Gene Editing: Scientific Basis and Clinical Potential

Kyriel Pineault
Research Associate, Imperial College London

Chaired by Uta Griesenbach
Professor of Molecular Medicine, Imperial College London
President of the British Society for Gene and Cell Therapy

Funded by

Coordinated by

Who are LAT and the ATTCs?

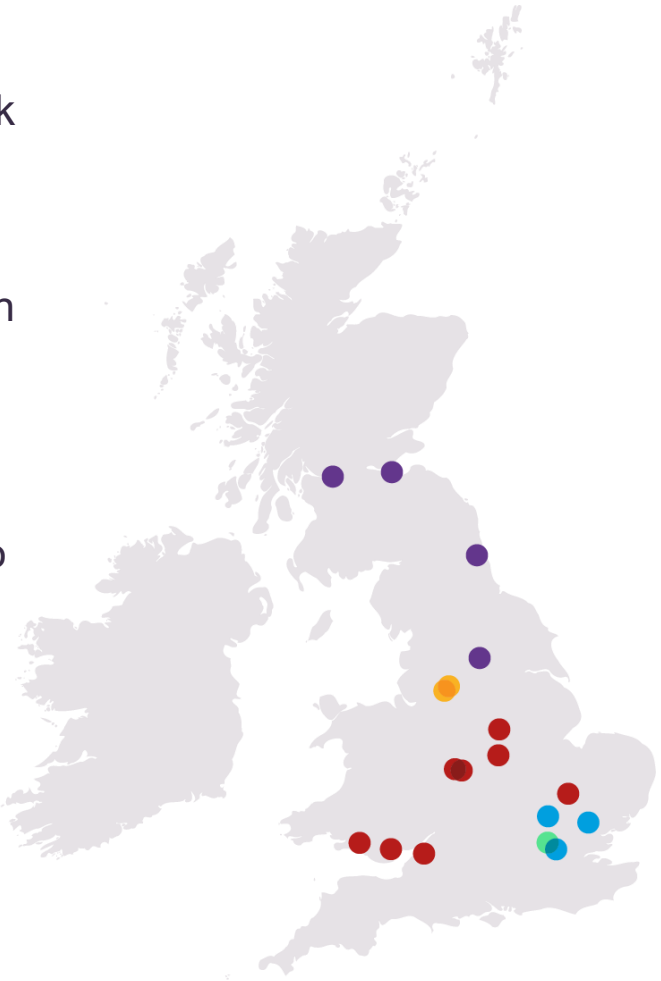
The ATTC (Advanced Therapy Treatment Centre) network is funded by Innovate UK and the Industrial Strategy Challenge Fund

London Advanced Therapies (LAT) is funded by Research England

The centres are working together, along with the Cell and Gene Therapy Catapult to specifically look at the training requirements for the current workforce and what needs to be put in place for them to be ready to deliver the treatments that are currently being developed.

This series of webinars is designed to help increase the awareness of advanced therapies and their impact in the clinic

Find out more at https://www.theattcnetwork.co.uk/



Coordinated by

Imperial College London

Gene Editing: Scientific Basis and Clinical Potential

Dr. Kyriel Pineault

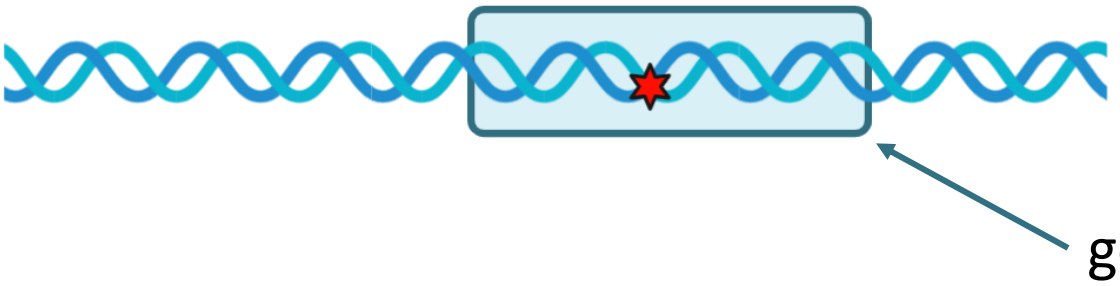
2021-02-09

Learning Objectives

- Introduction to gene editing systems
- Current clinical landscape
  - Diseases targets
  - Safety
  - Ethics
- Future perspective

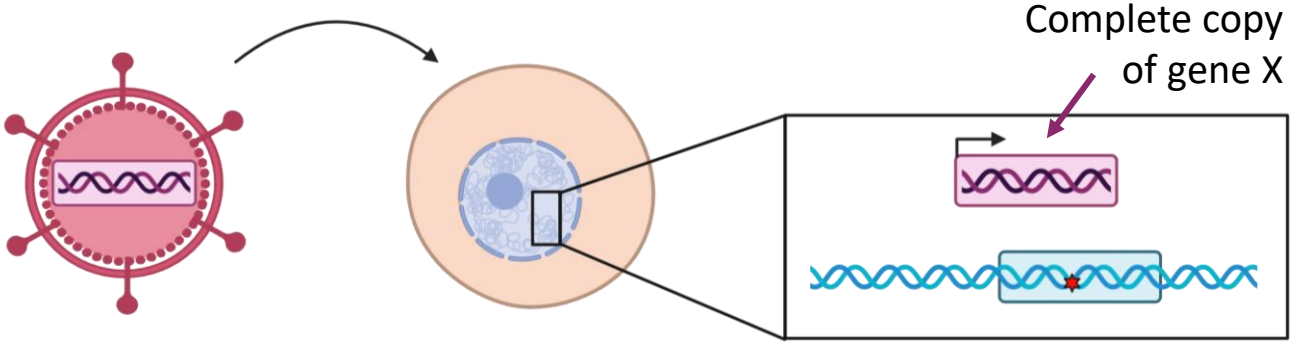
Gene Editing vs. Gene Therapy

Disease X



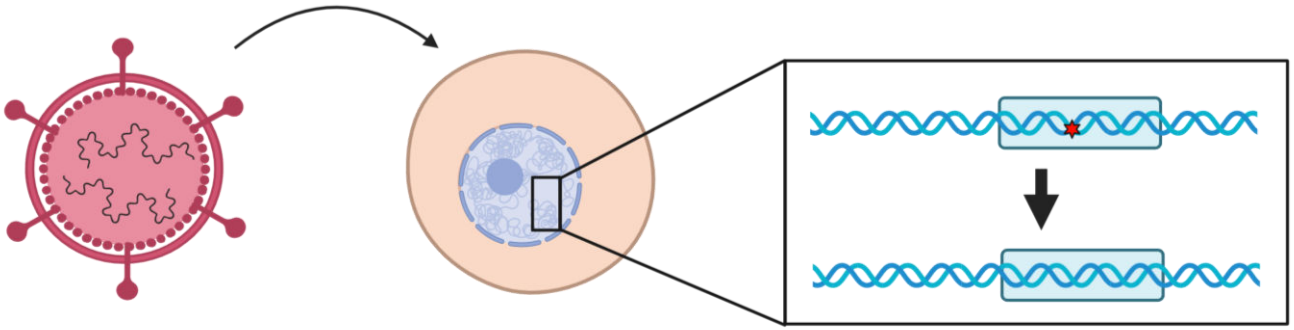
Gene Editing vs. Gene Therapy

Gene Therapy



Introduction of genetic material to compensate for an abnormal gene or to produce a beneficial protein

Gene Editing



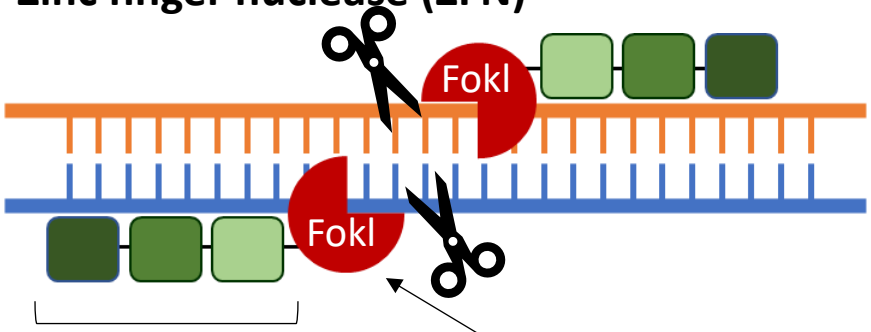
Targeted manipulation of genomic material to add, remove, or alter the sequence

Gene editing strategy design

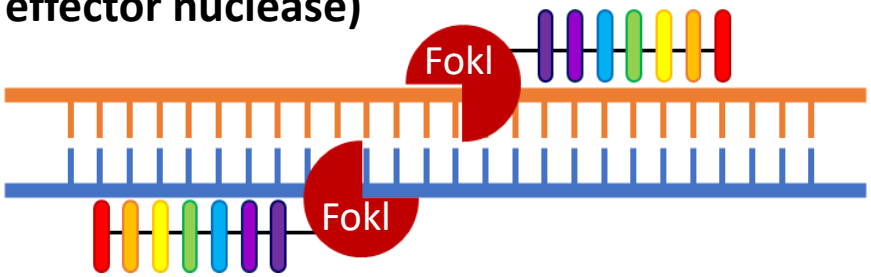
- Disease targets
  - ‘Single fix’ – treatment requires a one modification
  - Clear cell/organ target
- Gene editing system

Gene Editing Systems

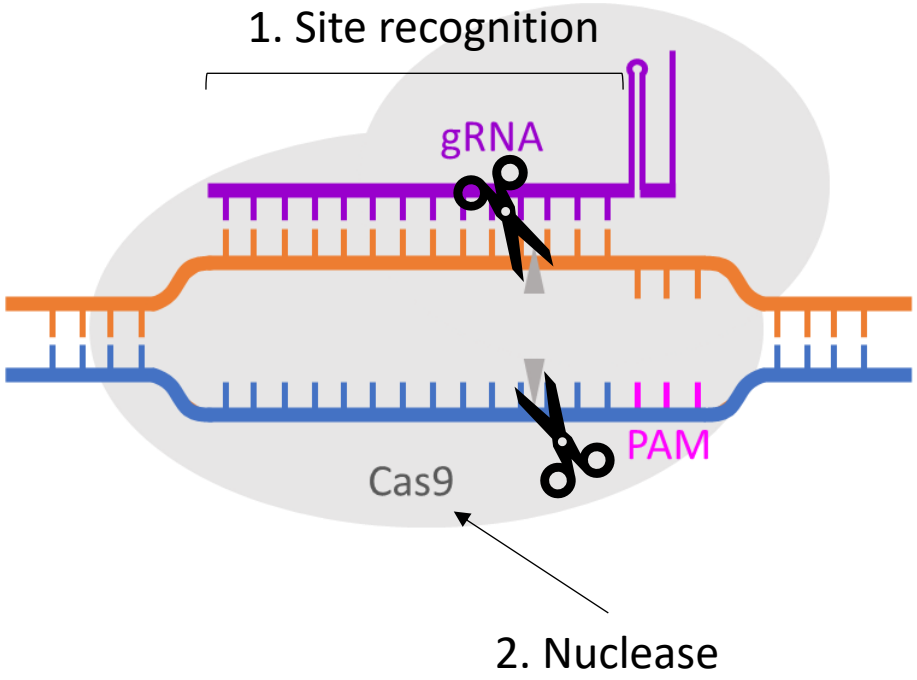
Zinc finger nuclease (ZFN)



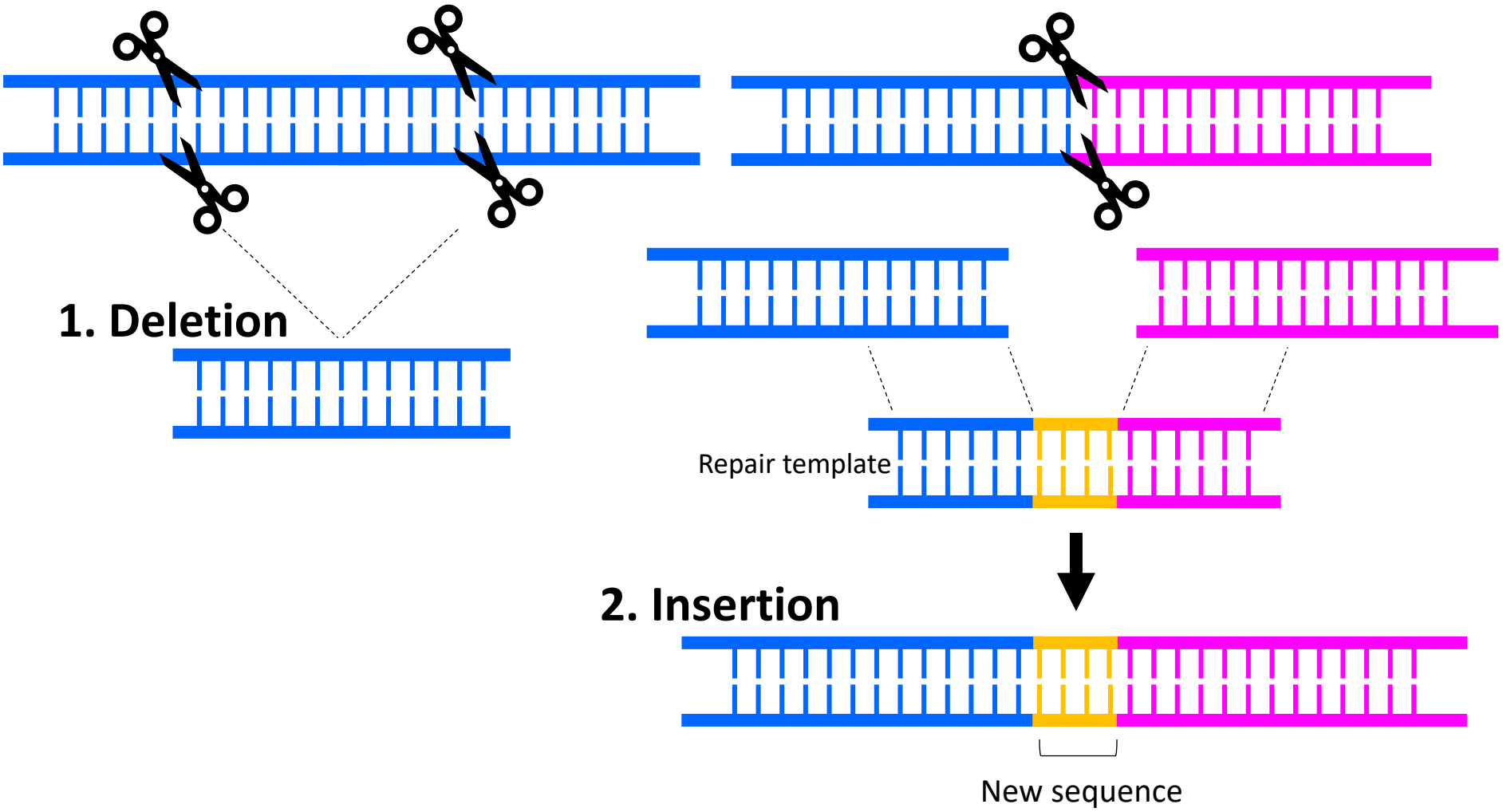
TALENs (Transcription activator-like effector nuclease)



CRISPR/Cas



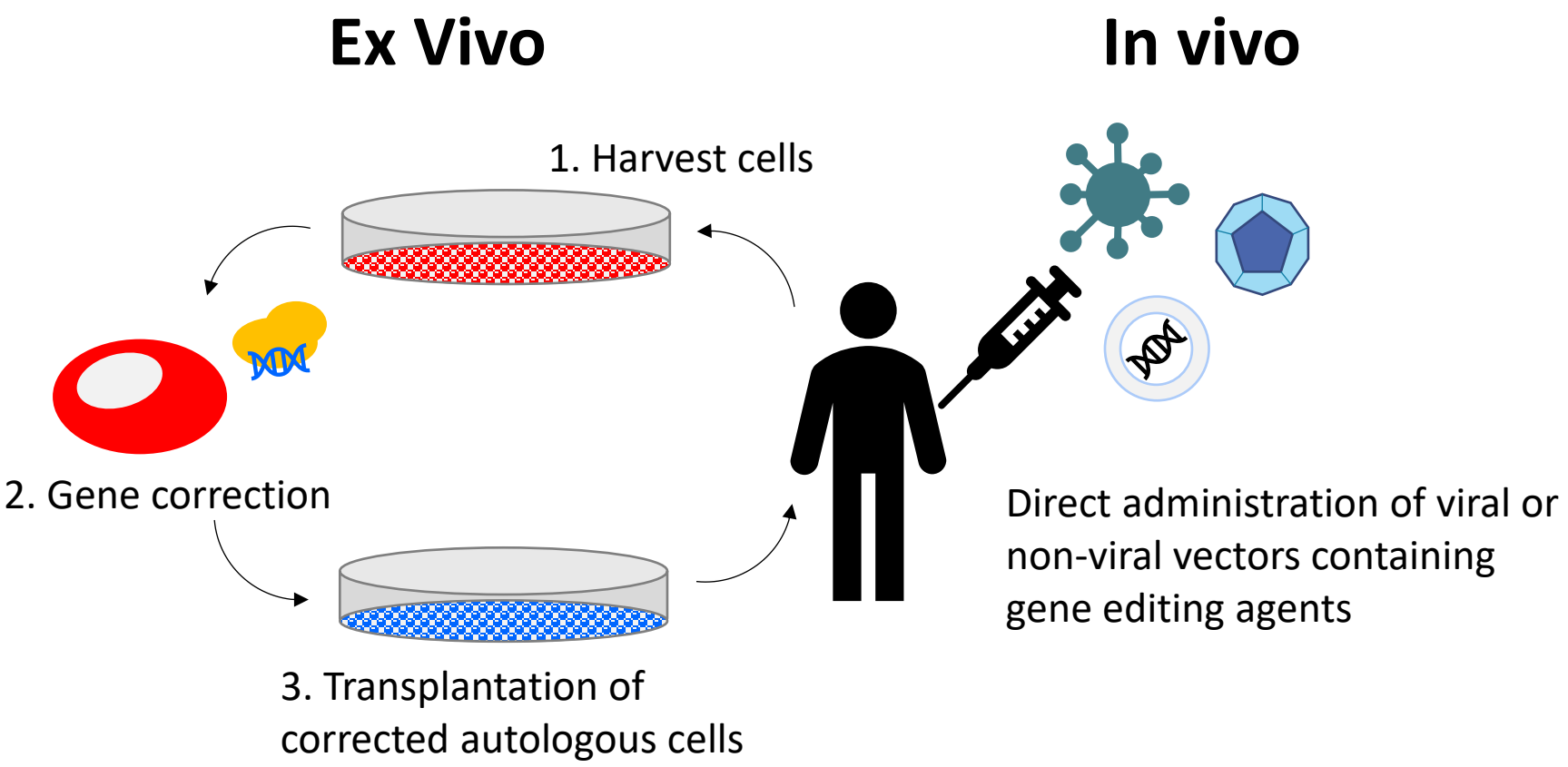
DNA Repair and Gene editing



Gene editing strategy design

- Disease targets
  - ‘Single fix’ – treatment requires a one modification
  - Clear cell/organ target
- Gene editing system
- Delivery system
  - Viral (Adenovirus, AAV, and Lentivirus)
  - Non-viral (nano particles, lipid particles, electroporation, etc.)

Delivery of Gene Editing Agents



Delivery Strategy

Advantages

Ex Vivo

- Precise control over edited cell type
- Quality control

In Vivo

- Broader potential cell targets
- Cell culture not required

Disadvantages

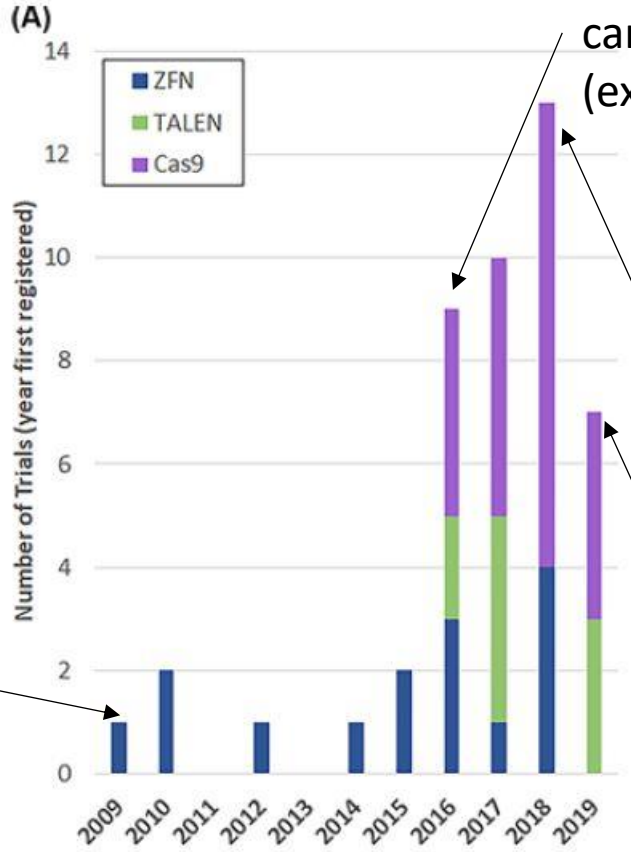
Ex Vivo

- Limited cell type options
- Culturing stem cells can change cell properties

In Vivo

- Low efficiency
- No quality control

Current Clinical Landscape



T cells for cancer therapy (ex vivo)

Haemoglobinopathies (ex vivo)

Congenital blindness (in vivo)

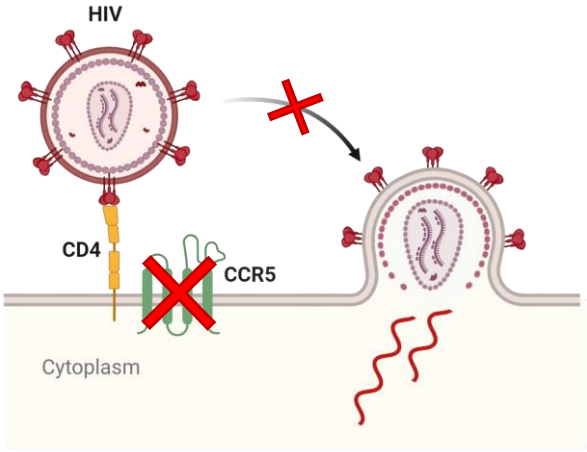
HIV-1 infection (ex vivo)

Kirakawa, *Bioscience Reports* (2020)

Case Study 1: HIV-1 infection treatment (ex vivo)

The ‘Berlin Patient’ (Timothy Ray Brown)

- HIV positive individual diagnosed with acute myeloid leukaemia
- 2007 he received a hematopoietic stem cell transplant from a donor with a homozygous CCR5 mutation

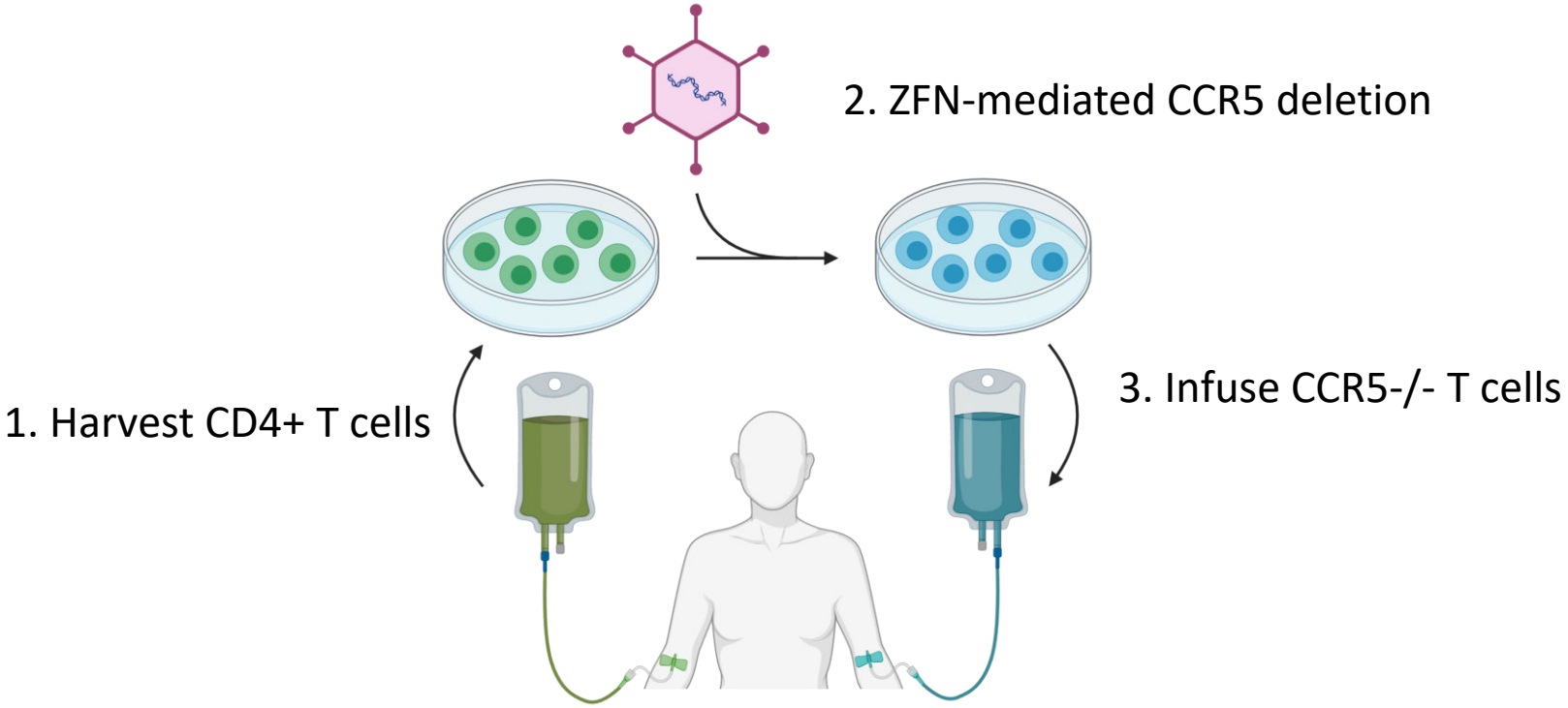


- Following transplant, patient was functionally disease free

Autologous HIV-infection resistant T cells

First gene editing study initiated in 2009

University of Philadelphia and Sangamo Biosciences



Future directions in HIV therapy

Phase 1

Primary objective: Safety	Yes, minimal adverse events
Engraftment	Yes, low levels
Viral load	No clear effect
Genotoxicity	None reported

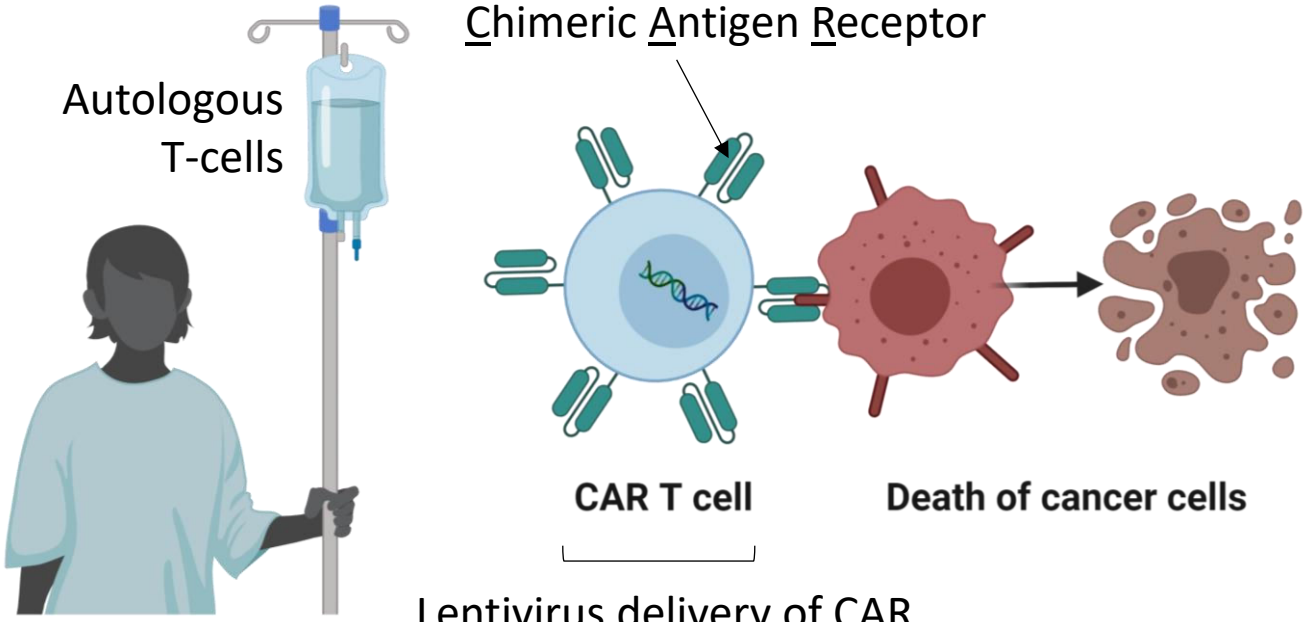
Tebas, P. *et al. N Engl J Med* (2014)

Phase 2

Objectives	Tolerability Efficacy
Strategy	T cells HSC (stem cells)
Genotoxicity	Long-term follow-up

Case Study 2: allogenic CAR T-cells (ex vivo)

Building on the success of the recently approved gene therapy, CAR T-cell products Kymriah (Novartis) and Yescarta (Kite Pharma)



Lentivirus delivery of CAR
(gene therapy/cell therapy)

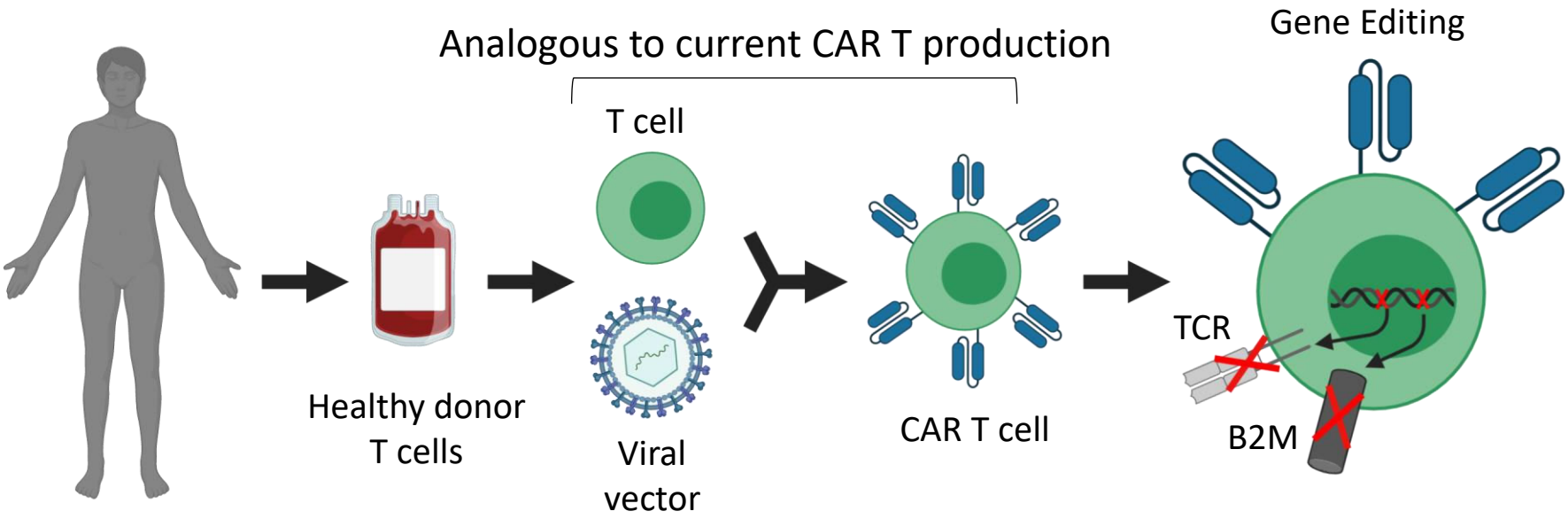
Autologous

↓

Allogenic
(off-the-shelf)

- Standard manufacture
- Available product
- Reduced cost

Universal (off-the-shelf) allogenic CAR T-cells



1. Deletion of T cell receptor (TCR)
   - Prevention of GvHD

2. Disrupt major histocompatibility complex (MHC)
   - Prevent transplant rejection

Universal CD19 CAR T cells for B cell leukaemia

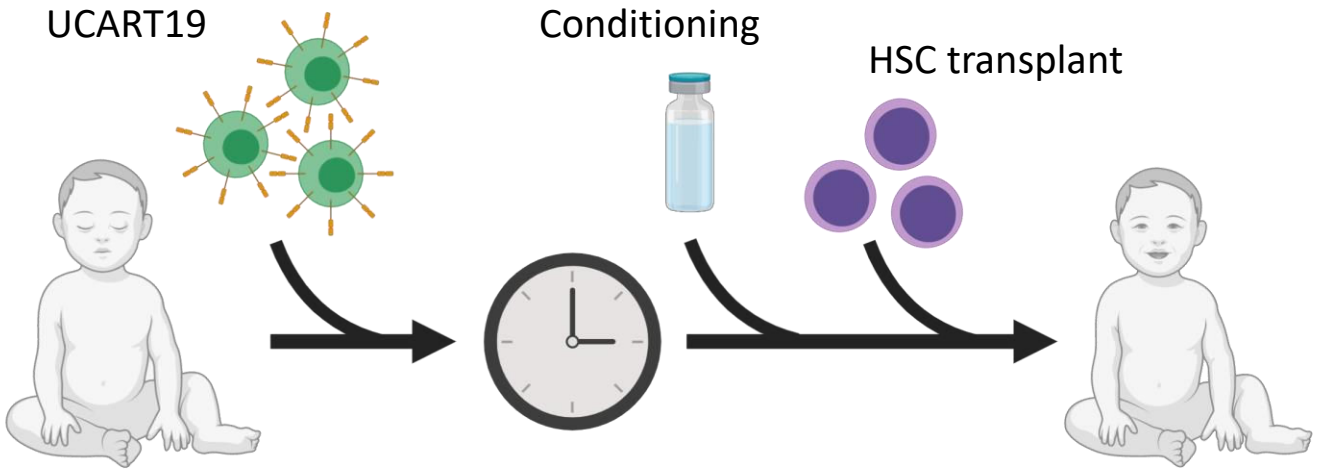
2015 Study (compassionate use)

Great Ormond Street Hospital, UCL, Cellectis

- 2 infants with relapsed refractory B-ALL
- Single dose of UCART19

Results

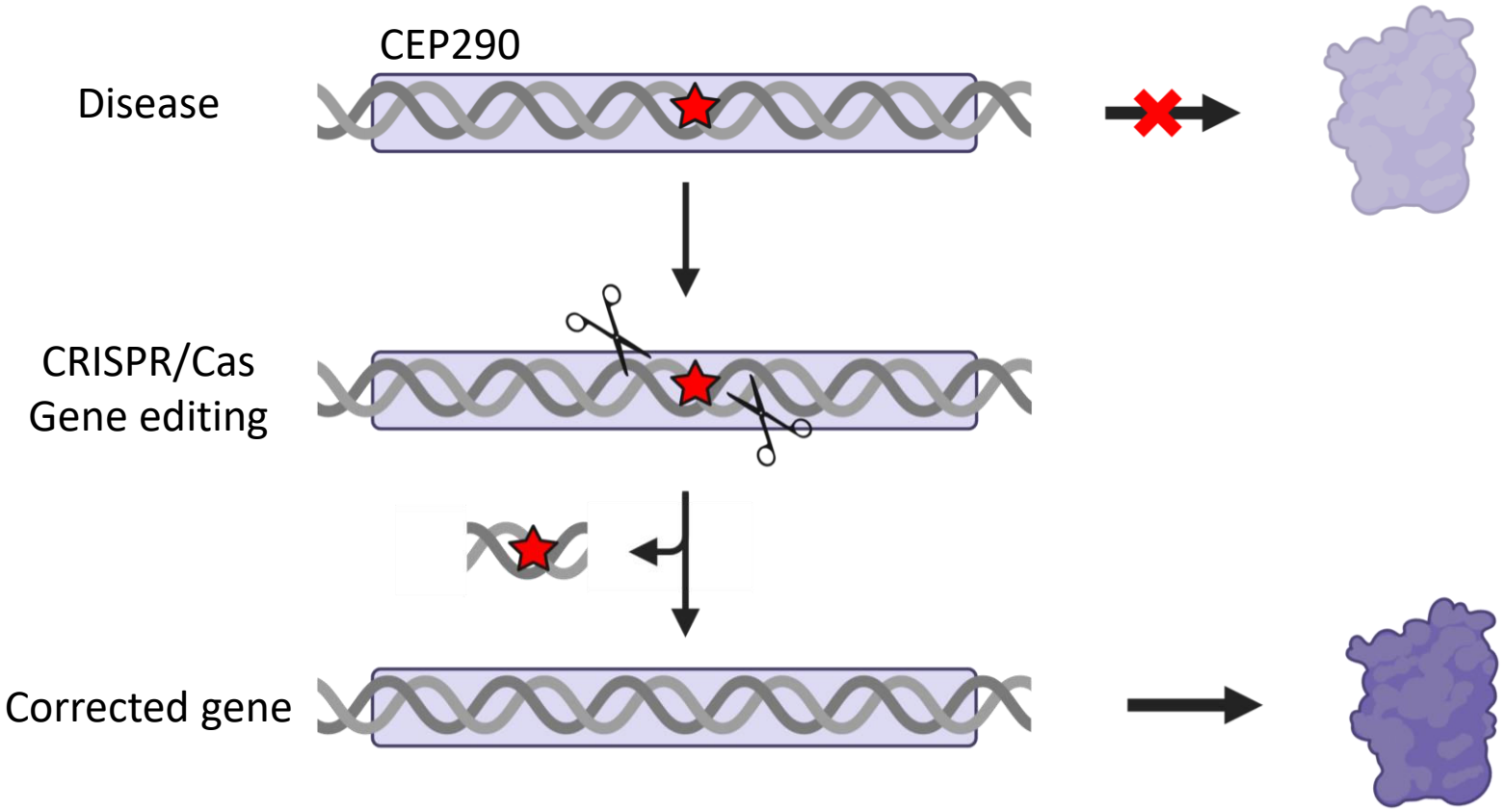
- Minor GvHD reaction
- UCART19 cells persist
- Disease remission



Qasim, W. *et al. Sci Transl Med* (2017)

Case Study 3: Congenital blindness (in vivo)

Leber congenital amaurosis 10

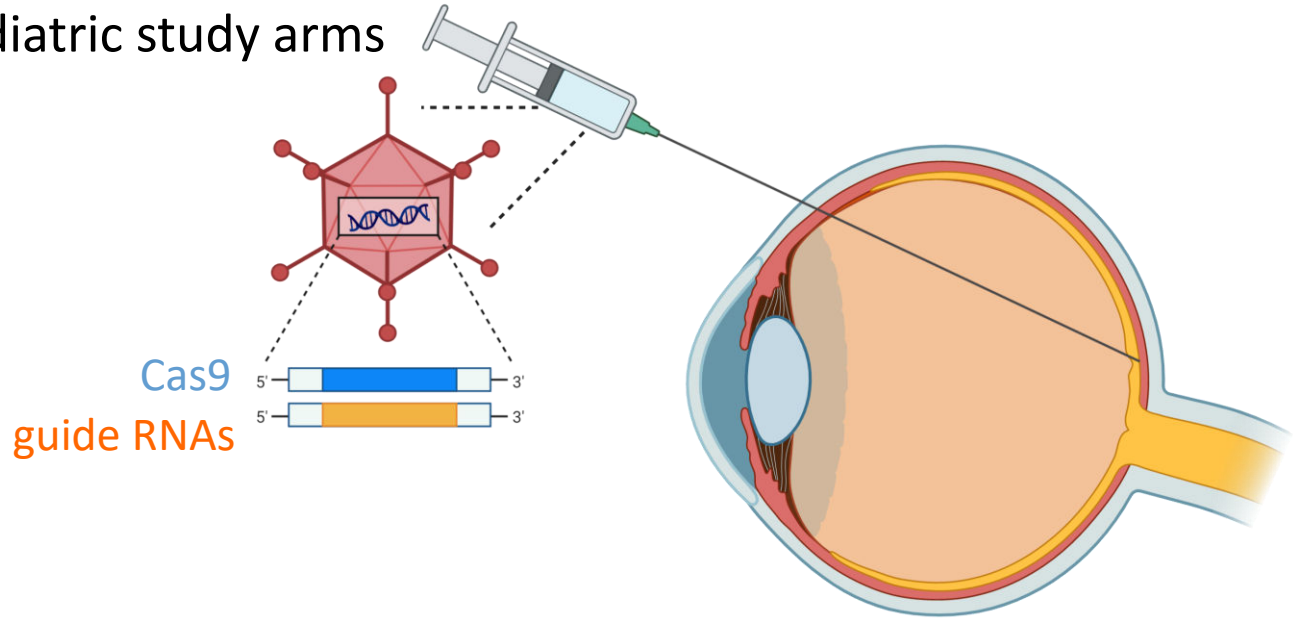


First in vivo gene editing with CRISPR/Cas

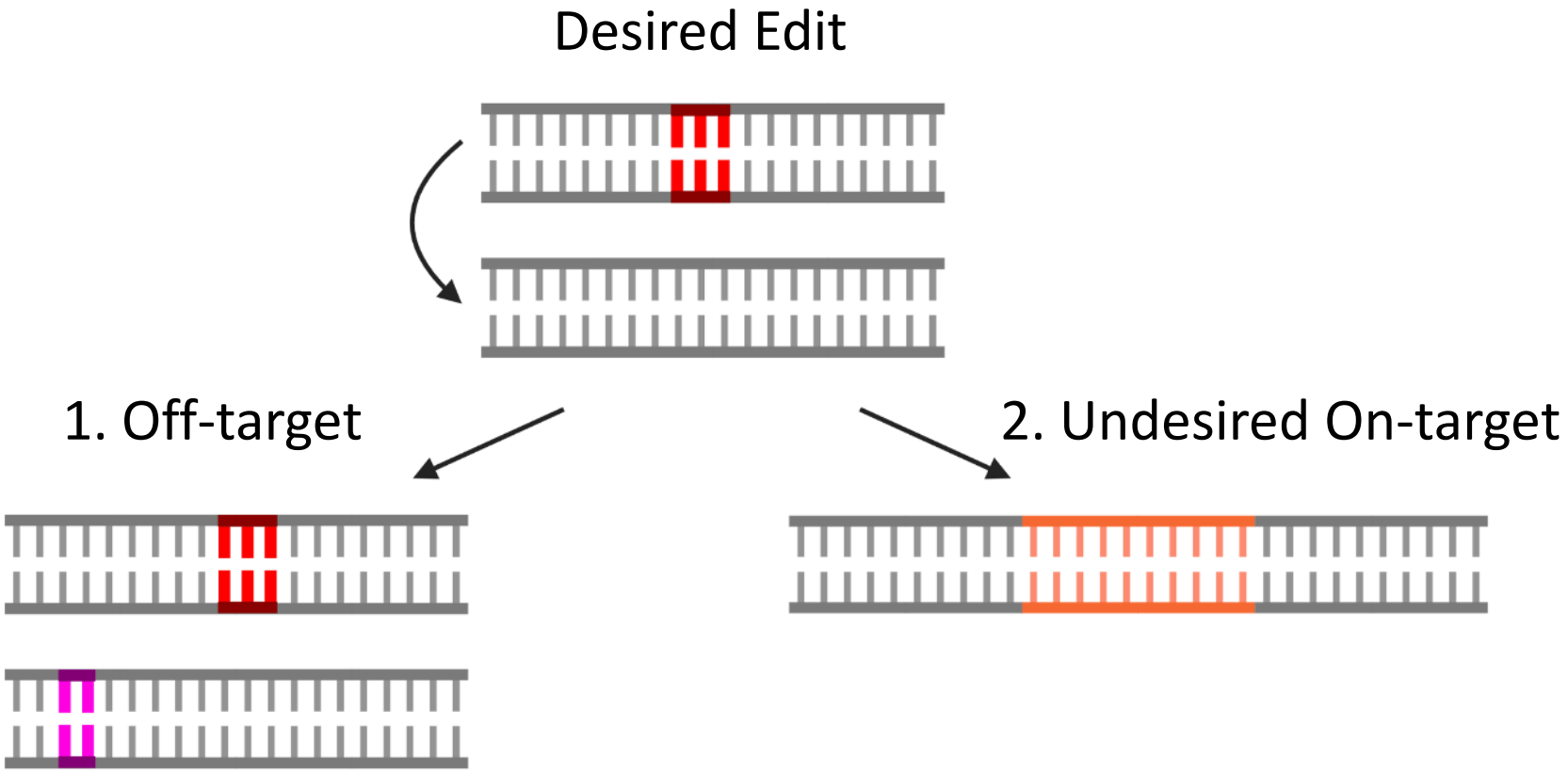
In vivo, AAV delivery of Cas9 + 2 gRNAs

Editas Medicine

- Phase 1 trial, 2019
  - Study planned to last through 2024
  - Adult and paediatric study arms



Safety: Edits Gone Wrong



Chinese Scientist Claims to Use Crispr to Make First Genetically Edited Babies

The researcher, He Jiankui, offered no evidence or data to back up his assertions. If true, some fear the feat could open the door to "designer babies."

NEWS · 28 NOVEMBER 2018 · CORRECTION 30 NOVEMBER 2018

CRISPR-baby scientist fails to satisfy critics

He Jiankui gives talk about controversial claim of genome editing babies, but ethical questions remain.

NEWS · 26 NOVEMBER 2018

Genome-edited baby claim provokes international outcry

The startling announcement by a Chinese scientist represents a controversial leap in the use of genome editing.

NEWS · 03 SEPTEMBER 2020

‘CRISPR babies’ are still too risky, says influential panel

The safety and efficacy of genome editing in human embryos hasn’t been proven, researchers warn.

NEWS GENETICS

Strict new guidelines lay out a path to heritable human gene editing

But scientists say making changes in DNA that can be passed on isn’t yet safe and effective

EDITORIAL · 13 MARCH 2019

Germline gene-editing research needs rules

In the wake of CRISPR babies, there is an urgent need to better regulate and debate whether, when and how related research should be done.

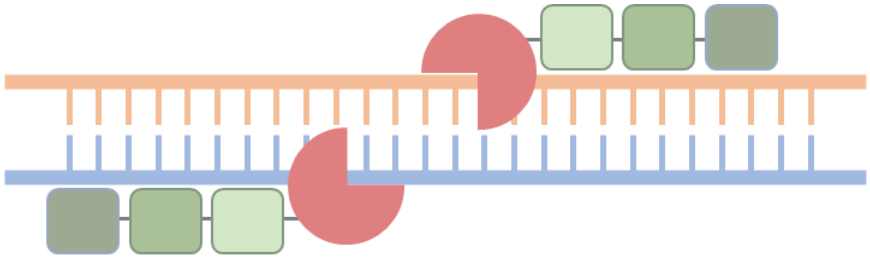
Advances in 5-10 years

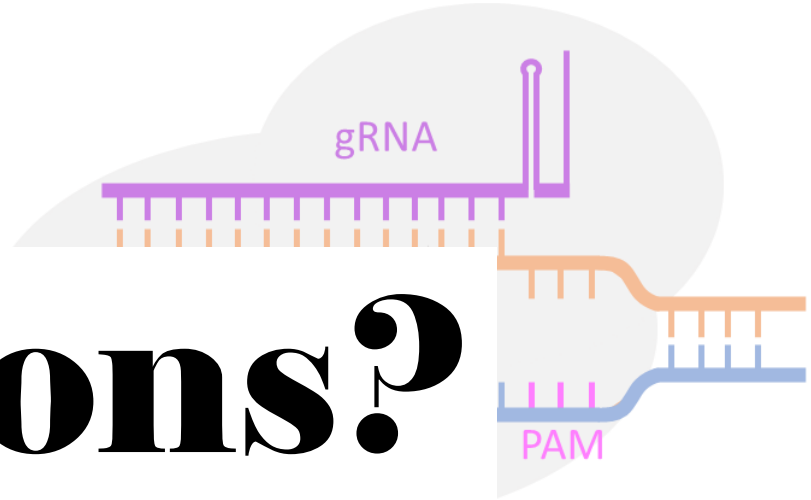
Advancing the Field

- Long-term safety data from Phase I trials
- Clinical testing of next generation editing tools

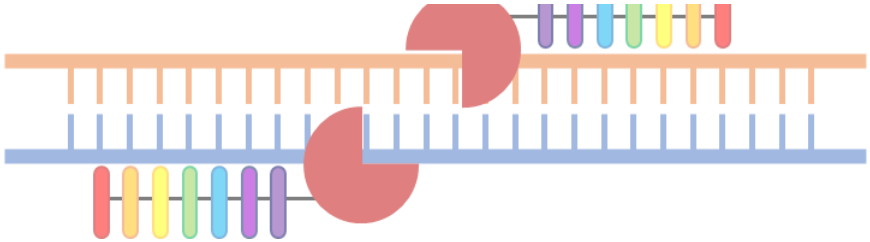
Moving to the Clinic

- T-cells for solid tumours
- Haemoglobinopathies: β-thalassemia and sickle cell disease
- Metabolic disorders: in vivo liver gene editing





Questions?



Images for this presentation were created with BioRender.com

Q&A

Advanced Therapy Treatment Centres

Please add any question you have into the Q&A box

Please fill in feedback survey, your input is really valuable to us

Next webinar,

Advanced therapy landscape

4pm 23rd February, Matthew Durdy (CEO, Cell and Gene Therapy Catapult)