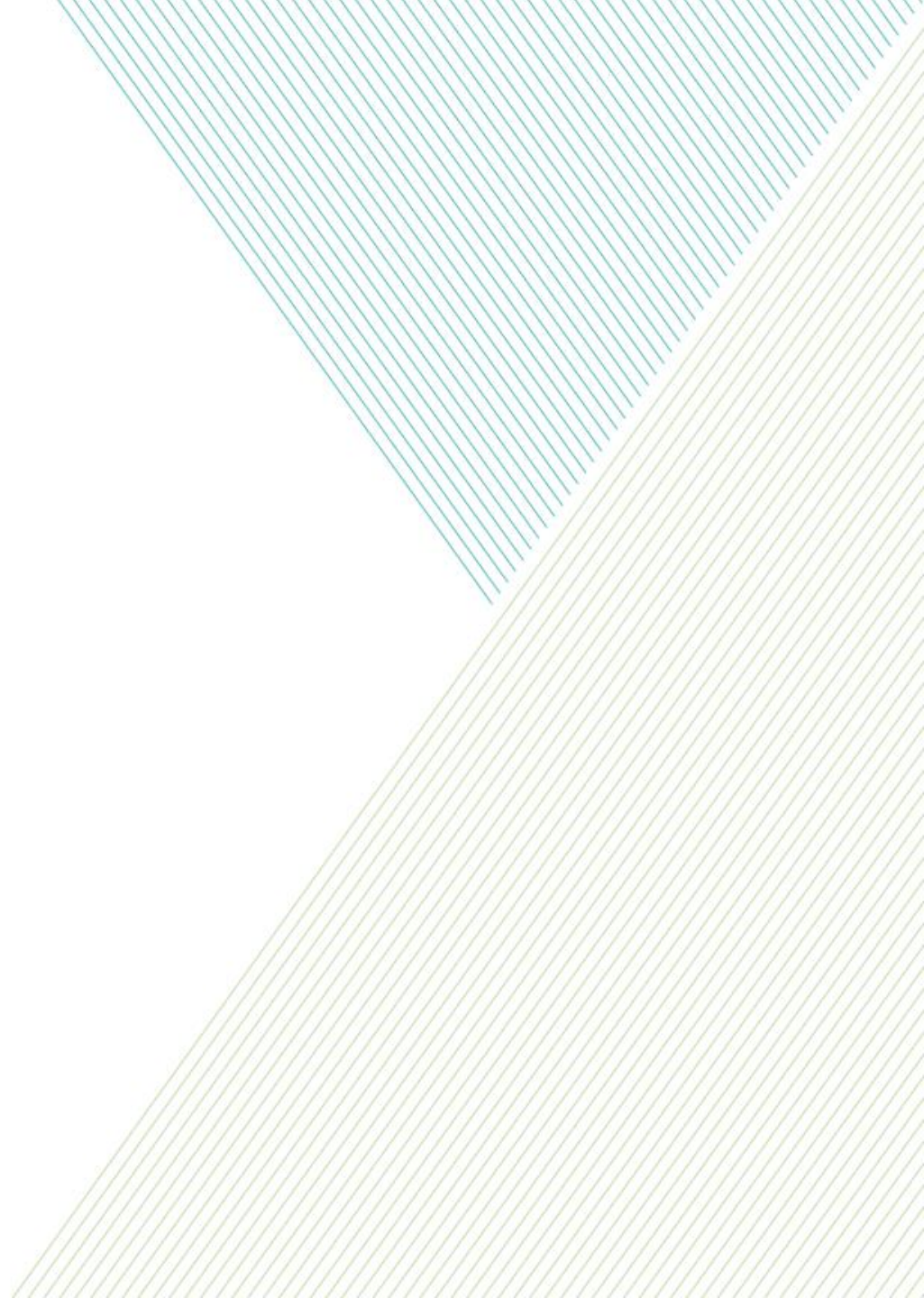
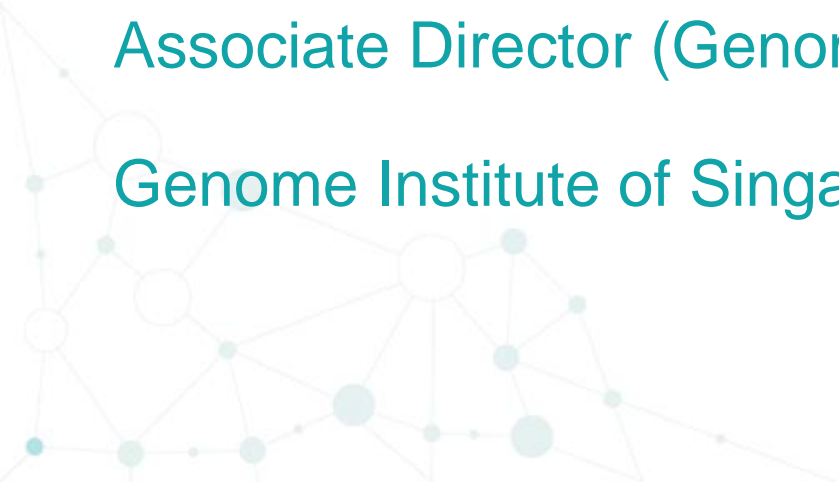


# Gene editing research and its bioethics

Chew Wei Leong

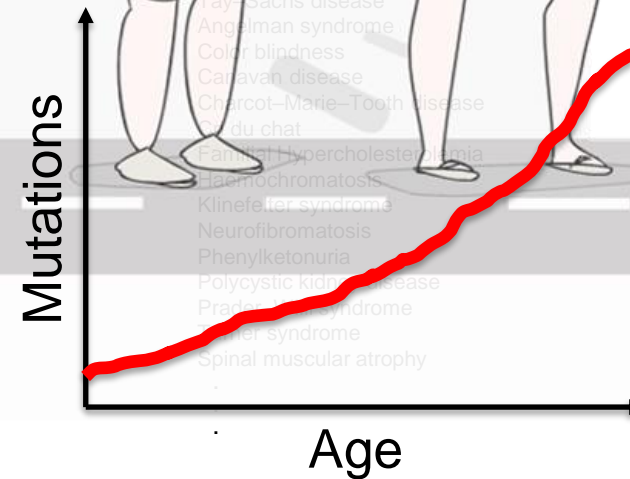
Senior Research Scientist  
Associate Director (Genome Design)

Genome Institute of Singapore



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

**Your DNA**

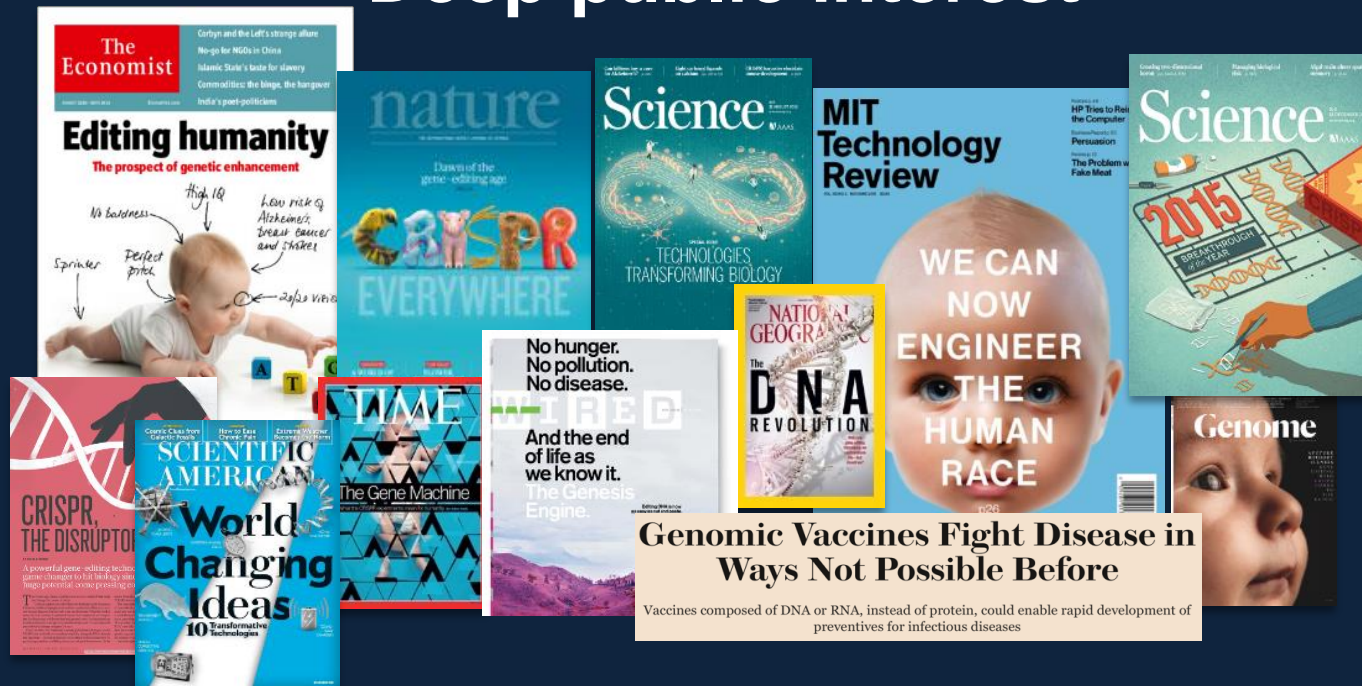




# Change DNA

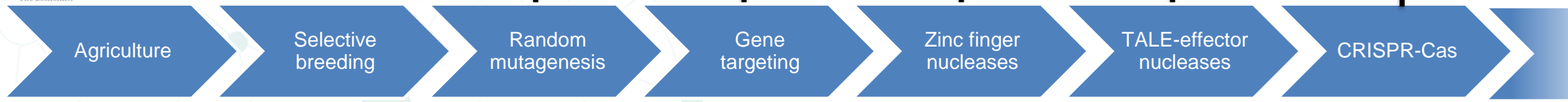
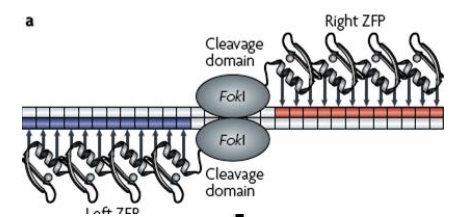
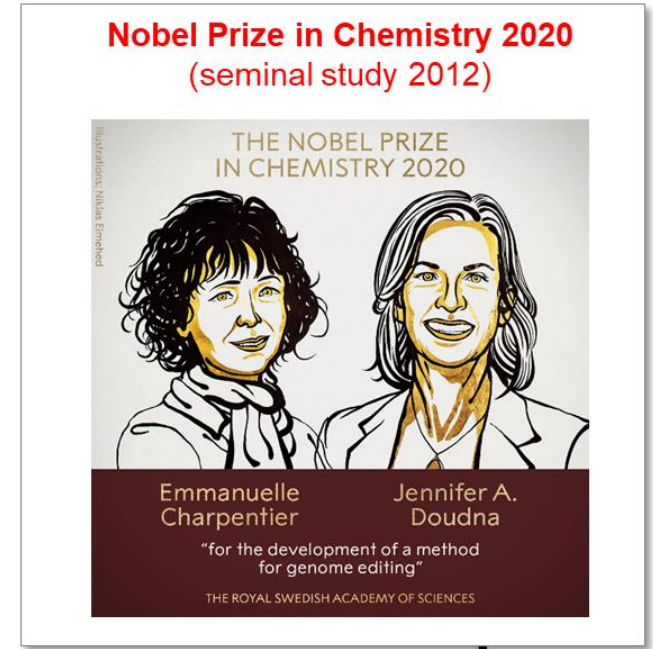
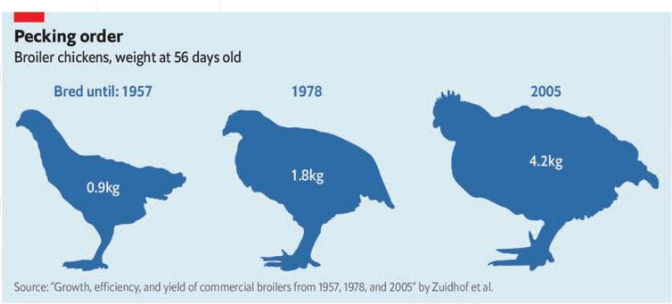
## The blueprint of life

### Deep public interest

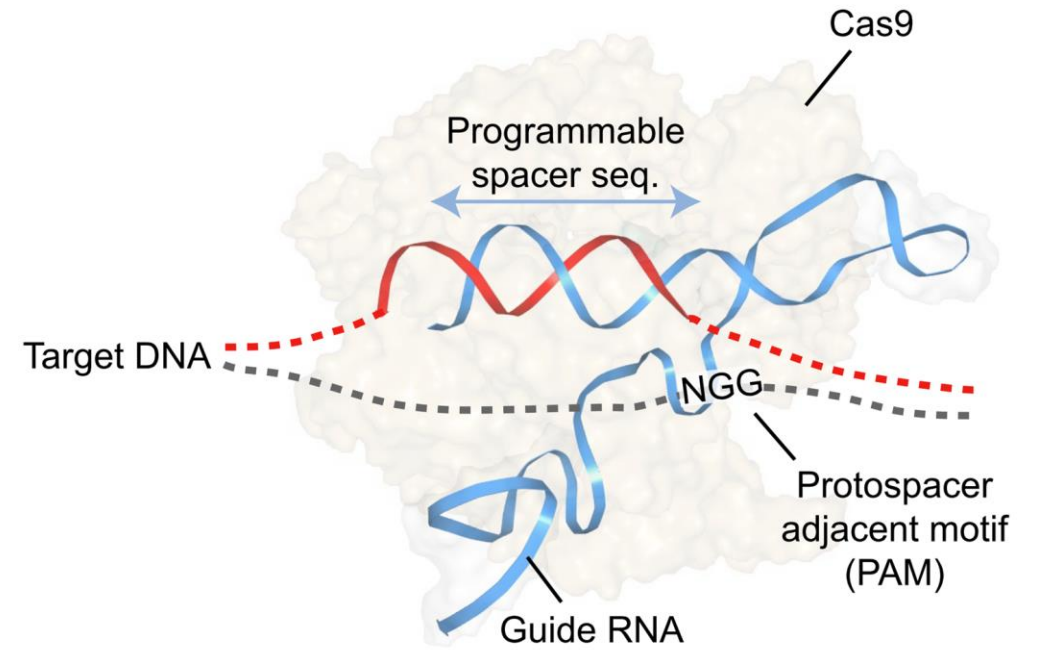
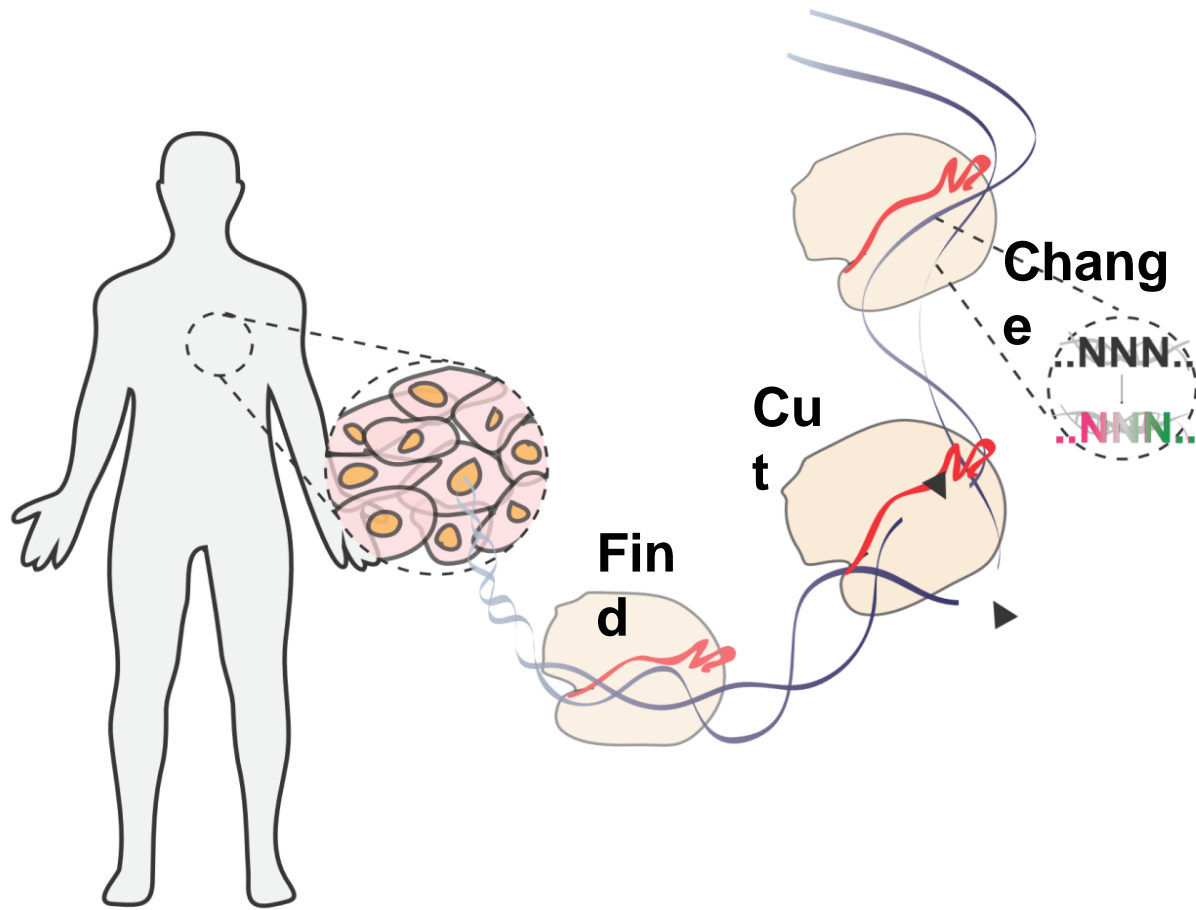




# A long history before the recent breakthroughs



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



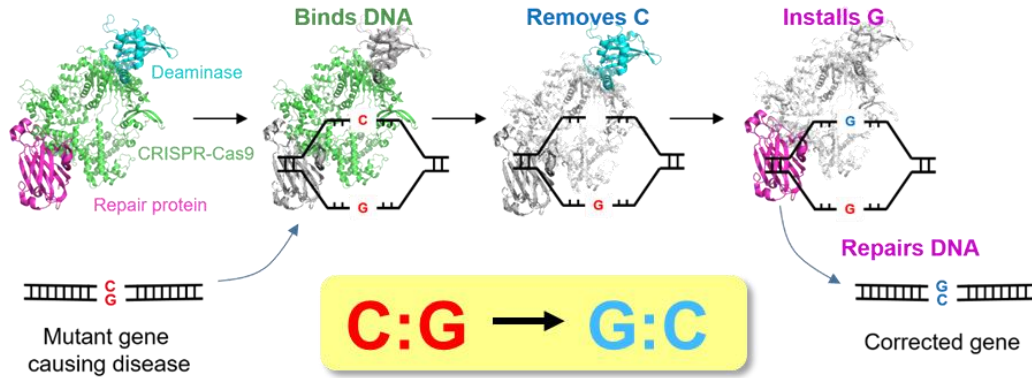
**Cas9 – targets DNA**

**Cas12 – targets DNA**

**Cas13 – targets RNA**

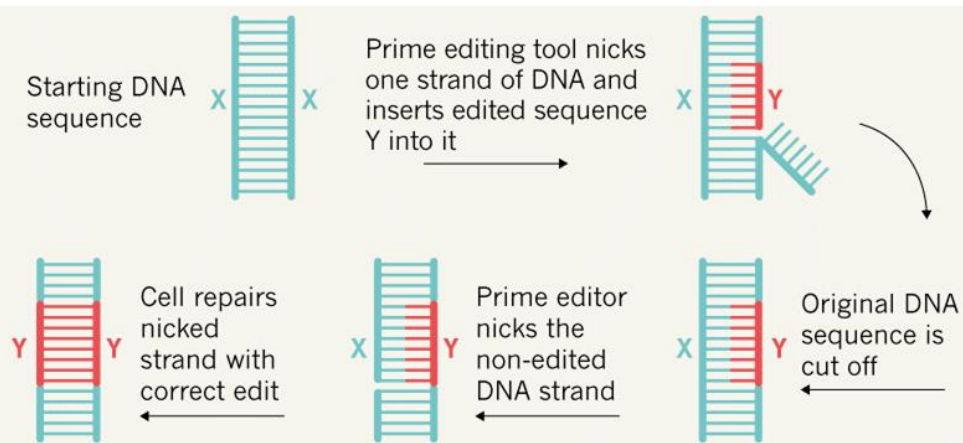
# CRISPR 2.0, 3.0,.... a right-click for biology

## Base editing



Chen et al., Nature Comms, 2021

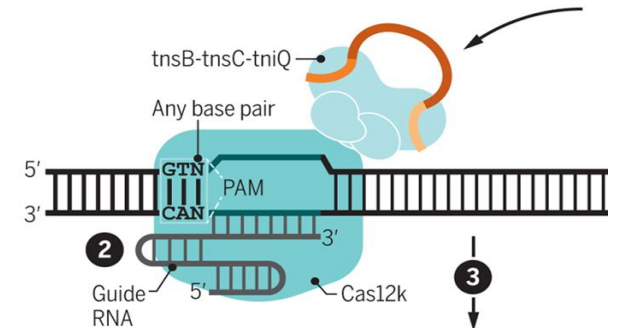
## Prime editing



©nature

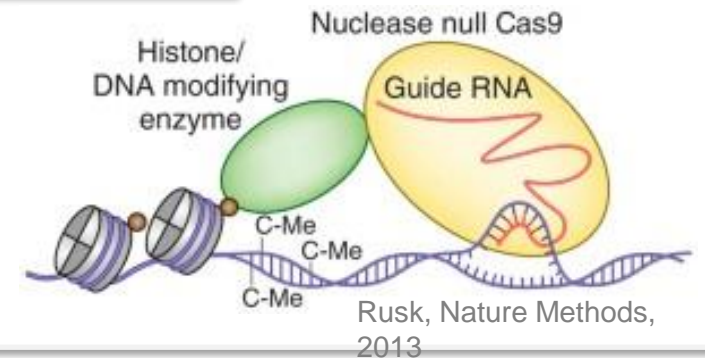
Anzalone et al., Nature, 2019

## Transposases



Klompe, Nature, 2019

## Epigenetic modifiers



Rusk, Nature Methods,  
2013

```

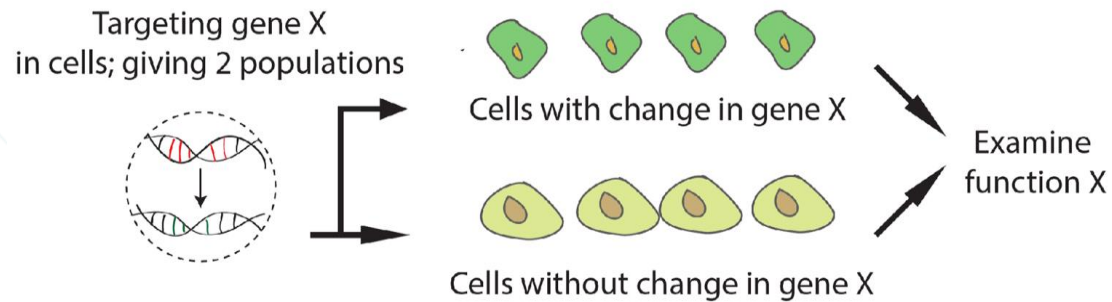
ATTCCTGGGGACTGTGGGGGGTGGTCAAAAGACCTCTATG
CCTGGGGCAGGGGGAGAACAGCCACCTCGTGACTGGG
GGGGCGGGACAGGGGGAGCCCTATAATTGGACAAGTCT
GGTGAAGGACGTCTTCCCCA
TCTAGAAAGAGCTGGGACCCCT
CTTGGGGAGAGGAGGAGCGGGC
GACGACCCGACCCGCTAGAAGC
CACGAGTTGTCACTATCATTTA
GGAGCCAGGGGCAGCGACACGC
ATAAATGGAACACGGCGCTTA
CTGGGACTGAGATGGAACCGG
TGGAATTTTCTATGGAGGCCG
ATGGGTTGGGGGCGGCTTGGTAAATGTGCTGGGATTAG
    
```



# Gene editing pervades biomedical research

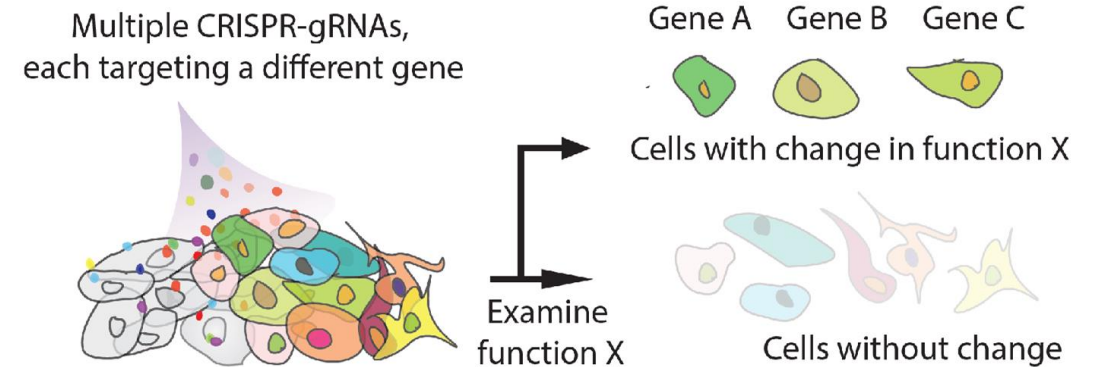
## Disease interrogation

How genes manifest function?



## Screens

Which genes responsible for function?



## Identified & deciphered many previously unknown genetics:

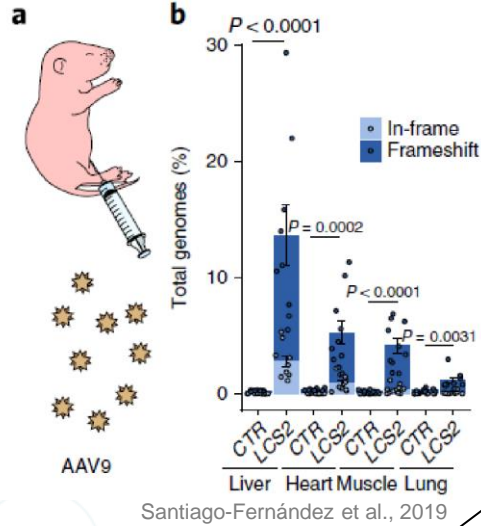
- Infections, genetic diseases, cancer vulnerabilities, fundamental biological insights...

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

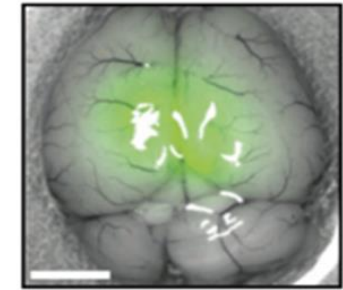
- Monogenic vs Polygenic
- Incomplete penetrance
- Incomplete knowledge

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

**Heart, aging (LMNA)**



**Brain (MECP2)**



Swiech et al., 2014

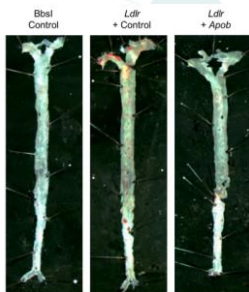
**Cataracts**



Wu et al., 2013

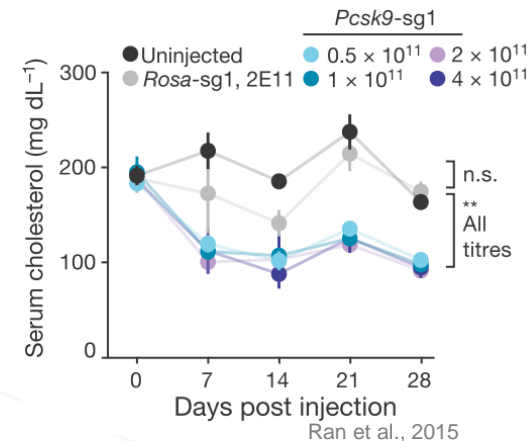
**Sickle cell anemia**  
**Hemophilia**  
**Thalassemia**  
**Cancer immunotherapy**

**Cardiovascular**

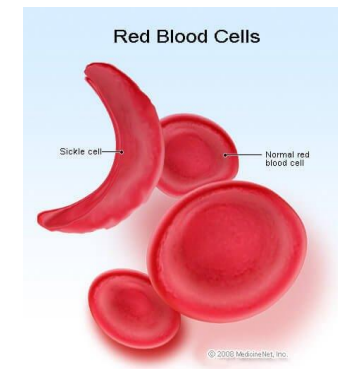
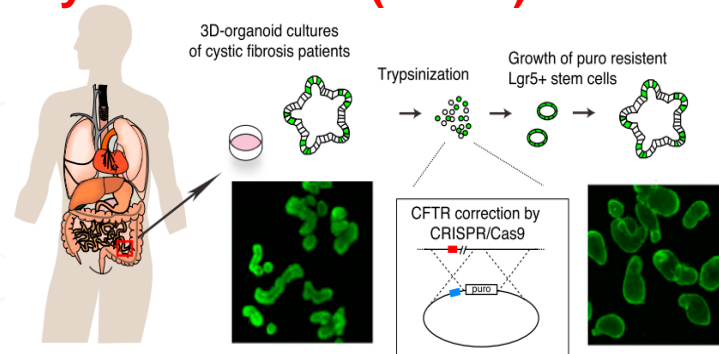


Jarrett et al., 2017

**Lowering cholesterol (PCSK9)**



**Cystic fibrosis (CFTR)**



<https://ghr.nlm.nih.gov/condition/beta-thalassemia>



# 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

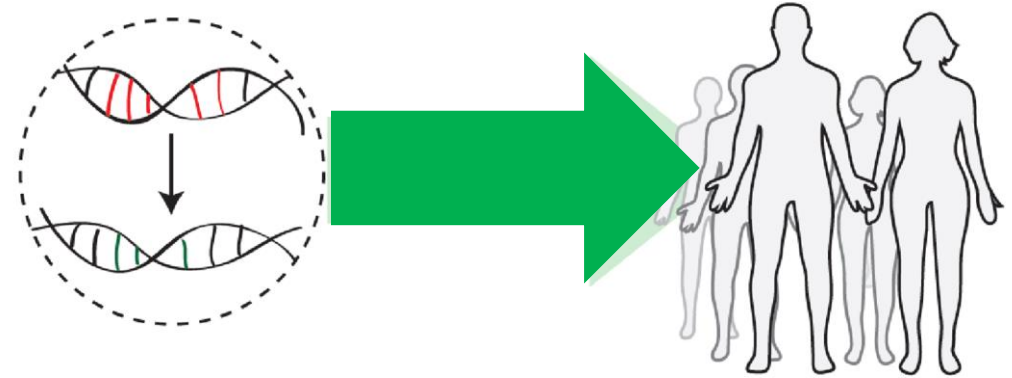
• May 10, 2021 5:00 AM ET



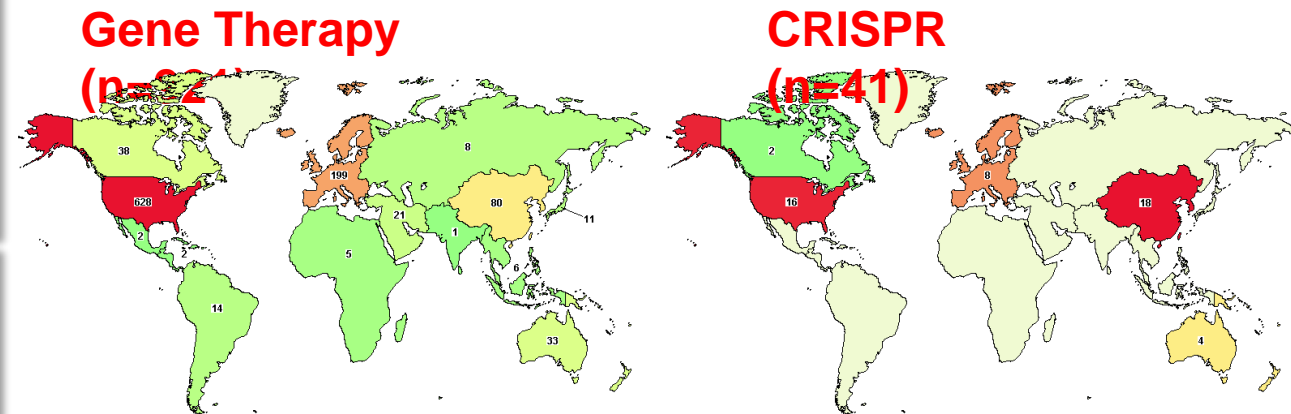
CRISPR gene editing proves safe in a clinical trial

• 10 FEBRUARY 2020

**nature**



**Clinical trials around the world**



# Gene editing across the whole body

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

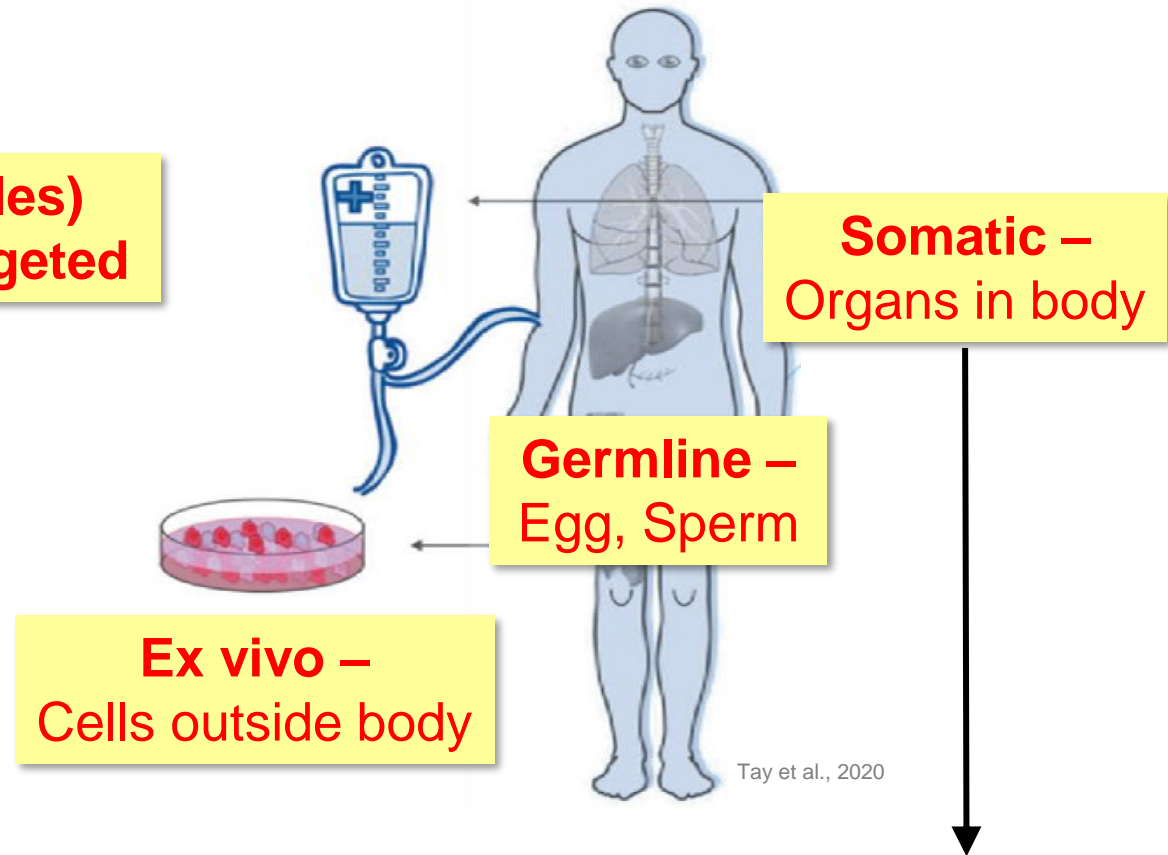
However,

## 1. Delivery is not 100% specific

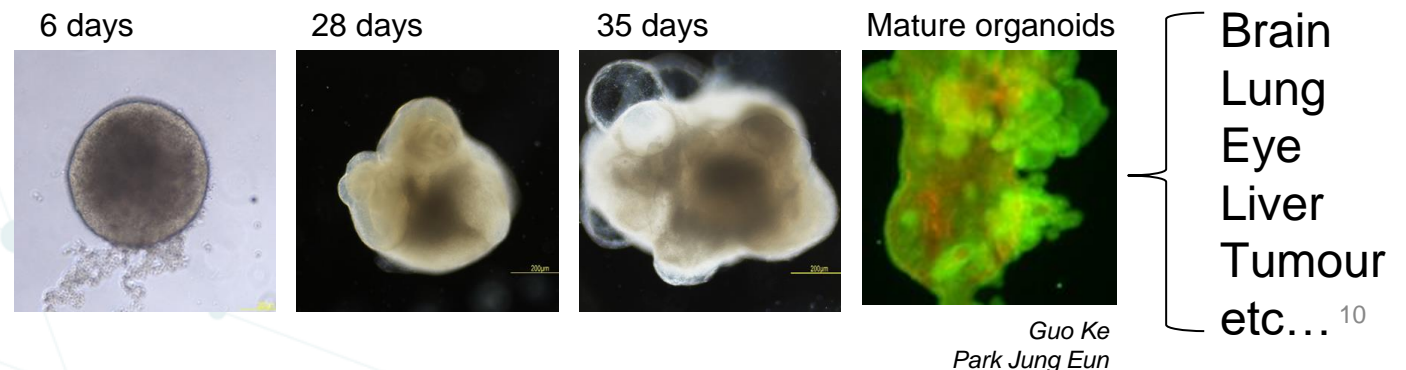
- Some cells might be unintentionally targeted – e.g. targeting liver but germline unintentionally targeted.

## 2. Delivery is not 100% efficient

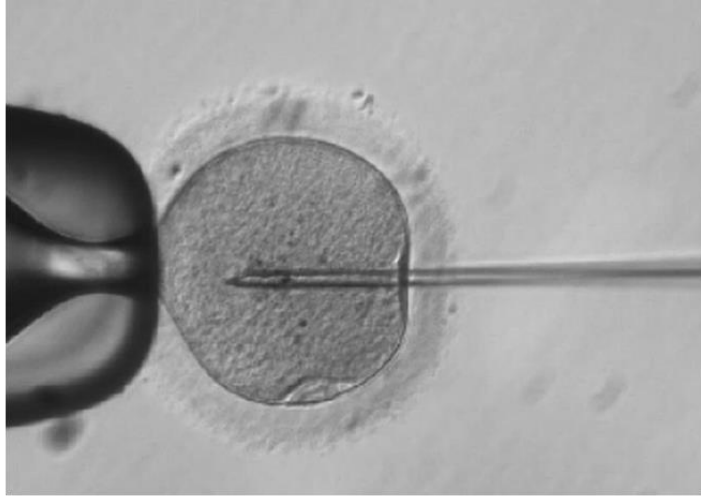
- Within each organ, some cells are treated successfully while some are not.
- In somatic organs: medically justifiable?
- In germline or embryos: mosaicism in the offspring where a mixture of cells with small genetic differences



## Modeling with mini human organs (organoids)



# Germline editing – very few studies

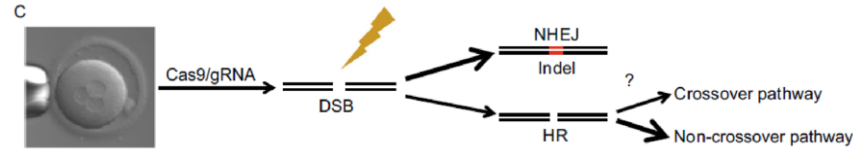


## Correction of a pathogenic gene mutation in human embryos

Hong Ma<sup>1\*</sup>, Nuria Marti-Gutierrez<sup>2\*</sup>, Sang-Wook Park<sup>2\*</sup>, Jun Wu<sup>3\*</sup>, Yeonmi Lee<sup>1</sup>, Keiichiro Suzuki<sup>1</sup>, Amy Koski<sup>1</sup>, Dongmei Ji<sup>1</sup>, Tomonari Hayama<sup>1</sup>, Riffat Ahmed<sup>1</sup>, Hayley Darby<sup>1</sup>, Crystal Van Dyken<sup>1</sup>, Ying Li<sup>1</sup>, Eunju Kang<sup>1</sup>, A.-Reum Park<sup>2</sup>, Daesik Kim<sup>1</sup>, Sang-Tae Kim<sup>2</sup>, Jianhui Gong<sup>4,6,7,8</sup>, Ying Gu<sup>5,6,7</sup>, Xun Xu<sup>5,6,7</sup>, David Battaglia<sup>1,9</sup>, Sacha A. Krieg<sup>9</sup>, David M. Lee<sup>9</sup>, Diana H. Wu<sup>9</sup>, Don P. Wolf<sup>1</sup>, Stephen B. Heitner<sup>10</sup>, Juan Carlos Izpisua Belmonte<sup>3</sup>, Paula Amato<sup>1,9</sup>, Jin-Soo Kim<sup>2,4</sup>, Sanjiv Kaul<sup>10</sup> & Shoukhrat Mitalipov<sup>1,10</sup> §

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 tripronuclear zygotes

Puping Liang, Yanwen Xu, Xiya Zhang, Chenhui Ding, Rui Huang, Zhen Zhang, Jie Lv, Xiaowei Xie, Yuxi Chen, Yujing Li, Ying Sun, Yaofu Bai, Zhou Songyang, Wenbin Ma, Canquan Zhou<sup>1,2</sup>, Junjiu Huang<sup>1,2</sup>

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 Kang<sup>1</sup> · Wenyin He<sup>1</sup> · Yuling Huang<sup>1</sup> · Qian Yu<sup>1</sup> · Yaoyong Chen<sup>1</sup> · Xingcheng Gao<sup>1</sup> · Xiaofang Sun<sup>1</sup> · Yong Fan<sup>1</sup>

- 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<sup>1-3</sup>. But t  
 they give scientists a good loo

- 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

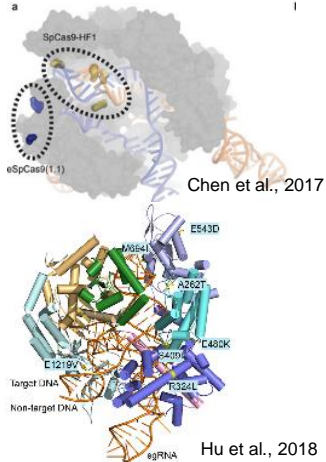
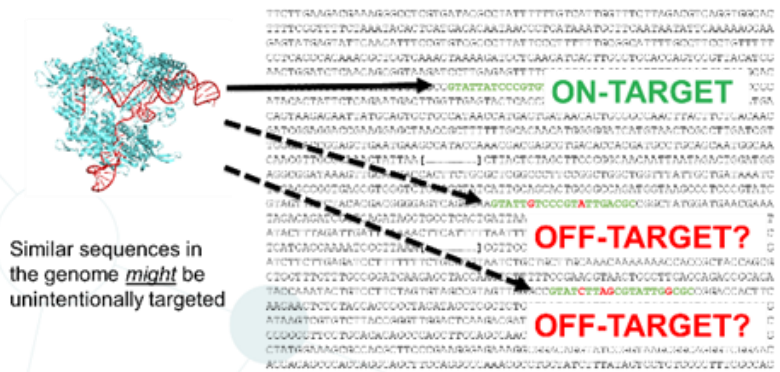


# Hard challenges are being worked on

## Safety

### Specificity

### Bioinformatics & Hyper-accurate CRISPR



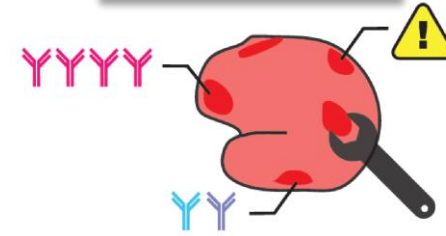
### Immune responses

Up to 96% of us might react adversely to **Engineered safer 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 1812 DECEMBER 7, 2017 VOL 377 NO 53

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

L.A. George, S.K. Sullivan, A. Giernasz, J.E.J. Rasko, B.J. Samelson-Jones, J. Ducore, A. Coker, L.M. Sullivan, S. Majumdar, J. Tittel, C.E. McGinnis, M.V. Ragni, A.Y. Luk, D. Hui, J.F. Wright, Y. Chen, Y. Liu, K. Wachtel, A. Winters, S. Tafelbacher, V.R. Arruda, J.C.M. van der Loo, D. Zervas, D. Tafelbaum, M.E. Carr, L.B. Couto, X.M. Anquaili, and K.A. High

**From 111 bleedings to 4**

The NEW ENGLAND JOURNAL of MEDICINE  
ESTABLISHED IN 1812 NOVEMBER 2, 2017 VOL 377 NO 52

Single-Dose Gene-Replacement Therapy for Spinal Muscular Atrophy

J.R. Mendell, S. Al-Zaidy, R. Shell, W.D. Arnold, L.R. Rodino-Knapic, T.W. Prior, L. Lowes, L. Alfano, K. Berry, K. Church, J.T. Kissel, S. Nagendran, J. L'Italien, D.M. Sproule, C. Wells, J.A. Cardenas, M.D. Hristova, A. Kasper, S. Comaras, L. Brown, S. Uthirak, C. Miravet, K. Meyer, K.D. Fouzi, A.H.M. Bughes, and B.R. Kasper

**From 0% survival to 100%**

MIT Technology Review The precision medicine issue

NOV 121 NOV 2017 \$9.99 USD \$10.99 CAD

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

**Should you?**

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

The AIs taking over from doctors Curing cancer with customized vaccines How to plan your digital afterlife

onasemnogene abeparvec-xioi ZOLGENSMA

Rx ONLY Suspension for intravenous infusion

2.0 x 10<sup>13</sup> 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**

5.5 mL



# 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...

The Straits Times, 1959



**SUPER BABIES  
-TO ORDER**

The Straits Times, 1980



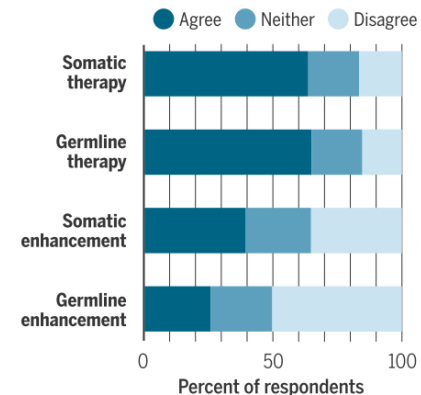
to making a quick buck? Few other developments etch so sharply the ethical, moral and social issues involved in the modern pursuit of scientific knowledge and its exploitation as does the fledging of the new industry of **BIOTECHNOLOGY and TELEMATICS. i.e. The Internet**

**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.**

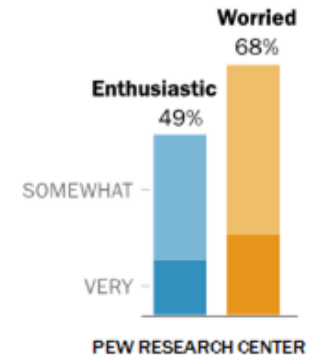
## Acceptance of gene editing

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



PEW RESEARCH CENTER

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



Centre for Biomedical Ethics  
Yong Loo Lin School of Medicine

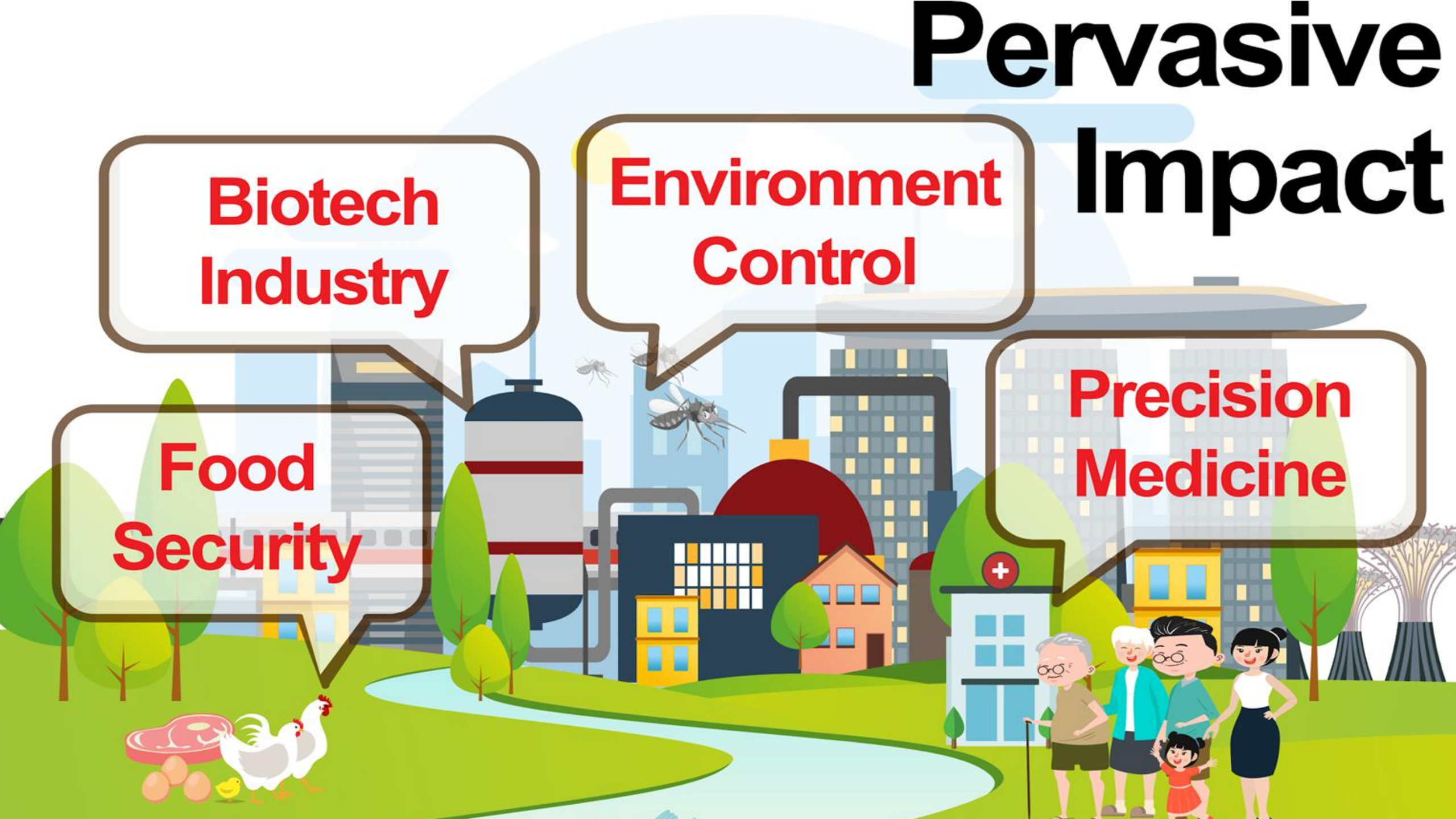
# Pervasive Impact

**Biotech  
Industry**

**Environment  
Control**

**Precision  
Medicine**

**Food  
Security**



**Thank you**

