A CRISPR way to understand genetic disease

Andrew Bassett

wellcome sanger institute

Human genome project – 13 years (1990-2003), $3 billion

Last year – 1 genome every 2 min (~5000 per week), ~$500

Variation

1 in every 1500 bases differs between individuals
i.e. we are 99.93% identical in DNA sequence
- 96% identical to a chimp
- 60% of genes are shared with a banana

But 3,000,000,000 bases of DNA, so around 2 million differences between two people

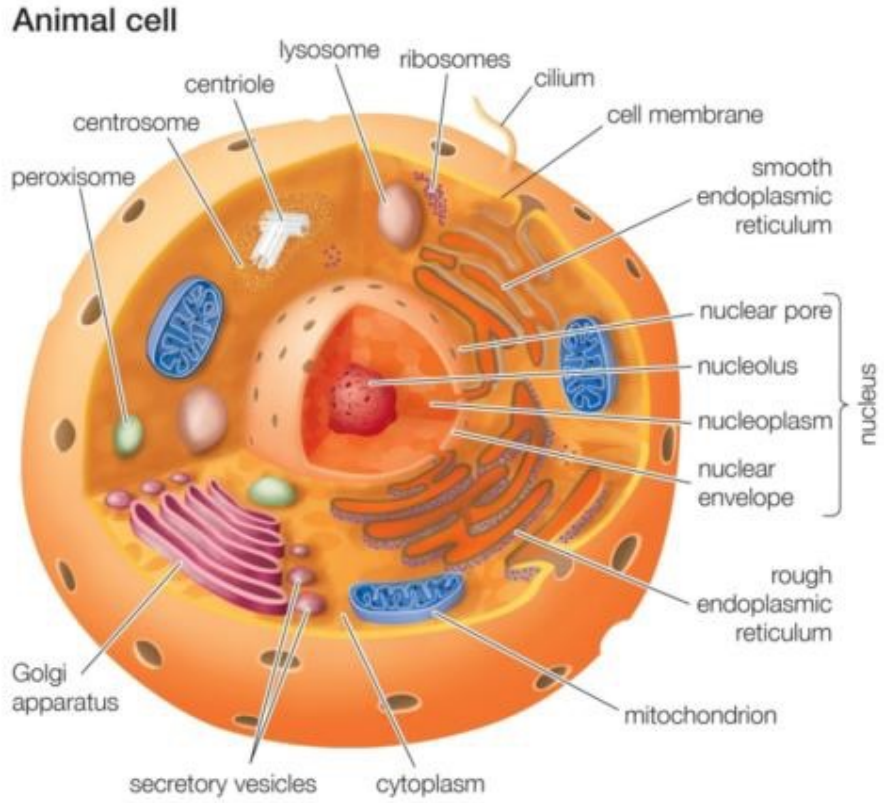
Around 2 m per cell! Packaged in a ~1 μm nucleus
Akin to trying to fit 24 miles of cotton into a tennis ball!

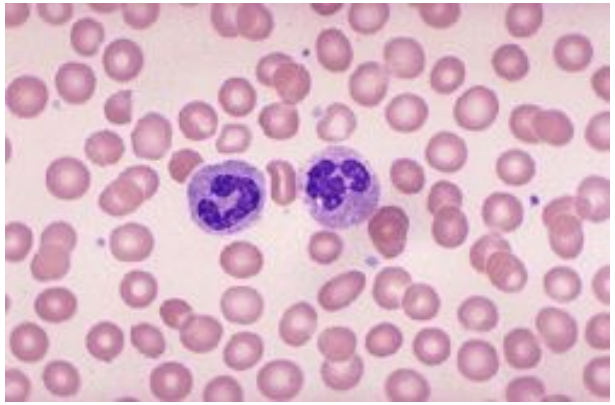
biobank uk
Improving the health of future generations

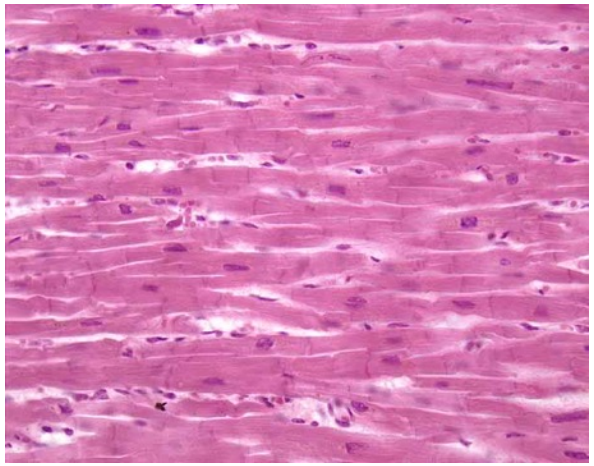

wellcome
sanger
institute
What do changes in the genome mean?
HiSeq X

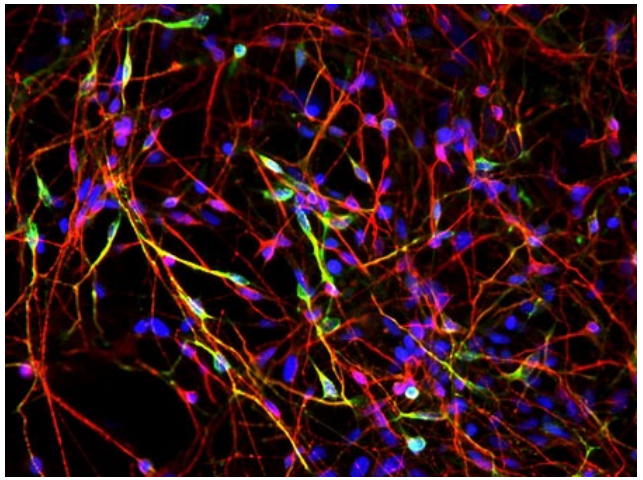
HUMAN CELL ATLAS

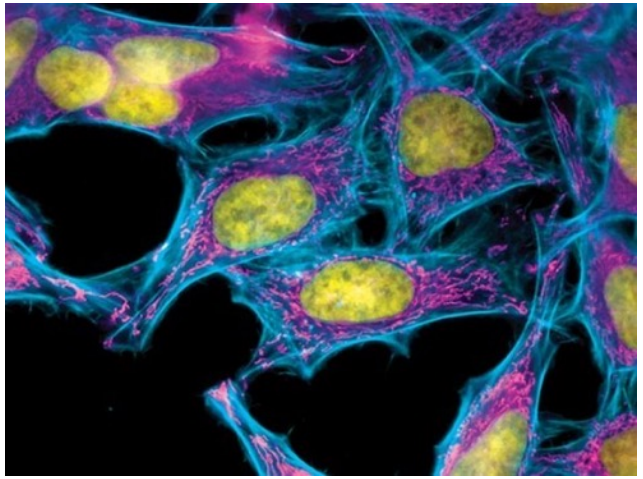
30,000,000,000,000 cells in a human DNA is identical, but cells are specialised

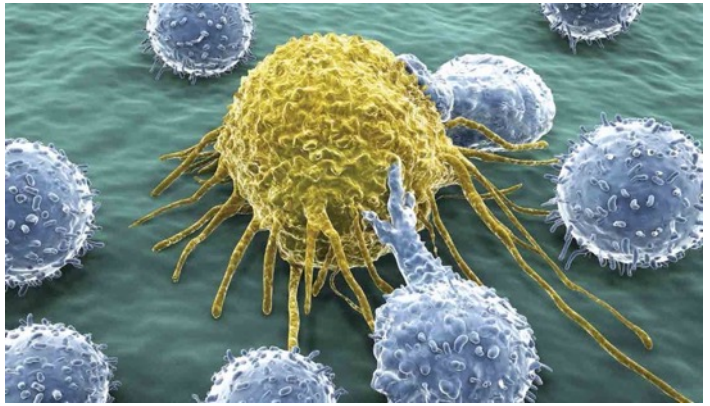






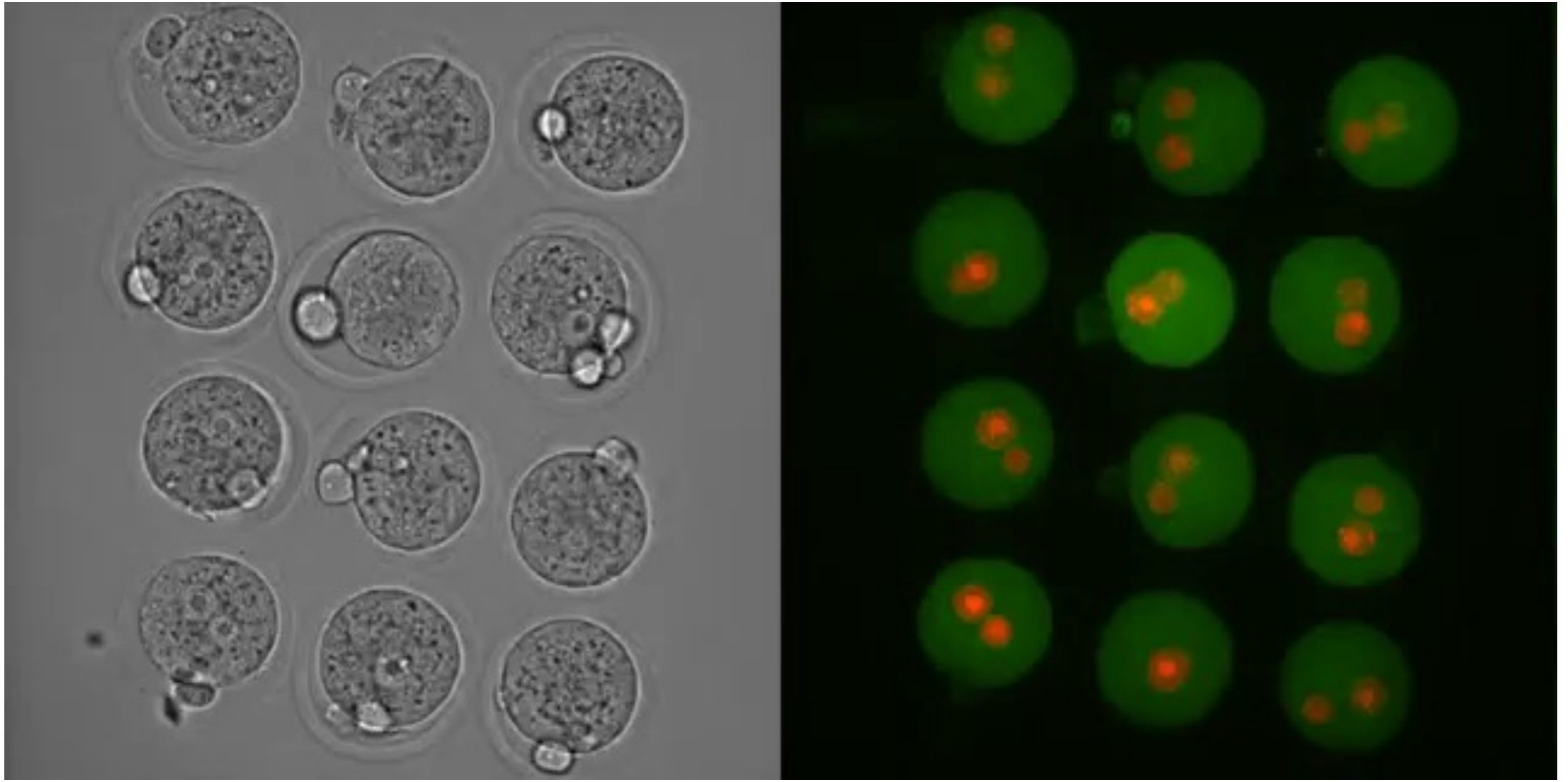




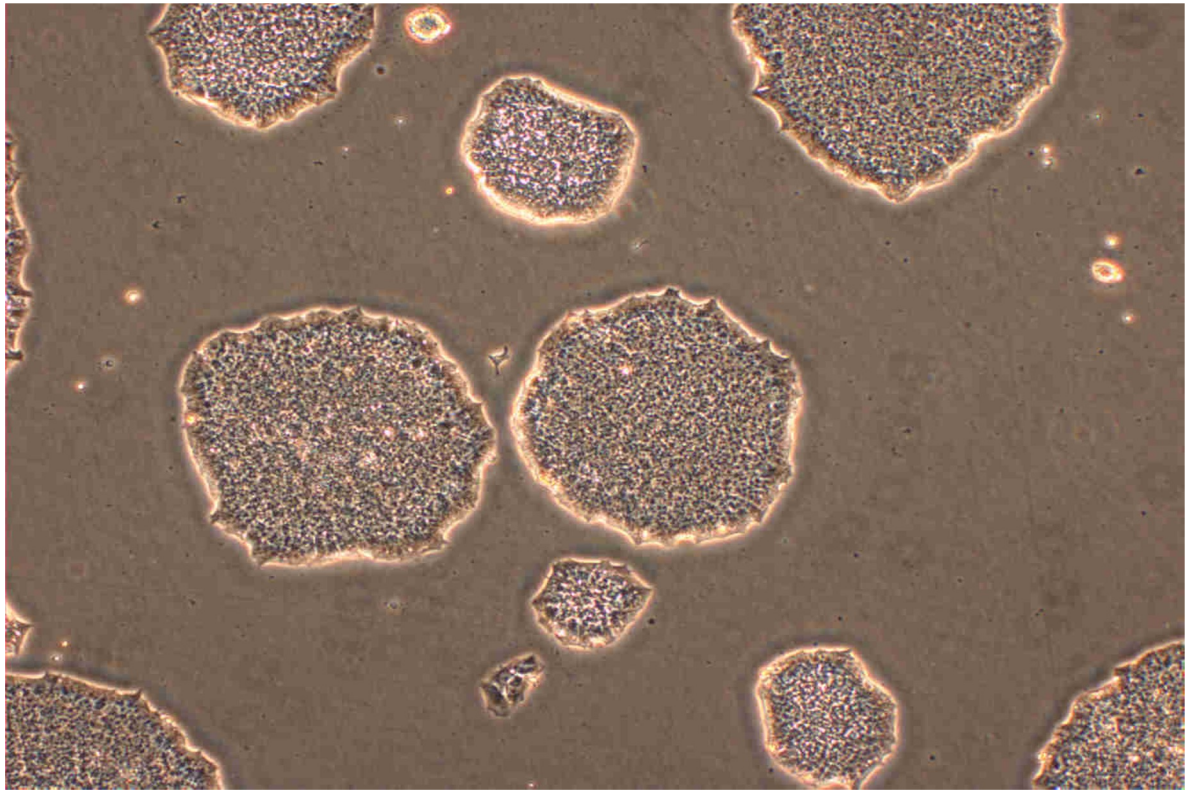


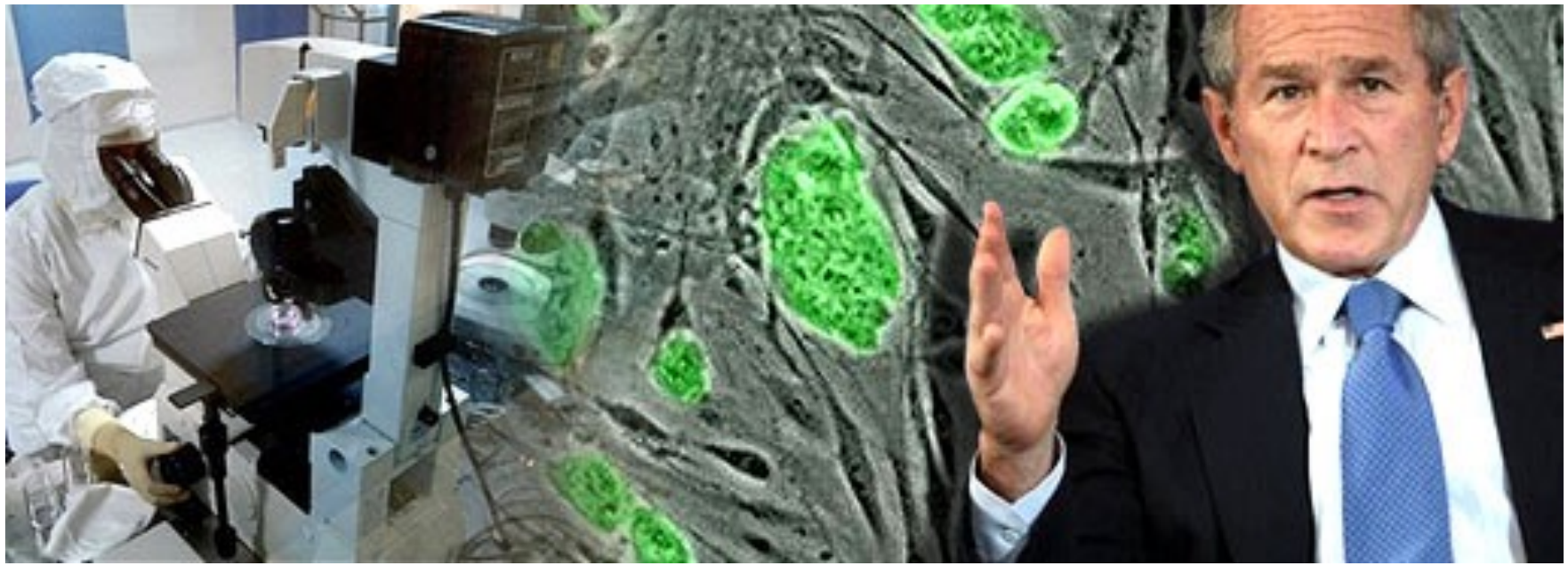
Pluripotent stem cells

All cells derived from a single fertilised egg cell

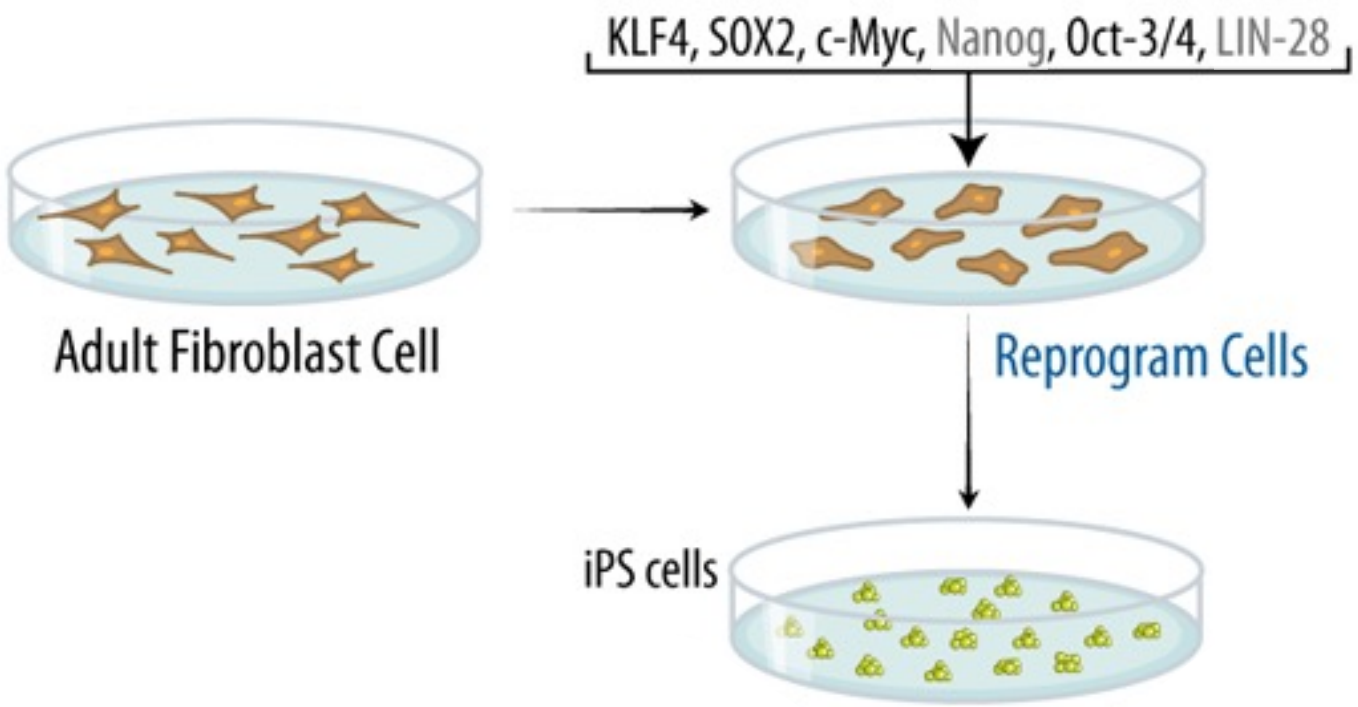


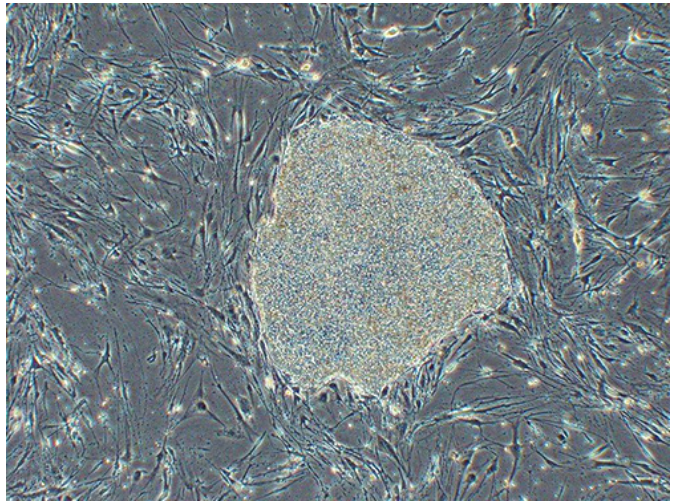

iPS





Induced pluripotent stem cells (iPSC) – Yamanaka 2007





HipSci HOME ABOUT US CELL LINES DATA

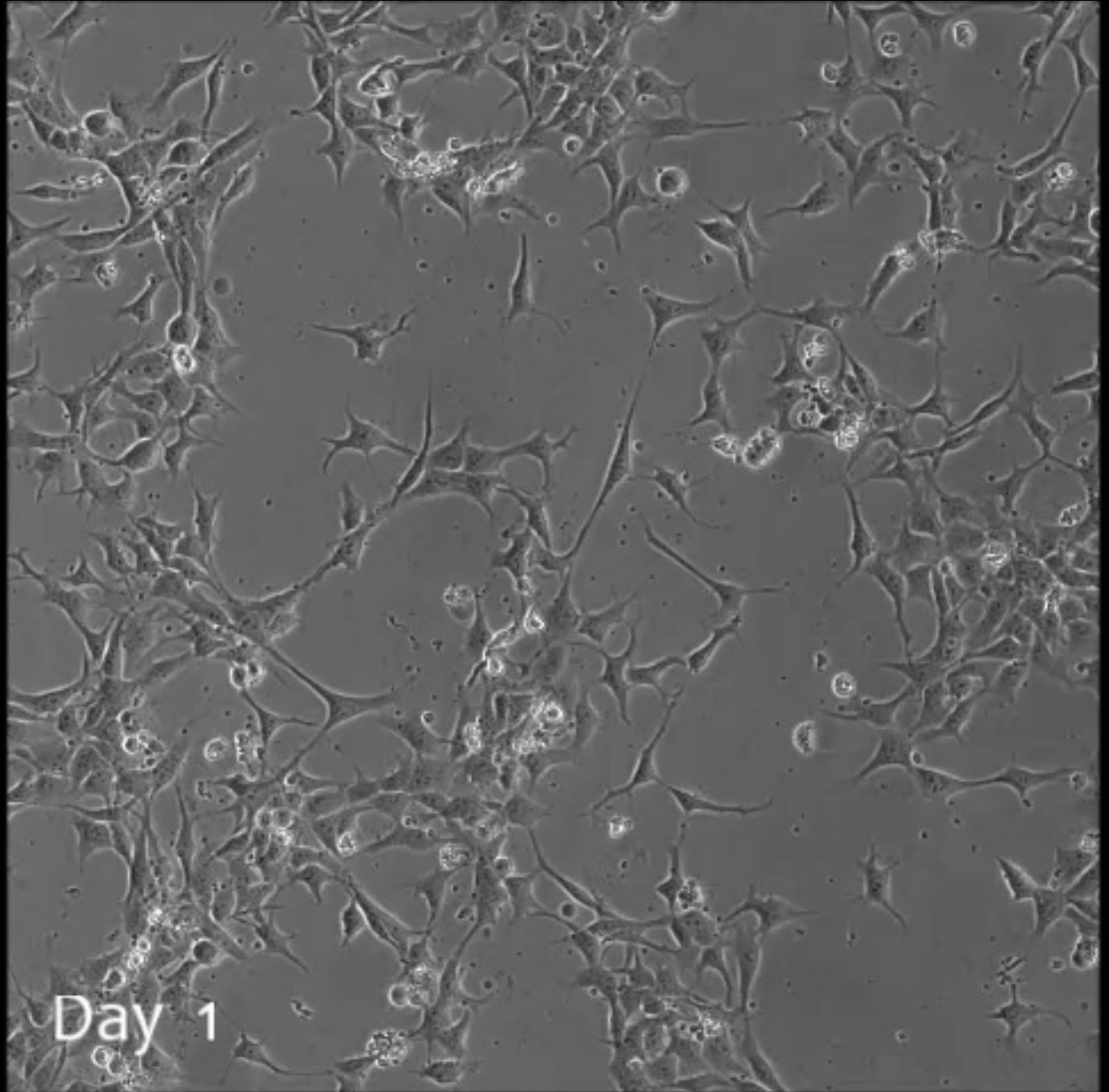
www.hipsci.org

HUMAN INDUCED PLURIPOTENT STEM CELL INITIATIVE

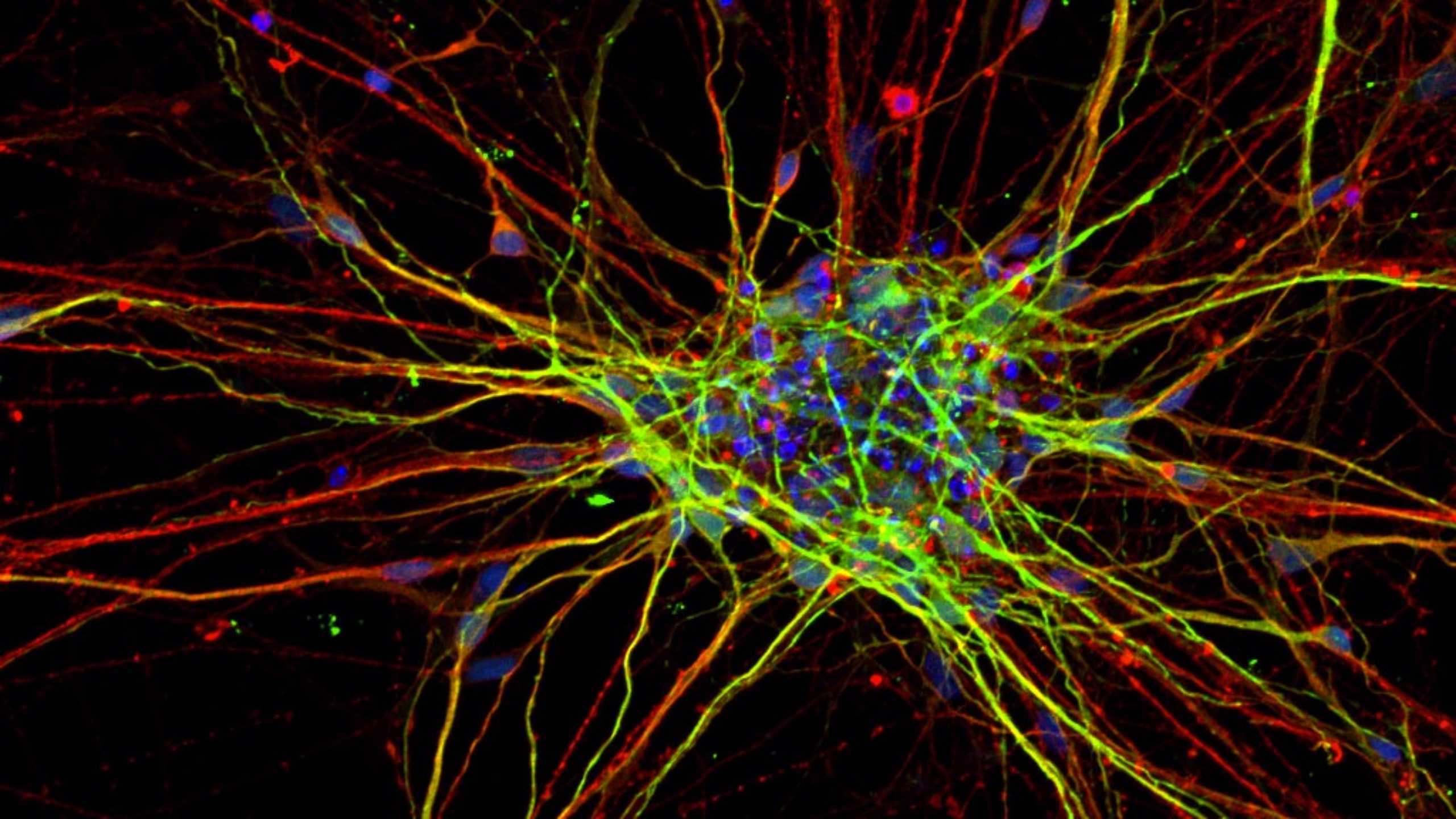
HIPSCI BRINGS TOGETHER DIVERSE CONSTITUENTS IN GENOMICS, PROTEOMICS, CELL BIOLOGY AND CLINICAL GENETICS TO CREATE A GLOBAL IPS CELL RESOURCE

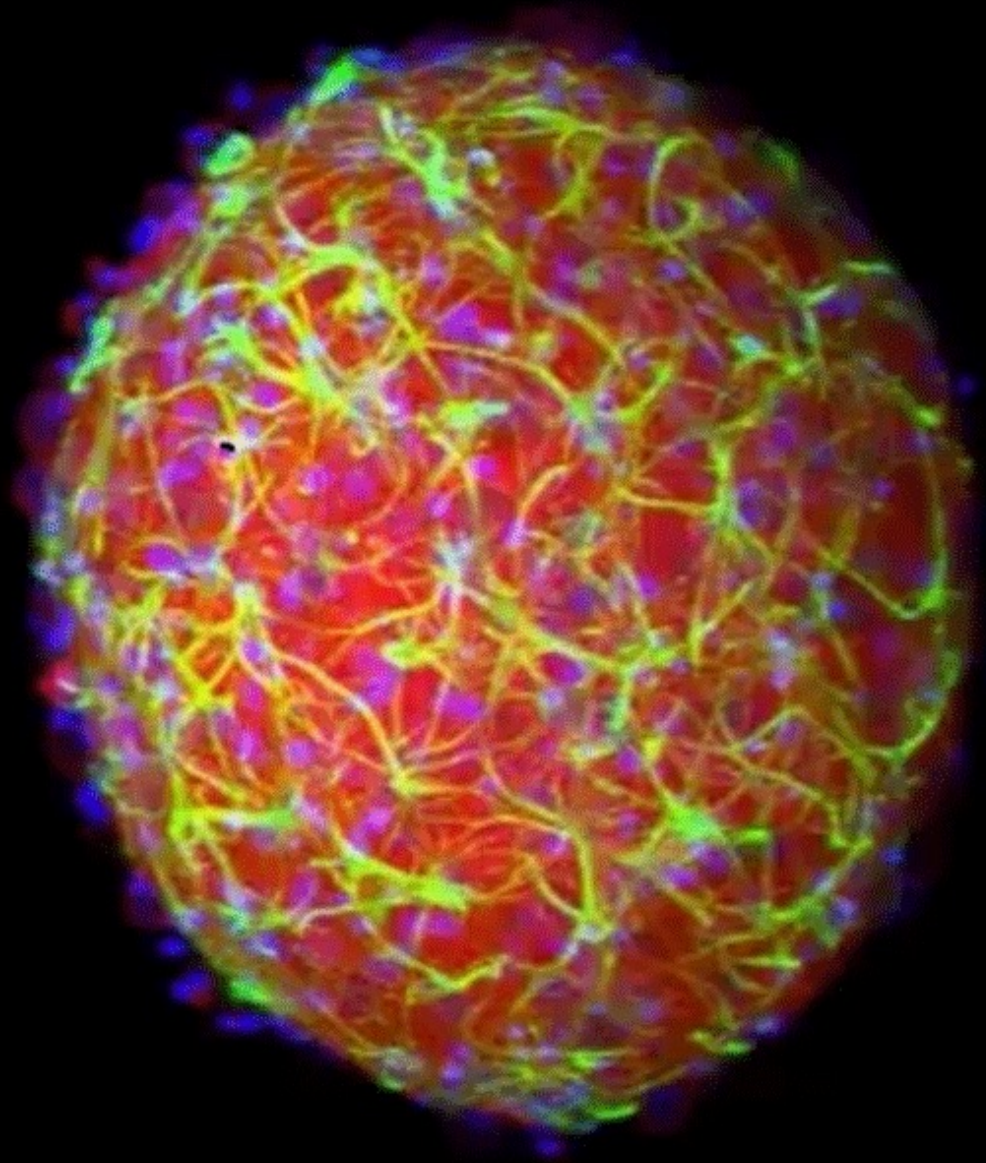
CELL LINES AND DATA BROWSER

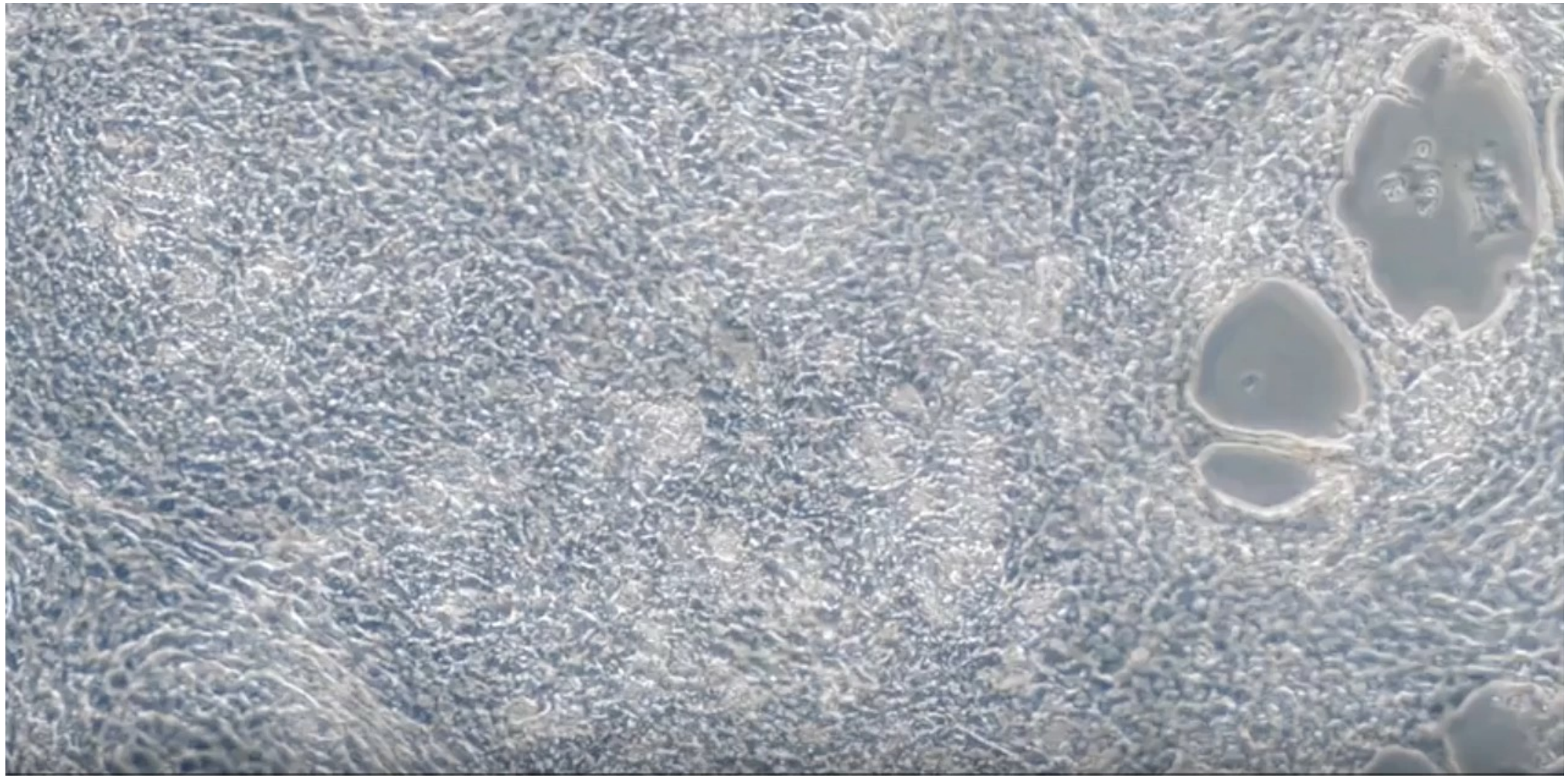
- Established in 2012 generate a large, well-characterized collection of iPS cells (>800x) for use in research.
- Two or three candidate iPSC cell lines from each donor (healthy or diseased), and initial characterisation of them



Mark Kotter







Video courtesy of Axol bioscience

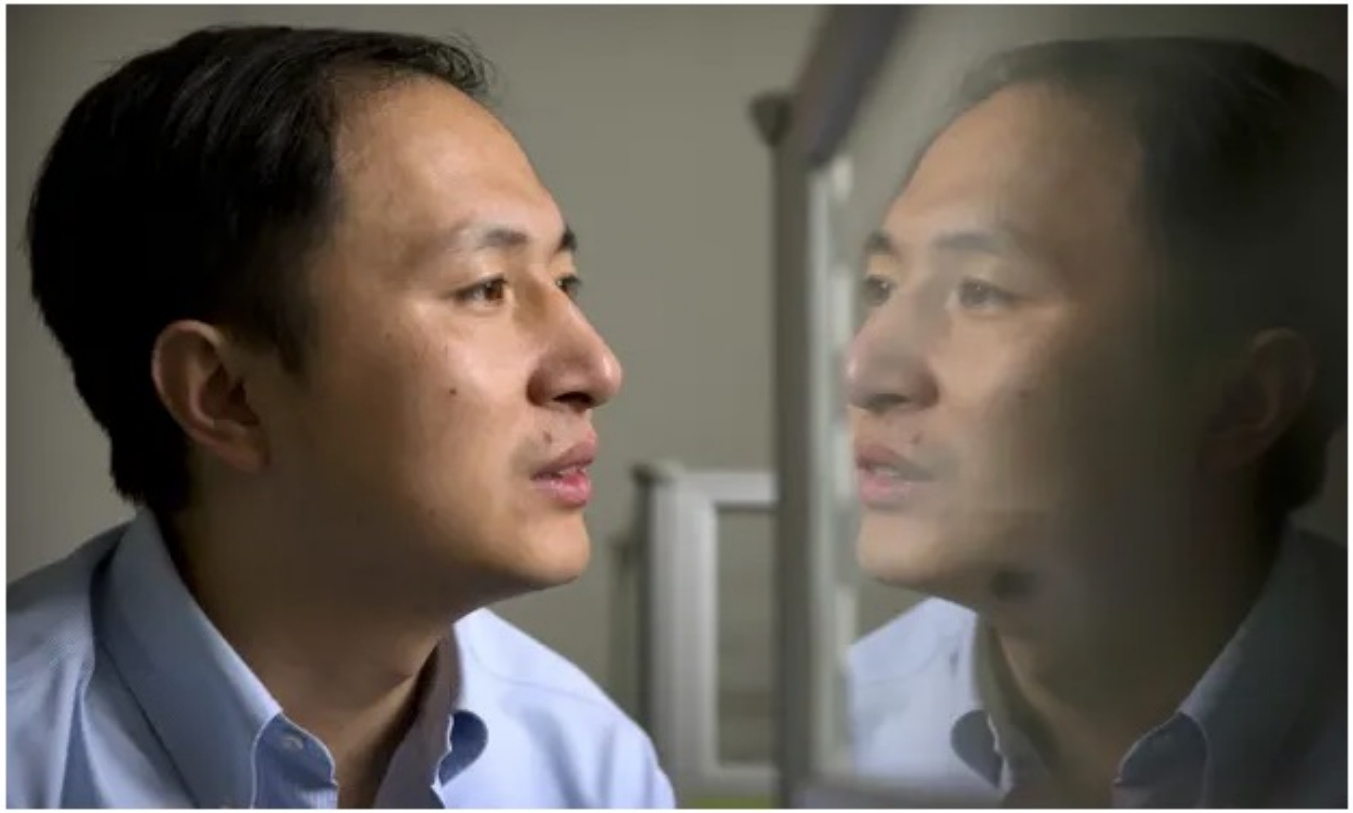
EVERYWHERE

Illustration by Chris Labrooy ©nature

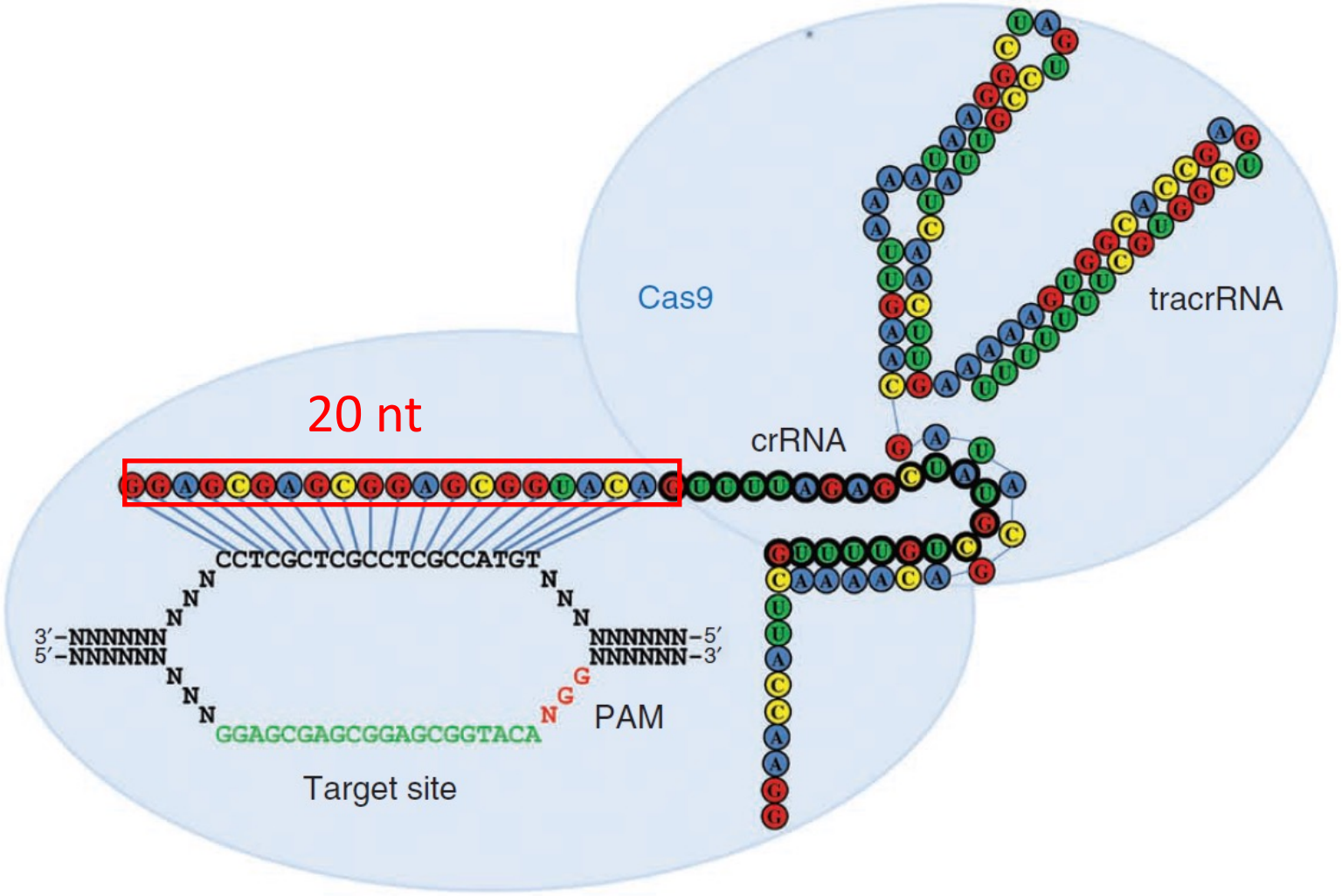
theguardian

'Of course it's not ethical': shock at gene-edited baby claims

Chinese geneticist He Jiankui's claim to have altered embryos prompts outcry from scientists



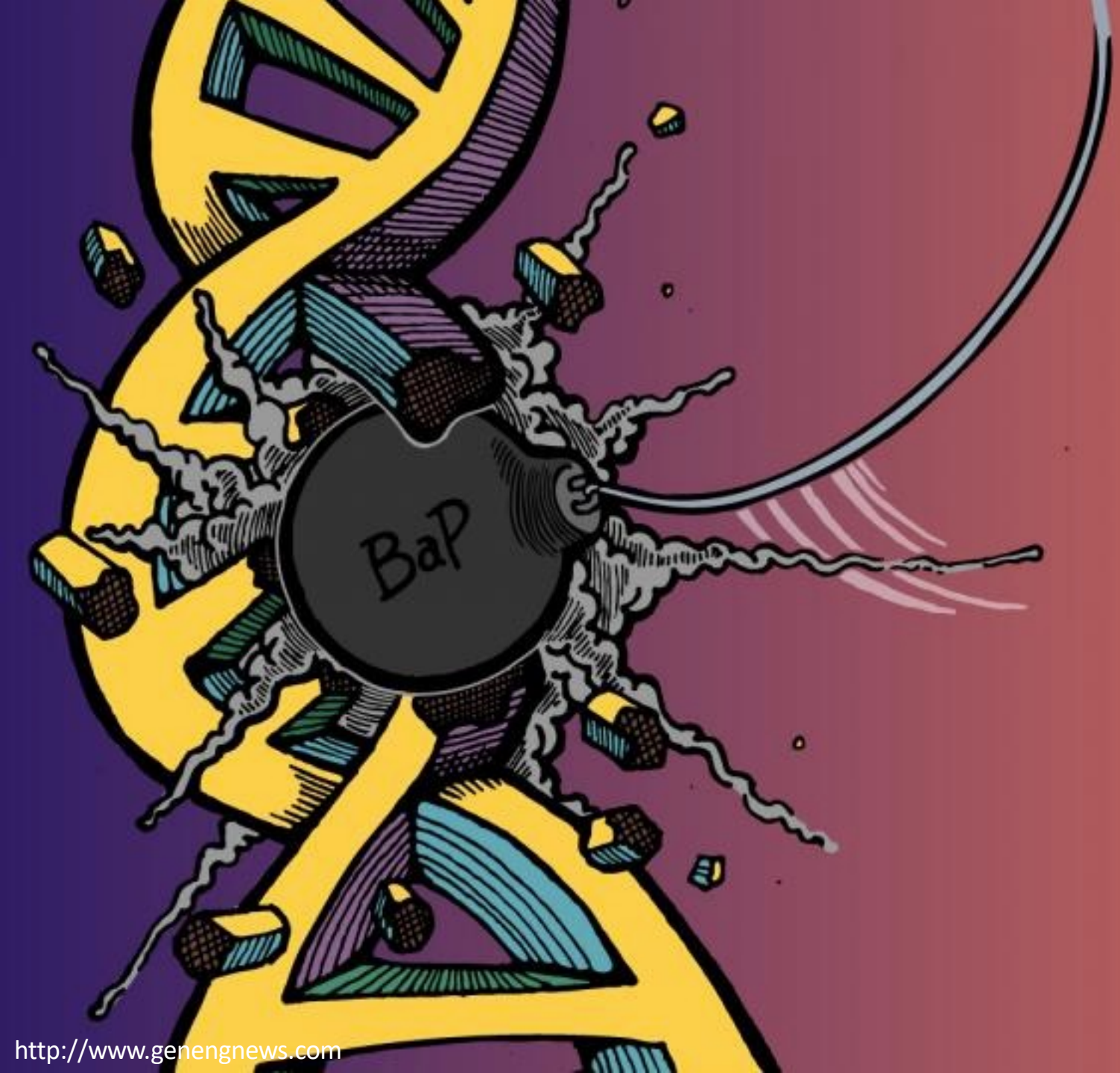
He Jiankui. Chinese authorities have ordered an investigation to verify his claims. Photograph: Mark Schiefelbein/AP

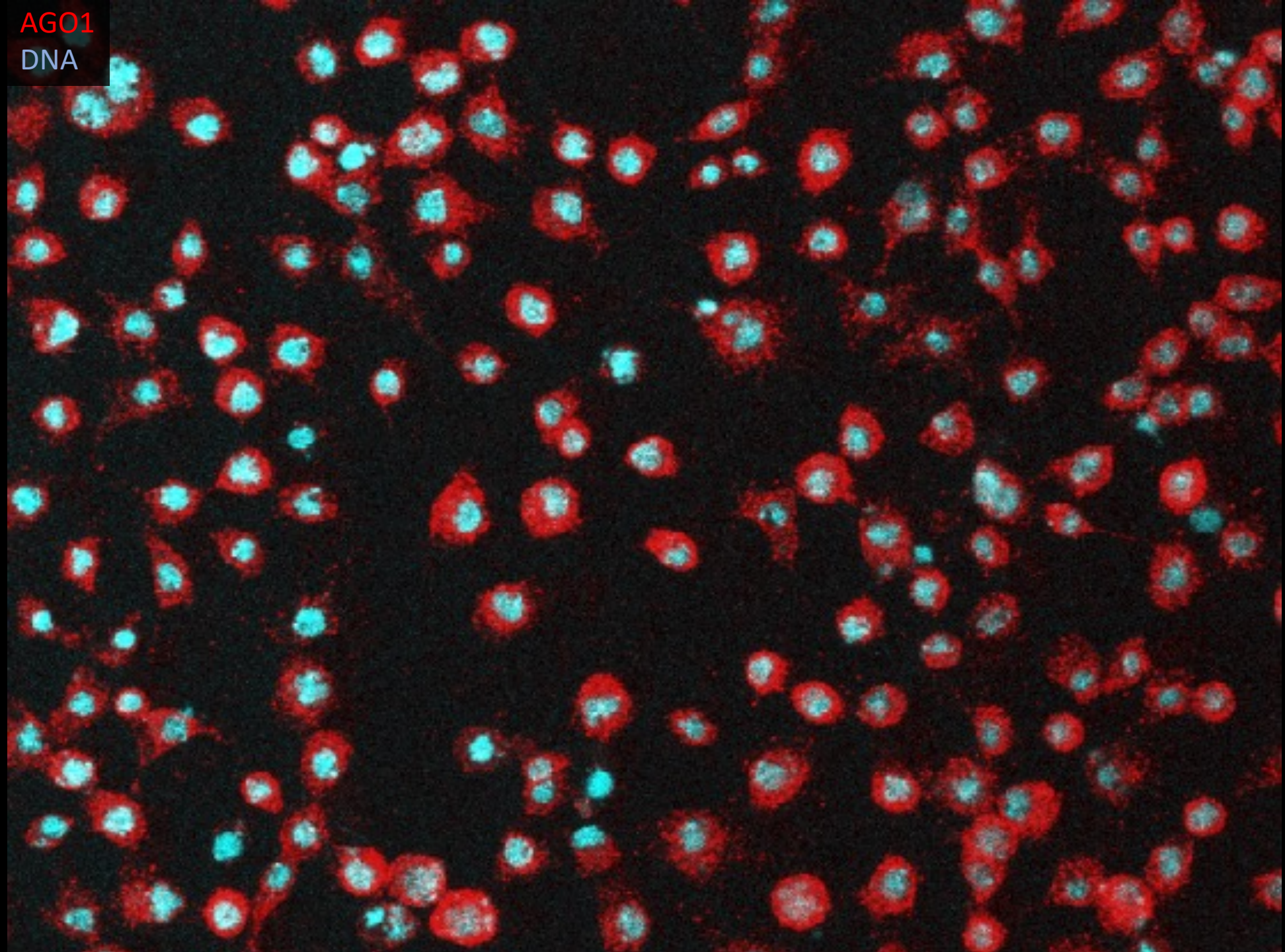


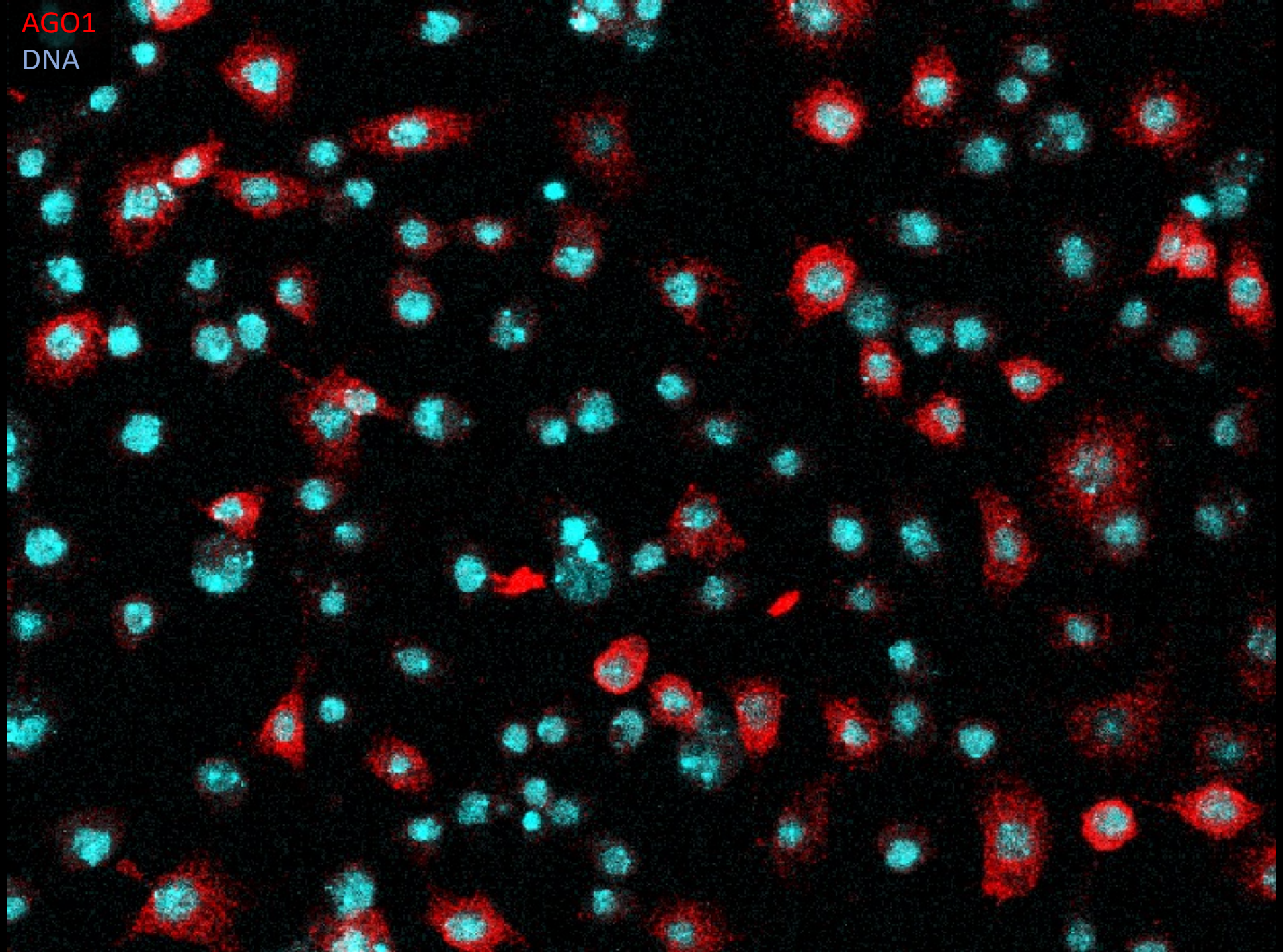
Target sequence PAM

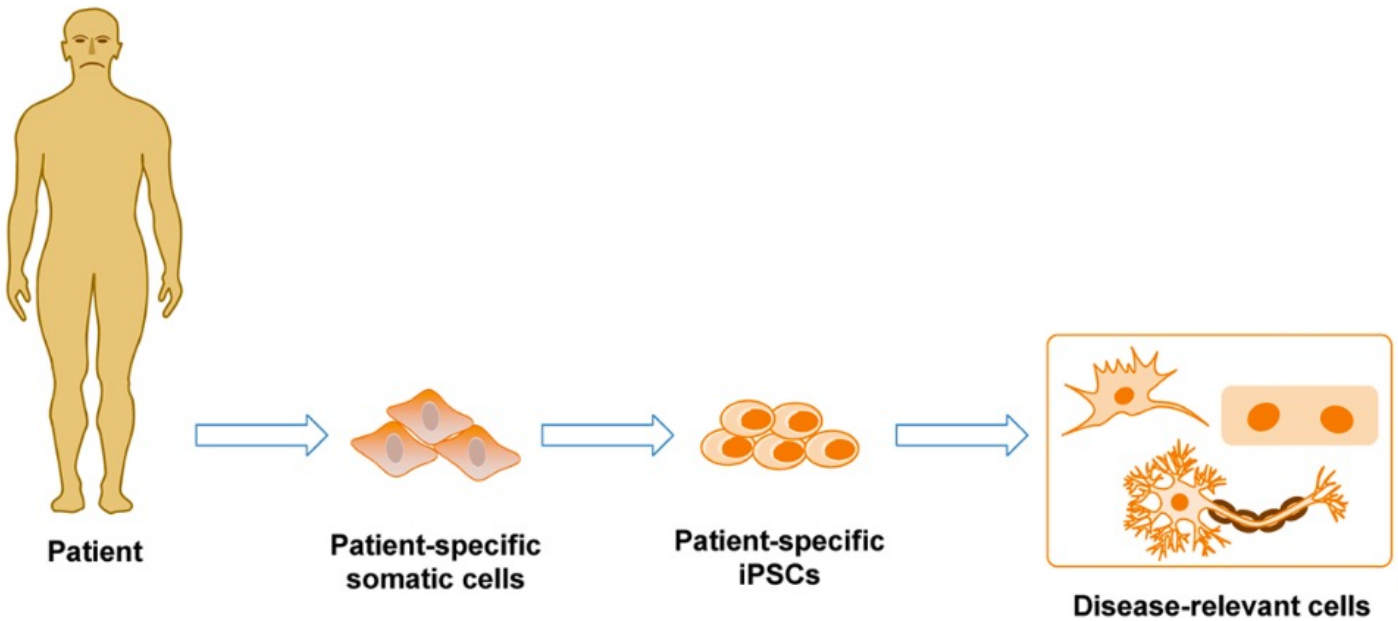
5′-AAACTTCAGGAGCGATATAGTTGGAGCCAGCTGGACTTTCCTTT-3′
3′-TTTGAAGTCCTCGCTATATCAACCTCGGTCGACCTGAAAGGAAA-5′


http://www.genengnews.com

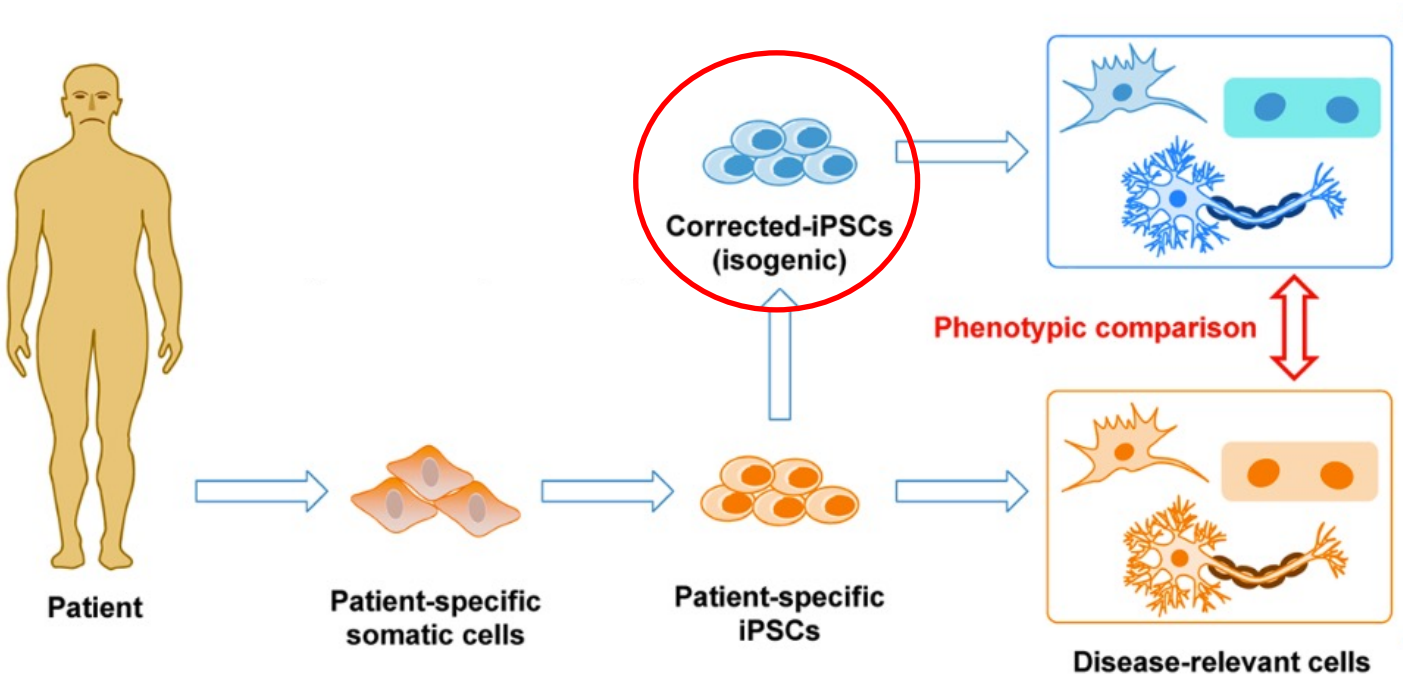



AGO1
DNA

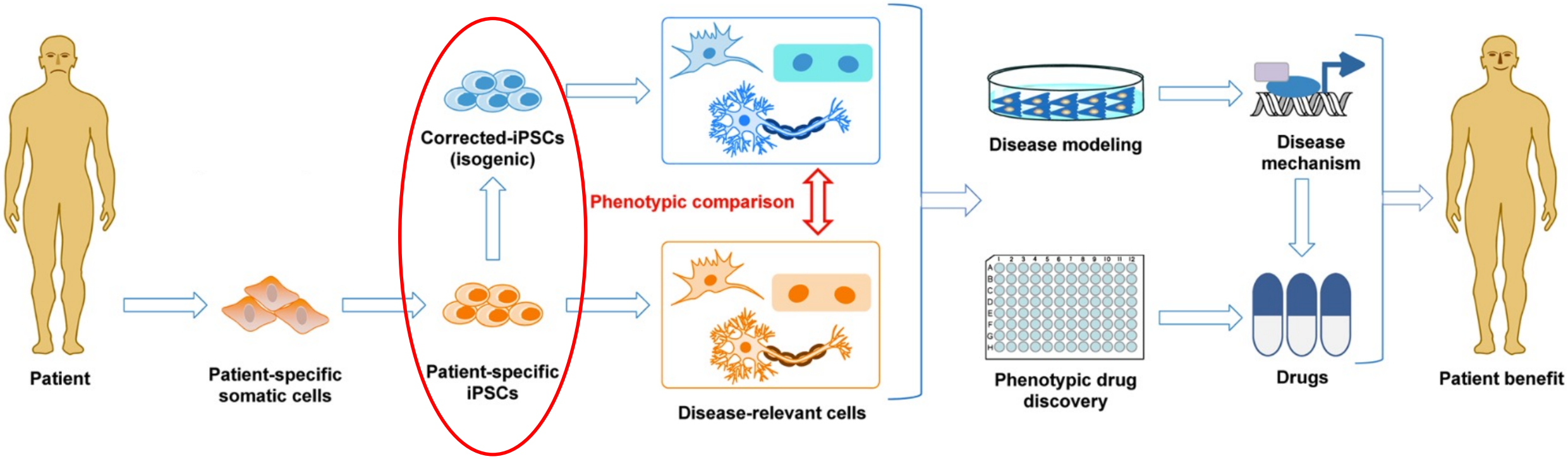

AGO1
DNA



Tang *et al* J Med Chem 2015

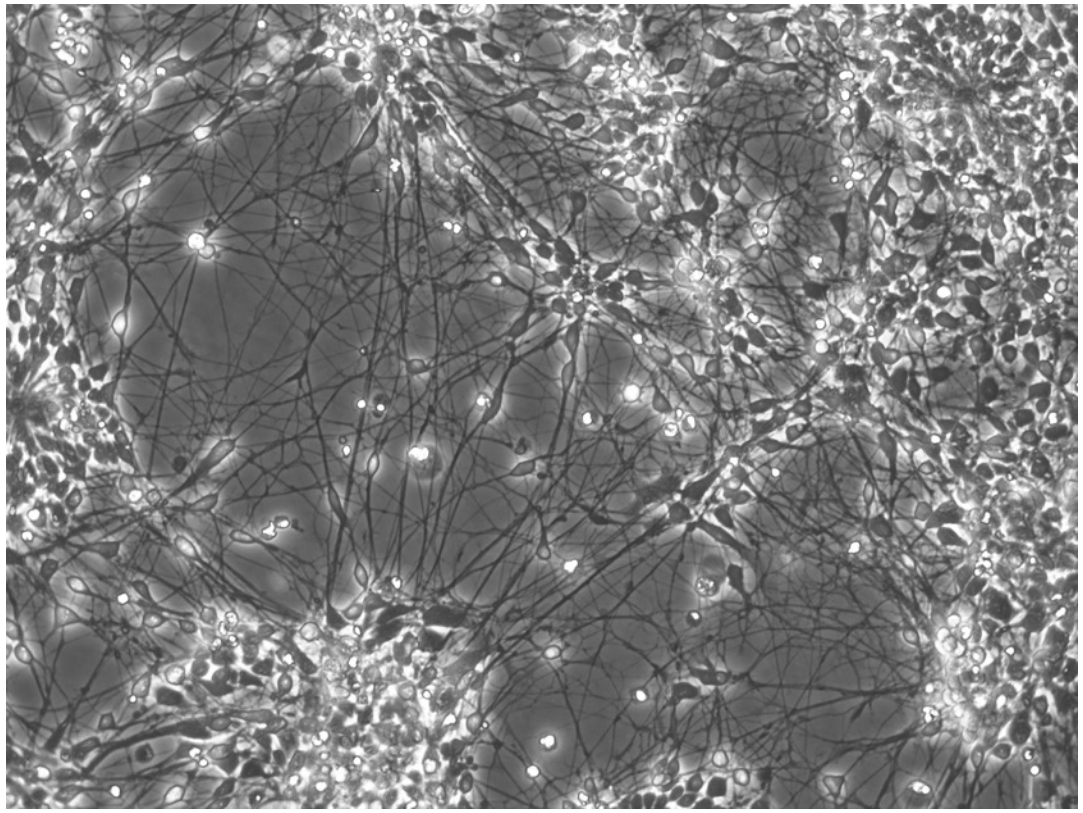


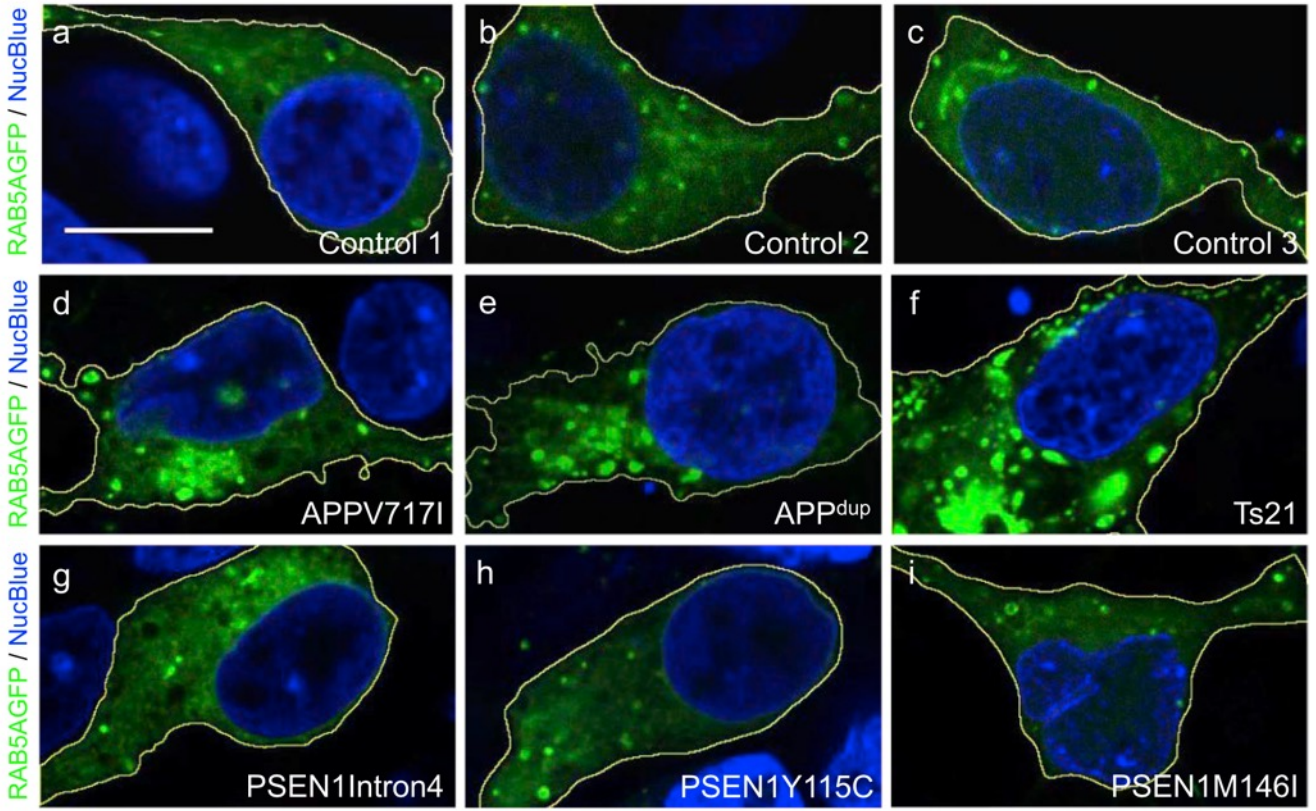
Tang *et al* J Med Chem 2015



Tang *et al* J Med Chem 2015

Alzheimer’s disease





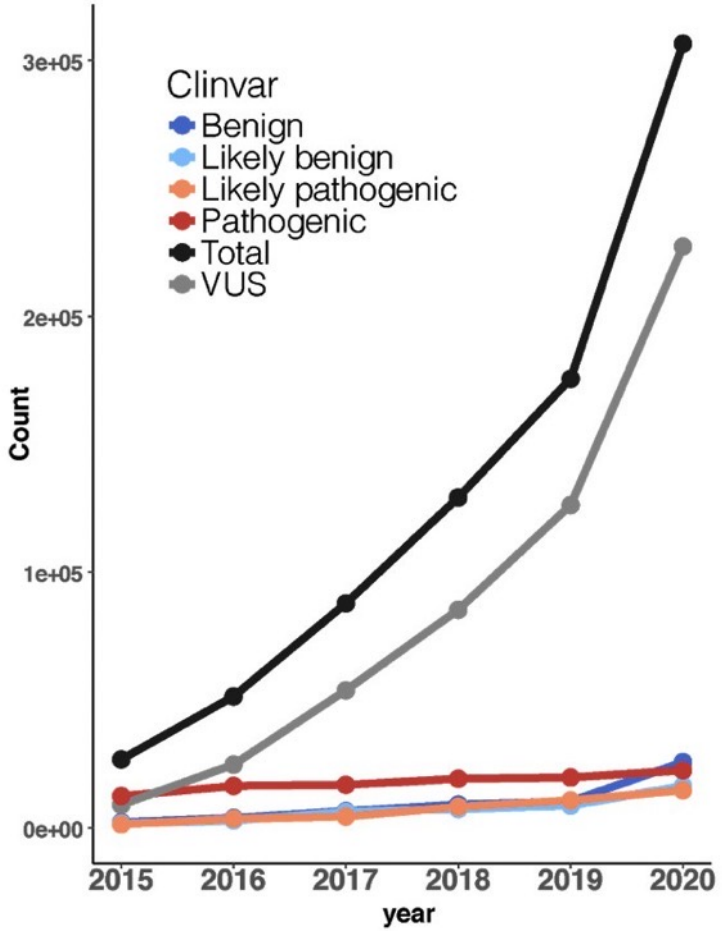
Rick Livesey, Lewis Evans

COSMIC
Catalogue Of Somatic Mutations In Cancer

TCGA

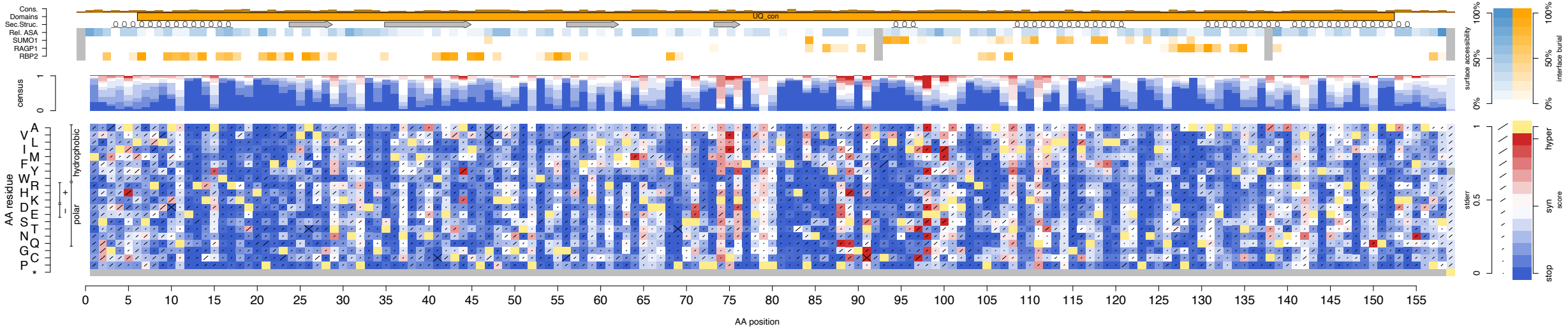
biobank uk

>500,000 disease-associated mutations
… expanding exponentially

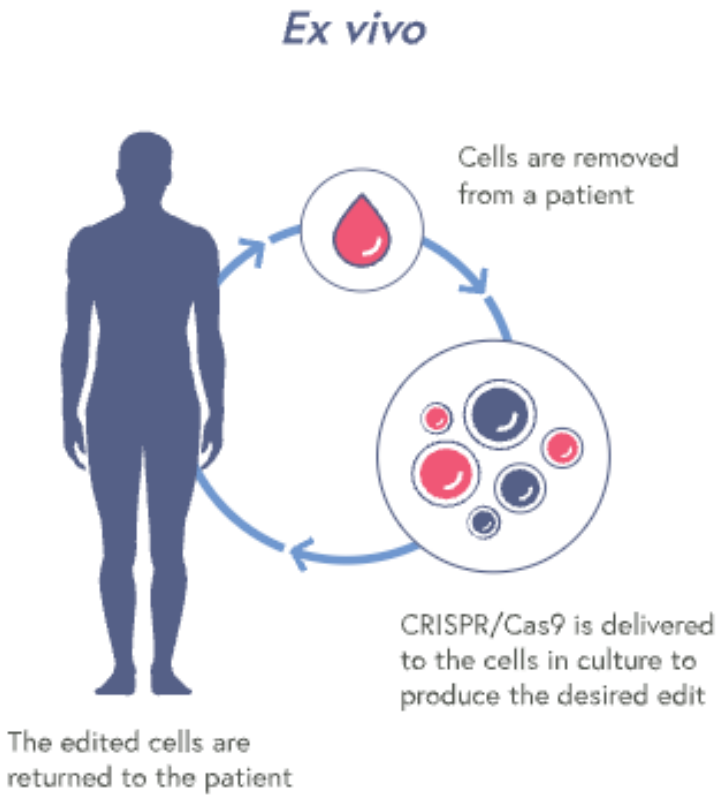


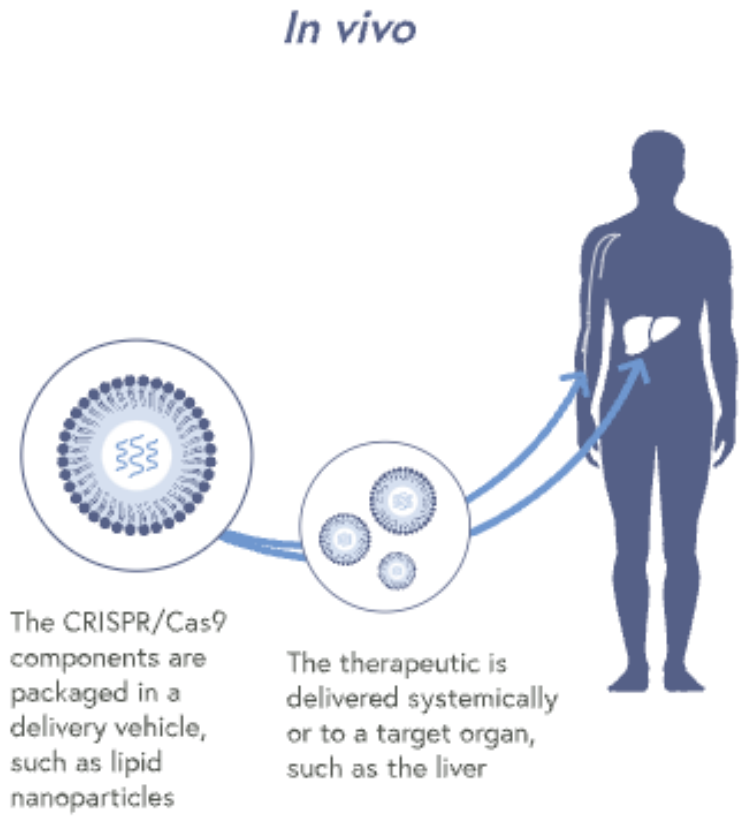
How do we understand these – one at a time is too slow
Working towards understanding all 3,000,000,000 bases in genome

Atlas of Variant Effects

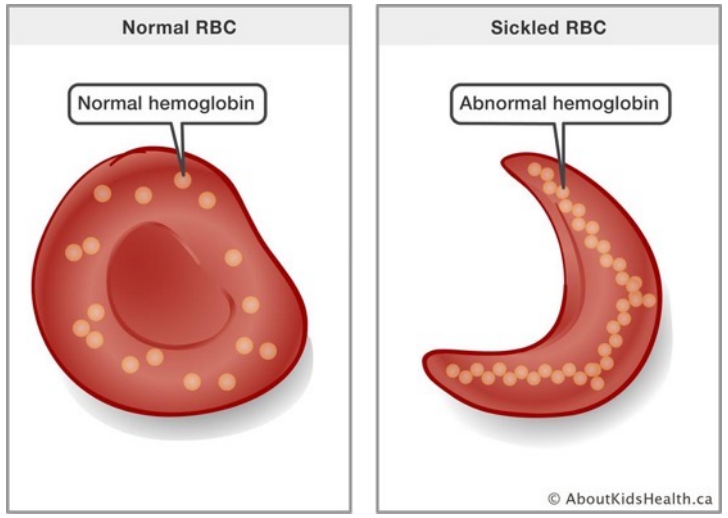


CRISPR as a drug





Sickle Cell Anaemia



1 base change in genome causes aggregation of haemoglobin
Blockages (VOC) caused by sickled blood cells 5-15x per year – cause pain and strokes

Vertex and CRISPR Therapeutics Present New Data in 22 Patients With Greater Than 3 Months Follow-Up Post-Treatment With Investigational CRISPR/Cas9 Gene-Editing Therapy, CTX001™ at European Hematology Association Annual Meeting

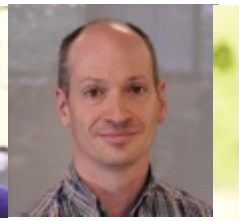
- Beta thalassemia: All 15 patients were transfusion independent after CTX001 infusion -
- Sickle cell disease: All seven patients were free of vaso-occlusive crises after CTX001 infusion -

After treatment, 16/17 (94%) patients had no VOC in 12 months!

Cellular and Gene Editing Research

Sarah Cooper
(sc34@sanger.ac.uk)

Michael Quail
(mq1@sanger.ac.uk)



Daniel Gitterman
(dg20@sanger.ac.uk)

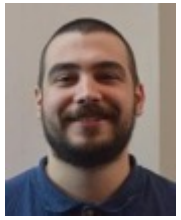
Qianxin Wu
(qw2@sanger.ac.uk)

Valentina Migliori
(vm14@sanger.ac.uk)

Andrew Trinh
(at29@sanger.ac.uk)

Filip Konopacki
(fk@sanger.ac.uk)

Chun Hao Wong
(cw24@sanger.ac.uk)



Ivan Gyulev
(ig8@sanger.ac.uk)

Michaela Bruntraeger
(mb27@sanger.ac.uk)

Aleks Gontarczyk
(ag33@sanger.ac.uk)

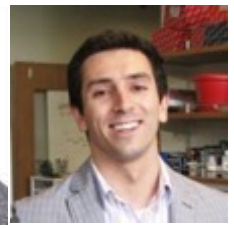
Sho Iwama
(si9@sanger.ac.uk)

HTSG / CellGen / CASM

Kenny Roberts

Tong Li

Kwasi Kwakwa

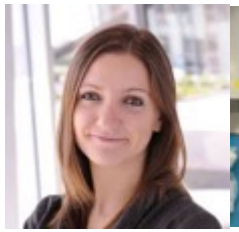


Omer Bayraktar

Lucy Yates

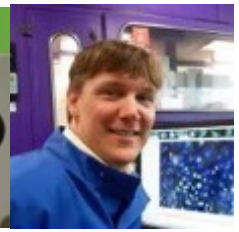
Mats Nilsson

OpenTargets Neurodegeneration



Gosia Trynka
(gosia@sanger.ac.uk)

Sally Cowley
(sally.cowley@path.ox.ac.uk)

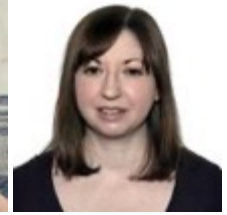


Daniel Ebner
(daniel.ebner@ndm.ox.ac.uk)

Marta Perez-Alcantara
(ma23@sanger.ac.uk)

Sam Washer
(sw30@sanger.ac.uk)
(sam.washer@path.ox.ac.uk)

Yixi Chen
(yc4@sanger.ac.uk)



Juliette Steer
(js47@sanger.ac.uk)

Leopold Parts
(lp2@sanger.ac.uk)

Florian Merkle
(fm436@cam.ac.uk)

Caia Dominicus
(cd8@sanger.ac.uk)

Diego Peretti
(dp25@sanger.ac.uk)

Shikha Kataria
(sk22@sanger.ac.uk)

Claudia Feng
(cf14@sanger.ac.uk)

Joseph McWilliam
(jm67@sanger.ac.uk)