols are addressed ▪ Comply with the *NIH Guidelines* in the conduct of recombinant or synthetic nucleic acid molecule research	▪ Comply with the *NIH Guidelines* in the conduct of recombinant or synthetic nucleic acid molecule research

Amendments to the *NIH Guidelines*

ENTITY	PREVIOUS RESPONSIBILITIES	RESPONSIBILITIES NOW
Novel and Exceptional Technology and Research Advisory Committee (NExTRAC) ~~RECOMBINANT DNA ADVISORY COMMITTEE (RAC)~~	▪ Responsibilities specified in the *NIH Guidelines* and committee charter ▪ Provide public forum for review of exceptional individual human gene transfer (HGT) protocols ▪ Provide advice on biosafety guidance and amendment of the *NIH Guidelines*	▪ Responsibilities specified in committee charter ▪ Provide advice to NIH Director on matters (scientific, ethical and social issues) related to the conduct and oversight of research involving emerging biotechnologies in biomedical sciences ▪ No review of individual protocols

Presentation Overview

- NIH OSP – Who We Are and What We Do
- Oversight of Human Gene Transfer (HGT) Research
  - Recent Amendments to the *NIH Guidelines*
- **Oversight of Emerging Technology**
  - **Evolution of the RAC > NExTRAC**
  - ***NIH Guidelines* for the 21st Century**

Introducing the NExTRAC

Novel and Exceptional Technology and Research Advisory Committee

- **Advise the NIH Director on scientific, safety, ethical and social issues associated with emerging biotechnologies**
  - **E.g., gene editing, gene drives, synthetic biology, neurotechnology, etc.**
  - **Cutting edge clinical applications?**
- **Facilitate transparent public discourse**

Inaugural Meeting of the NExTRAC

As part of the meeting, the NExTRAC will:

- **Receive its formal charge from Dr. Collins;**
- **Identify pathways for responsible innovation in emerging biotechnologies;**
- **Discuss characteristics of emerging biotechnologies; and**
- **Analyze proactive approaches to addressing scientific and societal implications of emerging biotechnologies**

Inaugural Meeting of the NExTRAC

December 5-6, 2019

NIH Campus, Bethesda

More information about the meeting, including a draft agenda and videocast information can be found at:

https://osp.od.nih.gov/biotechnology/novel-exceptional-technology-research-advisory-committee/

21st Century *NIH Guidelines*

"The *NIH Guidelines* cannot anticipate every possible situation…
As new techniques develop, the *NIH Guidelines* should be periodically reviewed to determine whether and how such research should be explicitly addressed.
It is the responsibility of the institution and those associated with it to adhere to the intent of the *NIH Guidelines* as well as to their specifics."

Some Questions…

- **We need to examine the current biosafety risk assessment framework to ensure we can adequately identify and manage potential safety issues posed by the application of emerging biotechnologies and new capabilities in the life sciences**
  - **What is future role of the *NIH Guidelines* within the overall context of the biosafety oversight system in the U.S.?**
  - **What is the future role of the RAC within this system?**

- **We need to develop flexible/dynamic oversight framework that evolves with the technology**
  - **How do we ensure our oversight system keeps current and allows science to proceed safely and responsibly?**

More Questions…

- **Scope of the NIH biosafety oversight system**
  - **What should be captured in our biosafety oversight system?**
  - **Need to focus on the applications of the technology, vs. technology itself?**

- **Appropriate levels of oversight (local/federal)**
  - **Do some of the routine research protocols employed today still require the level of oversight that is currently in place in the *NIH Guidelines*?**
  - **If we were to concentrate our oversight where it would be most beneficial from a risk management perspective, where might we focus our attention?**

Yet More Questions…

- How do we anticipate an emerging biotechnology that will create policy/safety/ethical/security challenges?
- Can potential risks posed by emerging biotechnologies and new capabilities be managed by the current NIH governance structure for biosafety oversight (i.e IBCs)?
- Is there a need for additional biosafety guidance to address new capabilities?
- When has an emerging technology “emerged”?

Emerging Technologies: Important Semantics

Technologies/Research Tools

• Genetic Engineering • Synthetic Biology •
• Gene Editing •

Tools ≠ Applications

Applications

• Somatic Gene Therapy • Germline Modification •
Antimicrobials • Organism Creation/Modification •
• Gene Drives •

Emerging Biotechnologies: The Promise…

Science

Brian Madeux, who has Hunter syndrome, has received a treatment aimed at editing the genome of his liver cells. AP PHOTO/ERIC RISBERG

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

By Jocelyn Kaiser | Nov. 15, 2017 , 6:00 PM

FDA U.S. FOOD & DRUG ADMINISTRATION

FDA approval brings first gene therapy to the United States

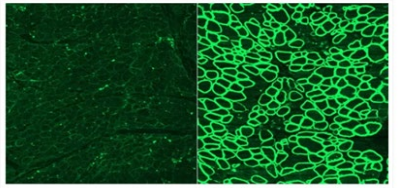
CAR T-cell therapy approved to treat certain children and young adults with B-cell acute lymphoblastic leukemia

For Immediate Release November 22, 2017

NIH Director's Blog

Gene Editing in Dogs Boosts Hope for Kids with Muscular Dystrophy

Posted on September 11th, 2018 by Dr. Francis Collins



Caption: A CRISPR/cas9 gene editing-based treatment restored production of dystrophin proteins (green) in the diaphragm muscles of dogs with Duchenne muscular dystrophy.
Credit: UT Southwestern

CRISPR and other gene editing tools hold great promise for curing a wide range of devastating conditions caused by misspellings in DNA. Among the many looking to gene editing with hope are kids with Duchenne muscular dystrophy (DMD), an uncommon and tragically fatal genetic disease 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.

CRISPR treatment for rare genetic eye disorder gains FDA study approval

Damian Garde | STAT | December 10, 2018

Days after a Chinese researcher incensed 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 stagecraft that marked the Chinese experiment, Editas Medicine went the old-fashioned way: waiting for approval from the Food and Drug Administration.

WIRED

MEGAN MOLTENI SCIENCE 01.16.19 04:30 PM

ANTIBIOTICS ARE FAILING US. CRISPR IS OUR GLIMMER OF HOPE

Antibiotic overuse has led to a growth in drug-resistant infections, which sicken more than two million people in the US each year and kill upwards of 23,000.

BJARTE RETTEDAL/GETTY IMAGES

Science

Genetically engineered piglets free of retroviral sequences may provide safer organs for human transplant. EGENESIS

CRISPR slices virus genes out of pigs, but will it make organ transplants to humans safer?

By Kelly Servick | Aug. 10, 2017 , 2:00 PM

Emerging Biotechnologies: The Peril…

The New York Times

As D.I.Y. Gene Editing Gains Popularity, 'Someone Is Going to Get Hurt'

By Emily Baumgaertner

May 14, 2018

The Telegraph

GM mosquitoes: playing with God or the only way to wipe out malaria?

By Sophie Arie

5 FEBRUARY 2019

Daily Mail .com

Controversial 'gene drive' research sparking ethical debate

By AFP

PUBLISHED: 06:08 EDT, 6 September 2016

Science

CRISPR—a weapon of mass destruction?

By Kelly Servick | Feb. 11, 2016 , 4:45 PM

c|net

The CRISPR machines that can wipe out entire species

BY JACKSON RYAN | 7 FEBRUARY 2019 12:00 AM AEDT

The New York Times Magazine

The Biotech Death of Jesse Gelsinger

By SHERYL GAY STOLBERG NOV. 28, 1999

Next Steps for the *NIH Guidelines*

- **Continue the important dialogue on issues related to emerging biotechnologies and the future direction of biosafety oversight**

- **Provide opportunities for stakeholders to provide input to NIH on a path forward in considering potential revisions to the *NIH Guidelines***

Parting Thoughts…

- Life sciences research is a vitally important endeavor that has contributed to biomedical and public health advances, improvements in agriculture, environmental quality, and much more.
- We can facilitate the conduct of beneficial biological research while maintaining a comprehensive biosafety oversight system to protect public health and national security.
- As a society, we must carefully consider aspects of emerging biotechnological capabilities, while maximizing the benefits of biotechnology for all humankind.

Parting Thoughts…

- Ideally, we need to develop a flexible and dynamic oversight framework that enables us to assess and manage potential risks posed by the application of emerging biotechnologies in a proactive way.

- It is vital we train our scientists to uphold the highest standards of biosafety as part of responsible conduct of research.

- We look forward to hearing from you as we consider how best to evolve our biosafety oversight framework into 21st Century.

Contact Us:

- About the changes or the *NIH Guidelines* in general:

NIHGuidelines@od.nih.gov

- Find us on the web at:

osp.od.nih.gov

Thank you for your attention!