

Engineering NK cells for cancer treatment: From bench to bedside

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Cancer Engineering: The Convergence of Engineering and Health to Advance Cancer Research and Care:

A Workshop

May 20-21, 2025

National Cancer Policy Forum

Board on Mathematical Sciences and Analytics

Board on Life Sciences

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

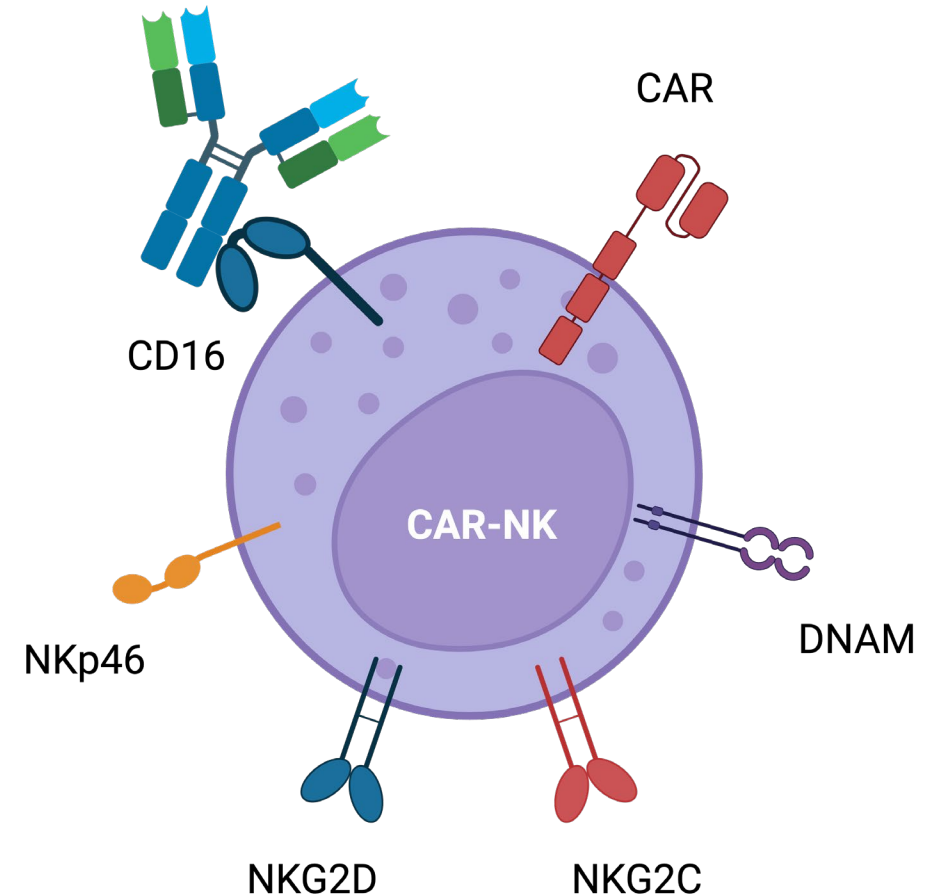
NK cells for allogeneic CAR therapy

Advantages:

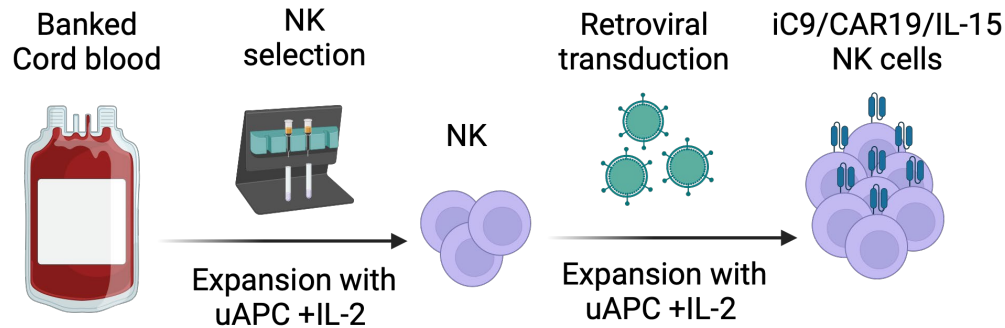
- Allogeneic: no GVHD --> off the shelf, lower cost
- Killing: CAR mediated + innate receptors
- Antibody-dependent cellular cytotoxicity (ADCC) through binding of CD16 on NK cells to antibody-bound target cells
- Safety: no CRS, no ICANS

Disadvantages:

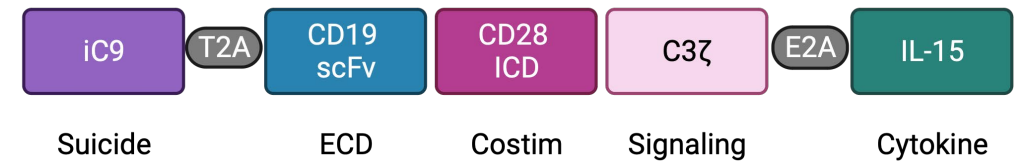
- Limited lifespan in the absence of cytokine support
- Unclear best starting population for manufacturing



First in-human trial of CAR19/IL-15 CB-NK cells in lymphoid malignancies (dose escalation phase)



Armored CAR



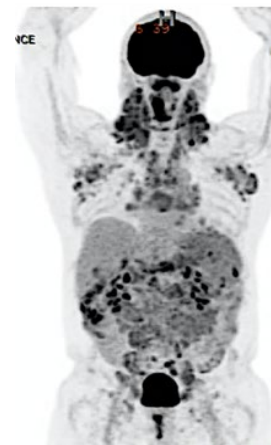
The NEW ENGLAND JOURNAL of MEDICINE

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 Kerbaui, 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., Rohitesh 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.

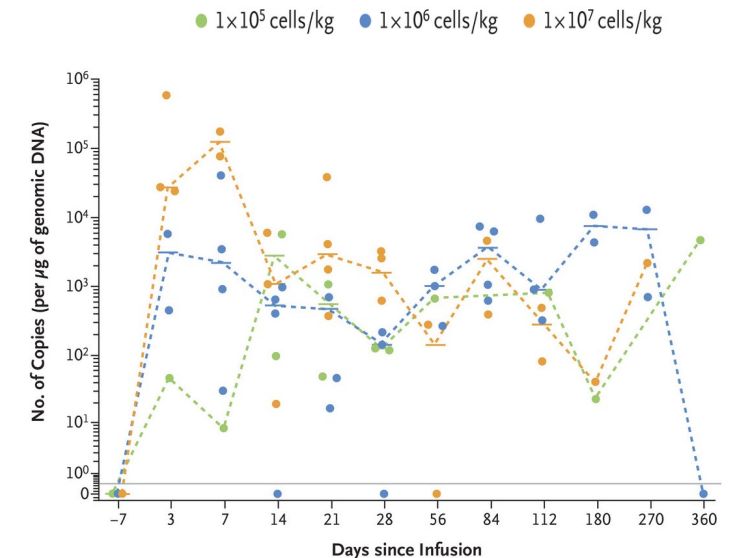
Pre-admission



Day 30 post CAR NK

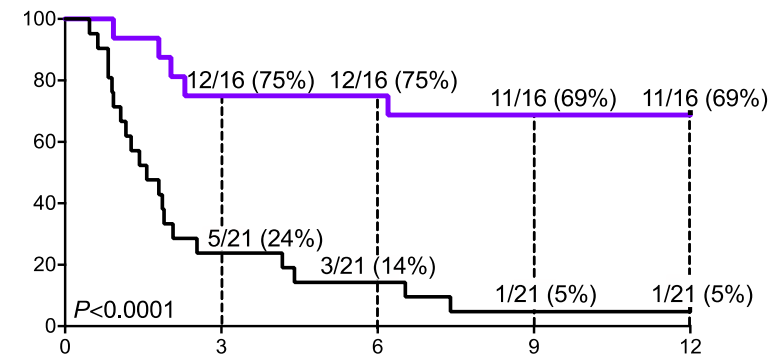
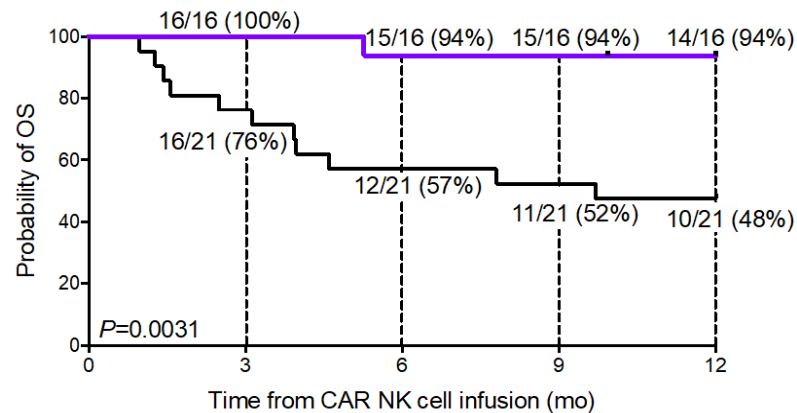
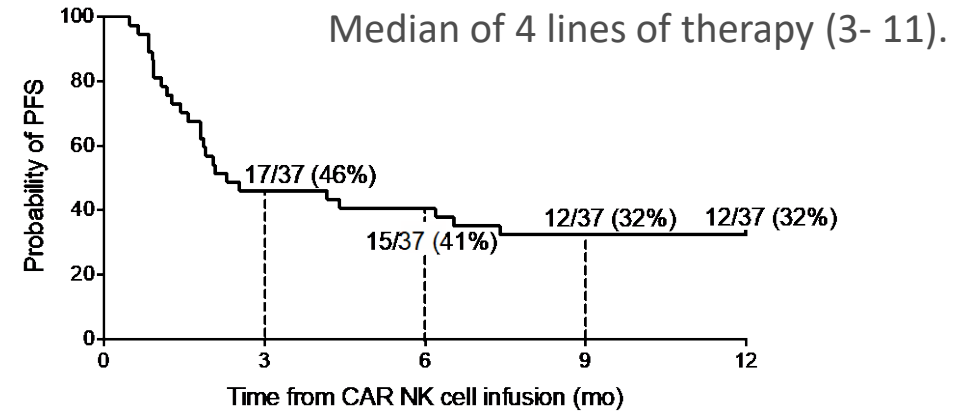
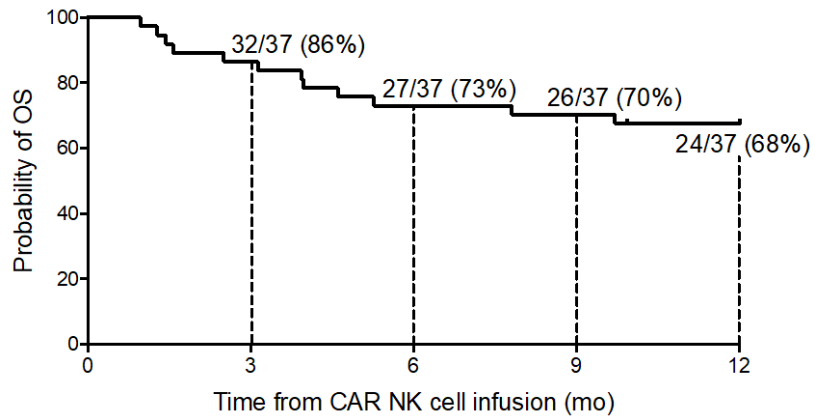


7/11 CR, No CRS, No
neurotoxicity, and No GvHD



CAR NK cells are detectable
> 12 months post infusion

CAR19 NK cell therapy results in durable responses in patients with lymphoid malignancies (n=37)



— Sub-Cs — Opt-Cs

Optimal cords:

Time to freezing ≤24hr; NRBC≤8E7

Suboptimal cords: Time to freezing >24hr; NRBC>8E7

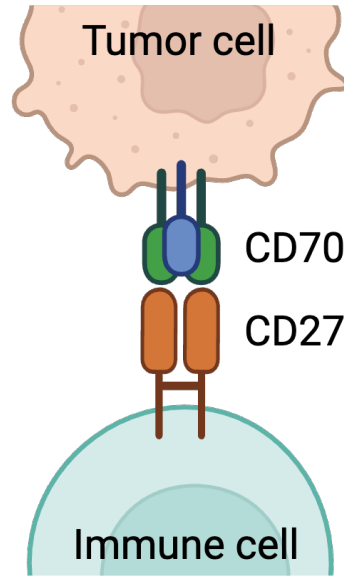
CD70 is a promising pan-cancer antigen

Ligand for CD27, and stimulates cells expressing CD27

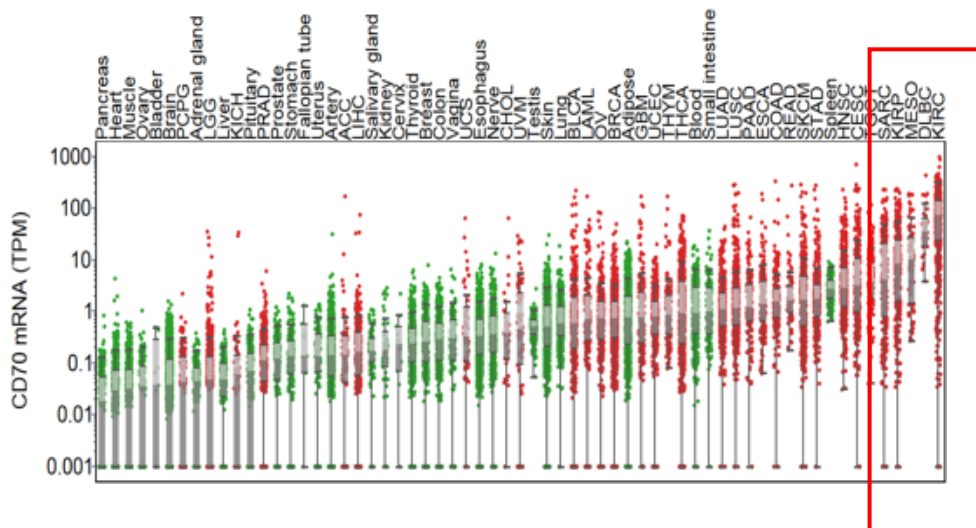
Generally absent in non-lymphoid normal tissues

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

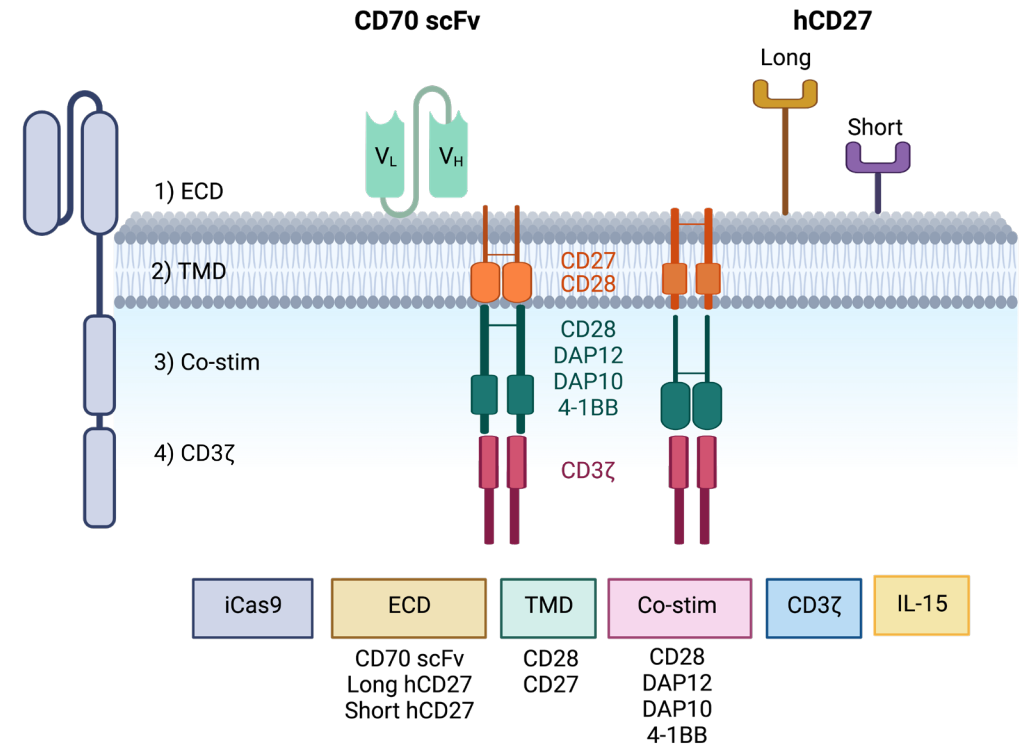
Cusatuzumab or ARGX-110 tested in multiple clinical trials



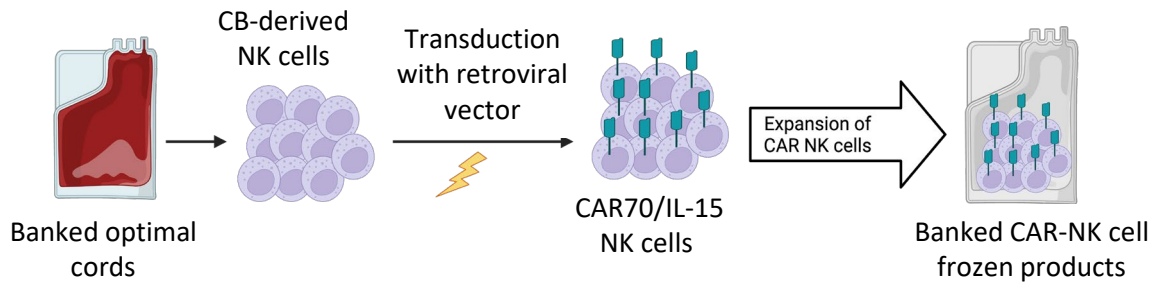
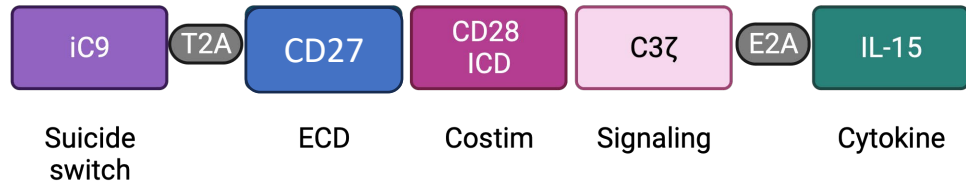
Sunil Acharya,
PhD



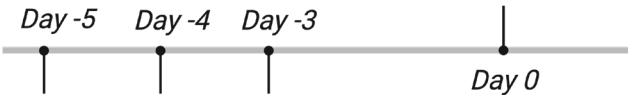
- Lymphomas
- Renal cell carcinoma
- Sarcoma
- Mesothelioma
- Nasopharyngeal carcinoma



CD70 is a promising pan-cancer antigen



Thaw and infuse
CD70 CAR NK cells



Cyclophosphamide 300 mg/m²

Fludarabine 30 mg/m²



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

Basket trial in hematologic malignancies
approved by IRB and FDA
(NCT05092451, IND 27757)

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

Patient with primary refractory high-grade B cell lymphoma-response to truly off-the-shelf HLA-mismatched, cryopreserved CD70 CAR-NK cells

38 year old male with primary refractory stage IV diffuse large B cell lymphoma (DLBCL) 5/2022

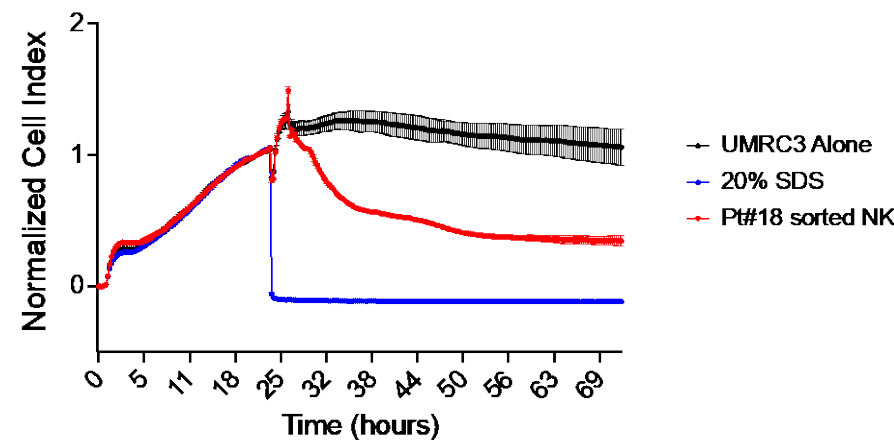
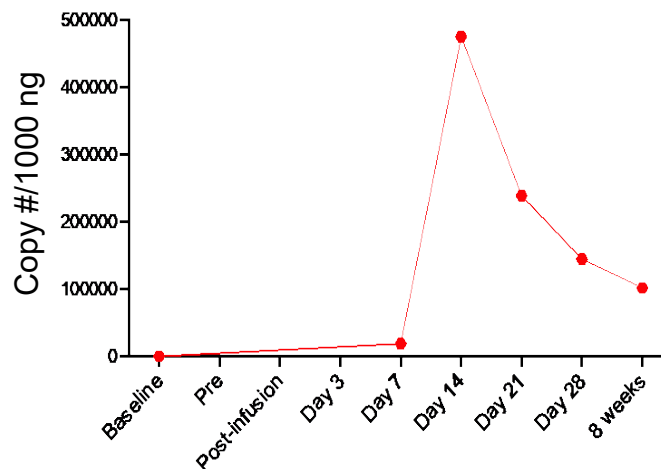
- R-EPOCH – no response
- RICE – progressive disease
- Revlimid + Ritux – progressive disease
- Pola-BR – progressive disease
- loncastuximab tesirine – progressive disease
- DHAX
- CD70 CAR NK cells 7/2024 (dose level 6)

→ **Complete remission**

Donor NK cell persistence

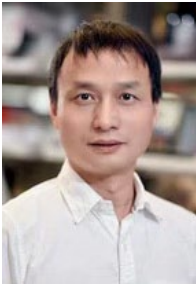
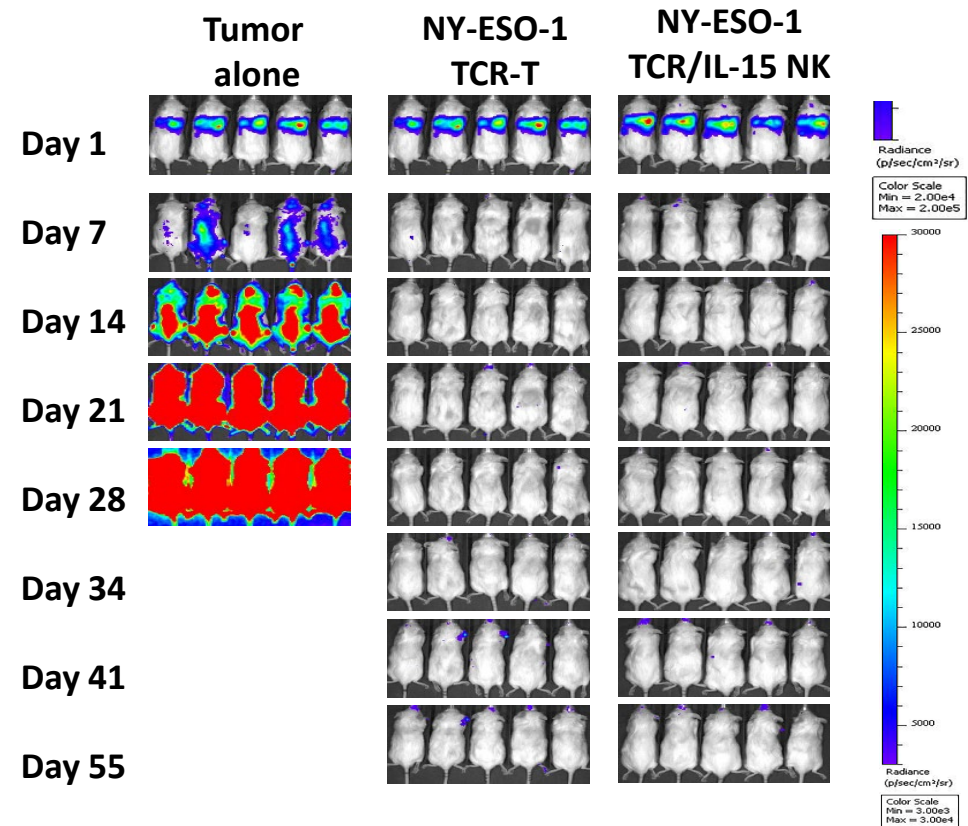
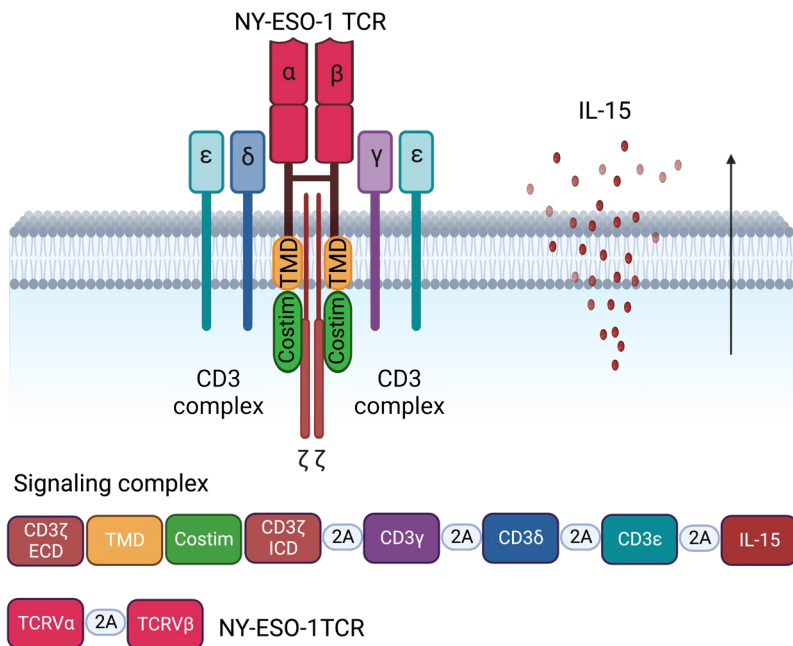
Pre-admission

Week 10



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
- NK cells do not 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)

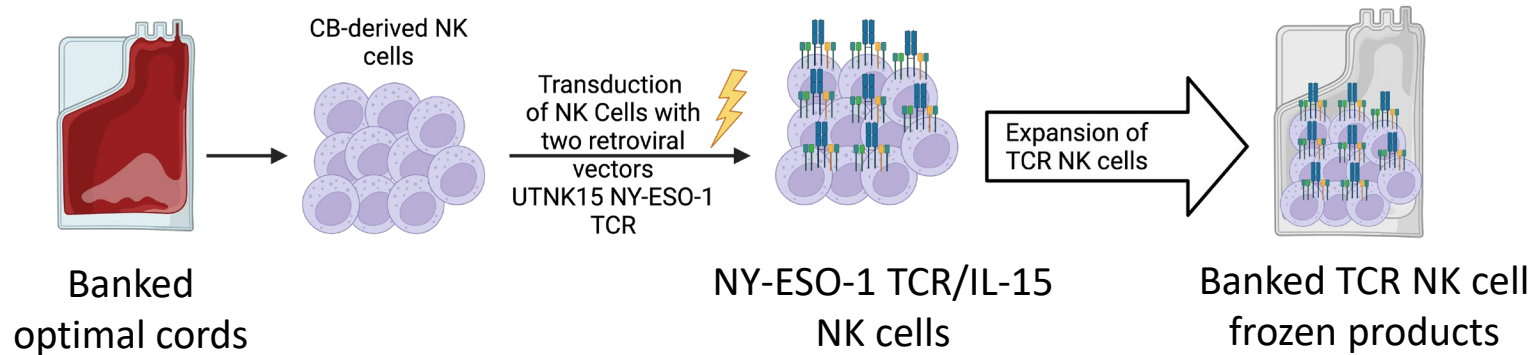


Bin Liu,
PhD



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



Thaw and infuse
TCR CAR NK cells



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



Christine Ye, M.D.
Lymphoma-myeloma

- 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 Livingston, MD
Sarcoma Medical Oncology

NY-ESO-1 Clinical Data: Response to CB NY-ESO-1 TCR/IL-15 NK cells in a heavily pretreated Multiple Myeloma patient

Patient summary:

64-year-old with **Multiple Myeloma**, IgA kappa subtype, R-ISS II, myeloma FISH panel showed del17p and t(4;14), BMB with 41% plasma cells → **High risk disease, double hit myeloma**, diagnosed in February 2018

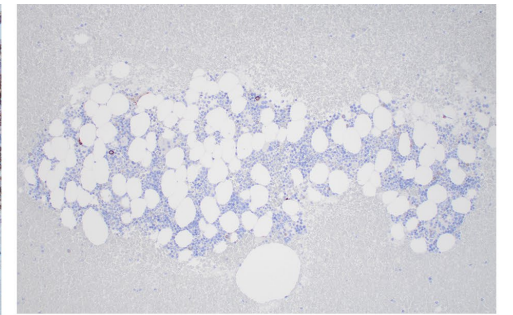
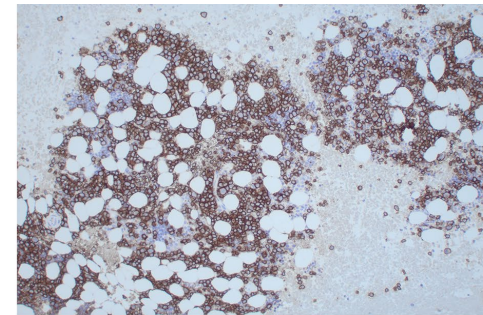
Treatment history:

1. KRD x 2 cycles
2. Autologous SCT
3. Revlimid maintenance
4. Protocol: 2018-0572 Cyclophosphamide, Fludarabine, and BCMA CAR-T cells
5. Daratumumab, Pomalidomide, and Dexamethasone
6. Talquetamab (Talvey)- BiTE (CD3 and GPCR5D)
7. CB-NK NY-ESO-1 TCR/IL-15: **DL1 80 x 10E6 frozen cells (transduction efficiency 27% = 22 x 10E6 flat dose TCR+ NK cells)**

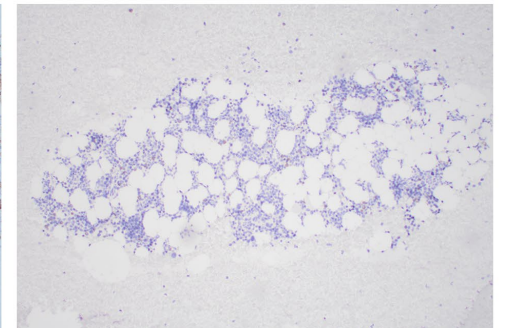
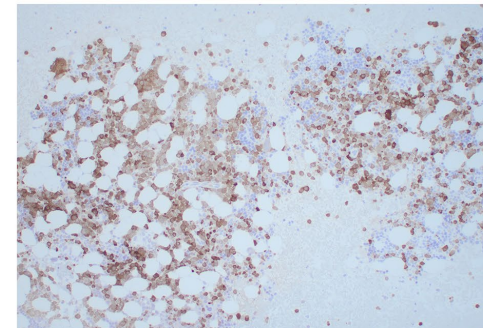
Response assessment:

- Bone marrow biopsy:
 - Plasma cell neoplasm (Pre-infusion) → **Normal bone marrow with no minimal residual disease (1 month post-infusion)**
 - **Percent NY ESO+ myeloma cells went from 100% to 0%**

CD138



NY-ESO

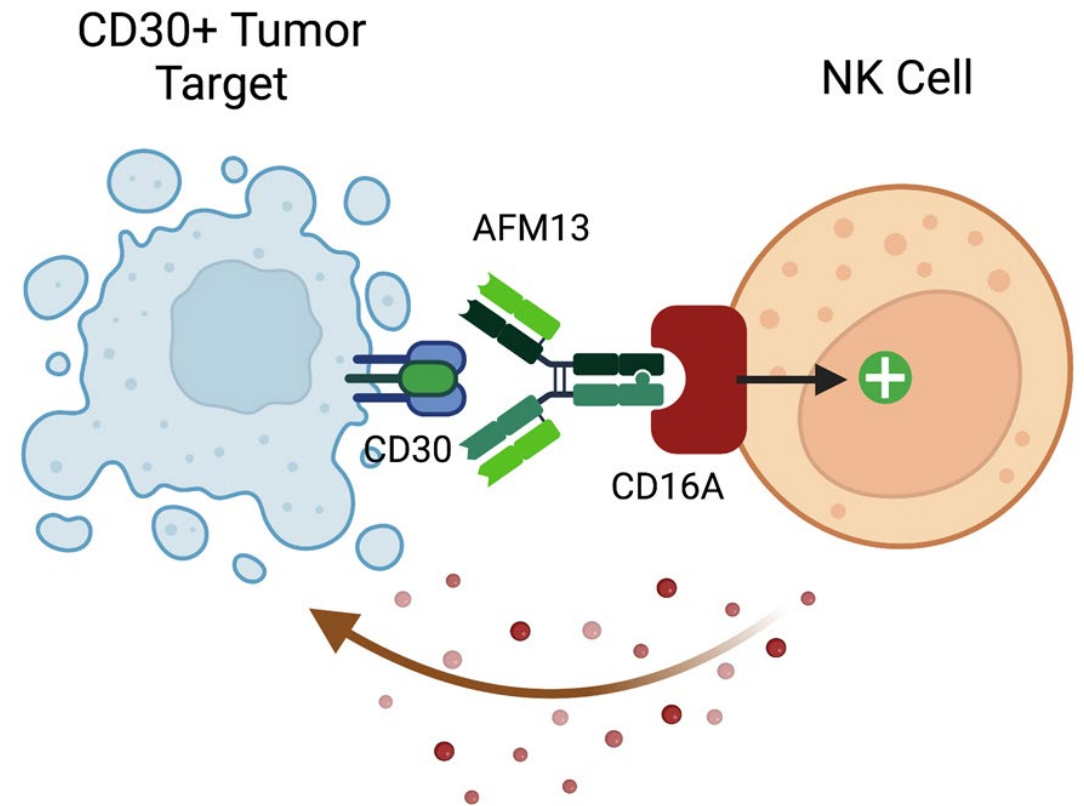


Courtesy Dr. Pei Lin

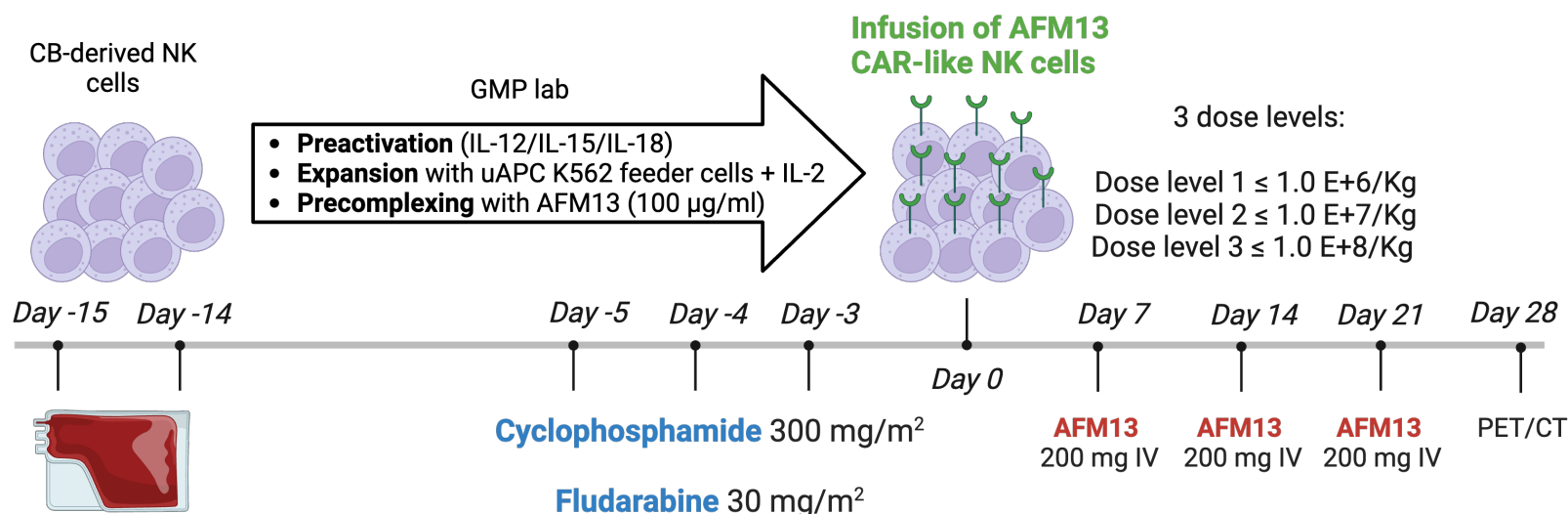
Antibody-armed NK cells

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



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

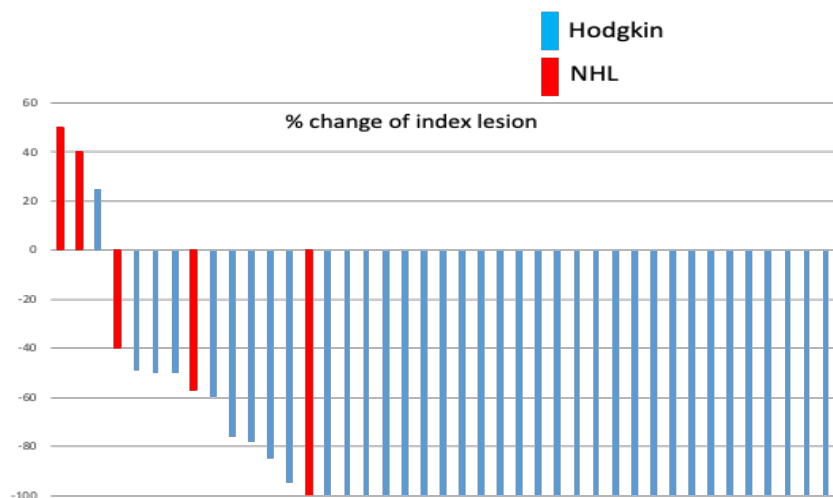


Median 7 prior lines of treatment



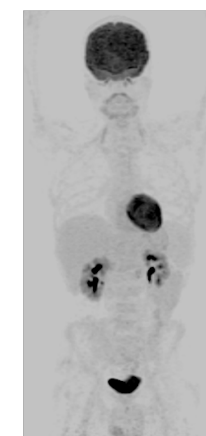
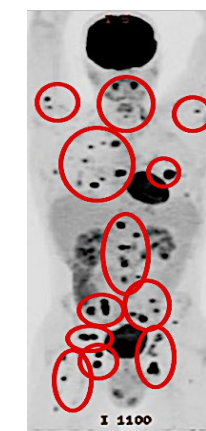
Yago Nieto, MD, PhD

- Responses evaluated by PET (Lyric criteria) on day 28 of each cycle
- 39/42 responses (**ORR 92.9%; CR 66.7%**)
- No cases of cytokine release syndrome (CRS), neurotoxicity (ICANS) or graft-vs-host disease (GVHD)

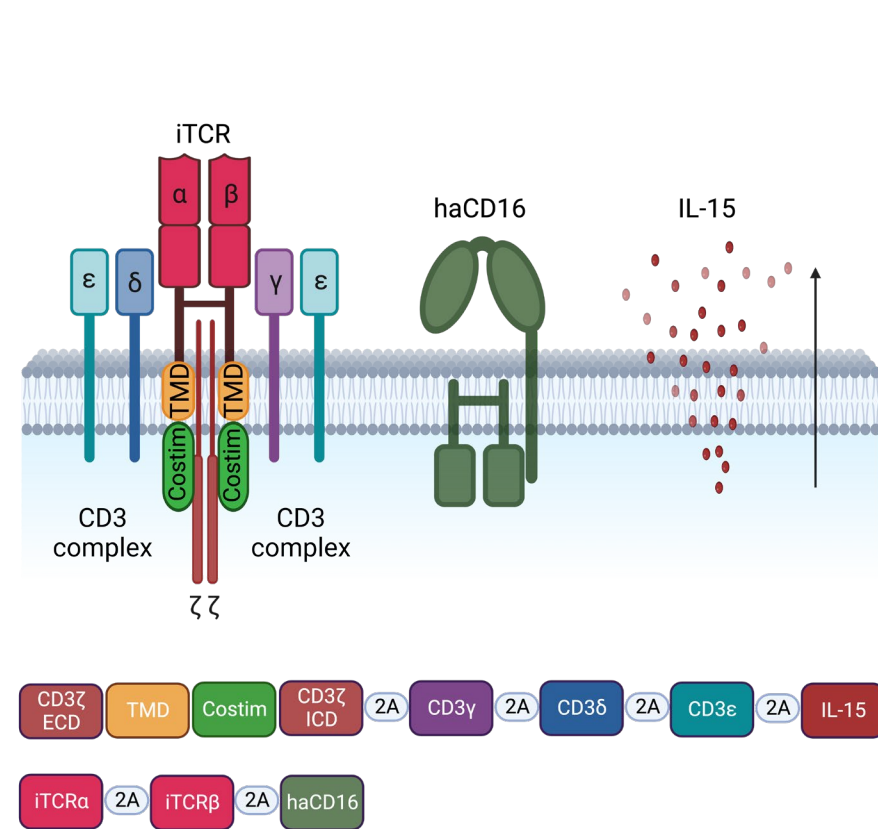


Pre-infusion

D30 post-infusion



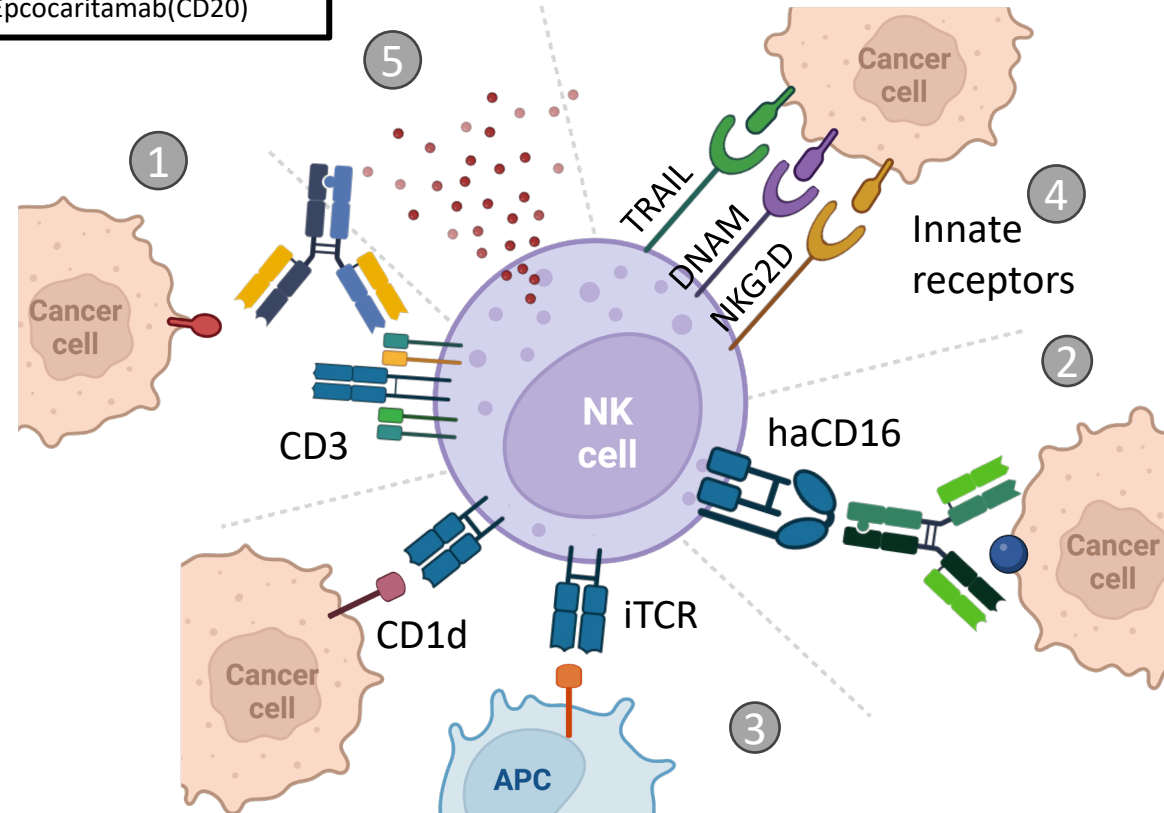
PluReceptor NK cells: A modular approach to multi-antigen targeting and enhancing NK cell persistence



T-cell engagers:

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

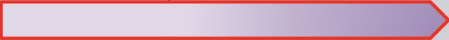
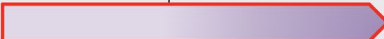
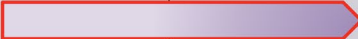
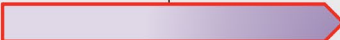

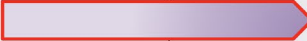
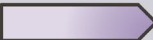
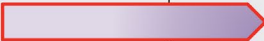
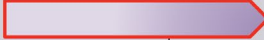



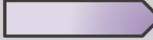


IL-15 (promotes NK cell persistence and *in vivo* expansion)



mABs:

Trastuzumab
 Rituximab
 Obinutuzumab
 Tafasitamab
 Imgatuzumab
 Cetuximab
 Pertuzumab
 Dinituximab
 Amivantamab
 Mogamulizumab

Current CAR NK cell pipeline at MDACC

Product	Indication	IND-Enabling	Phase I	PI
CD70-CAR-NK	Hematologic Malignancies			Dr. David Marin
	Solid Cancers			Dr. David Hong
TROP2-CAR-NK	PDAC and OC (IP)			Dr. Amir Jazaeri
	Solid Cancers (IV)			Dr. Ecaterina Dumbrava
	CRC (MRD; +Cetux)			Dr. Pia Morelli
CRISPR edited NK	GBM			Dr. Shiao-Pei Weathers
IL21 dual CAR-NK	GBM		Q1 2025	Dr. Fred Lang
NY-ESO TCR-NK	Solid Cancer			Dr. Andy Livingston
	Multiple Myeloma			Dr. Muzzafar Qazilbash
PRAME TCR-NK	AML			Dr. Jeremy Ramdial
	Uveal melanoma			Dr. Adi Diab
CD5-CAR-NK	Hematologic Malignancies			Dr. Chitra Hosing
PluraliNK	Multiple Myeloma		Q1 2025	Dr. Qaiser Bashir
	Lymphoma		Q1 2025	Dr. Yago Nieto
	Autoimmune diseases			Dr. Chitra Hosing and Dr. Shervin Assassi

Rezvani Lab

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Mayra Shanley
Pinaki Banerjee
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Sufang Li
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Dexing Fang
Mecit Kaplan
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Scott Kopetz
Fred Lang
Funda Meric
Anirban Maitra
Vinay Puduvalli
Shiao-Pei Weathers
And many others

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Stem Cell Transplant

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Rohtesh Mehta
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Amanda Olson
Betul Oran
Uday Popat
Muzaffar Quazilbash
Samer Srour
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Borje Andersson
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Christina Ganesh
Peggy LeCompte
Vivian Aljadhani
Yosra Aljawai
Warren Fingrut
George Chen

Rezvani Lab



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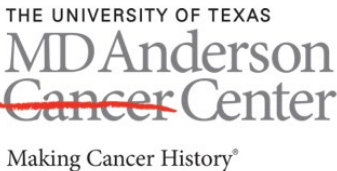
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NCI R01- CA061508

NCI P50CA127001

NCI- R01CA280827

NCI- P50CA281701



**MD Anderson
Moon Shots
Program**



GMP-CEG Group



CANCER PREVENTION & RESEARCH
INSTITUTE OF TEXAS

Patients and their families

The Marcus Foundation

Accelerator Fund

