

Gene editing research and its bioethics

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**Gene Editing Therapeutics find and rewrite
these causes of disease.**

Your DNA

Mutations ↑

Age →

Muscular Dystrophy
DMD mutation
N Engl J Med 2014; 371:e5

Breast Cancer

BRCA1 and BRCA2

N Engl J Med 2004;292(11):317-323

200 known genetic diseases

Sickle-cell disease

Haemophilia

Cystic fibrosis

Down syndrome

Cancer susceptibility

Tay-Sachs disease

Angelman syndrome

Color blindness

Caravan disease

Charcot-Marie-Tooth disease

Golu chat

Familial Hypercholesterolemia

Haemochromatosis

Klinefelter syndrome

Neurofibromatosis

Phenylketonuria

Polycystic kidney disease

Praetorius syndrome

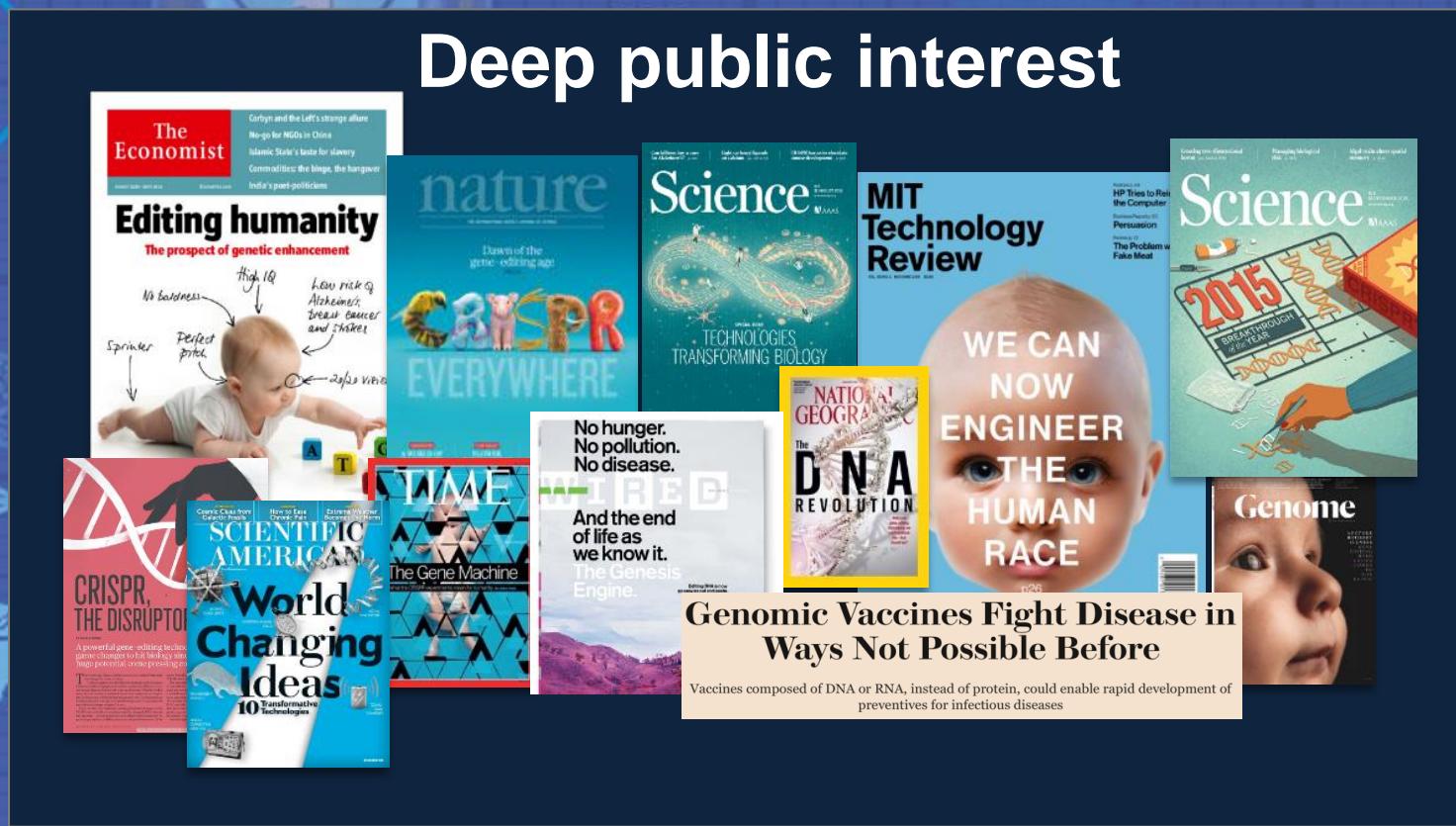
Spina bifida

Spinal muscular atrophy

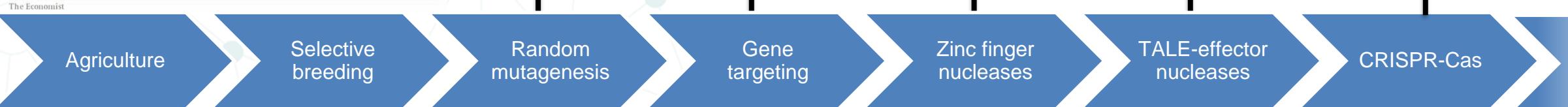
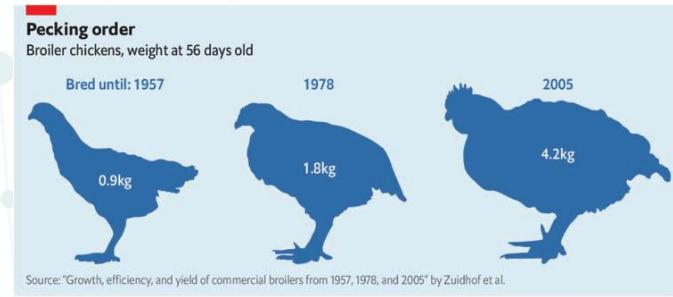
Change DNA

The blueprint of life

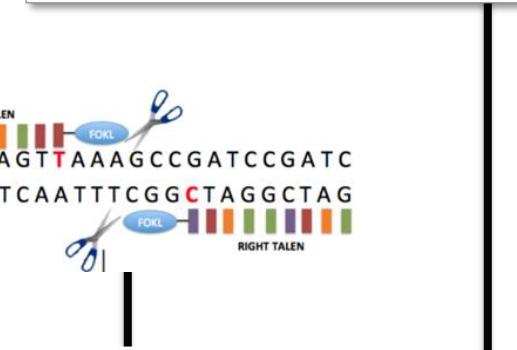
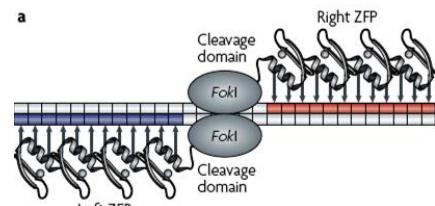
Deep public interest



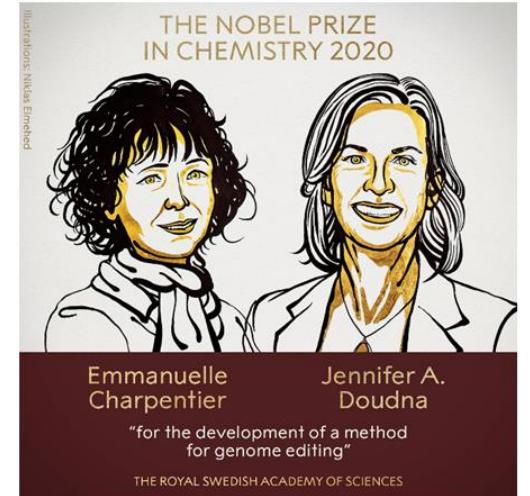
A long history before the recent breakthroughs



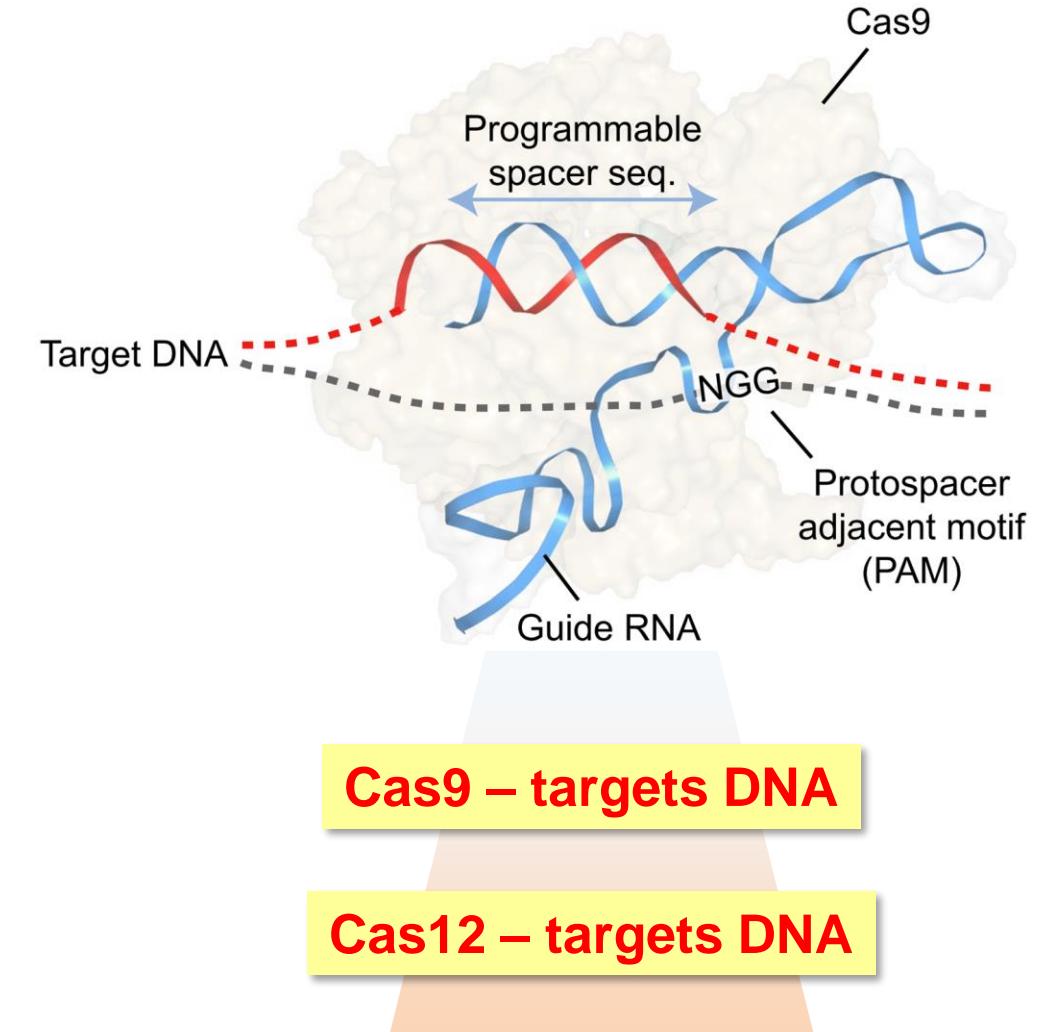
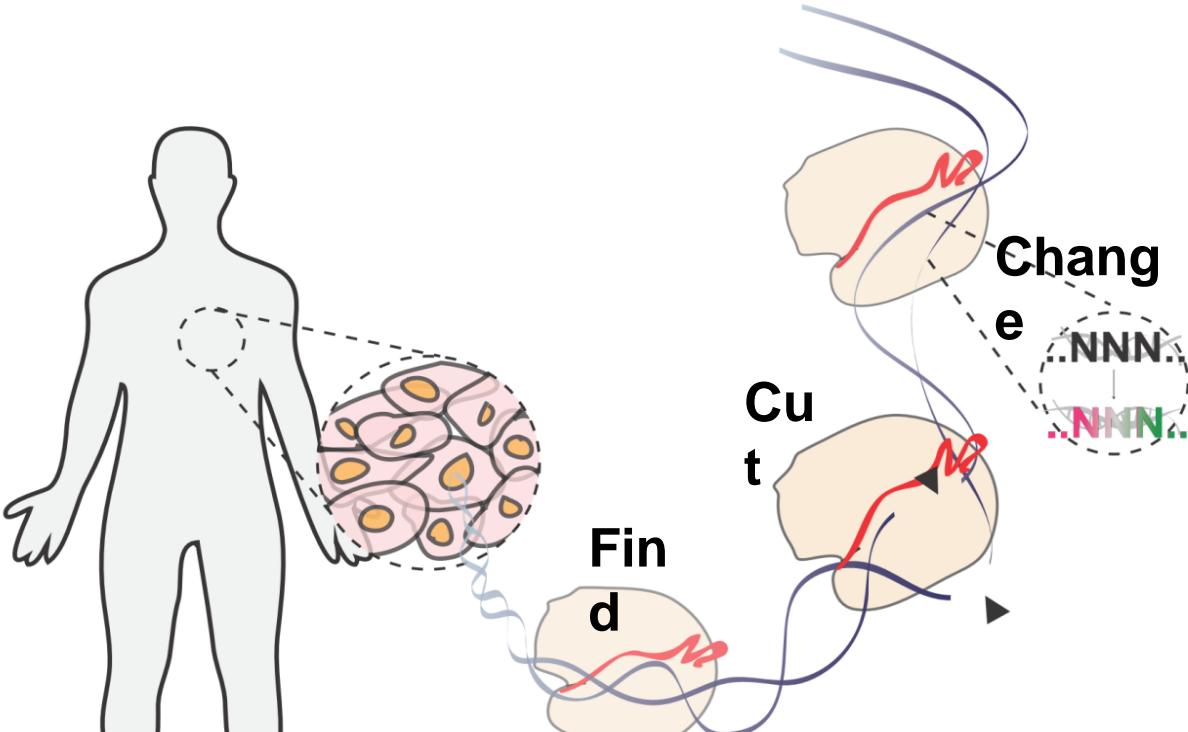
NOBEL PRIZE 2007
PHYSIOLOGY/MEDICINE



Nobel Prize in Chemistry 2020
(seminal study 2012)

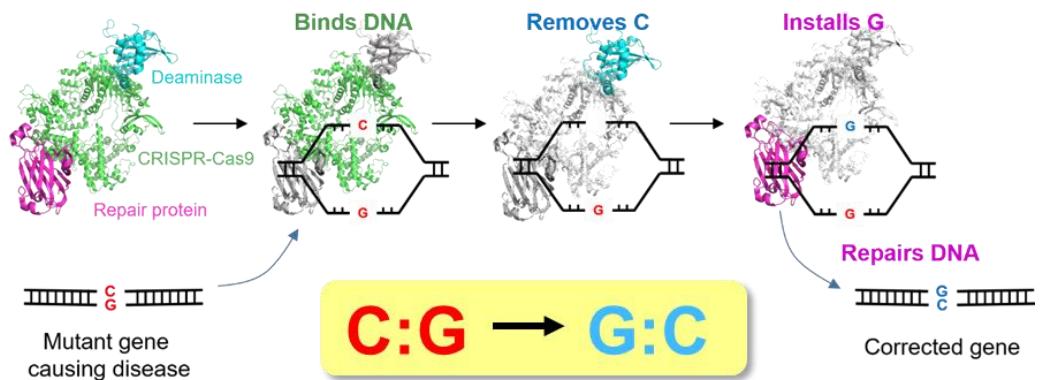


CRISPR-Cas (Cas9, Cas12, Cas13...)

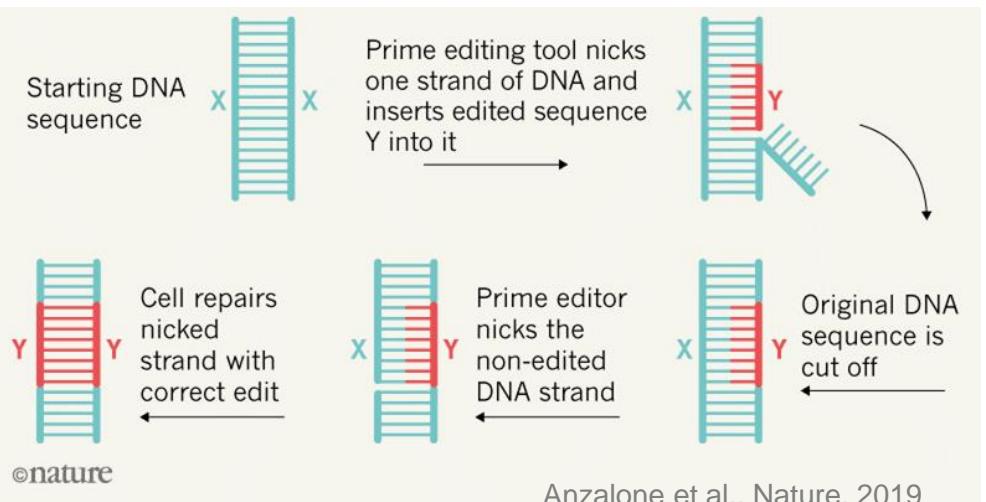


CRISPR 2.0, 3.0,... a right-click for biology

Base editing



Prime editing

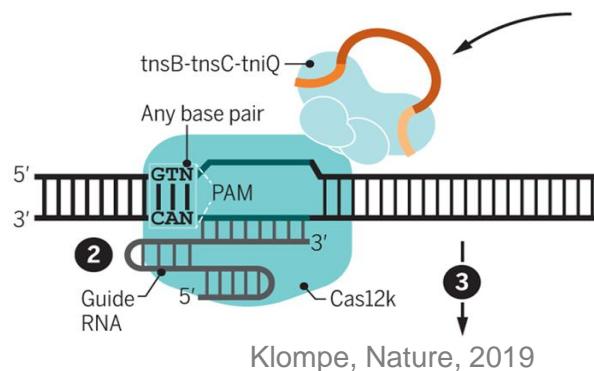


TCCTGGGGACTGTGGGGGTGGTAAAAGACCTCTATG
CCTGGGGCAGGGGGAGAACAGCCCACCTCGTACTGGG
GGGGCGGGACAGGGGGAGCCCTATAATTGGACAAGTCT
GGTGAAGGACGTCCCTCCCCAC
TCTAGAAAGAGCTGGGACCCTG
CTTGGGGAGAGGAGGGAGCGGGG
GACGACCCGACCCGCTAGAAGG
CACGAGTTGTCACTATCATTTA
GGAGCCAGGGCAGCGACACGG
ATAAATGGAACACGGCGCTTAZ
CTGGGACTGAGATGGAACCGGG
TGGAAATTCTATGGAGGCCGZ
ATGGGTTGGGGCGGCTTGGTAAATGTGCTGGGATTAG

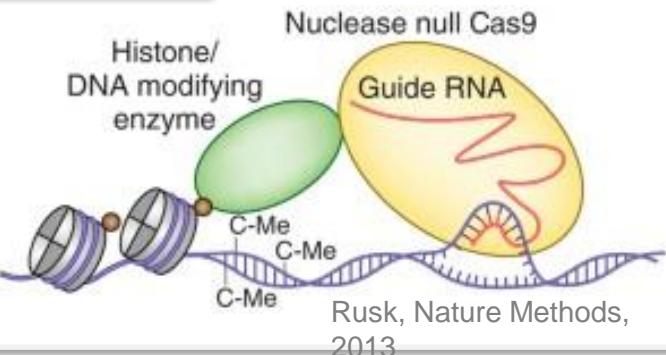
Context menu:

- Cut
- Copy
- Paste
- Font...
- Paragraph...
- Bullets
- Numbering
- Hyperlink...
- Look Up...
- Synonyms
- Translate
- Styles

Transposases



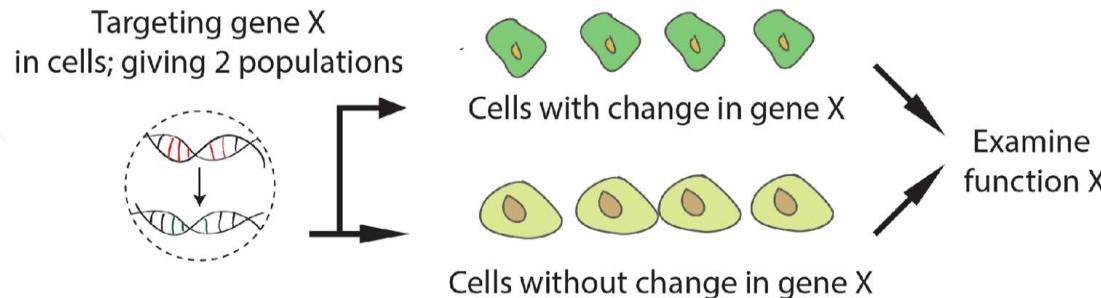
Epigenetic modifiers



Gene editing pervades biomedical research

Disease interrogation

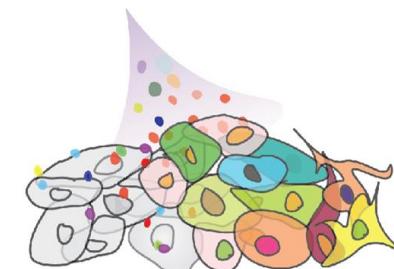
How genes manifest function?



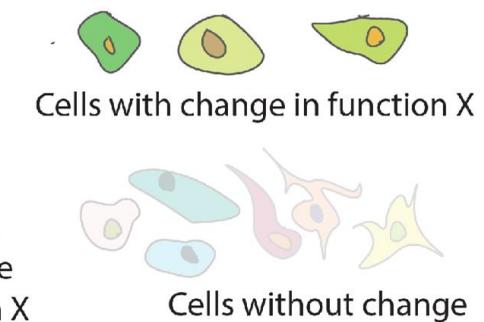
Screens

Which genes responsible for function?

Multiple CRISPR-gRNAs,
each targeting a different gene



Gene A Gene B Gene C



Identified & deciphered many previously unknown genetics:

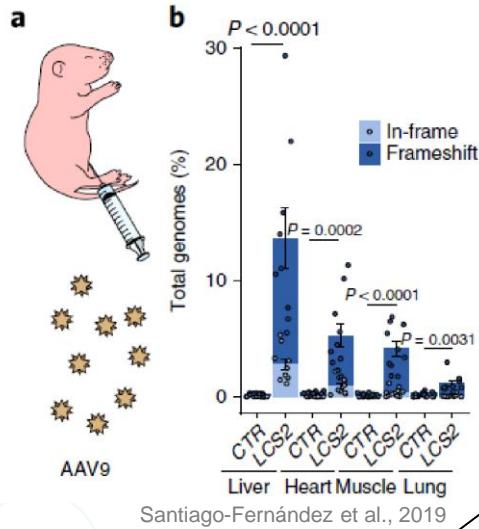
- Infections, genetic diseases, cancer vulnerabilities, fundamental biological insights...

- Can establish causality, but...
in vitro, ex vivo, animal models,
extrapolation

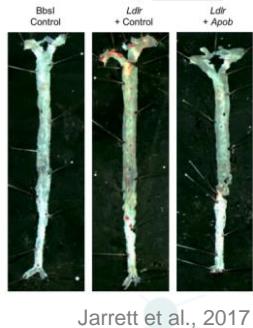
- Monogenic vs Polygenic
- Incomplete penetrance
- Incomplete knowledge

Treating the broad spectrum of genetic diseases (list goes on...)

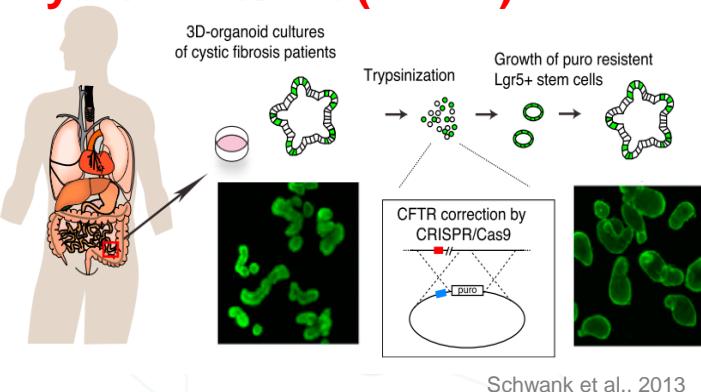
Heart, aging (LMNA)



Cardiovascular



Cystic fibrosis (CFTR)



Schwank et al., 2013

Ran et al., 2015

Days post injection

Serum cholesterol (mg dL⁻¹)

Pcsk9-sg1

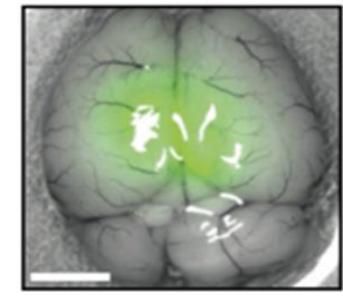
● Uninjected
● Rosa-sg1, 2E11
○ 0.5 × 10¹¹ ● 2 × 10¹¹
● 1 × 10¹¹ ● 4 × 10¹¹

Cataracts



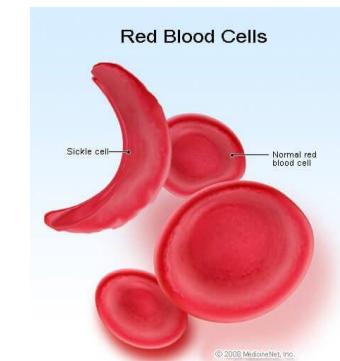
Wu et al., 2013

Brain (MECP2)



Swiech et al., 2014

Sickle cell anemia
Hemophilia
Thalassemia
Cancer immunotherapy



Gene editing is in the clinic

Multiple successful clinical trials,
even though still early phases

A Year In, 1st Patient To Get Gene
Editing For Sickle Cell Disease Is
Thriving

• June 23, 2020 5:04 AM ET



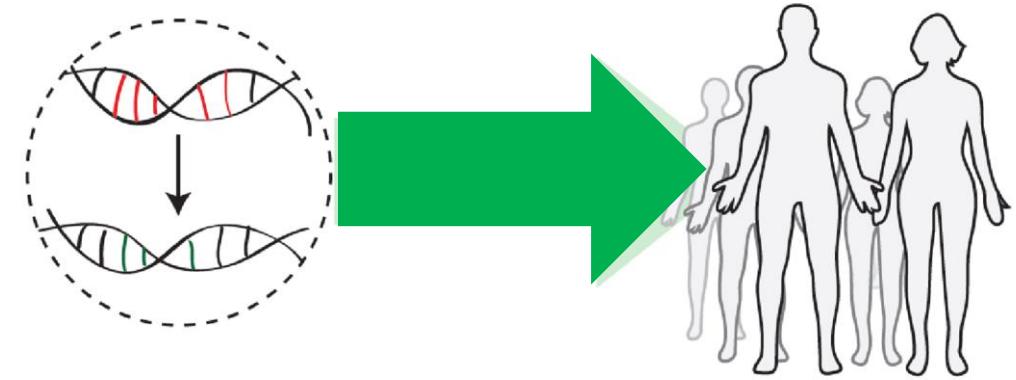
Blind Patients Hope Landmark
Gene-Editing Experiment Will
Restore Their Vision

• May 10, 2021 5:00 AM
ET

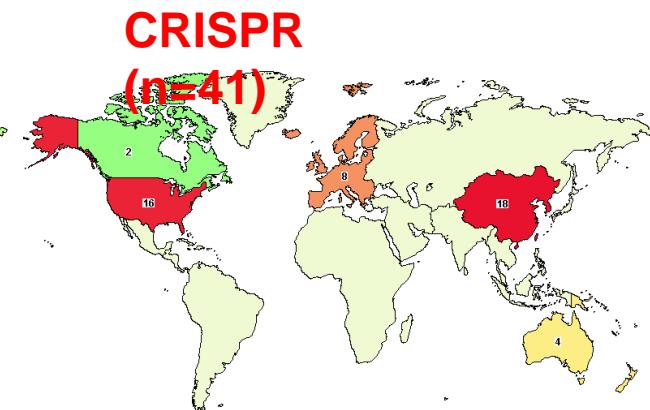
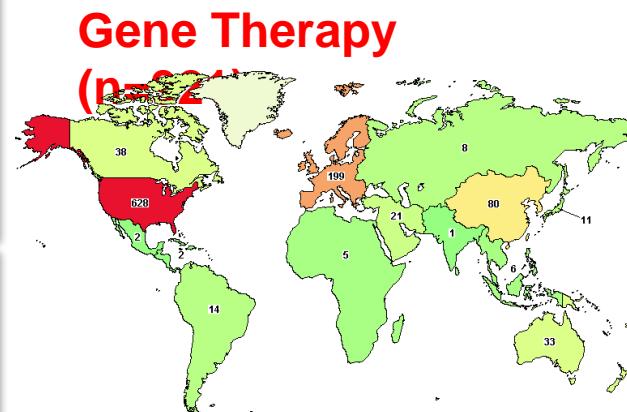


CRISPR gene editing proves safe in
a clinical trial

• 10 FEBRUARY 2020



Clinical trials around the world



Gene editing across the whole body

Delivery (viruses, liposomes, nanoparticles) determines which cells and organs are targeted

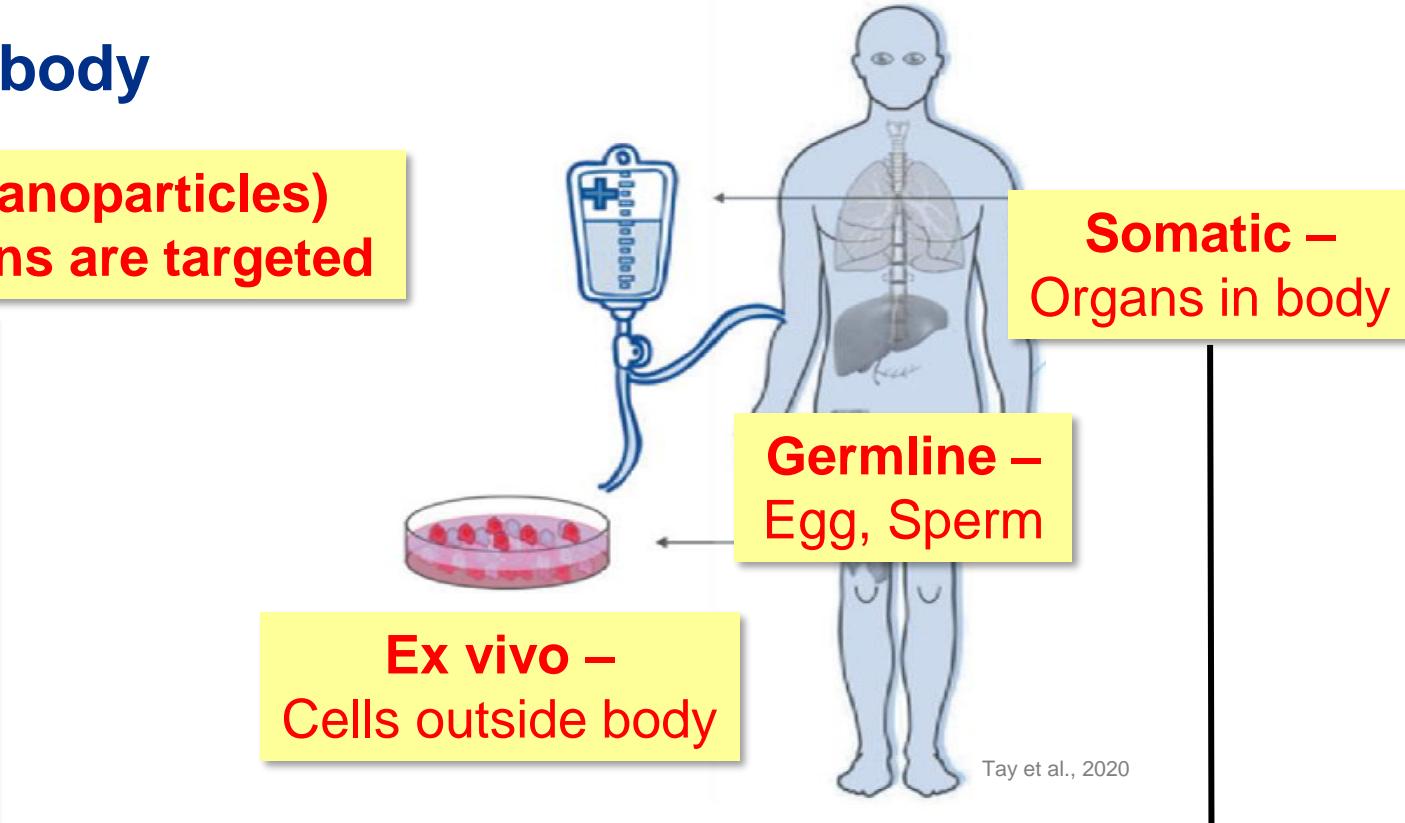
However,

1. Delivery is not 100% specific

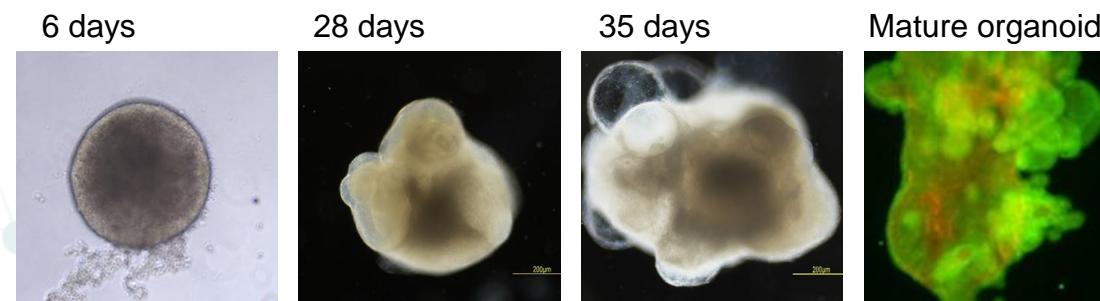
- Some cells might be unintentionally targeted – e.g. targeting liver but germline unintentionally targeted.

2. Delivery is not 100% efficient

- Within each organ, some cells are treated successfully while some are not.
- In somatic organs: medically justifiable?
- In germline or embryos: mosaicism in the offspring where a mixture of cells with small genetic differences



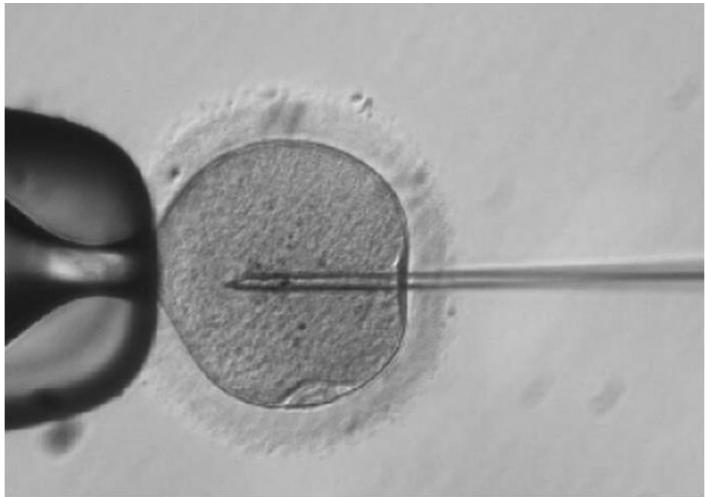
Modeling with mini human organs (organoids)



Guo Ke
Park Jung Eun

Brain
Lung
Eye
Liver
Tumour
etc...¹⁰

Germline editing – very few studies

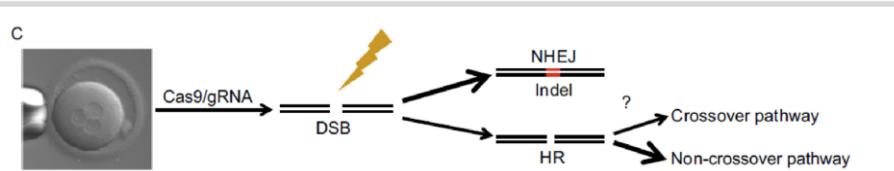


Correction of a pathogenic gene mutation in human embryos

Hong Ma^{1*}, Nuria Martí-Gutierrez^{2*}, Sang-Wook Park^{2*}, Jun Wu^{3*}, Yeonmi Lee¹, Keiichiro Suzuki³, Amy Koski¹, Dongmei Ji¹, Tomonari Hayama¹, Riffat Ahmed¹, Hayley Darby¹, Crystal Van Dyken¹, Ying Li¹, Eunji Kang¹, A-Reum Park², Daesik Kim⁴, Sang-Tae Kim⁵, Jianhui Gong^{5,6,7,8}, Ying Gu^{5,6,7,8}, Xun Xu^{5,6,7,8}, David Battaglia^{1,9}, Sacha A. Krieg¹, David M. Lee¹⁰, Diana H. Wu⁹, Don P. Wolf¹, Stephen B. Heintz¹⁰, Juan Carlos Izpisua Belmonte^{9,8}, Paula Amato^{1,9,8}, Jin-Soo Kim^{5,6,8}, Sanjiv Kaul^{10,8} & Shoukhrat Mitalipov^{1,10,8}

NATURE | VOL 548 | 24 AUGUST 2017

- Is efficient
- Copies maternal sequence
- Non-mosaic
- Well tolerated without apparent toxicity



CRISPR/Cas9-mediated gene editing in human triploid zygotes

Puping Liang, Yanwen Xu, Xiya Zhang, Chenchui Ding, Rui Huang, Zhen Zhang, Jie Lv, Xiaowei Xie, Yuxi Chen, Yujing Li, Ying Sun, Yaofu Bai, Zhou Songyang, Wenbin Ma, Canquan Zhou[✉], Junjiu Huang[✉]

Guangdong Province Key Laboratory of Reproductive Medicine, the First Affiliated Hospital, and Key Laboratory of Gene Engineering of the Ministry of Education, School of Life Sciences, Sun Yat-sen University, Guangzhou 510275, China

✉ Correspondence: hjunjiu@mail.sysu.edu.cn (J. Huang), zhouchanquan@hotmail.com (C. Zhou)

Received March 30, 2015 Accepted April 1, 2015

- Non-viable zygotes
- Editing found to be inefficient

J Assist Reprod Genet
DOI 10.1007/s10815-016-0710-8

TECHNOLOGICAL INNOVATIONS



Introducing precise genetic modifications into human 3PN embryos by CRISPR/Cas-mediated genome editing

Xiangjin Kang¹ • Wenyin He¹ • Yuling Huang¹ • Qian Yu¹ • Yaoyong Chen¹ •
Xingcheng Gao¹ • Xiaofang Sun¹ • Yong Fan¹

- Non-viable zygotes
- Editing found to be inefficient

CRISPR EDITING WREAKS CHROMOSOMAL MAYHEM IN HUMAN EMBRYOS

Studies showing large DNA deletions and reshuffling heighten concerns about heritable genome editing.

By Heidi Ledford

been peer-reviewed^{1–3}. But they give scientists a good look

- 3 studies
- Large deletions of DNA in embryos

- He Jiankui
- No scientific nor ethical merit
- Incomplete CCR5 knockout not anti-HIV
- Bypassed well-established norms & checks

Hard challenges are being worked on

Safety

Specificity

Similar sequences in
the genome might be
unintentionally targeted

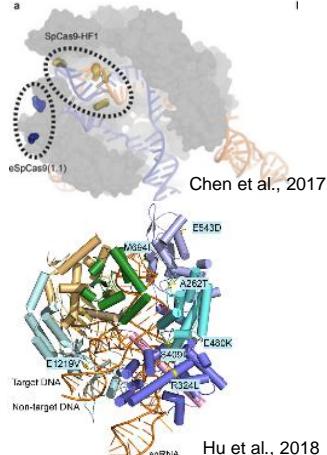


Immune responses

Up to 96% of us might react
adversely to ↑ Engine

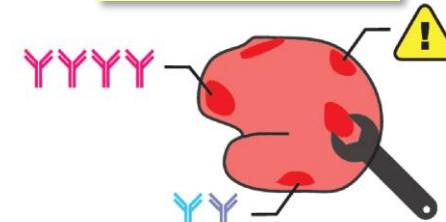
Engineered safer CRISPR

Bioinformatics & Hyper-accurate CRISPR



Efficacy

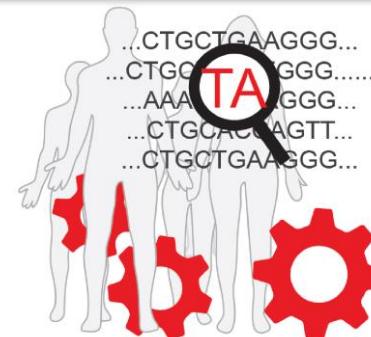
Machinery



Delivery



Understanding of mechanisms



Genetic therapies change lives... but...?

Hard challenges go beyond technology

Luxturna - Spark TX

"FDA experts offer a **unanimous endorsement**" – *Science*



Packshot of Luxturna, © Spark Therapeutics

Glybera – uniQure

"**First gene therapy approved**" – *Nature*



Packshot of Glybera, © uniQure B.V.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1822 VOL. 327 NO. 23 DECEMBER 7, 2017

Hemophilia B Gene Therapy with a High-Specific-Activity Factor IX Variant

L.A. George, S.K. Sullivan, A. Giermasz, J.E.J. Raskin, B.J. Samelson-Jones, J. Durone, A. Cuker, L.M. Sullivan, S. Majumder, J. Teitel, C.E. McGuire, M.V. Ragni, A.Y. Luk, D. Hui, J.F. Wright, Y. Chen, Y. Liu, K. Wachtel, A. Winters, S. Tiefenbacher, V.R. Aranda, J.C.M. van der Loos, O. Zelenka, D. Takefman, M.E. Carr, L.B. Couto, K.M. Angueta, and K.A. High

From 111 bleedings
to 4

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1822 VOL. 327 NO. 18 NOVEMBER 2, 2017

Single-Dose Gene-Replacement Therapy for Spinal Muscular Atrophy

J.A. Mendell, S. Al-Zaidy, R. Shieff, W.D. Arnold, J. Rodriguez-Gomez, T.W. Price, L. Lopez, L. Alfaro, S. Berry, K. Chisholm, J.T. Kuehn, S. Sridharan, J. T. Allen, D.M. Spudlak, C. Wells, J.A. Carpenter, M.D. Heiman, A. Kapoor, S. Concordia, L. Braun, S. Likhite, C. Miranda, K. Meyer, K.D. Foust, A.H.M. Burghes, and B.K. Kaizer

From 0% survival
to 100%

MIT Technology Review

\$2 million would save her life. Could you pay?



Should you?

Medicine is becoming hyper-personalized, hyper-accurate ... and hyper-unequal. p. 38

The AIs taking over from doctors

Curing cancer with customized vaccines

How to plan your digital afterlife



onasemnogene abeparvovec-xioi
ZOLGENSMA

Rx ONLY
Suspension for intravenous infusion.

2.0 x 10¹³ vector genomes/ml

See enclosed prescribing information for dosage and directions for use.

Contains no preservatives. Discard any unused portion.

Upon receipt store refrigerated at 2°C to 8°C (36°F to 46°F).

Must use within 14 days of receipt.

Store in the original carton until time of use.

DO NOT SHAKE DO NOT REFREEZE



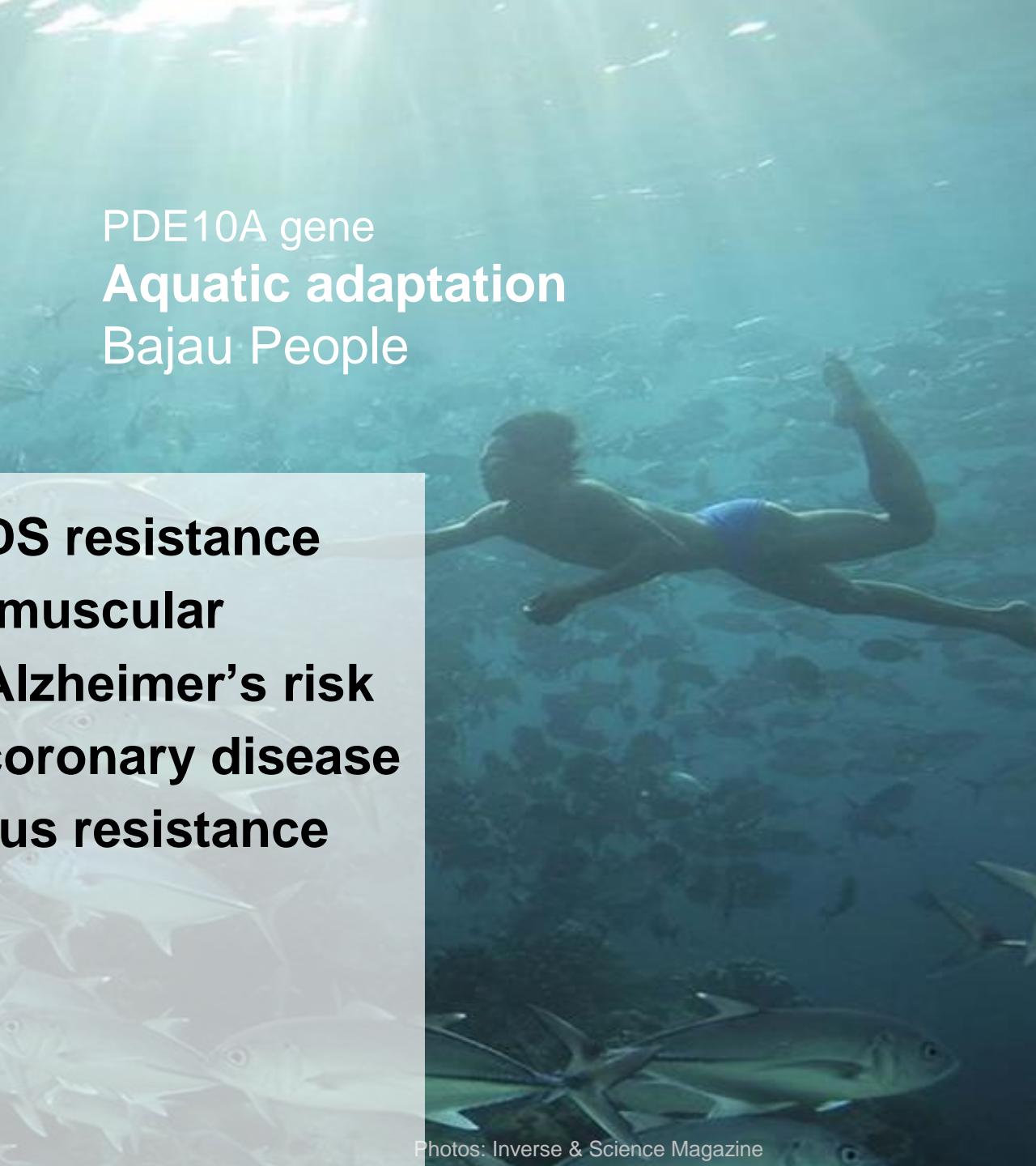
Impact (beyond) diseases

EPAS1, EGLN1, PPARA
genes

High altitude adaptation
Tibetans

PDE10A gene
Aquatic adaptation
Bajau People

- **CCR5 – HIV/AIDS resistance**
- **MSTN – Hyper-muscular**
- **APOE2 – Low Alzheimer's risk**
- **PCSK9 – Low coronary disease**
- **FUT2 – Norovirus resistance**
-
-
-



New medicines bring real challenges; Scientists can help to understand & unlock tremendous benefits

The Straits Times, 1976



Producing 'carbon copy'
human beings...

**SUPER BABIES
—TO ORDER**

The Straits Times, 1959



The Straits Times, 1980



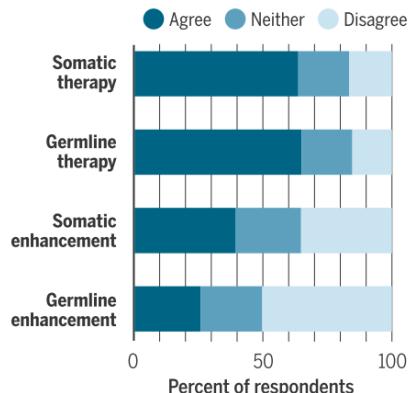
to making a quick buck? Few other developments etch so sharply the ethical, moral and social issues involved in the modern pursuit of scientific knowledge and its exploitation as does the fledging of the new industry of BIOTECHNOLOGY and TELEMATICS. i.e. The Internet

The same can said for telematics — that remarkable melding of computers and communications that promises to make the 80s as monumental an epoch in technology-driven social change as was the Industrial Revolution.

Perennial questions that go beyond technology development;
Scientists can help understand, progress, and unlock tremendous benefits.

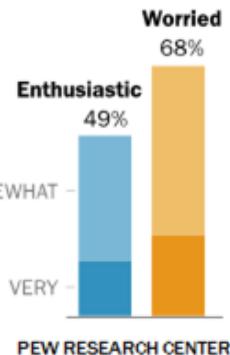
Acceptance of gene editing

A majority finds use of human genome editing for therapeutic purposes acceptable, including somatic and germline edits. Public opposition increases for applications aimed at enhancement.



SCIENCE 11 AUGUST 2017 • VOL 357 ISSUE 6351

Gene editing giving
babies a much reduced
disease risk



SOMEWHAT
VERY
PEW RESEARCH CENTER

Science, Health and Policy-relevant Ethics in Singapore (SHAPES)



Centre for Biomedical Ethics
Yong Loo Lin School of Medicine

Pervasive Impact

Biotech
Industry

Environment
Control

Food
Security

Precision
Medicine



Thank you

