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Genome Editing
Brief Overview

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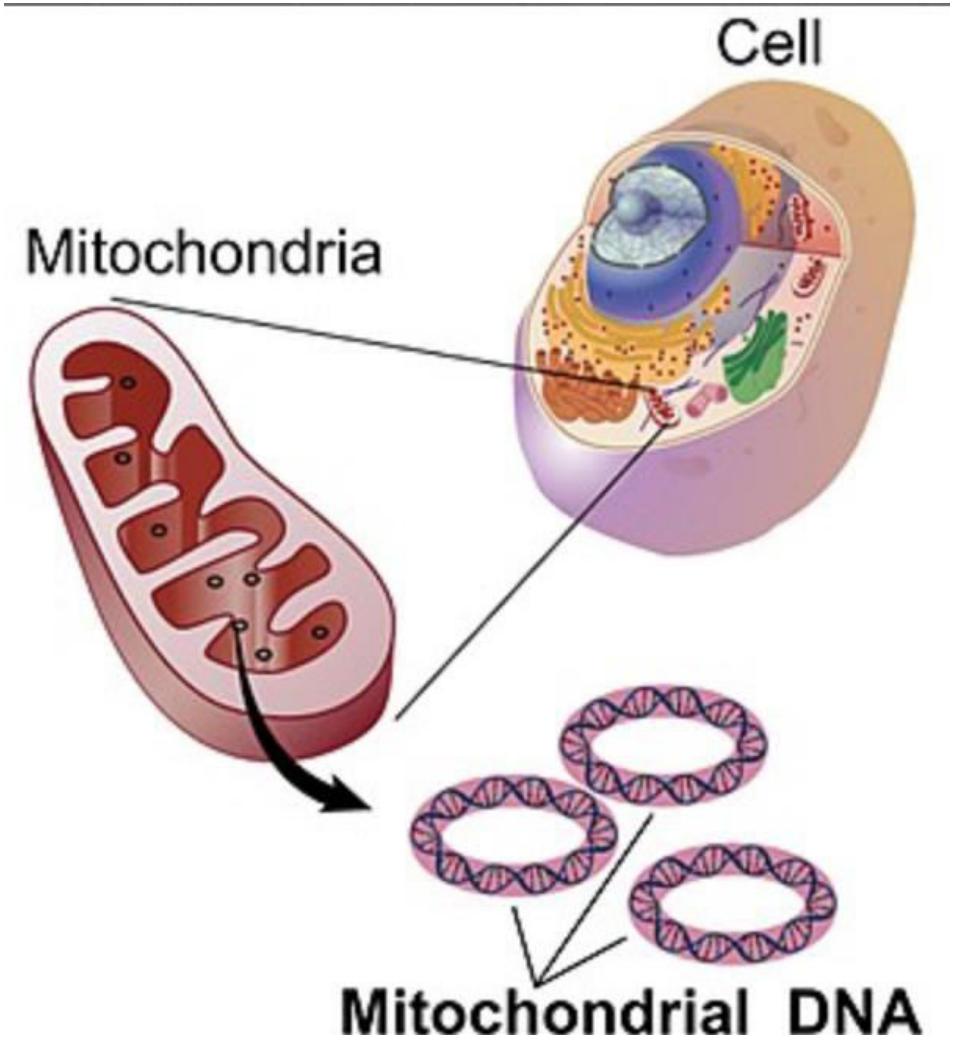
Centre for Research Ethics & Bioethics

Rare Disease 360 May 10-12 2018, Vienna

Genome Editing includes different categories of changes

- Site-specific changes in DNA in the nuclear genome
- Replace mitochondria (in fertilized eggs)



https://upload.wikimedia.org/wikipedia/commons/thumb/1/17/Mitochondrial_DNA_lg.jpg/300px-Mitochondrial_DNA_lg.jpg

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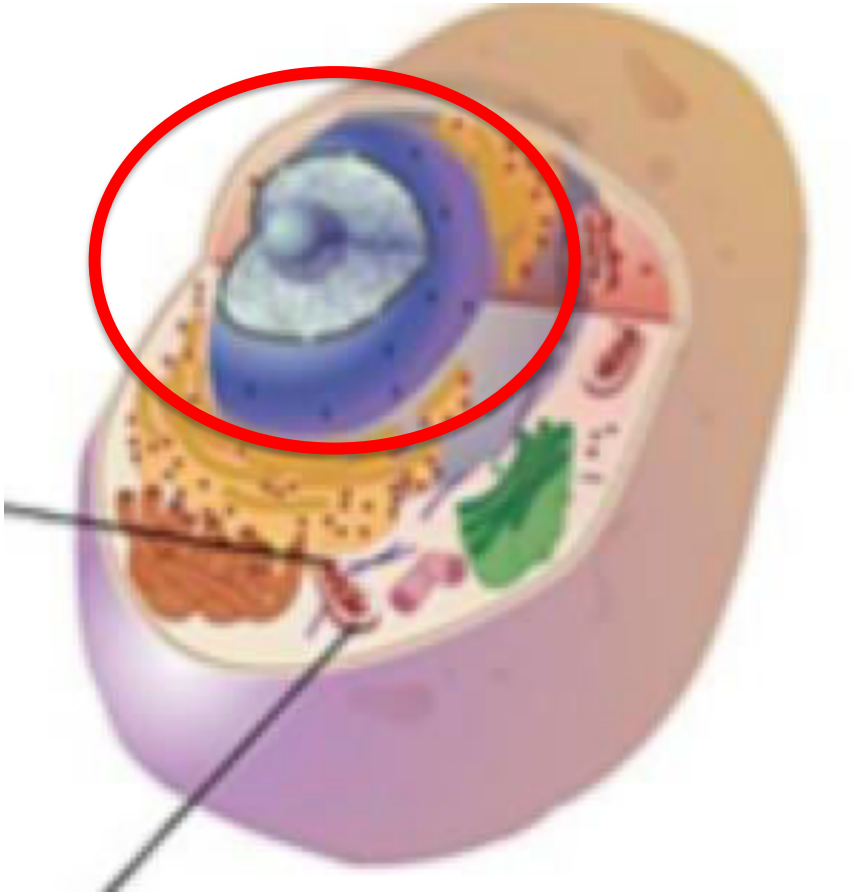

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What Tools/technologie are used?

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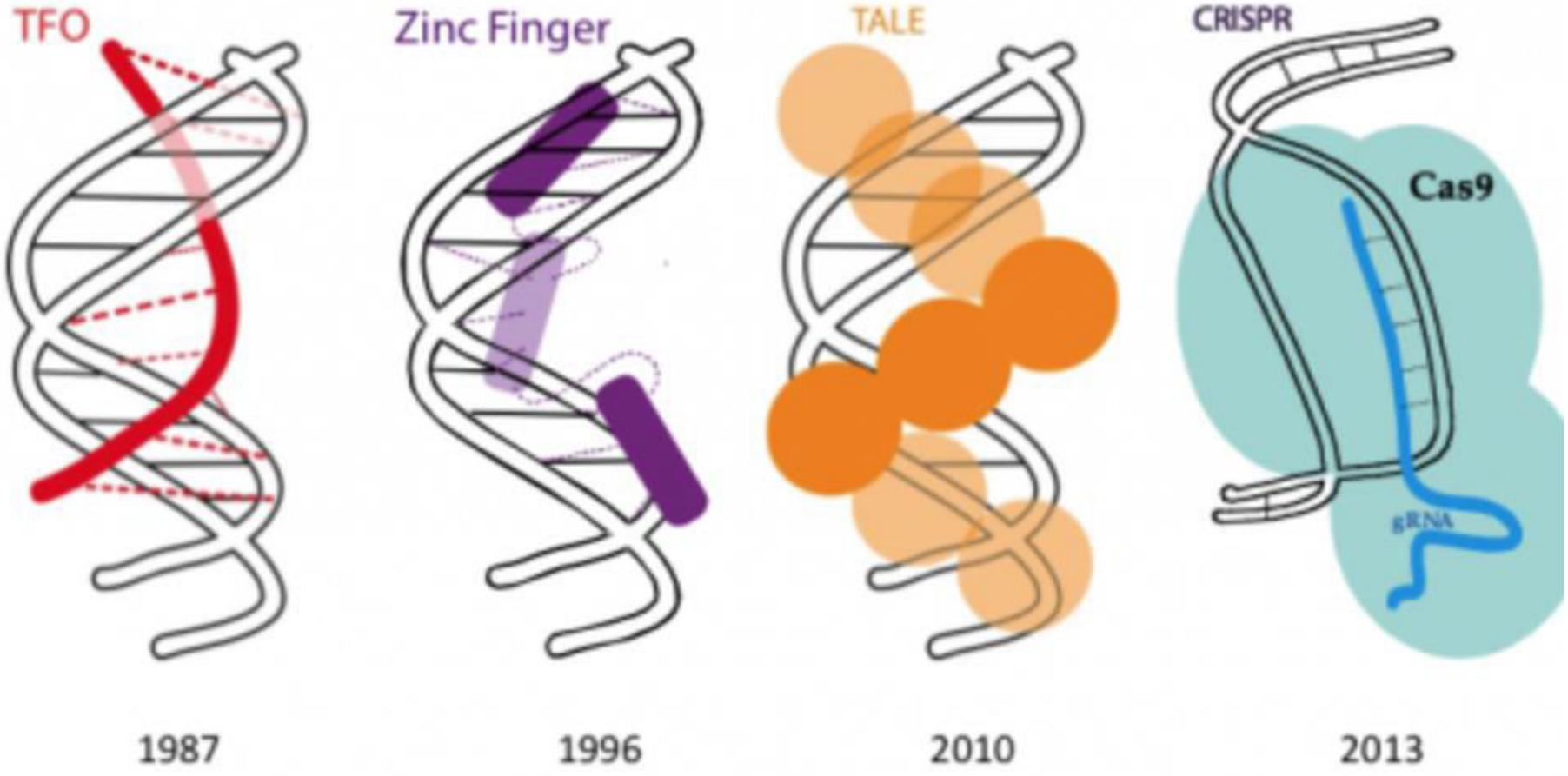
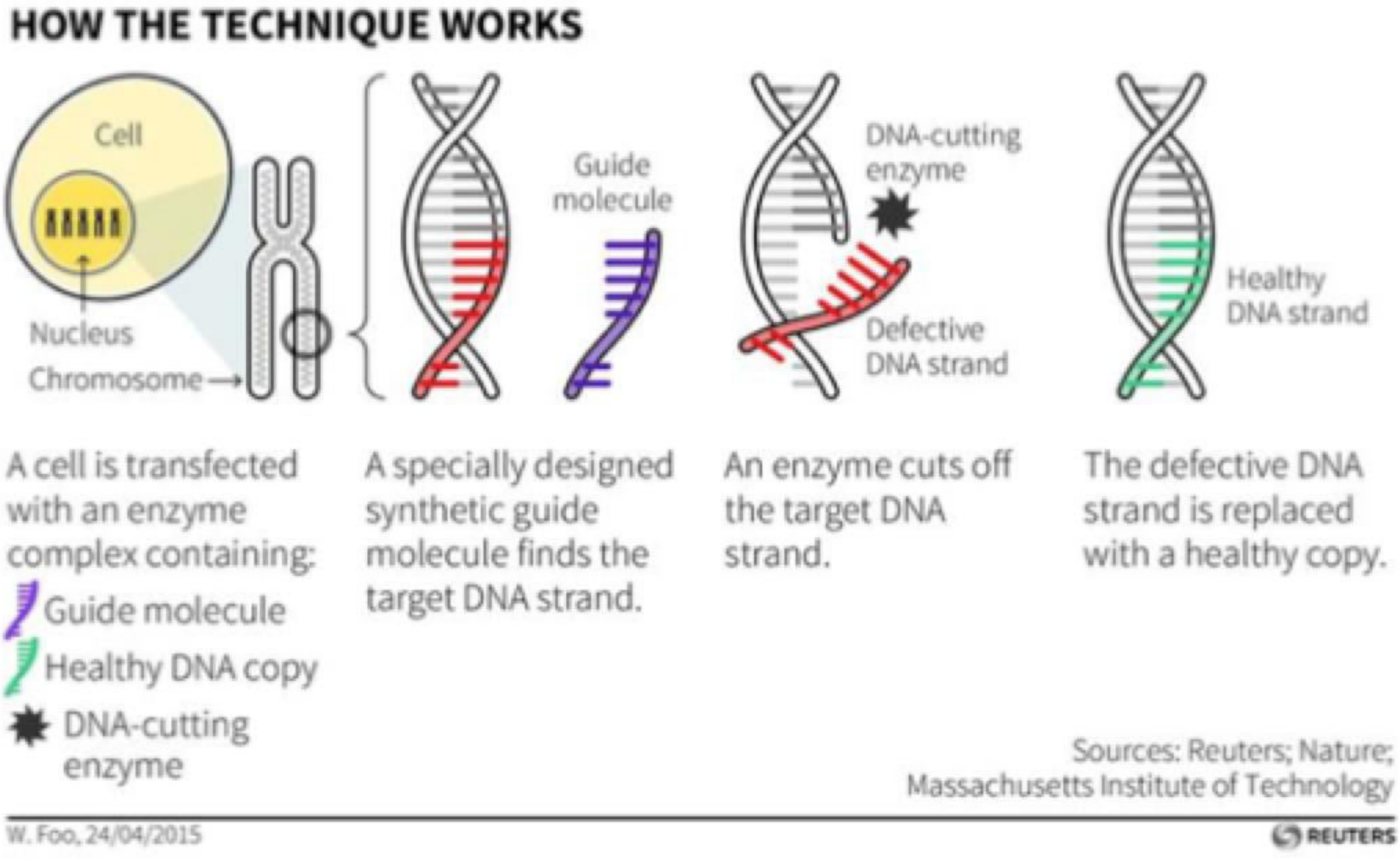
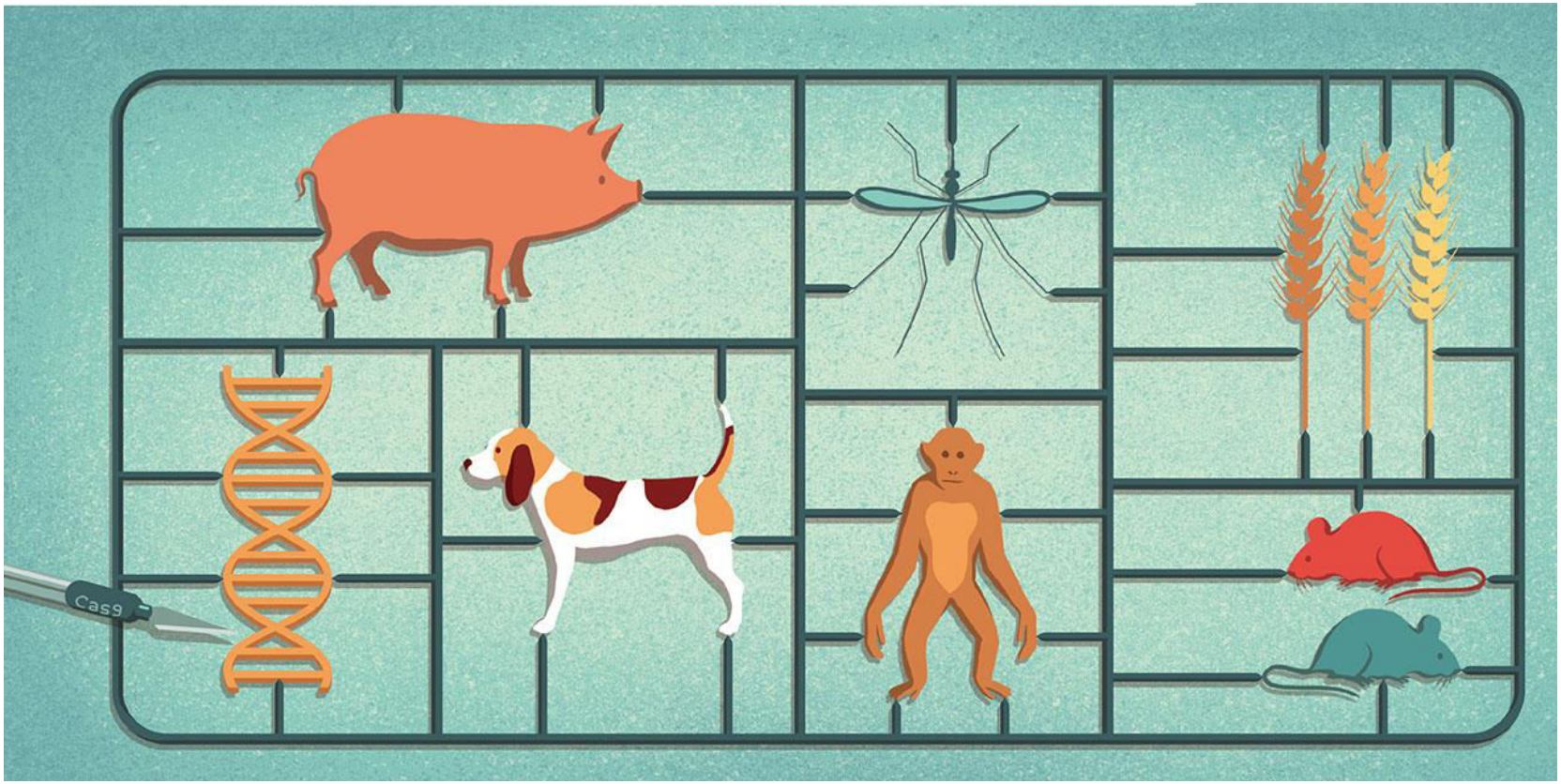


http://biophysique.mnhn.fr/site/Genome+Editing,+DNA+double-strand+break+Repair+and+cellular+Responses+(GE2R)

How it works

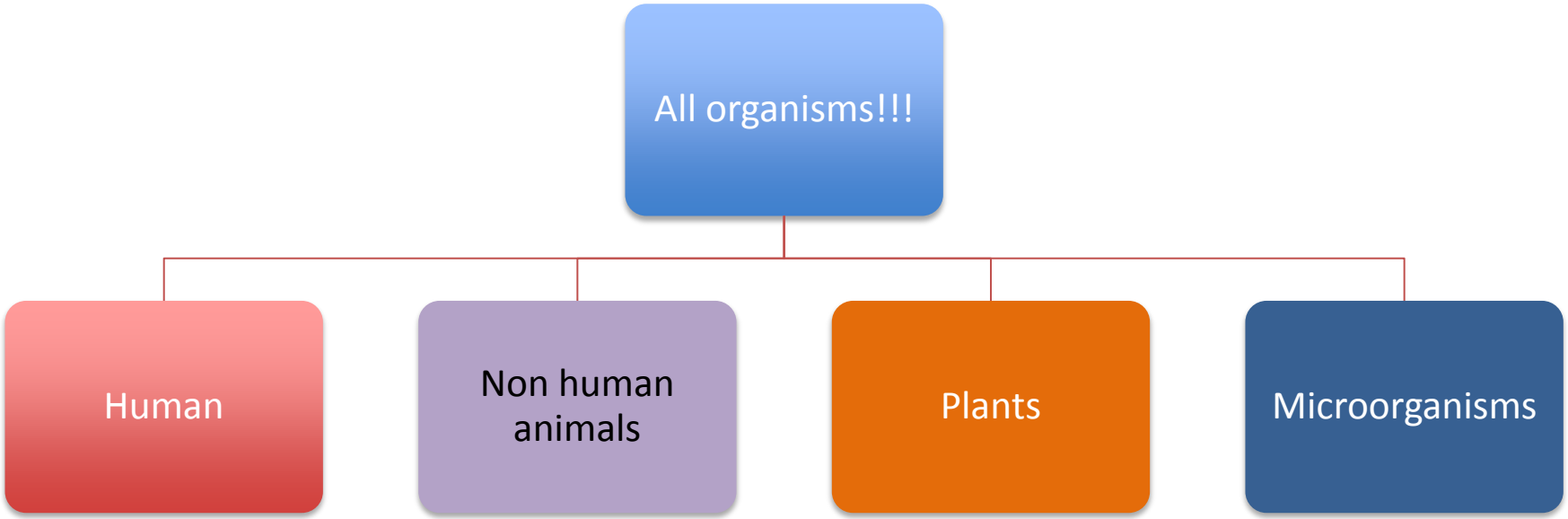

HOW THE TECHNIQUE WORKS
Cell
Nucleus
Chromosome
Guide molecule
DNA-cutting enzyme
Defective DNA strand
Healthy DNA strand
A cell is transfected with an enzyme complex containing:
Guide molecule
Healthy DNA copy
DNA-cutting enzyme
A specially designed synthetic guide molecule finds the target DNA strand.
An enzyme cuts off the target DNA strand.
The defective DNA strand is replaced with a healthy copy.
Sources: Reuters; Nature; Massachusetts Institute of Technology
W. Foo, 24/04/2015
REUTERS

Genome Modification can be used in many different types of organisms, including humans



http://science.sciencemag.org/content/350/6267/1456

Important to be context specific when discussing ethical, legal and social issues (ELSI)



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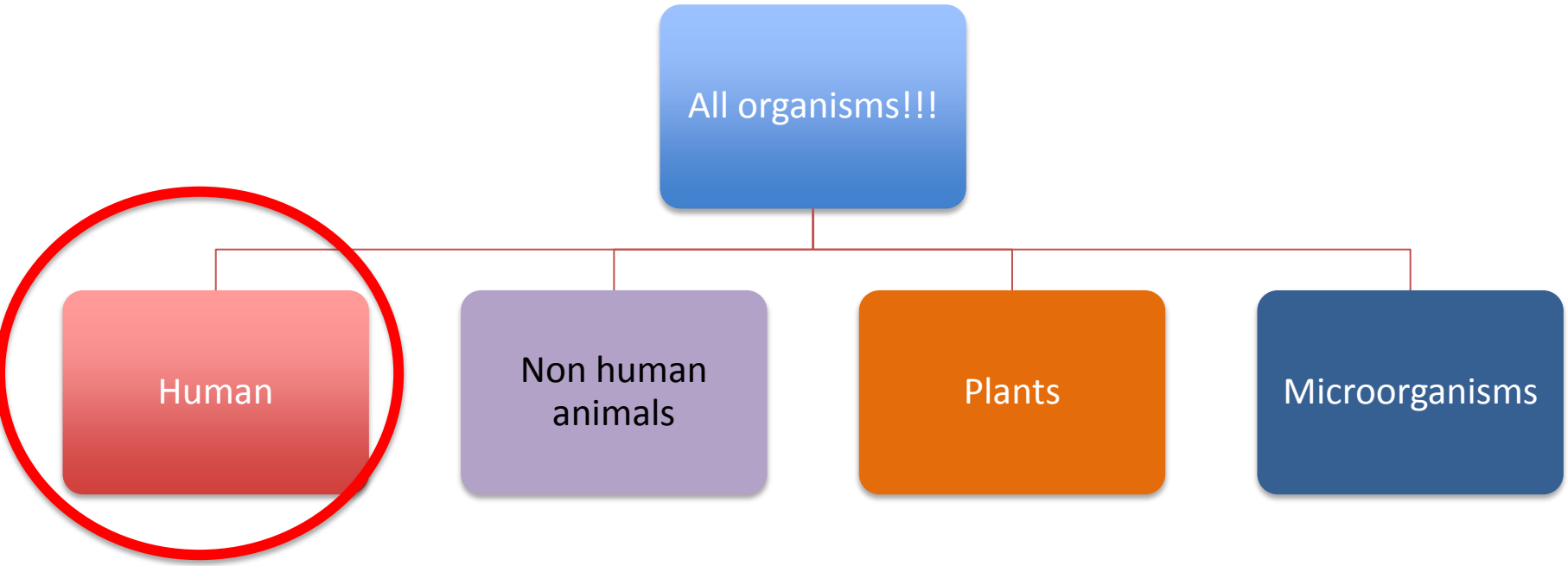
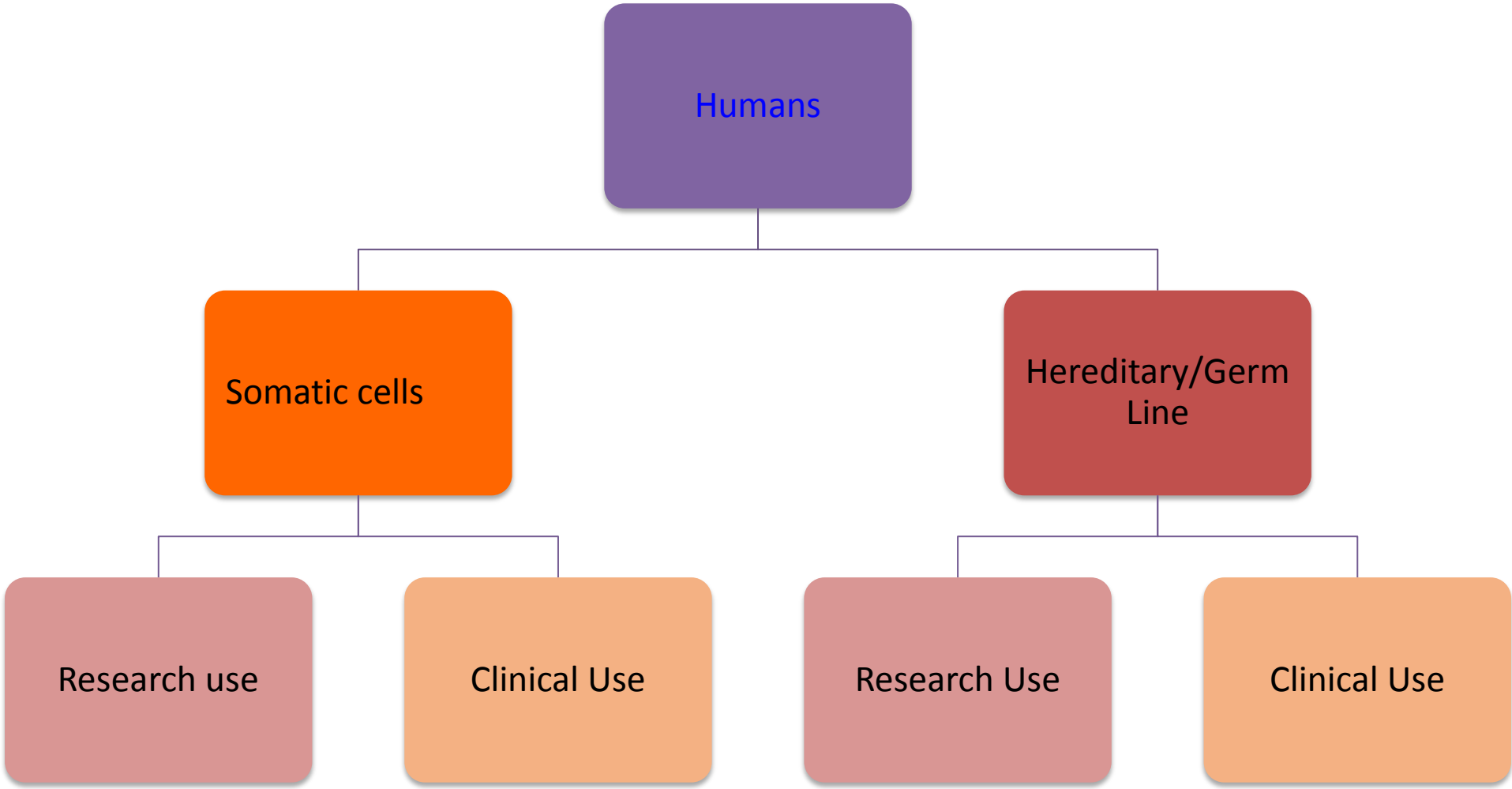
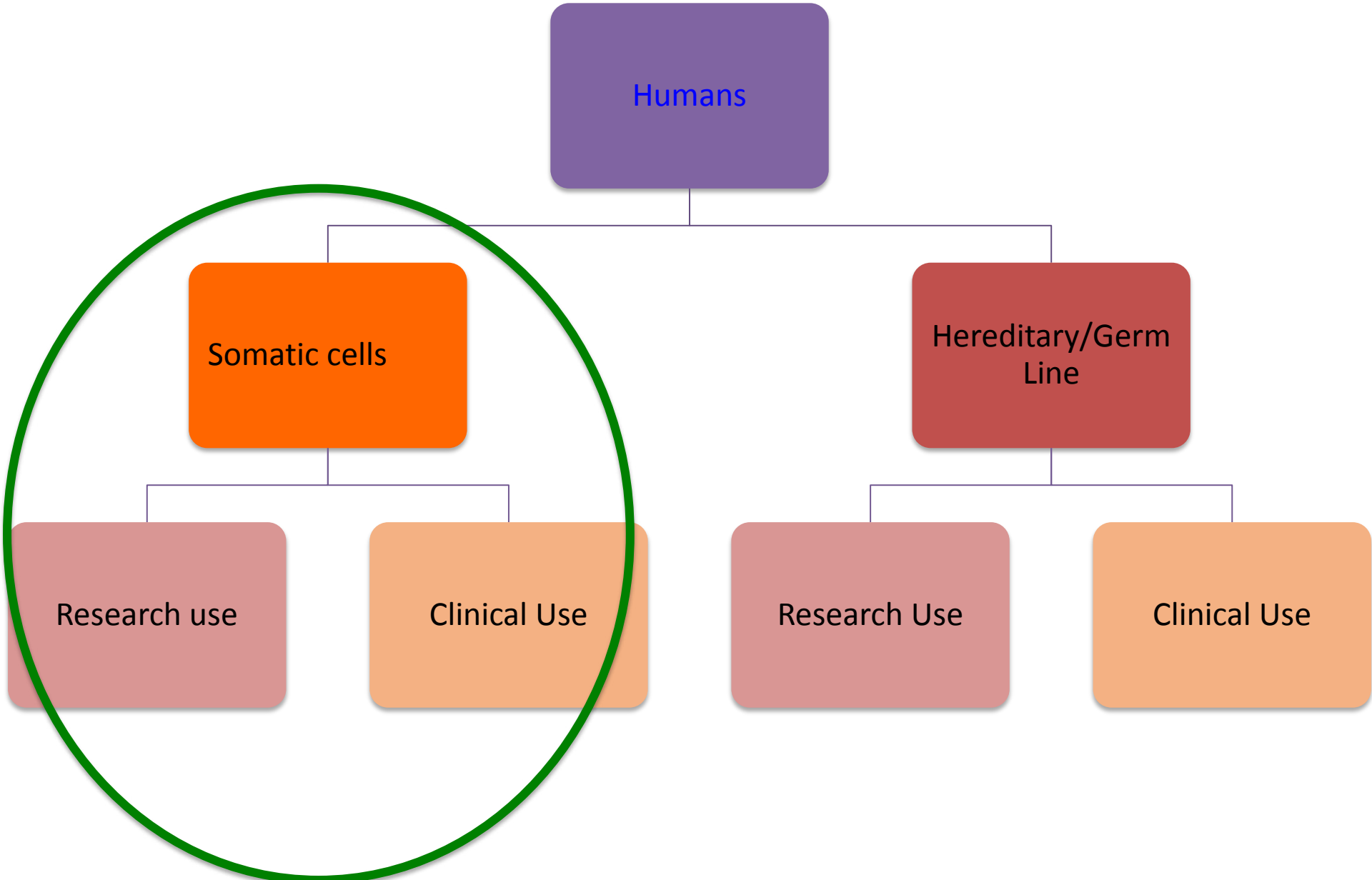



Humans
Somatic cells
Hereditary/Germ Line
Research use
Clinical Use
Research Use
Clinical Use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Somatic Genome Modification in humans is **now happening in**

- basic research

- in clinical trials, e.g. ZFN used to modify receptor in HIV infected cell

- in clinical use: compassionate (2015, baby with leukemia) use

  VS

  regular/standard of care

Somatic Genome Modification hints at the future

Target	Strategy
Viral infections	
HIV	Inactivating HIV receptors (CCR5, CXCR4)
	Knocking out essential host factors (LEDGF/p75)
	Excising viral genomes
	Targeted integration of antiviral factors
Hepatitis B virus	Inhibiting viral replication
Herpes simplex virus	Inhibiting viral replication
Human papilloma virus	Inactivating essential viral genes
T-cell immunotherapy	Knocking out endogenous T-cell receptors
	Knocking out self antigens
	Knocking out glucocorticoid receptor
	Knocking out checkpoint inhibitors
Hematologic disorders	
X-SCID	Gene correction in T cells and CD34+ HSCs
ADA-SCID	Gene modification in cell lines
RS-SCID	Gene correction in patient iPSCs
Sickle cell disease and β-thalessemia	Correction of β-globin mutations in iPSCs
	Correction of β-globin mutations in CD34+ HSCs

Adapted from Morgan L Maeder and Charles A Gersbach, 'Genome-Editing Technologies for Gene and Cell Therapy', YMTHE, 24/3 (2016),

Somatic Genome Modification hints at the future

Target	Strategy
	Inactivation of the enhancer of BCL11A
Liver-targeted gene editing	
Hemophilia	Targeted cDNA addition to endogenous gene
Enzyme replacement	Targeted gene addition to albumin locus for hemophilia and lysosomal storage disorders
Tyrosinemia type I	Gene correction in mouse liver
PCSK9	Gene disruption in mouse liver to lower cholesterol
α-1-antitrypsin deficiency	Gene correction in human iPSCs and differentiation into liver cells
Neuromuscular disorders	
Duchenne muscular dystrophy	Ex vivo targeted insertion of missing exons
	Ex vivo targeted insertion of a therapeutic minigene
	Ex vivo frameshift correction by NHEJ
	Ex vivo reading frame restoration by exon deletion
	In vivo reading frame restoration by exon deletion
Skin disorders	
Epidermolysis bullosa	Gene correction in fibroblasts and iPSCs
Ocular disorders	
Leber's Congenital Amaurosis type 10	Deletion of an aberrant splice site
Respiratory disorders	
Cystic fibrosis	Gene correction in stem cells
	Gene correction in mouse lung epithelium
Antimicrobials	
Bacterial infection	Reduction of bacteria in infection models

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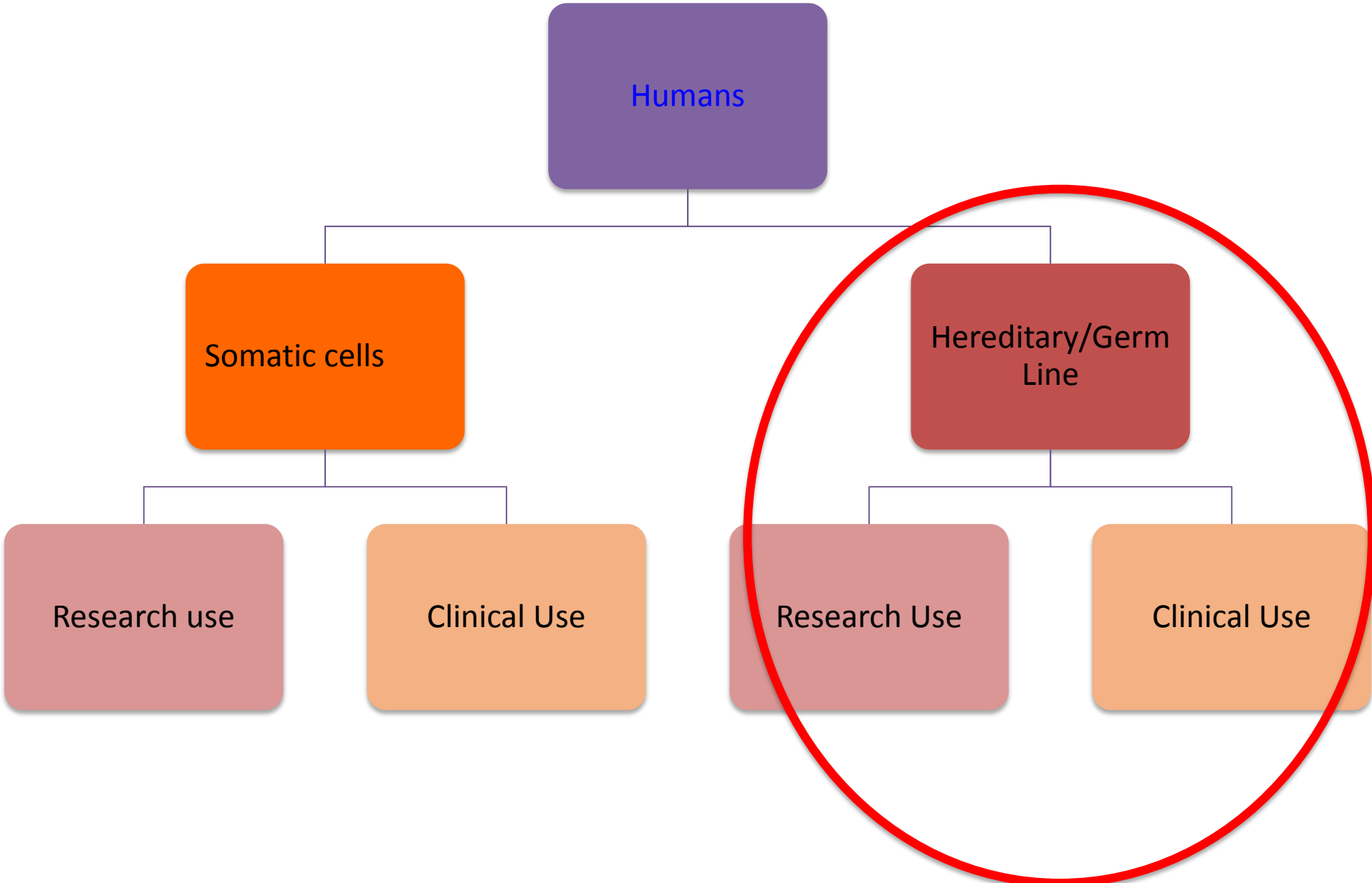
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Germ Line/Hereditary Genome Editing in human cells

Basic Research: regulated differently in different countries

- work ongoing in UK, Sweden, USA, China

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Clinical Trials in humans: not legally permitted in Europe

ch.18. article 90: “No gene therapy clinical trials may be carried out which result in modifications to the subject's germ line genetic identity.”

Thank you!

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sienna.
Technology, ethics and human rights

Vetenskapsrådet

Swedish Research Council

BBMRI-ERIC

Member:

- **PPPC ESHG**
- **ELSI board EIT Health**
- **Common Service ELSI BBMRI**
- **SAB PhenoMeNal**

wellcome trust sanger institute

Gene Therapy and Genome Modification? Where do they meet?

- Traditional gene therapy are vector-based or viral-based
  - Considered adding the “normal” DNA
- GM tools like CRISPR does not use these