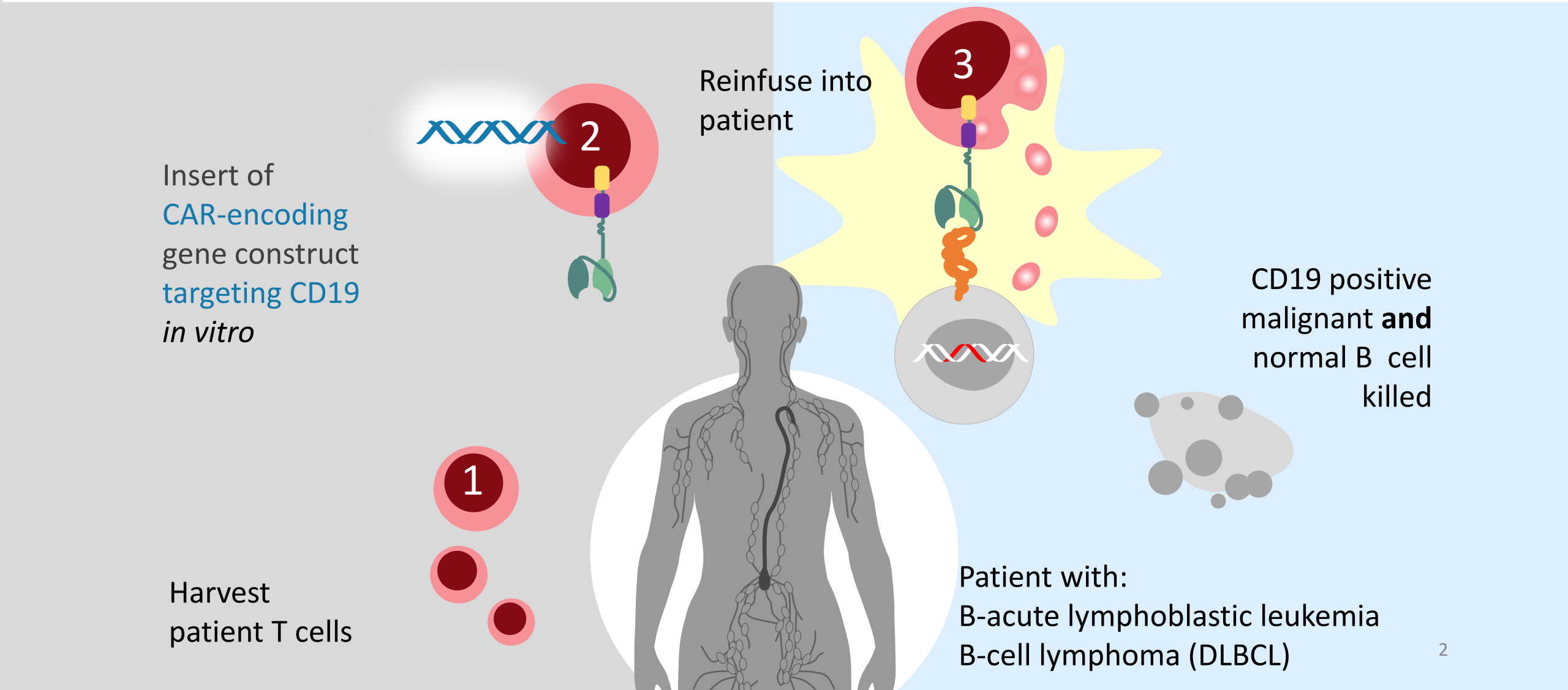
Genterapi – nye muligheter utviklet i Norge

Johanna Olweus

Seksjon for kreftimmunologi, Institutt for kreftforskning,
Oslo Universitetssykehus og Universitetet i Oslo

Oslo University Hospital

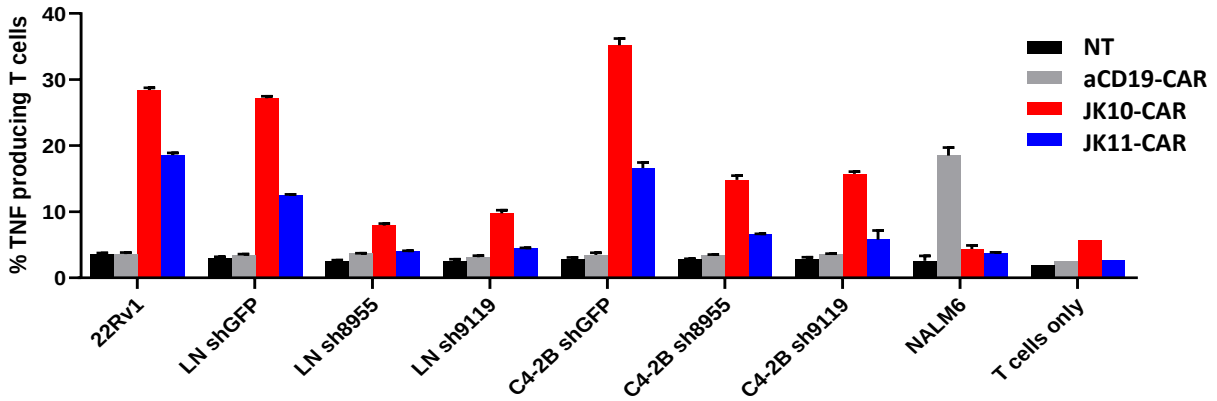
Background: CAR19 T cell-therapy can cure 40% of B cell malignancies



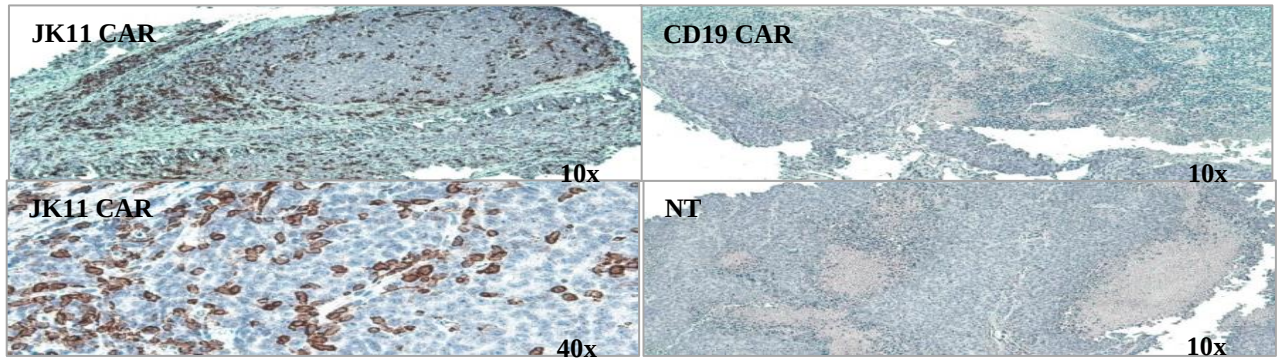
CAR T for treatment refractory prostate cancer

- Target antigen associated with tumor metastatis
- CAR T cells are highly specific, no cross-reactivity
- CAR T cells show potent anti-tumour activity in vitro and in mouse model

CAR T cells respond to tumor cells expressing the target, while control T cells do not



Animal model: JK11 CAR T cells infiltrate tumor, while control T cells do not



Experiments by Y Jin, Kyte Group

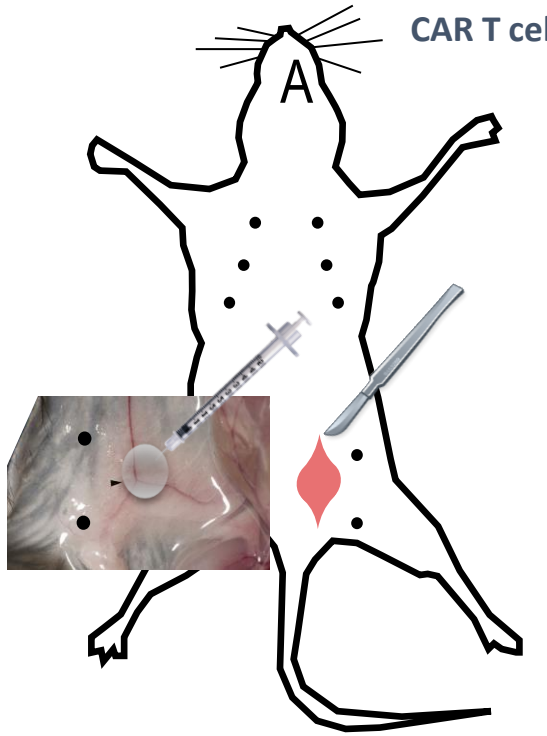
HELSE SØR-ØST

NORWEGIAN CANCER SOCIETY

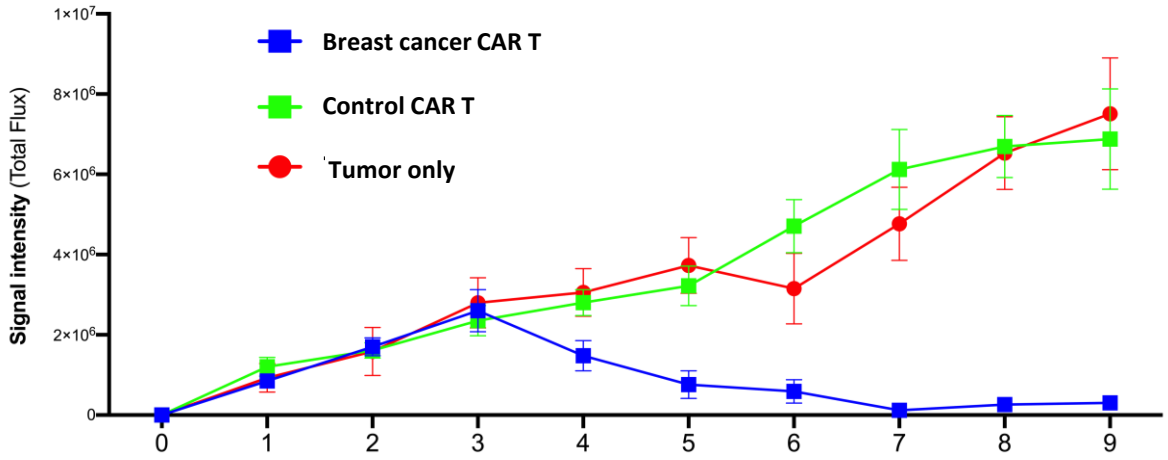
Kyte Group (*www.ous-research.no/kyte)*

CAR T cells targeting tumor-specific antigen expressed in aggressive and treatment refractory breast cancer

- Target antigen associated with tumor metastatis
- CAR T cells are highly specific, no cross-reactivity
- CAR T cells show potent anti-tumour activity in vitro and in mouse model



CAR T cells eliminates cancer in orthotopic (mammary fat pad) model of human breast cancer



Experiment by E Dorraji, Kyte Group

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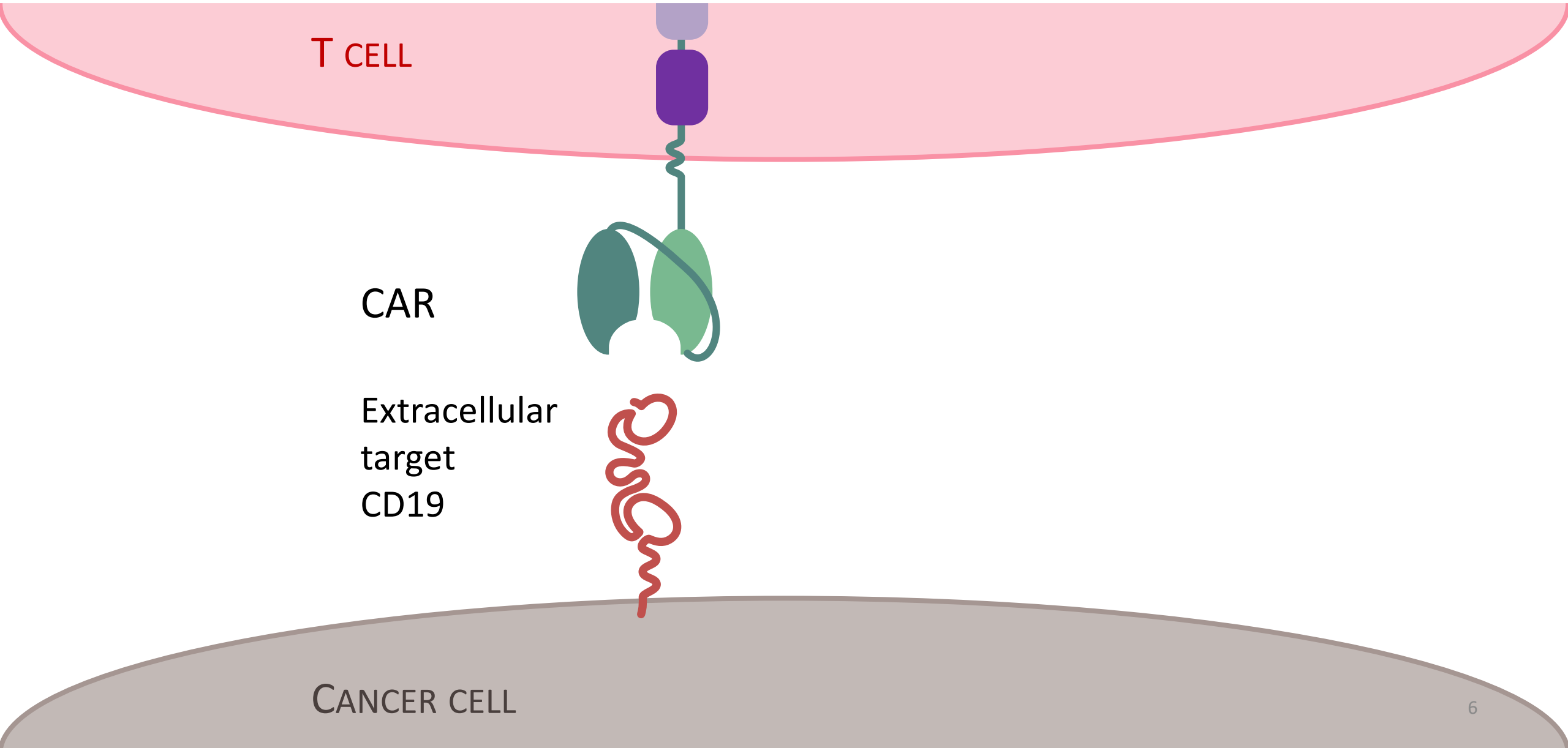
blood advances®

IMMUNOBIOLOGY AND IMMUNOTHERAPY | APRIL 12, 2019

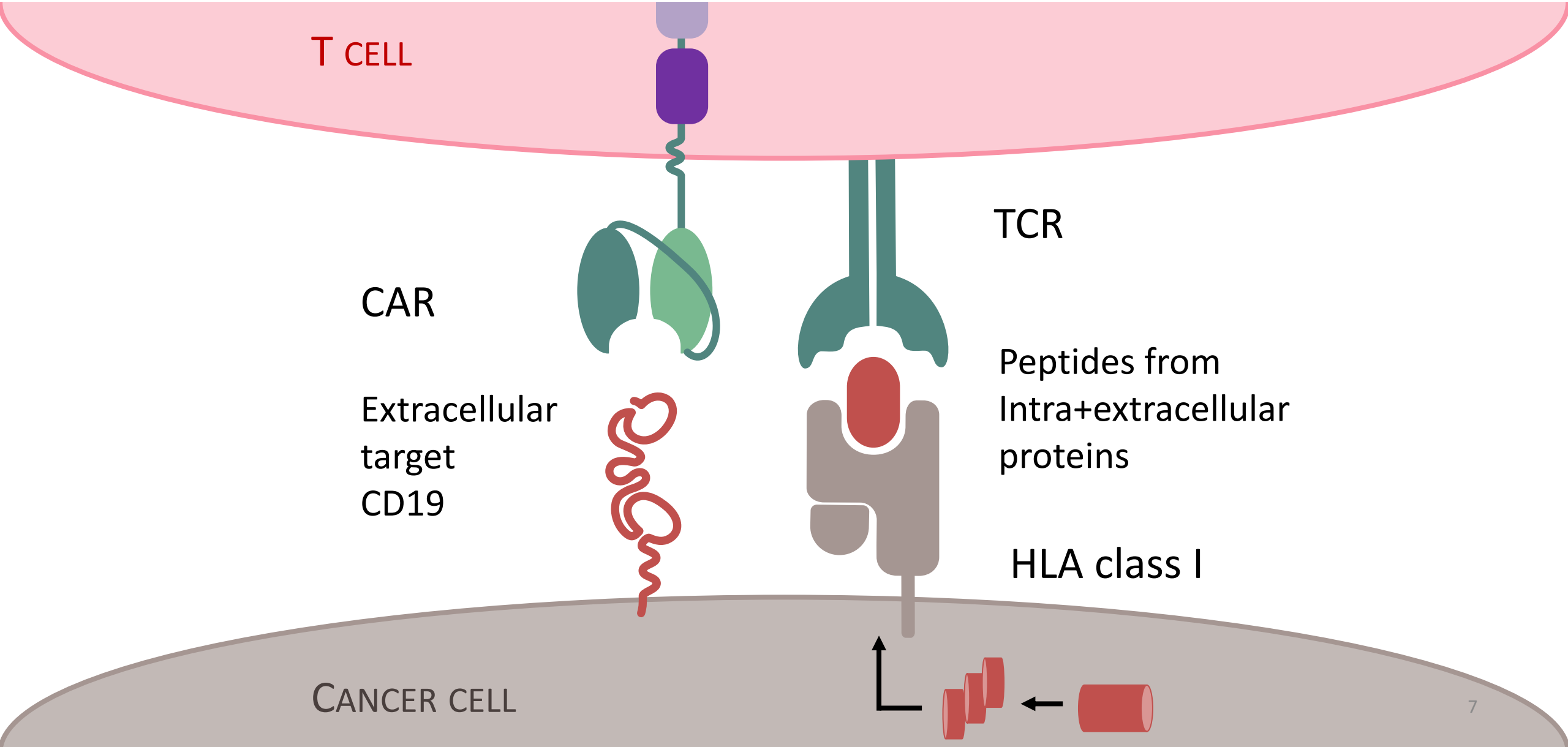
Preclinical development of CD37CAR T-cell therapy for treatment of B-cell lymphoma

Hakan Köksal, Pierre Dillard, Sarah E. Josefsson, Solrun Melkorka Maggadottir, Sylvie Pollmann, Anne Fåne, Yngvild Nuvin Blaker, Klaus Beiske, Kanutte Huse, Arne Kolstad, Harald Holte, Gunnar Kvalheim, Erlend B. Smeland, June H. Myklebust, Else Marit Inderberg, Sébastien Wälchli

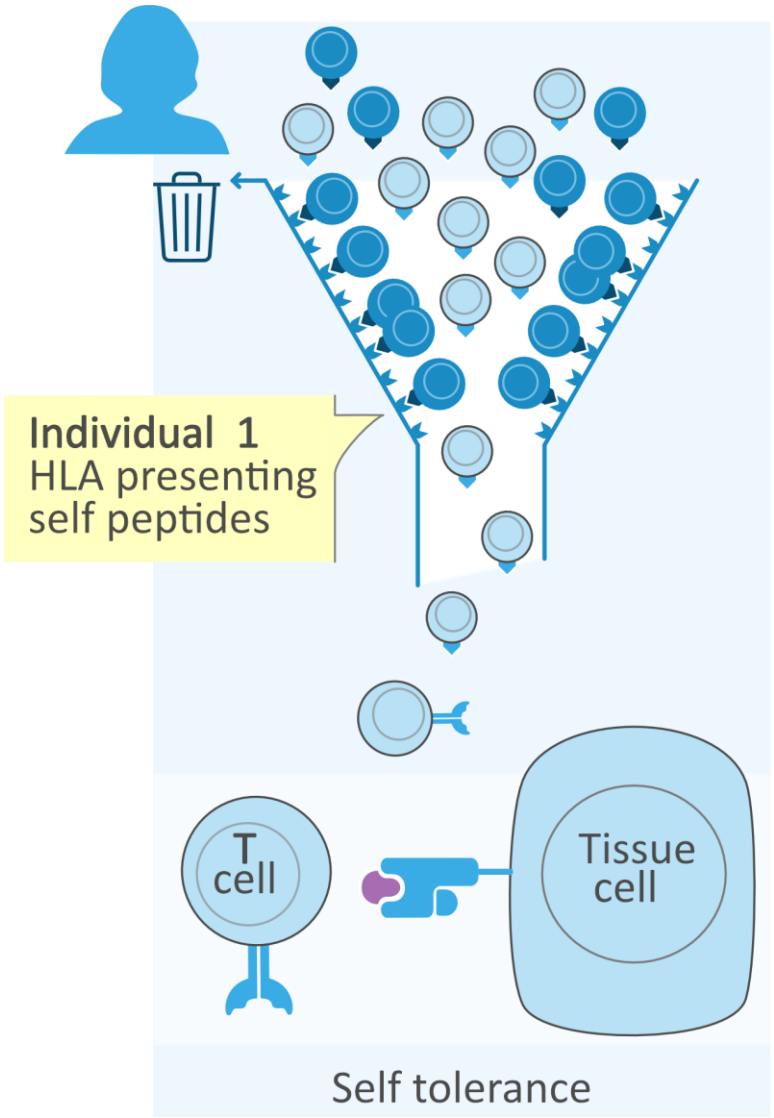
Tissue-specific self-antigens on the cell surface are rare



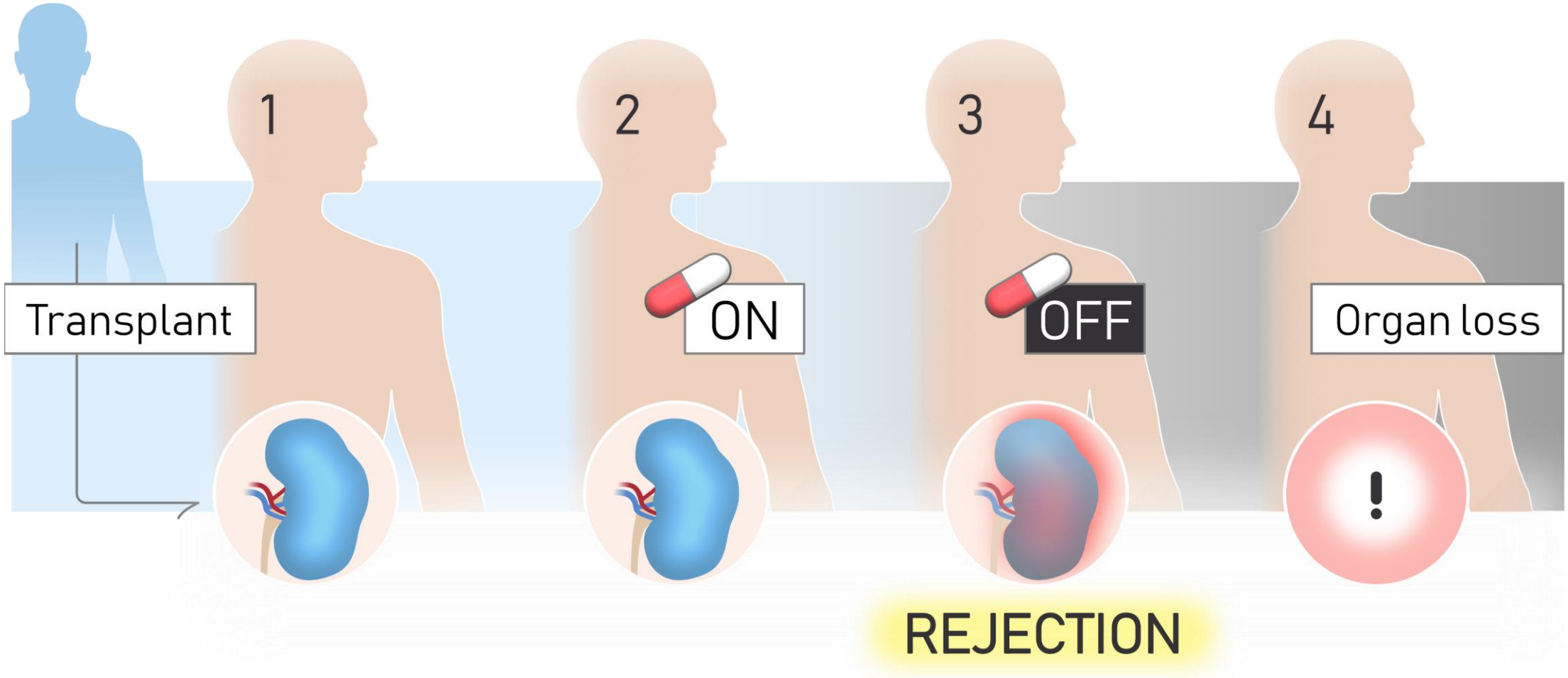
Can the success of targeting self be translated from CARs to T-cell receptors (TCRs)?



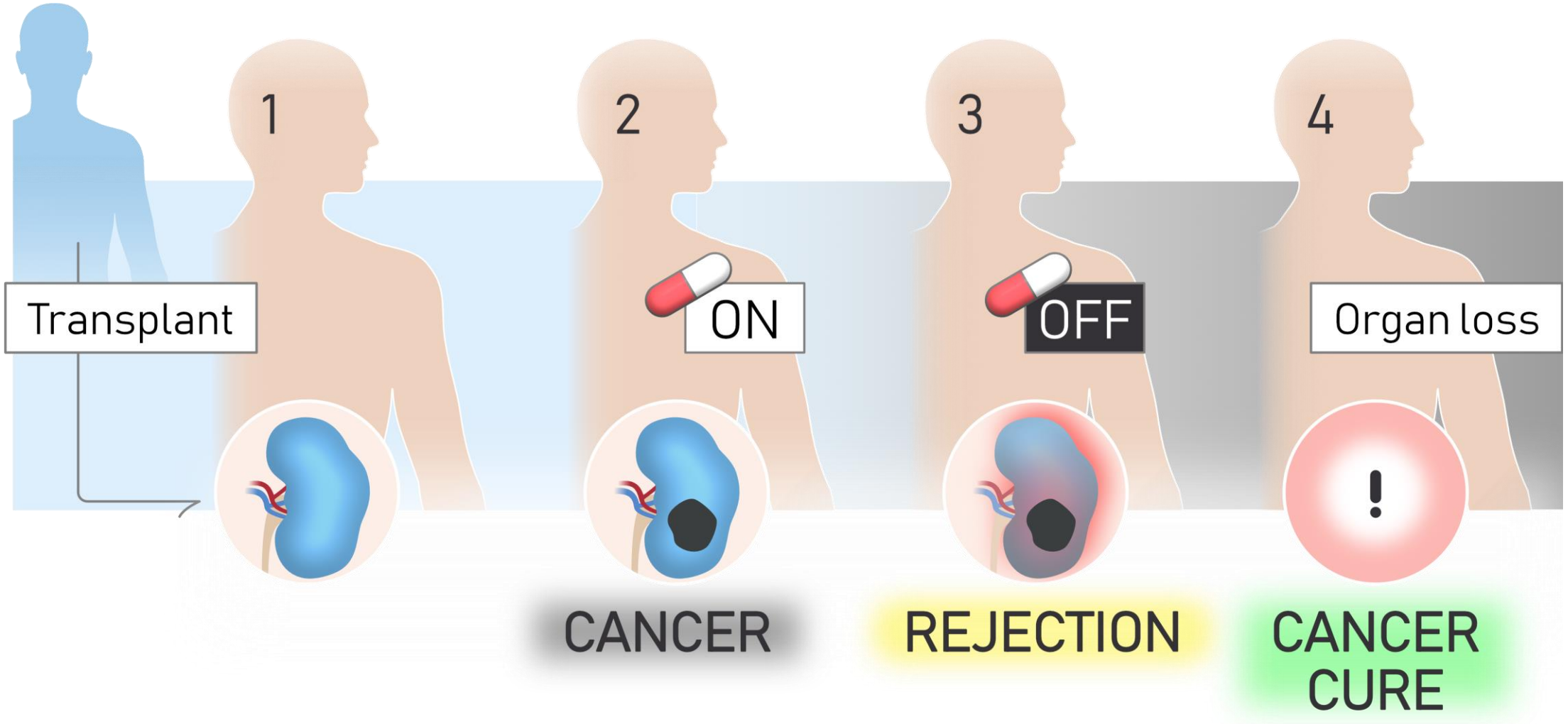
Self-reactive T cells are deleted in the thymus during development



Organ rejection – a strong T cell response

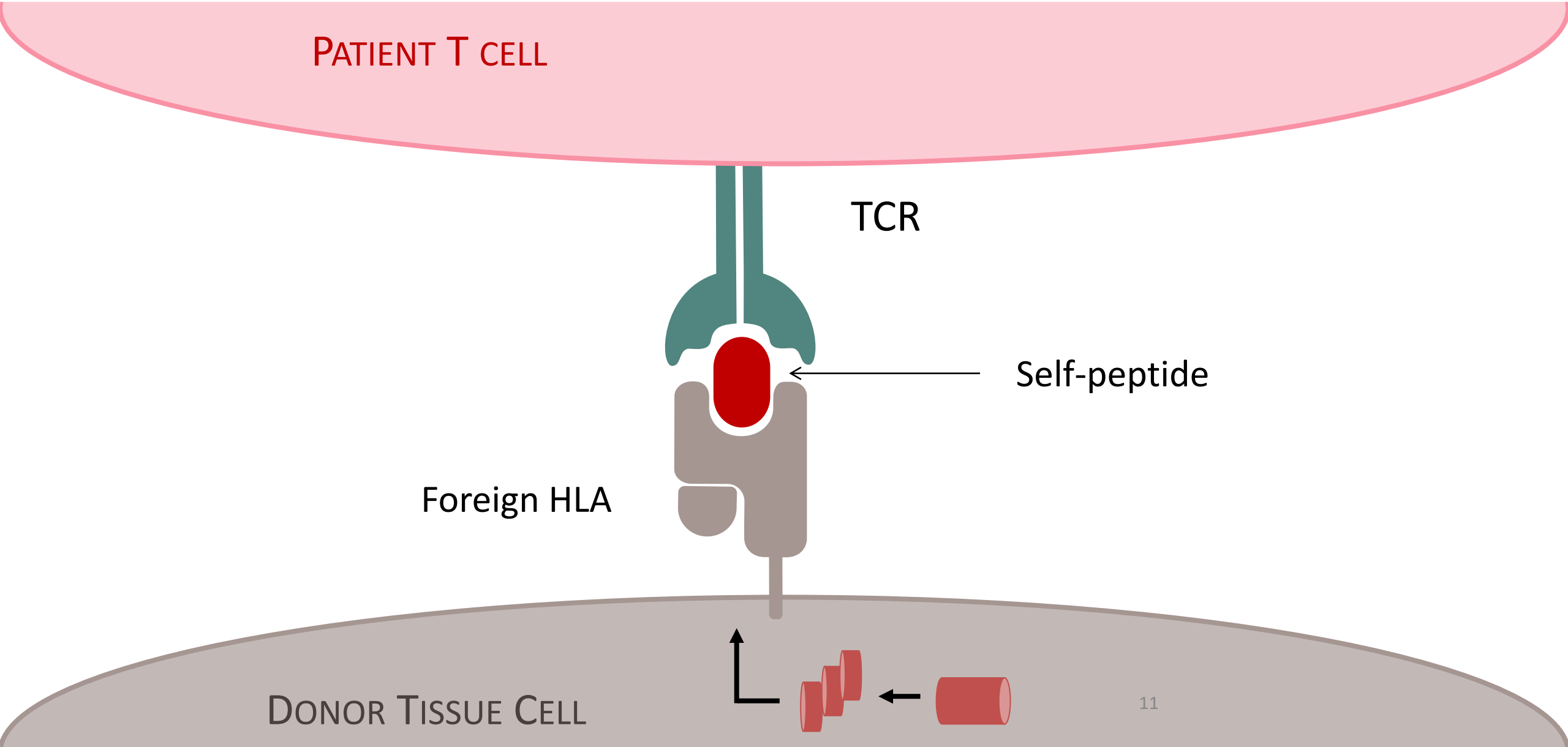


Rejecting cancer

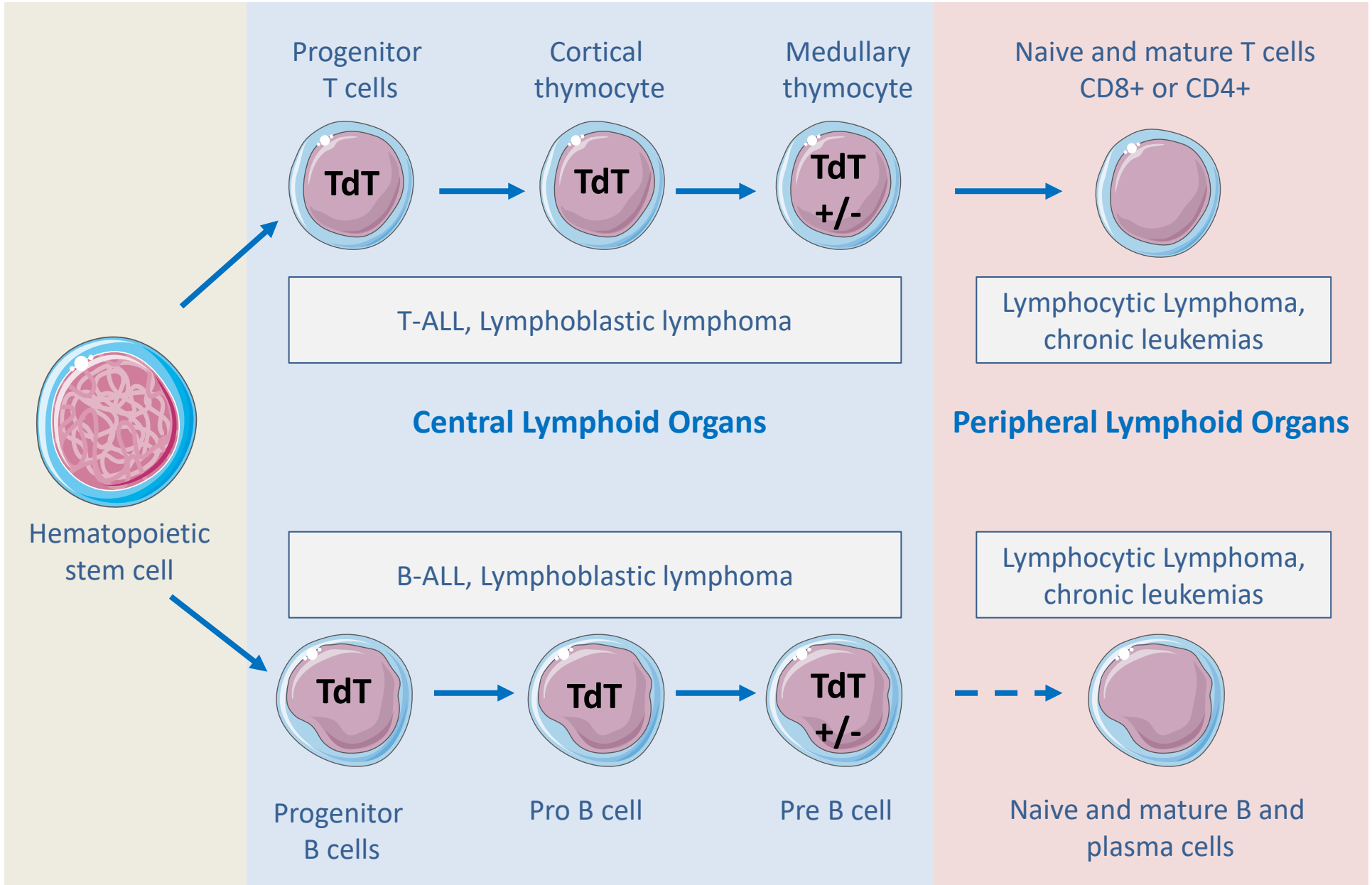


«Transmission of cancer from organ donors» I. Penn, Nefrologia, vol XV, 1995

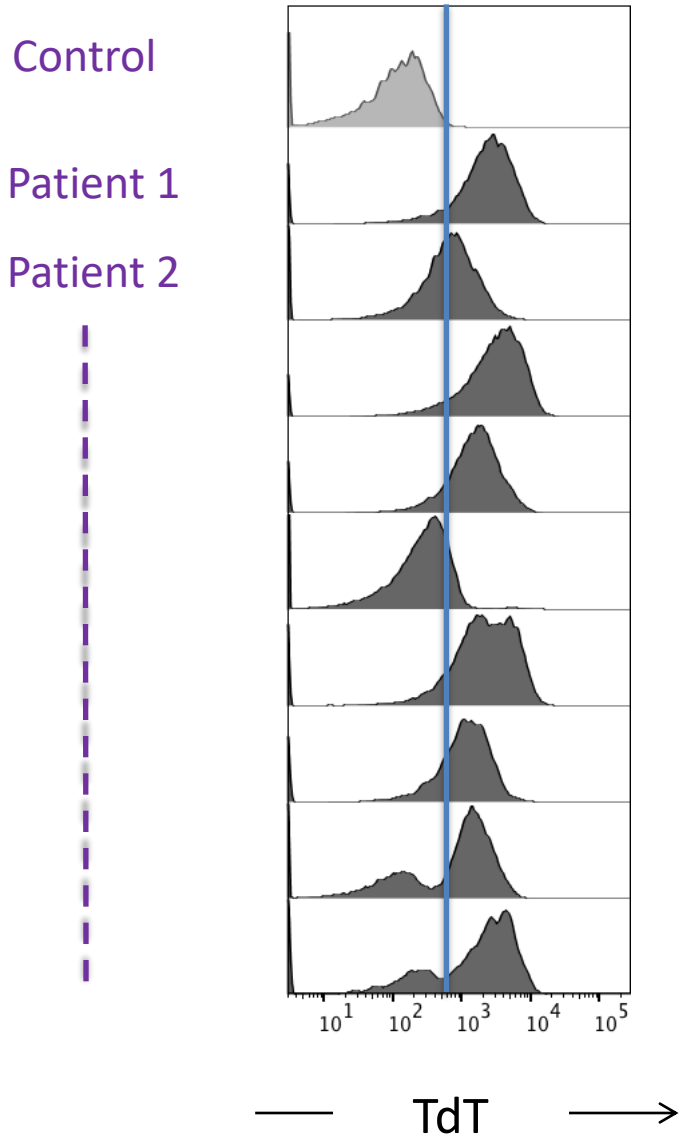
Exploit mechanism of organ rejection: T cells rejecting a single cell type



Terminal deoxynucleotidyl transferase (TdT) – a target for immunotherapy of B- and T-ALL

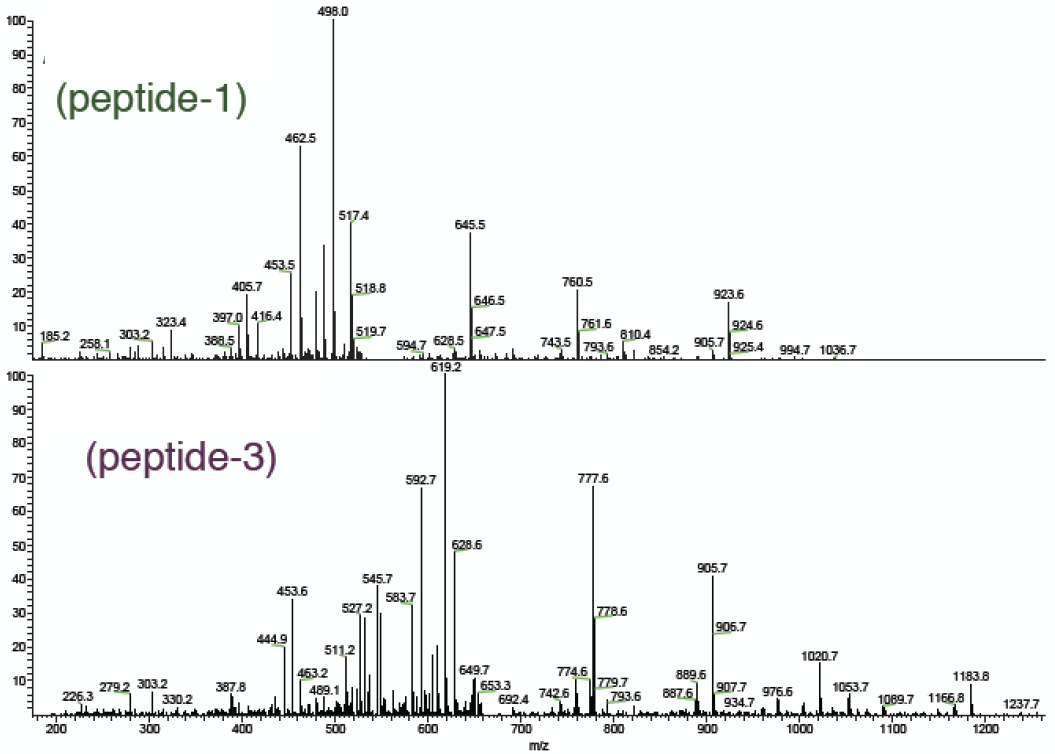


The majority of primary ALL are TdT+ and TdT-derived peptides are presented on HLA-A*02:01



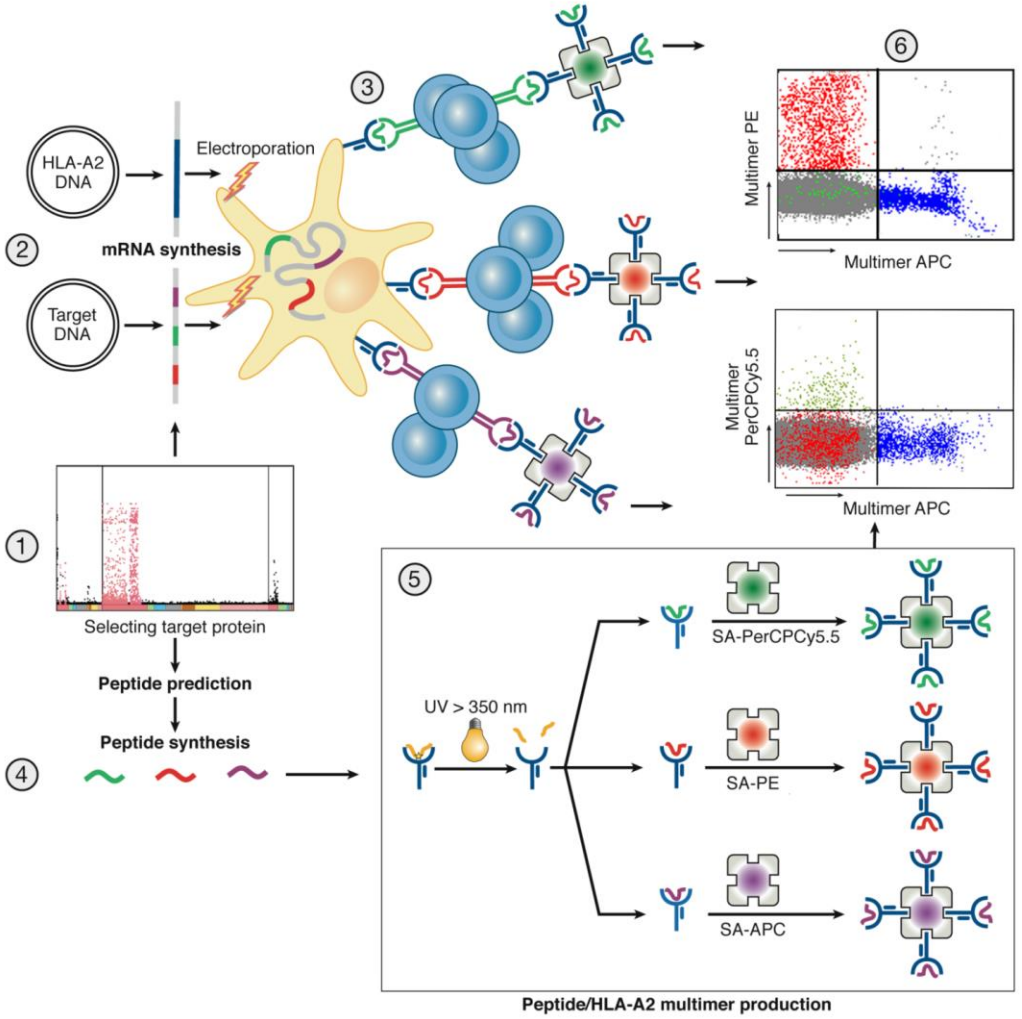
Muhammad Ali

Eirini Giannakopoulou

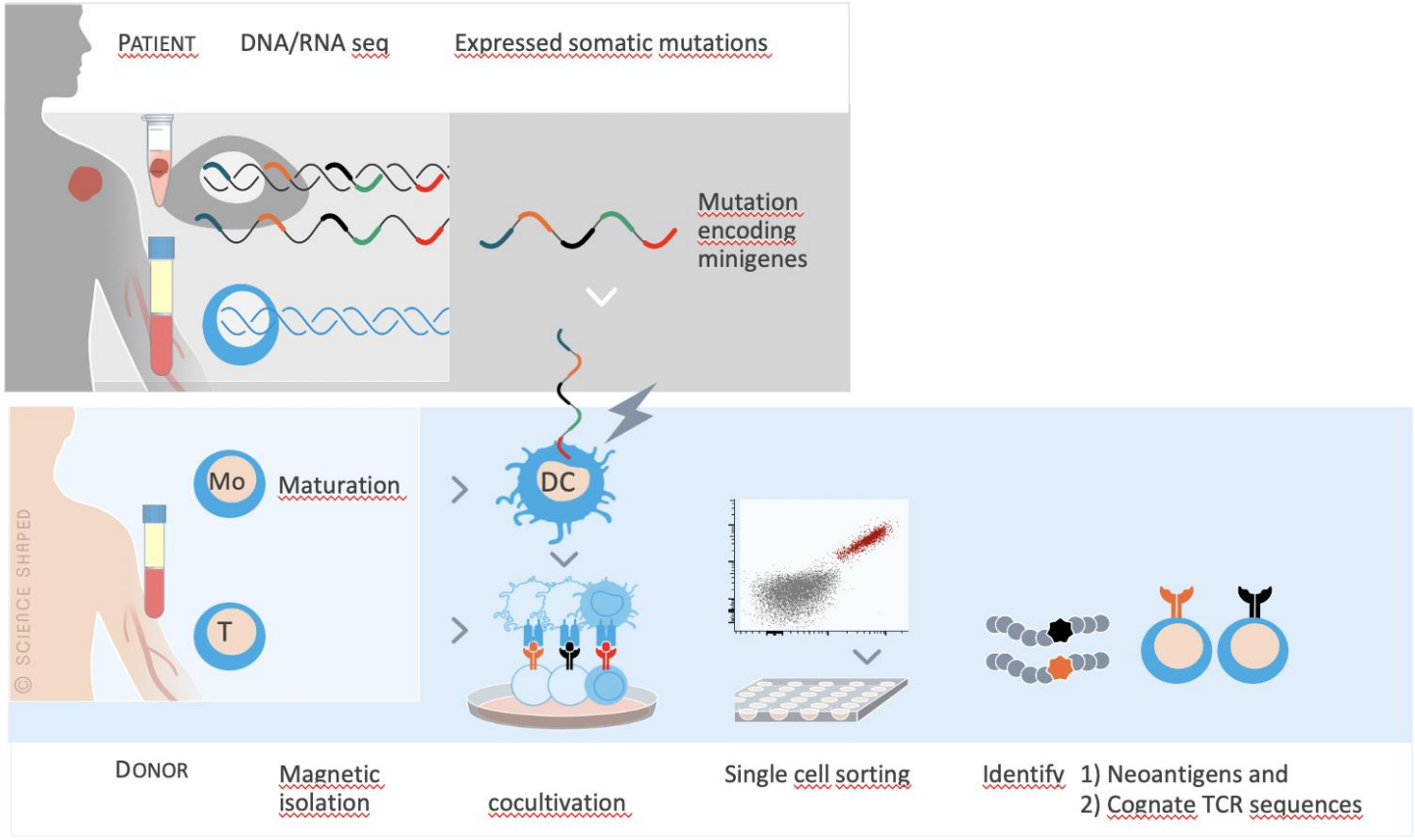


Ali/Giannakopoulou et al, Nature Biotechnology 2021

Identification of donor-derived TCRs that recognize TdT in context of foreign HLA-A*02:01



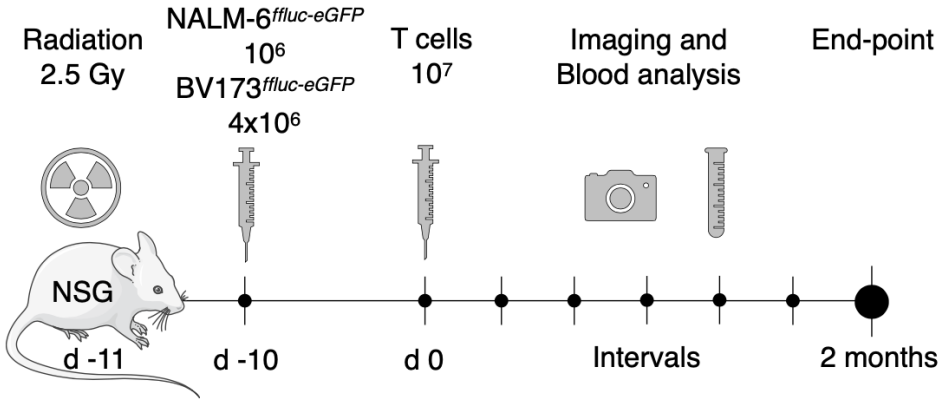
Kumari et al, PNAS 2014

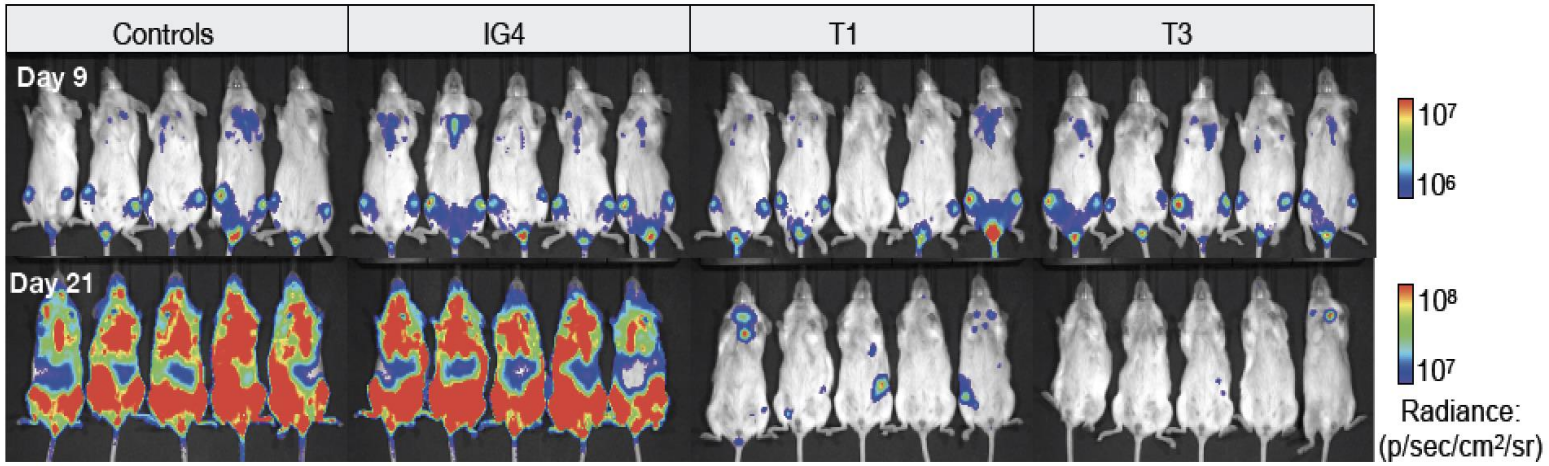


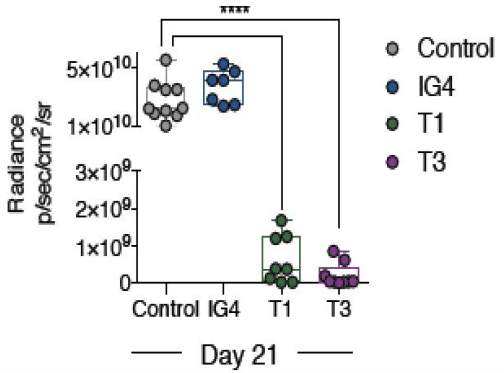
Strønen et al, Science 2016

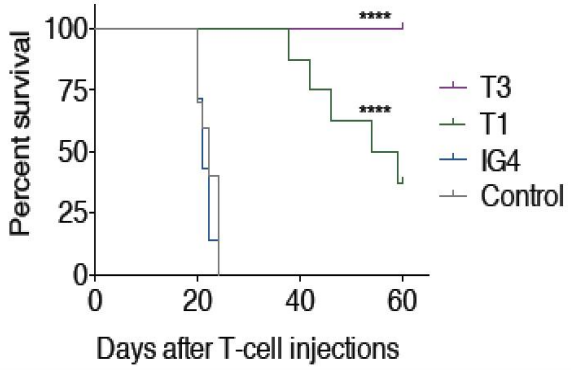
Ali/Foldvari/Giannakopoulou et al, Nature Protocols, 2019

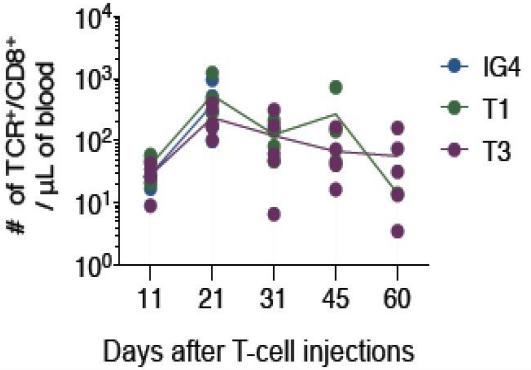
TdT TCRs mediate rejection of human leukemia *in vivo (BV173)*





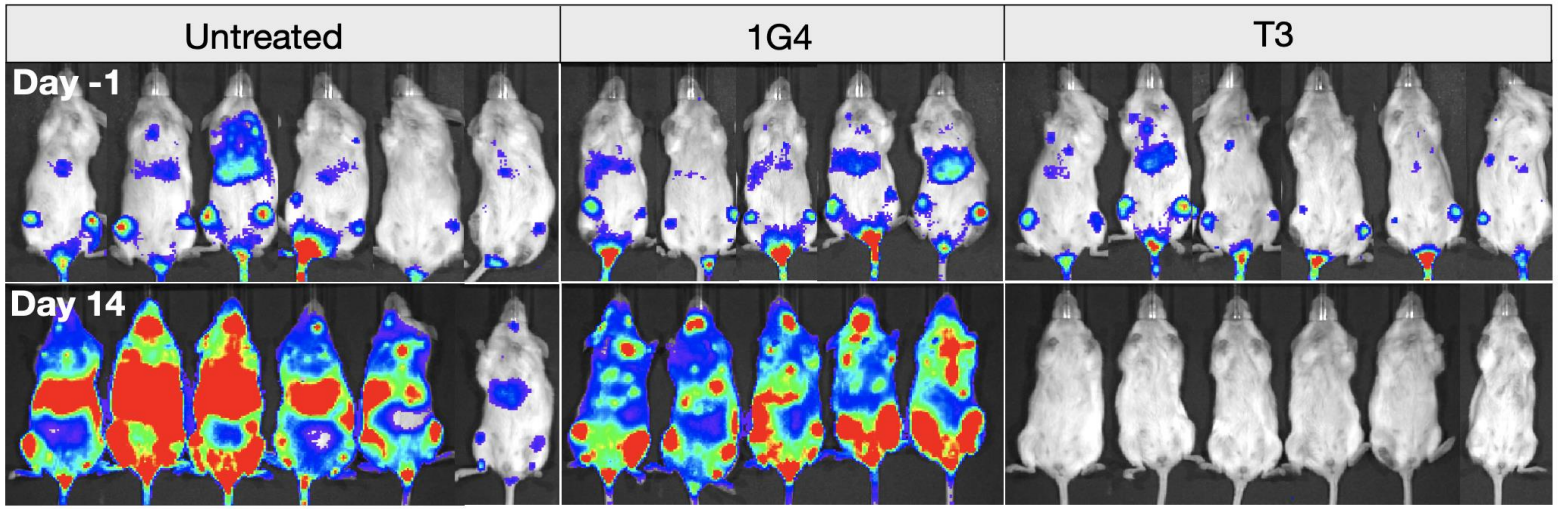


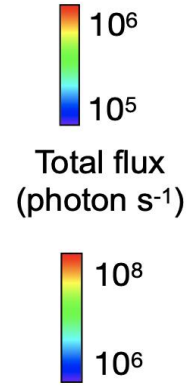


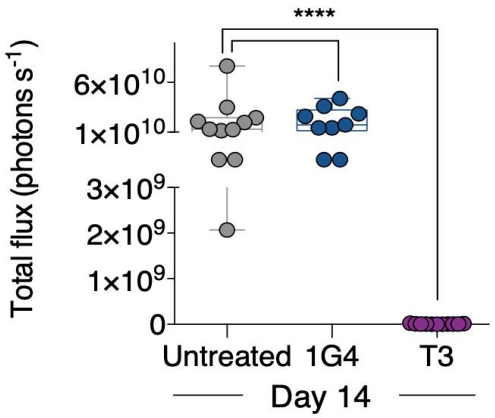


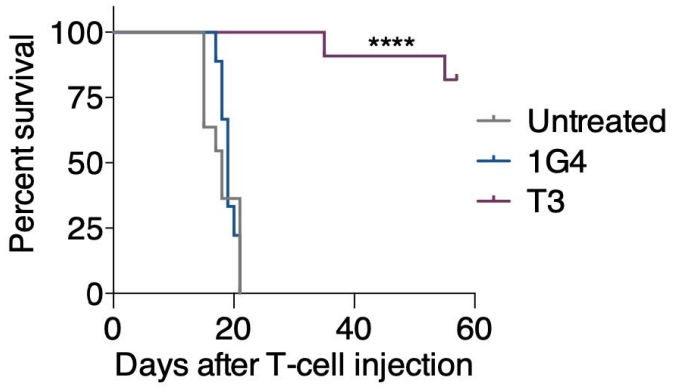
Ali/Giannakopoulou et al,
Nature Biotechnology 2021

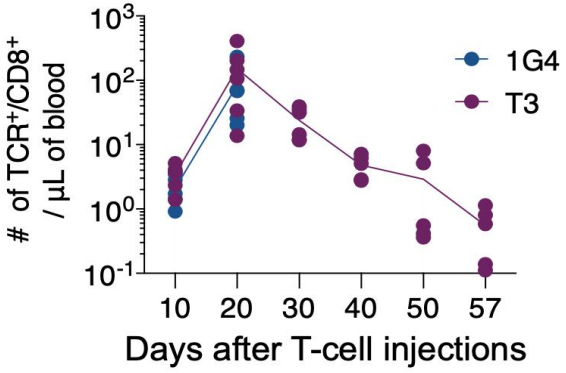
TdT TCRs eradicate human leukemia *in vivo (NALM-6)*









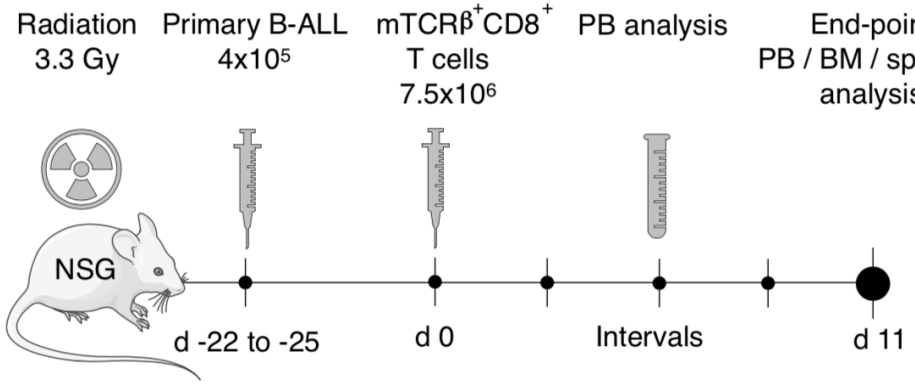


Ali/Giannakopoulou et al, Nature Biotechnology 2021

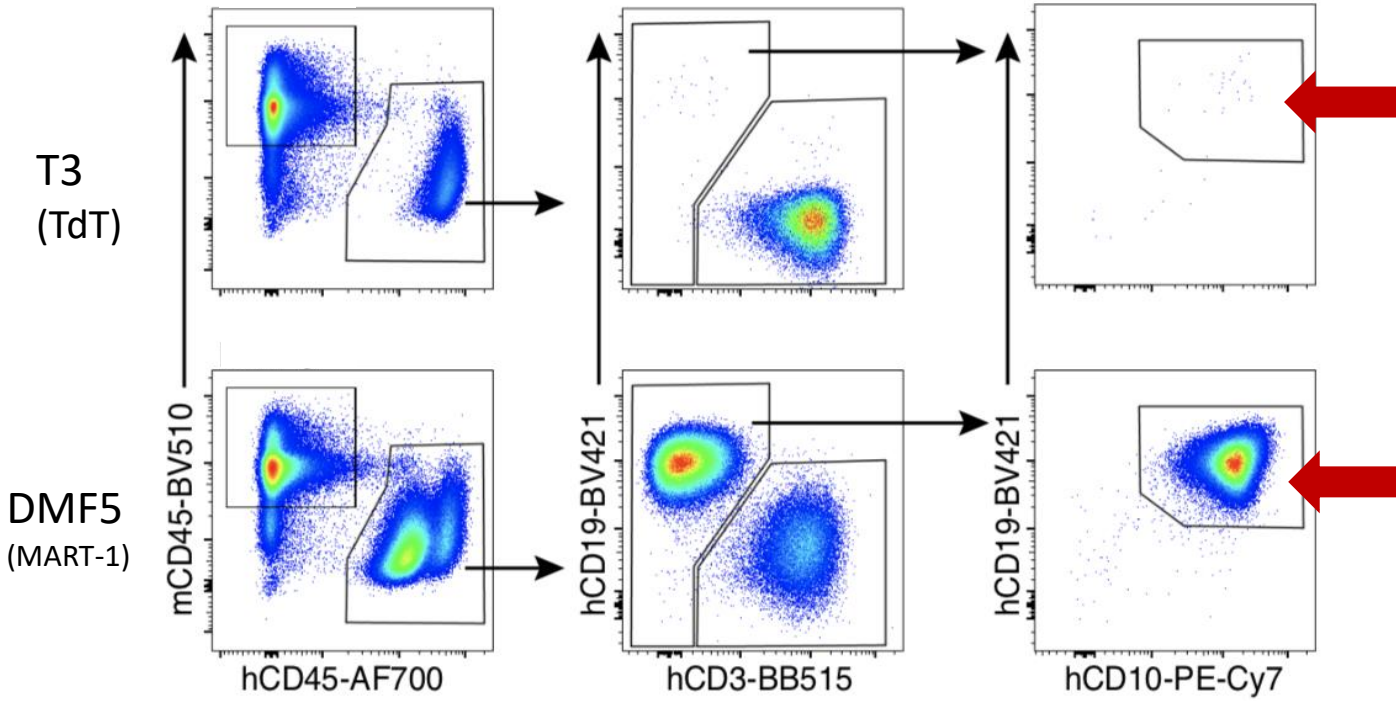
TdT TCRs efficiently eliminate primary B-ALL *in vivo*




Sten Eirik W. Jacobsen *Petter Woll* *Madeleine Lehander* *Stina Virding Culleton*

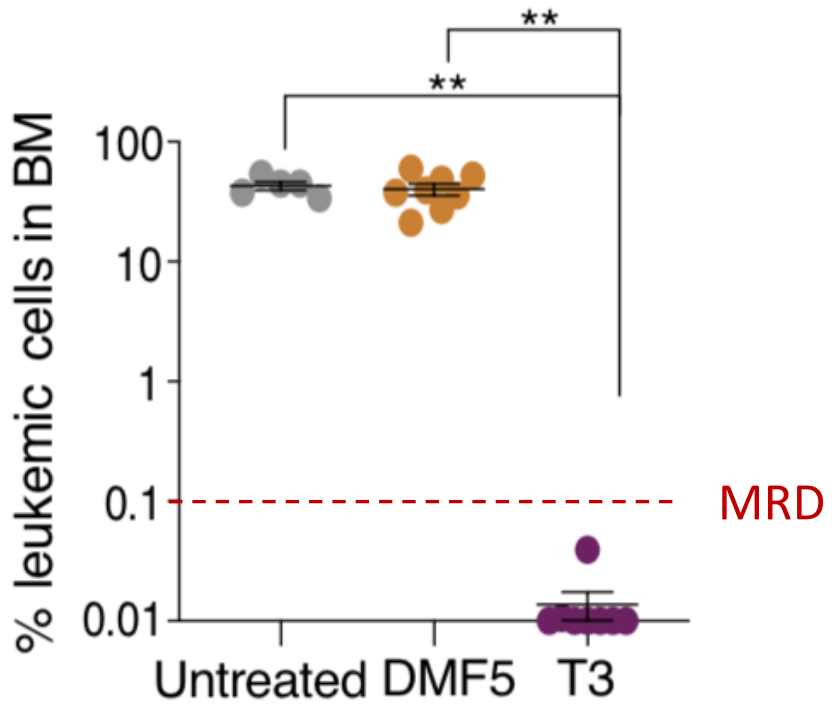


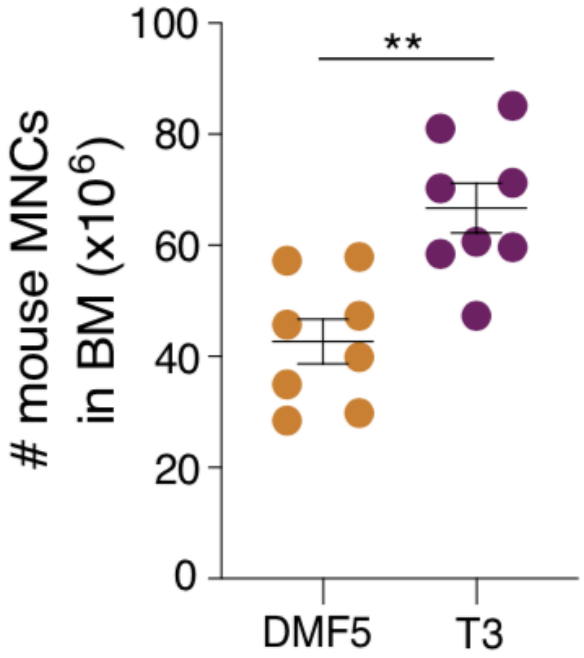
Bone marrow analysis – end of experiment



Ali/Giannakopoulou et al, Nature Biotechnology 2021

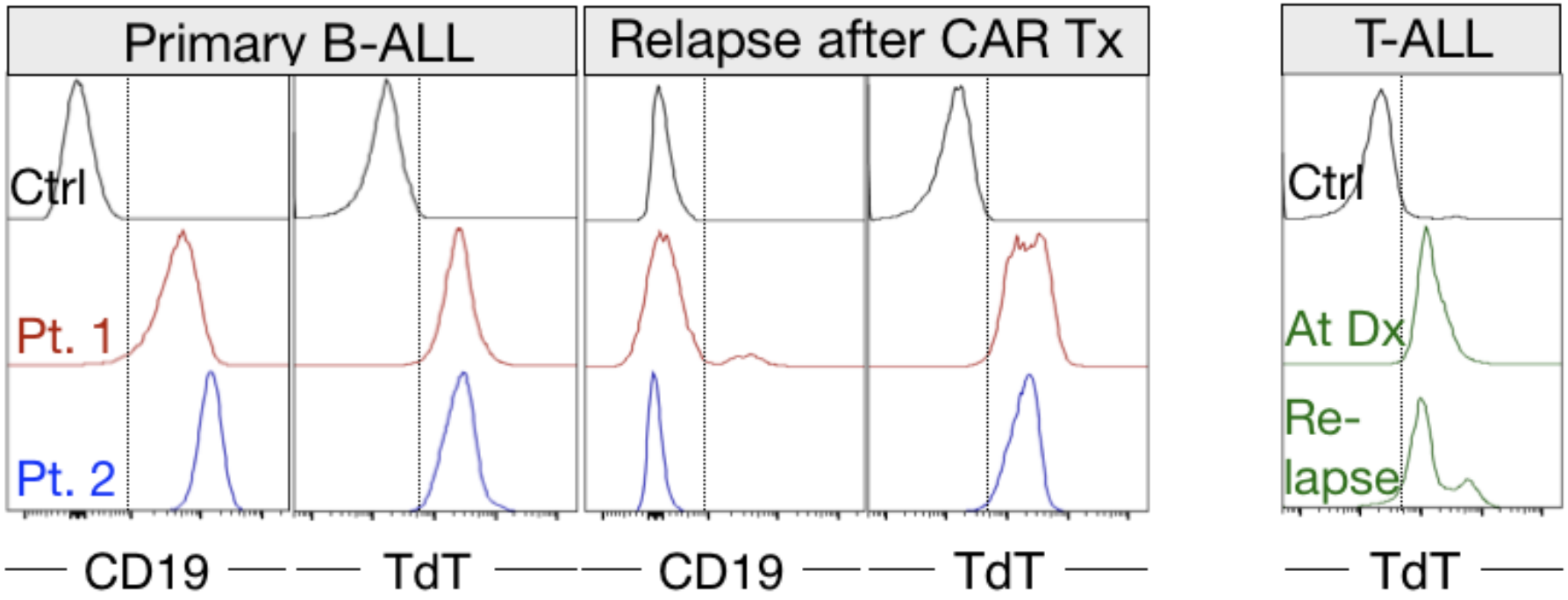
TdT TCRs efficiently eliminate primary B-ALL *in vivo* to minimal residual disease (MRD) negative levels in 11 days





Ali/Giannakopoulou et al, Nature Biotechnology 2021

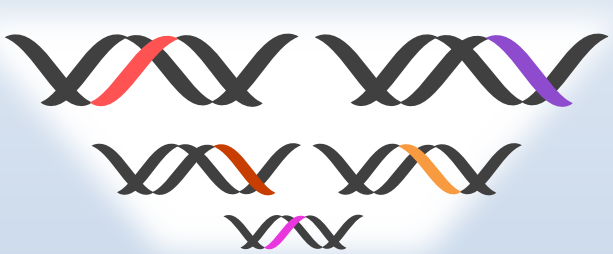
Patients relapsing from CAR19 T cell therapy with CD19 negative B-ALL, and relapsed T-ALL express high levels of TdT

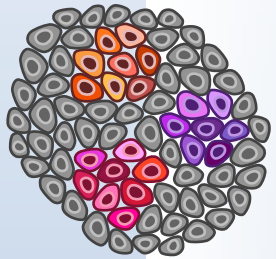


Ali/Giannakopoulou et al, Nature Biotechnology 2021

Selecting TCR targets

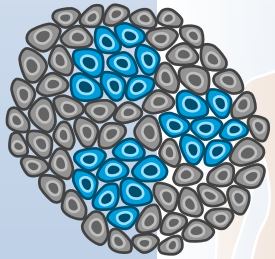
Private neoantigens





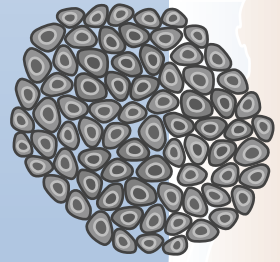
- Private
- Heterogeneous
- Low expression
- Low immongenicity

Shared neoantigens



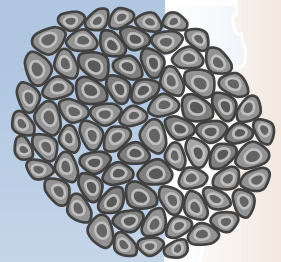
- Rare
- Heterogeneous
- Low expression
- Low immongenicity

Cancer/testis antigens

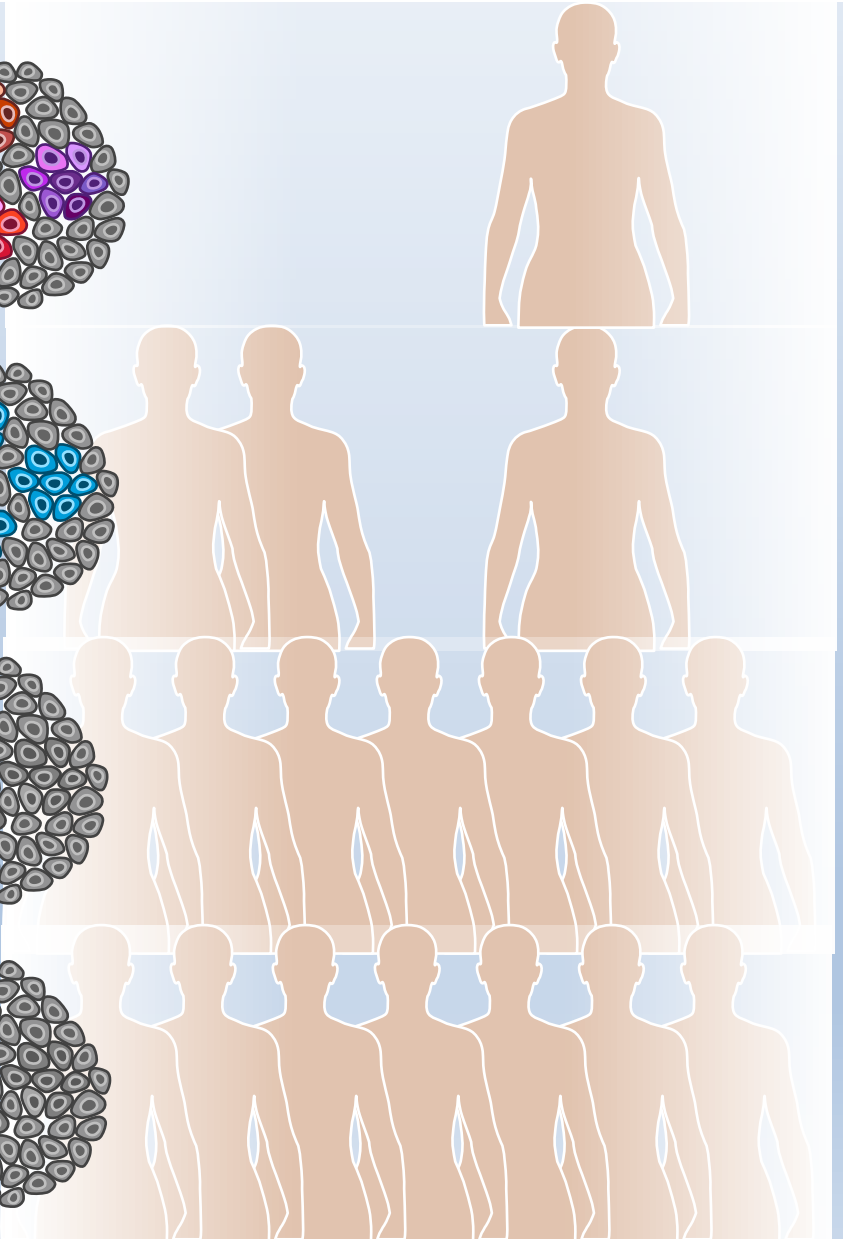


- Shared
- Heterogeneous
- Low expression

Tissue specific antigens

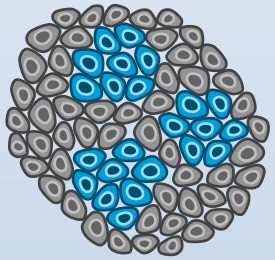


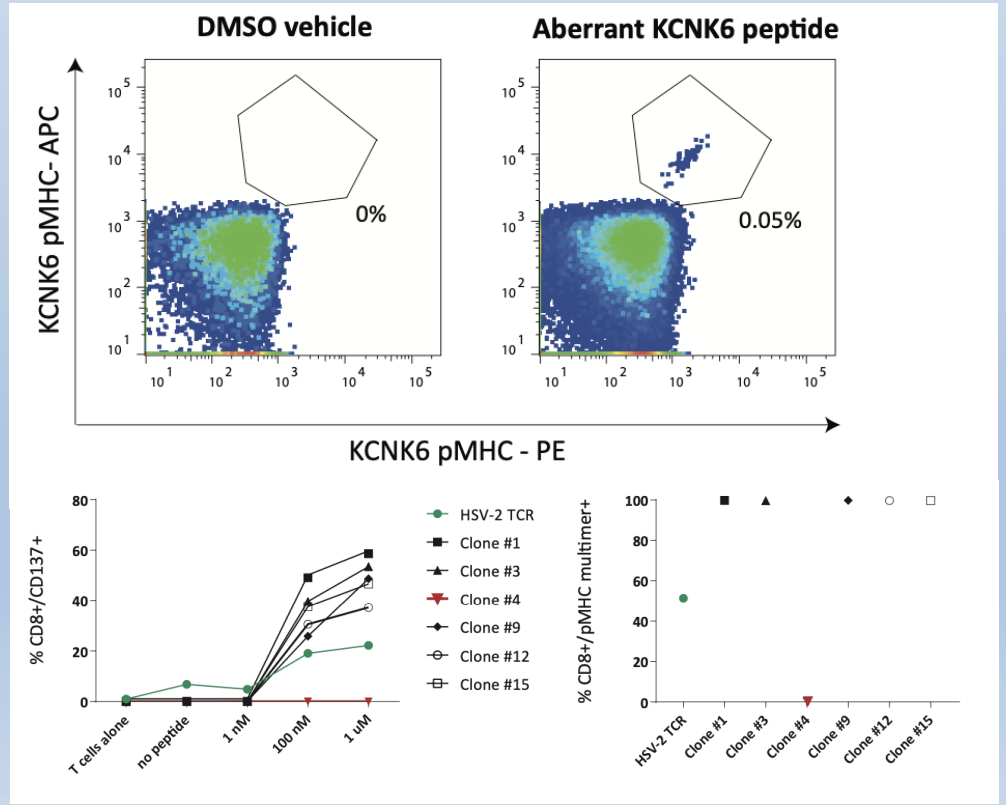
- Shared
- Homogeneous
- High expression



New shared targets? Translational mistakes

Translational mistakes





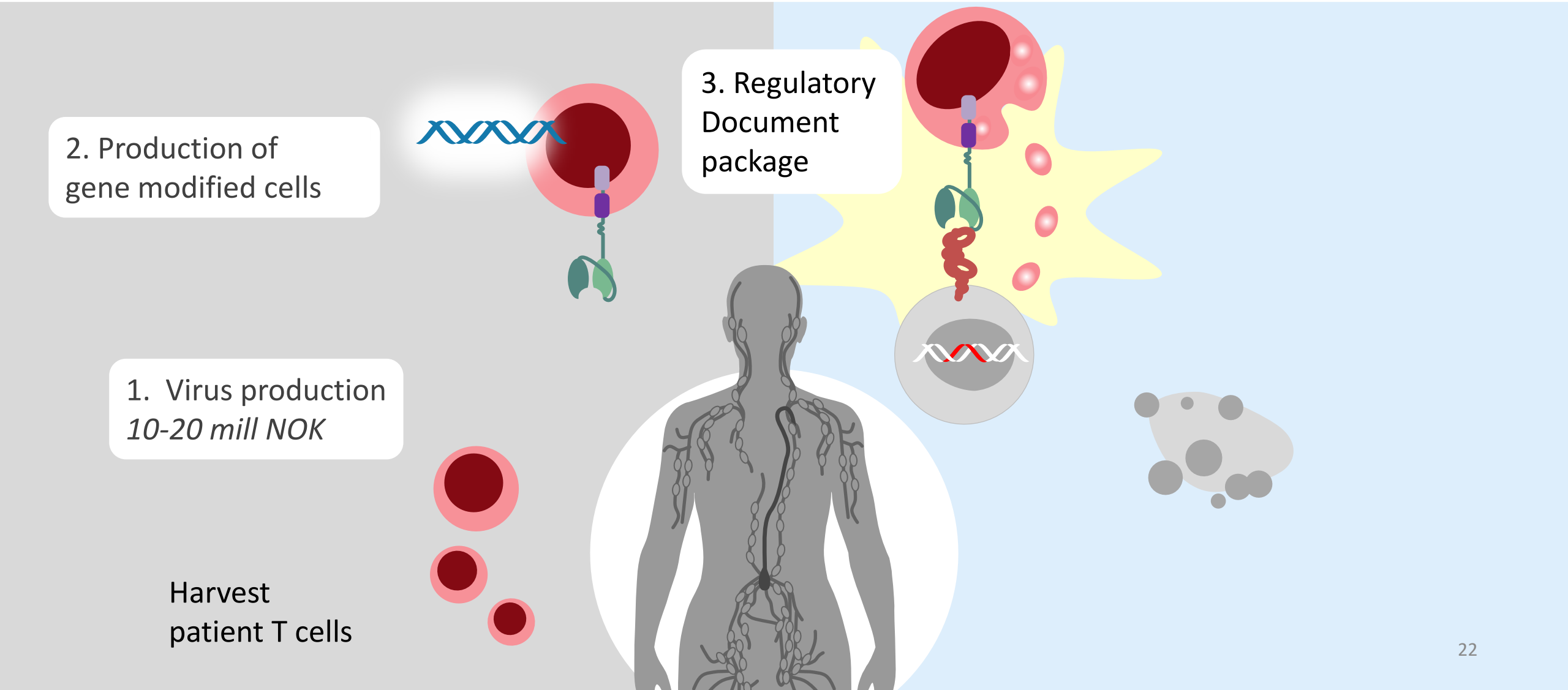
Bartok et al, Nature 2021

Pataskar et al, Nature 2022, in press

Morten M Nielsen

Maarja Laos

In house generated gene therapy – **bottle necks**



15. februar, 2022

nature biotechnology

Career Feature | Published: 15 February 2022

CAREER FEATURE

Assessing workforce needs for the emerging CAR-T cell therapy industry

Linda D. Ho, Hadassah L. Robbins & Aaron D. Levine ✉

Nature Biotechnology **40**, 275–278 (2022) | Cite this article

4 Altmetric | Metrics

"By 2025, the US Food and Drug Administration (FDA) expects to approve 10 to 20 cell and gene therapies annually[1]. However, development and, especially, manufacturing of these novel therapies is complicated and labor-intensive[2,3], which raises concerns that the lack of a skilled workforce may hinder growth of this field — potentially slowing development, raising costs and limiting the availability of novel therapies."

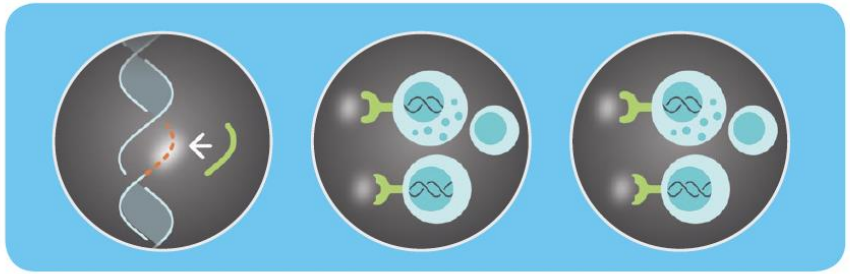
New Centre for Advanced Cell Therapy hosted by Division of Cancer Medicine, OUH

Cell and gene therapy form two of the most dynamic research areas world-wide and provide fundamentally new therapies for diseases without available treatment. Advanced Therapy Medicinal Products (ATMPs) typically target the underlying biology of the disease rather than the symptoms and therefore offer the possibility of cure. The development of new cell and gene therapies is spearheaded by the unprecedented clinical success of cancer immunotherapy, such as chimeric antigen receptor (CAR)-T cell therapy for B cell malignancies. In parallel, new advances in stem cell biology, including the possibility for differentiation of mesenchymal stem cells (MSCs), and of induced pluripotent stem cells (iPSC) reprogrammed from somatic cells, open up new possibilities to regenerate cells and tissues for the treatment of chronic diseases such as diabetes as well as various organ failures, including liver diseases. However, clinical-grade cell engineering and manufacturing represents a key bottleneck for the development of new cell and gene therapies. *"..clinical-grade cell engineering represents a key bottleneck for the development of new cell and gene therapies.."*

The academic leadership at ICR and the Department of Cancer Immunology has, together with the leadership at the OUH-CCC and the Department of Oncology and Section for Cell Therapy, outlined a path to restructure the cell therapy unit at OUH to meet the demands of the future and ensure that Norway stays at the international forefront in the development of cell and gene therapies. This effort has moreover been strengthened by the formation of a strategic research area in cell therapy at OUH (StratCell).

CRITICAL CONTRIBUTION FROM A PRIVATE DONOR CONSORTIUM

A donor consortium consisting of Svanhild and Arne Must´s Foundation for Medical Research (lead donor), RADFORSK oncology research fund and the Norwegian Cancer Society, has committed 50 MNOK to form a Centre for Advanced Cell therapy (ACT Centre) located in clean room facilities at the OUH. The investment is dedicated to the establishment of a center that will provide a new national service for the manufacturing of genetically engineered cells for therapy, under full-scale good manufacturing practices (GMP). The center will moreover include existing local competence in cell differentiation and manufacturing for production of other ATMPs to OUH.



Privat donasjon: 50 mill NOK til genterapi

Kreftforeningen
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Erik Must

Hans Peter Bøhn

Svanhild og Arne Musts fond for medisinsk forskning

RadForsk
Jonas Einarsson

KREFTFORENINGEN

RADFORSK

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Karolinska Institutet

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Sören Lehmann

Department of Haematology, Oslo University Hospital
Geir Erland Tjønnfjord

Department of Immunology, Oslo University Hospital
Liv Toril Osnes

THANK YOU!