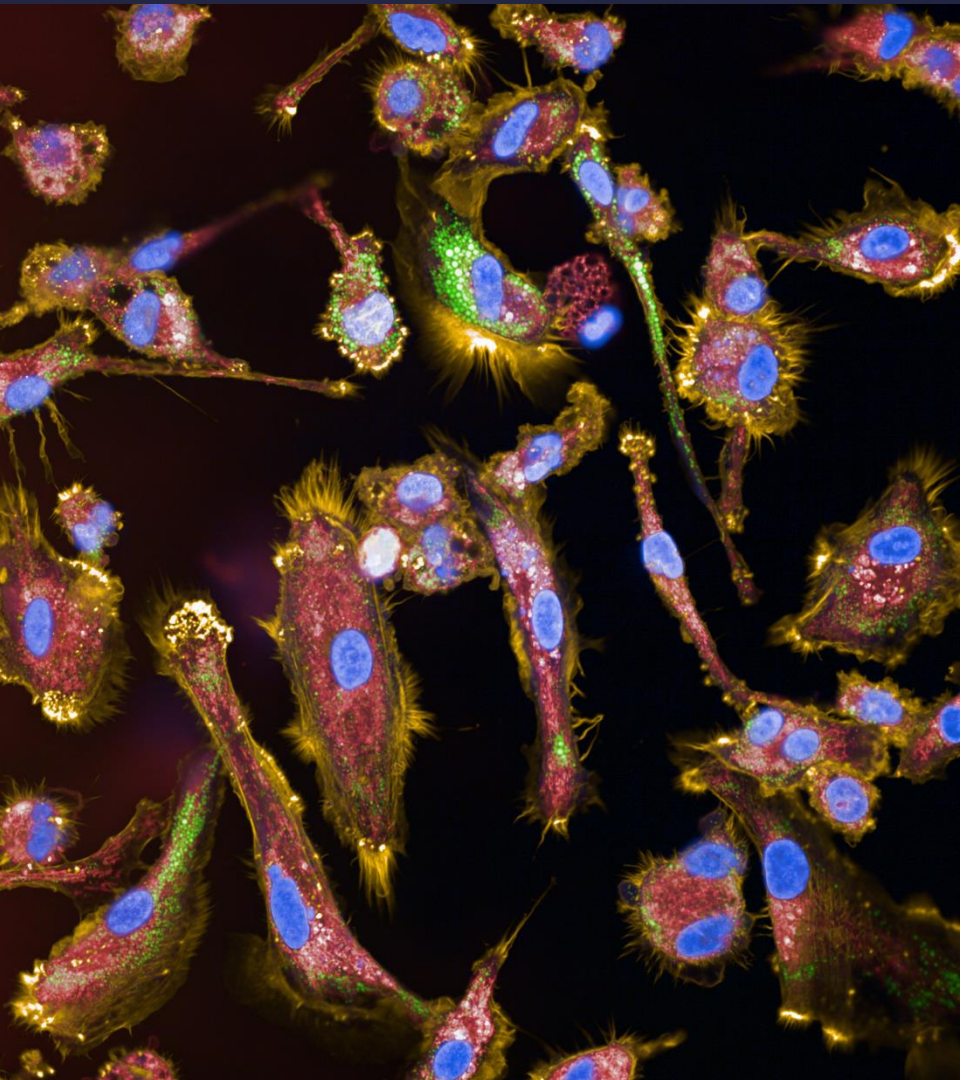
At The Cutting Edge: Applications of CRISPR

Dr Sam Washer
Postdoctoral Research Fellow
Gene Editing Research and Development

wellcome sanger institute



1. CRISPR
2. Editing Cell Lines
3. Research
4. Treating Human Disease
5. Next Gen CRISPR

wellcome sanger institute

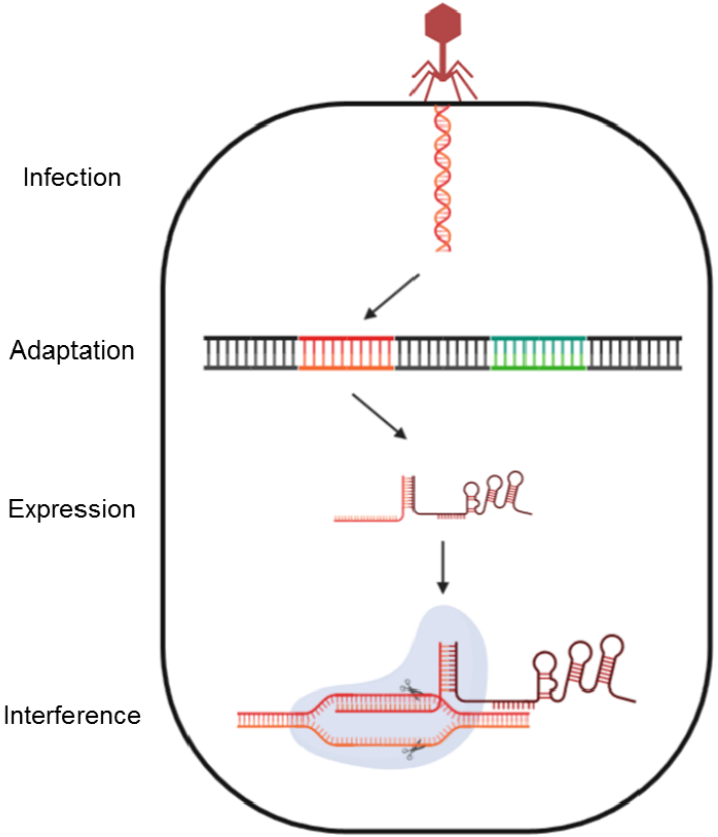
Why?

CRISPR

The molecular scissors transforming genetics

wellcome sanger institute

CRISPR - bacterial immune system



Clustered **R**egularly **I**nterspaced **S**hort **P**alindromic **R**epeats

Bacterial immune response to viruses

Three components:

- crRNA
- tracRNA
- Cas9

Sequence is 20bp

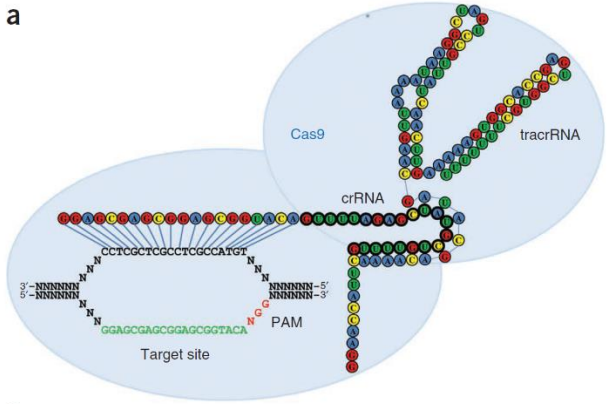
Requires a PAM (Protospacer Adjacent Motif)

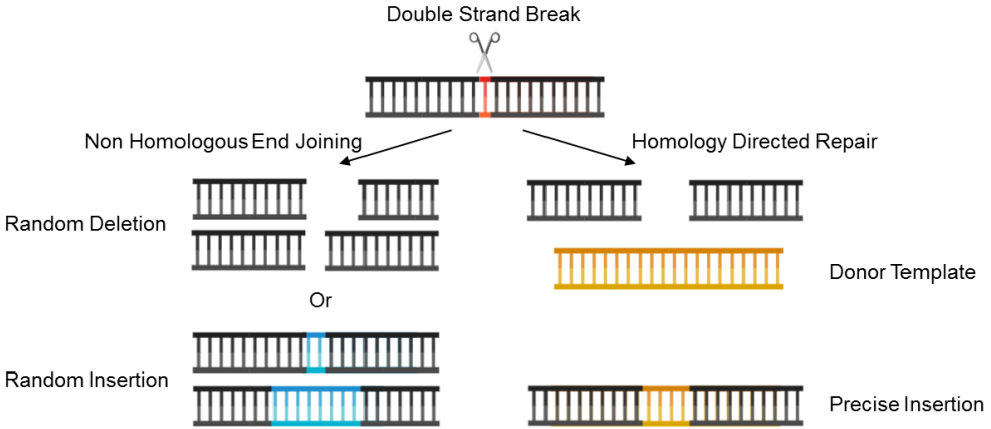
Induces a double strand break

Jennifer Doudna and Emmanuelle Charpentier – Nobel Prize Chemistry 2020

wellcome sanger institute

Cas9 causes a double strand break at precise locations

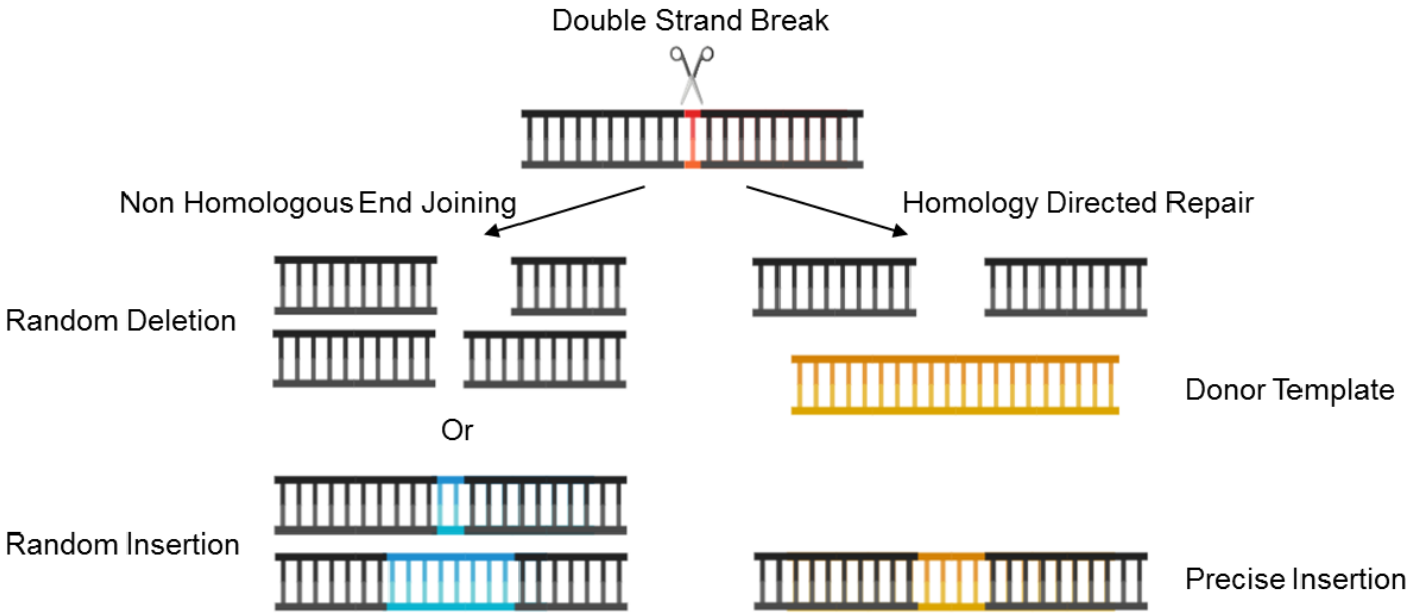




Non Homologous End Joining can result in a frameshift mutation and can stop protein translation
OR
Homology directed repair can correct mutated DNA back to healthy DNA

wellcome sanger institute

Editing Cells

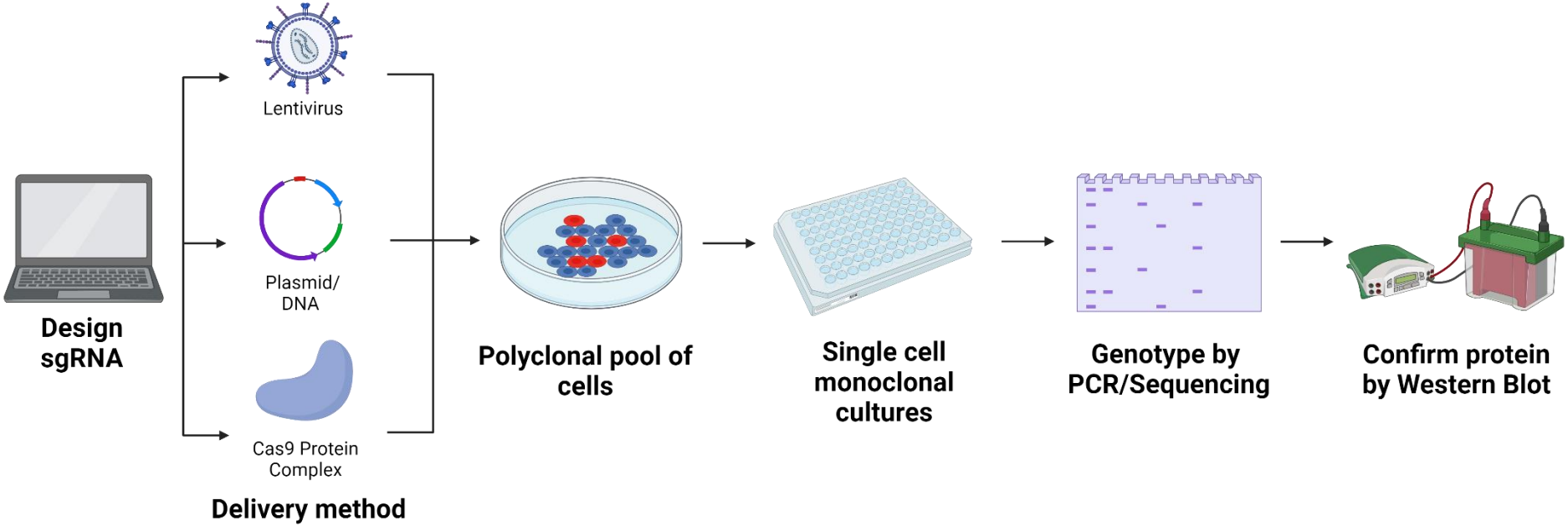


Genetic Knockout –
- What does the gene do?
- Removing disease causing alleles

Genetic Knock-in –
- Correcting disease causing mutations
- Generating reporter cell lines/models

wellcome sanger institute

How do we edit a cell?

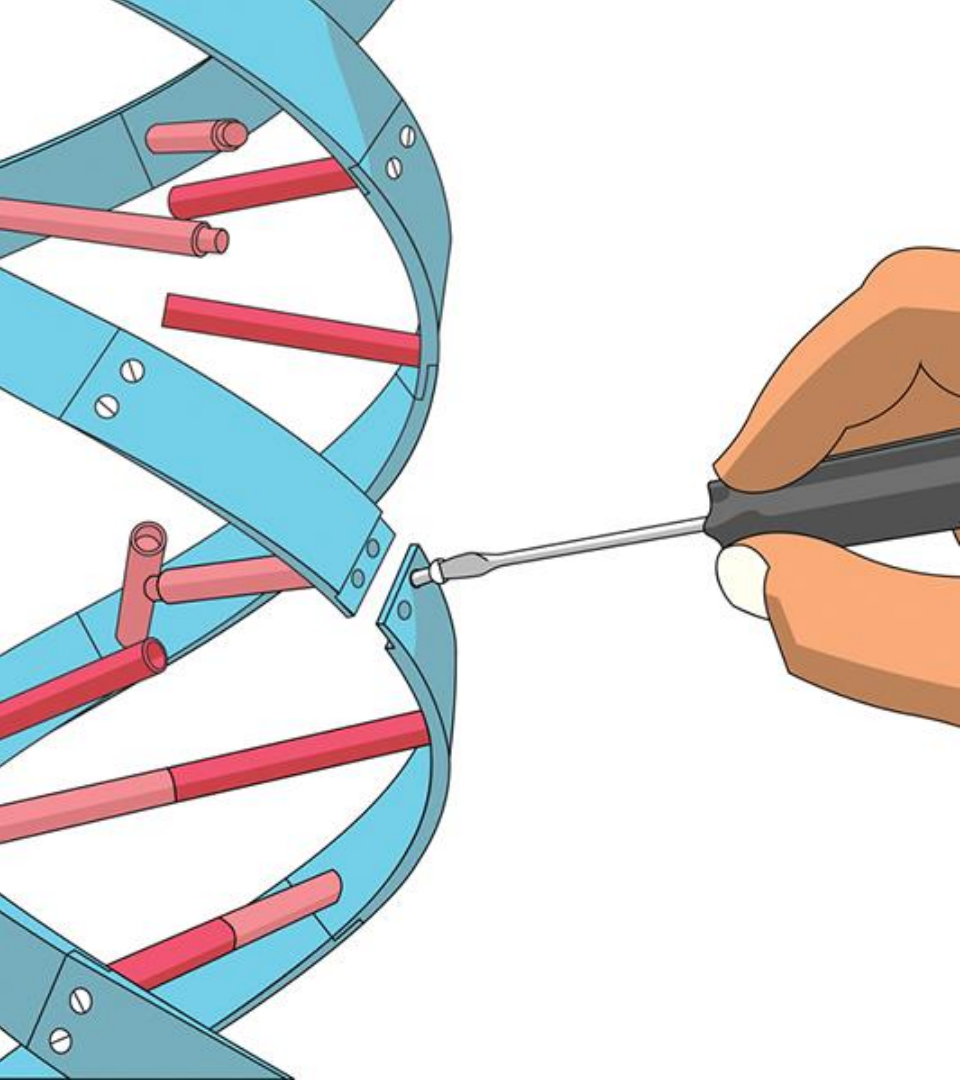


What research can we do with edited human cells?

wellcome sanger institute

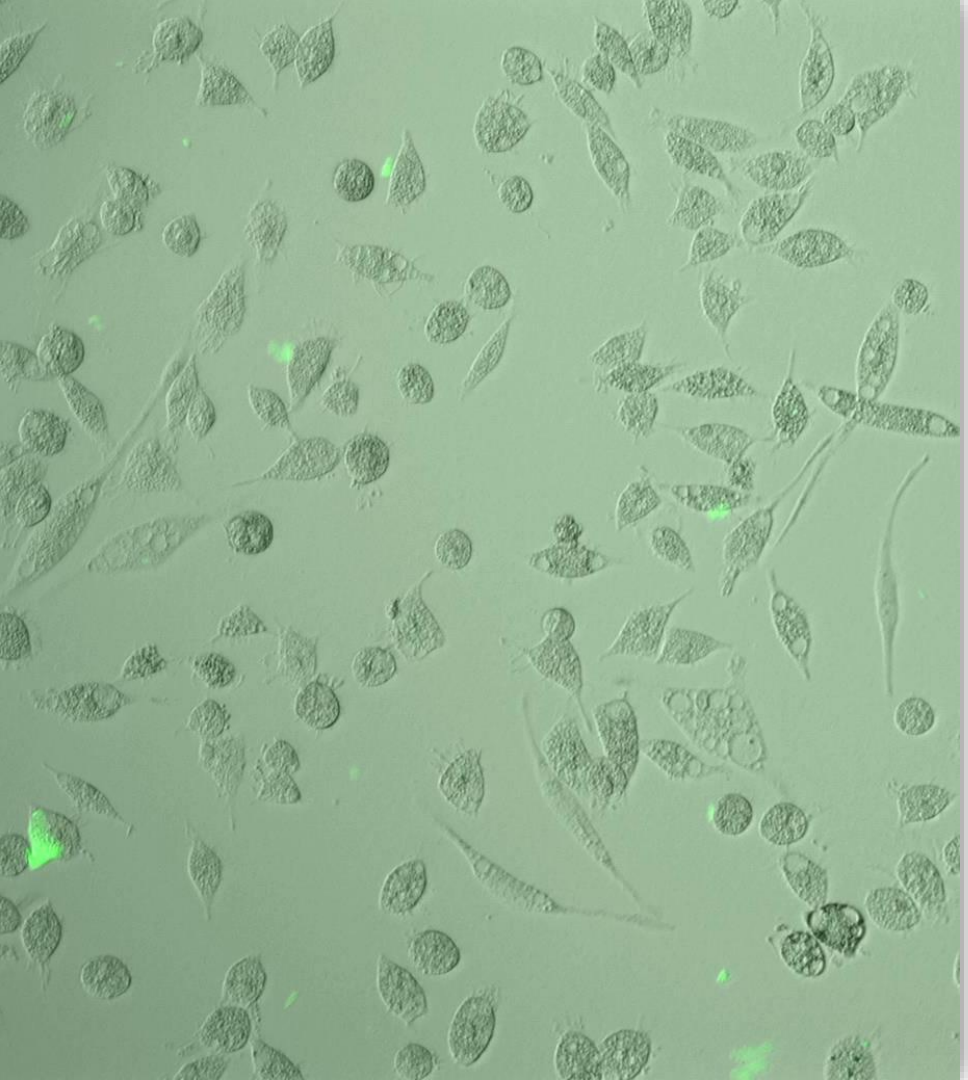
wellcome sanger institute

wellcome sanger institute



Basic biological understanding

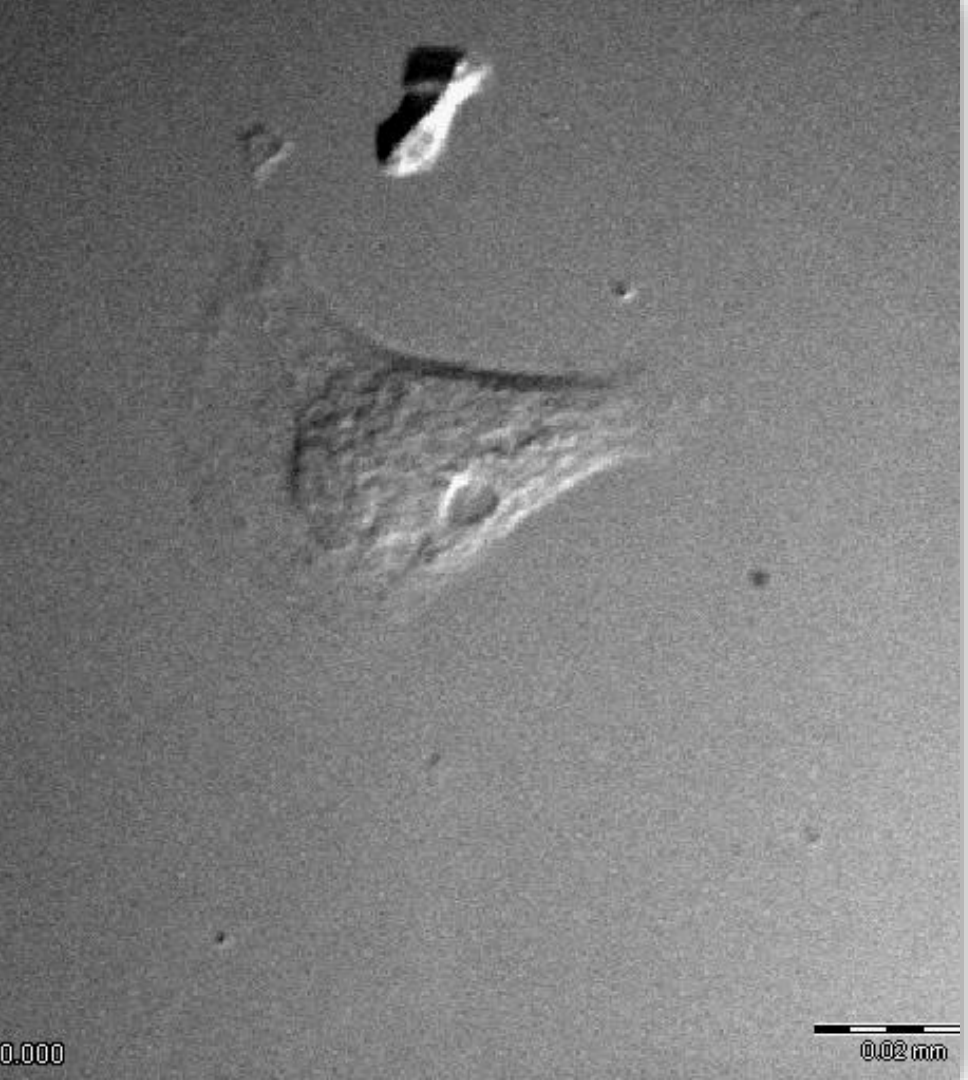
wellcome sanger institute



Discover what genes do

wellcome sanger institute

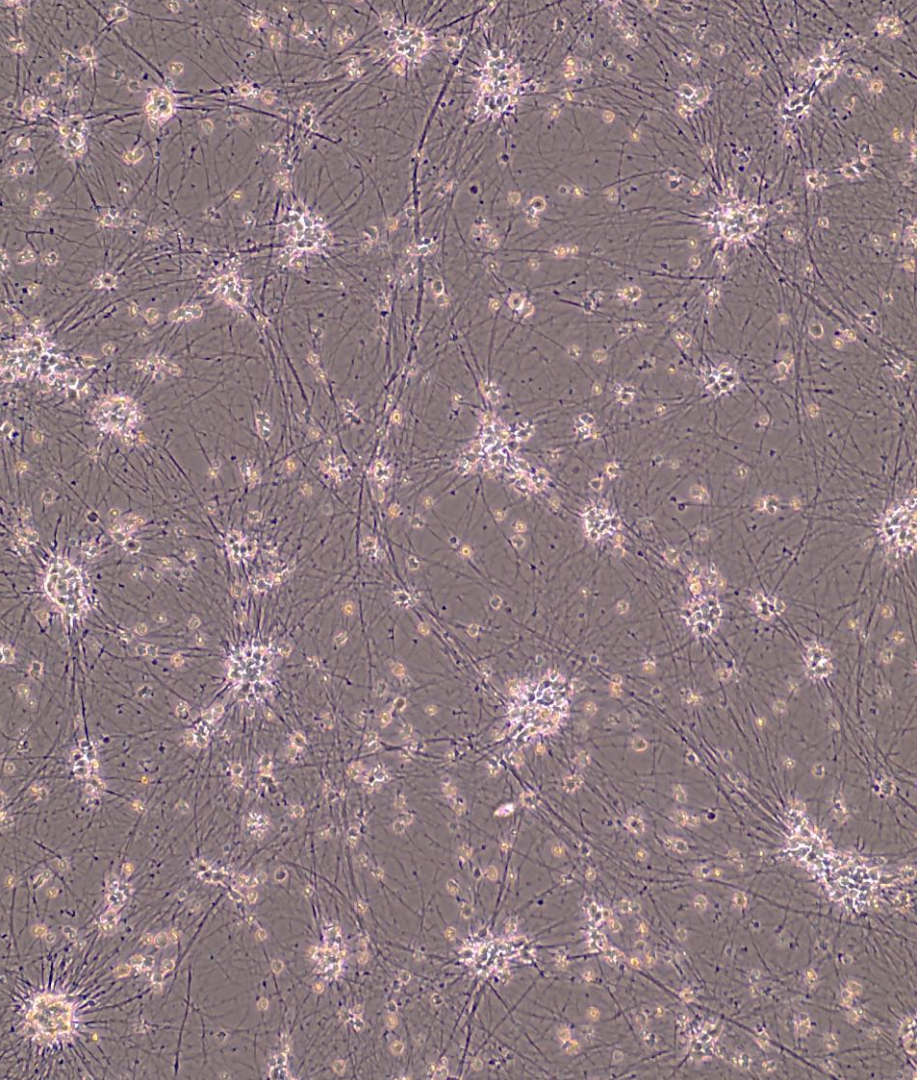
Walther Haenseler – University of Oxford



Discover what genes do

wellcome sanger institute

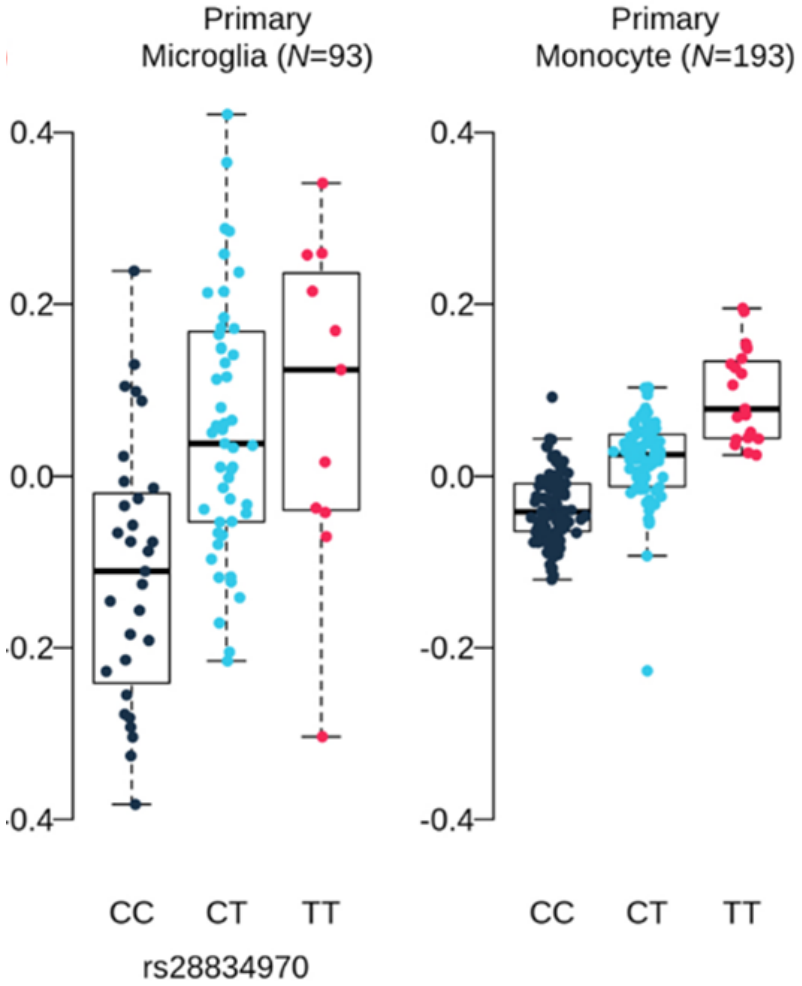
Frances Brook, Matt Daniels – University of Oxford



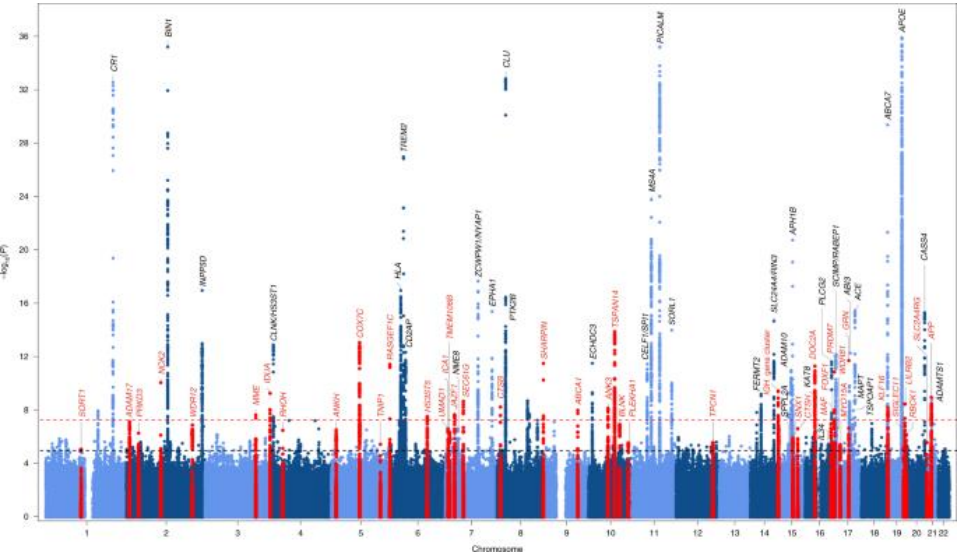
Discover what genes do

wellcome sanger institute

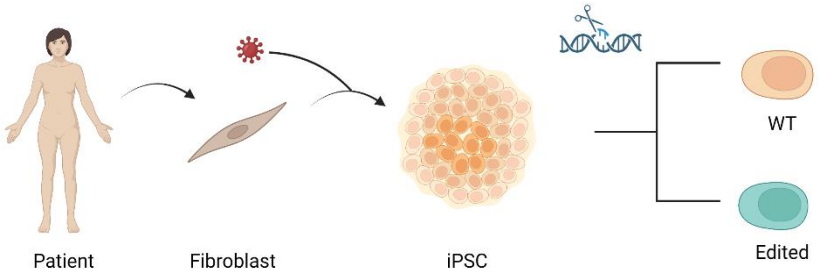
Sam Washer – Wellcome Sanger

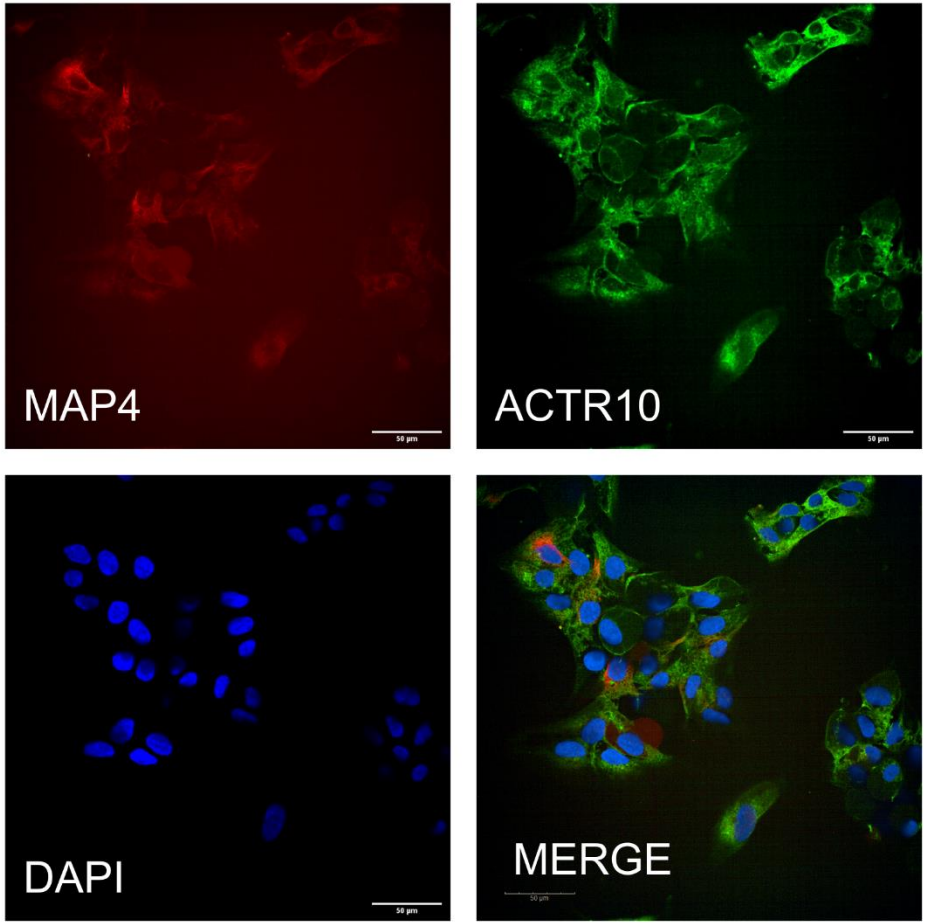


Explore genetic variation



Explore genetic variation

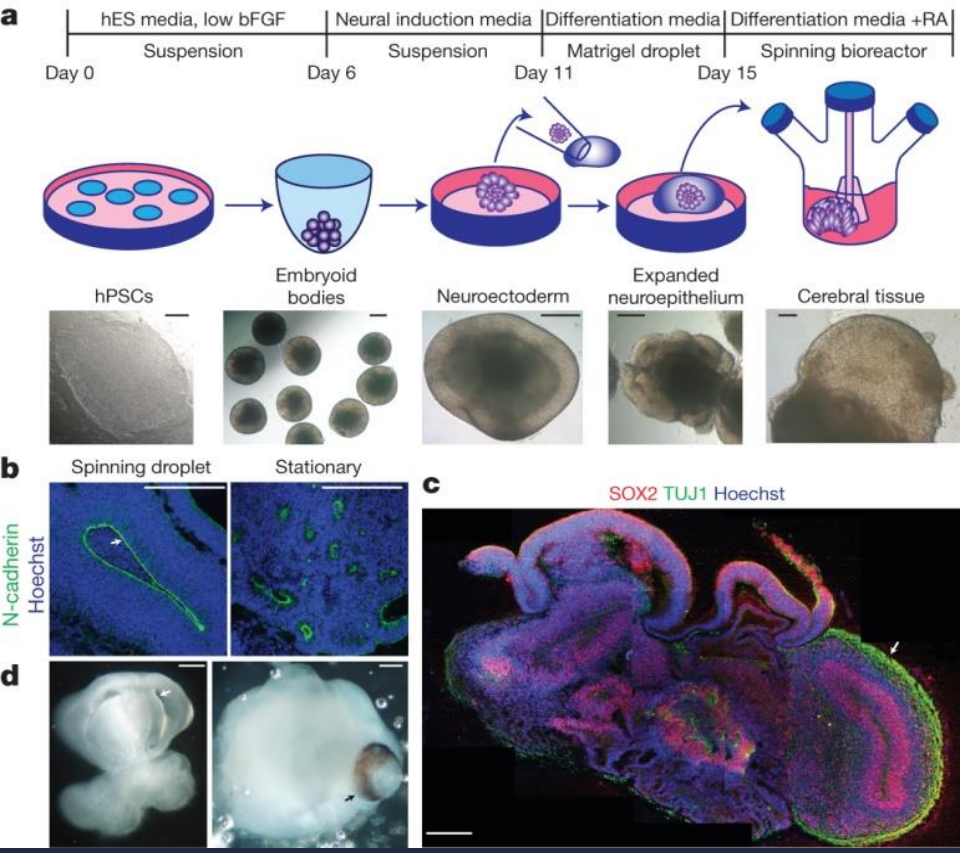




Generate reporter lines

Farming/Agriculture

wellcome sanger institute



Dive into the unknown

Lancaster et al 2013

How can CRISPR treat disease?

wellcome sanger institute

Case Study: Sickle Cell Anaemia

The first CRISPR treatment for a genetic disease

wellcome sanger institute

Treatments for Sickle cell

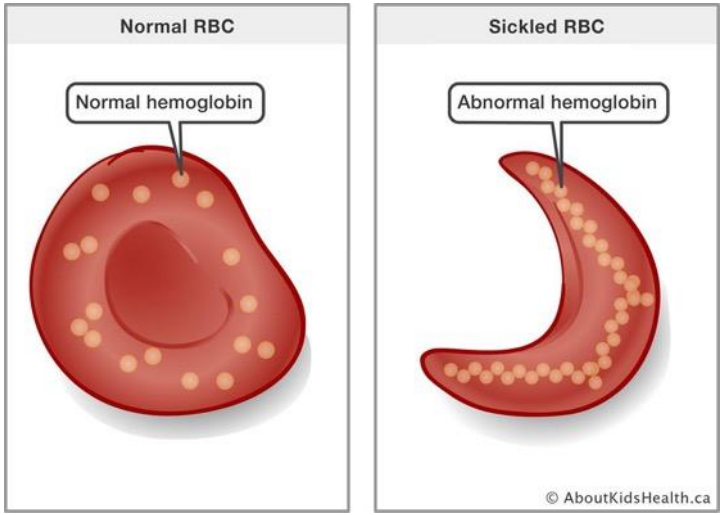
Genetic Disease – Autosomal Recessive

1 DNA base change causes haemoglobin to aggregate

GAG -> GTG

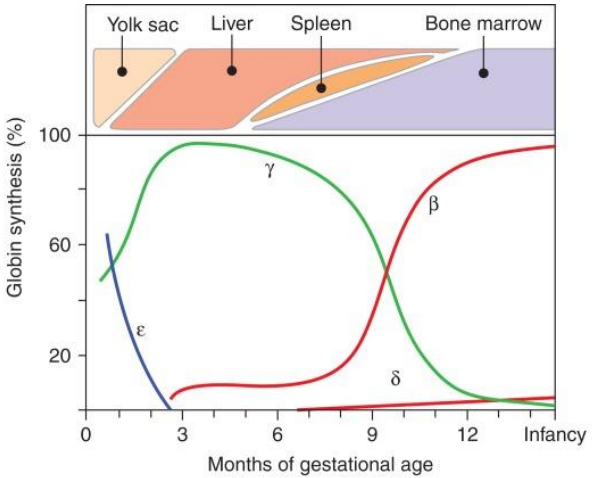
Glu -> Val

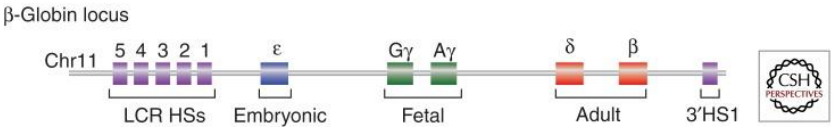
Blockages by sickled red blood cells can cause pain and strokes

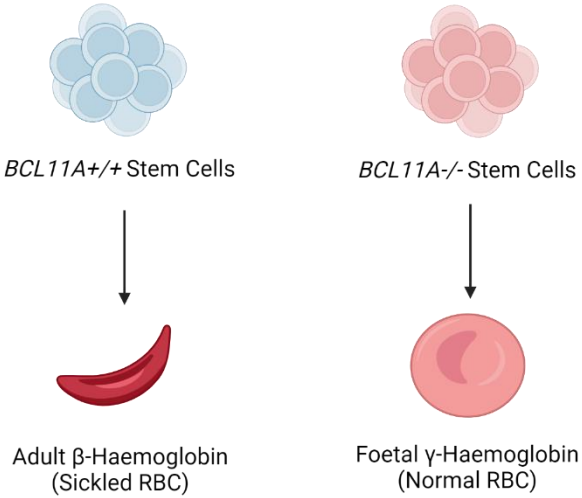


wellcome sanger institute

Treatments for Sickle cell

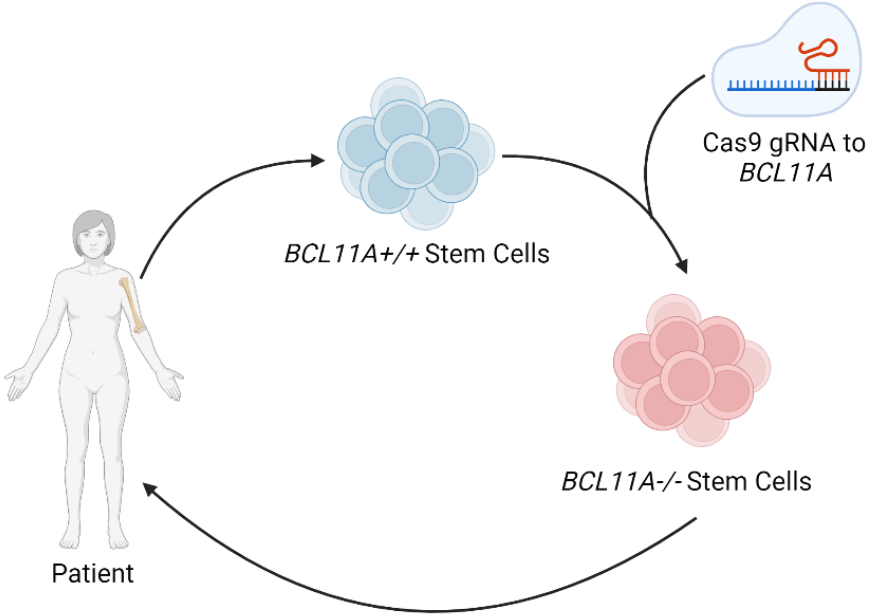






Sankaran & Orkin 2013

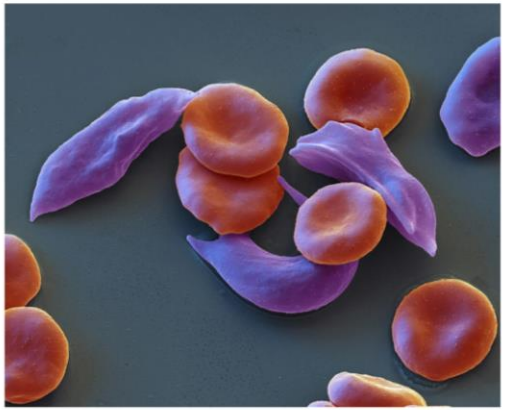
Treatments for Sickle cell



UK first to approve CRISPR treatment for diseases: what you need to know

The landmark decision could transform the treatment of sickle-cell disease and β-thalassaemia – but the technology is expensive.

By Carissa Wong



Sickle-cell anaemia is marked by red blood cells that are misshapen and sticky, affecting blood flow. Credit: Eye Of Science/SPL

28/29 patients treated were “cured”

wellcome sanger institute

Other genetic treatments?

Monogenic Disease

- Cystic Fibrosis
- Huntingtons
- Fragile X
- Duchenne Muscular Dystrophy

Polygenic Disease

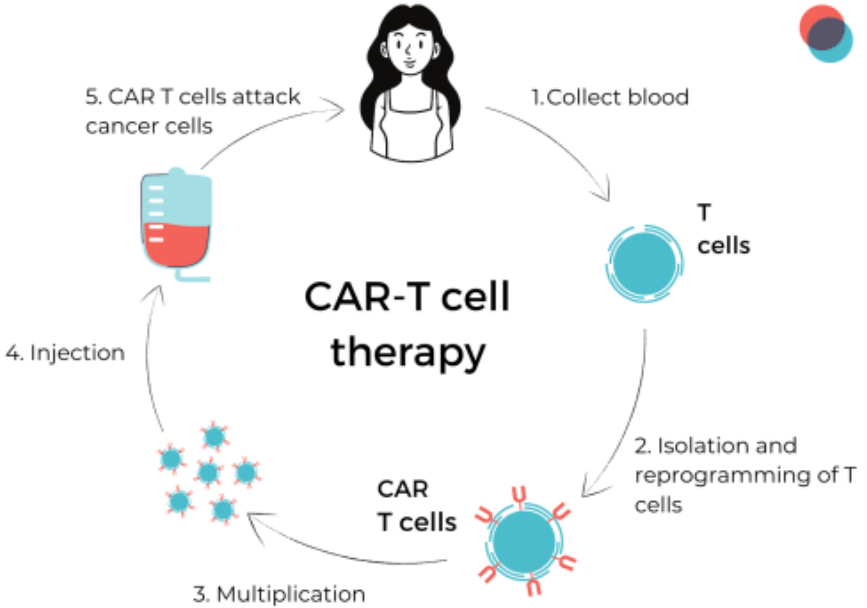
- Diabetes Type 1
- Cardiovascular disease

Infectious Disease

- HIV
- Hep B

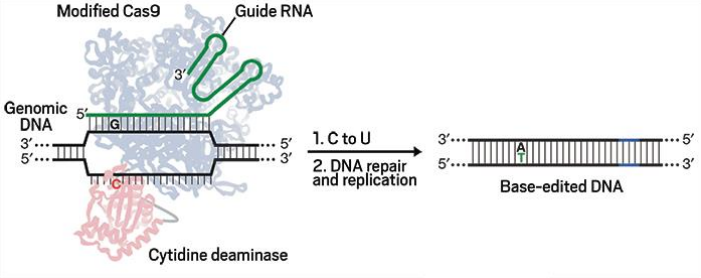
Cancers

- **CAR-T Therapy**

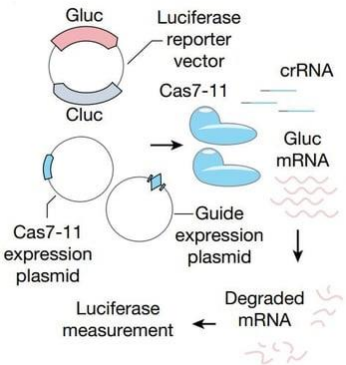


New CRISPR methods

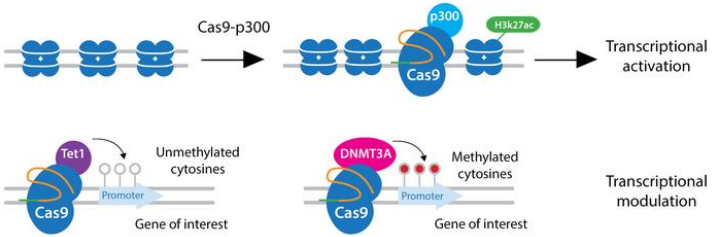
wellcome sanger institute



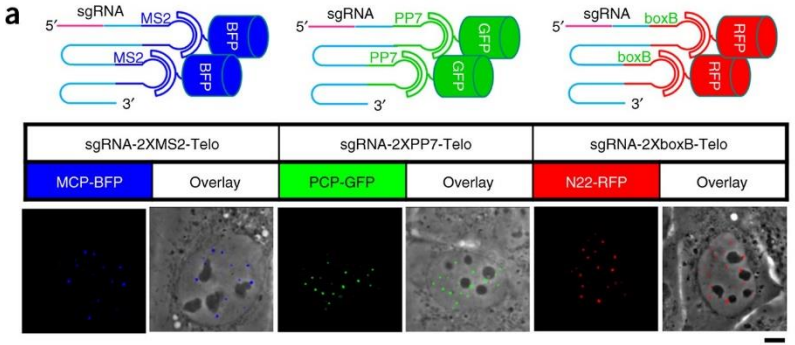
Base editors



RNA editors



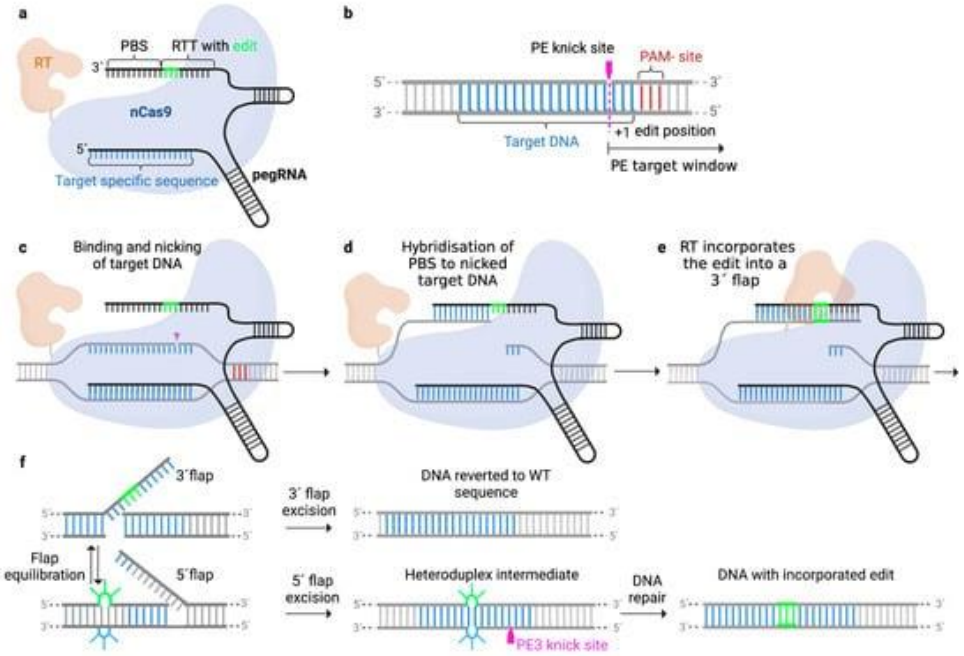
Epigenetic editors

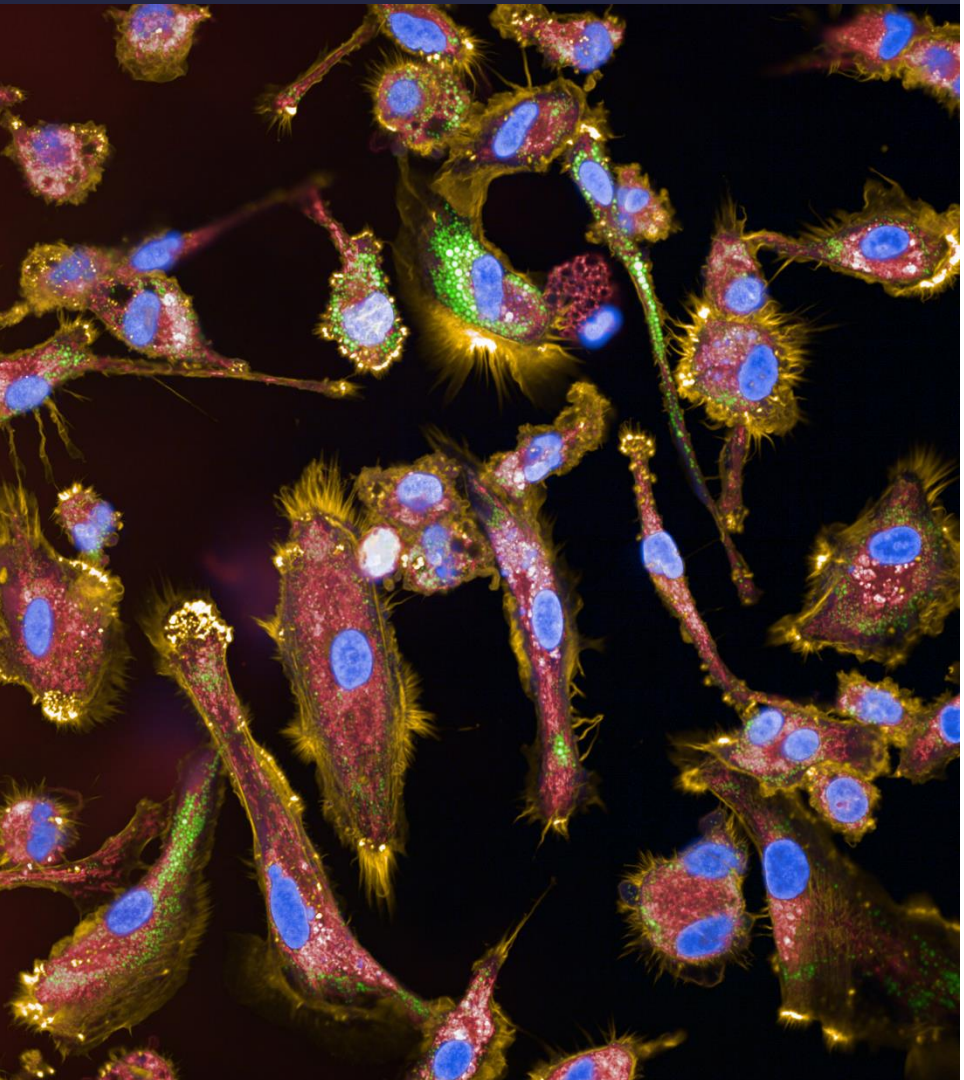


Visualisation

wellcome sanger institute

Prime Editing – The future?





1. CRISPR
2. Editing Cell Lines
3. Research
4. Treating Human Disease
5. Next Gen CRISPR

wellcome sanger institute