Metabolically enhanced CAR-T cell therapy

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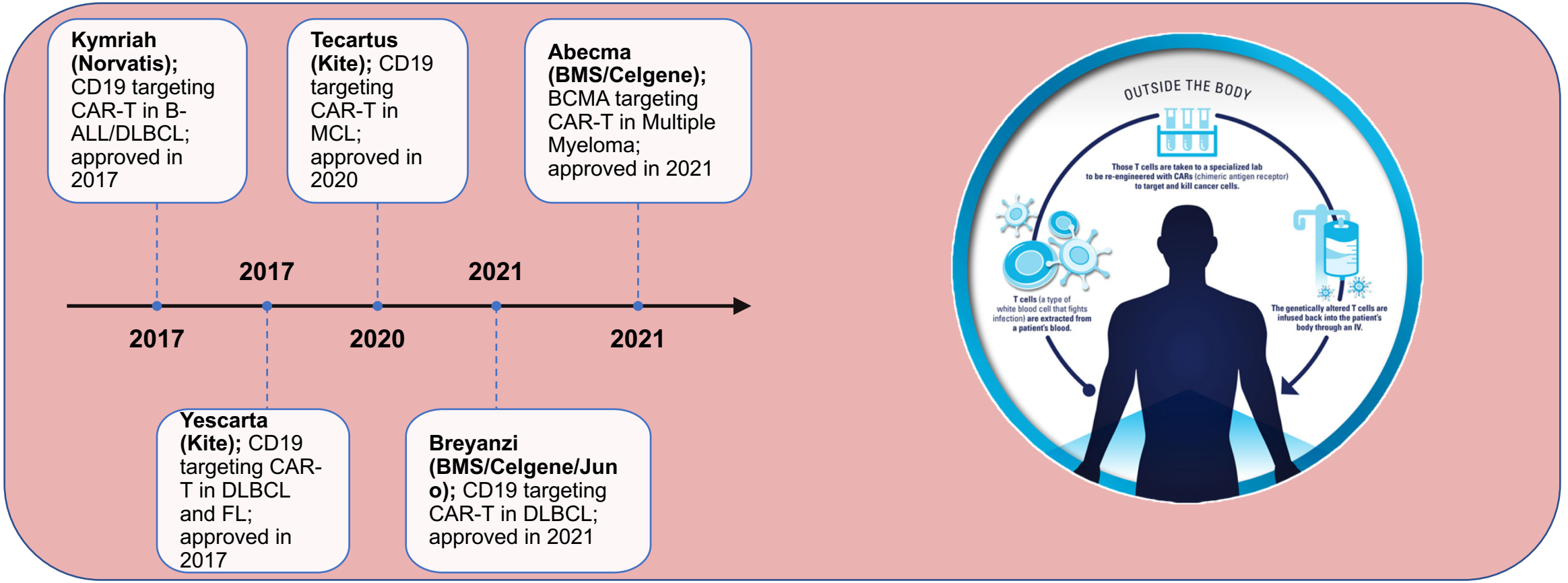
Cell therapies as revolutionizing cancer treatments



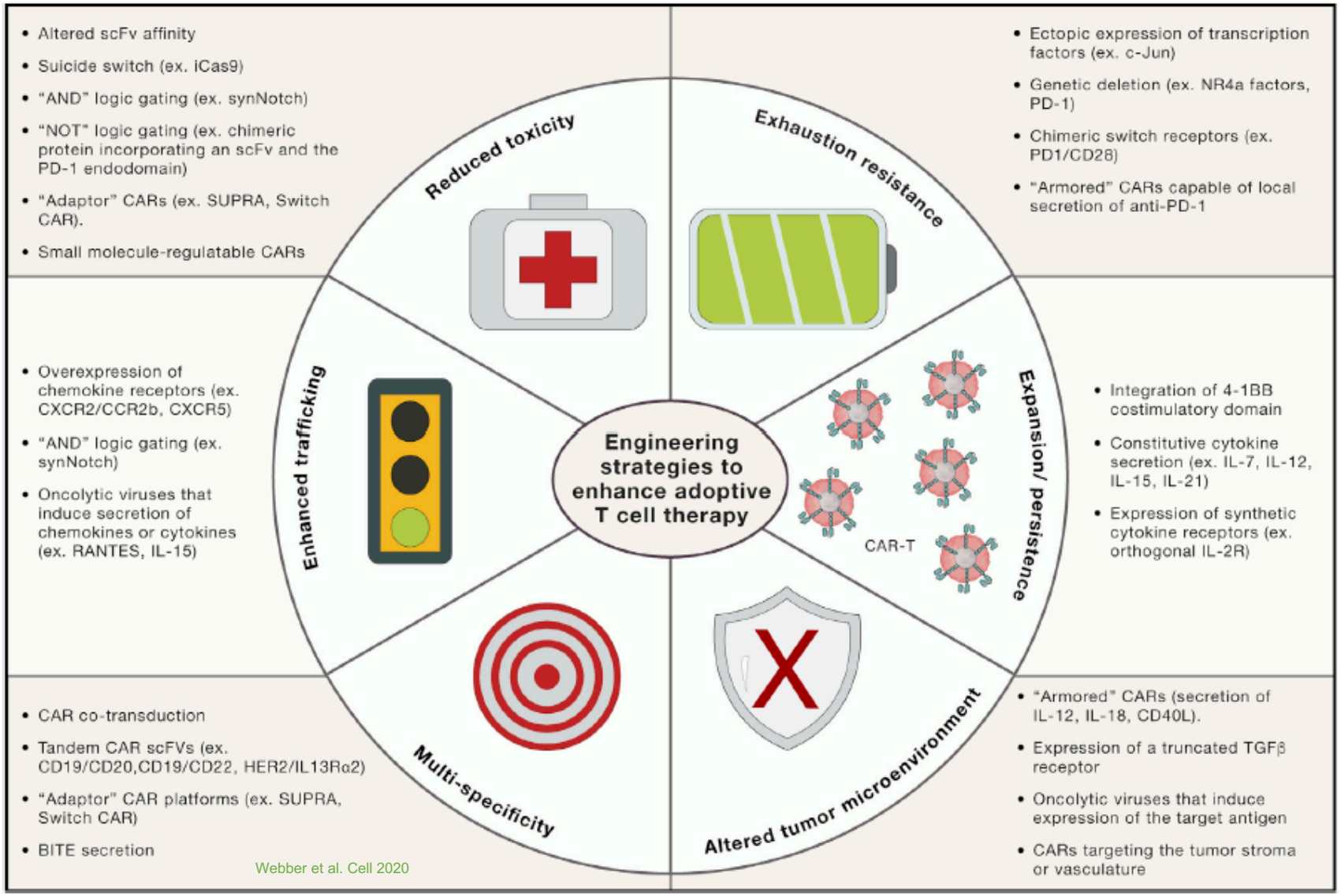
- Five FDA approvals and over 200 companies actively developing CAR-T cells.
- Approval in National Medical Products Administration in China.
- Multiple pharma and biotech companies in RnD.

Major challenges in cell therapy (example areas)

- Resistance & Efficacy
  - CAR-T therapies face resistant or refractory diseases, and lack efficacy in solid tumors
- Exhaustion & tumor microenvironment
  - CAR-T or CAR-NK cells face hostile TME and are easily exhausted, especially in solid tumors
- Durability
  - Adoptive transferred cells often perish before finishing off cancer cells; persistence need to be enhanced and optimized
- Manufacturing
  - Multiple steps required, logistic challenges for current autologous CAR-Ts
- Safety
  - Any grade CRS can occur; prevalent for all currently approved CAR-Ts
  - In certain cases, the toxicity of current CAR-Ts can be fatal

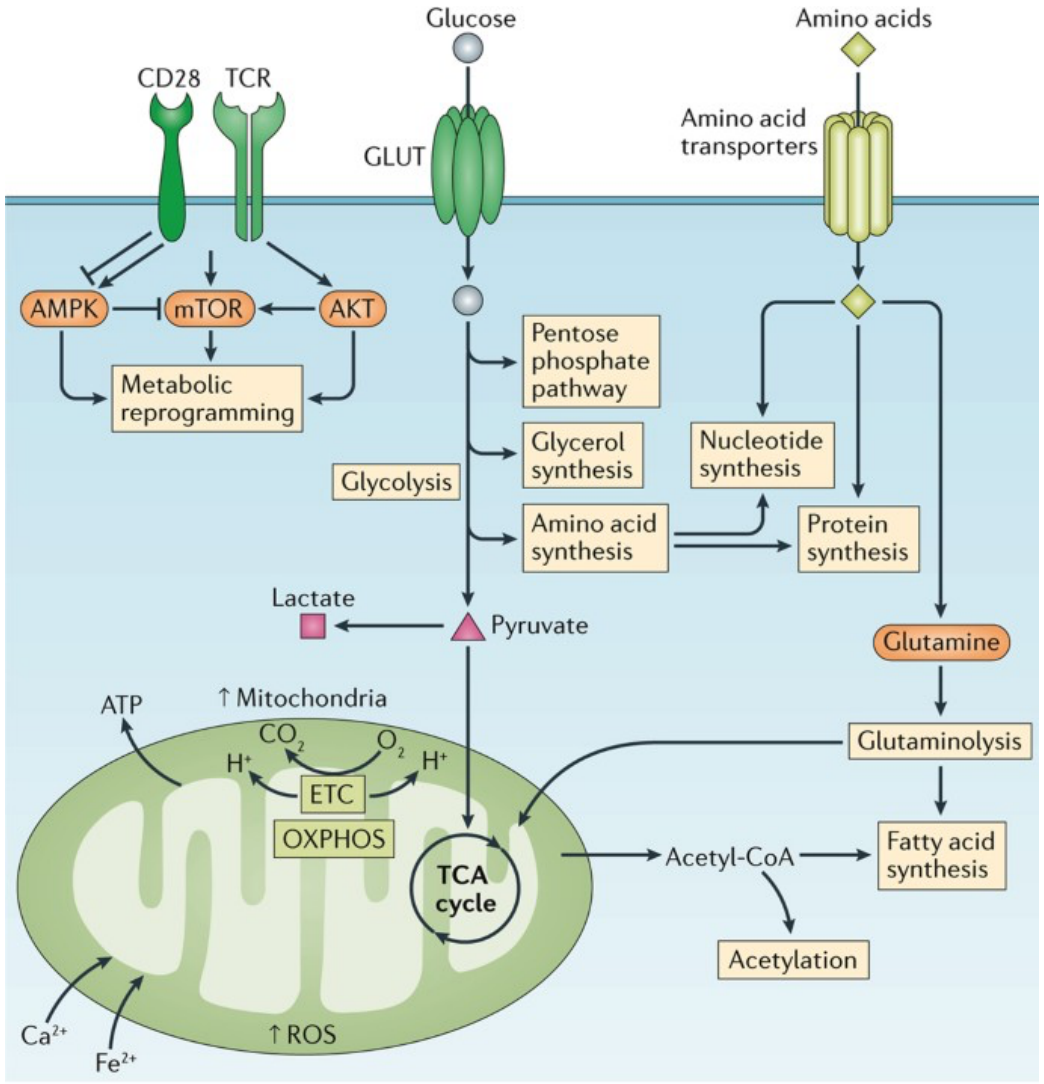
Unmet need for improved next-generation cell therapies that can overcome the outstanding problems.

Engineering approaches to build next-gen cell therapy



Webber et al. Cell 2020

Metabolism pathways are crucial for CAR-T function



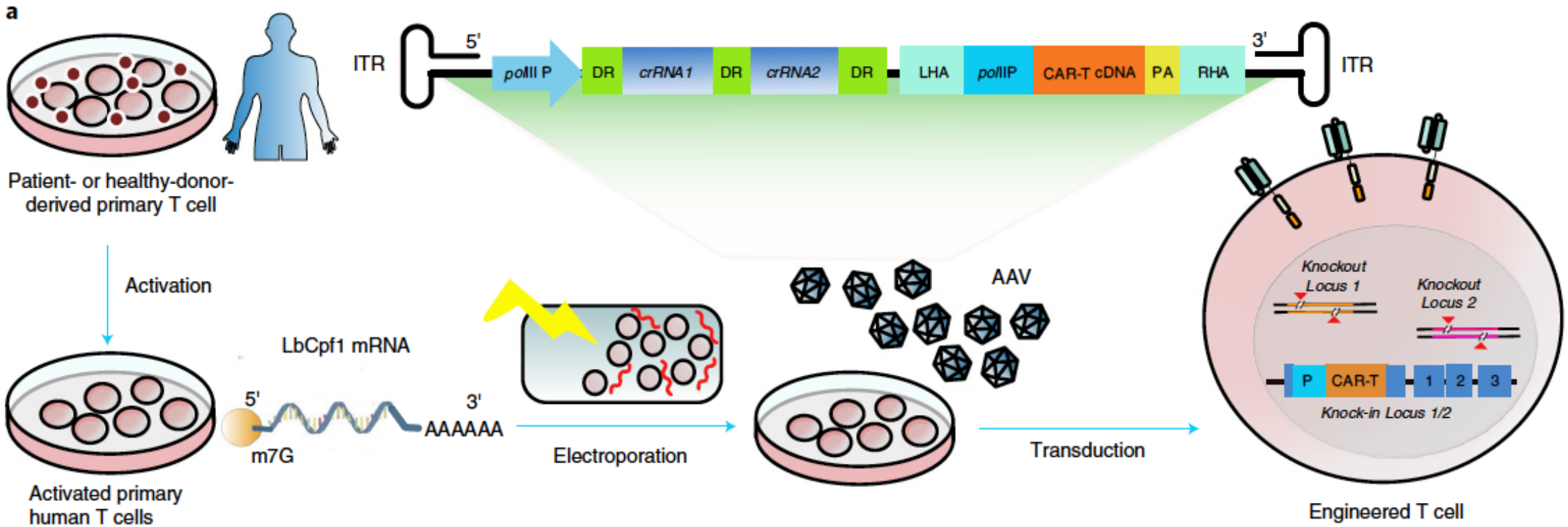
Nature Reviews | Immunology

Overall overall goals and differentiation

- Develop and harness transformative technologies for cell therapy innovations
- Engineering CAR-T cells with new tools
- Metabolically program CAR-T cells to enhance their anti-tumor efficacy
- Bring lead candidates to translation and clinic

- We have a Yale-IP, highly versatile CAR-T engineering platform (KIKO)
- We have novel candidates of proprietary Metabolically Engineered CAR-Ts

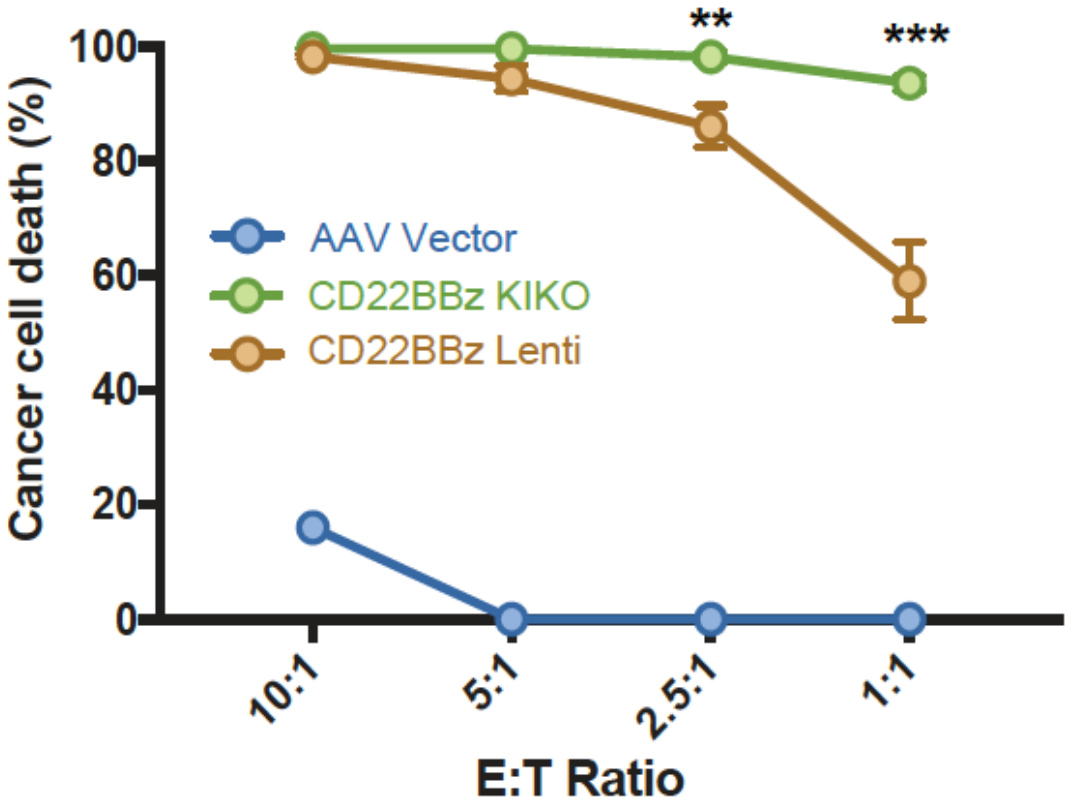
Technology platform – KIKO CAR-T engineering

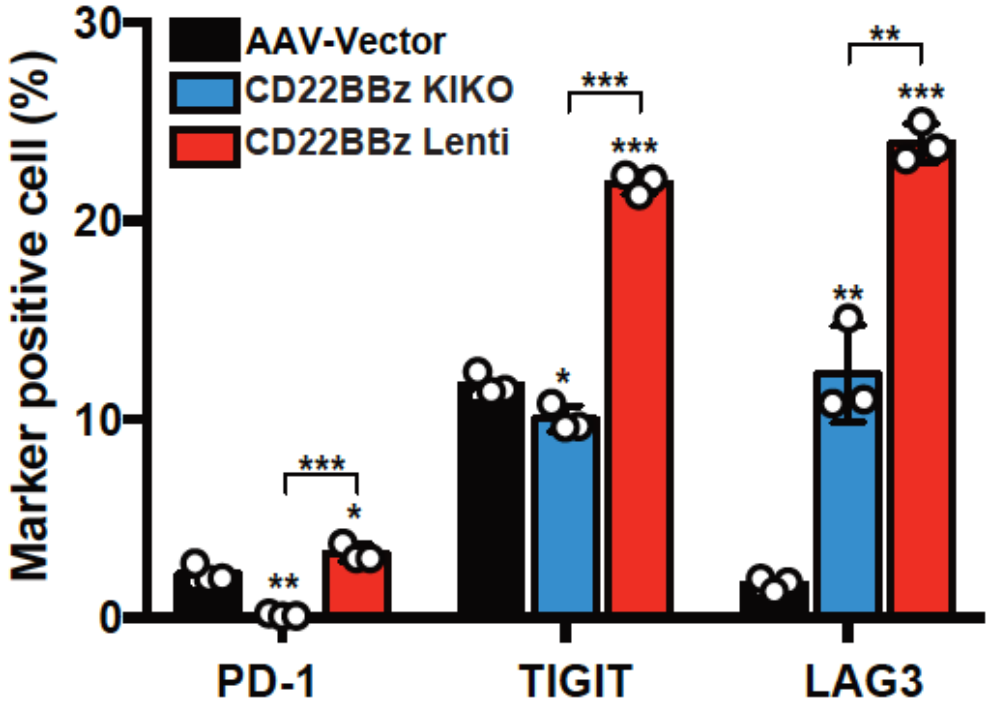


Dai et al. Nature Methods (2019)

KIKO takes on a novel "hybrid" approach of non-viral and viral strategy to **simplify** and **enhance** the efficiency of knock-ins and knock-outs. **(Plug-and-play CARs)**

CAR-T generated by KIKO outperforms lentiviral counterparts

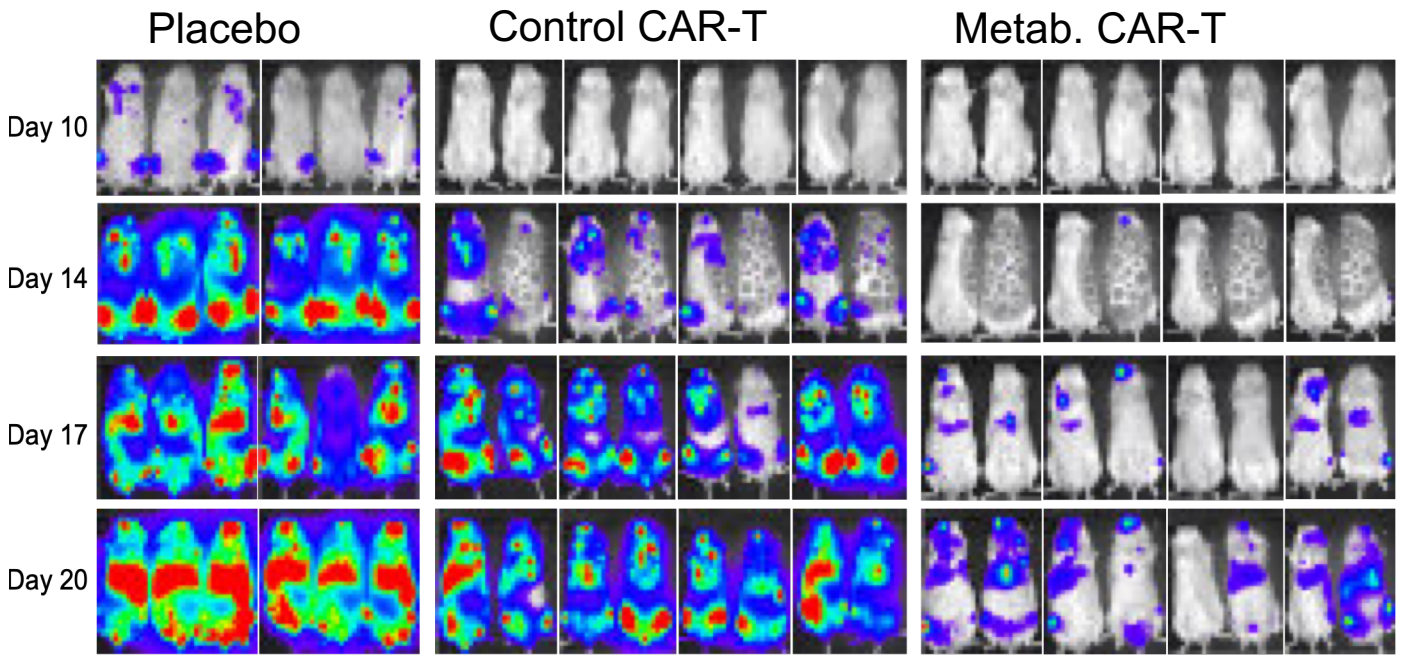




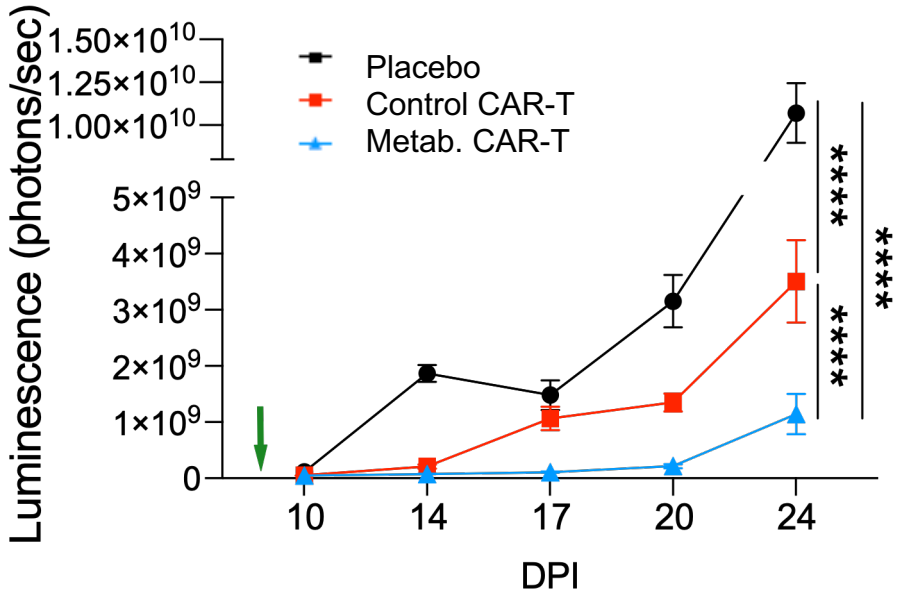
Comparison of KIKO with other gene editing technologies for cell therapy

	CAR-T cell viability and proliferation	Efficiency and accuracy	Resistance to exhaustion	Tumor killing efficacy
KIKO with AAV	High	High CAR KI% High gene KO%	Highest	Highest
Cas9 RNP with Donor DNA	Medium-High	Low-Medium KI% Medium-High KO%	Medium	High
Lentiviral	Medium-High	Random integration	Low	Medium
DNA/Transposon	Low	Random integration	Unknown	Unknown

Metabolically engineered CAR-T cells have enhanced *in vivo* efficacy and overcome therapeutic resistance



Chen lab, unpub.



Two-way ANOVA, $p < 0.0001$

Blavatnik Proposal

(Chen Metab. CAR-T)

Milestone (One lead Metab-CAR-T)	DNA Vector CMC	Viral Vector GLP Pilot Run	In-house viral vector validation	Efficacy validation	Initial Non-GLP prelim. Tox 1st model	Subtotal
Budget	110k	60k	20k	60k	50k	300k
Time	4 mo.	4 mo.	2mo.	3 mo.	2 mo.	15 months

Blavatnik Fund can help advance one lead first-in-class Metab. CAR-T program to IND-enabling stage