Gene Editing Clinical Progress and Regulatory Framework

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2020 Nobel Prize in Chemistry to Jennifer Doudna and Emmanuelle Charpentier for their pioneering work in 2012 on CRISPR gene editing

The Reality of Genetically Defined Diseases – Tremendous Need, Real Human Suffering

- It is estimated that more than 6,000 diseases are caused by genetic mutations
- These rare diseases affect approximately 1 out of 10 Americans and Europeans
- Only about 5 percent of these diseases have approved therapies
- Example: Sickle Cell Disease
  - Over 100,000 patients in the U.S., 50,000 in EU
  - Primarily African American (U.S.)
  - Deformed and diminished blood cells causing anemia, pain crises, organ failure, and mortality
  - Regular hospitalizations during crises
  - ~45 years median life expectancy

NORD®
National Organization for Rare Disorders

EURORDIS
RARE DISEASES EUROPE

SICKLE CELL DISEASE FOUNDATION

ORDI
Organization for Rare Diseases India

For too many of our patients, the status quo represents death or serious disability

Primer on Genomic Medicine

Gene therapy

- Adding a gene in an attempt to correct a mutation that leads to a serious or life-threatening condition

Gene editing

- An attempt to "repair broken genes" by precisely cutting DNA to disrupt, remove, or replace a mutation that leads to a serious or life-threatening condition

Both gene therapy and gene editing can be taken inside the body (in vivo) or outside the body (ex vivo)

Depending on the condition you are attempting to treat, you might use either a gene therapy or gene editing approach

Primer on Gene Editing

Gene editing platforms are unique biotechnologies that can target and edit DNA. Leading variations include:

Older technologies:	Zinc fingers, meganucleases, TALENs (1980s - 2000s)
Newer technology:	CRISPR, homologous recombination (2010 - 2015)
Newest technologies:	Base editing, PRIME editing (2015+)

Field of Gene Editing – Real Progress For Real Patients

NPR: In a 1st, Doctors In U.S. Use CRISPR Tool to Treat Patient With Genetic Disorder

July 29, 2019

AP Exclusive: US Scientists Try 1st Gene Editing in the Body

December 15, 2017

OHSU performs first-ever CRISPR gene editing within human body

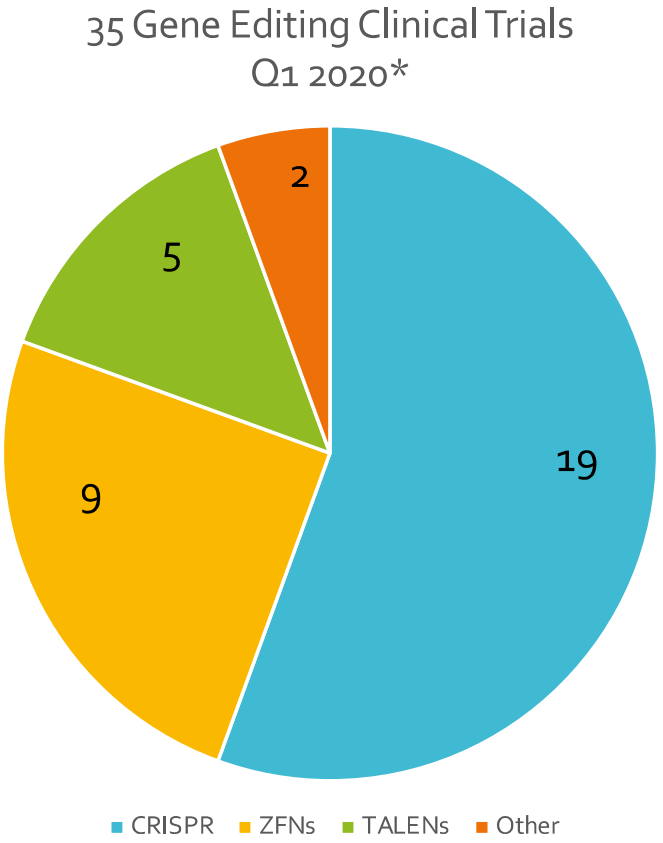
BRILLIANCE clinical trial aims to enable sight in people born with a blindness-causing mutation

March 4, 2020

Field of Gene Editing – Real Progress For Real Patients

Sangamo Therapeutics	
▪ Sickle Cell Disease/Beta Thalassemia	Phase 1/2
▪ MPS II	Phase 1/2
CRISPR Therapeutics	
▪ Sickle Cell Disease/Beta Thalassemia	Phase 1/2
▪ Cancer	
○ Non-Hodgkin Lymphoma (CTX-101)	Phase 1
○ Multiple Myeloma (CTX-120)	Phase 1
○ Solid tumors (CTX-130)	Phase 1
Editas Medicine	
▪ LCA10 (EDIT-101)	Phase 1/2
▪ Sickle Cell Disease/Beta Thalassemia	IND expected YE 2020
Intellia Therapeutics	
▪ ATTR	Expecting to dose Phase ½ by YE 2020

Field of Gene Editing – Real Progress For Real Patients



Leading disease areas:

- Hemoglobinopathies - 5
- Oncology – 16
- HIV/HPV - 7
- Ocular - 1
- Other diseases - 6

*Data compiled by Editas Medicine, based on analysis of clinicaltrials.gov

U.S. & EU Regulation of Somatic Cell Gene Editing Clinical Trials

- United States – robust regulatory framework
  - Both FDA and NIH jurisdiction
  - +40 years of biotech oversight
  - +30 years of gene therapy oversight
  - +15 years of gene editing oversight (zinc fingers)

FDA
Center for Biologics Evaluation and Research

- Europe – similar to the U.S. The European Commission requires gene editing products in somatic cells to undergo a centralized assessment of safety, efficacy, and quality by the European Medicines Agency (EMA)
  - Like in the U.S., this process is built upon decades of biologic experience and gene therapy experience

NIH
National Institutes of Health

- Within the EMA, the Committee for Advanced Therapies reviews applications for approval or rejection, and their decision is reviewed (and often ratified) by the Committee for Medicinal Products for Human Use (CHMP)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

November 2018: Hong Kong 2nd International Summit on Genome Editing

How is Germline Editing Clinical Application Treated– U.S.?

- Prohibited in the U.S.
- Longstanding FDA policy asserts jurisdiction over certain alterations to human embryos; requires IND (clinical trial)
- December 2015 – President Obama signs Appropriations bill that contains the Aderholt Amendment (R-AL)
  - Language expressly bars the FDA from considering requests to approve any clinical trials "in which a human embryo is intentionally created or modified to include a heritable genetic modification."
  - Indirect form of prohibition, via funding source cut-off
- June 2019 – House Appropriations Subcommittee removes Aderholt Amendment; later restored by full Appropriations Committee on a bipartisan basis

How is Germline Editing Clinical Application Treated – Europe?

(From Genetic Literacy Project)

- Europe – largely prohibited

- Regulatory and ethical guidelines for gene therapy/gene editing across the EU are guided by:
  1. The 2000 EU Charter of Fundamental Rights – Article 3 prohibits "eugenic practices, in particular those aiming at the selection of persons."; and

  2. The 1997 Convention on Human Rights and Biomedicine (Oviedo Convention) of the Council of Europe – ratified by 29 of the 47 European states, Oviedo requires that any therapy modifying the human genome "may only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendants."

- 18 European countries did not sign the Oviedo Convention, including Italy, Sweden, UK, Germany, Austria, and The Netherlands, in part because of the limits it puts on embryo research

How is Germline Editing Clinical Application Treated – Rest of World?

Genetic Literacy Project – Global Gene Editing Regulation Tracker

Global Governance of Germline Editing Clinical Application

- Russian scientist (2019) applies to regulators to permit editing embryos to eliminate rare hearing disorder

- World Health Organization
  - Peggy Hamburg (U.S.) and Edwin Cameron (South Africa) leading Commission on global governance
  - Report due Q1 2021
  - Focus on both somatic cell and germline editing

- Calls for a global moratorium
  - Eric Lander (Broad Institute) et al
  - ASGCT led letter to HHS Secretary Azar
  - WHO Director General's calls on regulatory agencies to prohibit clinical trials at this time (July 2019); not a moratorium per se

How Will Germline Editing be Treated In the Future?

- Question: "Do you want to be genetically engineered? "
  - Answer: The reality is, today you cannot do it legally in most of the world.
- But what about the future?
- Near-term: questions remain
  - WHO workstream (early 2021)
  - Russia in the future?
  - Future of the Aderholt Amendment? (Spring 2021 Appropriations Committee process?)
- Longer-term: challenges we may face when the science develops
  - What happens when there appears to be a relatively safe and effective application vs. a specific rare disorder?
  - "Ethics dumping" in lightly regulated markets and medical tourism for the affluent
  - Global governance for other provocative technologies – are we using gene editing to build for the future, or hide from it?

Global Governance/Regulation of Germline Genomic Editing Clinical Trials – Guardrails are Needed

Personal opinion:

- Gene editing field is flourishing…and this is a GREAT thing for patients!
  - Clinical trials enrolling, science advancing, new technologies are being pioneered, companies growing, companies raising funds to fuel more research

- Robust regulatory framework in place across most of the developed world; developing world could use more infrastructure (WHO process likely can help)

- Germline editing for clinical application
  - Science isn't ready & ethical clinical trials will be a challenge
  - I know of no companies doing work in this area
  - No country has expressly approved germline editing for clinical application
  - Some form of global guardrails are needed in the future – should not just be left country to country
  - Global moratorium would be helpful – give us time to convene, discuss, engage
  - Other technologies will develop in the years ahead that will make this moment look quaint by comparison; developing sound global governance now will better prepare us for this future