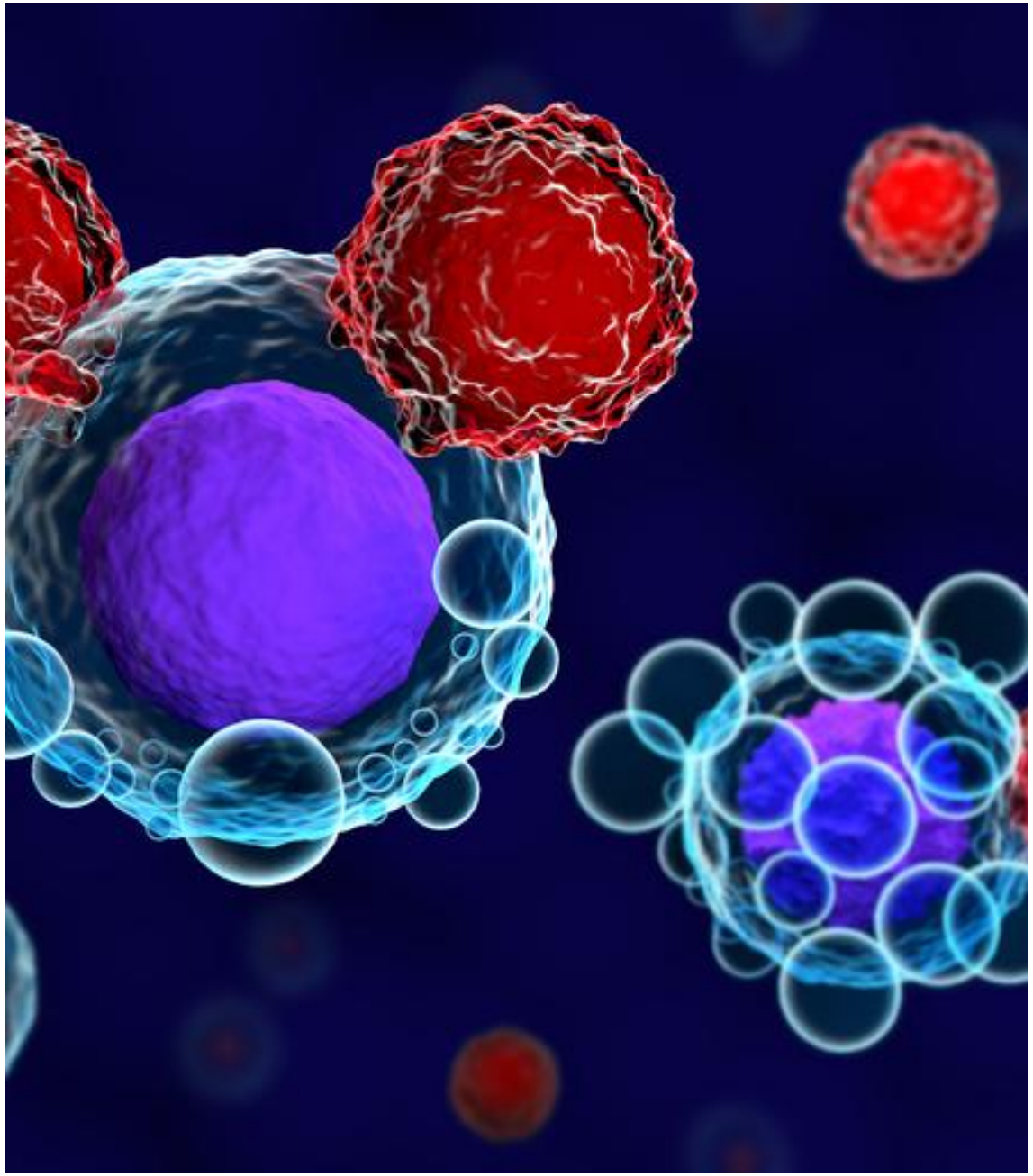


Credit: Getty Images/Melletios Verras

ICR The Institute of Cancer Research

UCLB UCL University College London

iTAG Platform:

Drug-inducible degron tags for adoptive cell-based immunotherapies

FURTHER FASTER TOGETHER
We are beating cancer

CANCER RESEARCH HORIZONS

Introduction

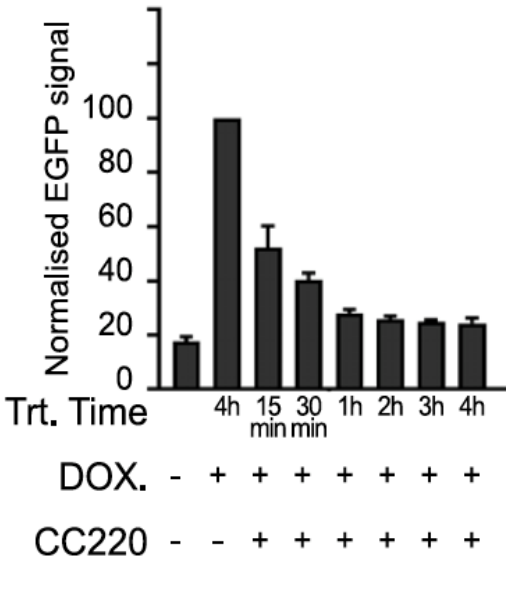
Researchers at the **Institute of Cancer Research (ICR)** and **University College London (UCL)** developed **iTAG, a drug-inducible degron tag platform useful for adoptive cell-based immunotherapies.**

- **iTAG** is a 60-amino-acid chimera from Ikaros and Zfp91 containing a central zinc-finger motif.
- **iTAG iMiDs/CeLMoDs based degron tag platform** constitutes a versatile tool to degrade targets across the murine and human proteome.
- **Greatest benefit: iTAG OFF-switches** enable pharmacologically controlled, reversible Chimeric Antigen Receptors (CAR) downregulation via targeted degradation, supporting both therapeutic use and manufacturing applications.

Rapid, efficient, selective and reversible degradation of target proteins fused with iTAG1 upon IMiD molecular glue treatment

Figure 1: iTAG induces rapid target degradation (i) at nM IMiD concentrations (ii), with effectiveness demonstrated *in vivo* (iii).

i.



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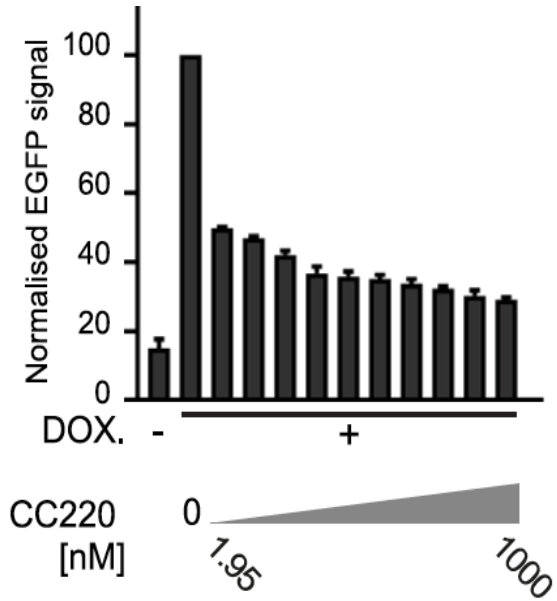

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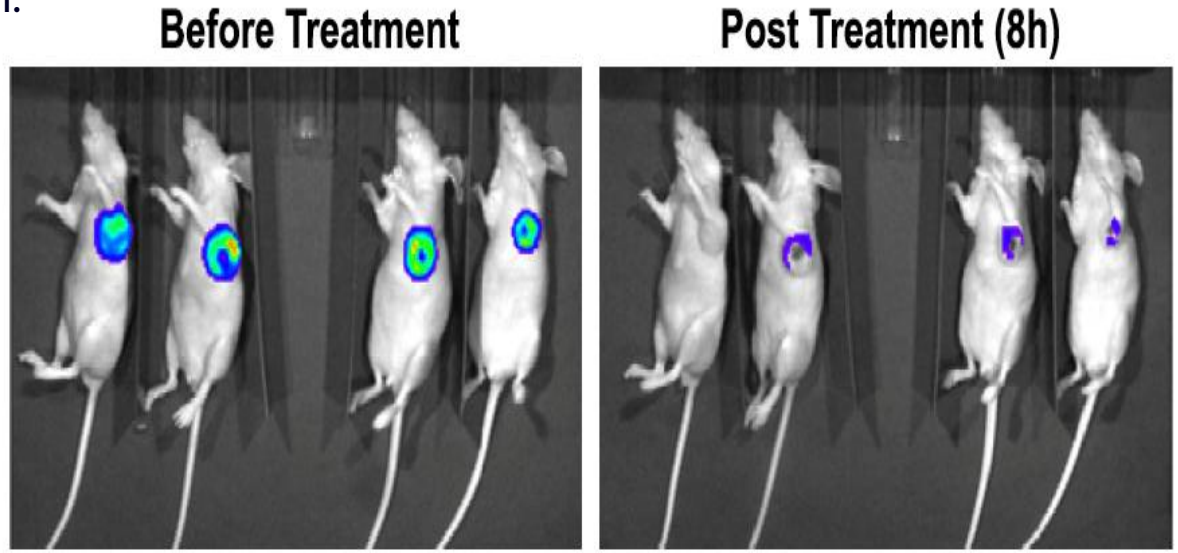


MDA-MB-231 tumour cells expressing FLuc-iTAG1

Challenge & Solution

Problem Addressed by iTAG2:

(1) **High intrinsic DNA-binding affinity of zinc-finger domains drives nuclear accumulation of fused proteins.**

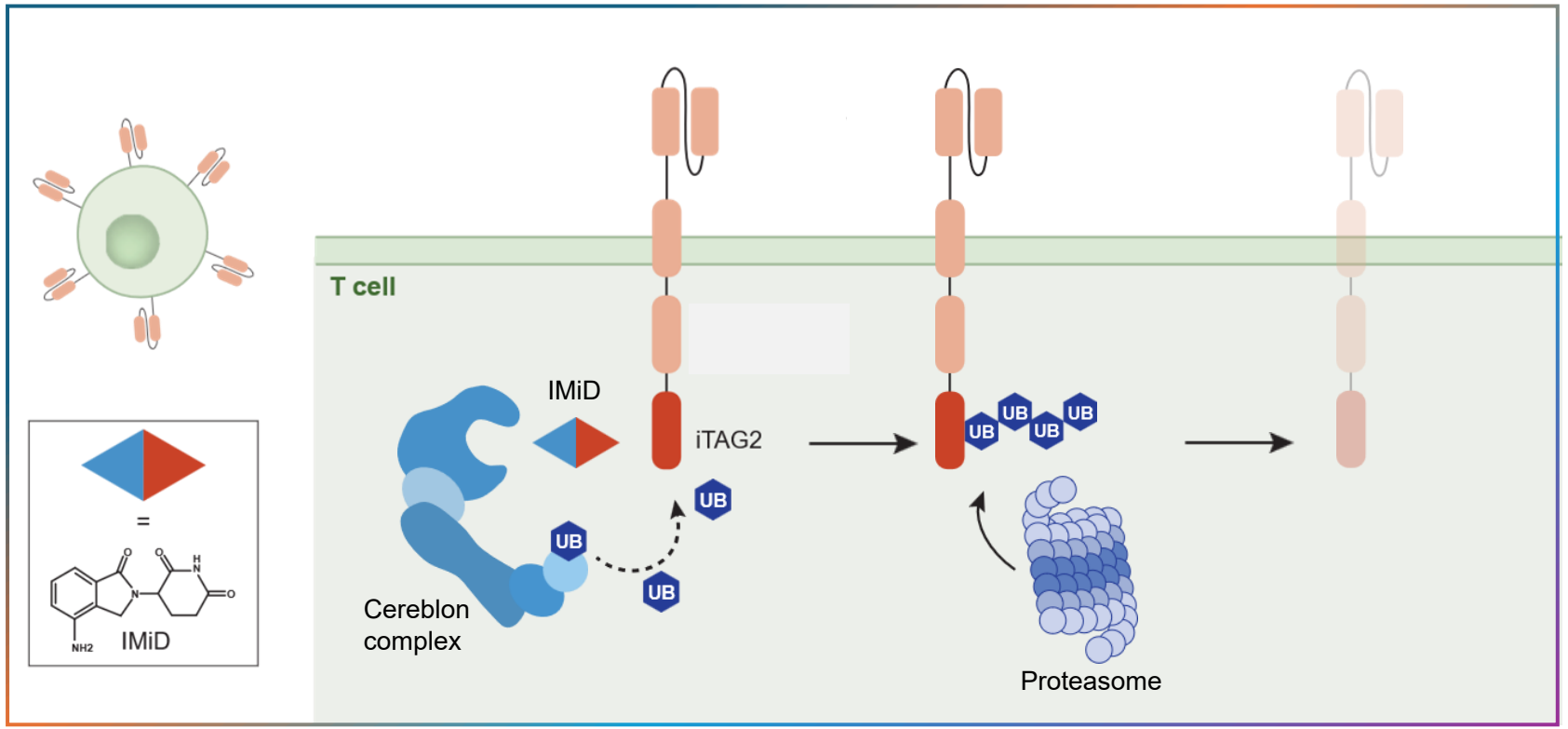
(2) **In solid tumours and blood cancers alike, CAR-T cell therapy** success can be challenged by multifactorial mechanisms; however, evidence suggests **dominant shared barriers are inadequate persistence and T cell exhaustion.**

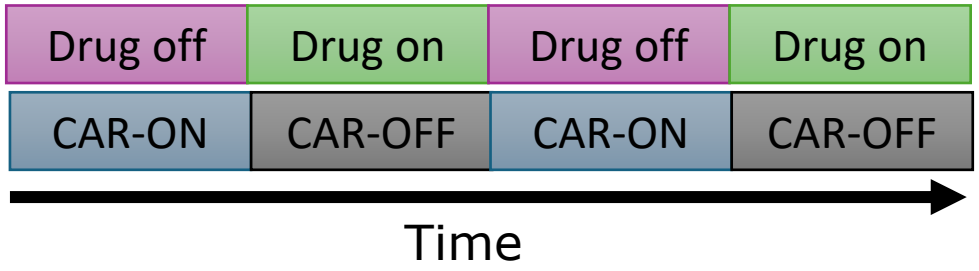
iTAG2 Key Features:

1. **ICR/UCL optimised iTAG2 enabling efficient incorporation into CAR-Ts**.
2. **iTAG OFF-switches** provide tuneable temporal control of CAR, with the aim of mitigating T-cell exhaustion while ultimately preserving CAR-T cell functionality and persistence post-infusion.

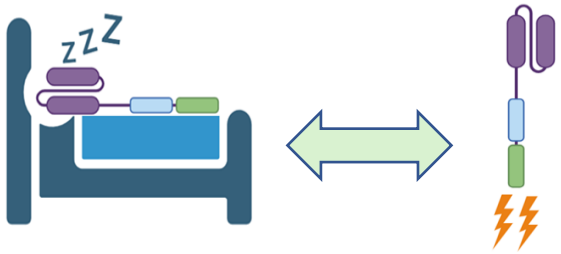
IMiD drug regulated CAR-T to reverse CAR signaling

Figure 2: iTAG OFF-SWITCH Design

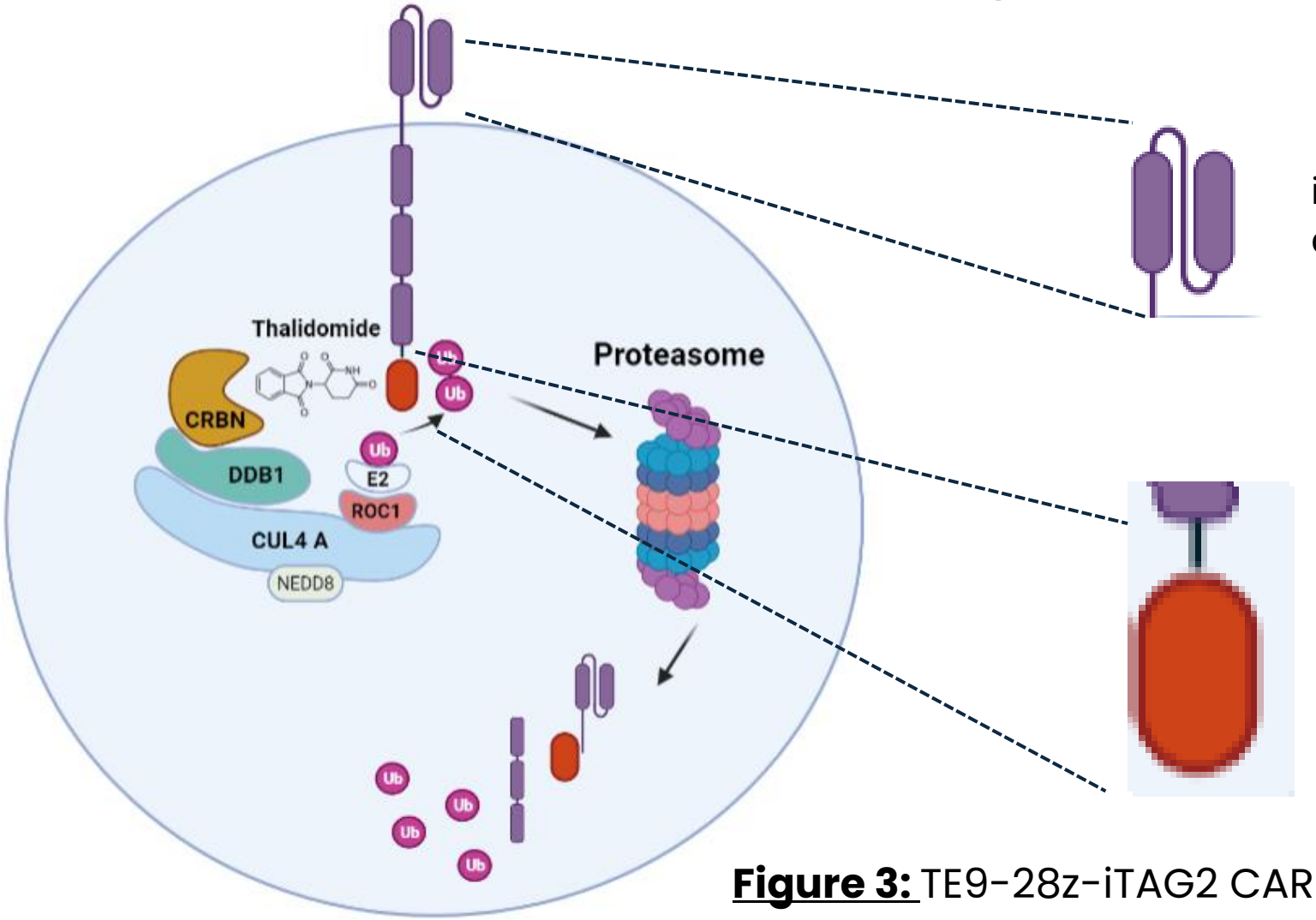




Optimised dosing and scheduling →



Developing a clinical candidate: anti-B7H3 iTAG2/IMiD-regulated CAR-T



ScFV =TE9 anti-B7H3:
intermediate affinity; fast on and off rates

iTAG2:
60 amino acid degron to allow drug regulated degradation

Figure 3: TE9-28z-iTAG2 CAR-T Schematic

Competing Approaches & Differentiation

iTAG2 outperforms other approaches, overcoming the limitations of SuperDegron, dTAGs or state-of-the-art PROTACs, by avoiding issues such as nuclear localisation of fused proteins and hook-effects, whilst ensuring suitable dosing and efficient modulation of the degradation of iTAG fused proteins (e.g., CARs).

- Abolishing the nuclear accumulation led to favourable cell surface expression of CAR construct and improved CAR-iTAG2 T cells functionality (data not shown, due for publication 2026).
- The *in-vitro* degradation of CAR-iTAG2 was found to be highly efficient at doses down to nM IMID/CELMOD doses.

Development Status

EARLY-STAGE CLINICAL TRIALS: anti-B7H3 iTAG2 CAR-T

1. "CARTUNE"

- Paediatric brain tumours expressing B7H3
- Phase I + expansion phase

2. "SWITCH"

- Extracranial paediatric brain tumours expressing B7H3
- Phase Ia/Ib

UCL will lead two translational clinical trials (CARTUNE and SWITCH) focused on anti-B7H3 CAR-Ts, initiation of first trial planned Q4 2026.

PRECLINICAL DEVELOPMENT AND ENGINEERING (ONGOING)

Next generation ITAG adoptive cell-based immunotherapies

- ICR and UCL are developing iTAG3 and additional regulatable iTAG-cell therapies to treat brain cancers. (Oxford-Harrington Award).
- UCL are optimising iTAG2/IMIDs in the manufacturing of CAR-T products, wherein this will be incorporated into clinical trials (e.g., CARTUNE).
- Further validation in additional CAR-Ts to expand iTAGs platform exemplification.

IP Status & Commercial Opportunity

Market Advantage:

Switch-control systems are predicted to deliver strong performance improvements over currently marketed CAR-T therapies and competing engineering approaches (Figure 8).

IP:

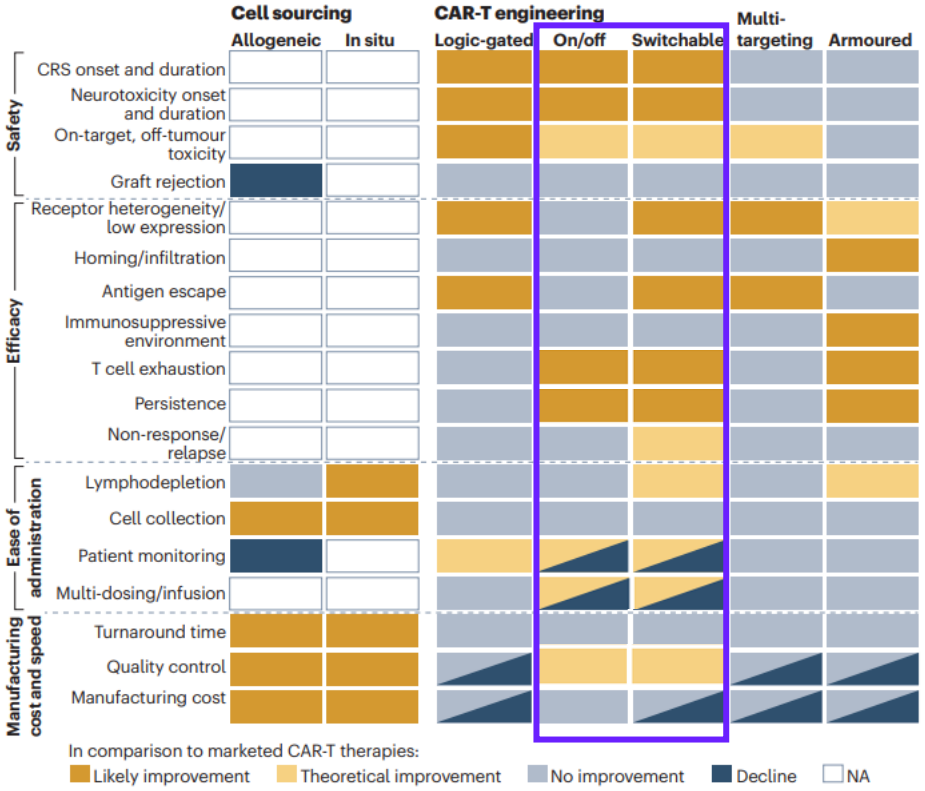
- Priority filed by CRH, ICR, UCLB on 7/11/2023 to cover iTAG (WO2024100392A1), N/R: EP, US, CN, JP, AU and KR.
- IPR for the anti B7H3 CAR-T, such as b7-h3 binders; (WO2024009075A1, filed 4/07/2022) vest solely with UCL/UCLB.
- IP packages available for licensing are expected to include patent families, know-how and arising clinical data.

SEEKING:

Co-development and licensing partners keen to integrate the iTAG platform into next-generation adoptive cell-based immunotherapies, particularly those targeting oncology indications and other applicable disease areas with unmet clinical need.

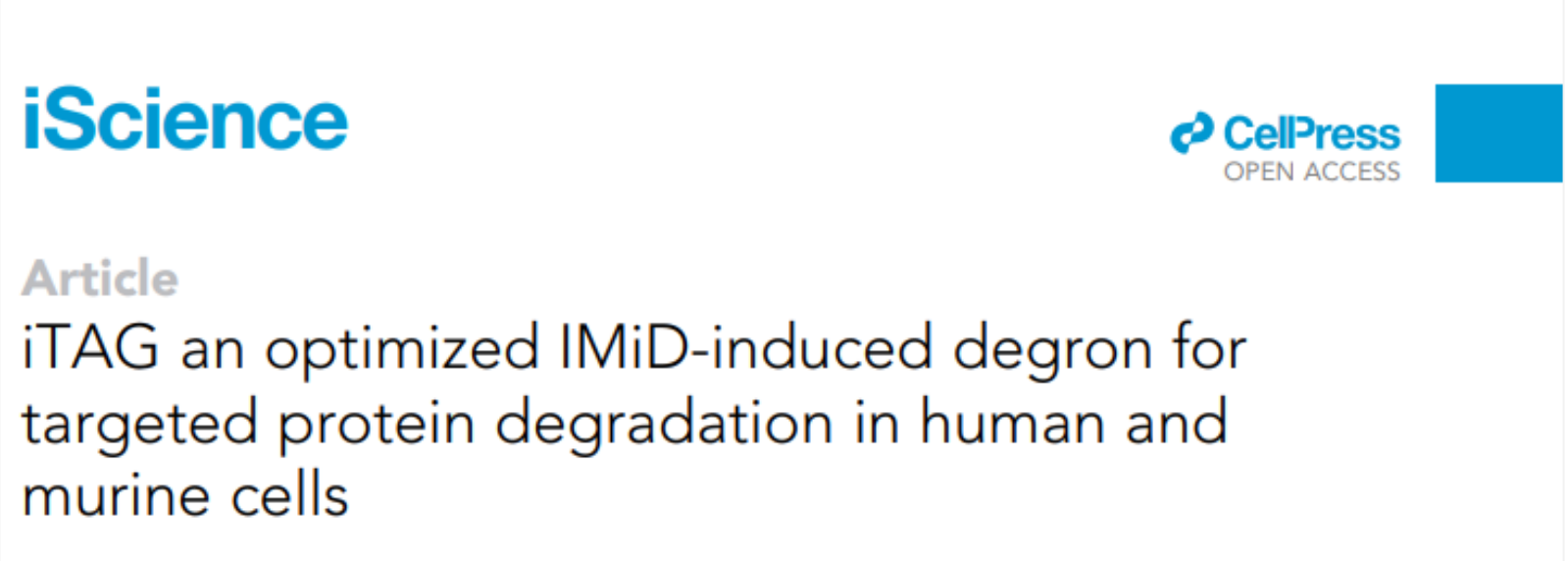
Figure 4: Impact of CAR-T therapy engineering innovations.

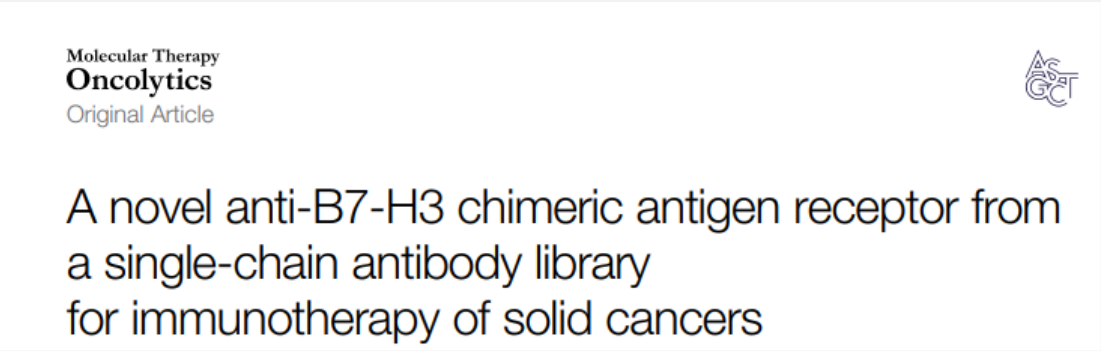
Adapted from Verma et al., 2023



Publications

Click textbox for link to publications









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