Genome Editing as a Medicine: Towards Health Justice

Fyodor D. Urnov, PhD
Professor of Molecular Therapeutics,
Department of Molecular and Cell Biology,
University of California, Berkeley

Scientific Director, Innovative Genomics Institute, UC Berkeley
Fyodor Urnov: disclosures

- **Cimeio Therapeutics**: SAB chair, paid advisor, hold equity
- **Ionis Pharmaceuticals**: paid advisor
- **Tune Therapeutics**: scientific co-founder, paid advisor, hold equity
- **Vertex Pharmaceuticals**: paid consultant on exa-cel program
“We have a responsibility to pursue CRISPR’s enormous potential to achieve previously impossible solutions to some of the world’s big challenges — solutions that will be available to anyone.”
Human Nature

Human Nature is a provocative exploration of CRISPR's far-reaching implications, through the families it's affecting, and the bioengineers who are testing its limits. How will this new power change our relationship with nature? What will it mean for human evolution? To answer these questions we must look back billions of years and peer into an uncertain future.

**** 148 IMDb 7.7 1 h 33 min 2020 13+

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CRISPRpedia is a free, textbook-style resource that explains and illustrates all things CRISPR.
CRISPR Clinical Trials: A 2023 Update

March 17, 2023 / Perspectives

By Hope Henderson
The invention of CRISPR gene editing gave us remarkable treatment powers, yet no one should do a victory lap. Scientists can rewrite a person’s DNA on demand. But now what? Unless things change dramatically, the millions of people CRISPR could save will never benefit from it. We must, and we can, build a world with CRISPR for all.

By Fyodor Urnov
Dr. Urnov is a professor of molecular and cell biology at the University of California, Berkeley, and a gene editor at its Innovative Genomics Institute.
Dec. 9, 2022
Fyodor Urnov
Imagine CRISPR Cures

Imaging CRISPR Cures | Fyodor Urnov | TEDxBerkeley

15K views 1 year ago
Fyodor Urnov explores the future of CRISPR and how it has the potential to save lives. Professor Fyodor Urnov is a Professor of Molecular and Cell Biology at the University of California, Berkeley, and is a Director at its Innovative Genomics Institute, leading the Center for Translational Genomics and directing the Technology & Translation division. A pioneer in the field of therapeutic genome editing, Fyodor's research focuses on advancing genome editing technology and pushing...
An IGI Task Force explored solutions to affordability and access challenges for genomic medicines

innovativegenomics.org/atf-report/

- **Dynamic cost-plus approach** anchoring price to COGS can drop prices by 10X
- **Manufacturing Innovation** Point-of-care manufacturing, automation, and platformization
- **Global access provisions** Empower TTOs to negotiate access into licensing agreements
- **A tripartite business model** Academic-Nonprofit-Public Benefit Corporation

Find the report here

Melinda Kliegman, Ph.D.
Director of Public Impact

Manar Zaghlula, Ph.D.
Policy & Engagement Manager
Leading causes of death in upper-middle-income countries

1. Ischaemic heart disease
2. Stroke
3. Chronic obstructive pulmonary disease
4. Trachea, bronchus, lung cancers
5. Lower respiratory infections
6. Diabetes mellitus
7. Hypertensive heart disease
8. Alzheimer’s disease and other dementias
9. Stomach cancer
10. Road injury

Number of deaths (in millions)

0 1 2 3 4

Noncommunicable Communicable Injuries


Leading causes of death in low-income countries

1. Neonatal conditions
2. Lower respiratory infections
3. Ischaemic heart disease
4. Stroke
5. Diarrhoeal diseases
6. Malaria
7. Road injury
8. Tuberculosis
9. HIV/AIDS
10. Cirrhosis of the liver

Number of deaths

0 200 000 400 000 600 000

Noncommunicable Communicable Injuries

What can genome editing do for human health?

No discernible effect of genetic variation on mortality from a given cause (224,000 deaths in US due to unintentional injuries in 2021).

Three types of connections:

1. Specific variants in a given gene causes a specific disease ($HBB$ E6V -> sickle cell disease) with very high (sometimes certain) likelihood.

2. Specific variants in a given gene strongly predispose to a given disease (BRCA1 -> breast cancer – ca 60-80% lifetime risk; ApoE4->AD 14x risk).

3. Cumulative effect of variants at many positions in the genome increase the risk of disease (~250 variants drive about 25% of IBD risk; ~100 variants drive about 40% of CAD risk) – “polygenic risk scores”
Diseases and human genetic variation

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All effect types are subject to modulation by environment/lifestyle + by other genes.

Data on all these effects informs development of molecular therapeutics.
Ca 6,000 Mendelian conditions affecting 350,000,000 people

OMIM®

An Online Catalog of Human Genes and Genetic Disorders
Updated August 23, 2023

Search OMIM for clinical features, phenotypes, genes, and more...

# 603903

SICKLE CELL DISEASE

Alternate title: sickle cell anemia

Phenotype-Gene Relationships

<table>
<thead>
<tr>
<th>Location</th>
<th>Phenotype</th>
<th>Phenotype number</th>
<th>Inheritance</th>
<th>Phenotype mapping key</th>
<th>Gene/Locus</th>
<th>Gene/Locus MIM number</th>
</tr>
</thead>
<tbody>
<tr>
<td>11p15.4</td>
<td>Sickle cell disease</td>
<td>603903</td>
<td>A8</td>
<td>2</td>
<td>HBB</td>
<td>141900</td>
</tr>
</tbody>
</table>

* 141900

HEMOGLOBIN—BETA LOCUS; HBB

HGNC Approved Gene Symbol: HBB

Cytogenetic location: 11p15.4  Genomic coordinates (GRCh38): 11:5,225,464-5,227,071 (from NCBI)

Gene-Phenotype Relationships

<table>
<thead>
<tr>
<th>Location</th>
<th>Phenotype</th>
<th>Phenotype Mapping key</th>
<th>Phenytoype Number</th>
<th>Inheritance</th>
<th>Phenotype Mapping Key</th>
</tr>
</thead>
<tbody>
<tr>
<td>11p15.4</td>
<td>Delta beta thalassemia</td>
<td>617794</td>
<td>AD</td>
<td>3</td>
<td></td>
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<tr>
<td>11p15.4</td>
<td>Beta-thalassemia, familial, 6</td>
<td>617790</td>
<td>AD</td>
<td>3</td>
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<tr>
<td>11p15.4</td>
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<td>141749</td>
<td>AD</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>11p15.4</td>
<td>Methemoglobinemia, beta type</td>
<td>617791</td>
<td>AD</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>11p15.4</td>
<td>Sickle cell disease</td>
<td>619043</td>
<td>AS</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>11p15.4</td>
<td>Thalassemia, beta</td>
<td>619042</td>
<td>AD</td>
<td>3</td>
<td></td>
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<tr>
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<td>Thalassemia beta, dominantly inherited</td>
<td>619042</td>
<td>AD</td>
<td>3</td>
<td></td>
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<tr>
<td>11p15.4</td>
<td>Thalassemia, beta</td>
<td>619042</td>
<td>AD</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

A number sign (#) is used with this entry because sickle cell disease is the result of mutant beta globin (HBB: 141900) in which the mutation causes sicking of hemoglobin.

https://www.omim.org/
https://www.omim.org/entry/603903
https://www.omim.org/entry/141900
Diseases and human genetic variation

No discernible effect of genetic variation on mortality from a given cause (224,000 deaths in US due to unintentional injuries in 2021).

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\textbf{All effect types are subject to modulation by environment/lifestyle + by other genes.}

Data on all these effects informs development of molecular therapeutics.
Even though it's a far-off prediction, it must be unsettling for you.

Yeah, there was an intensity to navigating it. Most of us, we like to avoid speaking about death in the hope that we'll somehow avoid it. We all have this belief that we'll figure it out. Then to all of a sudden be told some big indicators are actually pointing to this as the route which is going to happen, the reality of it sinks in. Your own mortality.
Chris Hemsworth is homozygous for the E4 allele of ApoE
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All effect types are subject to modulation by environment/lifestyle + by other genes. Data on all these effects informs development of molecular therapeutics.
Finding genetic signatures of complex disease

A Genome-Wide Association Study, often abbreviated as GWAS, is a method used in biomedical research to find connections between specific genetic variations and particular diseases or traits.

Here's a simple way to understand it:

1. **Genetic Variations**: Everyone's DNA contains small differences, which can influence how we look, how our bodies work, and our health. These variations are like tiny changes in a vast instruction manual.

2. **Comparing Groups**: In a GWAS, scientists compare the DNA of two groups of people: those with a certain trait or disease (like blue eyes or diabetes) and those without it.

3. **Looking for Patterns**: They scan the entire genome (all the genetic material) of each person, looking for specific genetic differences that are more common in the group with the trait or disease.

4. **Finding Links**: If a certain genetic variation is found more often in people with the condition, it suggests that this part of the genome might be related to developing that trait or disease.

5. **Understanding Risks**: This helps scientists understand which genes might contribute to diseases, how these genes work, and potentially how to predict, prevent, or treat these conditions.

Nice job, ChatGPT-4
Association mapping identifies haplotypes for disease susceptibility

$9.7 billion in 2022
Diseases and genome editing for them

1. Specific variants in a given gene causes a specific disease (*HBB* E6V -> sickle cell disease) with very high (sometimes certain) likelihood.

   Major progress for SCD, thalassemia, degenerative disease

2. Specific variants in a given gene strongly predispose to a given disease (BRCA1 -> breast cancer – ca 60-80% lifetime risk; ApoE4->AD 14x risk).

   Neurodegenerative disease trials – 3-5 years away

3. Cumulative effect of variants at many positions in the genome increase the risk of disease (~250 variants drive about 25% of IBD risk; ~100 variants drive about 40% of CAD risk) – “polygenic risk scores”

   First 10 subjects dosed for CAD
2020 Nobel Prize: Jennifer Doudna, IGI, UC Berkeley

Basic science discovery: 2012 -> CRISPR gene editing

Prize shared with Dr Emmanuelle Charpentier
0.3% of human genome

B-form DNA – 12 bp

6.6e9 bp diploid

in contrast to bacteria and yeast, HIGHLY resistant to targeted change
DSB – acutely genotoxic

Dividing human cells experience up to 50 DSBs per cell cycle

Multiple pathways of DSB-R highly conserved across evolution
Double Strand Break (DSB) Repair: Two Major Pathways

Schematic provided by Dr Lorraine Symington, Columbia University
DSB-driven editing

https://innovativegenomics.org/crisprpedia/
2012: Jennifer Doudna + Emmanuelle Charpentier
RNA-guided genome editing

A Programmable Dual-RNA–Guided DNA Endonuclease in Adaptive Bacterial Immunity

Martin Jinek, 1,2* Krzysztof Chylinski, 3,4* Ines Fonfara, 4 Michael Hauer, 2† Jennifer A. Doudna, 1,2,5,6‡ Emmanuelle Charpentier 4‡
How to program Cas9
How to program Cas9

sgRNA

SpyCas9 PAM: 5’ NGG 3’
How to program Cas9
"Considerable potential" in clinical data: a timecourse

Promising efficacy signals in clinical trial data for genome editing

A Programmable Dual-RNA-Guided DNA Endonuclease in Adaptive Bacterial Immunity

Martin Jinek,1,2,3 Krzysztof Chylinski,4,5,6 Ihsen Fonfara,4 Michael Hauer,4† Jennifer A. De等活动,5,6,7 Emmanuelle Charpentier†
“Considerable potential” made clinically real

Sickle Cell / Beta Thalassemia
CRISPRTX/Vertex Therapeutics
Cause: Point mutation in HBB / var.
Delivery: Ex-vivo, electroporation RNP
Phase 1/2

Transthyretin Amyloidosis (ATTR)
Intellia Therapeutics
Cause: Point mutation in TTR gene
Delivery: Lipid nanoparticle
Phase 1/2

Congenital Eye Disease (LCA10)
Editas Medicine
Cause: Point mutation in CEP290
Delivery: Direct injection, viral (AAV)
Phase 1/2

Approval in 2023!
Phase 3 trial!
Pediatric subject dosed!
“Considerable potential” – a portrait gallery
Editing in the clinic: ex vivo

Drugging the formerly undruggable
Sickle cell disease

NIH:

“Sickle cell anemia is the most common inherited blood disorder in the United States, affecting about 100,000 Americans or 1 in 500 African Americans. SCA is characterized by episodes of pain, chronic hemolytic anemia and severe infections, usually beginning in early childhood.”
Sickle cell disease – an unmet medical need of enormous urgency
Our genome encodes multiple beta-like globins
Clinical genome editing for SCD involves reactivating HbF
In a 1st, Doctors in U.S. Use CRISPR Tool to Treat Patient with Genetic Disorder

July 29, 2019 - 5:18 AM ET
Heard on Morning Edition

Victoria Gray, 34, of Forest, Miss., volunteered for one of the most anticipated medical experiments in decades: the first attempt to use the gene-editing technique CRISPR to treat a genetic disorder in the U.S.

A Young Mississippi Woman's Journey Through a Pioneering Gene-Editing Experiment

December 25, 2019 - 7:00 AM ET
Heard on All Things Considered

Victoria Gray, who has sickle cell disease, volunteered for one of the most anticipated medical experiments in decades: the first attempt to use the gene-editing technique CRISPR to treat a genetic disorder in the United States.
Victoria Gray has been cured of SCD by CRISPR – 2020
2023: transplantation of edited HSPCs resolves major symptoms SCD in 32 subjects
Panel Says That Innovative Sickle Cell Cure Is Safe Enough for Patients

The decision by an advisory committee may lead to Food and Drug Administration approval of the first treatment for humans that uses the CRISPR gene-editing system.

By Gina Kolata
Gina Kolata has reported on gene therapy for nearly 30 years and on sickle cell disease since 2018.
Oct. 31, 2023

A panel of experts said on Tuesday that a groundbreaking treatment for sickle cell disease was safe enough for clinical use, setting the stage for likely federal approval by Dec. 8 of a powerful new therapy.
RNA-guided targeted engineering without a DSB

2013
- Gene regulation
  - Gene repression
  - Temporary or persistent
  - Epigenetic modification or RNA targeting

2016
- Base editing
  - Single-base change by DNA nick
  - SNP reversal; gene KO
  - Permanent

2019
- Prime editing
  - Insertion, deletion, replacement
  - Nicks
  - Reverse transcriptase fused to Cas9 nickase with 3’ extended pegRNA guide
Base-edited CAR-T for pediatric leukemia

Figure 1. Base-Editing Donor T Cells to Target T-Cell Leukemia.
Unleashing CRISPR on Cancer

Base editing: Revolutionary therapy clears girl's incurable cancer

Dr. Waseem Qasim, a pediatric immunologist, discusses a recent study published in *The New England Journal of Medicine* that highlights the potential of CRISPR technology in treating a type of leukemia.

**Alyssa's Story**

Alyssa was a young girl who was diagnosed with leukemia. Despite trying multiple treatments, her condition remained resistant to conventional therapies. Dr. Waseem, who is the lead researcher on the study, shares how Alyssa's case evolved and the impact of CRISPR technology on her treatment.

**Hurdles in Treatment**

One of the major challenges in treating Alyssa was the development of resistance to standard treatments. The study found that CRISPR technology could effectively edit the genes responsible for this resistance, allowing doctors to introduce the right genetic material into Alyssa's immune cells to combat the disease.

**Outcome**

Alyssa's case is one of the first to demonstrate the potential of CRISPR technology in treating leukemia. The study not only showed promise in treating a patient with a rare and resistant form of the disease but also highlighted the need for further research to evaluate the technology's effectiveness in a broader patient population.

**Conclusion**

CRISPR technology represents a significant advancement in the field of oncology. Its potential to revolutionize cancer treatment by targeting specific genetic defects offers hope for patients who have exhausted conventional therapies. As research continues, it is anticipated that CRISPR will play an increasingly important role in oncology, providing new avenues for treating and potentially curing cancer.
Editing in the clinic: *in vivo*
Crispr’s Quest to Slay Donegal Amy

A trial using the gene-editing tool inside the body hints at treating, or even curing, a rare fatal disease—and is changing a community in the process.

Knockout blow for 'Donegal Amyloidosis'

Successful gene editing clinical trial for Donegal Duo


https://www.wired.com/story/crispr-treatment-donegal-amy/
Intellia Therapeutics – CRISPR KO for amyloidosis: In Vivo LNP-mRNA delivery
2022: Intellia Therapeutics
CRISPR-Cas9 can be programmed to cut a specific sequence of DNA in a patient by simply changing the guide RNA

Disease 1: TTR Amyloidosis
Gene: ATTR on chr 20a
93% target gene knockout in patient liver

Disease 2: Hereditary Angioedema
Gene: KLKB1 on chr 4
92% target gene knockdown in patient liver

Intellia Therapeutics Announces FDA Clearance of Investigational New Drug (IND) Application to Initiate a Pivotal Phase 3 Trial of NTLA-2001 for the Treatment of Transthyretin (ATTR) Amyloidosis with Cardiomyopathy
Human genetics identify target for CRISPR intervention in prevalent disease

Sequence Variations in PCSK9, Low LDL, and Protection against Coronary Heart Disease

Jonathan C. Cohen, Ph.D., Eric Boerwinkle, Ph.D., Thomas H. Moseley, Jr., Ph.D., and Helen H. Hobbs, M.D.

ABSTRACT

BACKGROUND
A low plasma level of low-density lipoprotein (LDL) cholesterol is associated with reduced risk of coronary heart disease (CHD), but the effect of lifelong reductions in plasma LDL cholesterol is not known. We examined the effect of DNA-sequence variations that reduce plasma levels of LDL cholesterol on the incidence of coronary events in a large population.

METHODS
We compared the incidence of CHD (myocardial infarction, fatal CHD, or coronary revascularization) over a 15-year interval in the Atherosclerosis Risk in Communities study according to the presence or absence of sequence variants in the proprotein convertase subtilisin/kexin type 9 serine protease gene (PCSK9) that are associated with reduced plasma levels of LDL cholesterol.

RESULTS
Of the 3363 black subjects examined, 2.6 percent had nonsense mutations in PCSK9; these mutations were associated with a 28 percent reduction in mean LDL cholesterol and an 88 percent reduction in the risk of CHD (P=0.008 for the reduction; hazard ratio, 0.11; 95 percent confidence interval, 0.02 to 0.81; P=0.03). Of the 9524 white subjects examined, 3.2 percent had a sequence variation in PCSK9 that was associated with a 15 percent reduction in LDL cholesterol and a 47 percent reduction in the risk of CHD (hazard ratio, 0.50; 95 percent confidence interval, 0.32 to 0.79; P=0.003).

88% reduction in disease risk
In vivo genome editing for CAD using LNP-Cas9 mRNA delivery

Sequential dosing in NHPs: >90% reduction of plasma PCSK9 protein followed by >90% reduction observed of plasma ANGPTL3 protein

Oct 23, 2023
Verve Therapeutics Announces Clearance of Investigational New Drug Application by the U.S. FDA for VERVE-101 in Patients with Heterozygous Familial Hypercholesterolemia
New Gene Editing Treatment Cuts Dangerous Cholesterol in Small Study

The trial involved only 10 patients, but it suggests cholesterol can be permanently reduced with a single treatment for patients at risk of heart disease.

And while more trials in a broader range of patients will need to be carried out, gene editing experts and cardiologists said the treatment had the potential to transform preventive cardiology.

“Even for seasoned veterans of this field like myself, this is a day we will look back on,” said Fyodor D. Urnov, a gene editor at the Innovative Genomics Institute in Berkeley, Calif. “I see today as crossing a Rubicon, in a good way. This is not a small step. It is a leap into new territory.”

Impressed with the data and the potential it shows, the pharmaceutical giant Eli Lilly paid $60 million to collaborate with Verve Therapeutics and opted to acquire additional rights to Verve’s programs for an additional $250 million. If the editing continues to look promising, Eli Lilly expects to help with larger studies.

“Until now, we thought of gene editing as a treatment we should reserve for very rare diseases where there is no other treatment,” said Dr. Daniel Skovronsky, Eli Lilly’s chief scientific and medical officer. “But if we can make gene editing safe and widely available, why not go after a more common disease?”
The invention of CRISPR gene editing gave us remarkable treatment powers, yet no one should do a victory lap. Scientists can rewrite a person’s DNA on demand. But now what? Unless things change dramatically, the millions of people CRISPR could save will never benefit from it. We must, and we can, build a world with CRISPR for all.

By Fyodor Urnov
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Dec. 9, 2022
U.S. Approved Gene Therapies

- Kymriah (2017)
- Yescarta (2017)
- Luxturna (2017)
- Zolgensma (2019)
- Tecartus (2020)
- Breyanzi (2020)
- Abecma (2021)
- Carvykti (2022)
- Zynteglo (2022)
- Skysona (2022)
- Hemgenix (2022)
- Adstiladrin (2022)
- Vyjuvek (2023)
- Elevidys (2023)
- Roctavian (2023)
$2.9 million

BioMarin said Roctavian's $2.9 million price tag reflects “the possibility of freedom from years” of infusions, which cost about $800,000 annually for a typical patient. The price is less than the $3.5 million announced last year for a similar gene therapy for hemophilia B, a less common form of the disease.  

$2.9 million gene therapy for severe hemophilia is approved ...

$3.2 million

Sarepta's (ticker: SRPT) $3.2 million one-time treatment—which will be marketed under the name Elevidys—is the first gene therapy approved to treat DMD, a progressive and fatal condition that manifests in early childhood. The $3.2 million price tag makes Elevidys one of the most expensive medicines in the world.  

Sarepta's $3.2 M Gene Therapy Just Got Approved ... - Barron's
Fyodor Urnov @UrnovFyodor · Sep 22, 2021
Dr. Bennett is a hero and inspiration to all of us in cell and gene therapy for taking Luxturna from preclinical to approval (a "yes we can" moment for the field).
I'm excited she's taking on other indications in the eye space - unmet need is huge.

Helaine Fonseca @helaine_fonseca
Tenho duas filhas com indicação para receberem #Luxturna, no Brasil me foi negado judicialmente e recentemente foi negado a incorporação ao SUS, preciso de ajuda para ter acesso a esse tratamento.
Me ajudem!