New Drugs in Hematology
January 15-17, 2024
BOLOGNA, ROYAL HOTEL CARLTON

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

CAR Natural Killer Cells: a new frontier for cancer immunotherapy

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Disclosures

- Scientific founder- Syena

- License agreement and research agreement:
  - Takeda to develop CB-CAR NK cells for the treatment of B-cell malignancies and other cancers, which creates an institutional conflict of interest under MD Anderson policy
  - Affimed

- SAB:
  - AvengeBio, Bayer, Caribou Biosciences, GemoAb, GSK, Navan Technologies, Virogin Biotech, Bit Bio Limited, Innate Pharma

Challenges to the use of allogeneic donors for CAR therapy

- Risk of GVHD (with allogeneic T cells)
- Limited persistence
    - intrinsic to some cells (e.g. NK cells)
    - Rejection (HLA-mismatch between donor and recipient)
- Choice of cell type (αβ T vs γδ T vs NK vs iNKT vs macrophages vs CIK etc)
- Choice of donor
    - Not all donors are created equal!

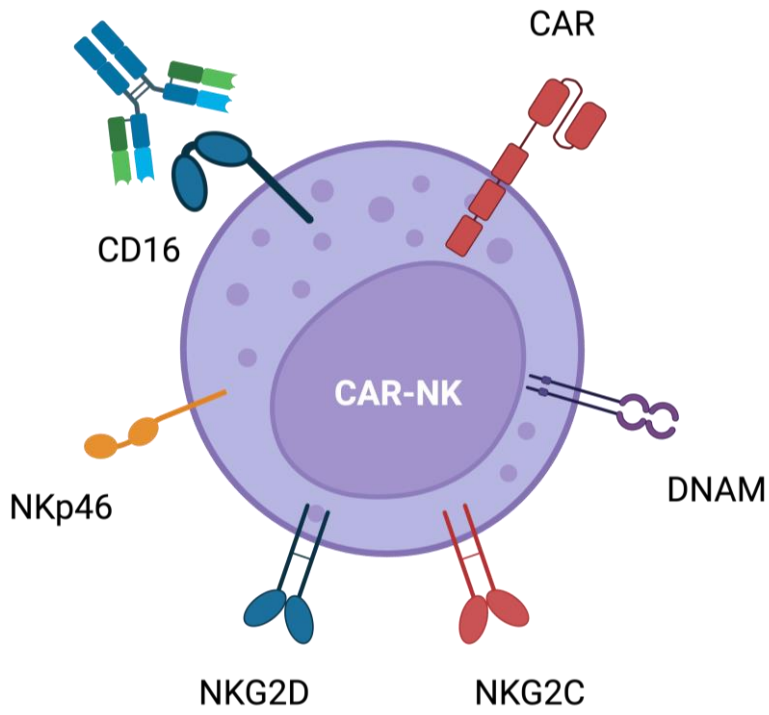
NK cells for allogeneic CAR therapy

Advantages:

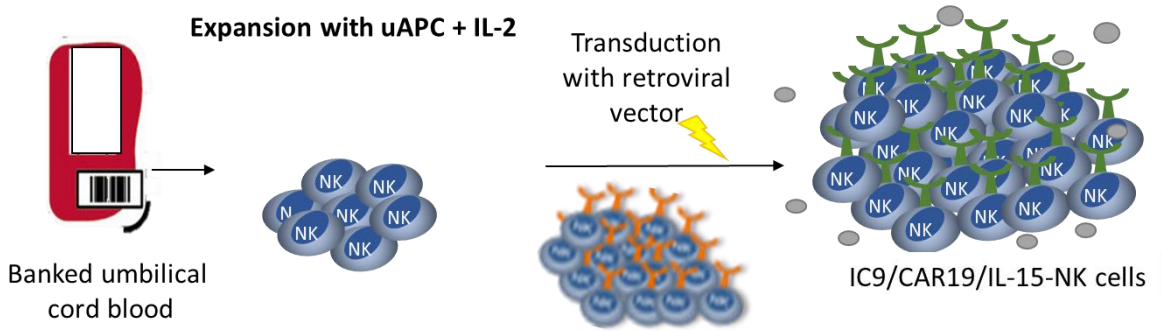
- Allogeneic: no GVHD --> off the shelf, lower cost
- Killing: CAR mediated + innate receptors
- Antibody-dependent cellular cytotoxicity (ADCC) through binding of CD16 on NK cells to antibody-bound target cells
- Safety: no CRS, no ICANS

Disadvantages:

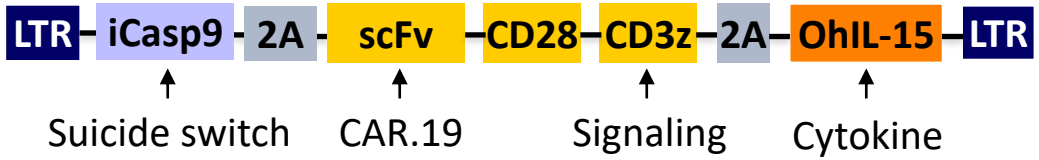
- Limited lifespan in the absence of cytokine support
- Unclear best starting population for manufacturing



First in-human trial of CAR19/IL-15 CB-NK cells in lymphoid malignancies



Armored CAR



Generously provided by Pietro Dotti, MD

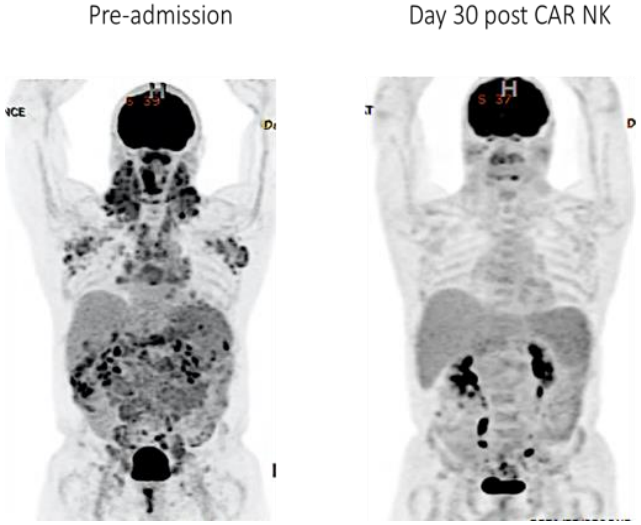
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

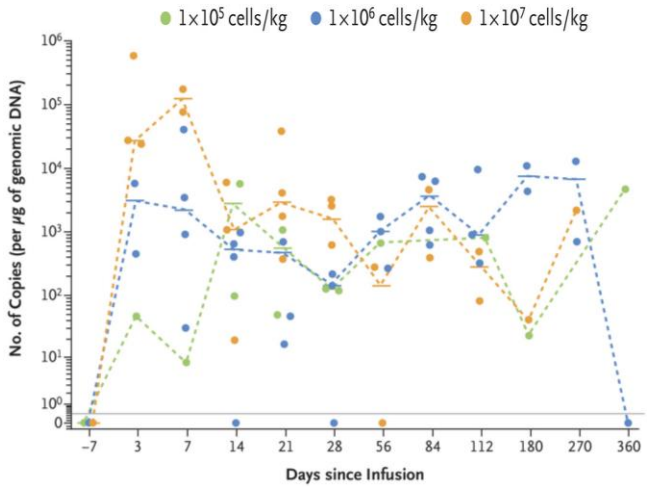
Use of CAR-Transduced Natural Killer Cells in CD19-Positive Lymphoid Tumors

Enli Liu, M.D., David Marin, M.D., Pinaki Banerjee, Ph.D., Homer A. Macapinlac, M.D., Philip Thompson, M.B., B.S., Rafet Basar, M.D., Lucila Nassif Kerbauy, M.D., Bethany Overman, B.S.N., Peter Thall, Ph.D., Mecit Kaplan, M.S., Vandana Nandivada, M.S., Indresh Kaur, Ph.D., Ana Nunez Cortes, M.D., Kai Cao, M.D., May Daher, M.D., Chitra Hosing, M.D., Evan N. Cohen, Ph.D., Partow Kebriaei, M.D., Rohtesh Mehta, M.D., Sattva Neelapu, M.D., Yago Nieto, M.D., Ph.D., Michael Wang, M.D., William Wierda, M.D., Ph.D., Michael Keating, M.D., Richard Champlin, M.D., Elizabeth J. Shpall, M.D., and Katayoun Rezvani, M.D., Ph.D.

N Engl J Med. 2020 Feb 6; 382(6): 545–553.



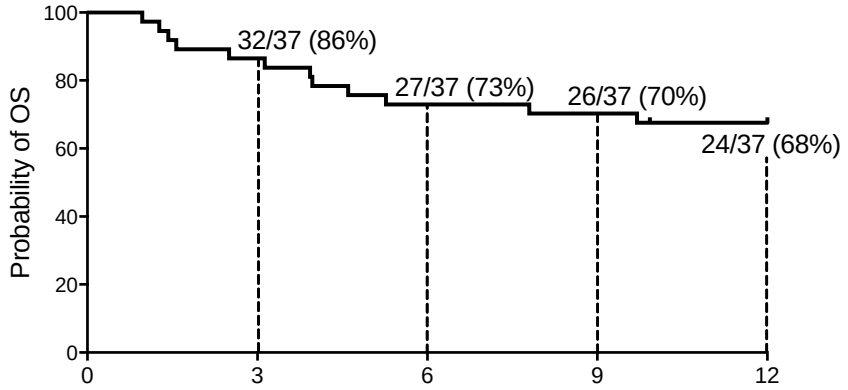
7/11 CR, no CRS, no neurotoxicity, and no GvHD

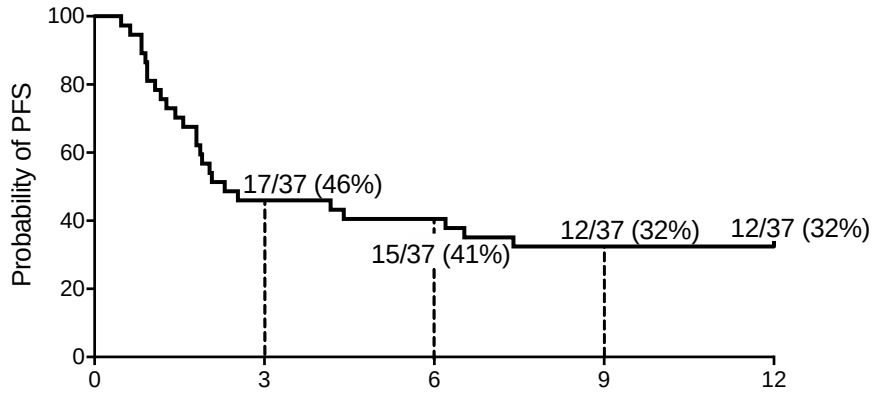


CAR-NK cells are detectable up to 12 months post-infusion

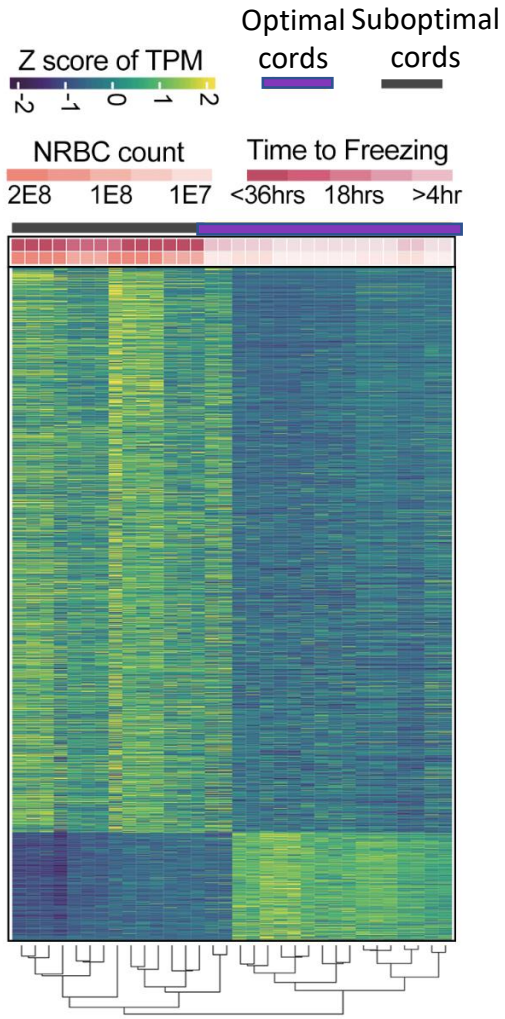
Liu et al. & Rezvani *N Engl J Med*, 2020

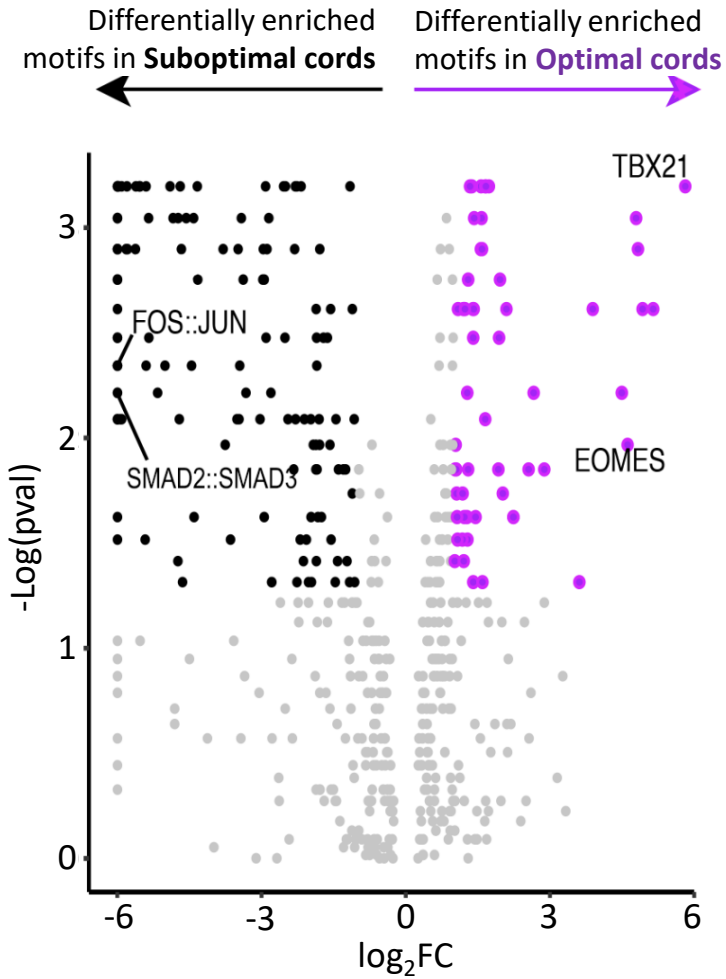
Cord Quality is the most important determinant of durable response after CAR19/IL-15 NK cell therapy

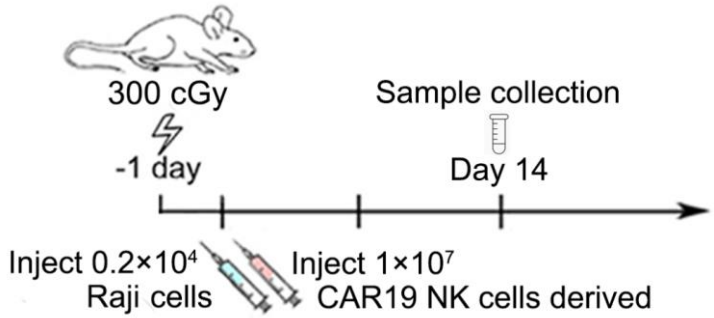


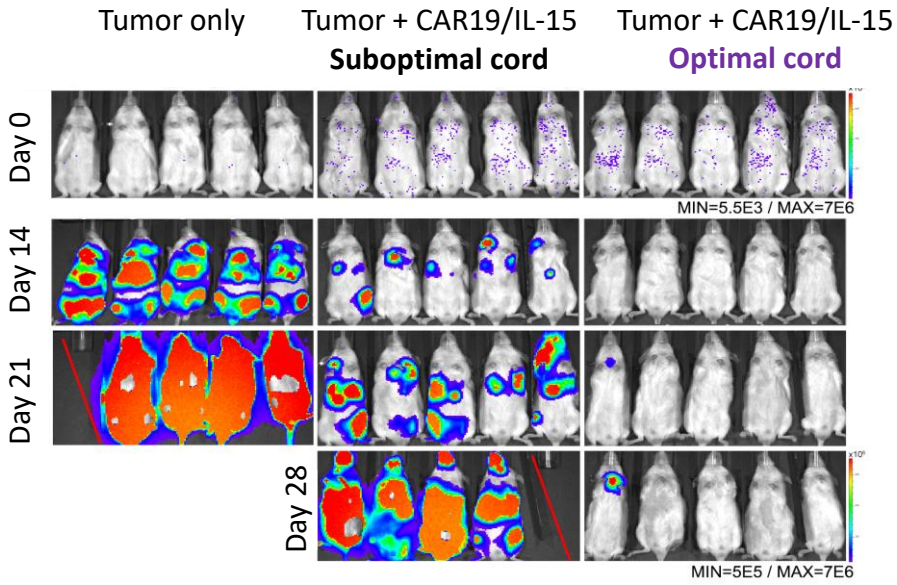


NK cells from optimal cords vs. suboptimal cords have distinct effector functionality potency









Provisionally accepted, *Nature Medicine 2023*

Can CAR-NK cells be applied beyond $CD19^+$ malignancies?

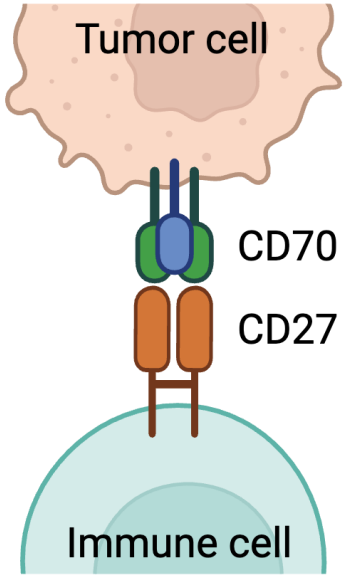
CD70 is a promising pan-cancer antigen

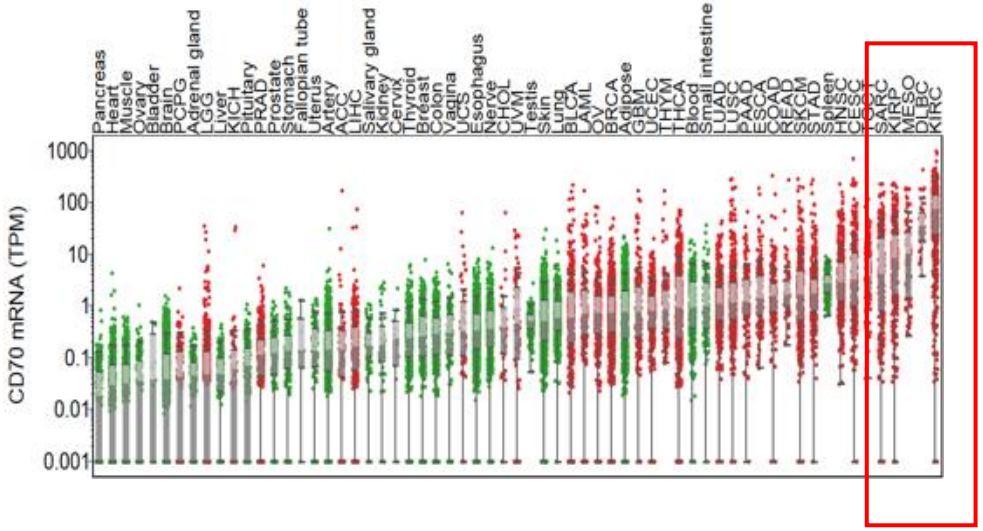
Ligand for CD27, and stimulates cells expressing CD27

Generally absent in non-lymphoid normal tissue

Constitutively expressed on many hematological malignancies and considerable fractions of solid carcinomas

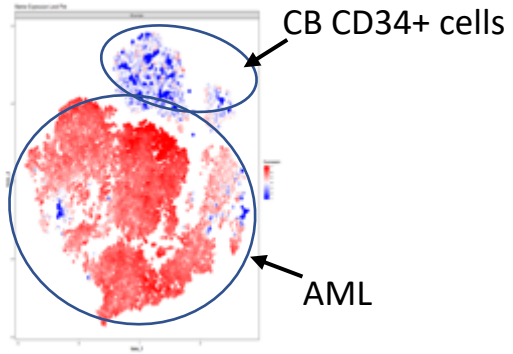
Cusatuzumab or ARGX-110 tested in multiple clinical trials

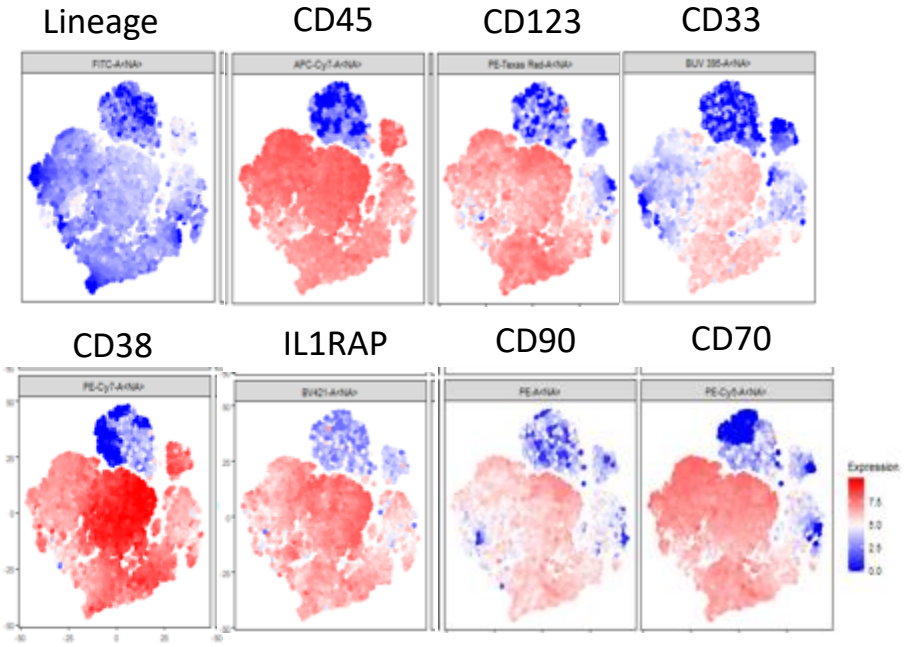




- Lymphomas
- Renal cell carcinoma
- Sarcoma
- Mesothelioma
- Nasopharyngeal carcinoma

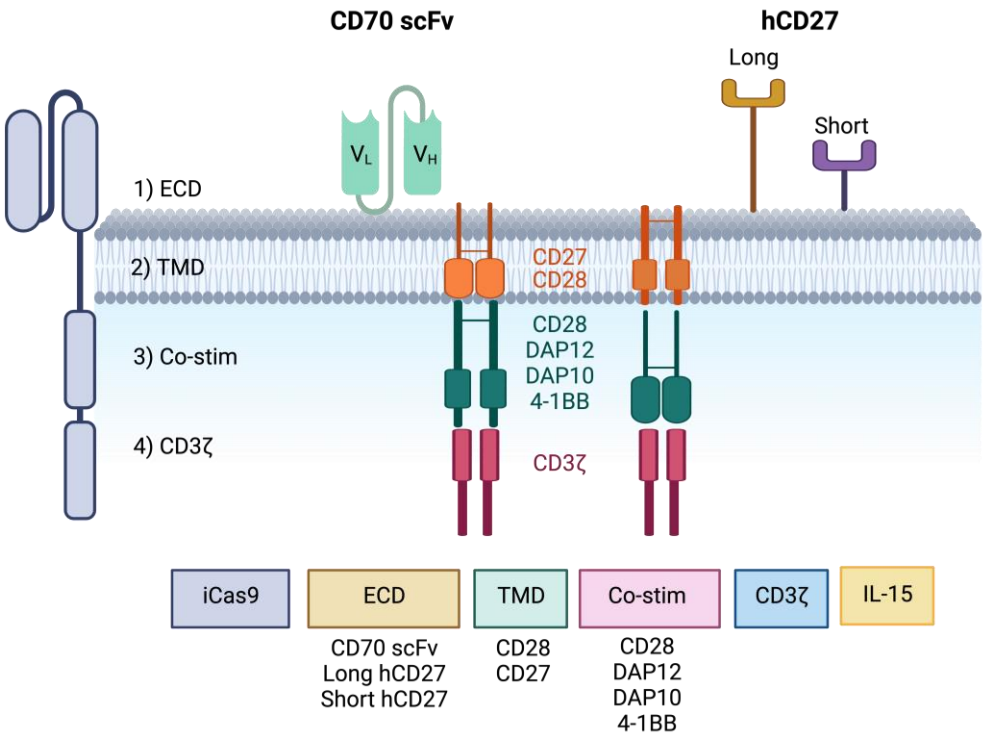
CD70 is expressed in primary AML samples (MDACC; n=54)

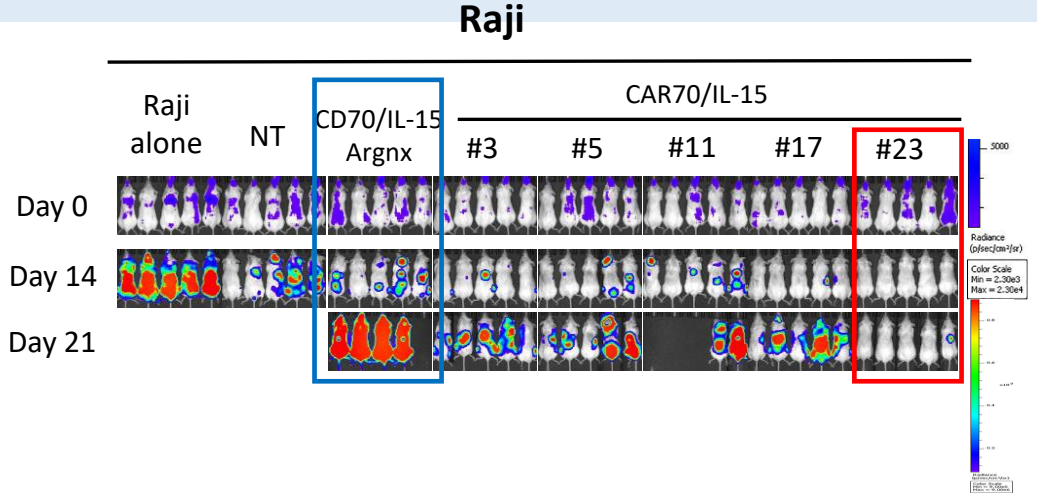


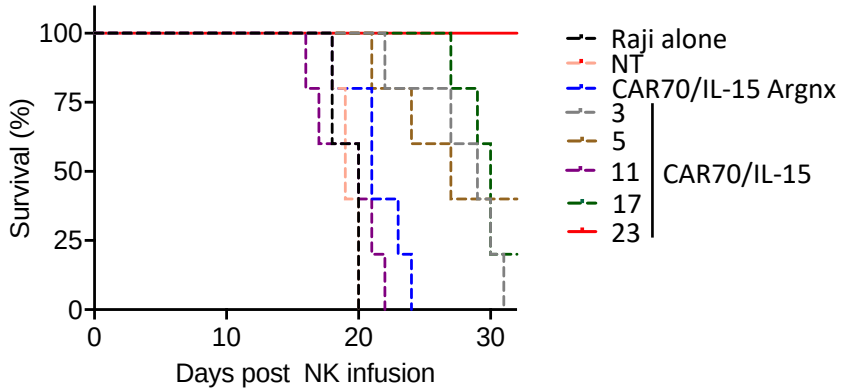


Data by Drs. Bijender Kumar, May Daher and Rafet Basar

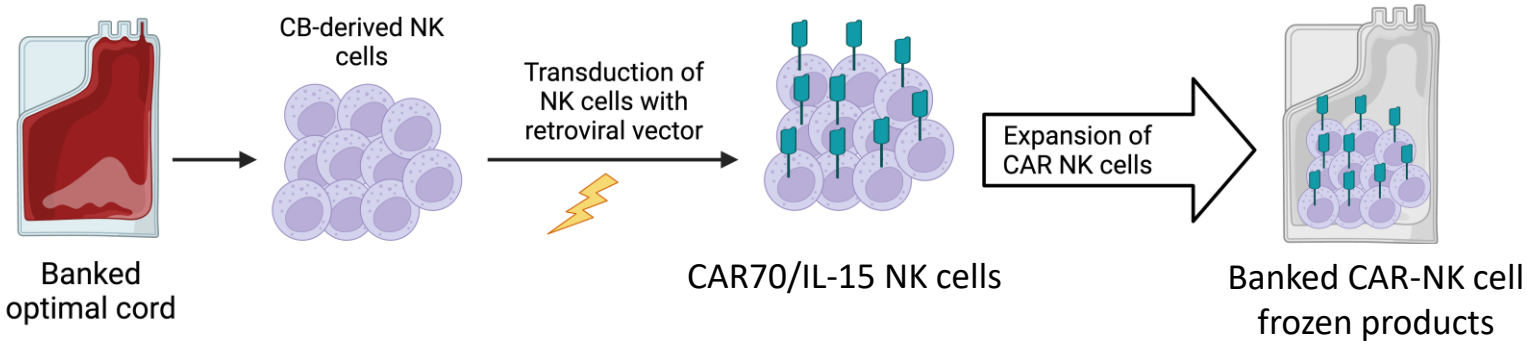
Designed and tested 34 different CD70 targeting CAR constructs based on human CD27 receptor sequence



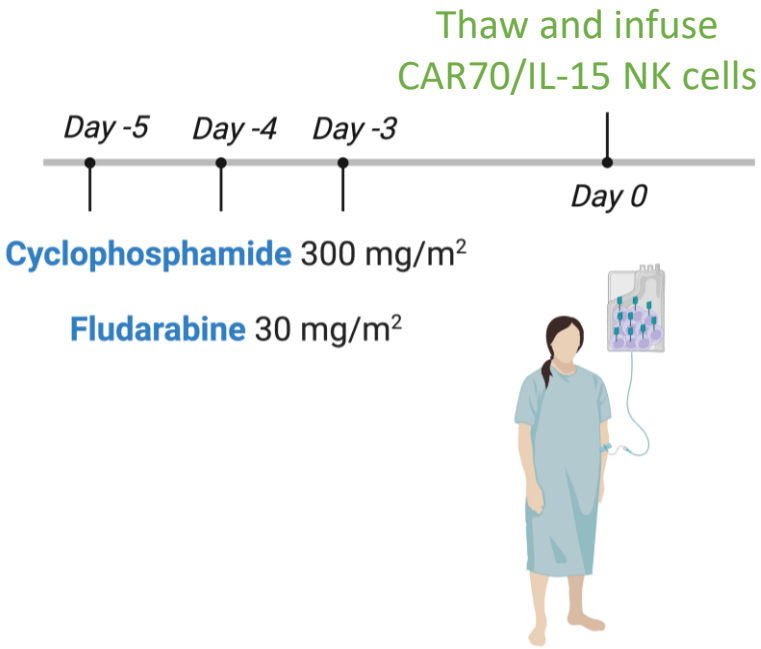




Clinical translation: Phase I/II clinical trial evaluating the safety and efficacy of CAR70/IL-15 NK cells for cancer immunotherapy



250 patient doses manufactured and frozen from two cord blood units
CAR transduction efficiency 58% and 77%



Basket trial in hematologic malignancies approved by IRB and FDA (NCT05092451, IND 27757)- dose level 3 complete

6 dose levels:

Dose level -1: 4.0 E+6
Dose level 1: 8.0 E+6
Dose level 2: 4.0 E+7
Dose level 3: 8.0 E+7
Dose level 4: 4.0 E+8
Dose level 5: 8.0 E+8
Dose level 6: 4.0 E+9

David Marin, MD
Stem Cell Transplant and Cellular Therapy

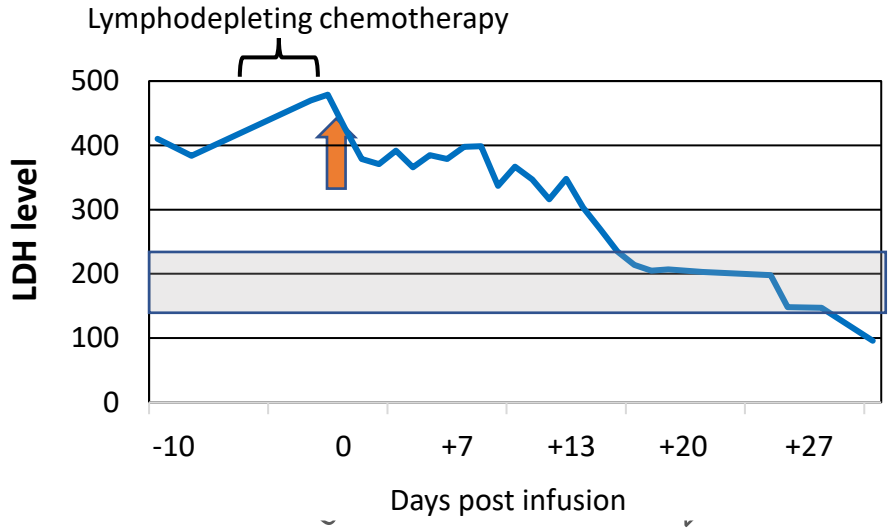
Clinical protocol in renal cell carcinoma, mesothelioma, and osteosarcoma approved by IRB and FDA (NCT05703854, IND 29057)

David Hong, MD
Department of Investigational Cancer Therapeutics

Patient response to truly off-the-shelf HLA-mismatched, cryopreserved CAR70/IL-15 NK cells-patient with classical HL

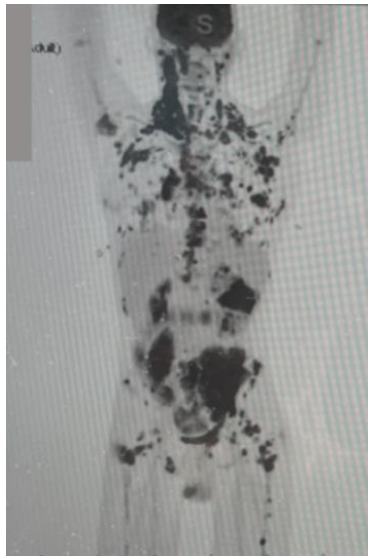
24 yr old male
Diagnosed with Stage IV classical HL – widespread LN and bones

- ABVD x 6 → CR
- 3 months later - relapsed disease
- GDP x 2 → CR → ASCT
- 1 month post ASCT- relapsed HL
- Brentuximab + Nivo → CR
- 2 months later- Haplo-SCT (Flu/Cy/TBI)- complicated by cGVHD eyes and mouth
- 10 months later- relapsed
- Camidanlumab (anti-CD25 ADC) – NR
- RT left flank/kidney
- **CAR-NK cell infusion (Flat dose: 8M NK cells)**

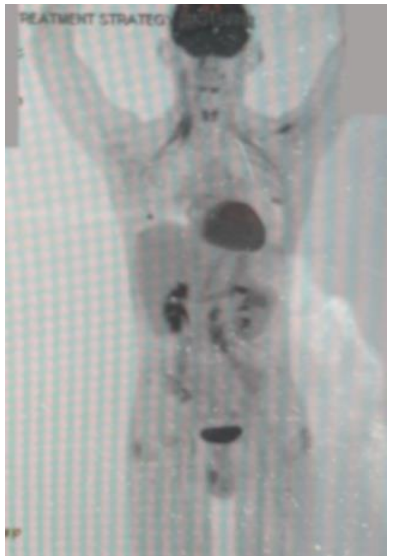


Patient with classical HL

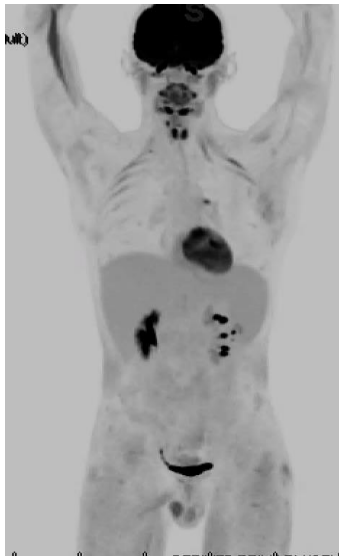
Pre-infusion



D30 post-infusion



D60 post-infusion

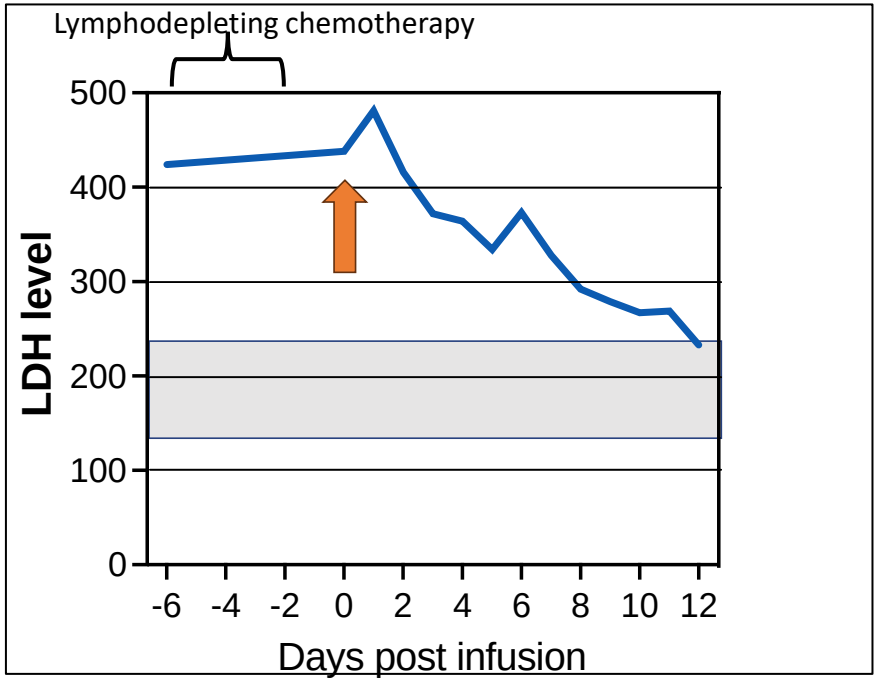


Currently at dose level 4
Responses observed in 8/10 patients (7 of 8 with HL)

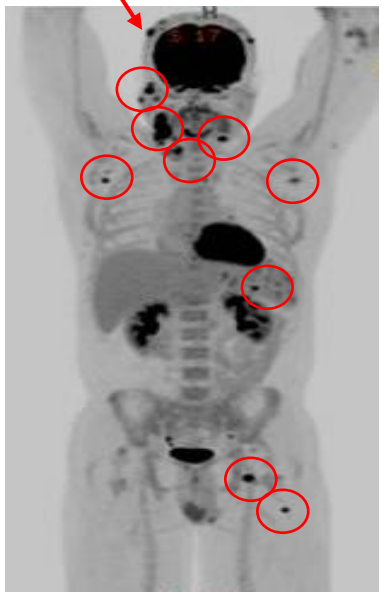
Patient response to truly off-the-shelf HLA-mismatched, cryopreserved CAR70/IL-15 NK cells-patient with refractory CTCL

Patient with refractory cutaneous T-cell lymphoma (CTCL)

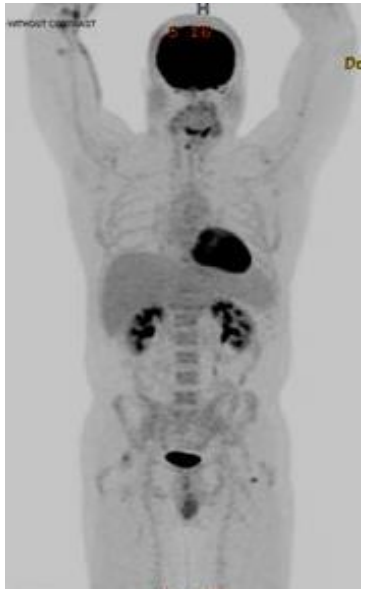
- S/p EPOCH, BV-CHP, Romidepsin, ICE, pralatrexate, Duvelisib, GDP, mogamulizumab
- **CAR-NK cell infusion** (**First patient treated at dose level 4: 4E8**)
- No toxicity



Pre-infusion

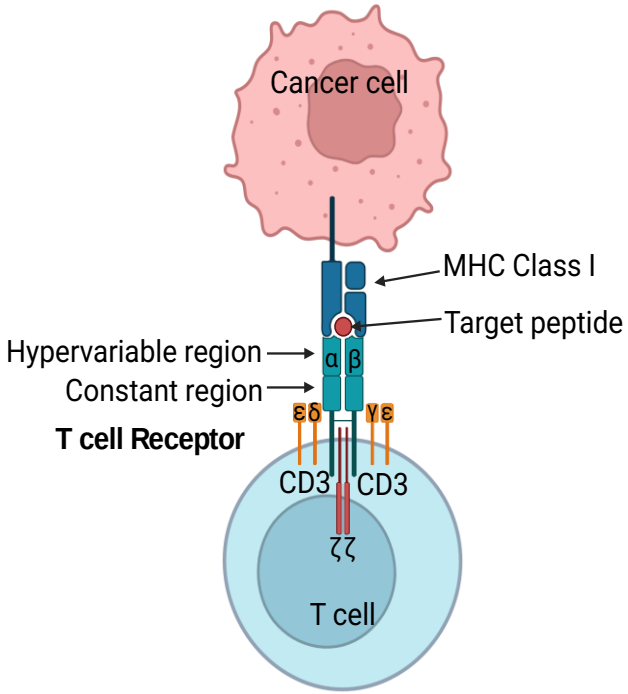


D30 post-infusion



T-cell receptor-based therapy

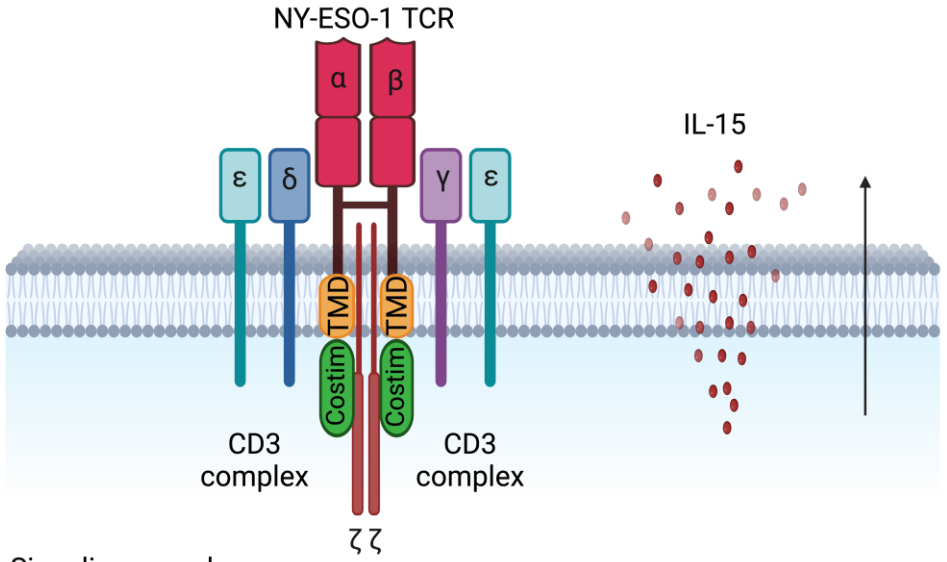
- TCRs recognize a greater number of intracellular tumor-specific/associated/neo-antigens that are not targetable by immunoglobulins or CARS
- Majority of cancer antigens belong to this category



- NK cells do no express TCR: no risk of mispairing
- No risk of GVHD
- 40–90% of human tumors are MHC class I deficient-harness the innate ability of NK cells to recognize class I deficient tumors (missing-self)
- NK cells can be successfully transduced to express a TCR. *Mensali N, et al. EBioMedicine.; Parlar A, et al. Eur J Immunol. 2019;. Morton LT et al. J Immunother Cancer. 2022*

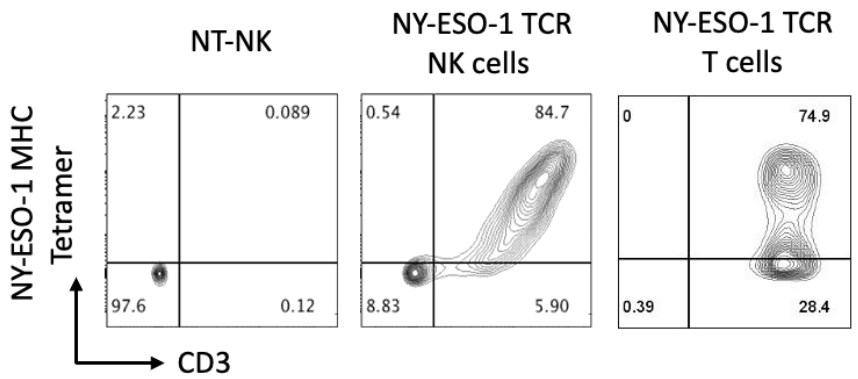
Potential for ‘off-the-shelf’ product, thus increasing accessibility and reducing cost

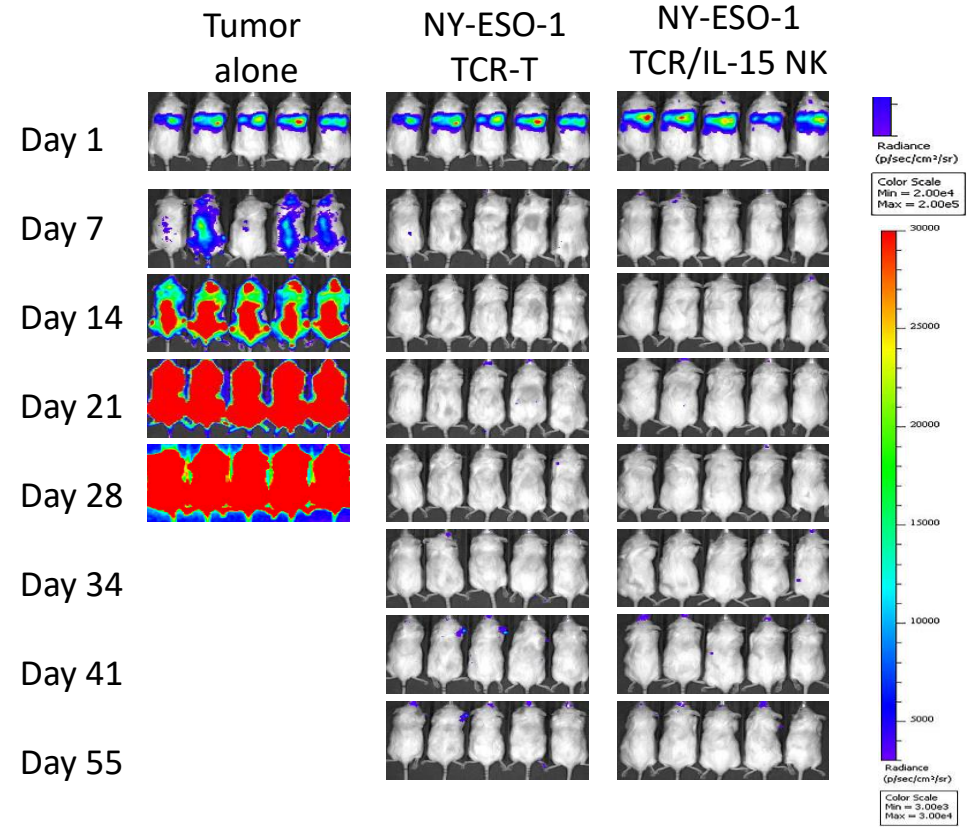
NY-ESO-1 TCR/IL-15 NK cells and NY-ESO-1 TCR T cells show similar *in vivo* anti-tumor activity

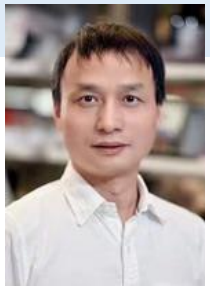


Signaling complex

NY-ESO-1TCR



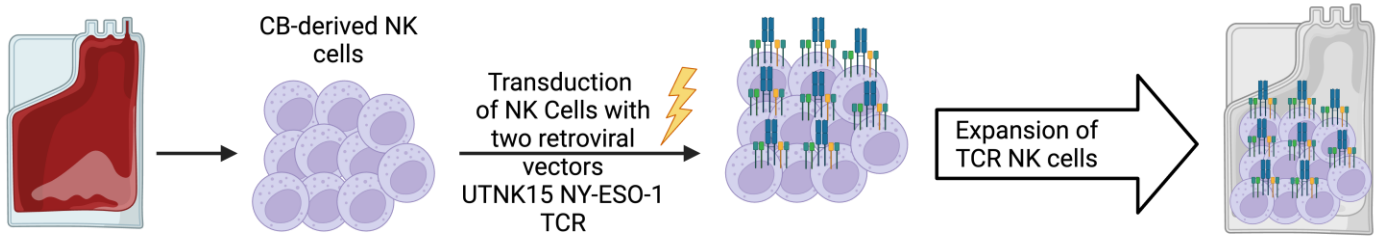




Bin Liu, PhD

Rafet Basar, MD

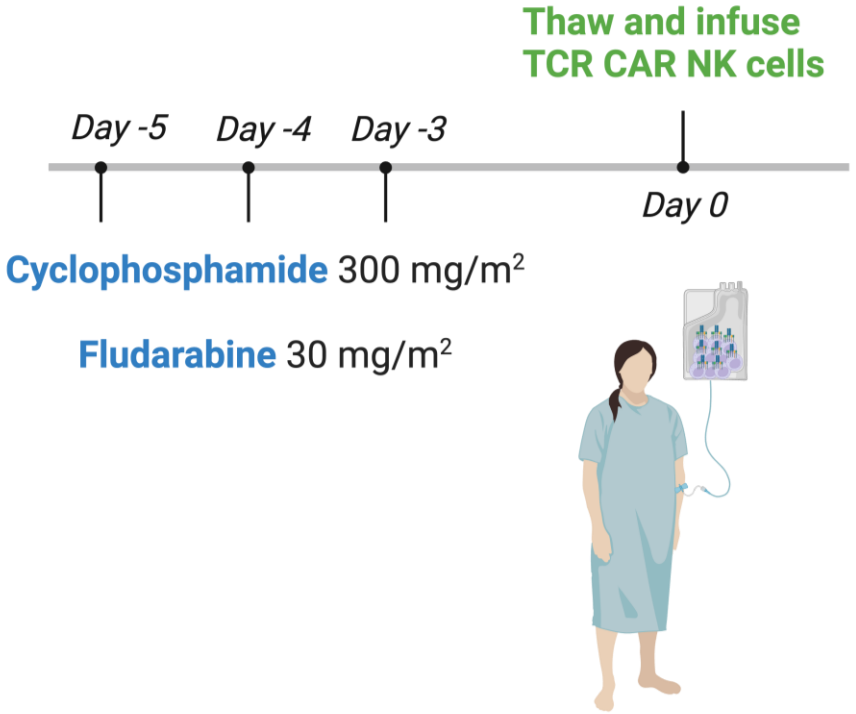
Phase I clinical trial evaluating the safety and efficacy of NY-ESO-1 TCR/IL-15 NK cells for cancer immunotherapy-FDA approved; IND 29522 and IND 29526



Banked optimal cords

NY-ESO-1 TCR/IL-15 NK cells

Banked TCR NK cell frozen products

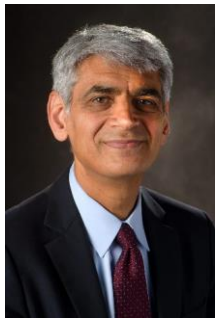


Phase I clinical trials:

- **Trial for multiple myeloma (IND 29526)**

4 dose levels:

Dose level -1: 2.53 E+7
Dose level 1: 8.0 E+7
Dose level 2: 2.53 E+8
Dose level 3: 8.0 E+8
Dose level 4: 2.53 E+9



Muzaffar H. Qazilbash, MD
Stem Cell transplant

- **NY-ESO+ synovial sarcoma and myxoid liposarcoma (IND 29522, NCT06083883)**

4 dose levels:

Dose level -1: 8.0 E+6
Dose level 1: 8.0 E+7
Dose level 2: 4.0 E+8
Dose level 3: 8.0 E+8
Dose level 4: 4.0 E+9

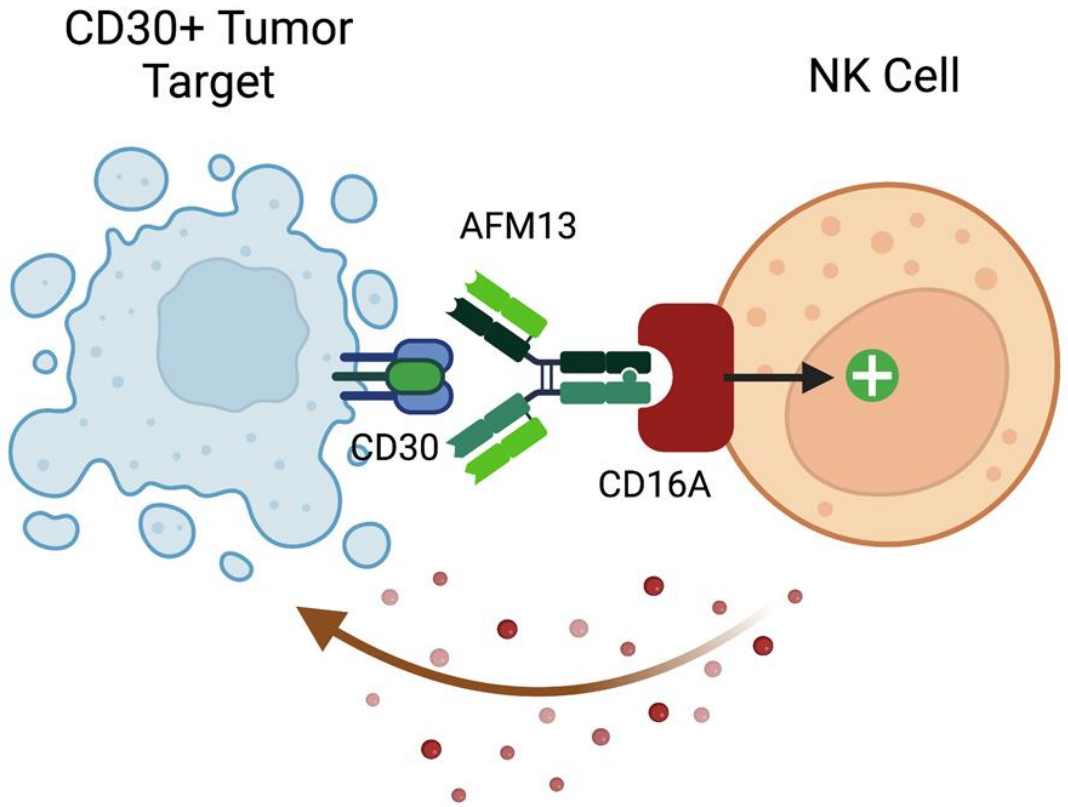
Andy Livingstone, MD
Sarcoma Medical Oncology

Antibody-armed NK cells

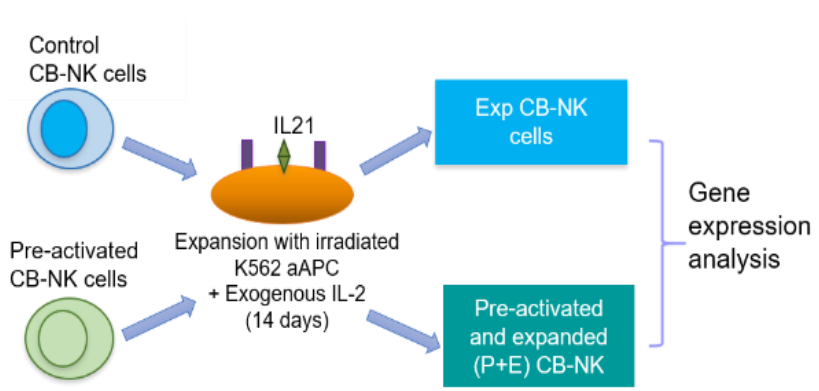
Hypothesis:

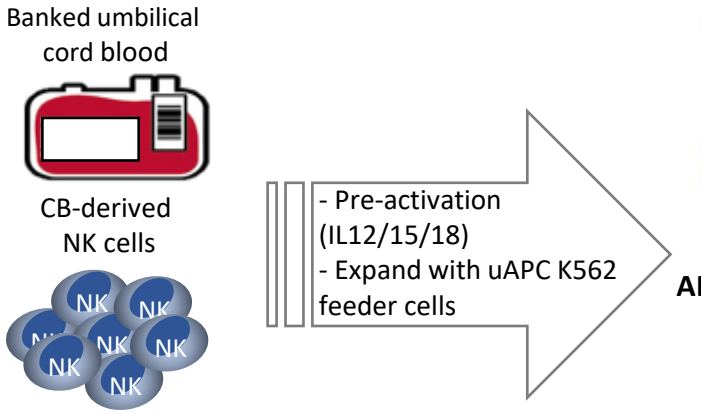
1. Pre-complexing NK cells with bispecific antibodies or FC-enhanced antibodies prior to infusion facilitates CAR-like responses by NK cells

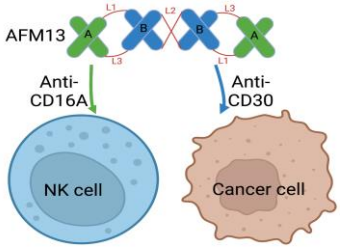
2. Potency of NK cells can be enhanced by pre-activation with inflammatory cytokines



IL-12/15/18 pre-activated and *ex vivo* expanded CB-NK cells have upregulation of genes related to JAK-STAT signaling and IFN-γ response





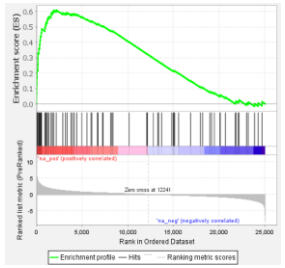


AFM13 is a tetravalent bi-specific anti-CD30::CD16 ICE®

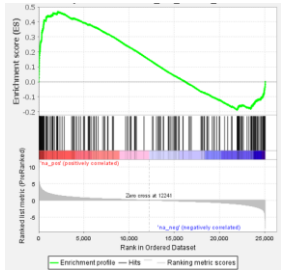
Precomplex with AFM13

Lucila Kerbauy, MD, PhD

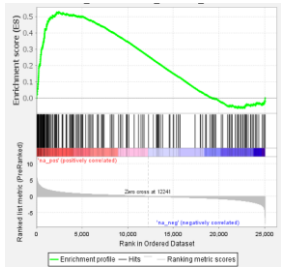
IL-6/JAK/STAT3 Signaling



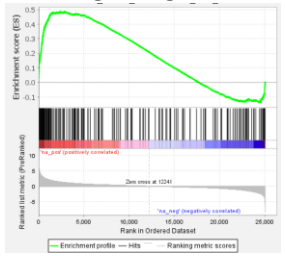
IL-2/STAT5 Signaling



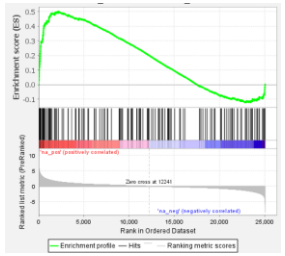
IFN-γ Response



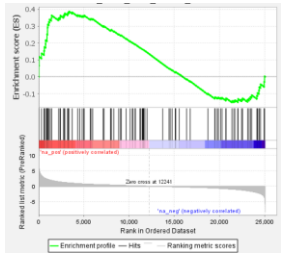
TNF-α signaling via NFKB

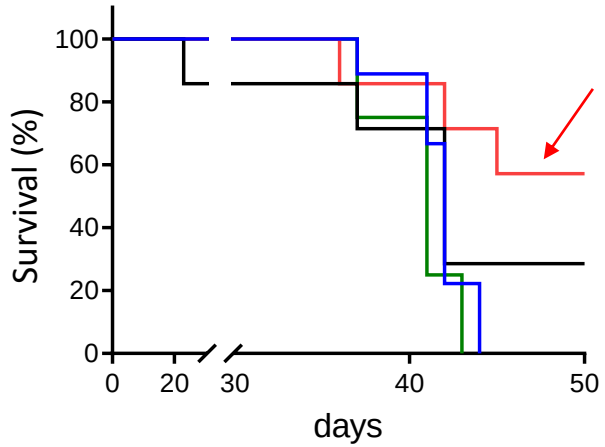


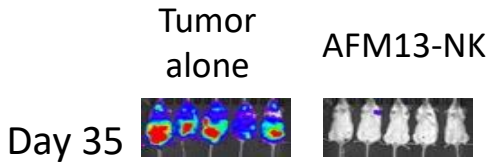
Inflammatory Response



PI3K/AKT/MTOR Signaling



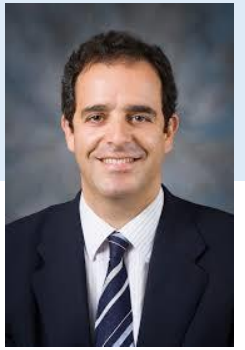




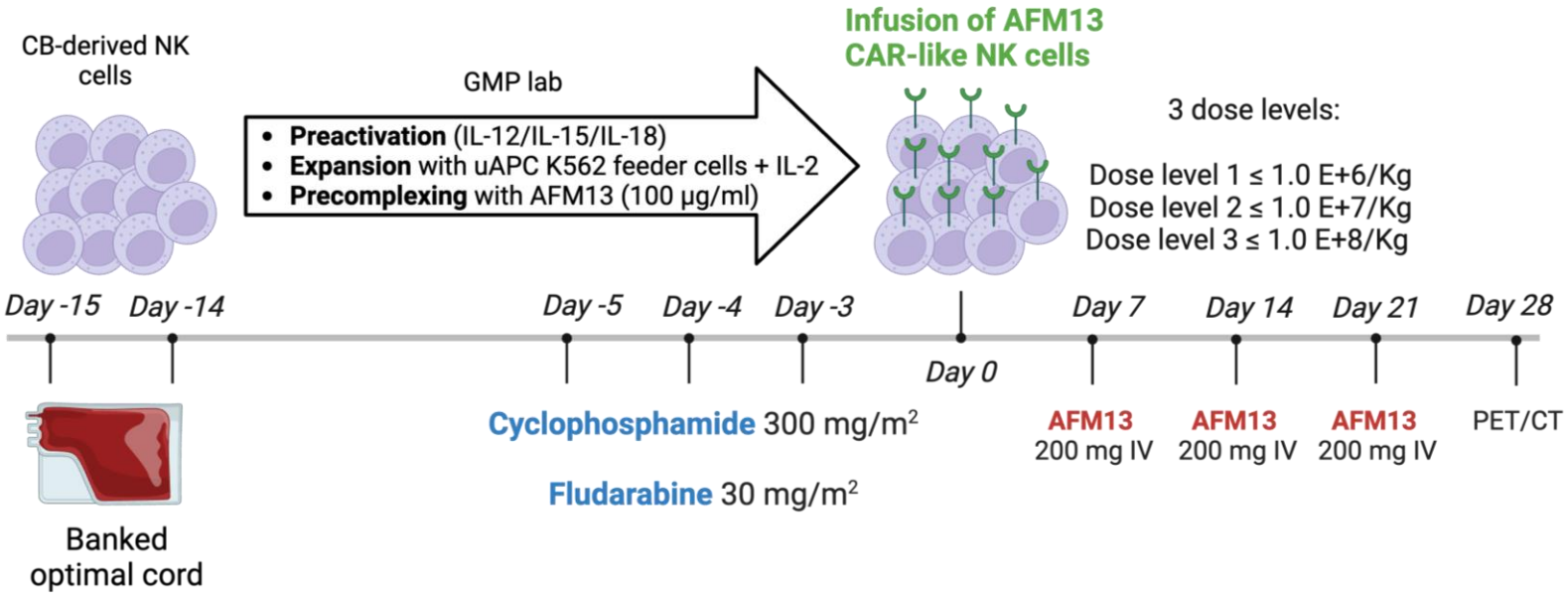
Kerbauy, Marin et al, Fehniger & Rezvani; *Clin Cancer Res*, 2021

Clinical trial of AFM13-complexed CAR-like memory CB-NK cells for Refractory/Relapsed CD30+ Malignancies- approved by FDA; NCT04074746; IND 19221

Data presented ASH 12/2023



Yago Nieto, MD, PhD



Relapsed/refractory classical Hodgkin, ALCL , PTCL or B-NHL refractory or intolerant to brentuximab

Baseline characteristics	N=42
Age, median (range)	43 (20–75)
Gender (male/female)	27/15
Diagnosis (Hodgkin / T-NHL)	37/5
No. prior lines therapy, median (range)	7 (1–14)
Prior brentuximab vedotin (anti-CD30 mAb)	42
Prior anti-PD-1	39
Prior SCT (autologous / allogeneic /both)	25 (15 / 4/ 6)
Prior cellular therapy (CD30.CAR-T)	4
No. prior relapses/progressive disease, median (range)	5 (1–14)
Progressive disease after immediately prior therapy	41 PD, 1 SD

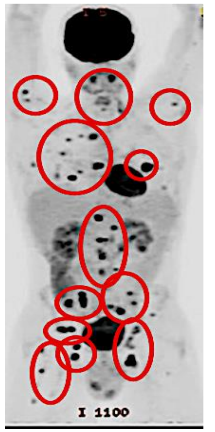
Anti-tumor activity of AFM13-complexed CAR-like memory CB-NK cells

- Responses evaluated by PET (Lyric criteria) on day 28 of each cycle
- 39/42 responses (ORR 92.9%; CR 66.7%)
- Among patients treated at the RP2D (N=36):
  - **94.4% ORR**
  - **72.2% CR**
- No cases of cytokine release syndrome (CRS), neurotoxicity (ICANS) or graft-vs-host disease (GVHD

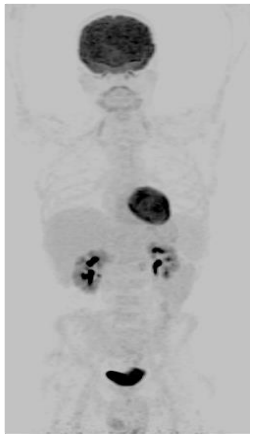
27 y/o male, with Hodgkin in PD after 8 lines of therapy:

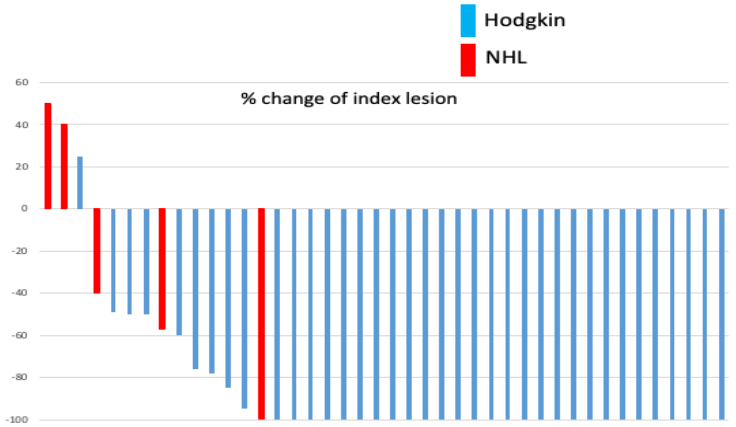
- ABVD, ICE, brentuximab vedotin, nivolumab, CAR-T, anti-CD137, benda/BBV and allogeneic SCT)

Pre-infusion

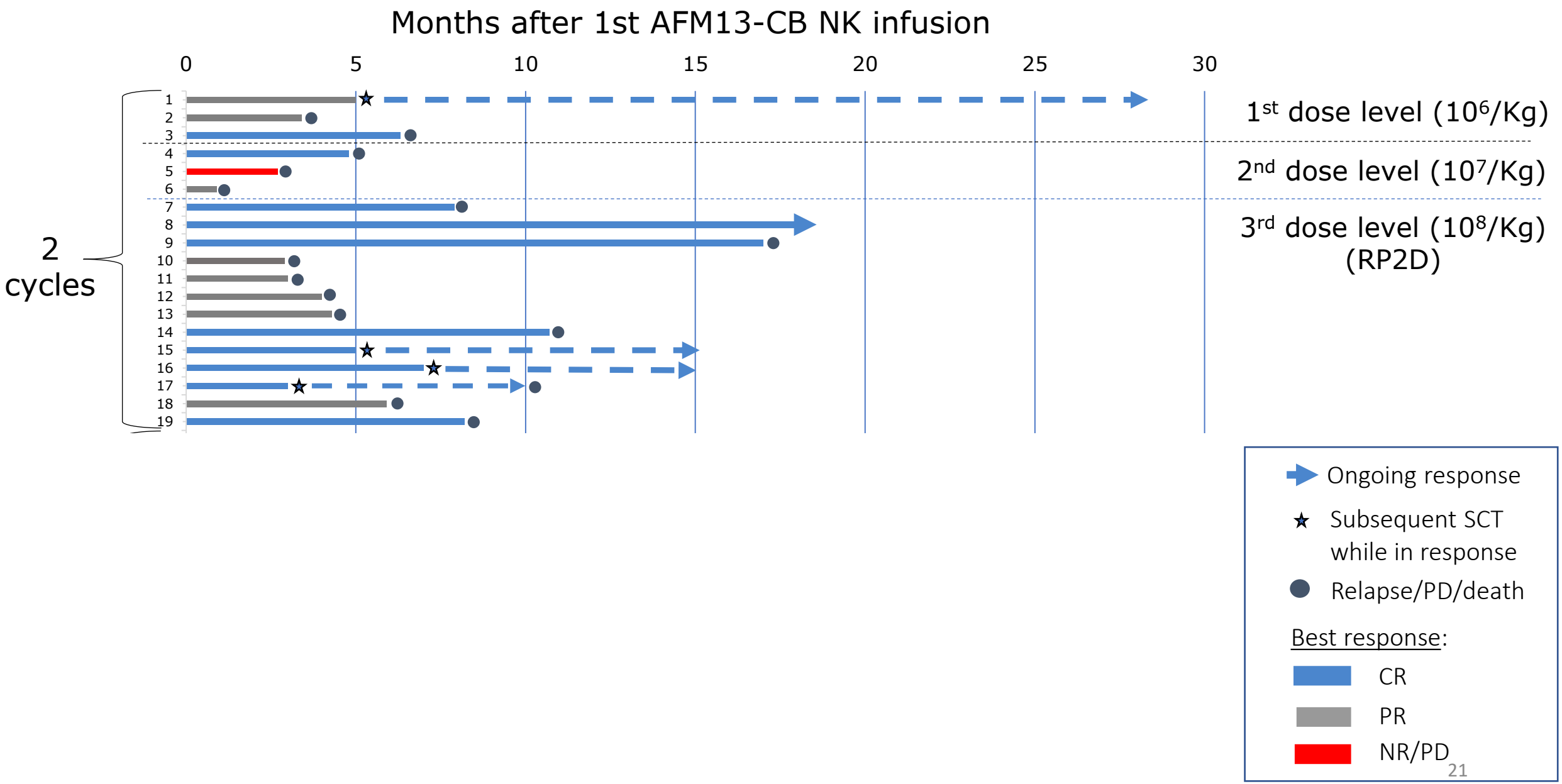


D30 post-infusion

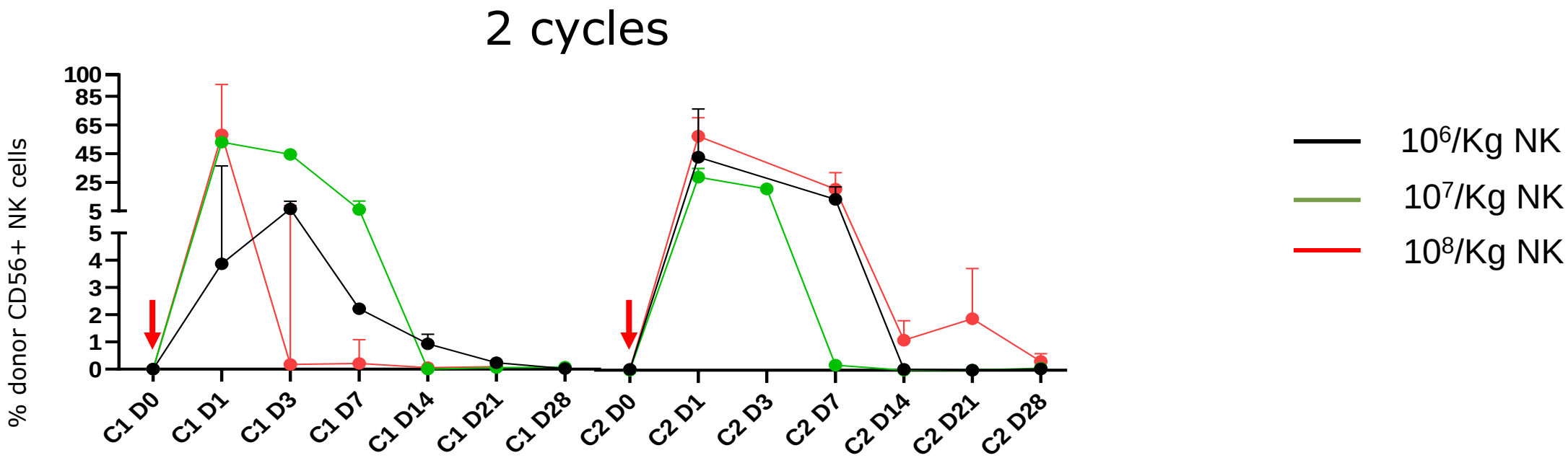




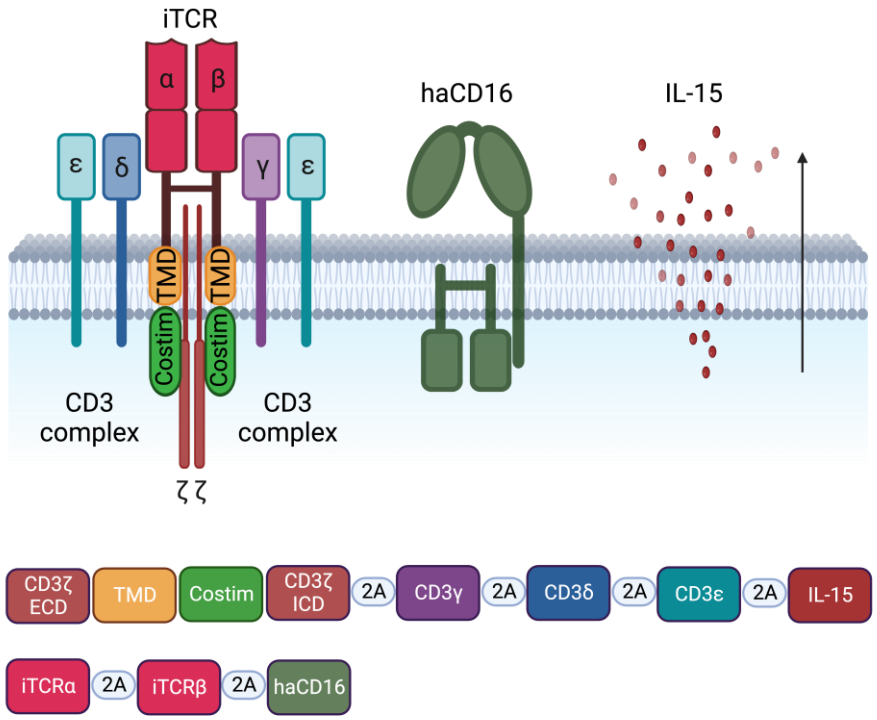
Duration of responses



Blood levels of donor NK cells



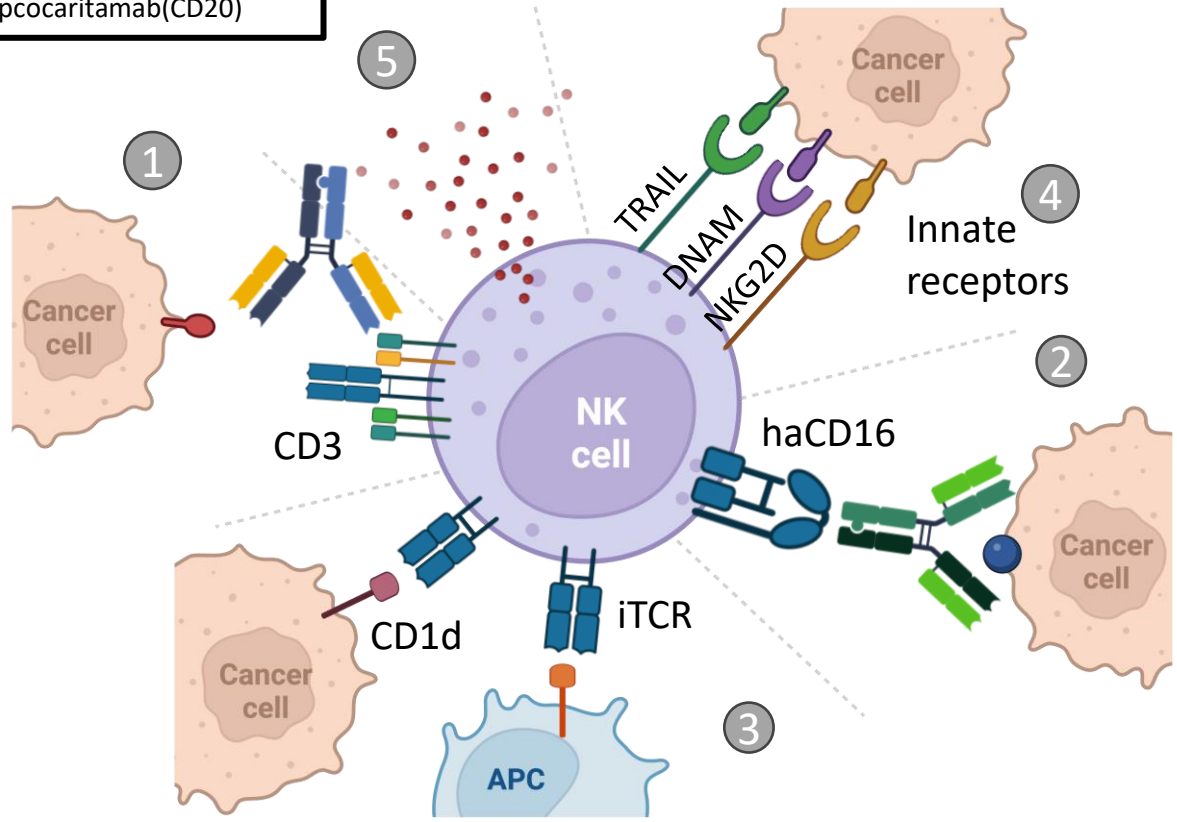
PluReceptor NK cells: A modular approach to multi-antigen targeting and enhancing NK cell persistence



T-cell engagers:

Blinatumumab(CD19)
Teclistamab(BCMA)
Talqutamab(GPRC5D)
Elranatamab(BCMA)
Cevostamab(FcRH5)
Mosenutuzumab(CD20)
Glofitamab(CD20)
Epcocaritamab(CD20)

IL-15 (promotes NK cell persistence and *in vivo* expansion)



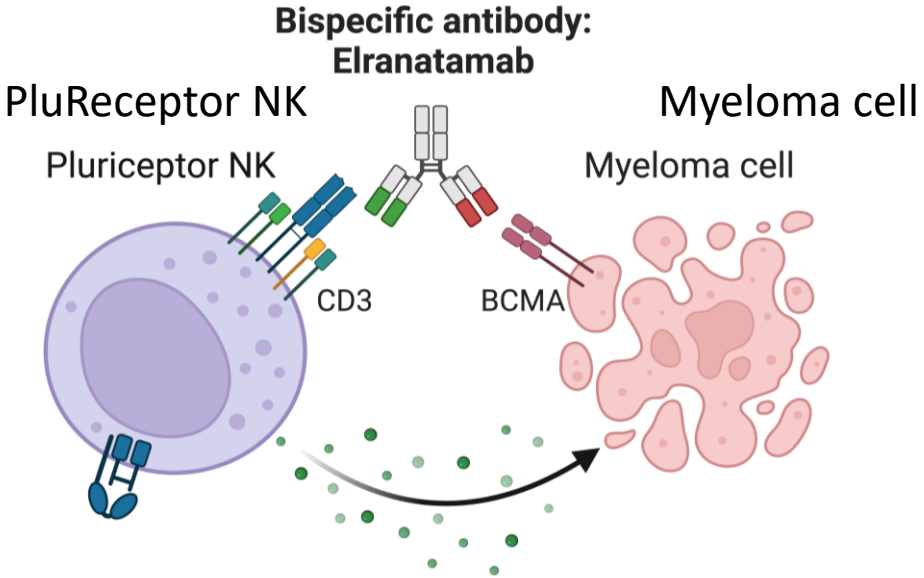
mABs:

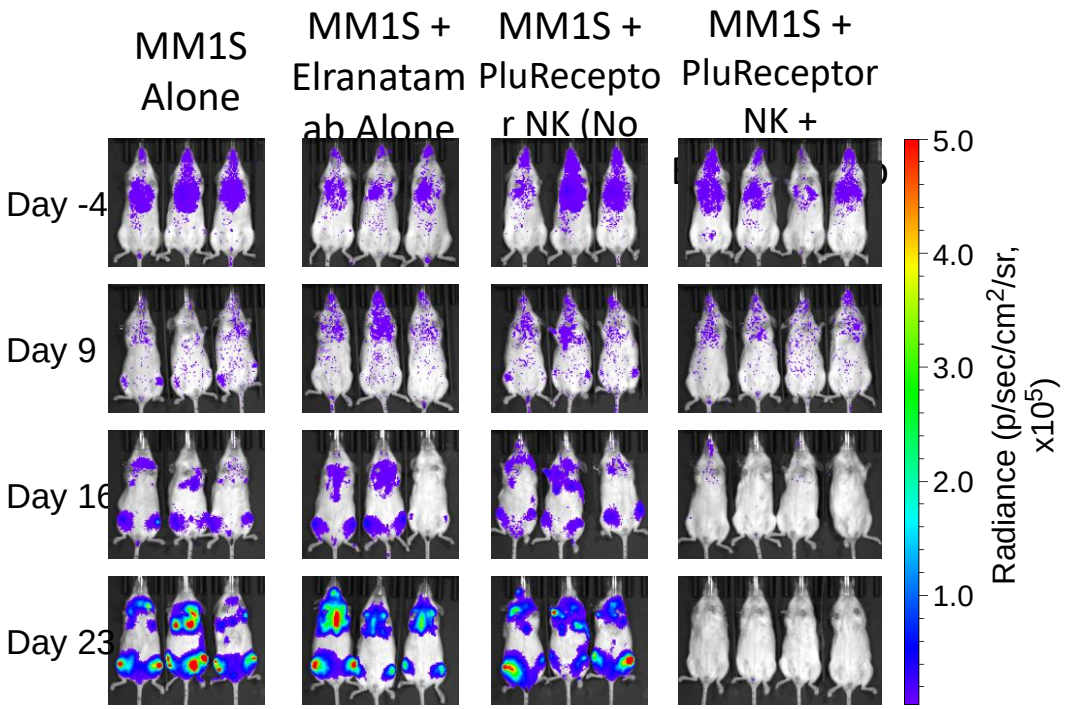
Trastuzumab
Rituximab
Obinutuzumab
Tafasitamab
Imgatuzumab
Cetuximab
Pertuzumab
Dinituximab
Amivantamab
Mogamulizumab

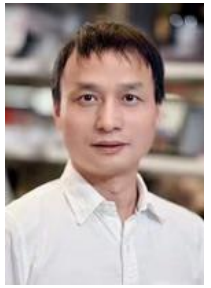
ADCs:

Gemtuzumab-Ozagamicin
Brentuximab-Vedotin
Transtuzumab-emtansine
Inotuzumab ozogamicin
Mexetumomab pasudotox
Polatuzumab vedotin
Enfortumab vedotin
Trastuzumab deruxtecan
Sacituzumab govitecan
Belantamab mafoditin-blmf
Loncastuximab tesirine-lpyl
Tisotumab vedotin-tftv

PluReceptor NK cells in combination with Elranatamab show superior anti-tumor activity in an immunodeficient NSG mouse model of multiple myeloma





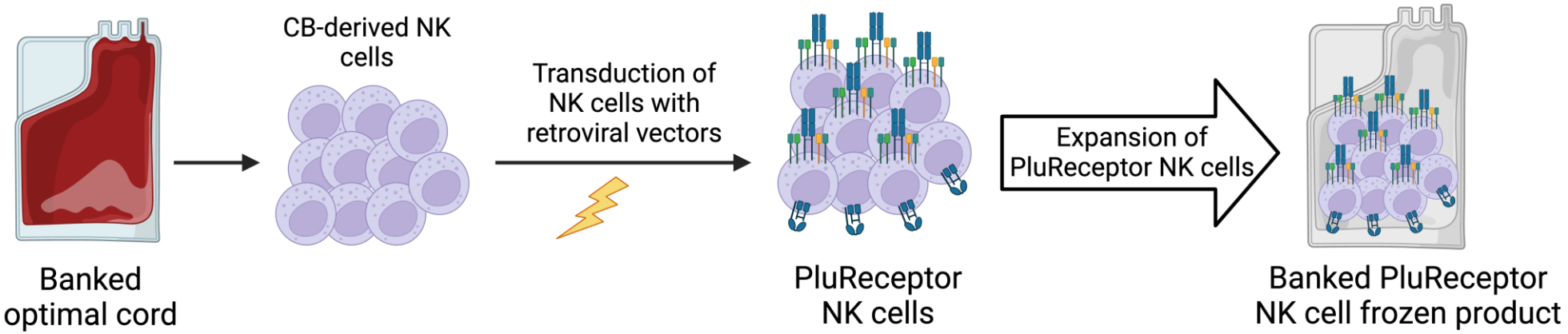


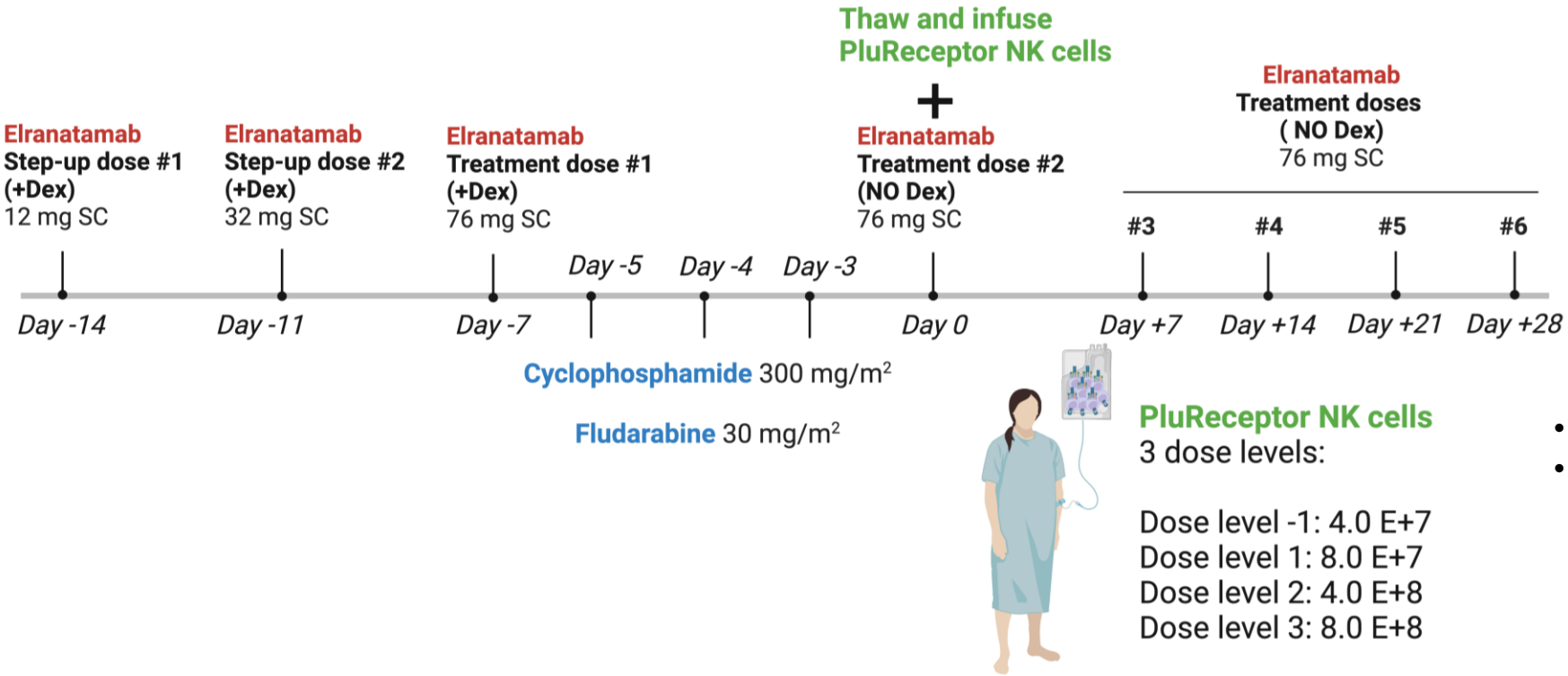
Bin Liu, PhD

Rafet Basar, MD

Clinical trial of PluReceptor CB-NK cells + Elranatamab for refractory/relapsed multiple myeloma

Qaiser Bashir, MD





PluReceptor NK cells
3 dose levels:

Dose level -1: 4.0 E+7
Dose level 1: 8.0 E+7
Dose level 2: 4.0 E+8
Dose level 3: 8.0 E+8

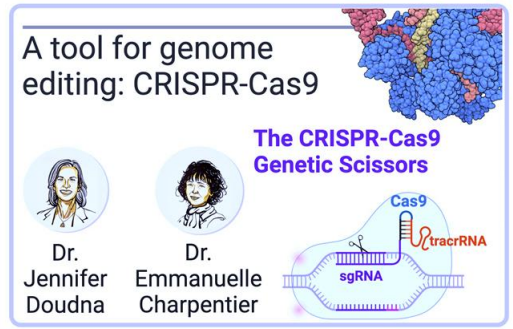
- GMP-grade virus manufacturing complete
- FDA submission underway

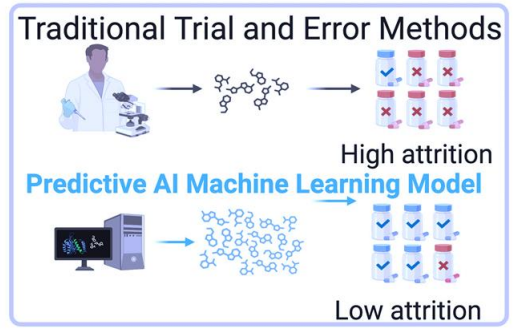
Future Directions

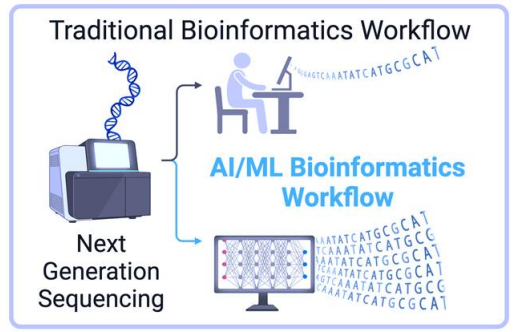
Combinatorial strategy:

- CARs or TCRs that target more than one antigen
- Combine CAR/TCR engineering with bispecific engager/antibody loading
- Cytokine engineering and/or pre-activation
- Combining CAR engineering with CRISPR gene editing
- Combine with checkpoint inhibitors/immunomodulatory drugs/ radiotherapy

1. Increased understanding of cell biology and immunology
2. Increased understanding of synthetic biology
3. Advances in manufacturing
4. Leveraging knowledge from Big Data
5. Promise of AI







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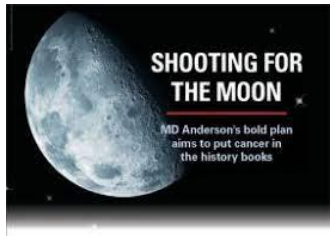

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