# Welcome to the Webinar!

# Human Genome Editing: Latest Developments and Advancements

**Thursday, February 22, 2018 at 10:30am PT/1:30pm ET**

*Co-hosted by:*
*The National Academy of Sciences (NAS) and the National Academy of Medicine (NAM)*
*and*
*Biotechnology Innovation Organization (BIO)*

**Presenters:**

- Matthew Porteus, *Stanford University*
- Sandy Macrae, *Sangamo Therapeutics*
- Peter Marks, *U.S. Food and Drug Administration*

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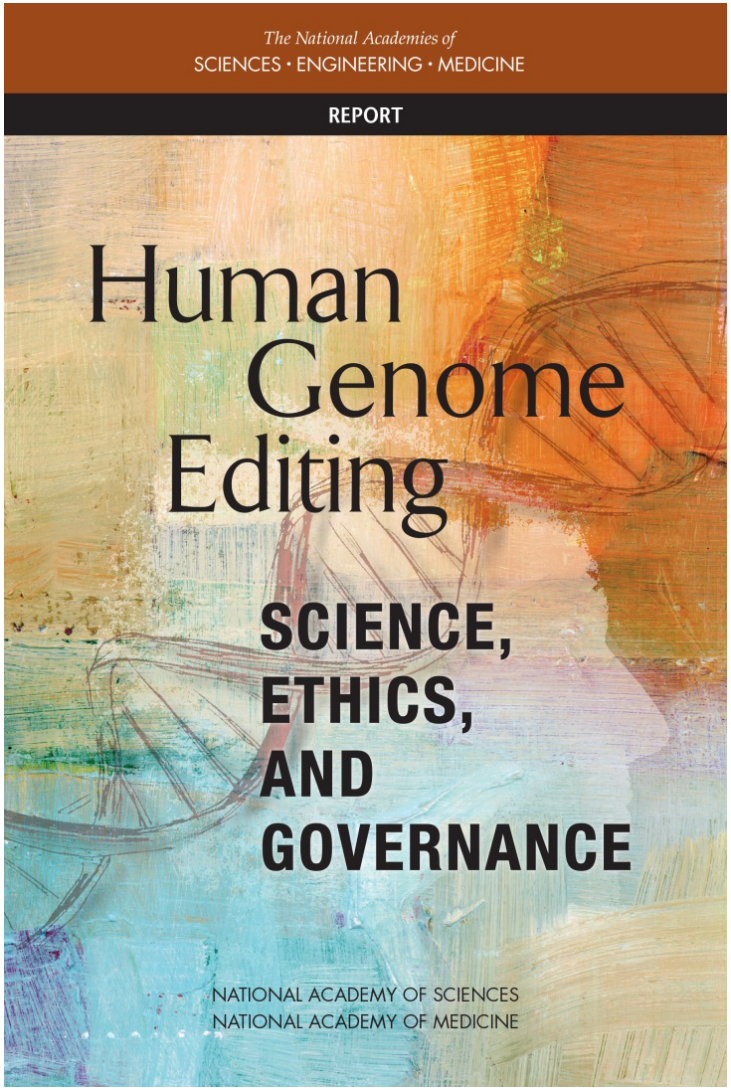


# Highlights of the Report: Somatic Therapy

**Matthew Porteus, MD, PhD,**
Stanford University; and
Committee member, *Human Genome Editing: Science, Ethics, and Governance*

# Consensus Study Charge

- Assess scientific aspects of human genome editing:
  - Current state of the science
  - Potential clinical applications
  - Efficacy and potential risks to humans
  - Standards for quantifying potential "off-target events"
- Do current ethical and legal standards adequately address human genome editing?
- What are the prospects for harmonizing policies?
- Are there overarching principles or frameworks for oversight?



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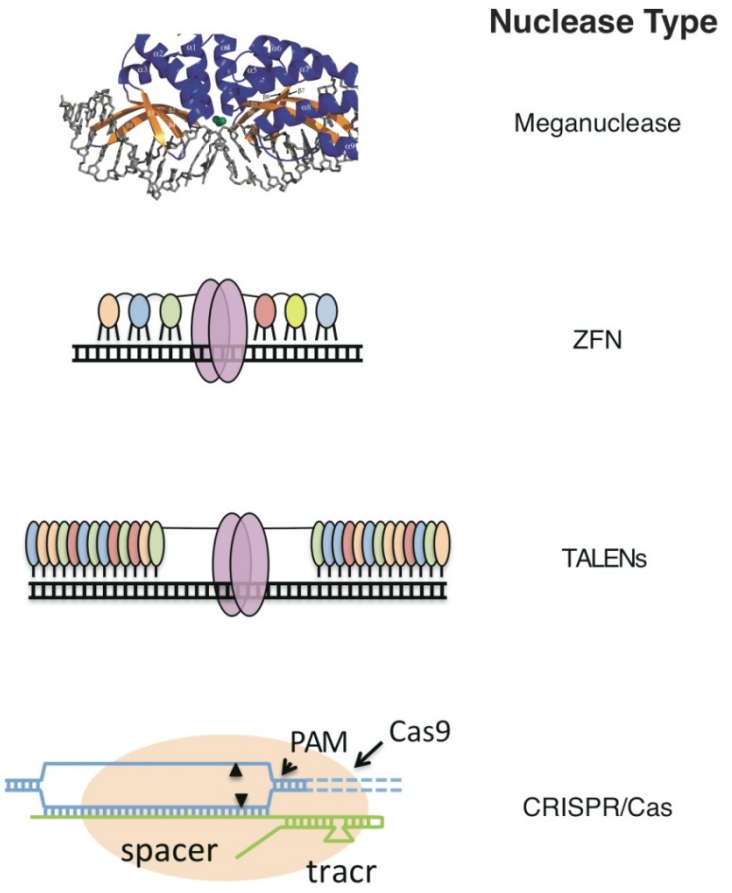
# Genome Editing

- Can add, delete or inactivate a gene, or make targeted alterations
- Not a new concept; already in use
- Specific DNA recognition precisely targets DNA cutting
- Cellular repair mechanisms introduce changes
- CRISPR/Cas9 a recent focus of attention
  - RNA-guided rather than protein-guided like earlier editing tools
  - Explosion of use in basic research demonstrates rapid advances possible




Carroll, D. 2014. *Annual Review of Biochemistry* 83:409-439



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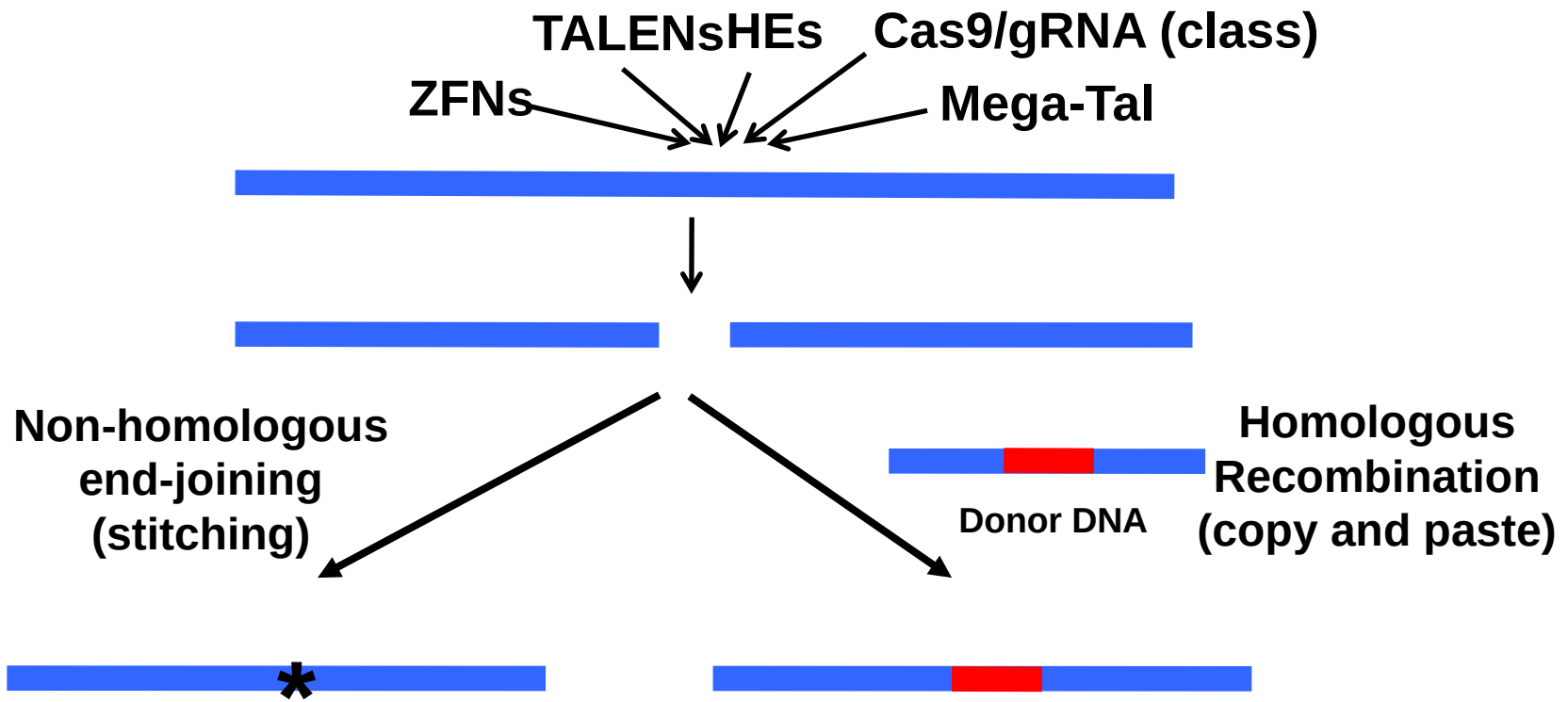
# Genome Editing is the *Controlled Mutagenesis* of the Genome

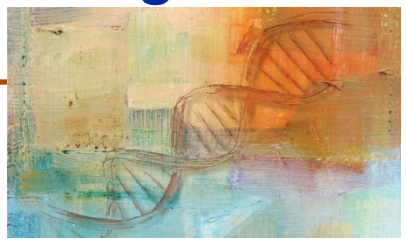



**Precise Spatial Modification**

**Precise Spatial AND Nucleotide Modification of Genome**

## Method to Break Things

## Method to Fix Things





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# A New Tool for Gene Therapy

- Approaches for somatic interventions:
  - outside the body (*ex vivo*) by removing cells, editing, and reinserting them
    - Ex: editing blood cells for cancer immunotherapy or HIV treatment
    - Ex: editing blood cells for sickle cell disease, thalassemias
  - directly in the body (*in vivo)* by injection; carries more technical challenges at this time
    - Ex: editing liver cells for hemophilia
    - Ex: editing muscle cells for muscular dystrophy





# Example of Huntington's Disease

About **30,000** Americans have HD. **200,000** more are at risk.

**BASIC RESEARCH**

Scientists are already researching how to "delete" the genetic abnormality that causes HD.

**SOMATIC THERAPIES**

"Somatic cells" make up the tissues of the body. One day, doctors might be able to use genome editing techniques in somatic cells to treat someone with HD.

**GERM CELL THERAPIES**

"Germ cells" are reproductive cells that give rise to sperm or eggs. Therefore, characteristics of germ cells get passed to the next generation. One day, doctors might be able to use genome editing techniques in germ cells to ensure that parents with HD don't pass the disease to their children.



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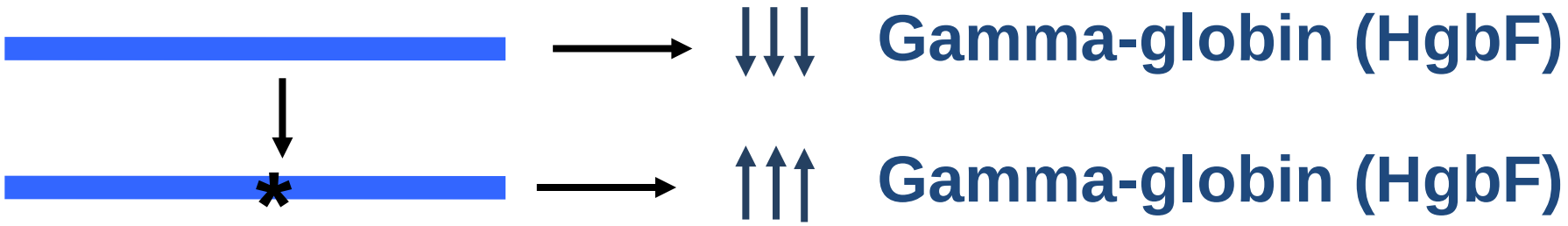
# Example of Sickle Cell Disease

- About 100,000 people in the United States have Sickle Cell Disease with ~5,000 new births per year
- Median Life Expectancy is mid-40s
- Autosomal recessive disease caused by a single nucleotide change in a single gene (*HBB* gene)
- Higher levels of fetal hemoglobin can cause marked improvement in disease course. No symptoms if hereditary persistency of fetal hemoglobin (HPFH).
- Bone marrow transplant can cure the disease.

# Two Approaches to Treating Sickle Cell Disease Using Genome Editing (Ex vivo editing of Somatic Cells)

1. Inactivate a gene that represses fetal hemoglobin (NHEJ)




2. Directly correct *HBB* gene (HDR)

**HgbS** → **HgbA**

**CCT GTG GAC** → **CCT GAG GAC**



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# Selected Report Recommendations

- Genome editing in the context of basic research and somatic gene therapy is valuable and adequately regulated.
  - Ethical norms and regulatory regimes at local, state, and federal levels; use these existing processes to oversee.
- Limit clinical trials or therapies to treatment and prevention of disease or disability at this time.
- Evaluate safety and efficacy in the context of risks and benefits of intended use.
- Efficiency, specificity, and off-target events must be evaluated in the context of the specific intended use and method. No single standard can be defined at this time.



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# Report Key Messages

- Somatic therapy should be used only for treatment and prevention of disease and disability.
- Should not be tried for enhancement at this time; do not extend without extensive public engagement and input.
- Heritable genome editing needs more research before it might be ready to be tried; public input and engagement also essential.
- Heritable editing must be approached cautiously and according to strict criteria with stringent oversight.

> It is essential that **transparent** and **inclusive** public policy debates precede any consideration of whether to authorize clinical trials for indications that go beyond treatment or prevention of disease or disability.



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# Germline Editing of CCR5 to create "HIV Resistant" Babies violates these criteria.

- There are reasonable alternatives.
- CCR5 positivity is not a serious disease (it is normal).
- Not known if being CCR5 negative is safe in all parts of the world (reasons to think it will not be).

**Should not be confused with somatic cell editing to inactivate CCR5 in someone who is HIV infected.**




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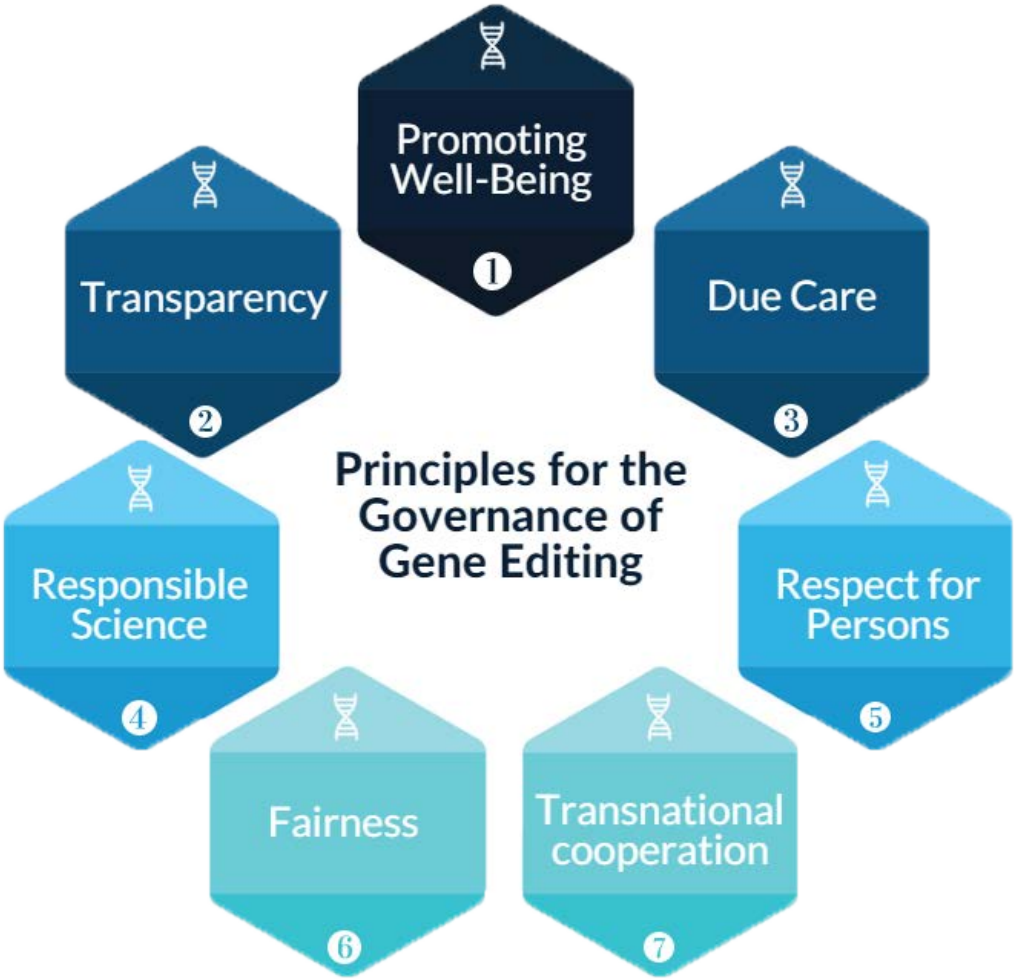
# Overarching Principles for Governance of Human Genome Editing




*Any nation considering governance of human genome editing can incorporate these principles—and the responsibilities that flow therefrom—into its regulatory structures and processes.*



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**Report, Handouts, and Archived Report Release Video Available:**
www.nationalacademies.org/gene-editing/consensus-study

**Sponsors:** FDA, DARPA, Greenwall Foundation, MacArthur Foundation & Wellcome Trust



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**BIO Representative:**

**Sandy Macrae, MB, ChB, PhD**
CEO, Sangamo Therapeutics



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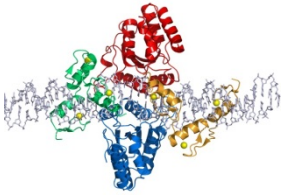
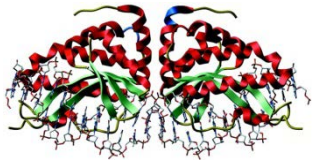
# First…
# What Exactly Is Genome Editing?

- Designed or RNA-guided nucleases to recognize and cut a specific DNA sequence

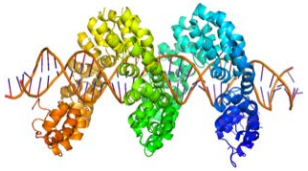
**Zinc Finger Nucleases**



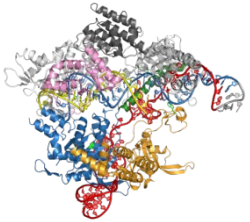
**Meganucleases**



**TALE Nucleases (TALENs)**



**CRISPR/Cas9 and CRISPR/Cpf1 Nucleases**



- Cell's DNA repair machinery repairs the cut
- May revise, remove, or replace a gene, depending on editing strategy

Epinat et al., *NAR* 2003



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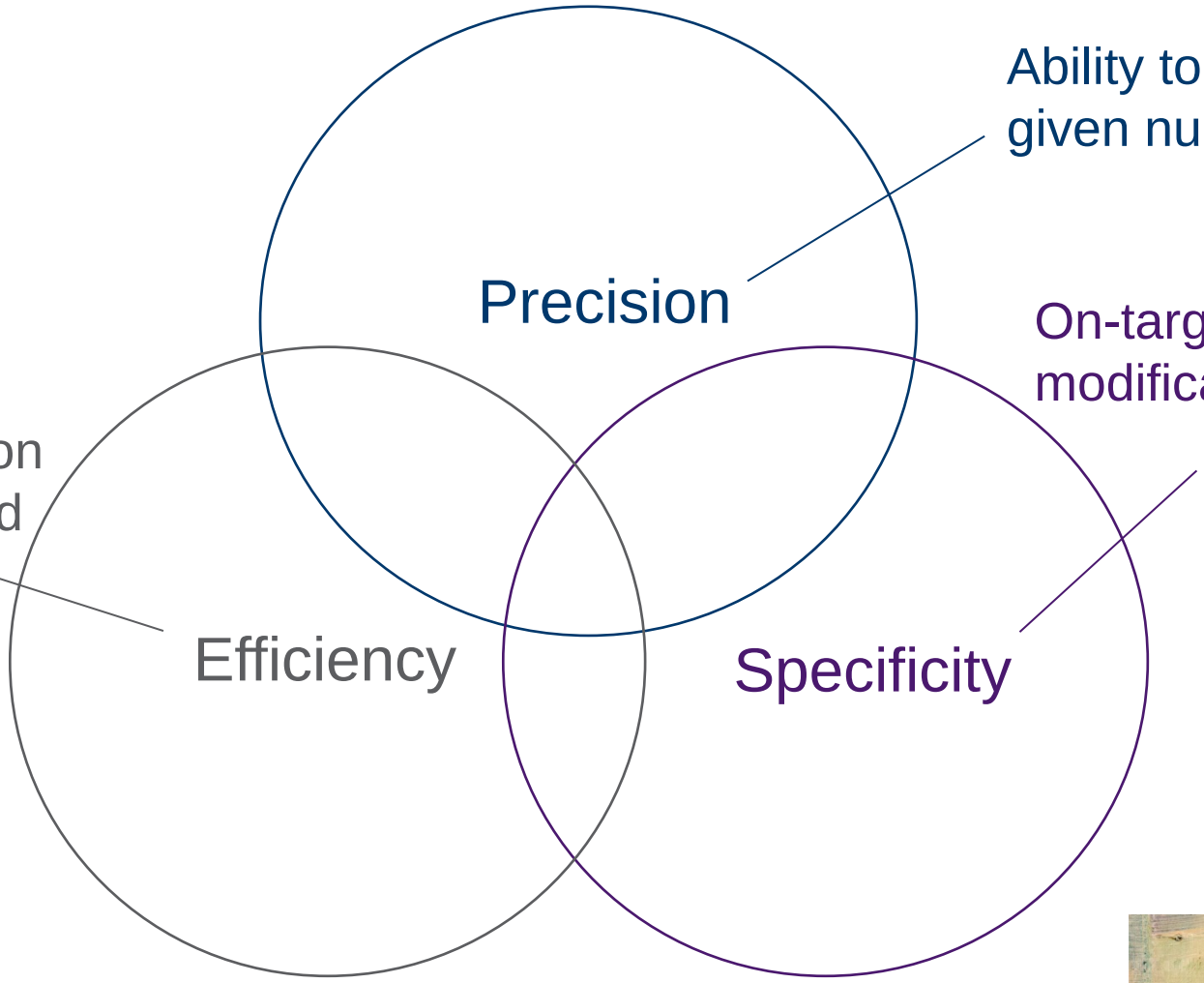
# Many Companies Are Developing Genome Editing Medicines

| Company | Technology |
|---|---|
| Biogen | rAAV |
| bluebird bio | megaTALs |
| Caribou Biosciences | CRISPR/Cas9 |
| Cellectis | TALEN |
| CRISPR Therapeutics | CRISPR/Cas9 |
| Casebia Therapeutics | CRISPR/Cas9 |
| Editas Medicine | CRISPR/Cas9 |
| Homology Medicines | AAVHSCs |
| Intellia Therapeutics | CRISPR/Cas9 |
| LogicBio Therapeutics | GeneRide™ |
| Poseida Therapeutics | Footprint-Free™ |
| Precision BioSciences | ARCUS |
| Sangamo Therapeutics | Zinc Finger Nucleases |
| Universal Cells | rAAV |

# Optimizing Technology For Therapeutic Genome Editing




Epinat et al., *NAR* 2003



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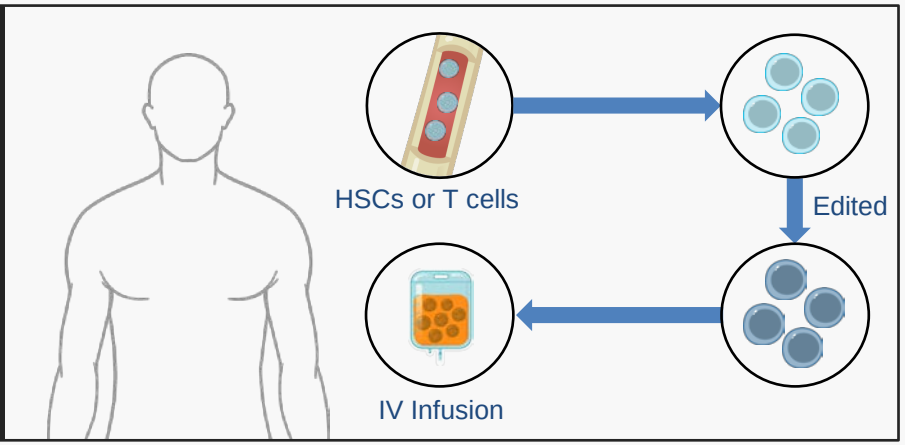
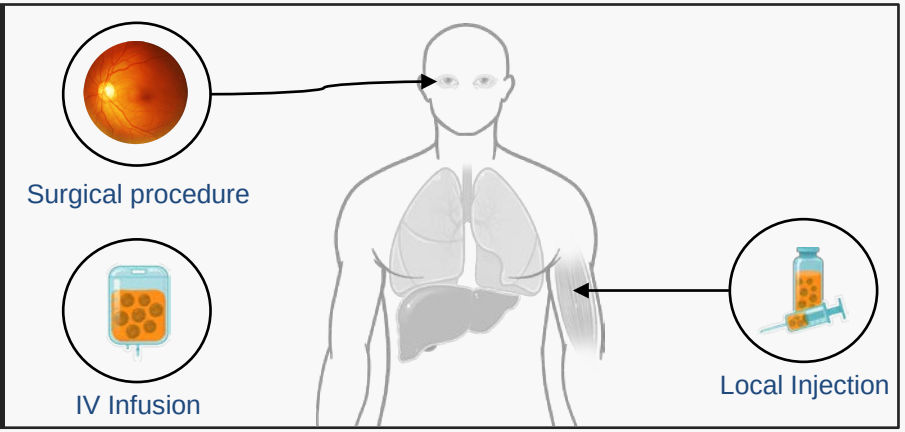
# What Might Genome Editing Medicines Look Like?

*Ex vivo*:
Editing performed on cells outside the body then infused as treatment




*In vivo*:
Editing performed on cells inside the body after delivery to the source



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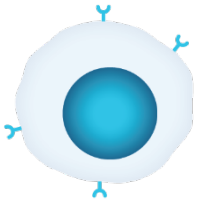
# Research into Delivery Methods to Edit Genes in Any Tissue or Cell

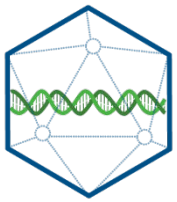
## *Novel Delivery Technologies*

### *Ex Vivo* Delivery



- Avoids need for electroporation to deliver mRNA to cells
- Eliminates need for viral delivery of donor DNA

### Novel AAV Vectors



- Solves for tissue specific route of administration
- Reduces impact of neutralizing antibodies

### Lipid Nanoparticles

- Tissue specificity (e.g., liver) and allows for re-dosing for clinical control
- Eliminates issue of neutralizing antibodies



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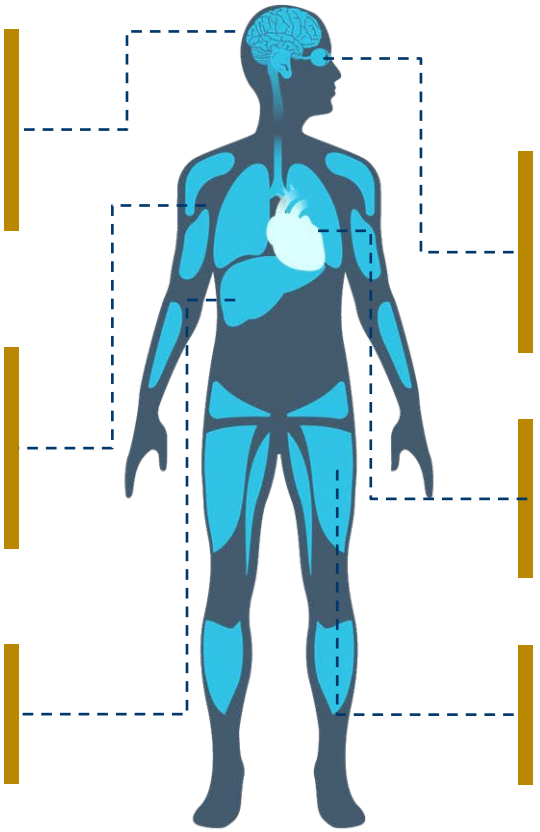
# Goal for Therapeutic Genome Editing: Target Any Disease in Any Tissue or Cell

**Central Nervous System**
*Huntington's Disease*
*Parkinson's Disease*
*Alzheimer's Disease*

**Lungs**
*Cystic Fibrosis*
*Chronic Obstructive Pulmonary Disease (COPD)*
*Asthma*

**Liver**
*Familial Amyloid Polyneuropathy*
*Non-alcoholic Steatohepatitis (NASH)*



**Eyes**
*Stargardt's Disease*
*Leber's Congenital Amaurosis*
*Neovascular AMD*

**Heart**
*Congenital Heart Disorders*
*Chronic Heart Failure*

**Muscles**
*Duchenne's Muscular Dystrophy*



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# Layers of Protection in the Development of Genome Editing Treatments

- Industry Social Contract for Somatic Editing
  - NIH Recombinant DNA Advisory Board (RAC)
    - FDA/EMA
      - Institutional Review Board (IRB)
        - Patient Consent





# Together we are focused on making medicines to provide patients a brighter future



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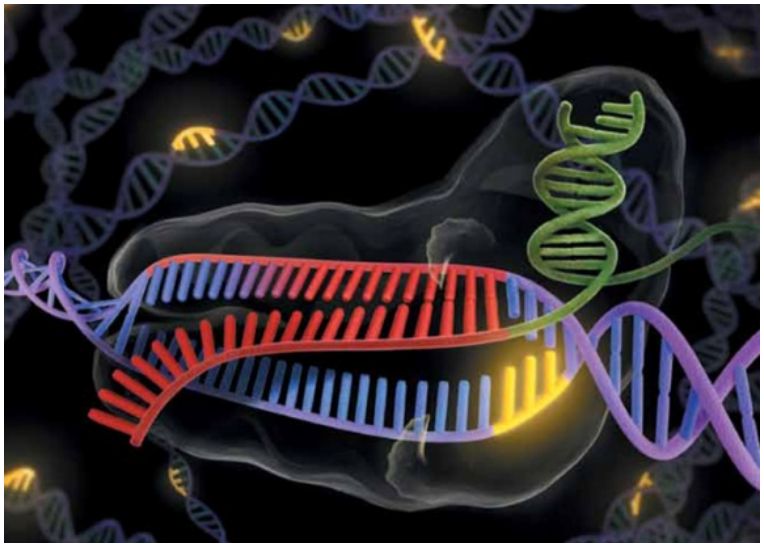
# Human Genome Editing: A Regulatory Perspective



**Peter Marks, MD, PhD,**

Director, Center for Biologics Evaluation and Research, FDA



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# Potential for Genome Editing

Possible to modify somatic cell or germline genomes through relatively efficient targeted genetic modification

- Insert a replacement for a defective or missing gene at a specific site in the genome
- Inactivate a gene that is causing disease through its expression of a product
- Correct single (or possibly multiple) nucleotide errors in the genome

# Biologic Product Evolution

| Proteins purified from plasma | Recombinant Proteins | Cell and Gene Therapies |
|---|---|---|
| 1960 | 1990 | 2020 |

Example:

| | | |
|---|---|---|
| Factor VIII Concentrate (licensed) | Recombinant Factor VIII (licensed) | Factor VIII Gene Therapy (in development) |

# Regulation of Gene Editing

FDA regulates somatic and germline gene modifications used as therapeutics in humans

- Includes modification of cells prior to administration and the direct administration of gene therapy vectors
- Somatic cell versus germline editing relevant, as by law FDA cannot currently accept an application for a product that involves heritable genetic modification

# Regulatory Considerations

- Science-based approach to regulation
- Nature of editing
  - Inactivation, insertion, modification
- Safety considerations
  - Percent cleavage at on- and off-target sites
  - Profile of insertions and deletions and types of mutations generated
- Somatic cell versus germline modification
- Benefit-risk analysis

**We will now begin Audience Q&A.**

**Please submit your questions.**



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# Thank you!

**To read the NAM/NAS report, please visit: www.nationalacademies.org/gene-editing/consensus-study**

**To learn more about BIO, please visit: www.bio.org**



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