NK cell Engineering Strategies for the Management of Advanced Cancer

2025 Cell Coast Conference

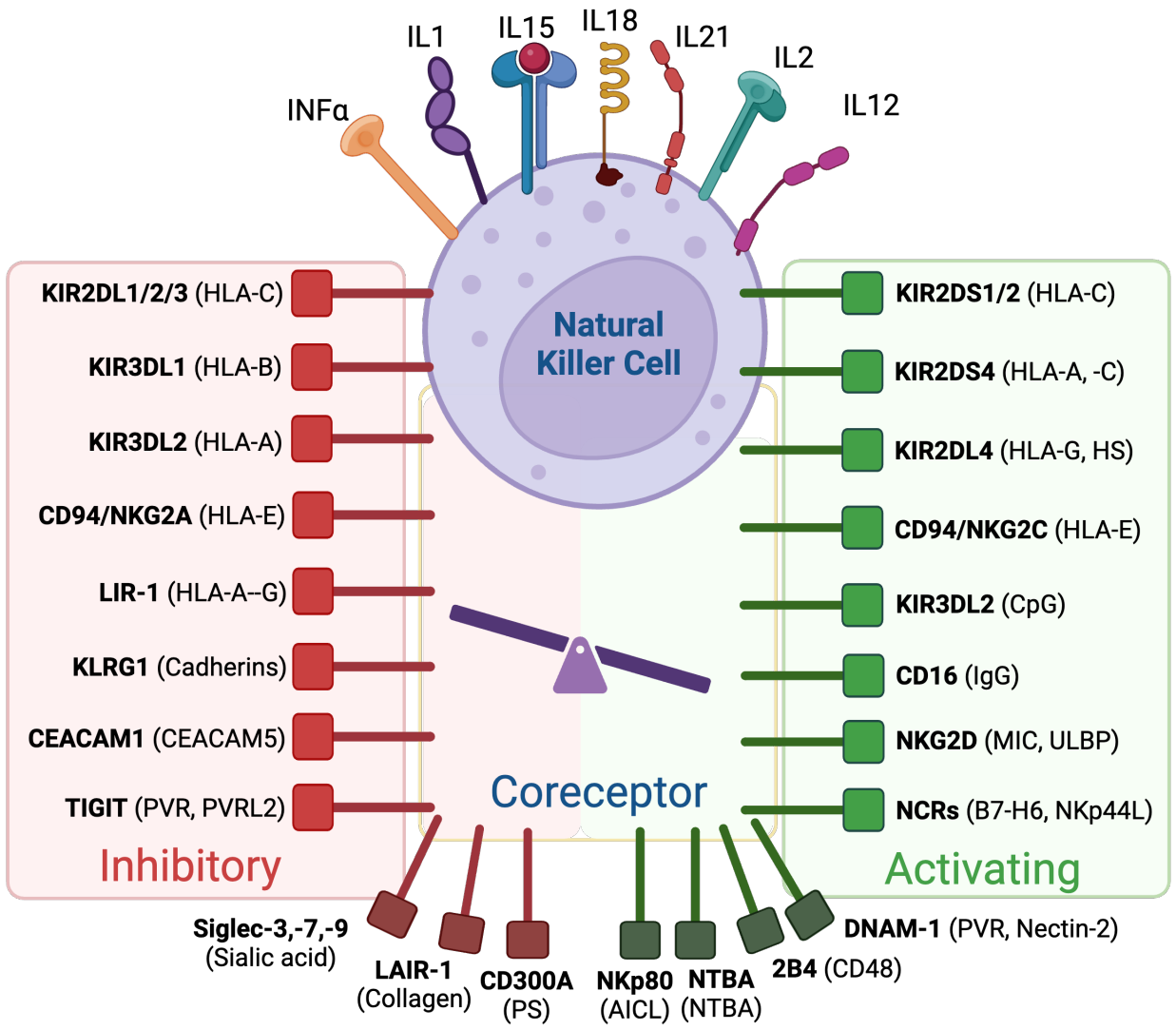
10.18.2025

MAY DAHER, MD

Associate Director, Translational Research, Institute for Cell Therapy Discovery & Innovation
Associate Professor of Medicine, Department of Stem Cell Transplantation and Cell Therapy
MD Anderson Cancer Center
Houston, TX, USA

What are Natural Killer (NK) cells?

- Innate immune system
- CD56+CD3-
- Differentiate in the BM
- No antigen priming
- No/low risk of GVHD
- Recognition takes place through complex array of receptors



Limitations of adoptive NK cell Therapy

- Limited persistence in the absence of cytokine support
- Lack of antigen specificity
- Functional decline following cryopreservation
- Limited tumor infiltration
- Adoptive infusion of non-engineered NK cells showed limited clinical efficacy

Strategies to enhance adoptive NK cell antitumor potential

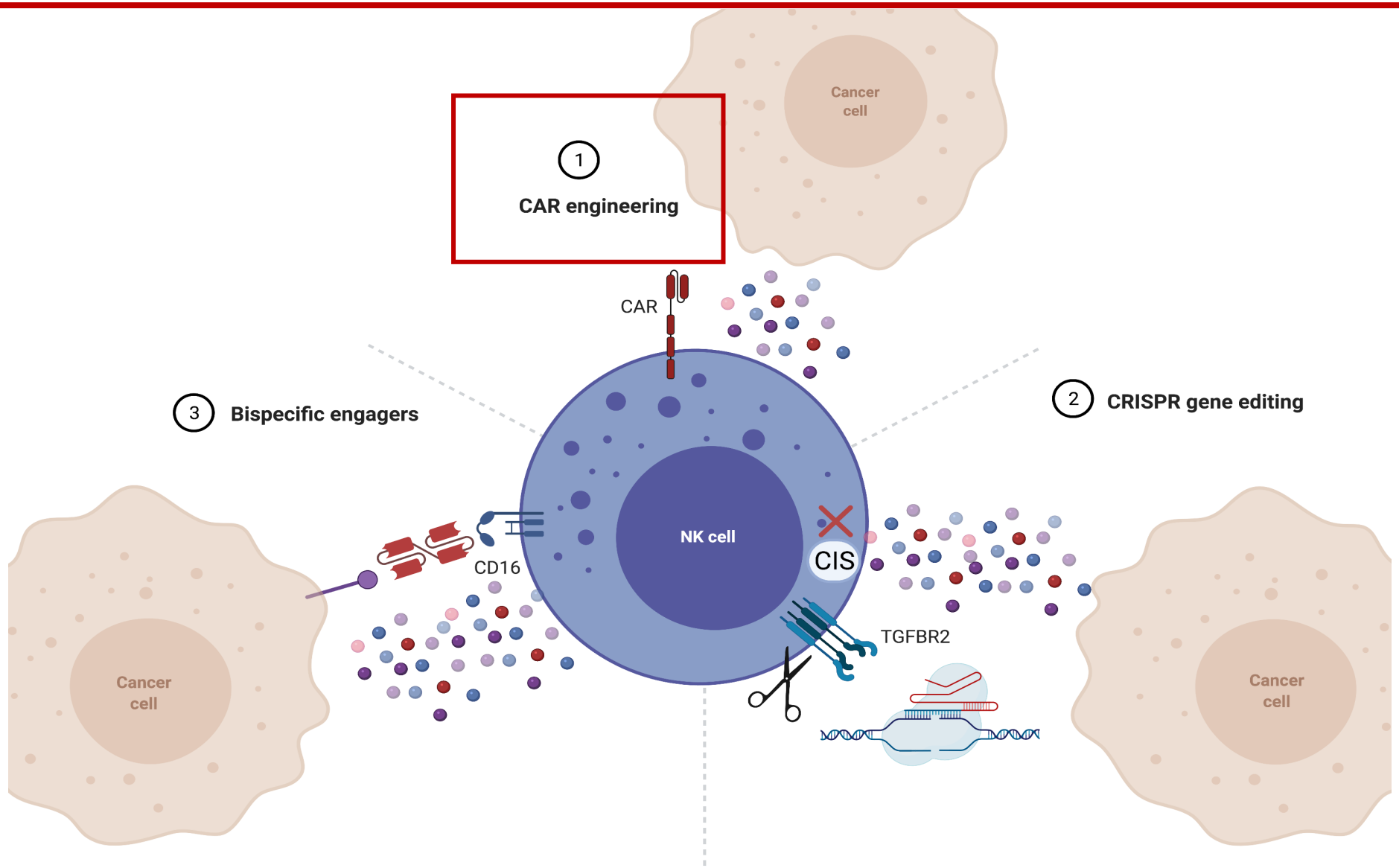


Figure made in Biorender

Challenges of autologous CAR-T therapy

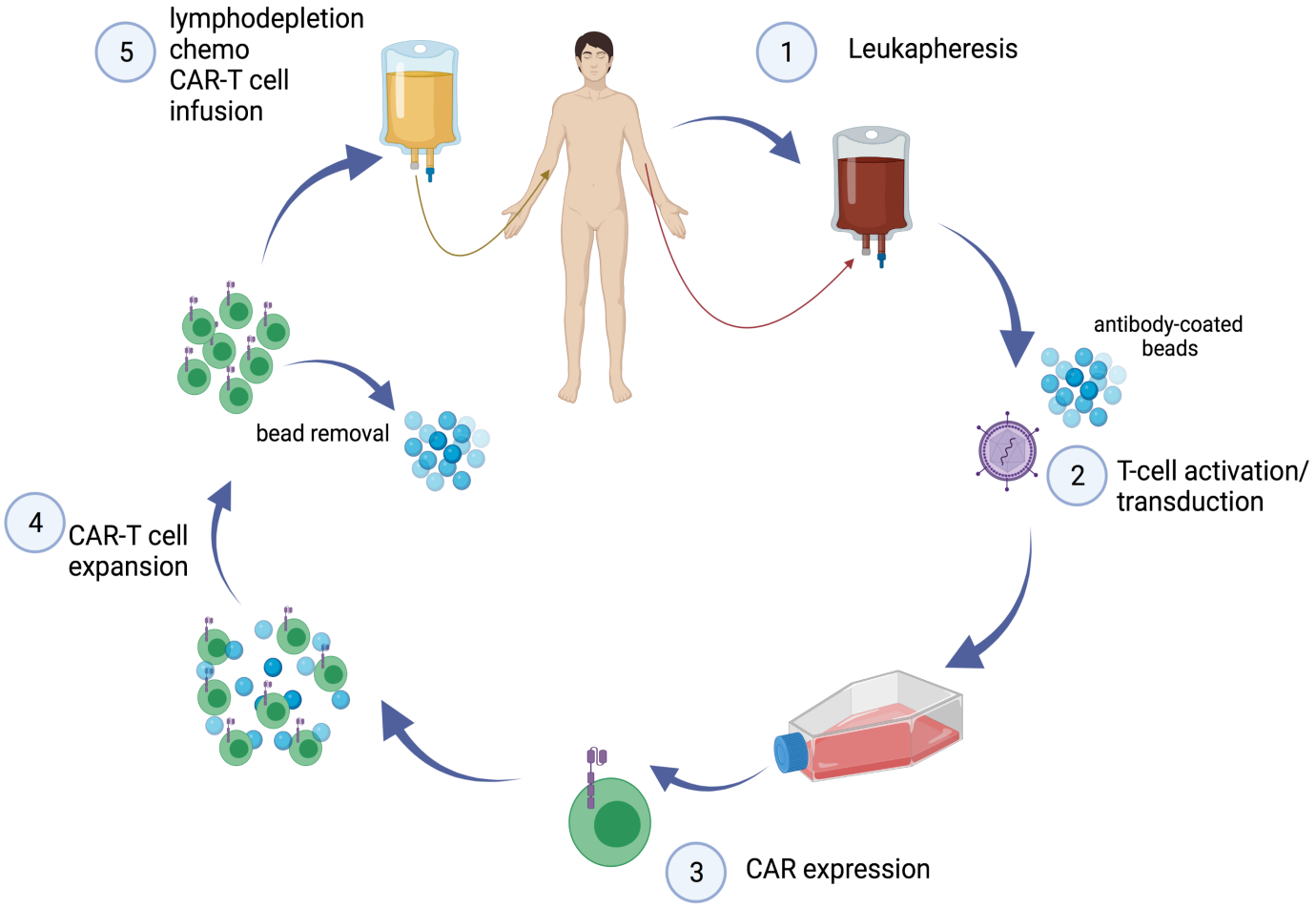


Figure made in Biorender

Autologous CAR-T still have a **number of limitations:**

- Patients progress or die while waiting (~10-20%) or manufacturing failure (~5-7%)
- Patient-to-patient variability- “Health of T cells”
- Costly, complicated manufacturing
- Commercial challenges

Autologous vs allogeneic CAR products

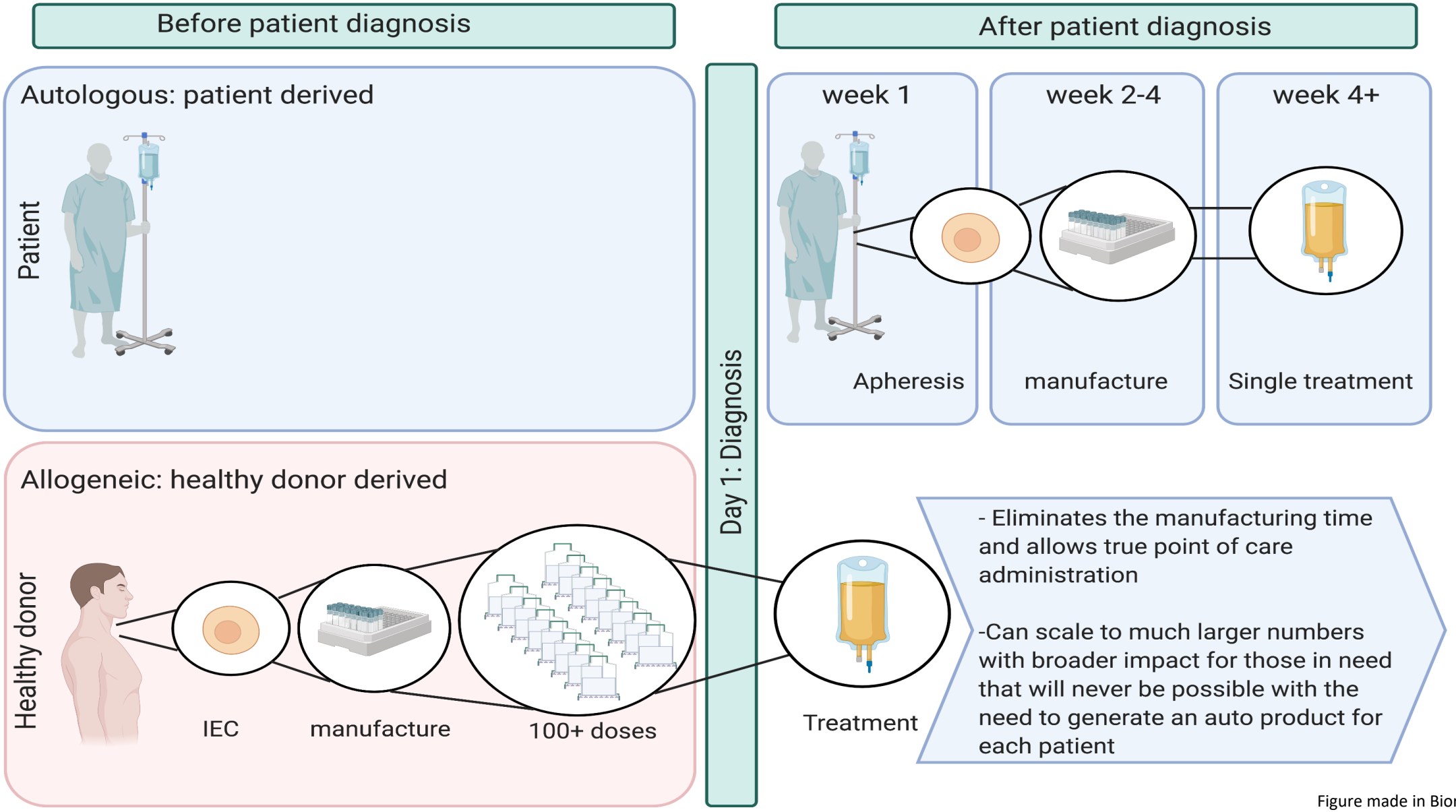
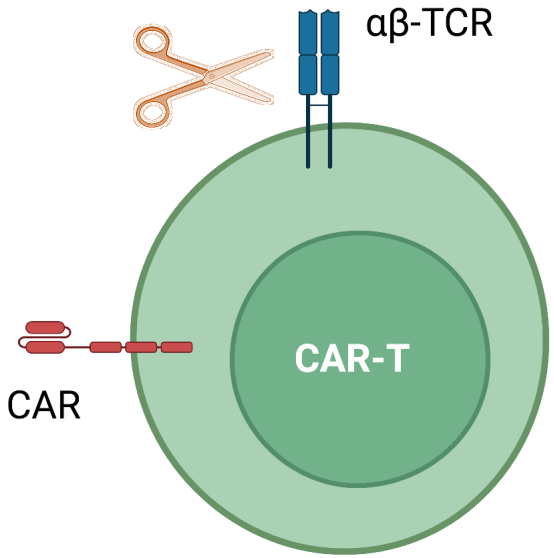
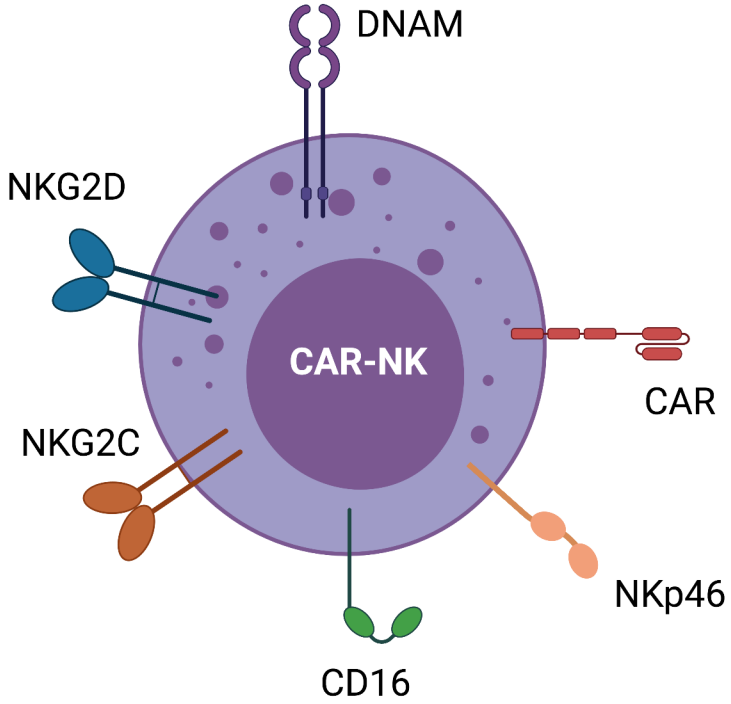


Figure made in Biorender

Advantages of NK cells over T cells for CAR therapy





Allogeneic: GVHD

Killing: CAR mediated

Toxicity: CRS, ICANS

Allogeneic: no GVHD-->off the shelf, lower cost

Killing: CAR mediated + innate receptors

Safety: no CRS, no ICANS

Allogeneic sources of NK cells for CAR engineering

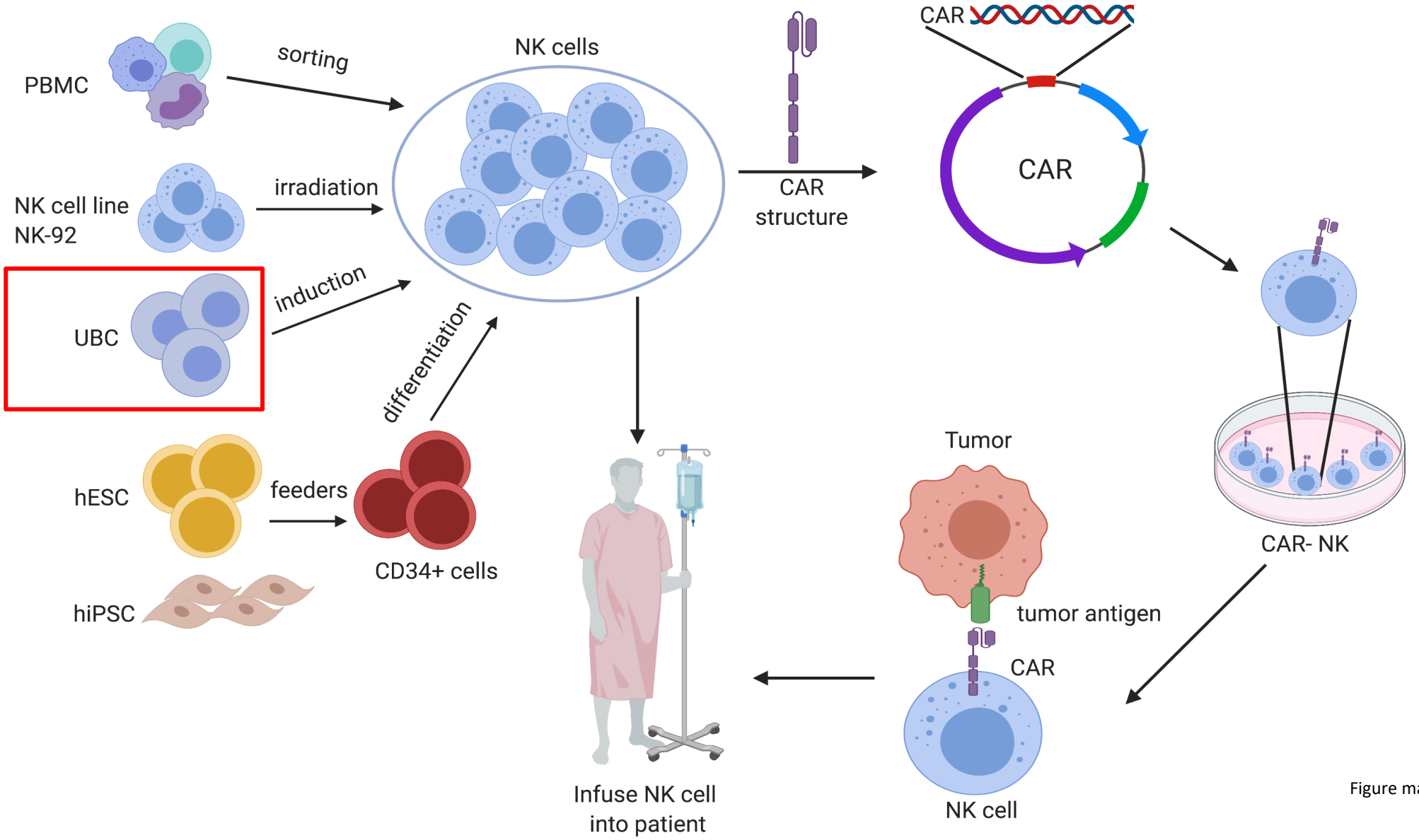


Figure made in Biorender

MD Anderson Cord Blood Bank (established and lead by Dr. EJ Shpall since 2005)

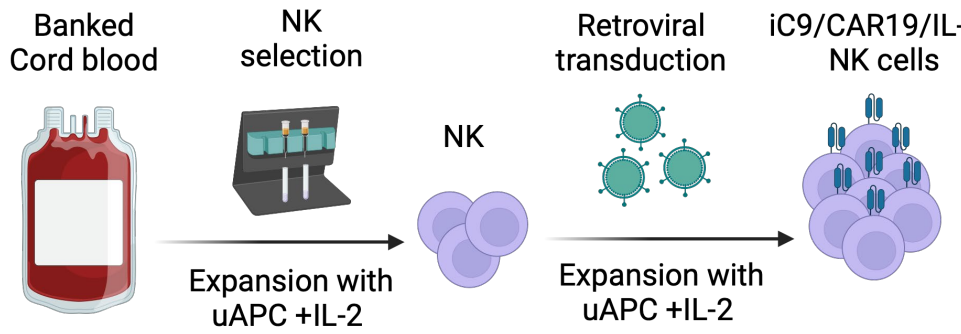
THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

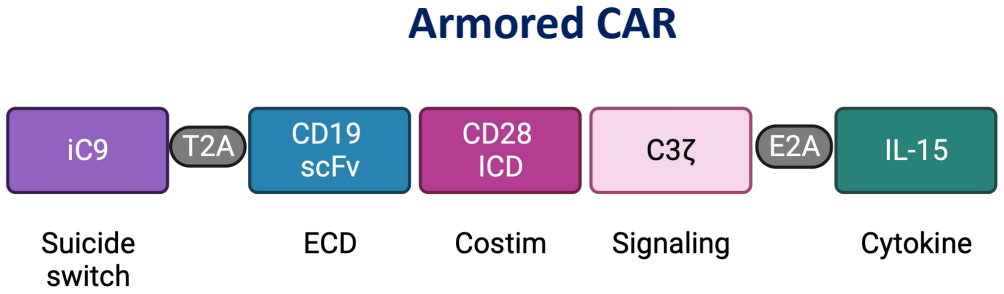
- No. Units Collected: 103,980
- No. Units Stored: 34,119
- No. Units Transplanted: 2,109
- No. Units for Research: 18,768
- No. Minority Donor Units: 72%
- Partners:
  - The Woman's Hospital of Texas
  - BCM/Harris Health Ben Taub Hospital
  - Memorial Hermann Medical Center
  - Memorial Hermann Southwest
  - Memorial Hermann Memorial City
  - Memorial Hermann Woodlands
  - St. Joseph Medical Center
  - St. John's and Providence (Detroit)

Characteristics of iC9/CAR.19/IL15-transduced CB-NK cells generated from 5 different CB units after 14 days of culture

	Starting Cell Number ($\times 10^6$)	NK Fold Expansion	NK Absolute Count at Day14 ($\times 10^8$)	CAR Transduction Efficiency (%)
>100 doses of CAR NK cells can be generated from one cord blood unit				
CAR-CBNK#2	20	843.7	170	87.4
CAR-CBNK#3	20	7369.6	1530	64.4
CAR-CBNK#4	20	2514.3	500	47.8
CAR-CBNK#5	20	2221.8	440	67.5
Median	**20**	**2221.8**	**440**	**66.6**

First In-human Trial of CAR19/IL15 CB-NK Cells in Lymphoid Malignancies (dose escalation phase)





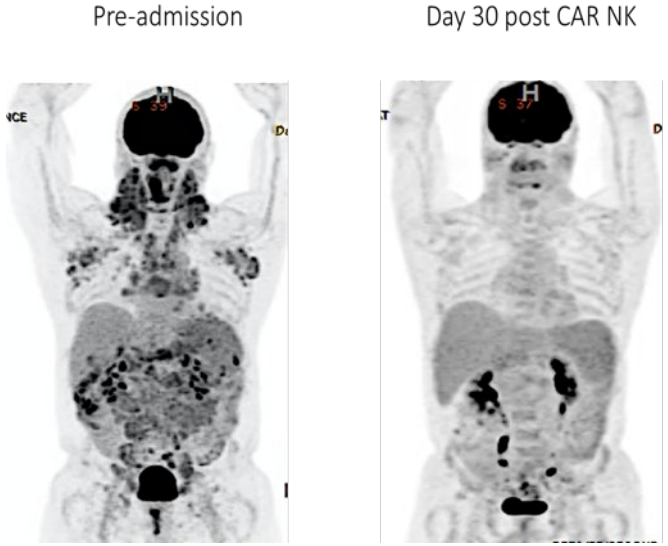
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

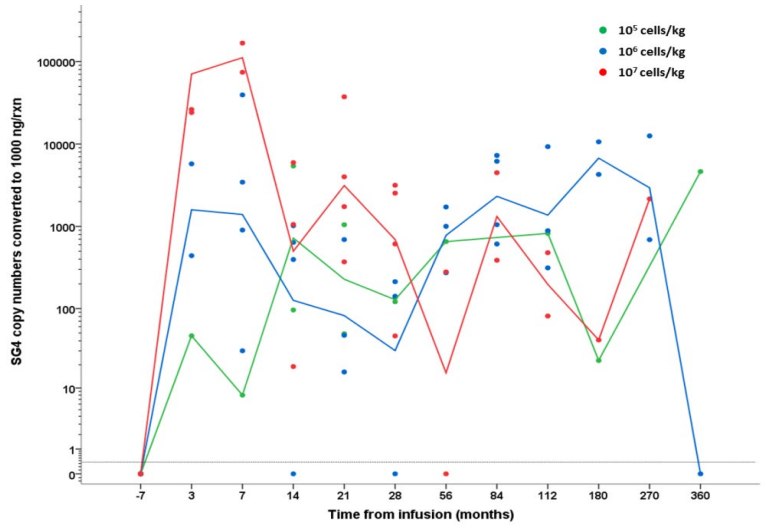
Use of CAR-Transduced Natural Killer Cells in CD19-Positive Lymphoid Tumors

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.



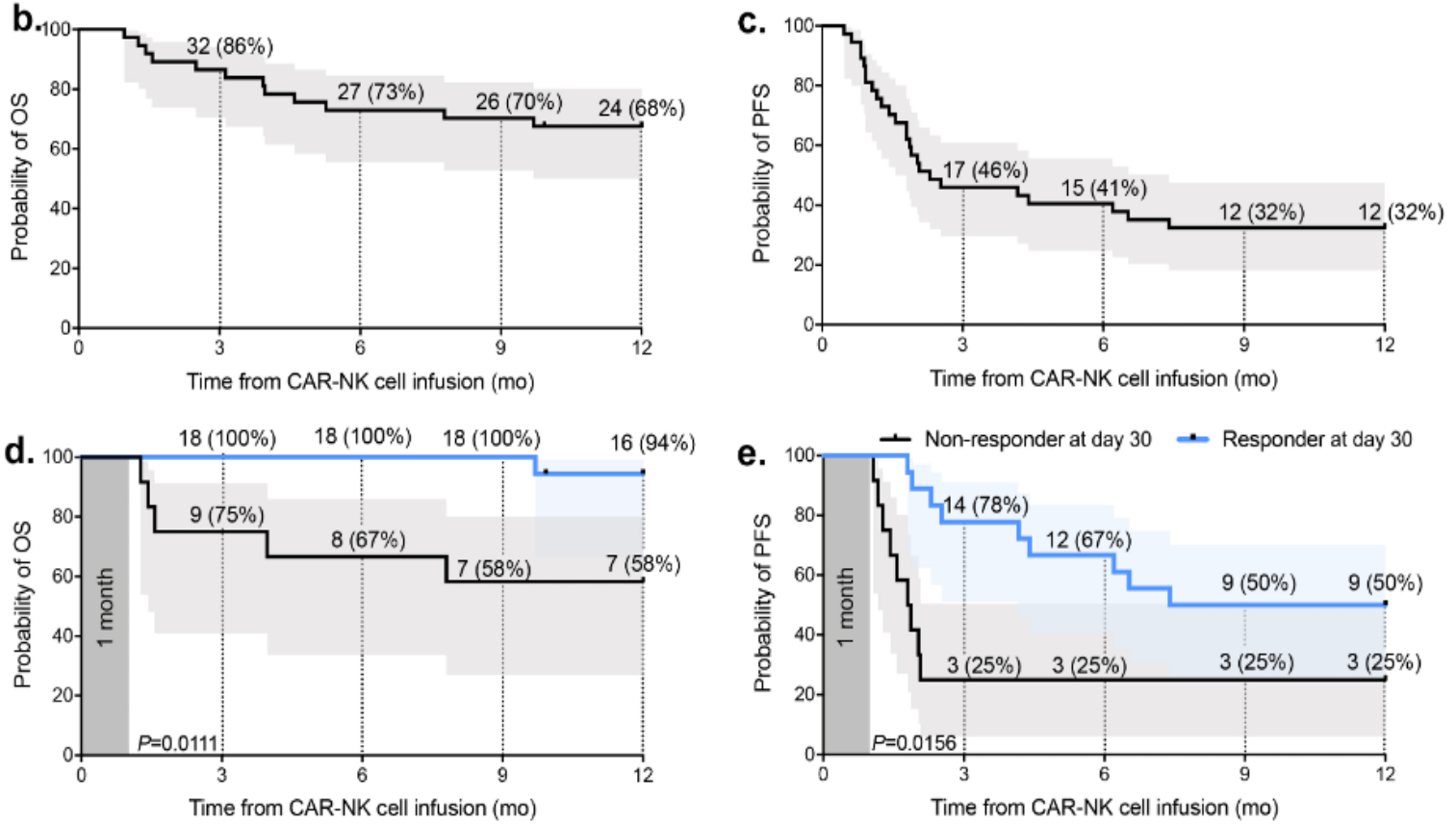
7/11 CR, No CRS, No neurotoxicity, and No GvHD



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

CAR NK cells are detectable > 12 months post infusion

First In-human Trial of CAR19/IL15 CB-NK Cells in Lymphoid Malignancies (dose expansion phase)



For the 37 patients:

- The day 30 and day 100 OR rates were 48.6% (95% CI= 31.9-65.6) for both
- The day 30 and day 100 CR rates were 27% (95% CI= 13.8-44.1) and 29.7% (95% CI= 15.9-47.0)

- 1 year PFS 32%, 1 year OS 68%

Marin, Li, Basar, Rafei, Daher &Rezvani et al. Nature Medicine 2024.

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

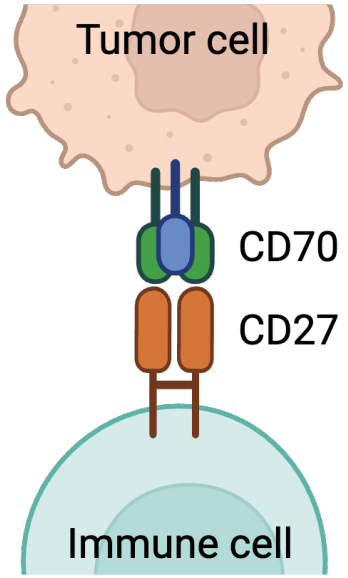
CD70 is a promising pan-cancer antigen

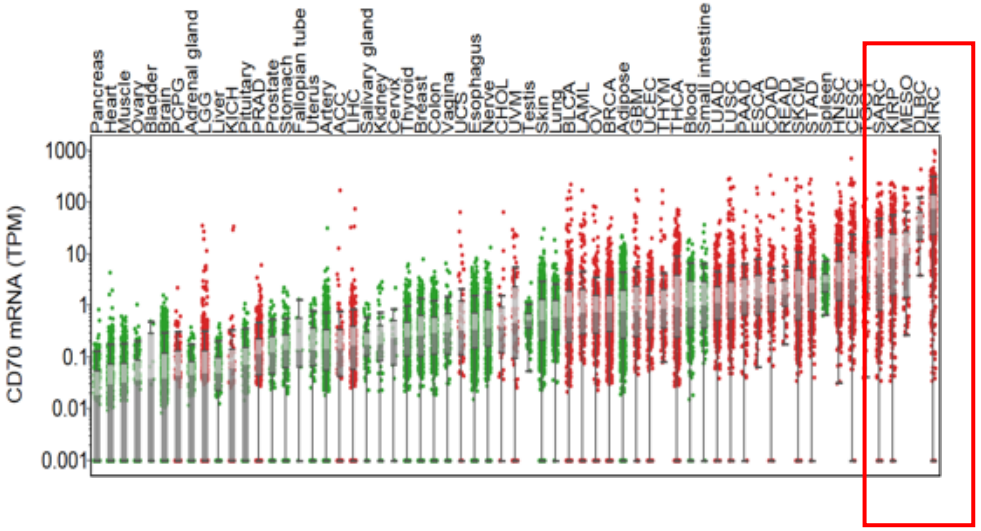
Ligand for CD27, and stimulates cells expressing CD27

Generally absent in non-lymphoid normal tissue

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

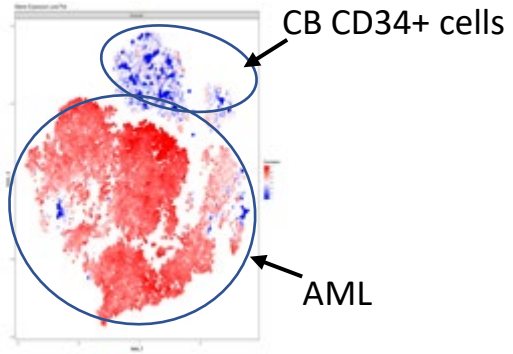
Cusatuzumab or ARGX-110 tested in multiple clinical trials

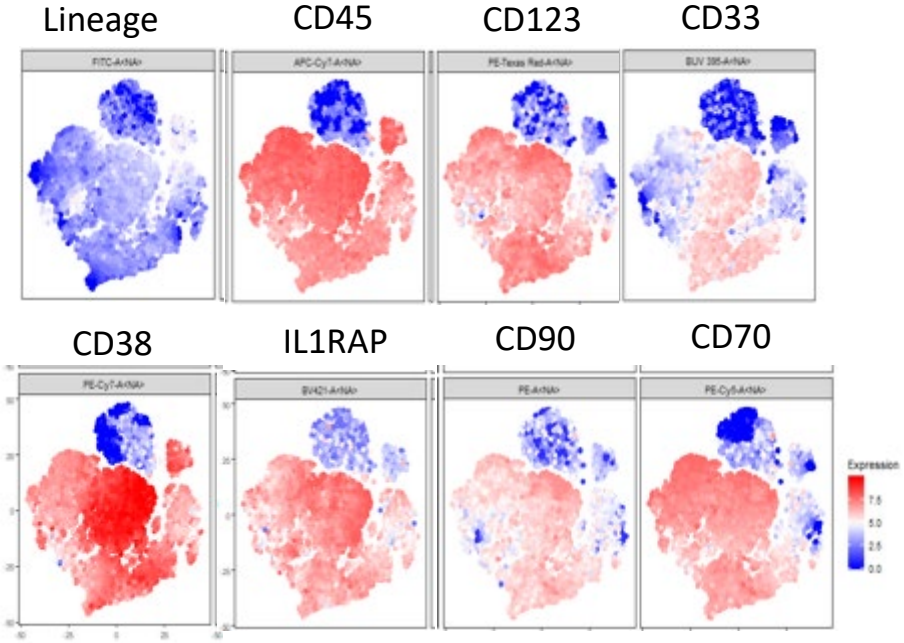




- Lymphomas
- Renal cell carcinoma
- Sarcoma
- Mesothelioma
- Nasopharyngeal carcinoma

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

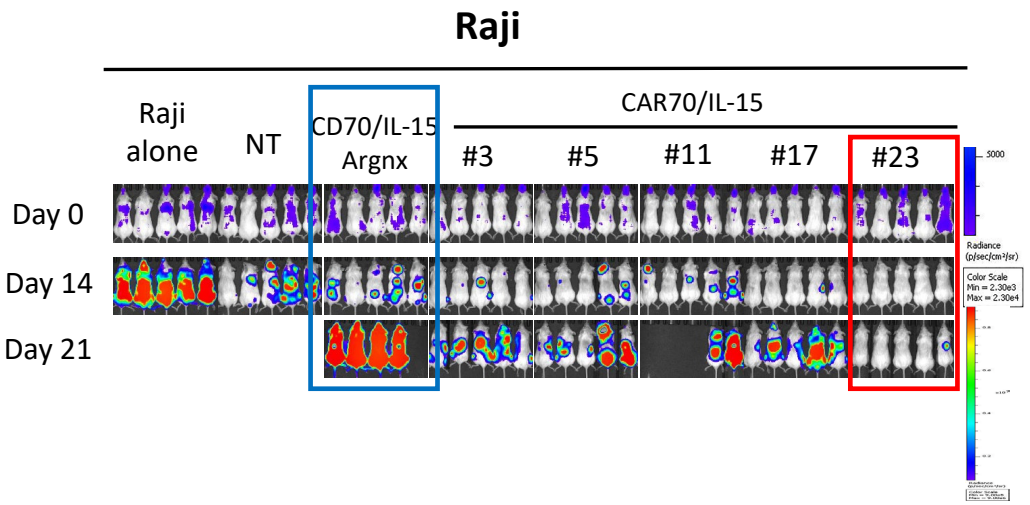


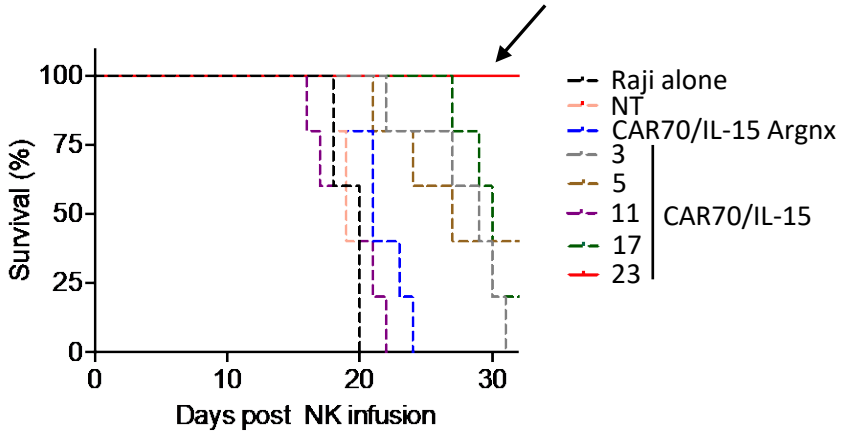


Data by Drs. Bijender Kumar, May Daher and Rafet Basar

CAR70/IL-15 NK cells show safety and superior anti-tumor activity in an aggressive CD70+ Raji (Burkitt lymphoma) mouse model and in an AML model

Controls: ARGXCD70-Cusatuzumab | Argnx



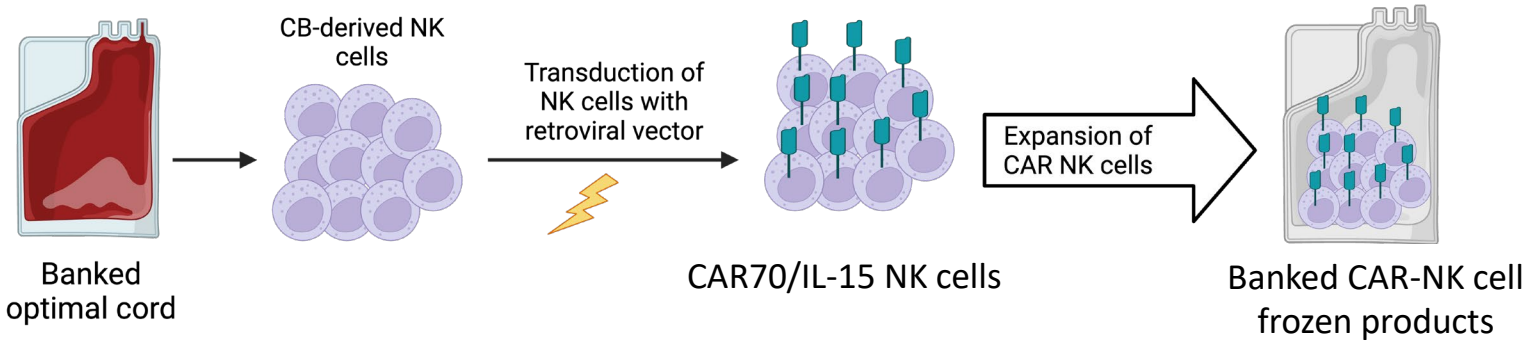


Sunil Acharya, PhD

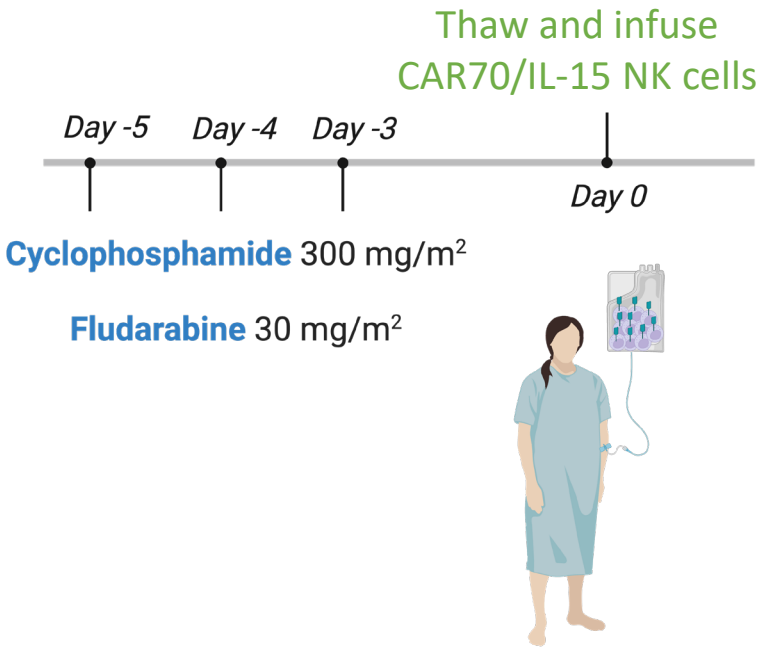
Rafet Basar, MD

Acharya et al., Cancer Discovery 2024

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

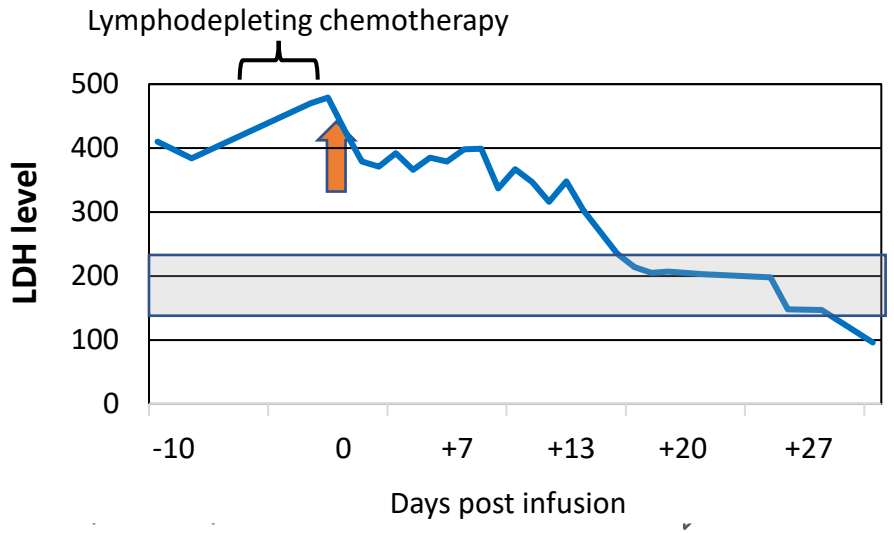
Clinical protocol in renal cell carcinoma, mesothelioma, and osteosarcoma approved by IRB and FDA (NCT05703854, IND 29057)

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

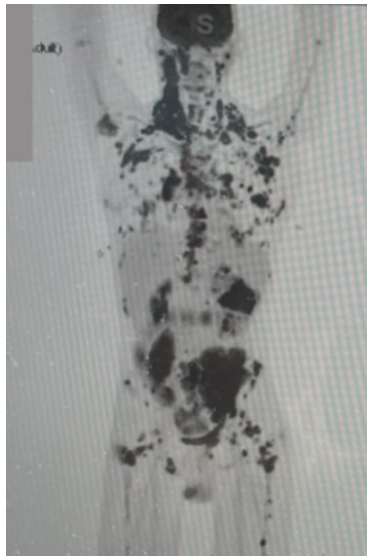
24 yr old male
Diagnosed with Stage IV classical HL – widespread LN and bones

- 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)**



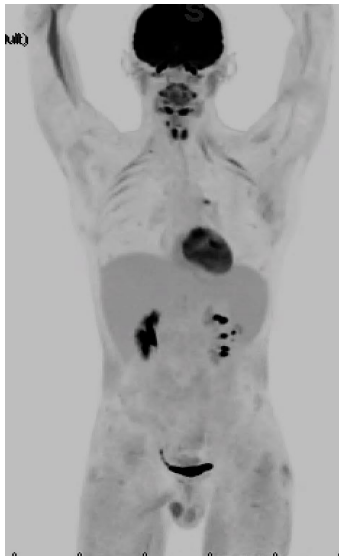
Patient with classical HL

Pre-infusion



D30 post-infusion

D60 post-infusion

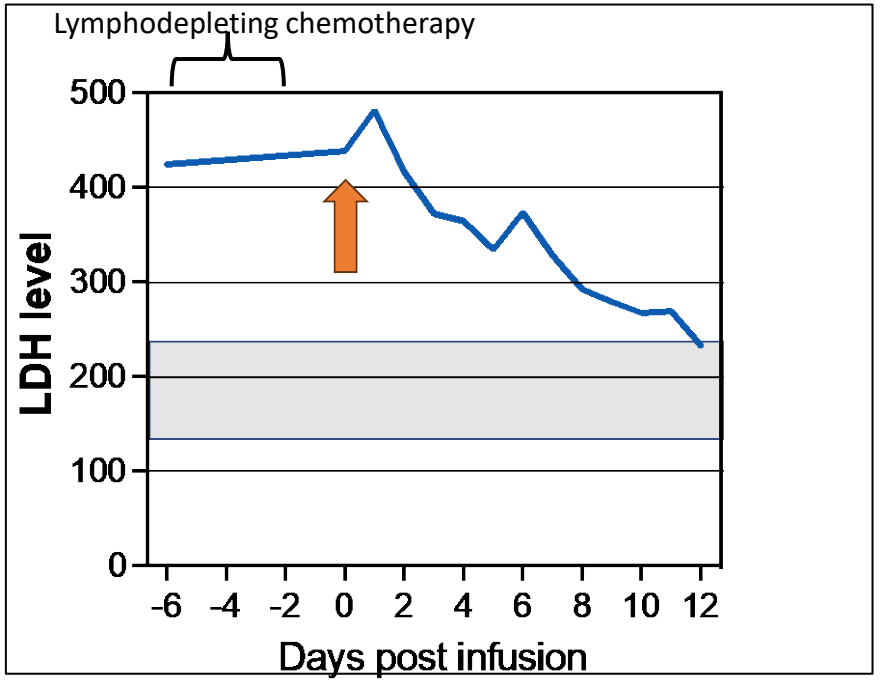


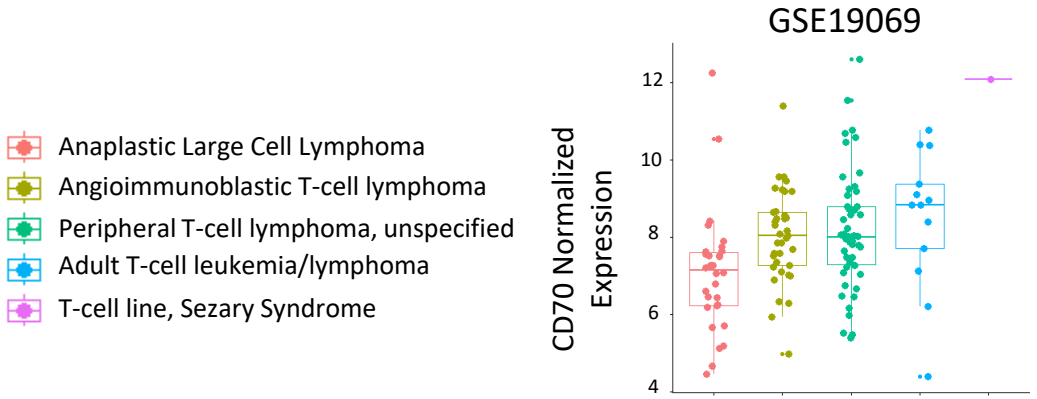
Dose level 4 completed
Responses observed in 10/12 patients

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

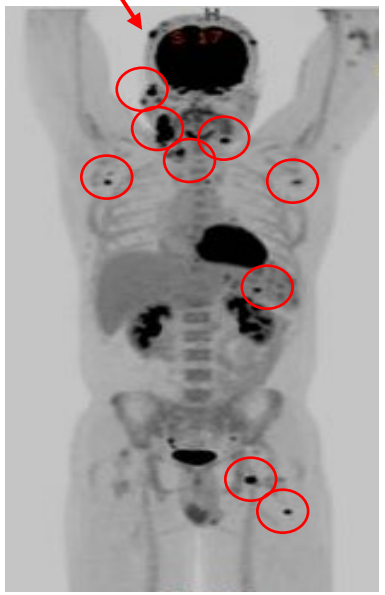
Patient with refractory cutaneous T-cell lymphoma (CTCL)

- 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

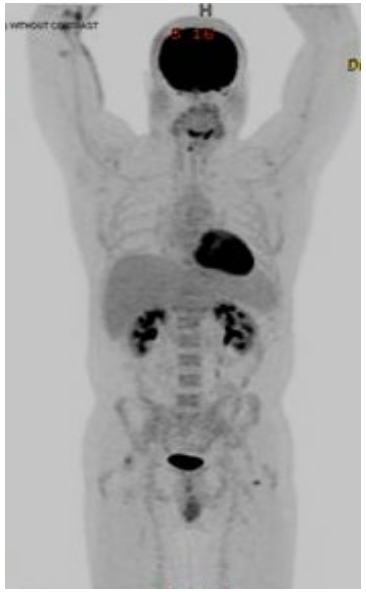




Pre-infusion



D30 post-infusion

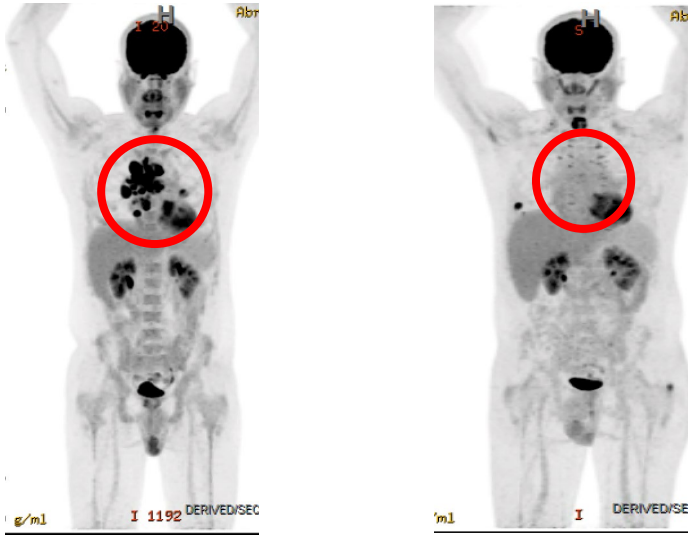


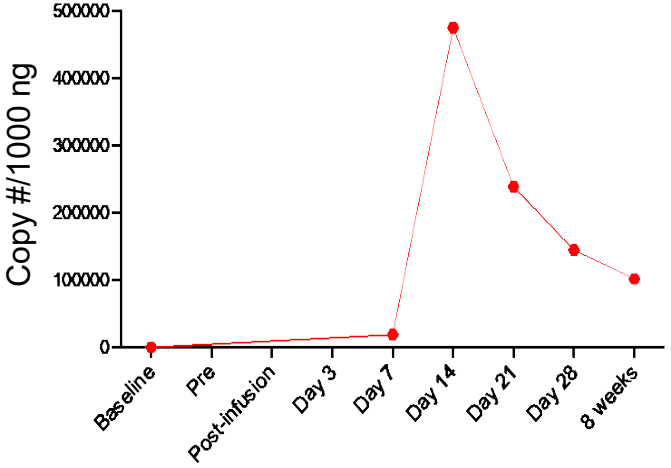
CAR70/IL-15 NK cells persist and remain functional in patients

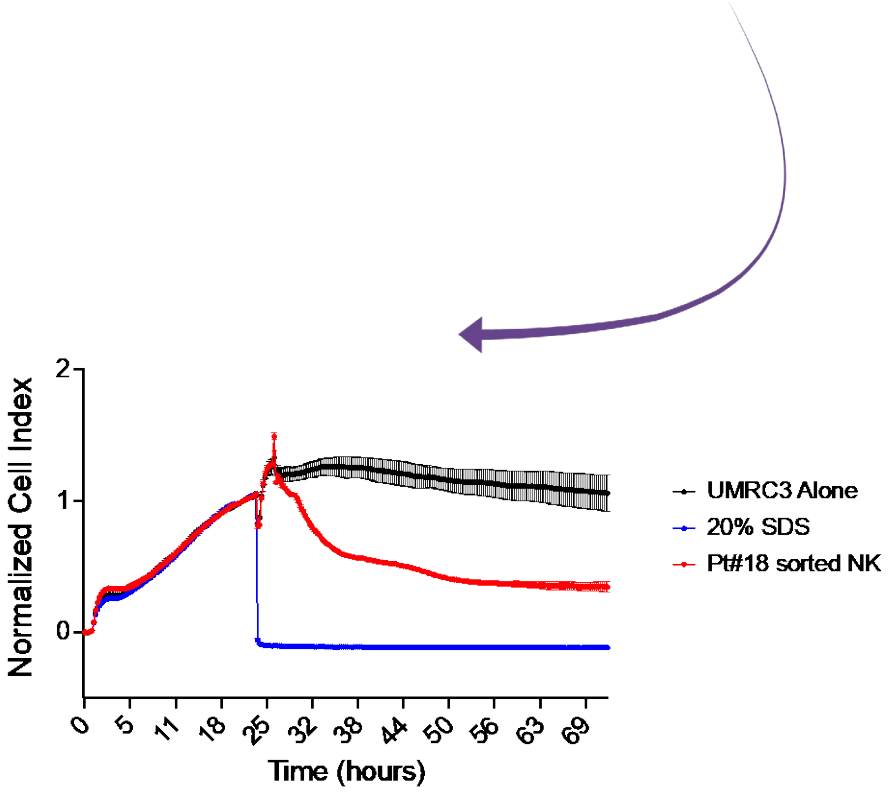
38 year old male with primary refractory stage IV diffuse large B cell lymphoma (DLBCL) 5/2022

- 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 → **Complete remission**

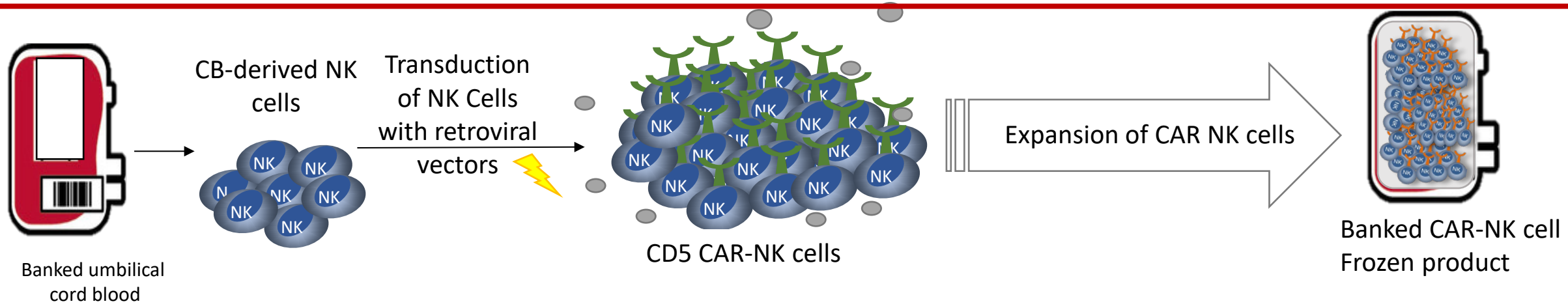
Week 10 post-infusion

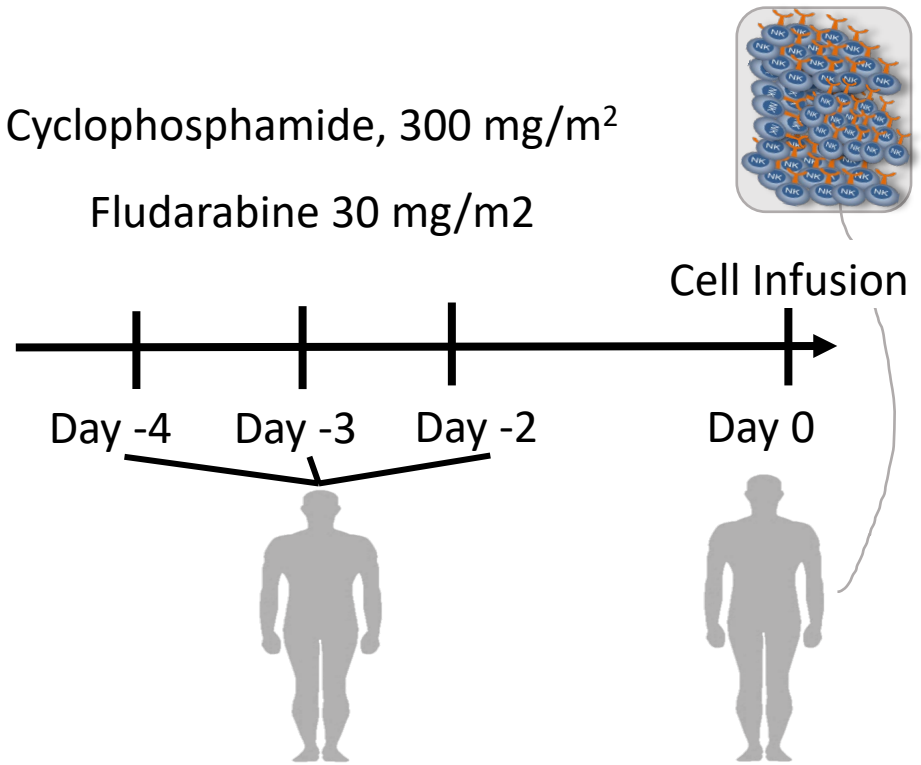






Clinical translation: Phase I/II clinical trial evaluating the safety and efficacy of CD5 CAR-NK cells for cancer immunotherapy



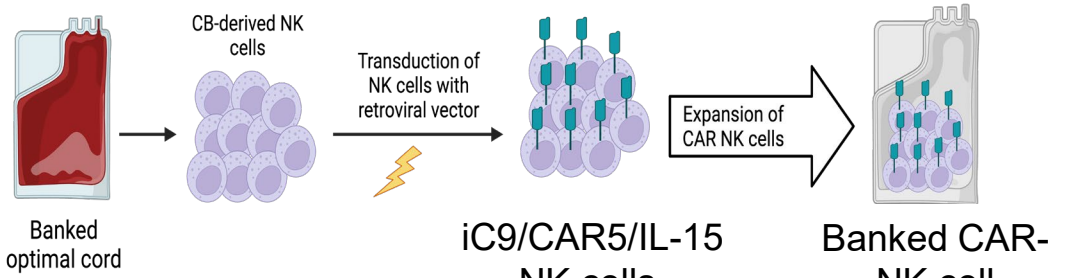


4 dose levels.
40x10e6,
120x10e6,
400x10e6,
1.2x10e9.

Phase I/II clinical trial:

- CD5+ hematologic malignancies (T cell lymphomas/leukemias, MCL, CLL)
- Primary objectives: safety, optimal cell dosing, efficacy
- Secondary objectives: response rates, OS, PFS, persistence of CAR-NK cells, comprehensive correlative studies

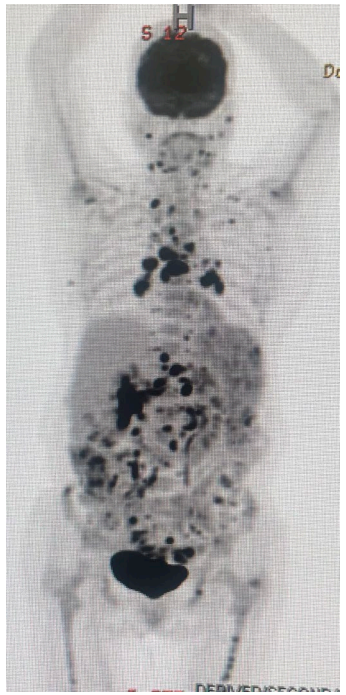
Response to off-the-shelf CD5 CAR-NK cells



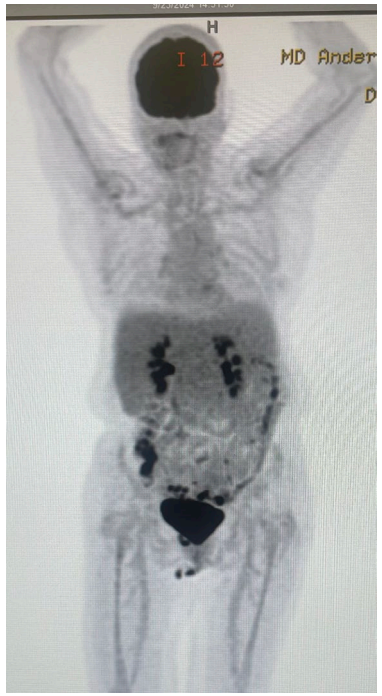
74 yr old female with T-cell lymphoma

Disease failed to respond to 5 different type of chemotherapy

Pre-infusion



D30 post-infusion



Responses observed in **2 / 3** patients

Strategies to enhance adoptive NK cell antitumor potential

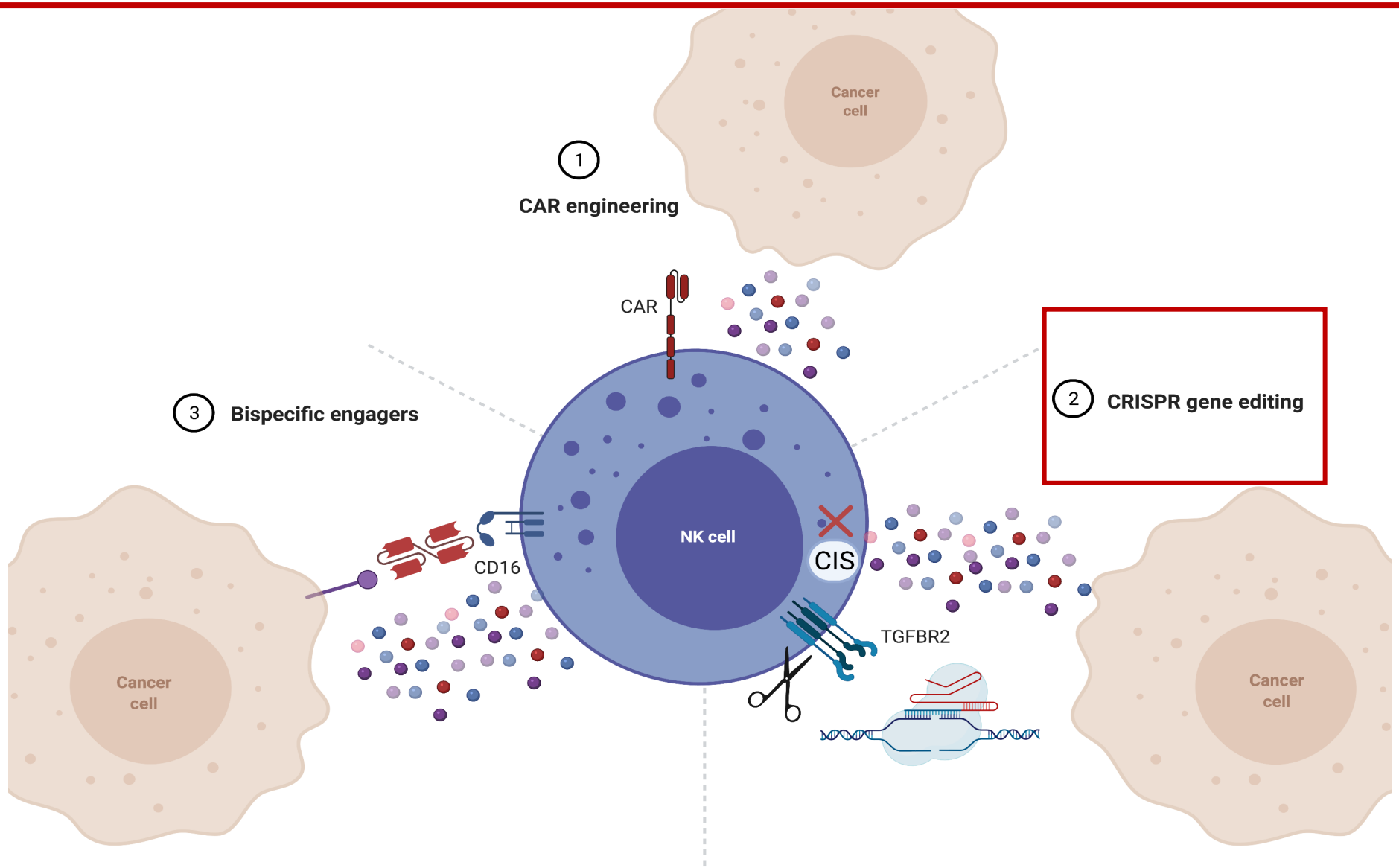
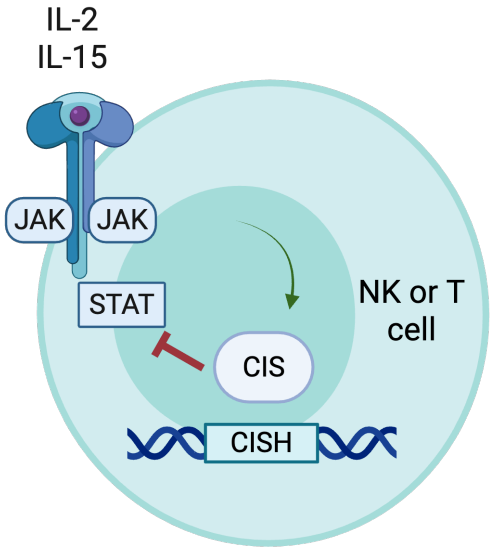


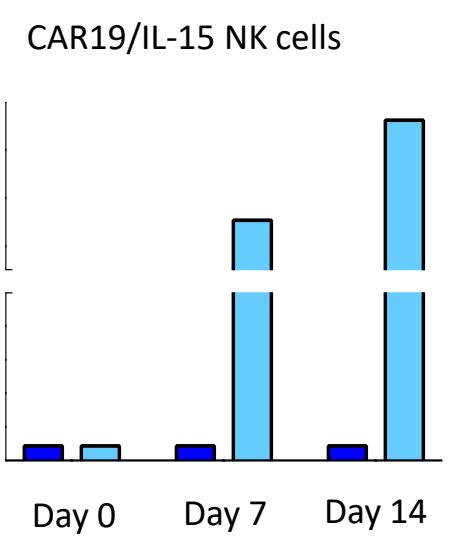
Figure made in Biorender

Deletion of CIS enhances the fitness and anti-tumor activity of CAR-NK cells

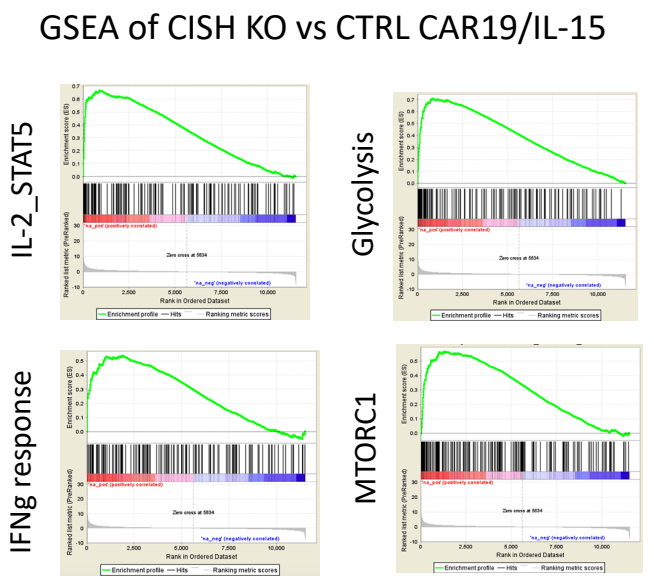
A



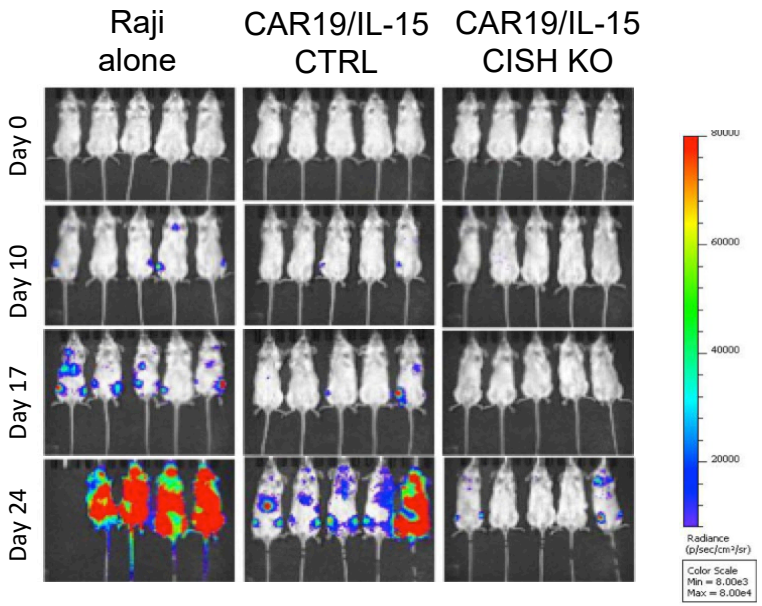
B



C

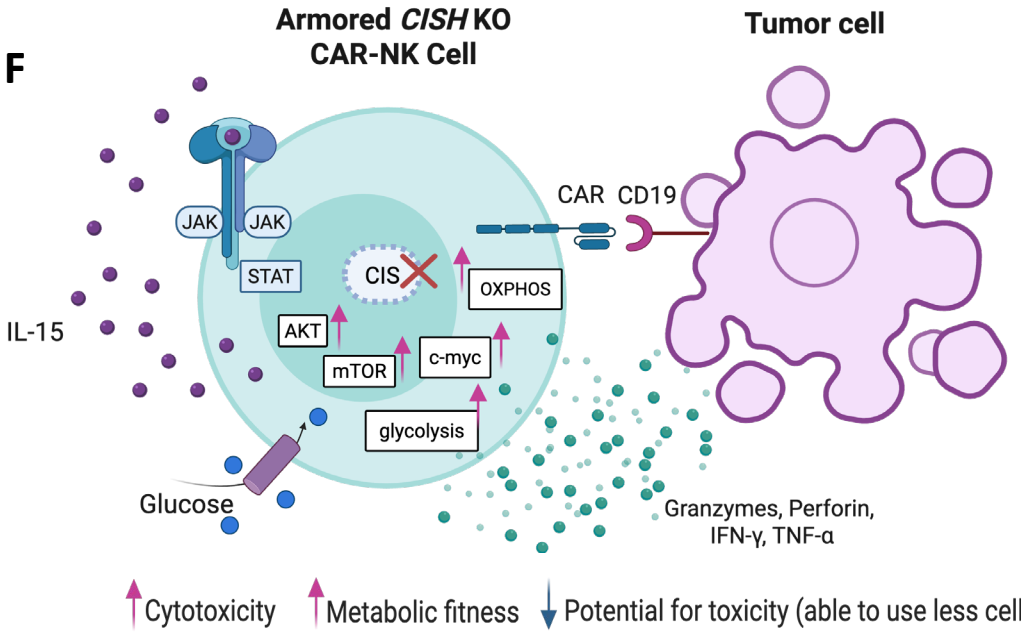


D



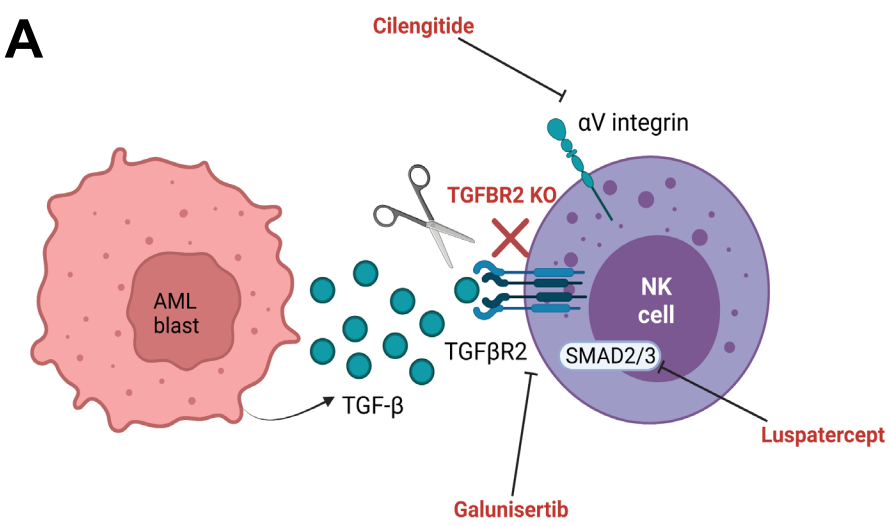
E

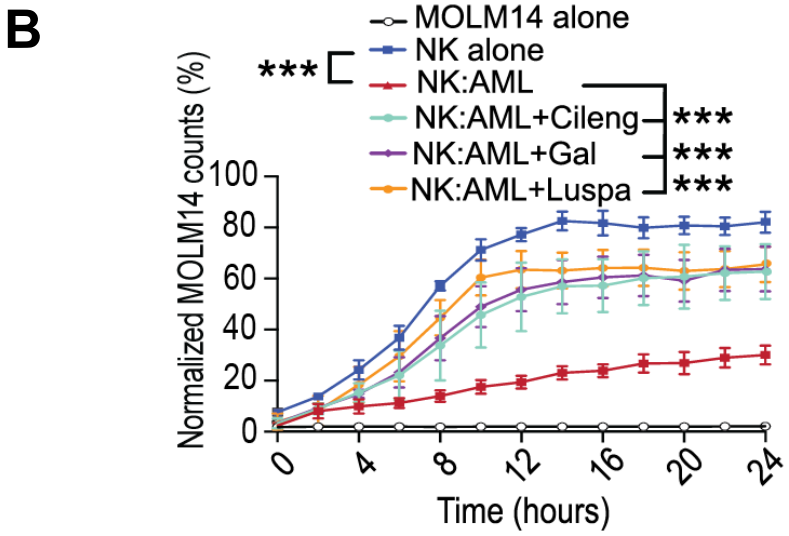
F

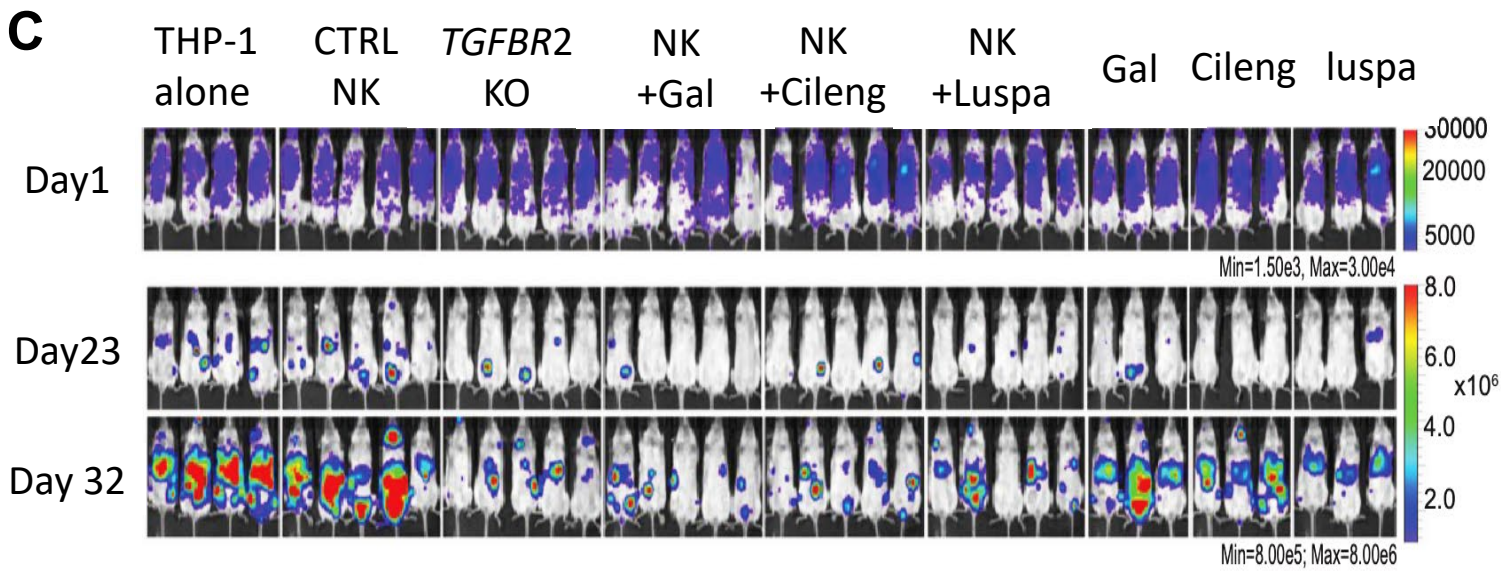


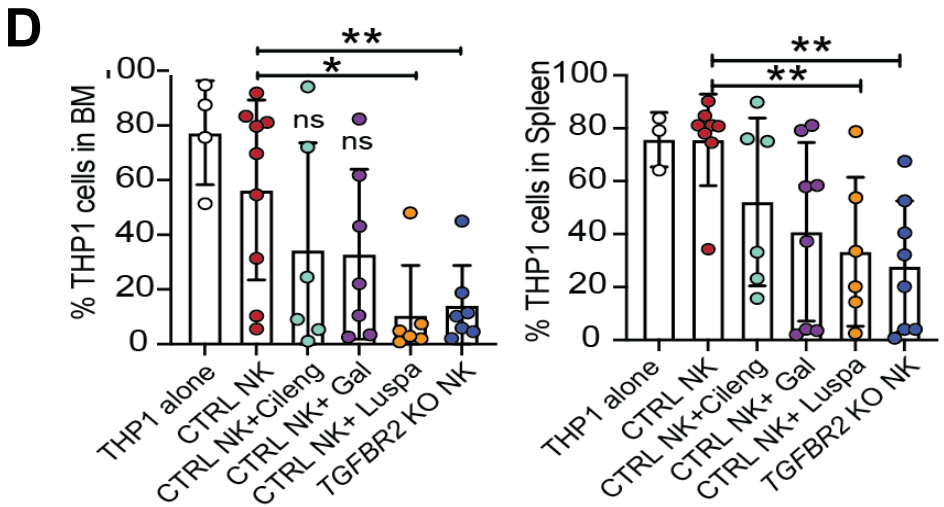
Daher et al & Rezvani. Blood 2021. 137(5):624-636

TGF-β pathway inhibition can prevent AML induced NK cell dysfunction



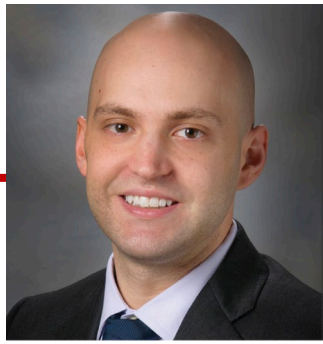




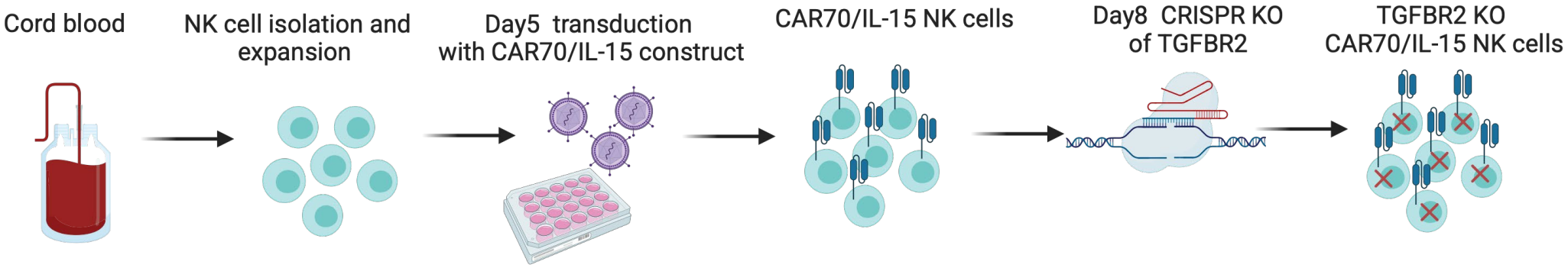


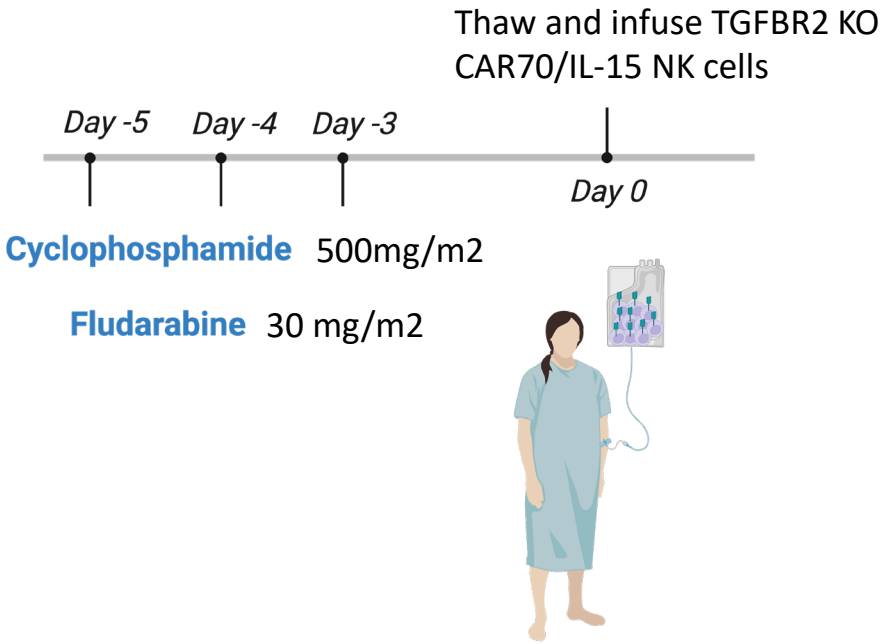
Kumar, Singh & Daher et al. Science Translational Medicine, 2024.

Off-the-shelf *TGFBR2* KO CAR70/IL-15 NK cells for the treatment of relapsed/refractory AML (IND 31339, Protocol 2024-1967)



Nick Short, MD





Dose Level	Cryopreserved Transduced Cells Dose for Treatment
Dose Level -1	1.3×10^7
Dose Level 1	4×10^7
Dose Level 2	1.3×10^8
Dose Level 3	4×10^8

Conclusions

- Cord blood is an attractive allogeneic source of NK cells
- NK cells are promising alternative vehicles for cell therapy
- Various strategies can be employed to enhance the efficacy of adoptive NK cell therapy including CAR engineering and CRISPR gene editing
- Multiple ongoing trials testing the safety and efficacy of various NK cell engineered products against various malignancies

Institute for Cell Therapy Discovery and Innovation
Katy Rezvani

Stem Cell Transplant
Elizabeth J. Shpall
Richard Champlin
David Marin

Faculty
Sairah Ahmed
Gheath AlAtrash
Amin Alousi
Paolo Anderlini
Borje Andersson
Qaiser Bashir
Stefan Ciurea
Chitra Hosing
Jin Im
Partow Kebriaei
Issa Khouri
Rohtesh Mehta
Jeff Molldrem
Yago Nieto
Amanda Olson
Betul Oran
Uday Popat
Muzaffar Quazilbash

Research Nurses:
Bethany Overman
Glenda Woodworth
Becky Mc Mullin

SCT staff

MD Anderson Cord Blood Bank
Jeff Wison
Erin Eaton CB staff

MD Anderson CEG GMP Facility
Mariam Ammari
Sheetal Rao
Indresh Kaur
Enrique Alvarez
Daniel Esqueda
Suzanne Dworsky
GMP Techs

Leukemia Department
Hagop Kantarjian
Guillermo Garcia Manero
Hussein Abbas
Simona colla
Nick Short

Genomic Medicine Department
Kunal Rai
Anand Singh

Bioinformatics group
Huihui Fan
Ken Chen
Vakul Mohanty
Merve Dede
Jinzhuang Dou

Lab colleagues
Rafet Basar
Nadima Uprety
Sunil Acharya
Mayra Shanley
Bijender Kumar
Ye li
Ana Karen Nunez Cortes
Maliha Munir
Madison Moore
Silvia Tiberti
Paul Lin
Bin Liu
Pinaki Banerjee
Alexander Biederstadt
Silvia Tiberti
Mayela Mendt
Bingqian Hu
Francia Reyes Silva
Elif Gokdemir
Enli Liu
Sonny Ang
Mecit Kaplan
Junjun Lu
Sufang Li
Xingliang Guo
Jiang Xin Ru
Luis Feliciano Muniz
Gary Deyter

Previous lab colleagues
Lucila Kerbauy
Francesca Lim

DKMS
WE DELETE BLOOD CANCER

sitc
Society for Immunotherapy of Cancer

NCI R01- CA280827-01

SITC Amgen grant

Andrew Sabin Foundation

MD Anderson MDS/AML Moonshot
MD Anderson Lymphoma Moonshot