آزمایشگاه طب بازساختی و نوآوریهای پزشکی
再生医療学医薬基盤研究室

The **First** *(TvAI)* **Skyroom**
International **Virtual Congress on** the practical Application of Artificial Intelligence in **Medical Sciences**

Date & Time: 1-5 February 2025 (09:00 Am - 12:00)

Artificial Intelligence and Future of Biodesign

Hosein Shahsavarani, Ph. D

Principal investigator, Lab. of Regenerative Medicine & Biomedical Innovations

Biodesign and genome editing in news

Baby mice have been made with two mums and no dad

Russian biologist plans more CRISPR-edited babies

The proposal follows a Chinese scientist who claimed to have created twi embryos last year.

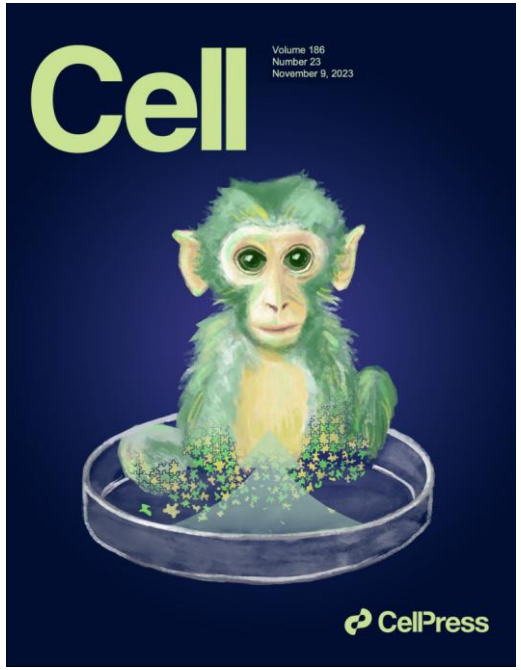
By David Cyranoski

A Russian scientist says he is planning to produce gene-edited babies, an act that would make him only the second person known to have done this. It would also fly in the face of the scientific consensus that such experiments should be banned until an international ethical framework has agreed on the circumstances and safety measures that would justify them.

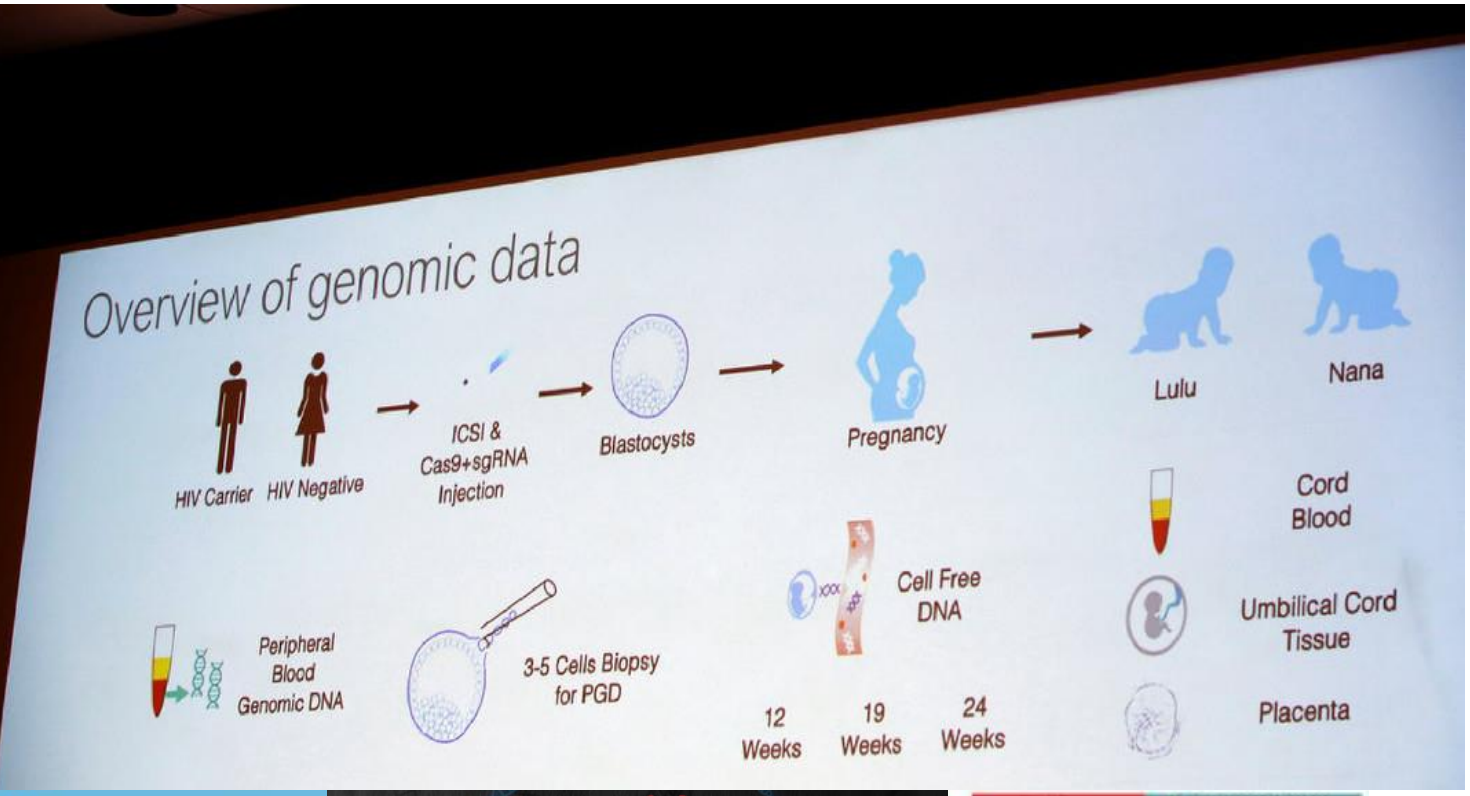
Chinese scientists report first live birth of chimeric monkey

Source: Xinhua Editor: huaxia 2023-11-14 17:58:15

Baby mice have been made with two mums and no dad



World's First Genetically Edited Babies Using CRISPR



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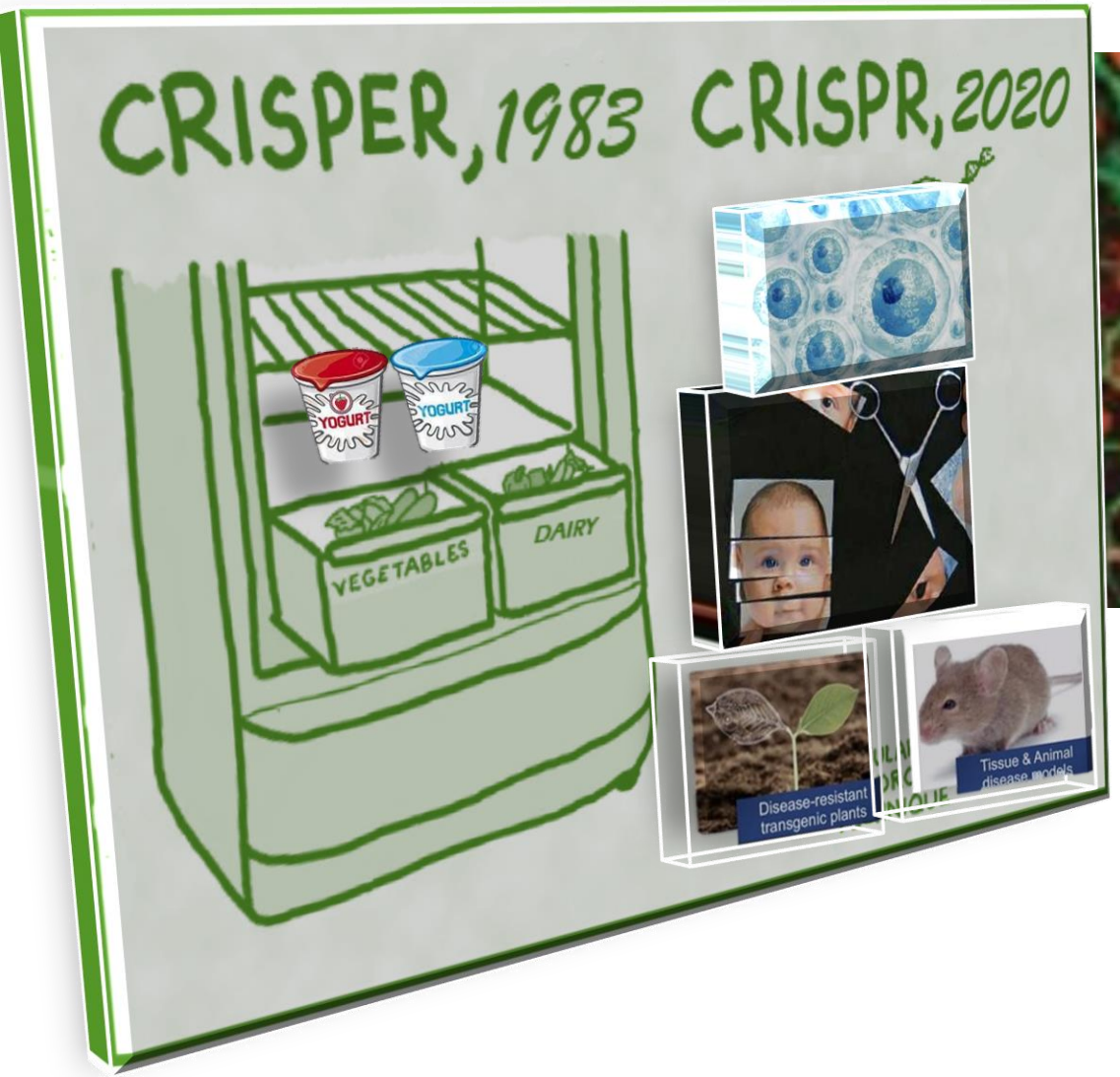
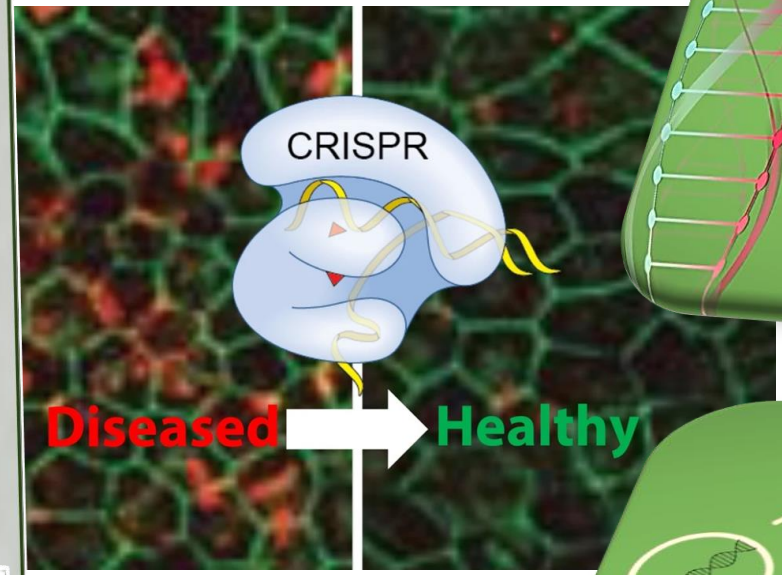
NEWS · 10 JUNE 2019

Russian biologist plans more CRISPR-edited babies

The proposal follows a Chinese scientist who claimed to have created twins from edited embryos last year.

From bacterial immune system to genome editing

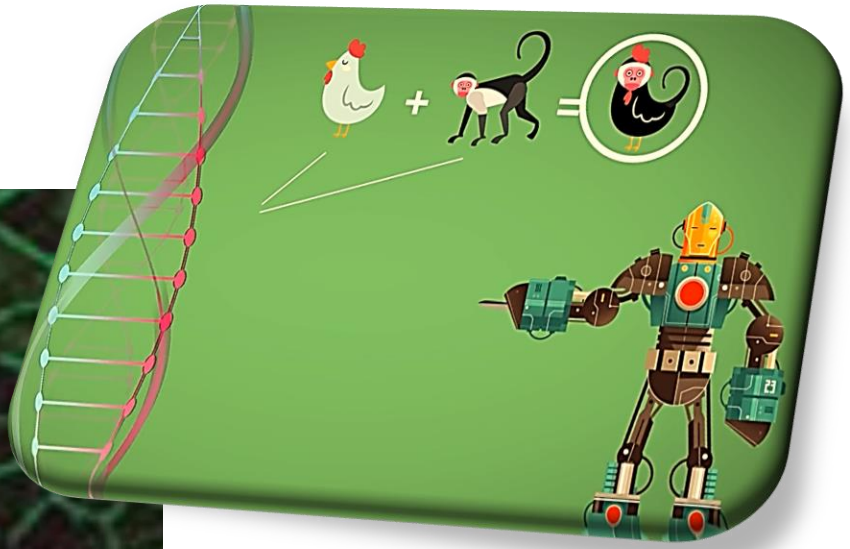




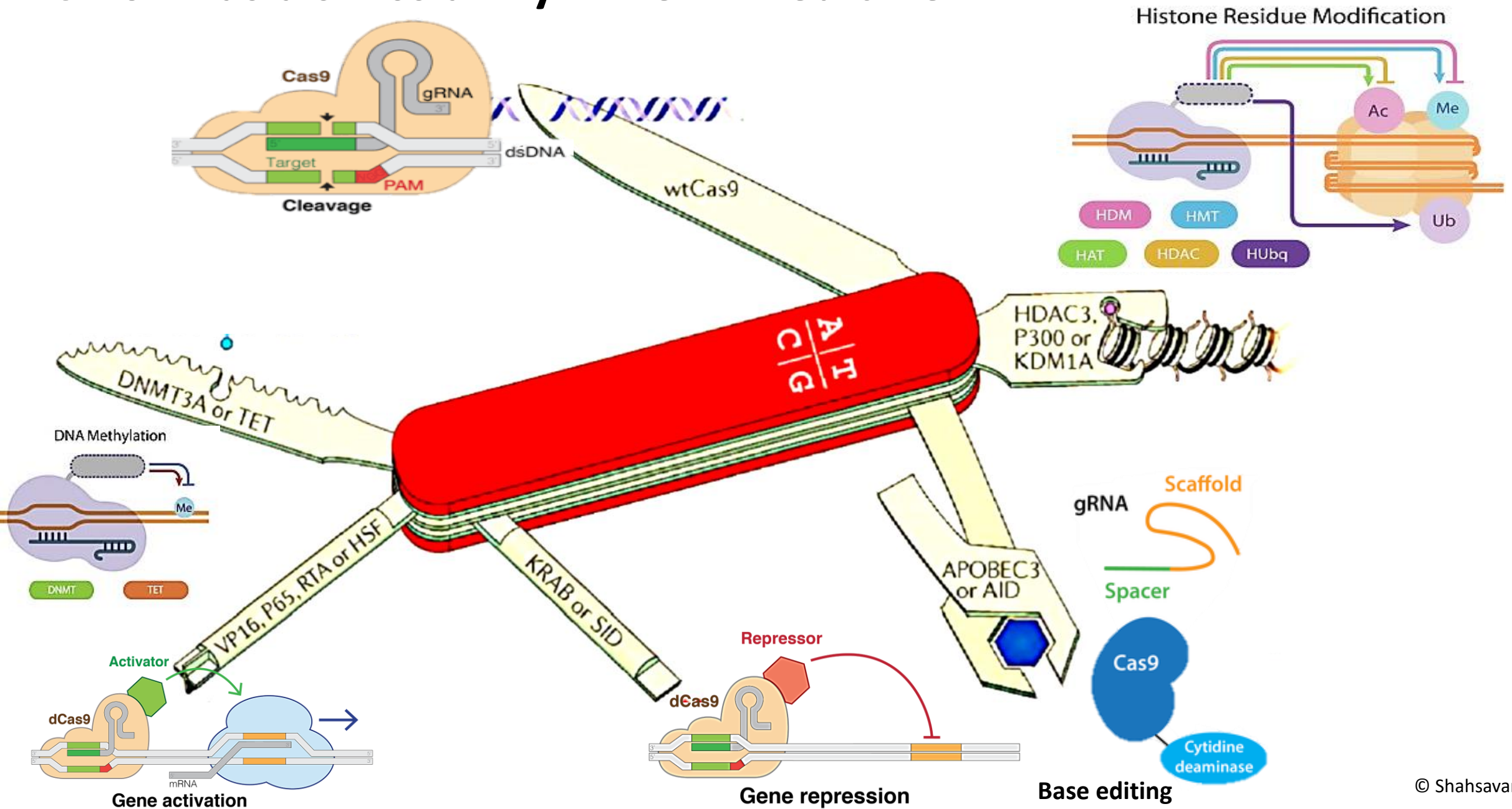
We may be nearing the beginning of the end of inheritable disease.

Jennifer Doudna

Future

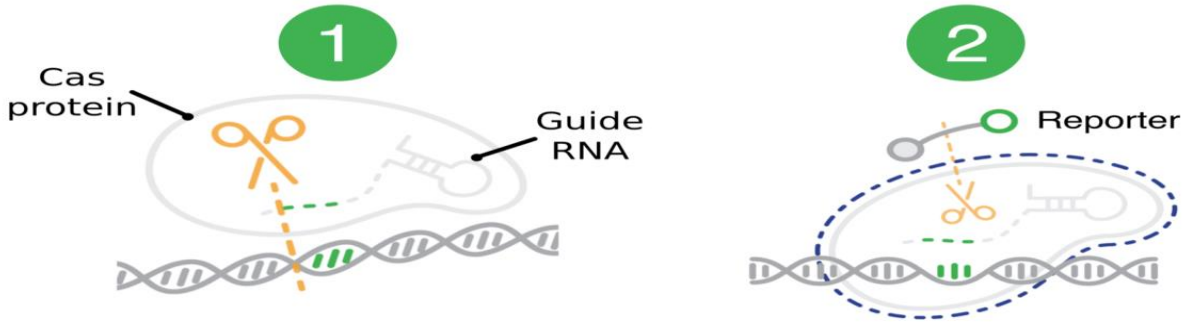


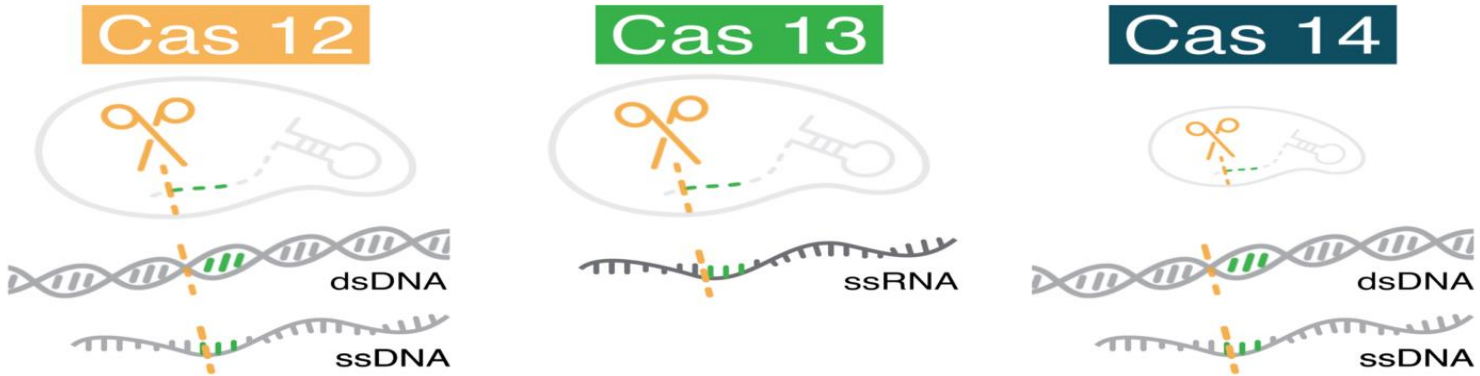
CRISPR as a swiss army knife in medicine

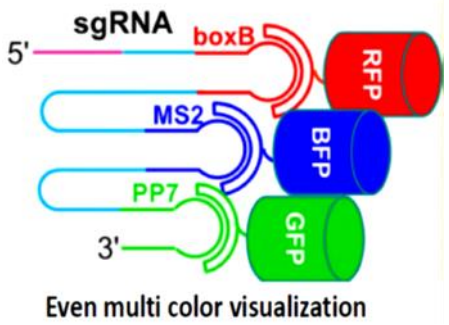


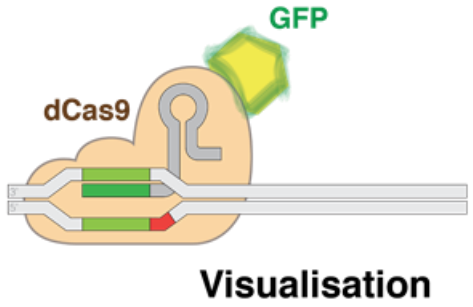
New generations and applications of CRISPR

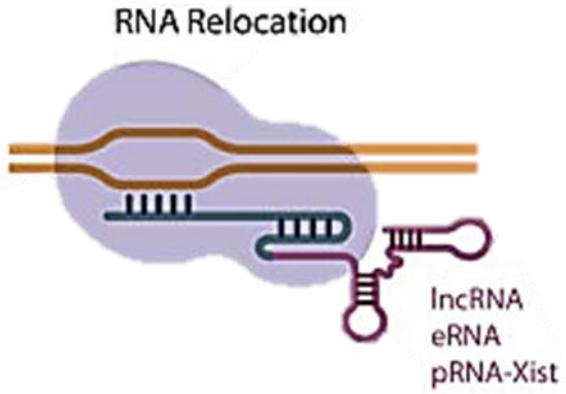
- CRISPRainbow
- Single base editing
- Temporal control of CRISPR
- Multiplexed editing
- RNA editing
- RNA relocation
- enChIP

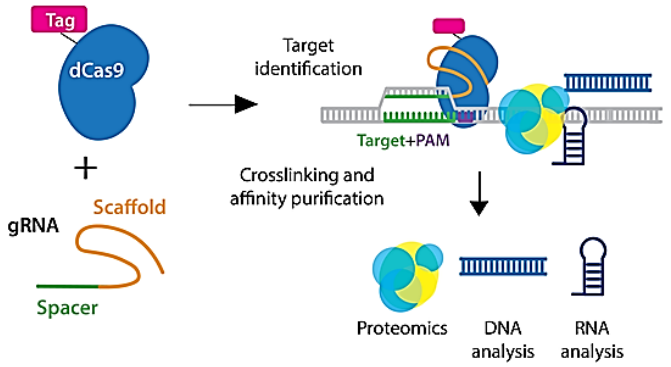












Clinical Human Applications of CRISPR

- ❑ **Viral infections: HIV, HSV, VZV**
  - ✓ **Inserted viral genome could be removed**

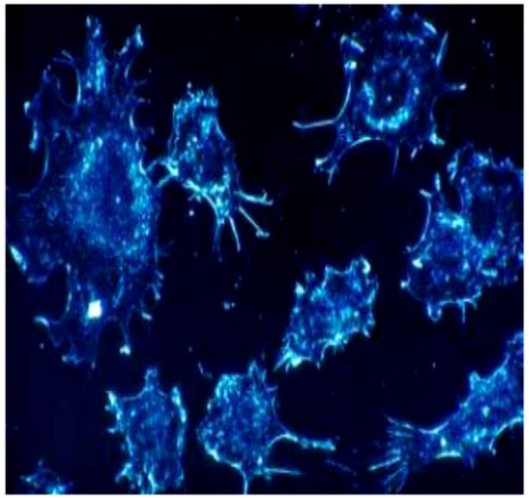
by altering immune cells

- ✓ **Human embryos: Kang &colleagues inserted the CCR5Δ32 allele into early human 3PN embryos**

- ❑ **Genetic diseases**
  - ✓ **Remove or add the sequence that is causing the disease**

- ❑ **Cancer**

Mutation driven cancers



- ❑ **Transplantation**
  - ✓ **Gene editing of mismatched human or even non-human mammals as potential organ donors**
  - ✓ **Editing will reduce risk of immune responses and rejection when using mismatched organs/tissues/cells**

Kang, X. et al. J Assist Reprod Genet 33, 581, 2016

A Crack in Creation: The New Power to Control Evolution

- **Liang et al using human tripronuclear zygotes cleaved the HBB gene with a CRISPR/Cas9- mediated system**
  - **Low efficiency and edited embryos were mosaic with off target cleavage**

- **Other clinical trials forthcoming:**
  - ✓ **Editas**
  - ✓ **CRISPR Therapeutics**
  - ✓ **Caribou Biosciences**
  - ✓ **Intellia Therapeutics**

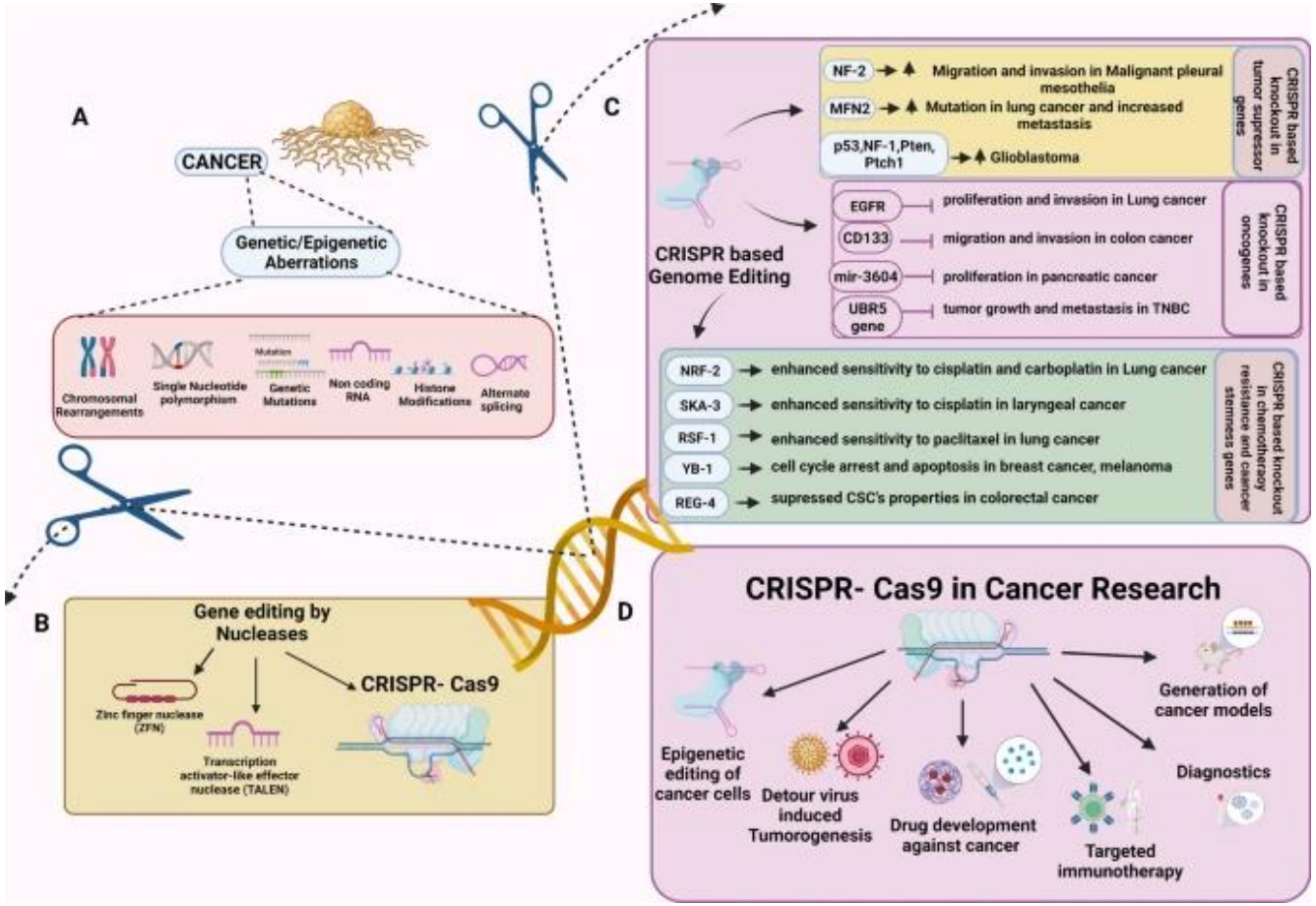
Cancer trials

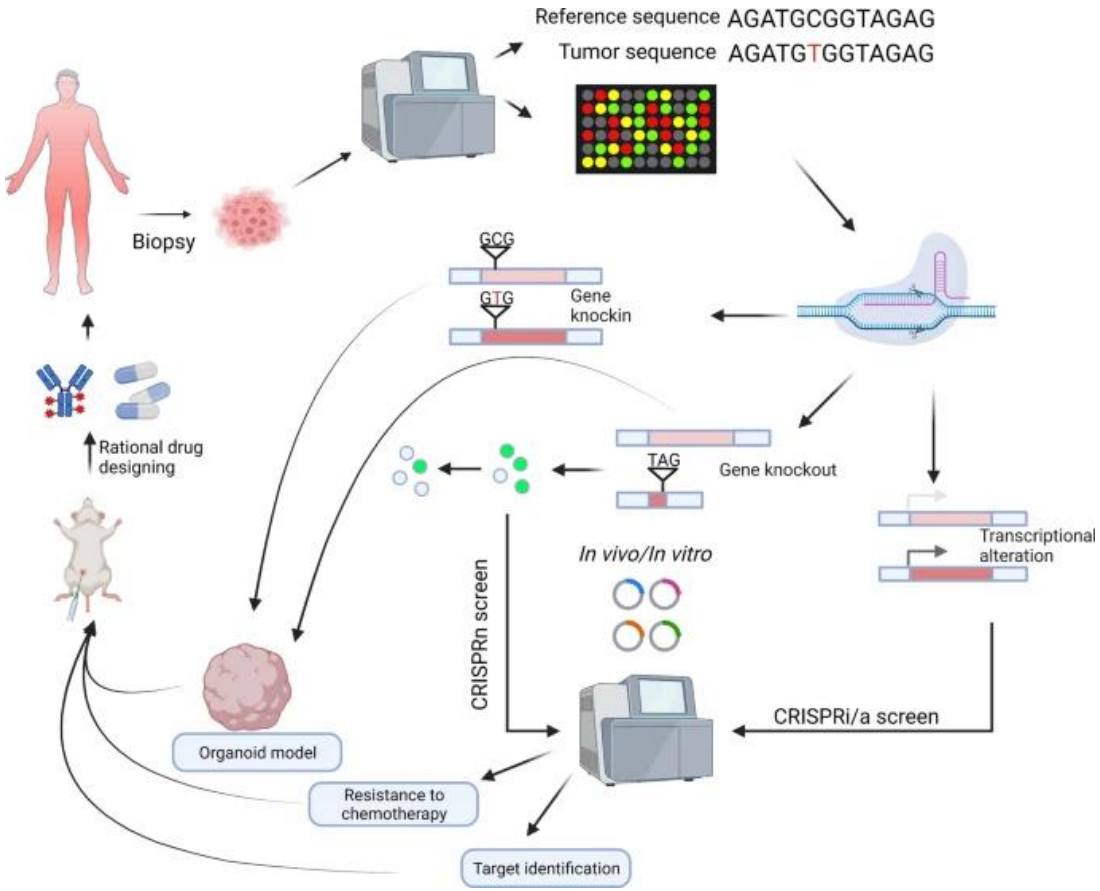
1	Not yet recruiting	**PD-1 Knockout Engineered T Cells for Metastatic Non-small Cell Lung Cancer** **Condition:** Metastatic Non-small Cell Lung Cancer **Interventions:** Drug: Cyclophosphamide; Other: PD-1 Knockout T Cells; Drug: Interleukin-2
2	Not yet recruiting	**PD-1 Knockout Engineered T Cells for Castration Resistant Prostate Cancer** **Condition:** Hormone Refractory Prostate Cancer **Interventions:** Biological: PD-1 Knockout T Cells; Drug: Cyclophosphamide; Drug: IL-2
3	Not yet recruiting	**PD-1 Knockout Engineered T Cells for Muscle-invasive Bladder Cancer** **Condition:** Invasive Bladder Cancer Stage IV **Interventions:** Biological: PD-1 Knockout T Cells; Drug: Cyclophosphamide; Drug: IL-2
4	Not yet recruiting	**PD-1 Knockout Engineered T Cells for Metastatic Renal Cell Carcinoma.** **Condition:** Metastatic Renal Cell Carcinoma **Interventions:** Biological: PD-1 Knockout T Cells; Drug: Cyclophosphamide; Drug: IL-2

Source: Clinicaltrials.gov, Sept 2016

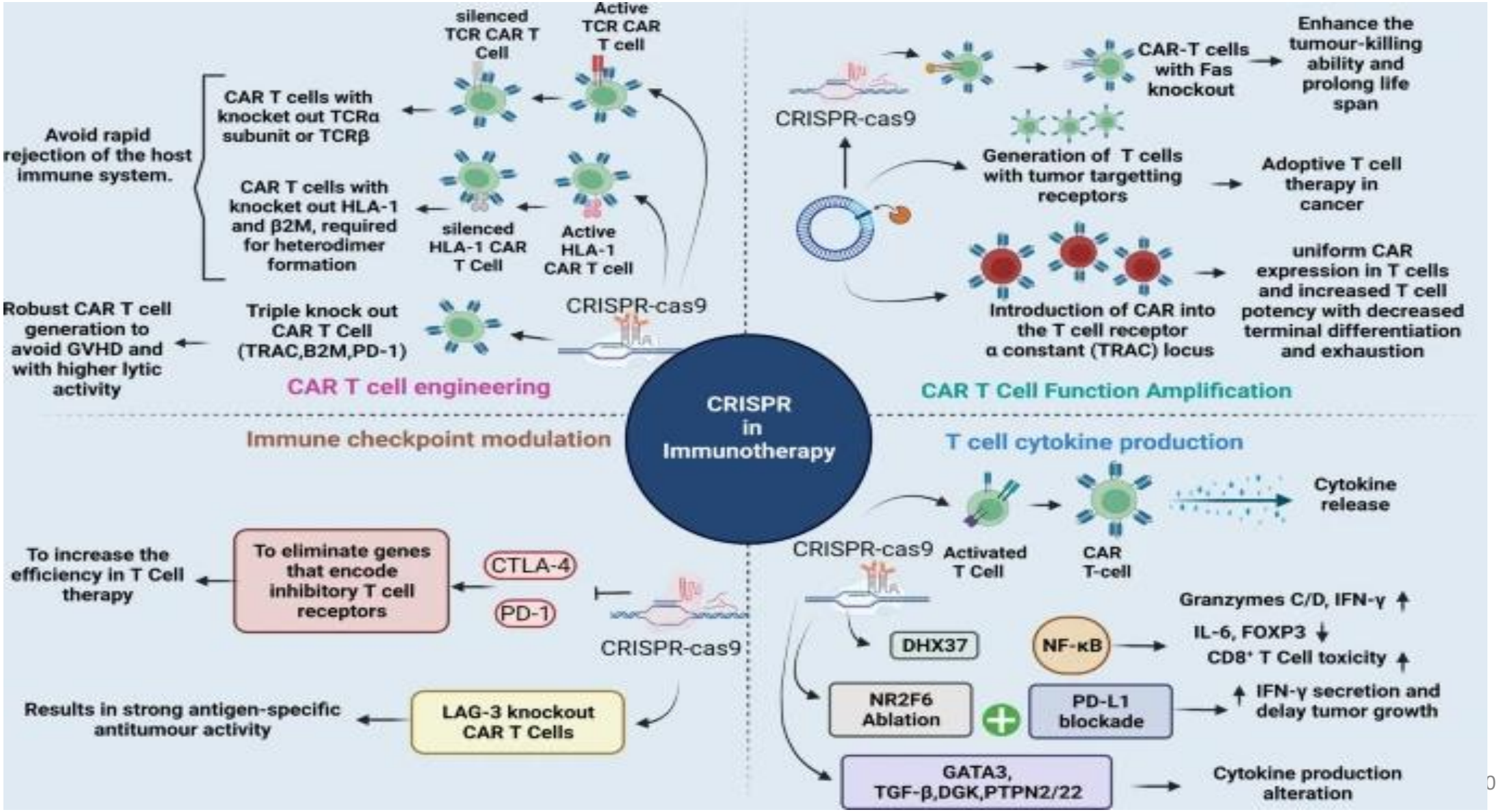
Liang et al, *Protein and Cell* 2015

A paradigm shift in cancer therapeutics

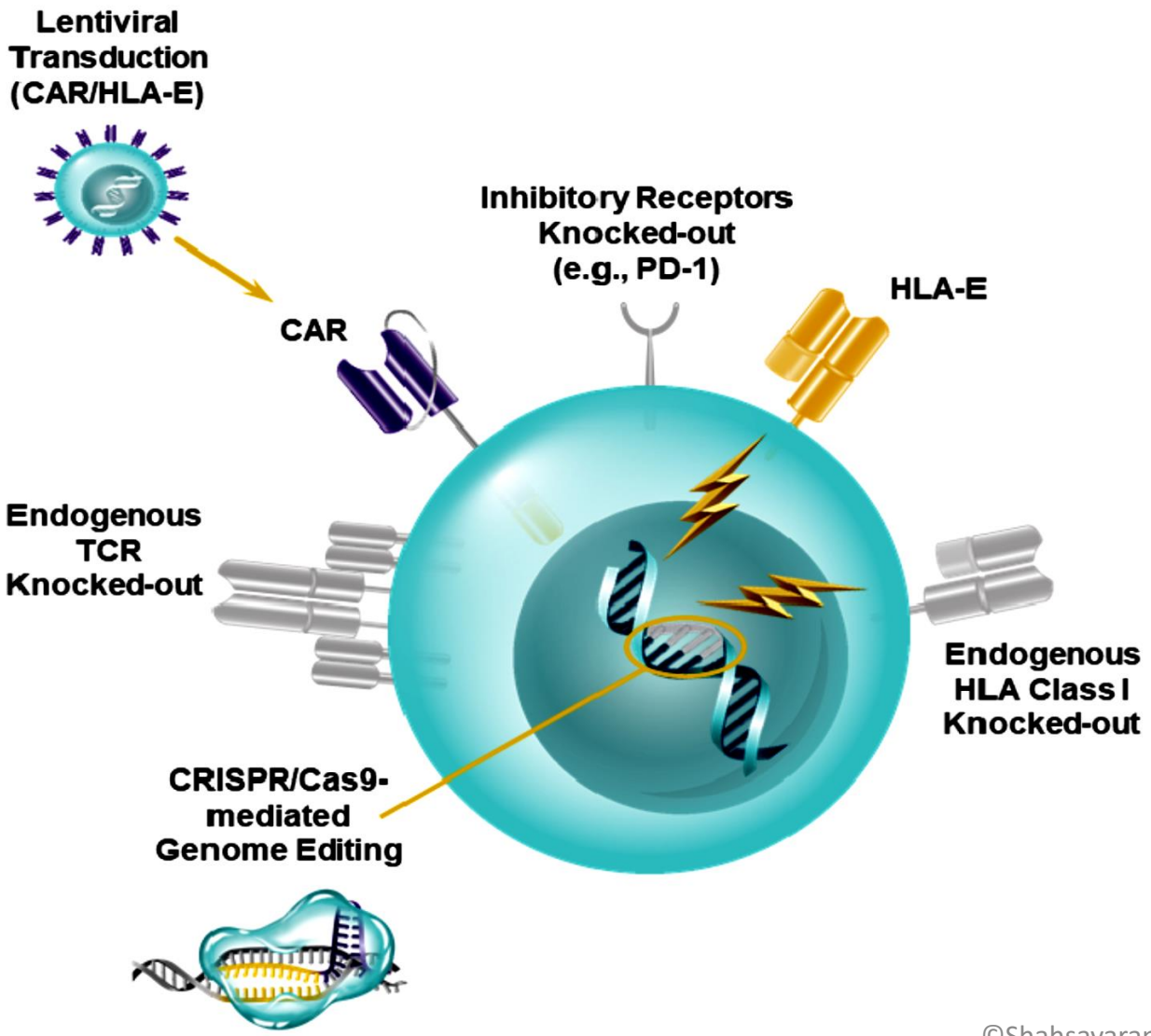


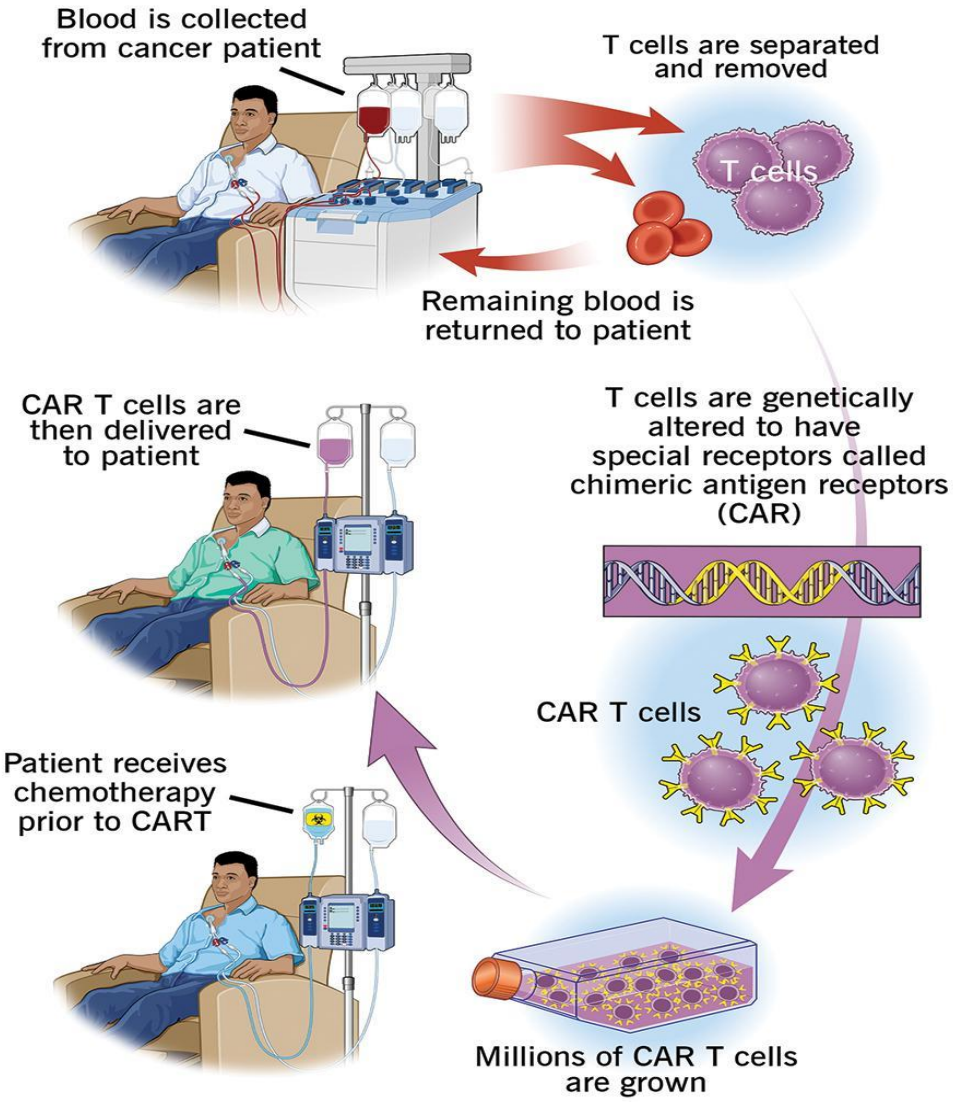


CRISPR in immune therapy



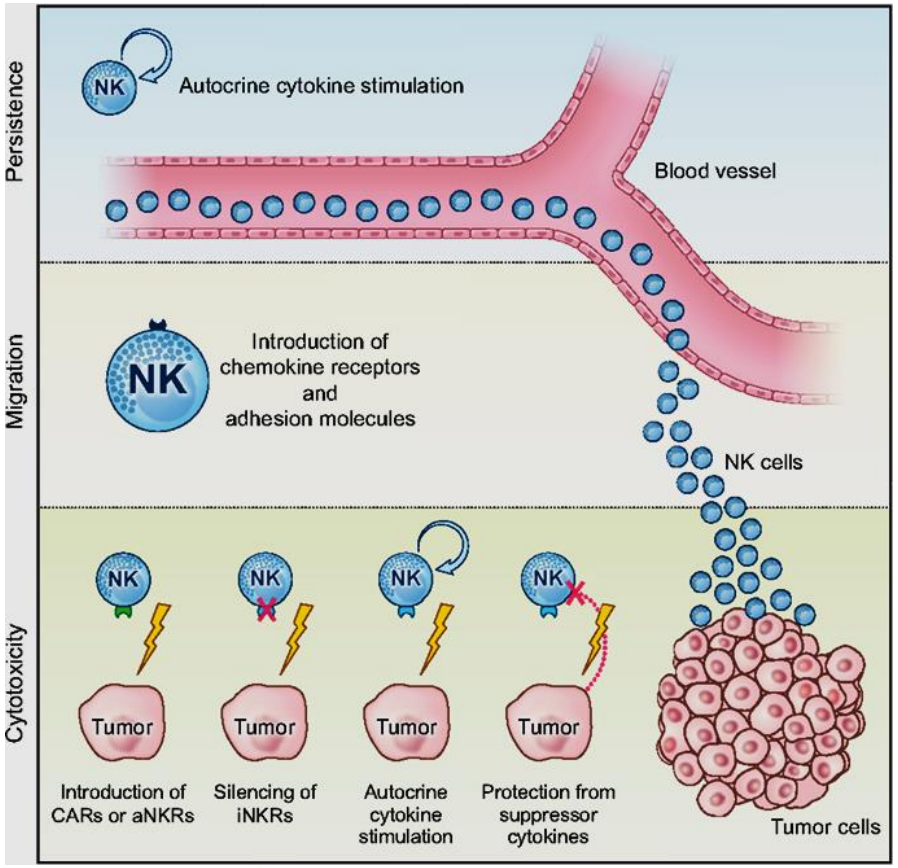
Advancing CAR T cell therapy with CRISPR/Cas9

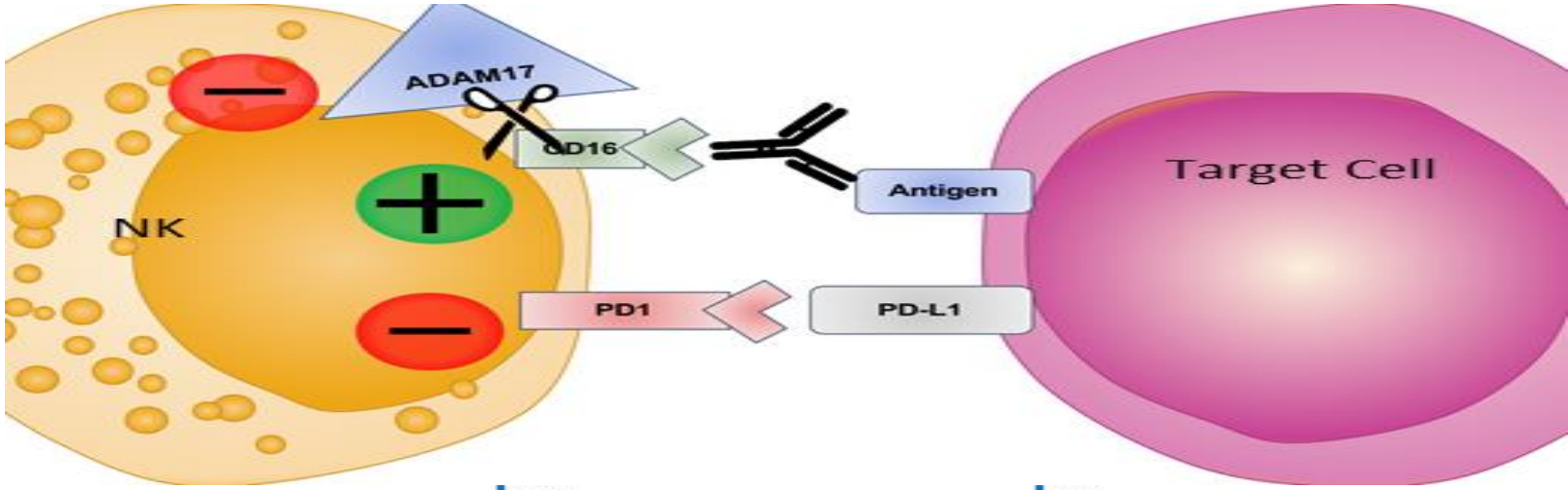


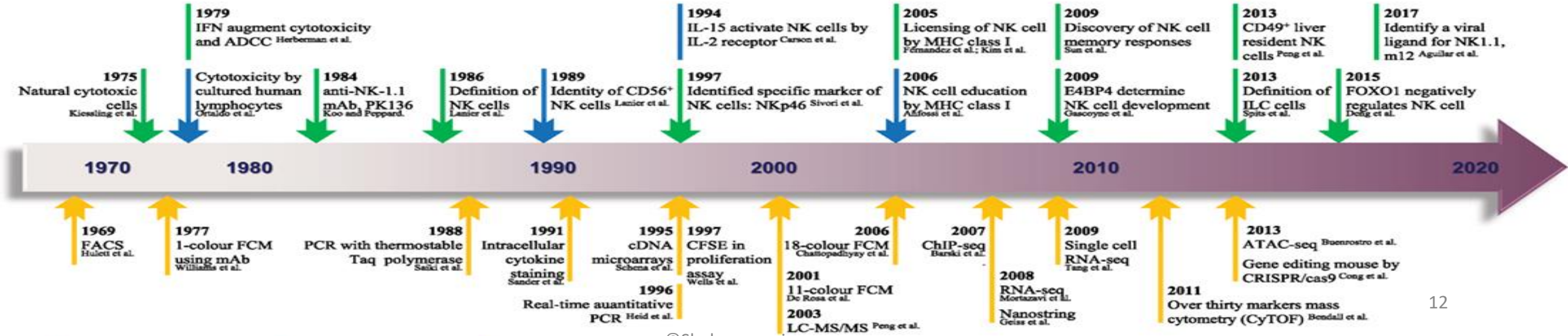


Hum Vaccin Immunother. 2019;15(5):1126-1132. doi: 10.1080/21645515.2019.1571893

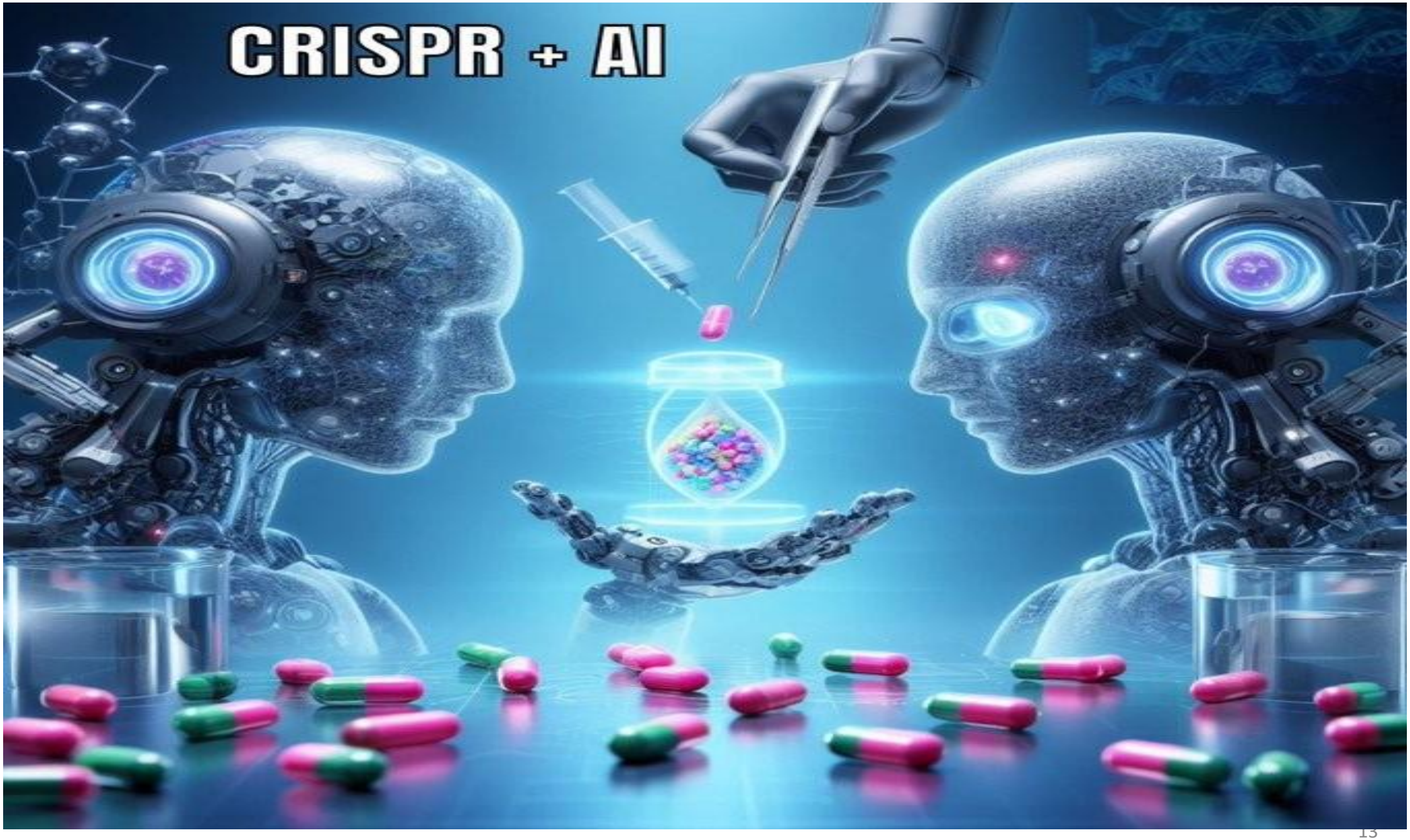
The next great cancer immunotherapy:
CRISPR engineered natural killer cells



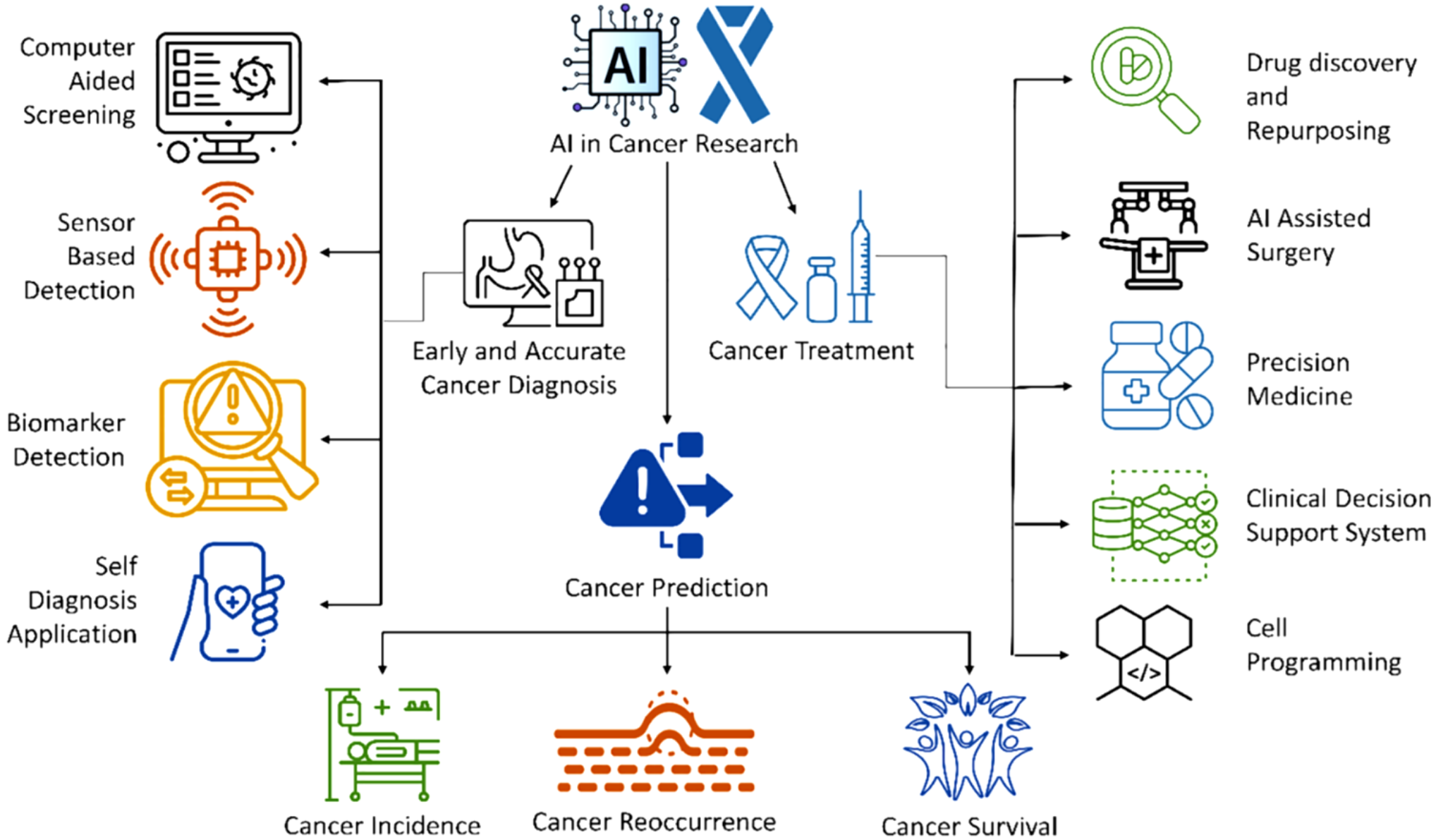


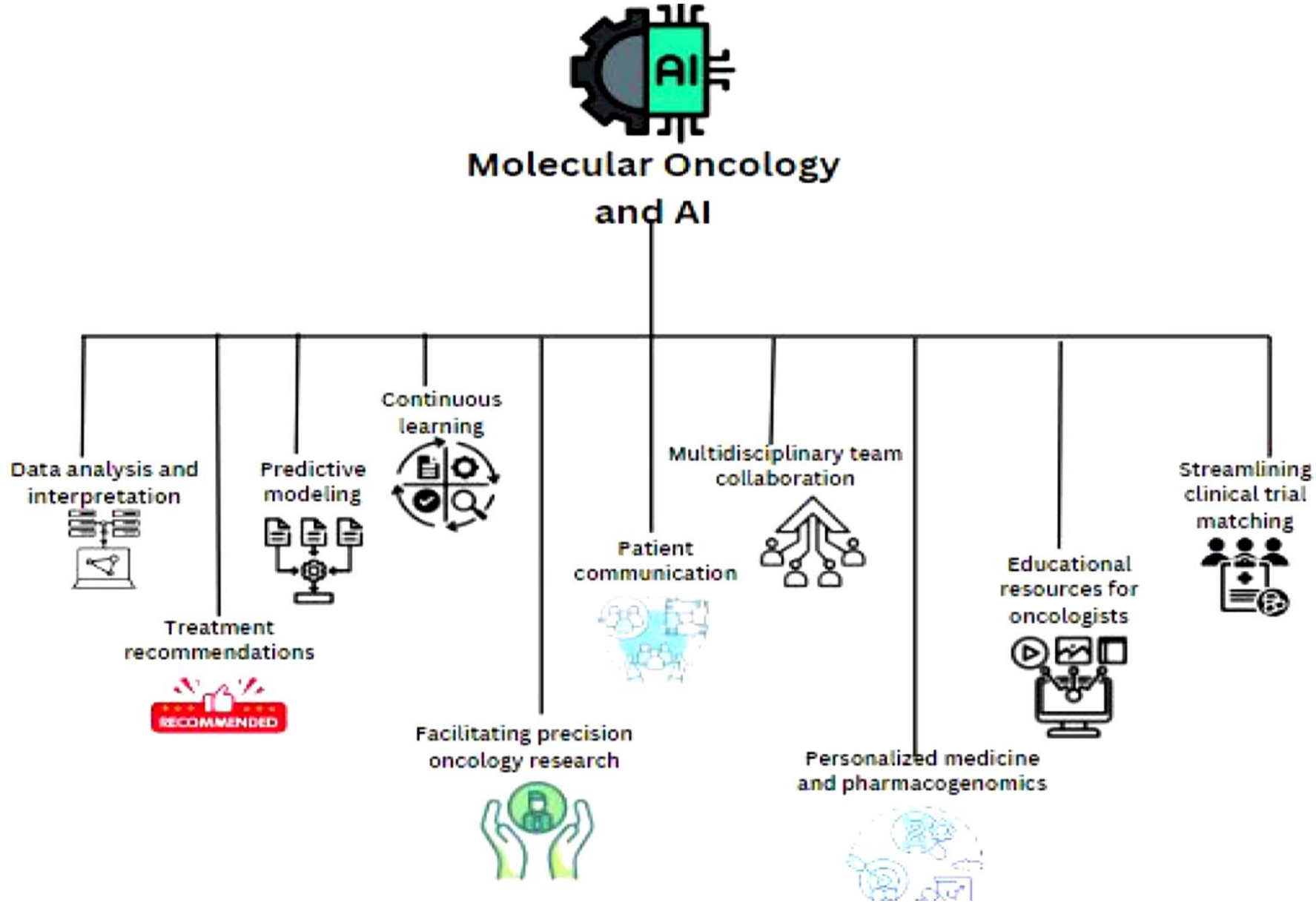


www.bloodjournal.org/content/128/22/2724

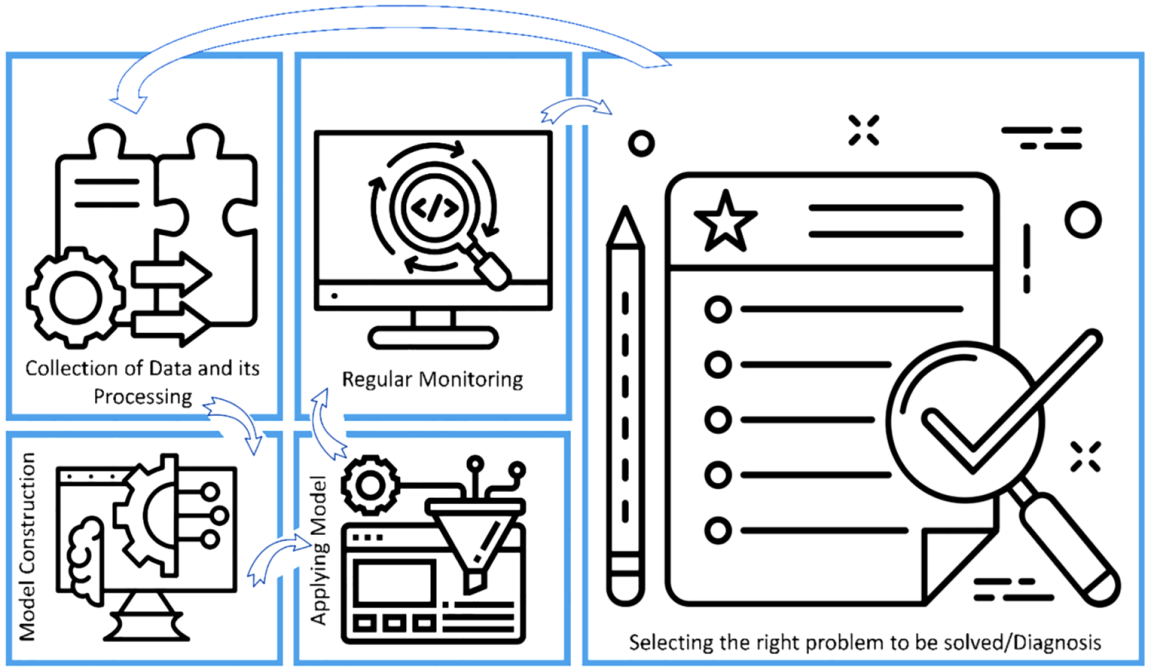

CRISPR + AI

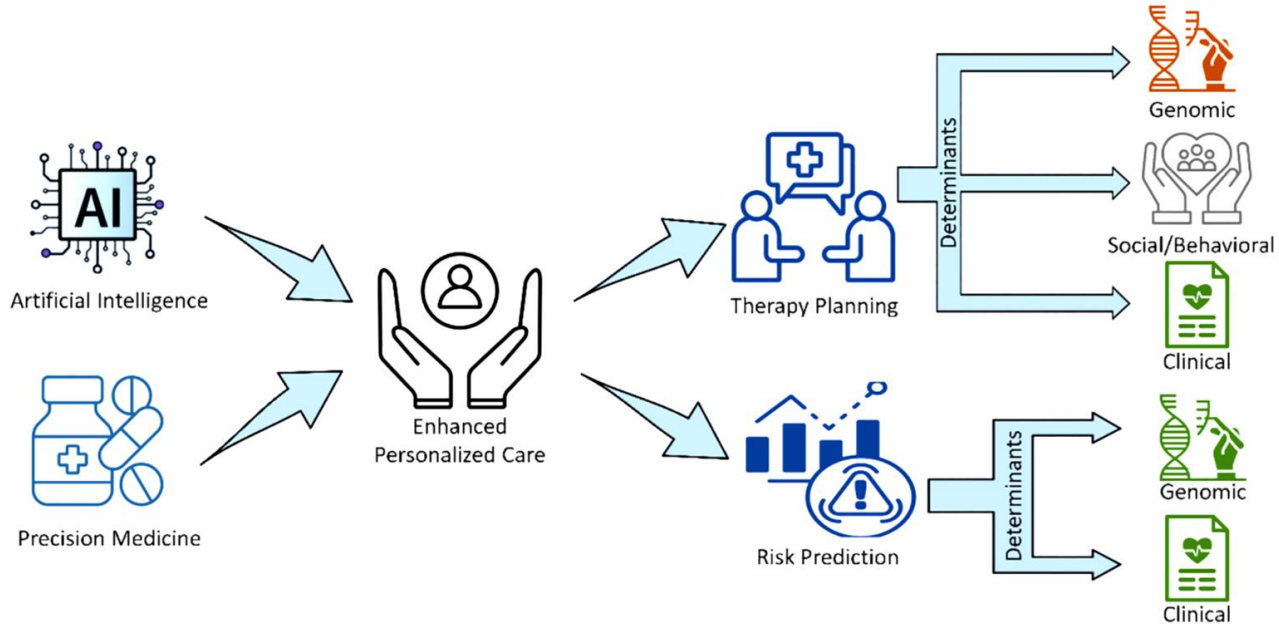
AI in chimeric antigen receptor-based therapies



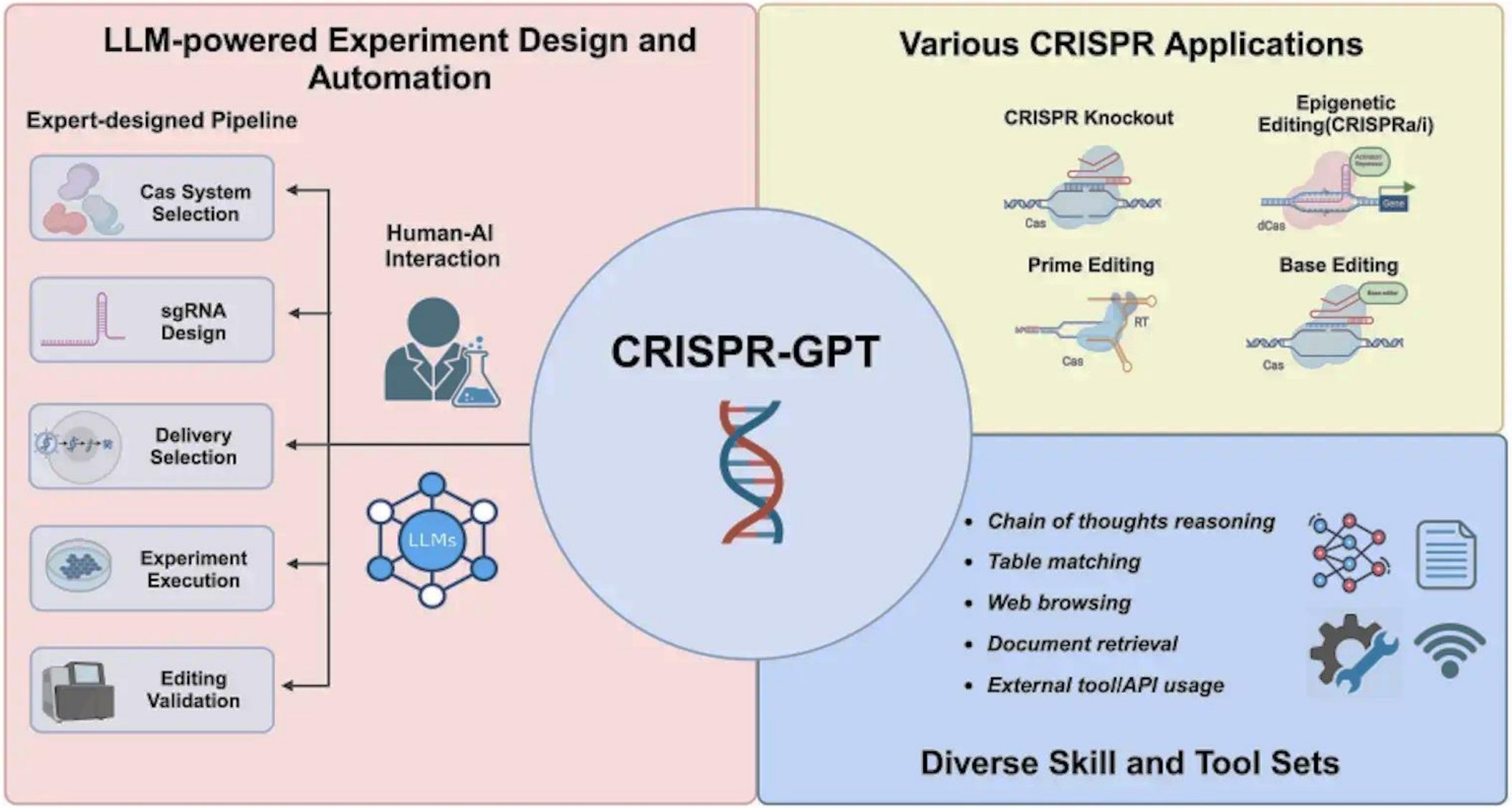

AI
Molecular Oncology and AI
Data analysis and interpretation
Predictive modeling
Continuous learning
Multidisciplinary team collaboration
Streamlining clinical trial matching
Treatment recommendations
RECOMMENDED
Patient communication
Educational resources for oncologists
Facilitating precision oncology research
Personalized medicine and pharmacogenomics

Steps involved in AI-based models for diagnosis in healthcare.

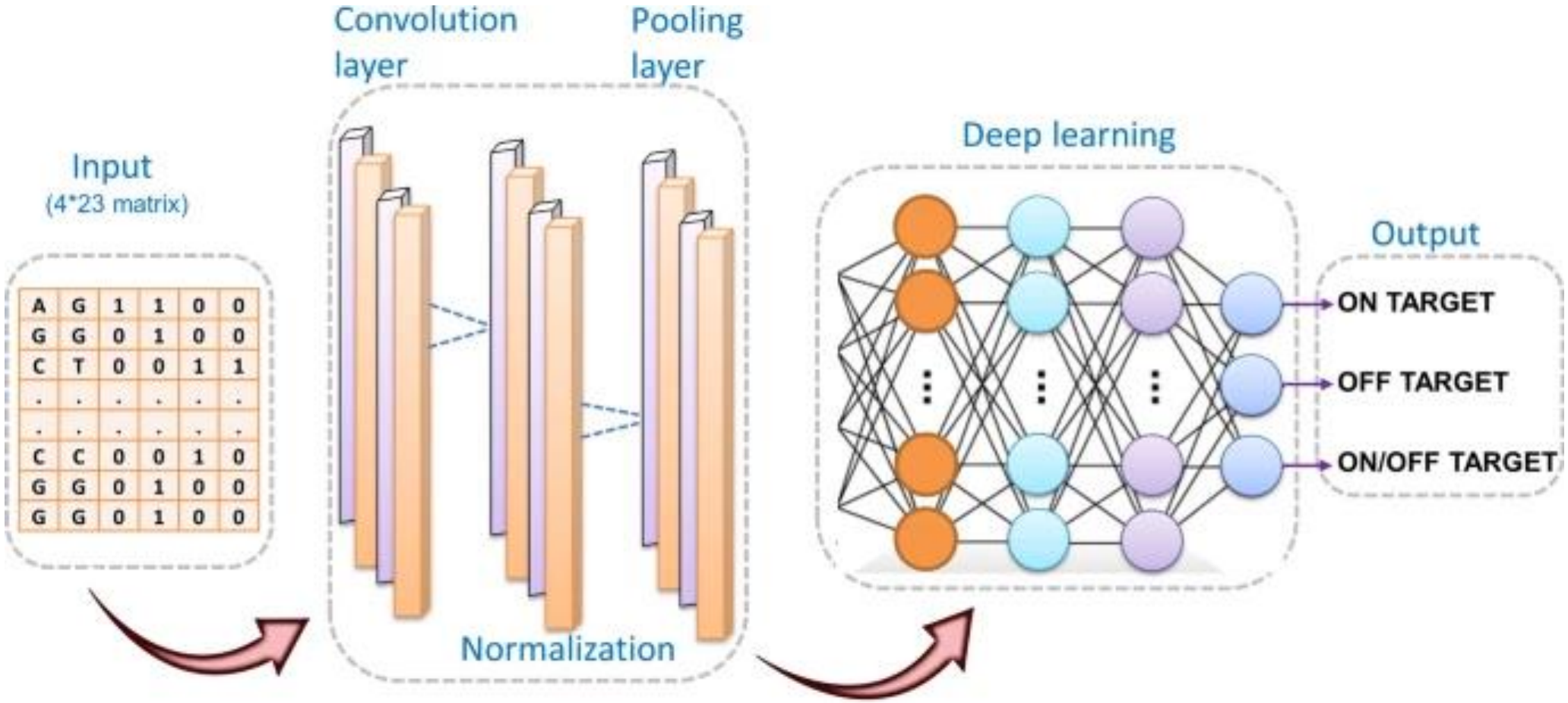




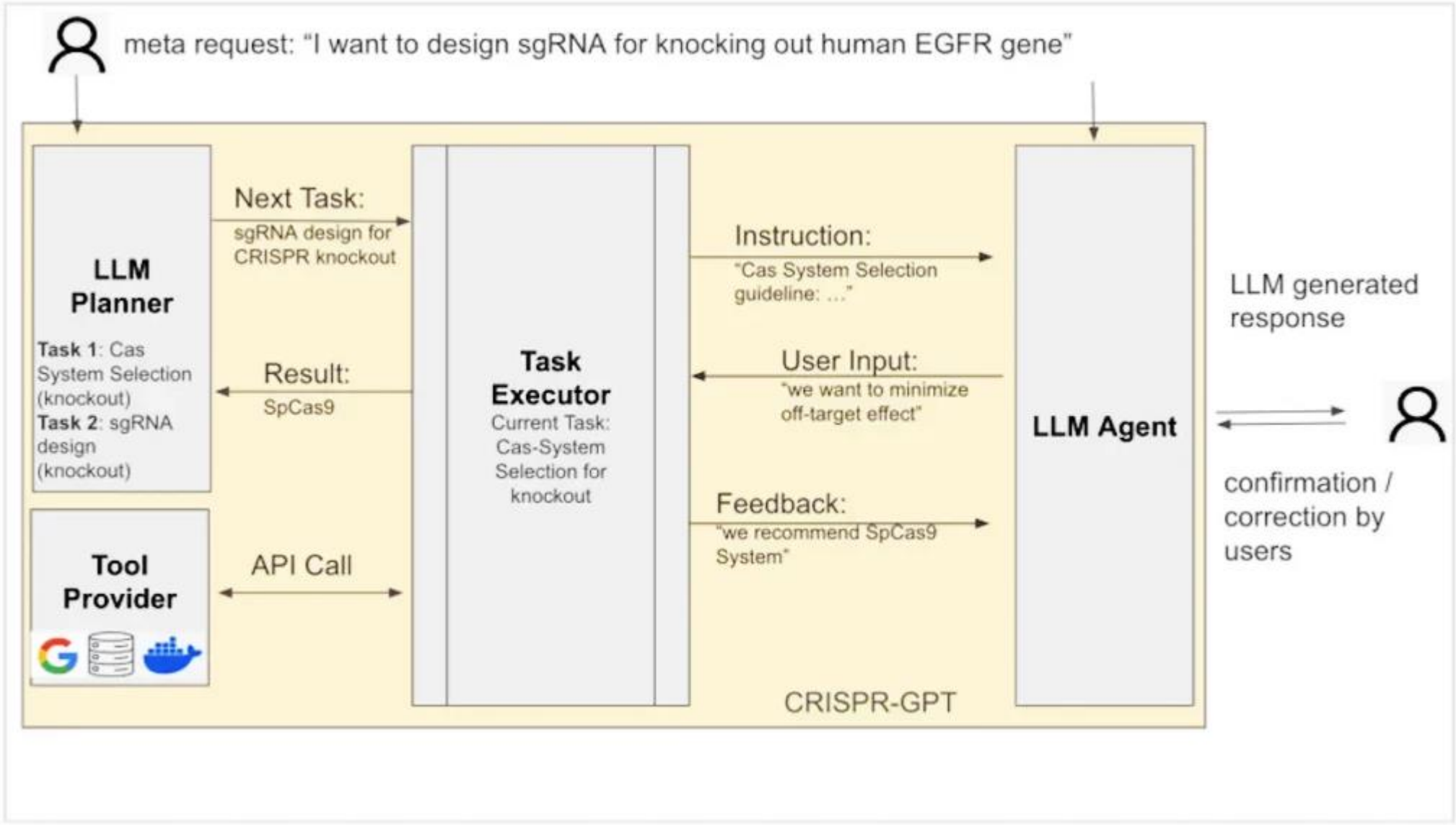
CRISPR-GPT, the Future of Efficient CRISPR Experiment Design



CRISPR/Cas9 deep learning architecture.



Developing apps for beginners



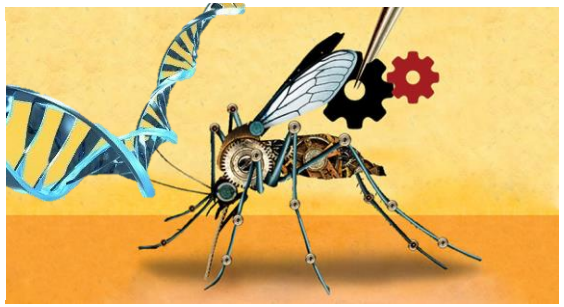
CRISPR application for eradication of infection disease

MEGAN MOLTENI SCIENCE 09.24.2018 11:00 AM

2018

Here's the Plan to End Malaria With Crispr-Edited Mosquitoes

Target Malaria hopes to eradicate Africa's malaria-carrying mosquitoes. But when manipulating the fate of a species, moving slowly is a virtue.



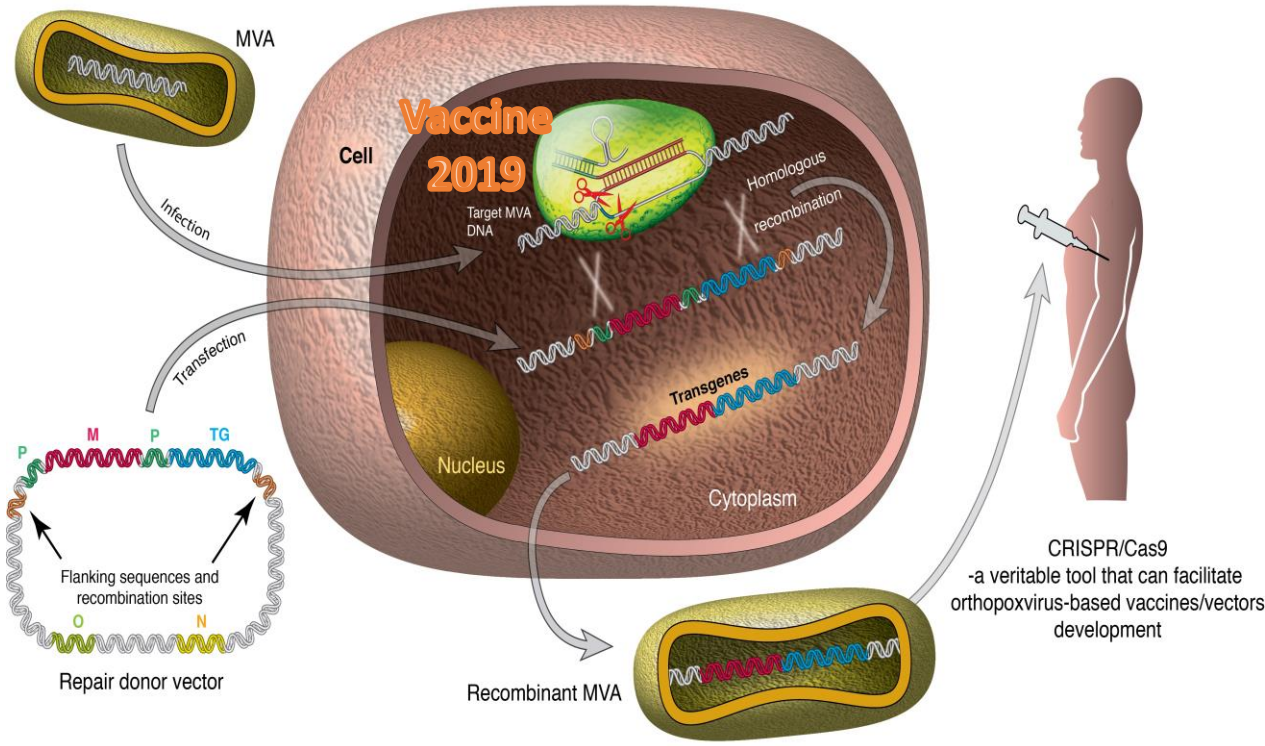
The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT September 2019

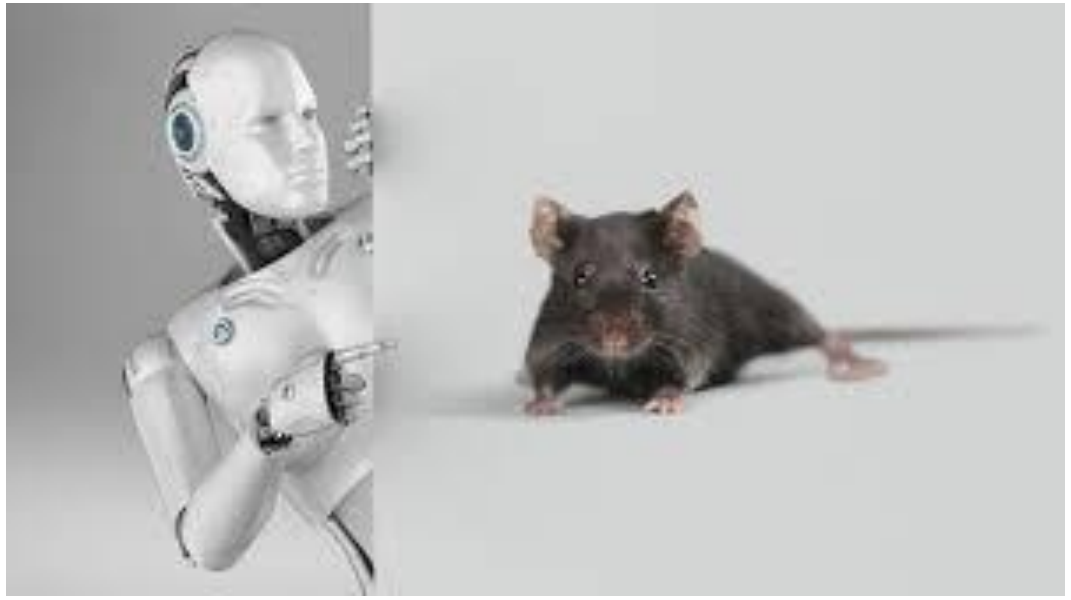
CRISPR-Edited Stem Cells in a Patient with HIV and Acute Lymphocytic Leukemia

N ENGL J MED NEJM.ORG

The New England Journal of Medicine

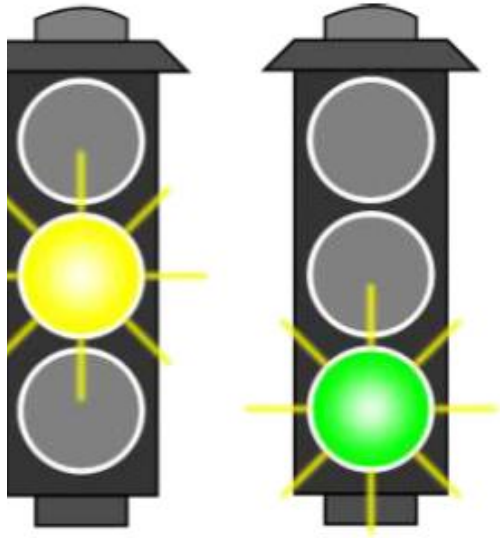


Artificial Intelligence as a Replacement for Animal Experiments?



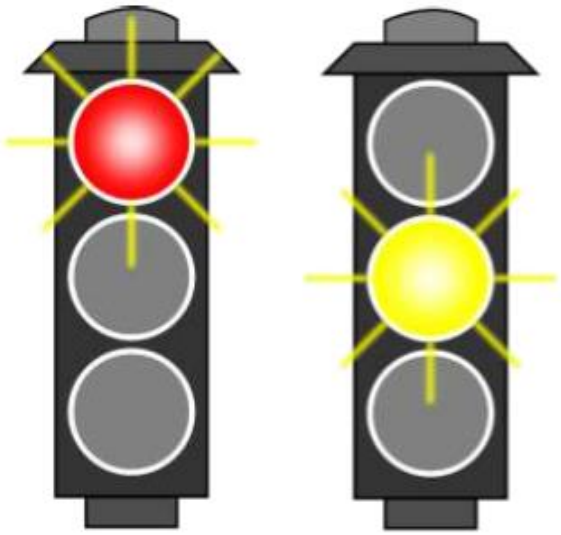
Limitless application

- Drug development – optimize biotech manufacture
- Disease models
- Ecological vector control – mosquito sterilization
- Biofuels
- Agriculture – modification of crop strains or animals



The NIH recombinant advisory Committee has Approved the First US Trial

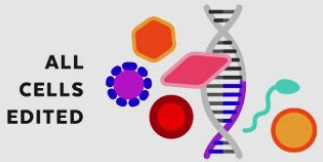
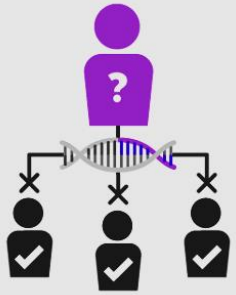
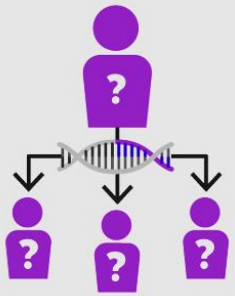
The University of Pennsylvania:
combination of PD-1 and NY-ESO-1 and LAGE-1 in human cancer



Clinical Development Considerations for Gene Editing Technology

- Therapies may provide life-long cure through a single treatment
- CRISPR technology has made gene-editing much more accessible and has broadened the range of targets
- Regulatory and ethical frameworks
- Bring new therapies to the clinic via a safe and rapid pathway

SOMATIC GENE EDITING VS. GERMLINE GENE EDITING

	SOMATIC GENE EDITING	GERMLINE GENE EDITING
EDIT	 Somatic therapies target genes in specific types of cells (blood cells, for example).	 Germline modifications are made so early in development that any change is copied into all of the new cells.
COPY	 The edited gene is contained only in the target cell type. No other types of cells are affected.	 The edited gene is copied in every cell, including sperm or eggs.
RISKS **NEXT GENERATION**	 Any changes, including potential off-target effects, are limited to the treated individual. The edited gene is not passed down to future generations.	 If the person has children, the edited gene is passed on to future generations.
CONSENSUS	 Somatic cell therapies have been researched and tested for more than 20 years and are highly regulated.	 Human germline editing is new. Heritability of germline changes presents new legal and societal considerations.

Ethical Concerns

Non-Therapeutic Use / Enhancement

- International Summit on Human Gene Editing (Dec 2015)
  - Concerns over germ line editing – need for an ongoing forum
- NAS/NAM Meeting (April 2016)
  - All aspects of human germline editing, consequences, regulation and potential applications
  - Committee assembled to perform a year-long in-depth study
- EU CT Directive (2001/20/EC) does not allow germ line editing (Article 9)
- NIH RAC will not review proposals on germ line editing
- Eugenic practices prohibited:
  - Oviedo Convention
  - Convention on Human Rights and Biomedicine (1997)
  - Article 3(2) of the Charter of Fundamental Rights of EU prohibits eugenic practices

Regulatory Challenges

Somatic Cell Therapies

- CRISPR/Cas-based gene editing of somatic cell therapies will use in vivo or ex vivo strategies
- Current regulations for gene therapy and cell therapy will regulate CRISPR-based therapies
- Regulators will need to stay up to date with rapid technology advances
- Pathways to market will need to be flexible and allow timely patient access to therapies

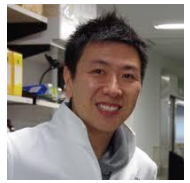
Safety and Efficacy

- Off-target effects/genotoxicity
  - Improvements in targeting of CRISPR/Cas9 system
    - Methods to assess genome-wide off-target effects
    - Need to ensure there is no detectable germ line modification
- Efficacy
  - Single administration may be sufficient but need to consider multiple treatments
  - Control of CRISPR/Cas editing
- Animal models
  - Significant area for regulators and companies

Acknowledgement

Dr. Kazemi

Dr. Kouichi Hasegawa



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Dr. Peter David Gee

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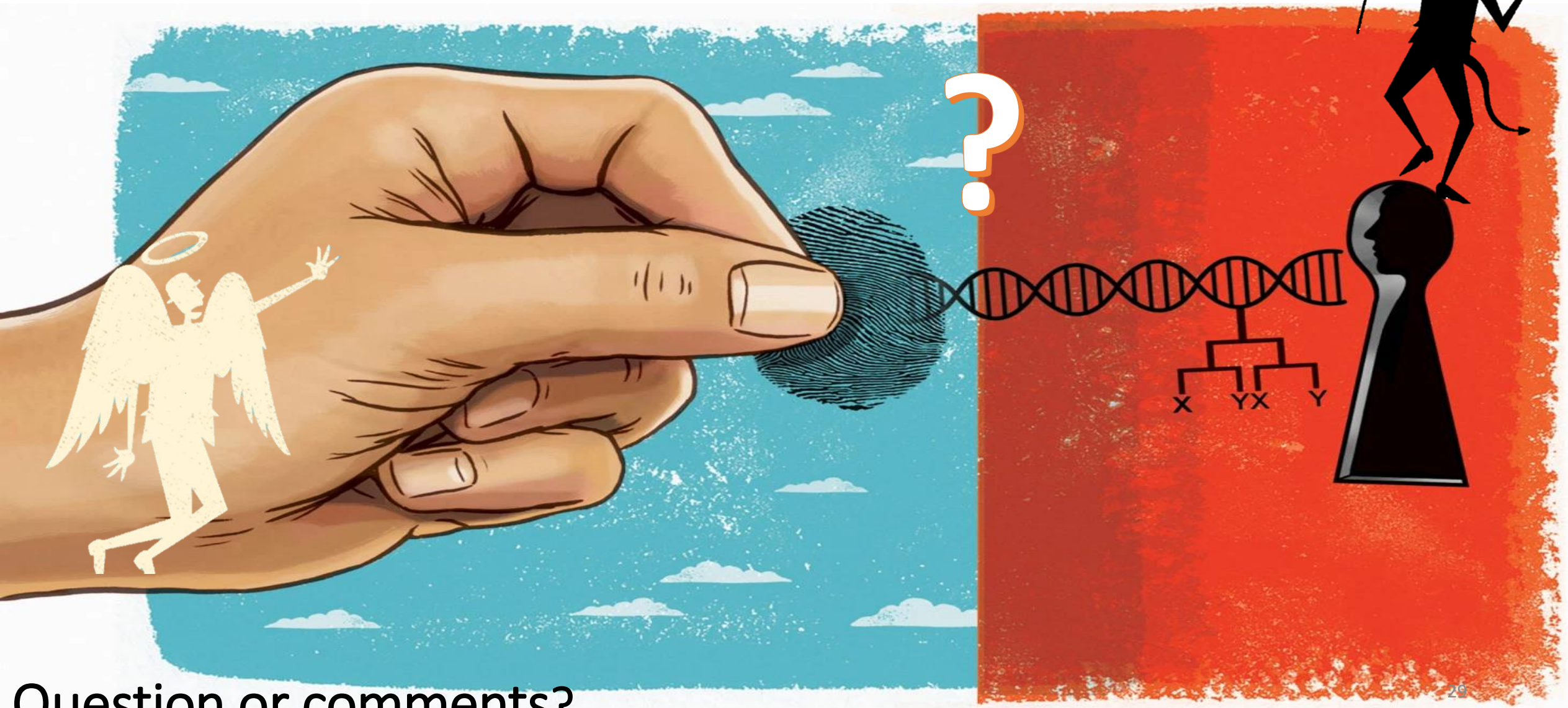
Kouichi Hasegawa

Hosein Shahsavarani

Thank you very much for your kind attention.



Question or comments?