What Adult Transplanters can Learn from Pediatric Transplanters and Vice Versa

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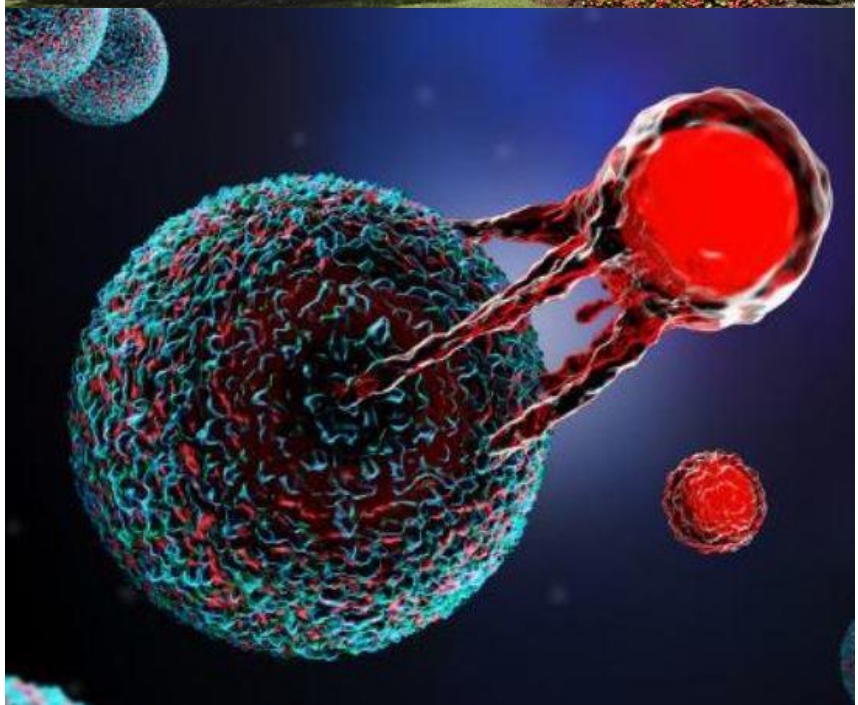


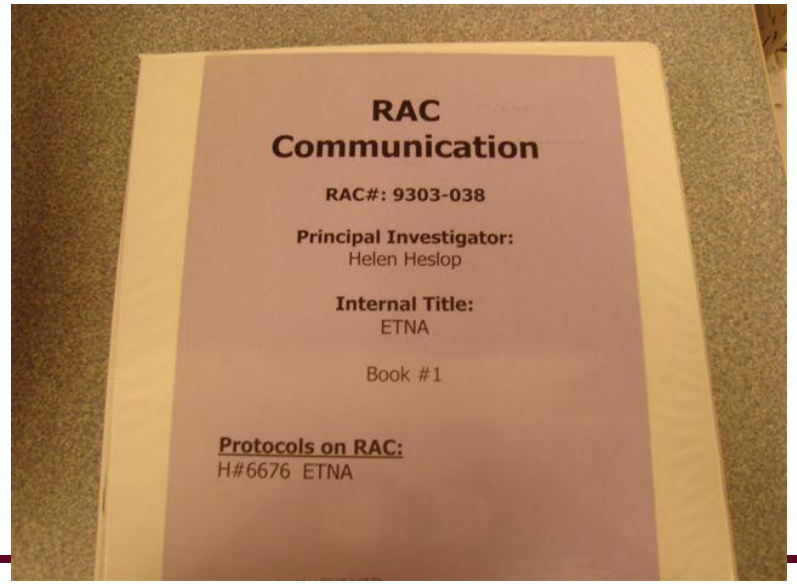
Disclosures

Catherine Bollard, M.D., FRACP, FRCPA.

- Co-Founder: Catamaran Bio (completed)
- SAB Member: Minovia TX Ltd
- Board of Directors: Cabaletta Bio
- Stock/ownership: Repertoire Immune Medicines
- Royalties: Cellmedica
- Honoraria: Novartis
- DSMB: SOBI (term completed)
- Patent applications for TAA-T and CAR-TA

sitc 1985 35th ANNIVERSARY 2020

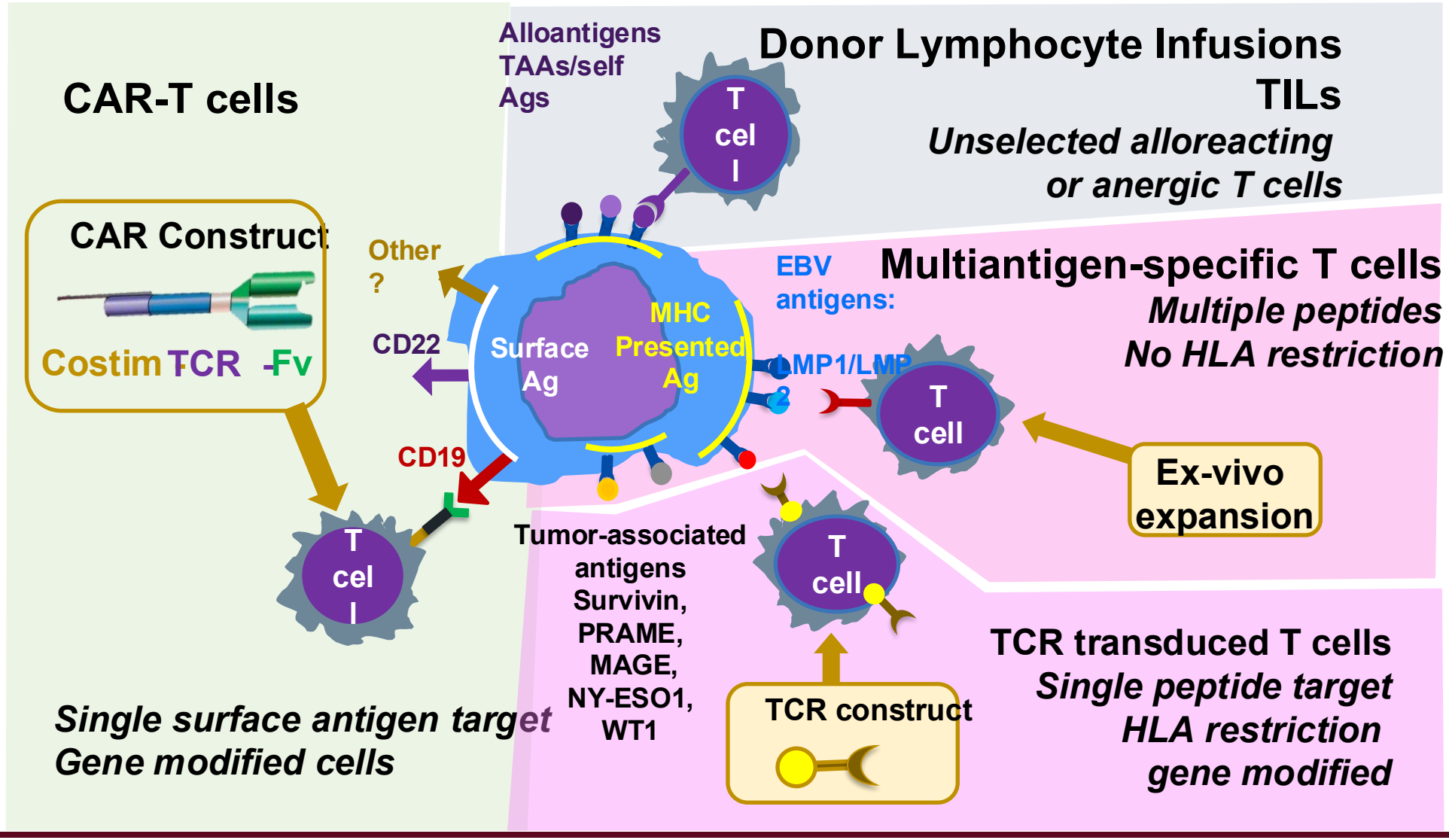
1985: Tumor Infiltrating lymphocytes (TILs)



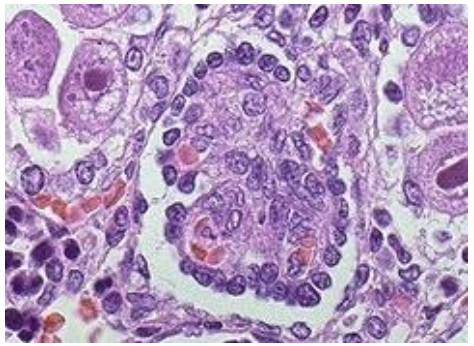
1993: Virus specific T cells (VSTs)

GW

T Cell Effectors

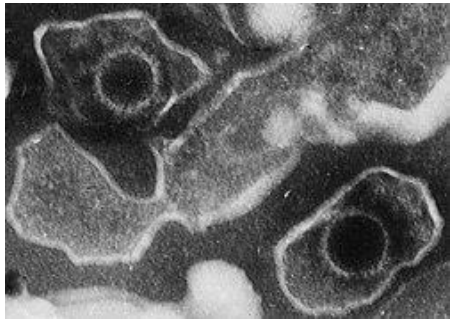


Development of Virus-specific T cell Immunotherapy



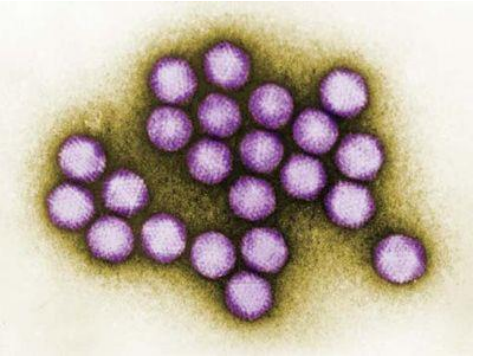
1992: CMV-specific T cells developed with CMV infected fibroblasts (Riddell *et al*)

1995: Epstein-Barr virus-specific T cells produced with EBV-LCL for Pediatric PTLD (Heslop *et al*)

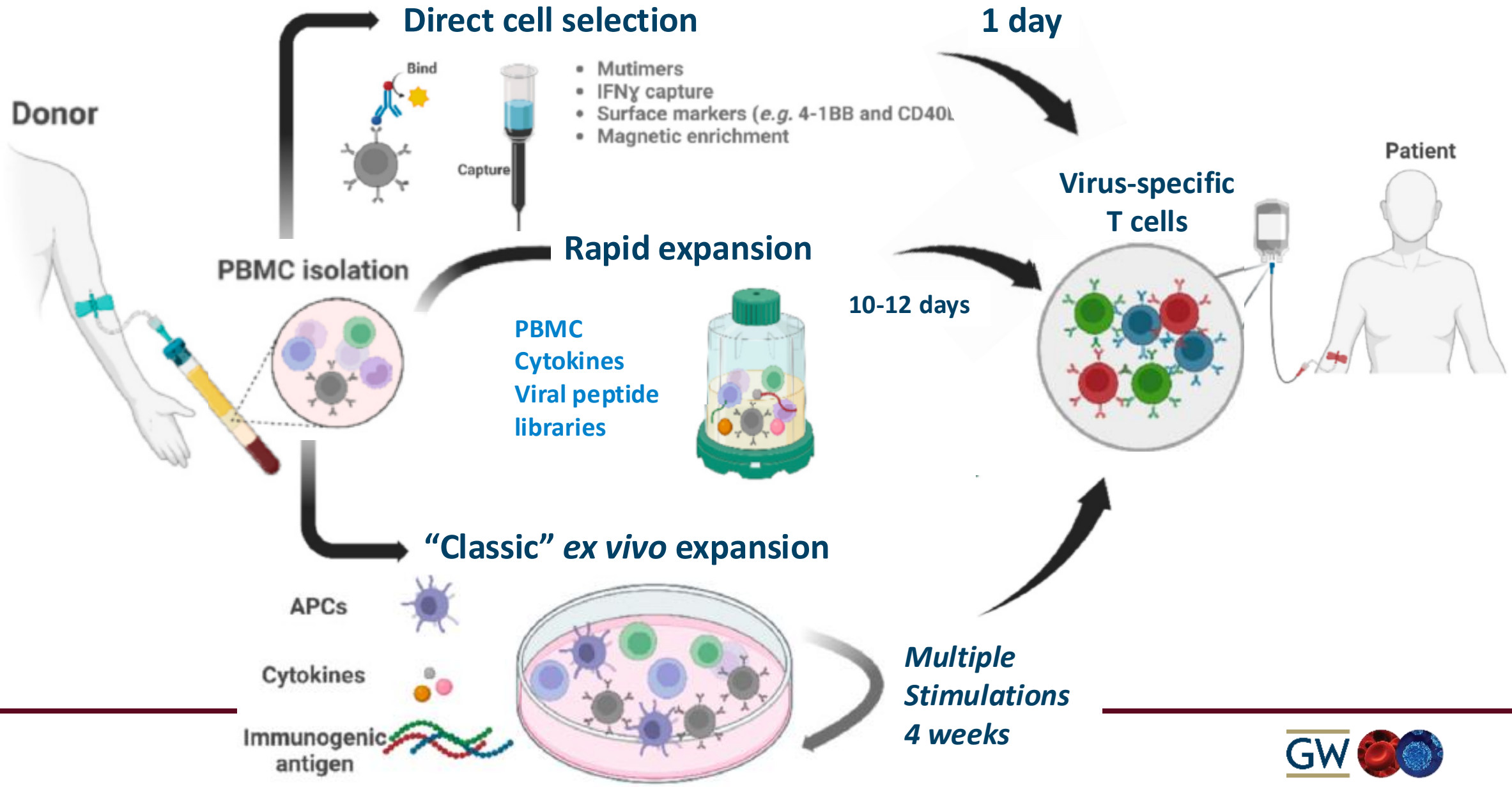


2006: Production of CMV/EBV/Adenovirus specific T cells using Ad5f35-pp65 chimeric vector (Leen *et al*)
2007: Off the shelf VSTs (Haque et al)

2012: Production of rapid VSTs using peptide libraries (Gerdemann *et al*)
2013: Clinical use of Cord Blood derived VSTs (Hanley *et al*)
2017: CD137 selected products (Gottlieb, Blyth *et al*)

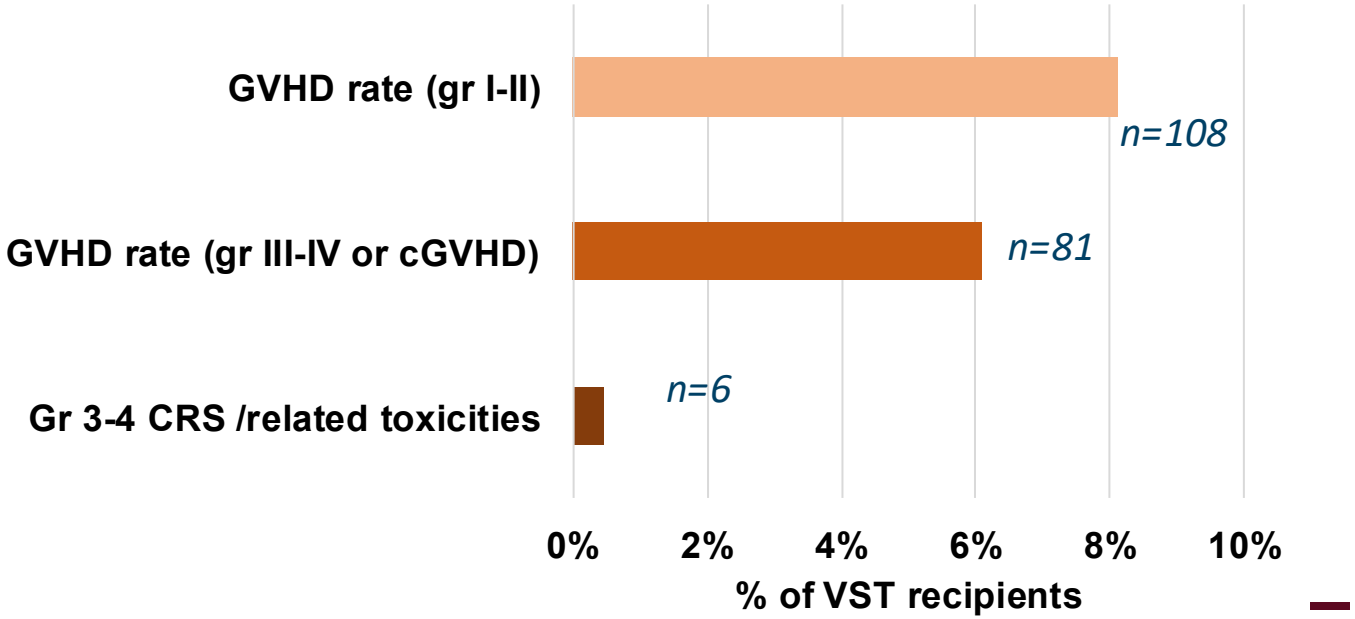


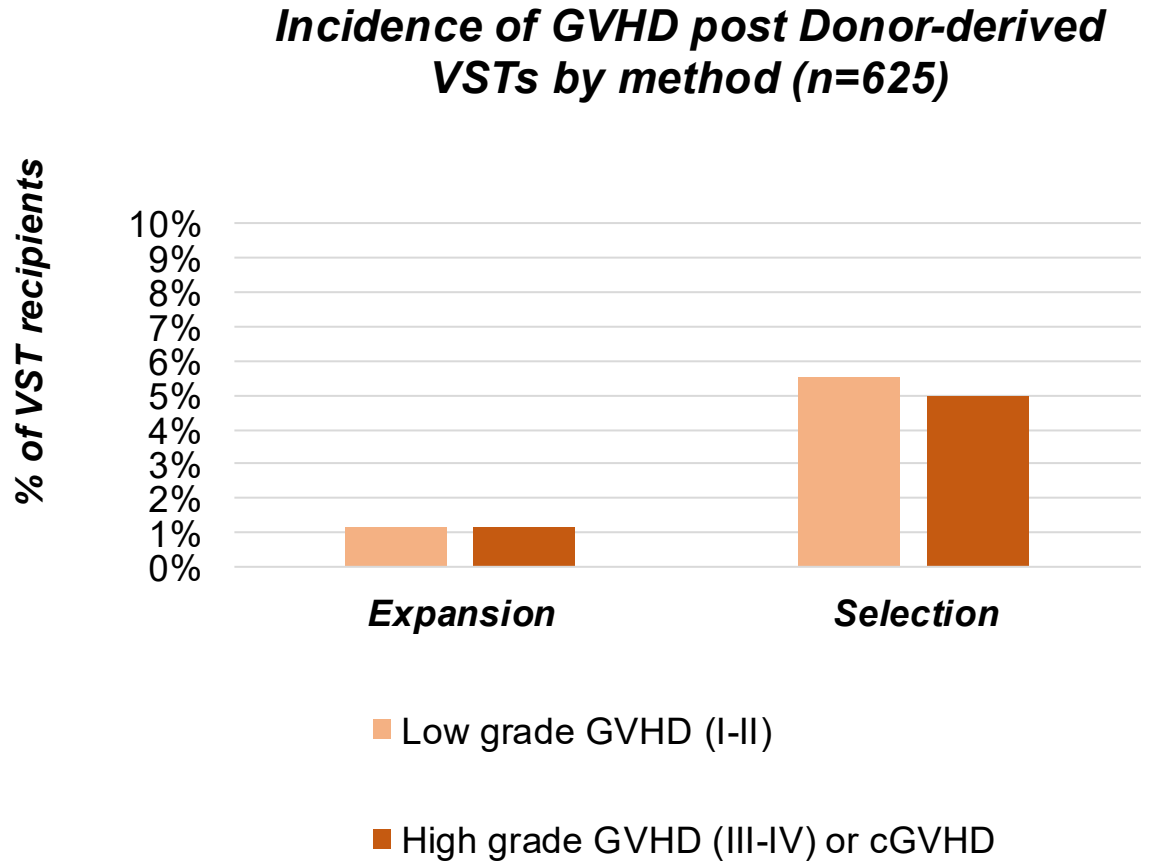
Production of Virus-specific T cells



VSTs have minimal related toxicity

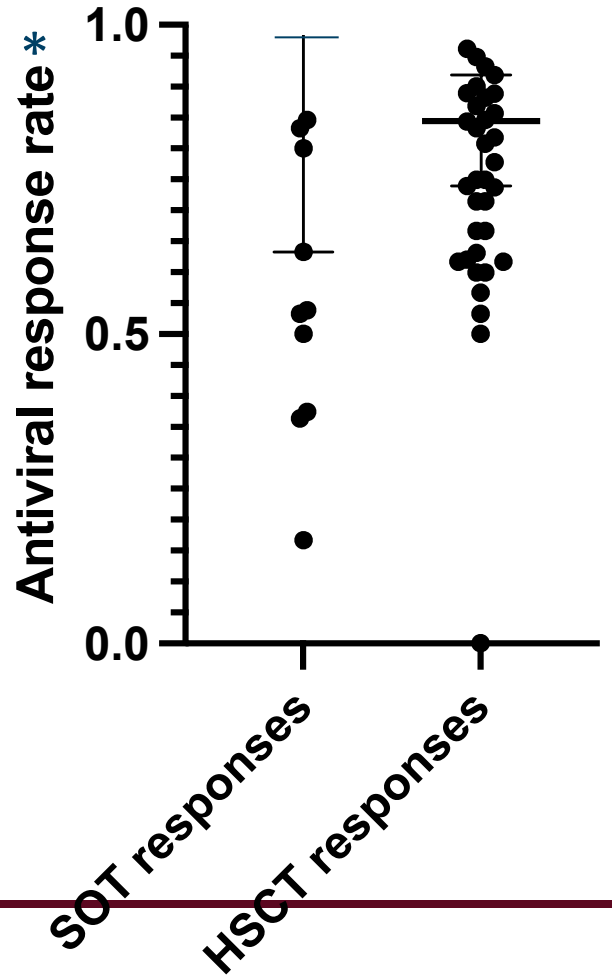
- *De novo* GVHD is uncommon, even with mismatched VST
- Cytokine release syndrome(CRS): <1% of VST infusions



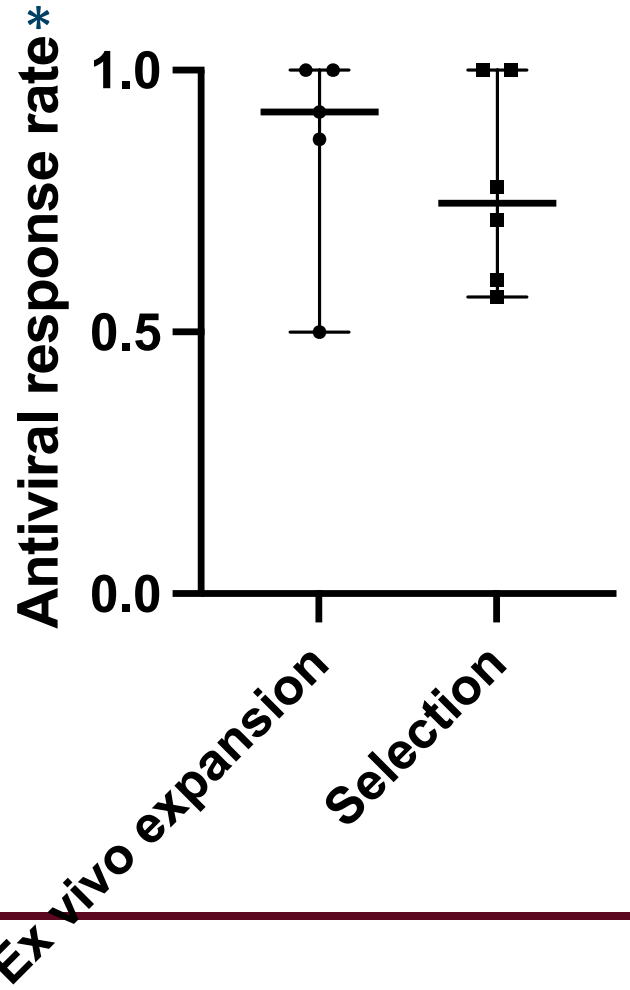


VSTs: effective in multiple settings

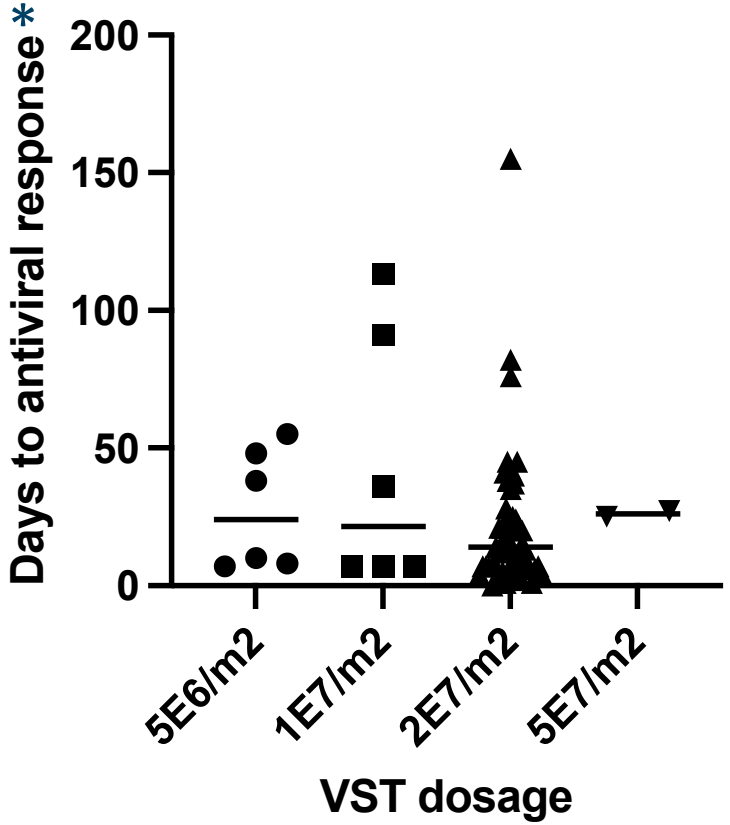
Efficacy in SOT versus HSCT recipients



Efficacy of expanded vs selected VSTs (n=625)



VST efficacy by dose (n=67)



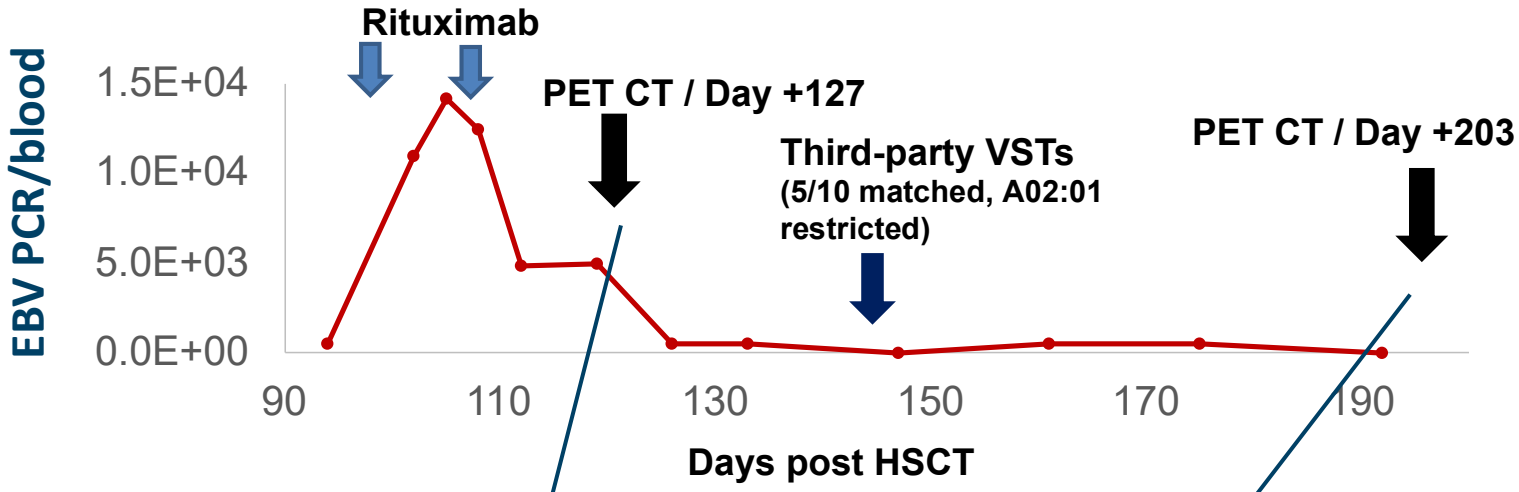
Response definitions:** sustained improvement in viral load and symptoms. - **Keller et al, unpublished data

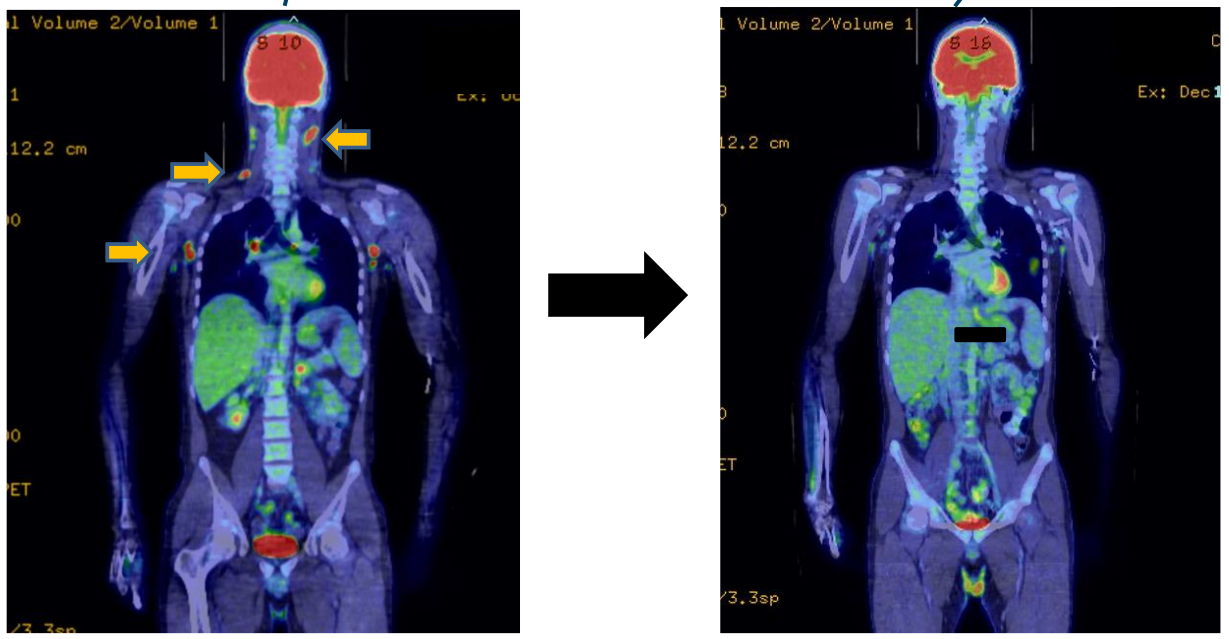
Select Third party VST Clinical Trials

Application	Study	Target	n	Serious adverse events	Clinical Results
SOT	Haque et al. 2007	EBV	33	None	52% PR/CR
HSCT	Leen et al. 2013	CMV, EBV, Adv	50	8 cases GvHD (2 *de novo*)	74% CR/PR
HSCT	Withers et al. 2017	CMV, EBV, Adv	30	2 cases of de novo GVHD	93% CR/PR
HSCT	Galletta et al. 2023	CMV/EBV/Adv/ BKV	63	2 cases of GVHD	63% CR/PR
HSCT	Pfeiffer et al 2023	CMV/EBV/Adv/ HHV6/BKV	58	1 with gr3 GVHD, 2 with gr2 GVHD	95% CR/PR overall
HSCT	Prockop et al 2023	CMV	67	1 de novo GVHD	64% CR/PR
SOT	Wistinghausen et al 2024	EBV	15	3 episodes of graft rejection, none likely VST related	70% response (ND), 20% (r/r disease)
HSCT/SOT	Nikiforow et al 2024	EBV	26	1 case Gr3 GI-GHVD	65% CR/PR overall
HSCT	Keller et al 2024 x2	CMV, EBV, Adv	51	CRS in 1, TA-GVHD in 1 Neurological disease in 2 No de novo GVHD	65% CR/PR overall

Third party VSTs Effectively Treat EBV PTLD

19 yr old with EBV-PTLD Post BMT

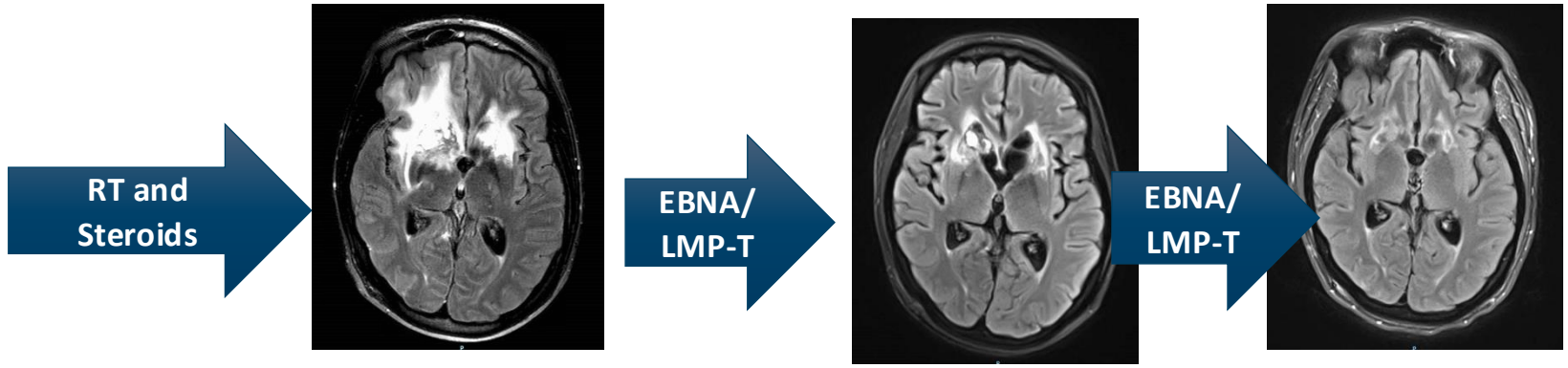




Keller *et al Nat Comm* 2024

CNS Disease Successfully Treated with 3rd party EBV-directed T cells

87% CR/PR after SOT or BMT (MSKCC, BCM, CNMC)



Prockop et al, JCI 2020
Bollard et al, ASHI 2017 Keller et al, ESID 2017

Pakakasama S et al, Transplantation. 2004

Future Considerations
Third Party Virus-specific T cells

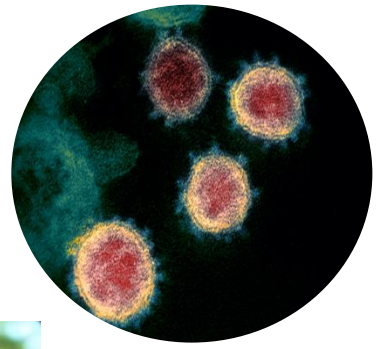
- **Multiple academic studies in single/small/multi center and in cooperative group / consortium settings for post BMT/SOT patients – (**PBMTC/PIDTC: Keller et al, Nature Com 2024 and COG: Wistinghausen et al, Blood Adv 2024 and BMT-CTN: in progress)

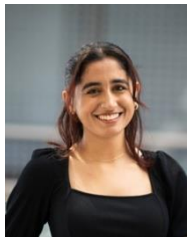
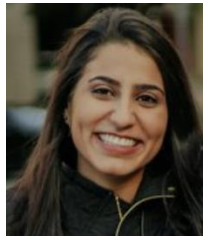
- **Third party and donor-derived virus (including EBV) specific T cells (VSTs) effective in clearing Viral disease after BMT (approx 70% overall)** (Keller and Bollard, Blood 2020 and Keller et al, Nat Communications 2024)

- EMA approved Atara product **Ebvallo™ (tabelecleucel) for PTLD** → Results from Allovir studies (not EBV alone) stopped for futility

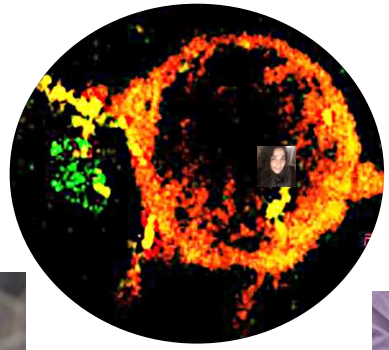
VST Program Goals at CNH

Expanding viral targets

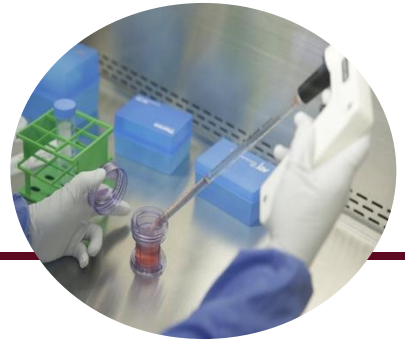
Improving efficacy

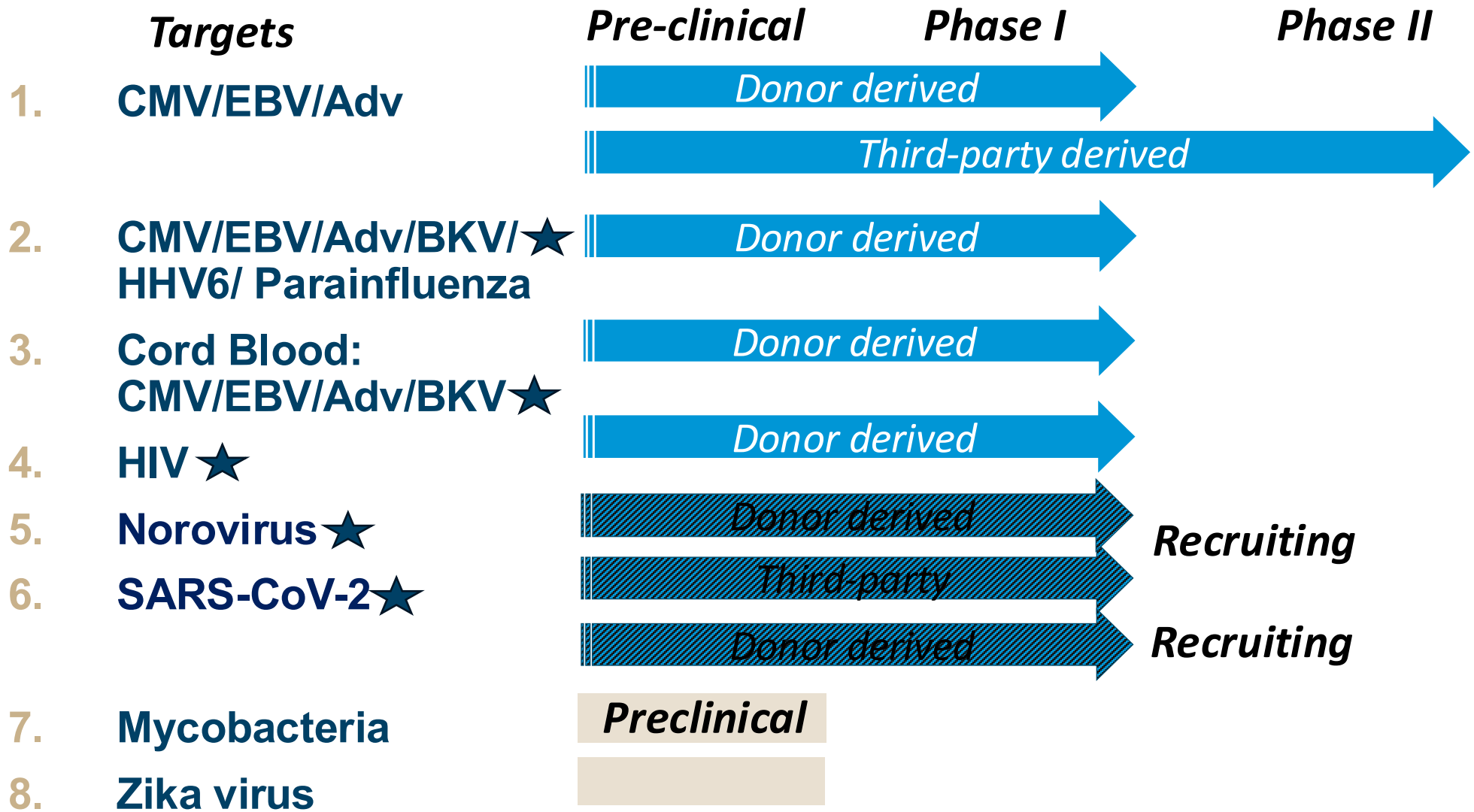


Enhancing Use & Accessibility





Antiviral Pipeline at CNH



★ *First in human studies*

Can we Leverage the Antigen Specific T cell Platform Beyond Viruses?

Antigen specific T Cells - Targeting Tumor associated Antigens (TAA)

Targeting TAAs in Heme Malignancies – The Shortlist

Goswami et al, Leukemia 2014 *Rooney et al, Imm Rev 2014*	AML	CML	ALL	CLL	HL	NHL
WT1	+	+	+			
Proteinase 3	+	+				
PRAME	+	+	+		+	+
RHAMM	+	+	+	+		
Aurora A Kinase	+	+	+			
MAGE	+	+		+	+	+
MPP11				+		
HAGE	+	+				
BCR/ABL	+	+		+		
NY ESO 1		+				+
BMI-1		+		+		
Telomerase	+	+	+	+		
Fibromodulin				+		
Syntaxin				+		
SSX					+	+
Survivin	+	+	+	+	+	+

Use of Donor-derived WT-1 specific T Cells for Acute Leukemia

- 11 patients infused with HLA-A*0201-restricted WT1-specific donor-derived CD8+ T cell clones
- No attributed toxicities/GVHD
- 2 clinical responses
- 3 patients at high risk for relapse remain in CR
- CTLs generated in the presence of IL-21 remained detectable long-term

Studies using WT1 specific T cells generated using overlapping peptides ongoing at MSKCC

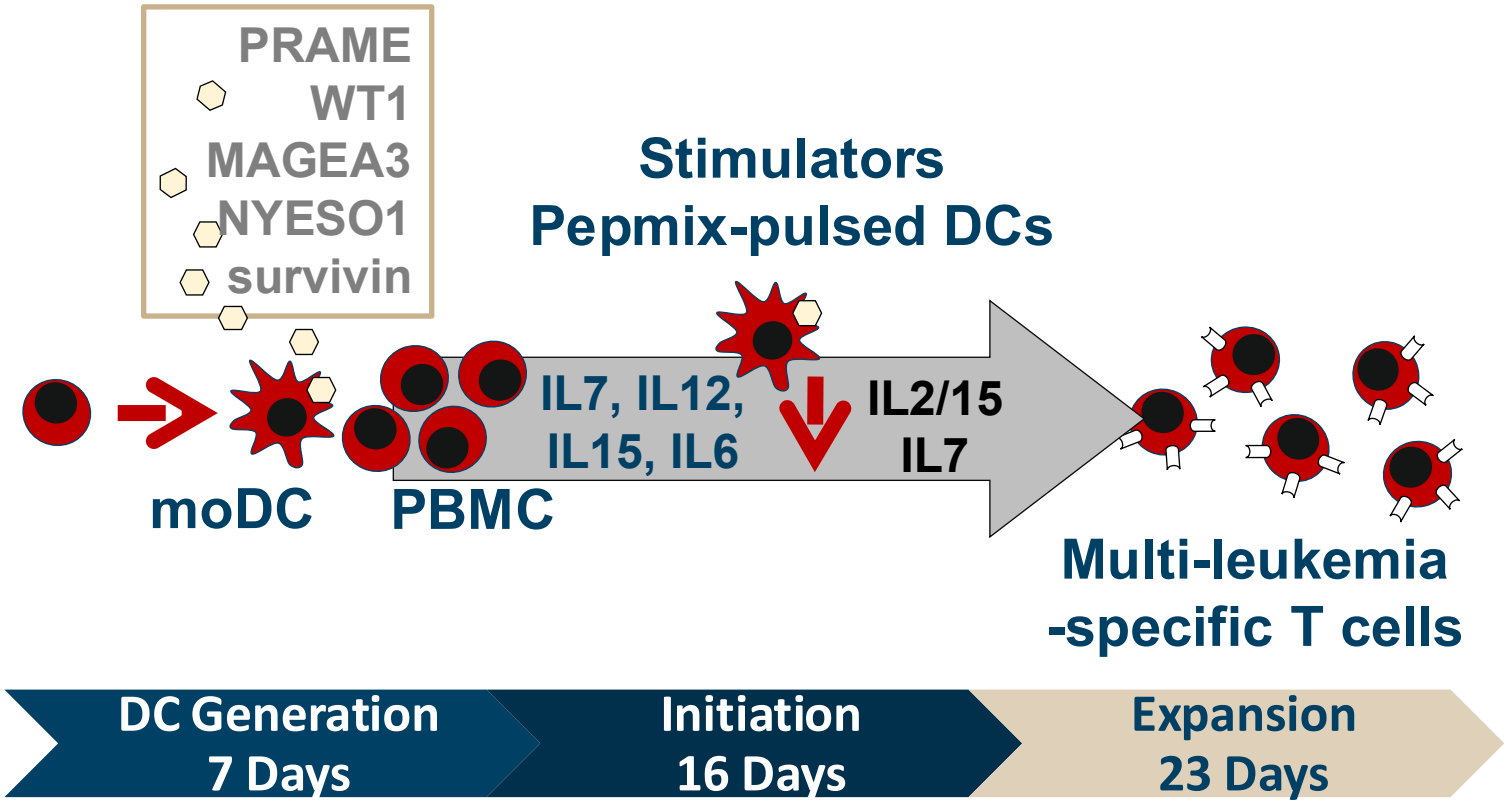
(Koehne and O'Reilly)

Chapuis and Greenberg. ***Sci Trans Med.*** **2013**

Children's National

GW

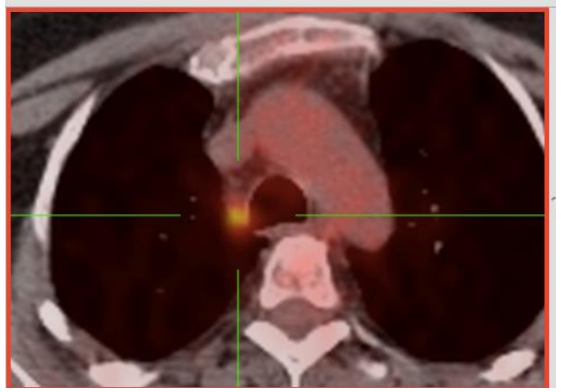
Clinical Use of Multi TAA T Cells for Leukemia and Lymphoma



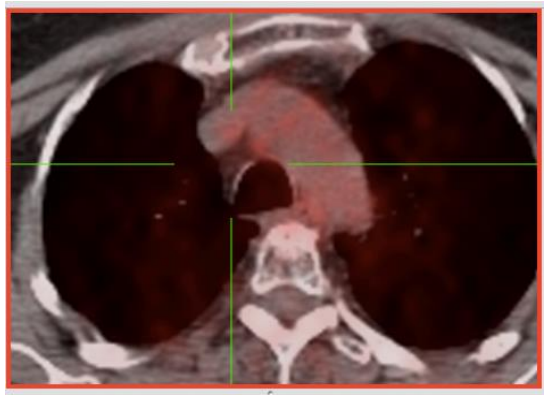
Weber et al, *CCR*. 2013, Weber et al, *Leukemia*. 2013, Gerdemann et al, *Mol Ther.* 2012

Autologous Multi-TAA Specific T Cells Are Safe with Disease Responses in vivo for Lymphoma

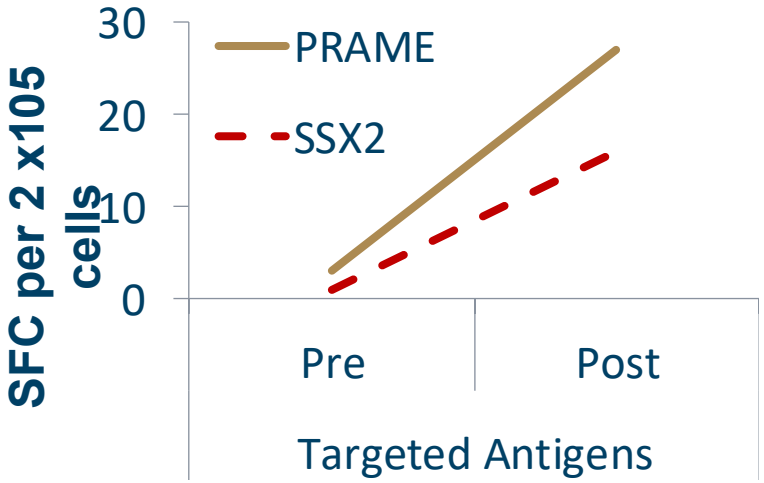
Pre TAA-T



Post TAA-T + RT

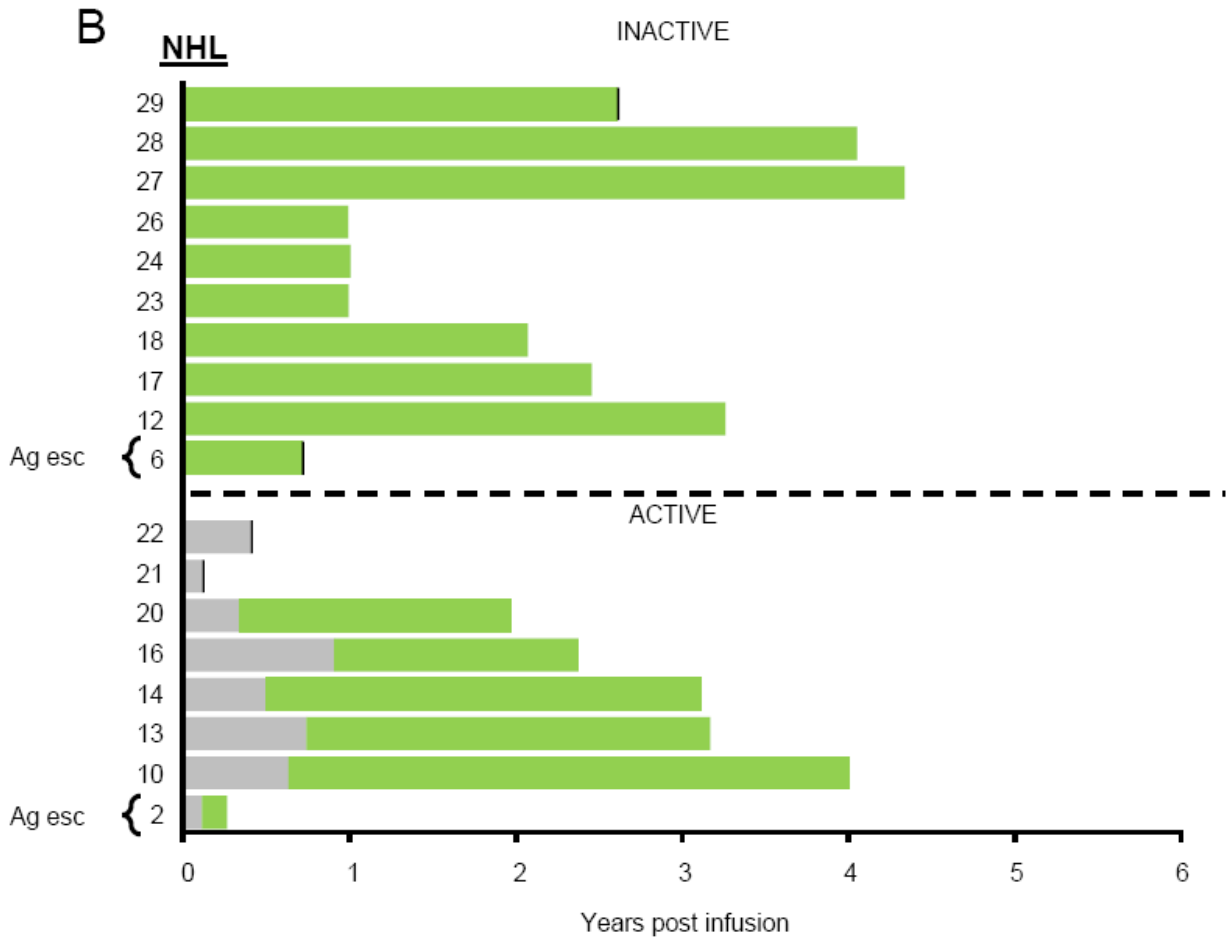


32 patients – med 3 prev Rxs
No lymphodepletion
No toxicity
14 HL – 2/7 CR
18 NHL – 4/8 CR



Vasileiou et al, JCO 2021

Autologous Multi-TAA Specific T Cells Are Safe with Disease Responses in NHL



17 DLBCL
1 ALCL
2 double hit NHLs
in “inactive” group

4 double hit NHLs
in “active” group

Vasileiou et al, JCO 2021

Summary- Use of Autologous TAA-T as Treatment for Relapsed Blood Cancers

- TAA-T cells can be generated from relapsed /refractory patients and NHL and HL (and also solids tumors – ***Hont et al JCO 2019***)
- Autologous TAA-T are safe for patients with relapsed HL/NHL and also solid tumors
- Opportunity for Neoantigen specific –T cells ***(Rood/Bollard labs Nature Comm 2022 and IND 28415)***
- TAA-T cells also show early evidence of efficacy including post nivolumab ***(Dave et, al Blood Adv 2021)***

→ opportunity for further combination therapies such as post BMT?

TAA-T for AML after Allogeneic SCT – Phase I Study established Saftey

TAA: WT1 NyESO PRAME Survivin Dose escalation 5 x 10^6 → 1x 10^7 → 2 x 10^7 /m^2

27 enrolled

20 treated

13 HIGH RISK for relapse ADJUVANT

- 3 CR2/3
- 3 FLT3-ITD
- 3 MDS tAML
- 2 MLL-r
- 1 Ph+
- 1 DNMT3a

8 CCR
4 Relapsed

7 RELAPSE /ACTIVE DISEASE POST SCT >d30

- 5 30-70% blasts in BM
- 2 extramedullary relapse

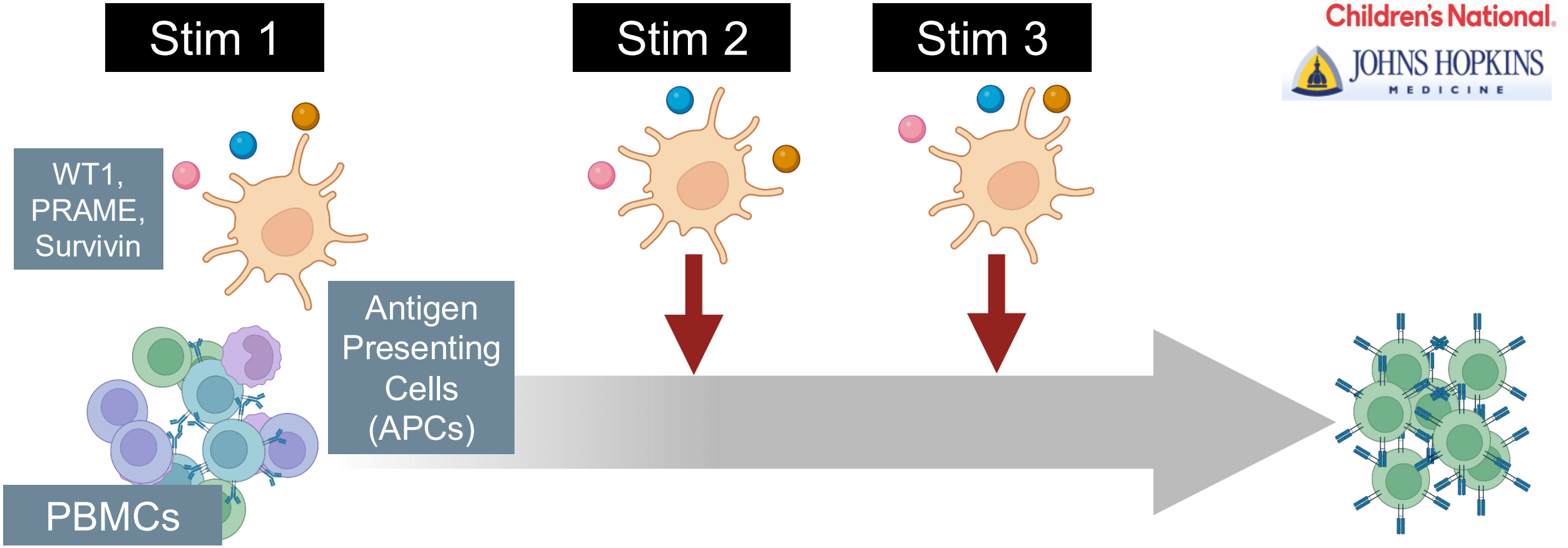
1 CR
1 PR
4 NR
1 NE

Lulla et al , TCT meeting 2019 and Blood 2020

TAA-T At Children's National- Evaluating in a Phase 2 study

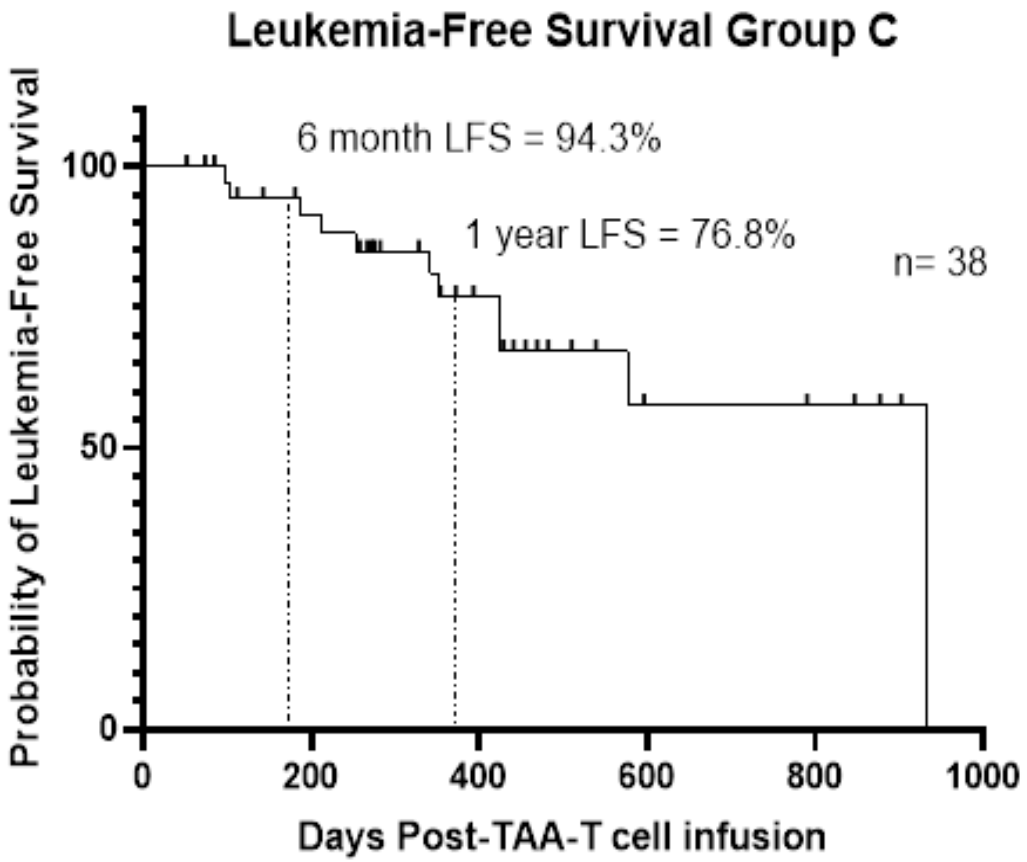
Children's National

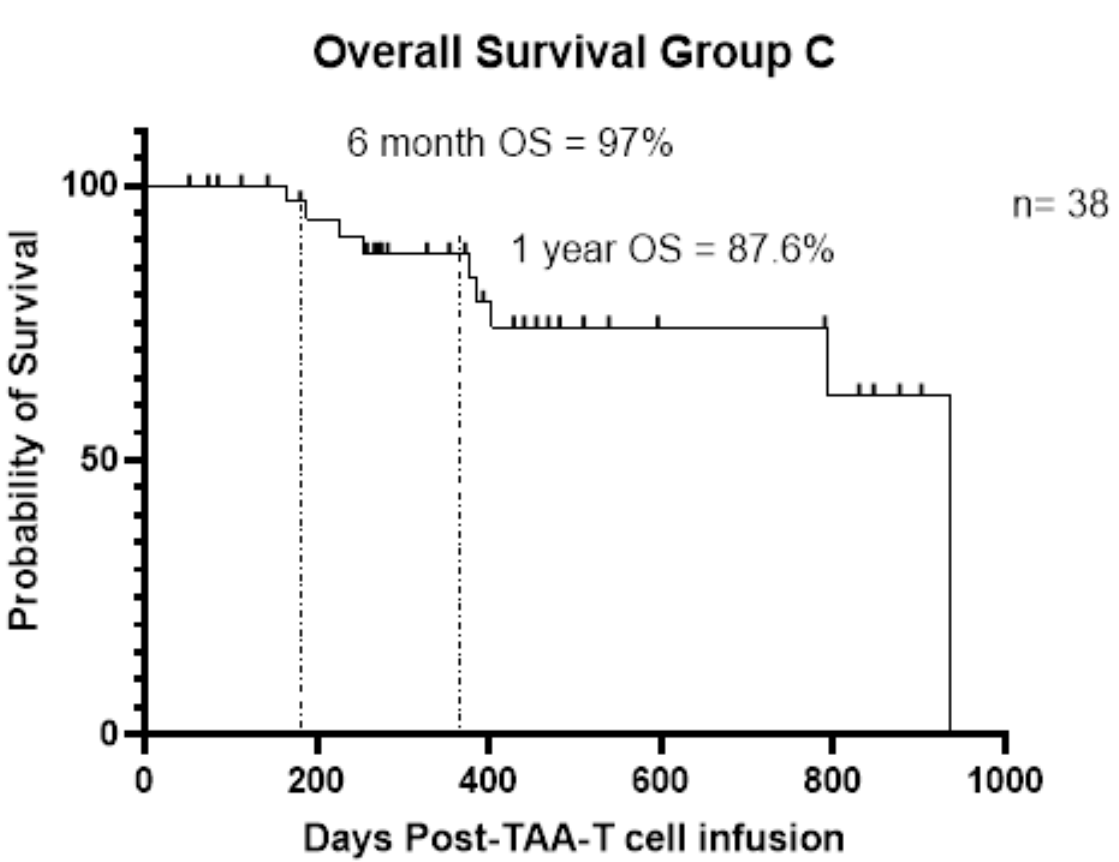
JOHNS HOPKINS MEDICINE



Kinoshita et al, Blood Advances 2022
Unpublished data
Keri Toner and Hannah Kinoshita

Phase 2 study - Post-transplant TAA-T for high-risk AML/MDS may reduce risk of relapse





Hannah Kinoshita

Keri Toner

Kinoshita et al, Blood Advances 2022
Unpublished data
Keri Toner and Hannah Kinoshita

Primary Endpoint Based on improving historical data: >40% LFS at 1 year

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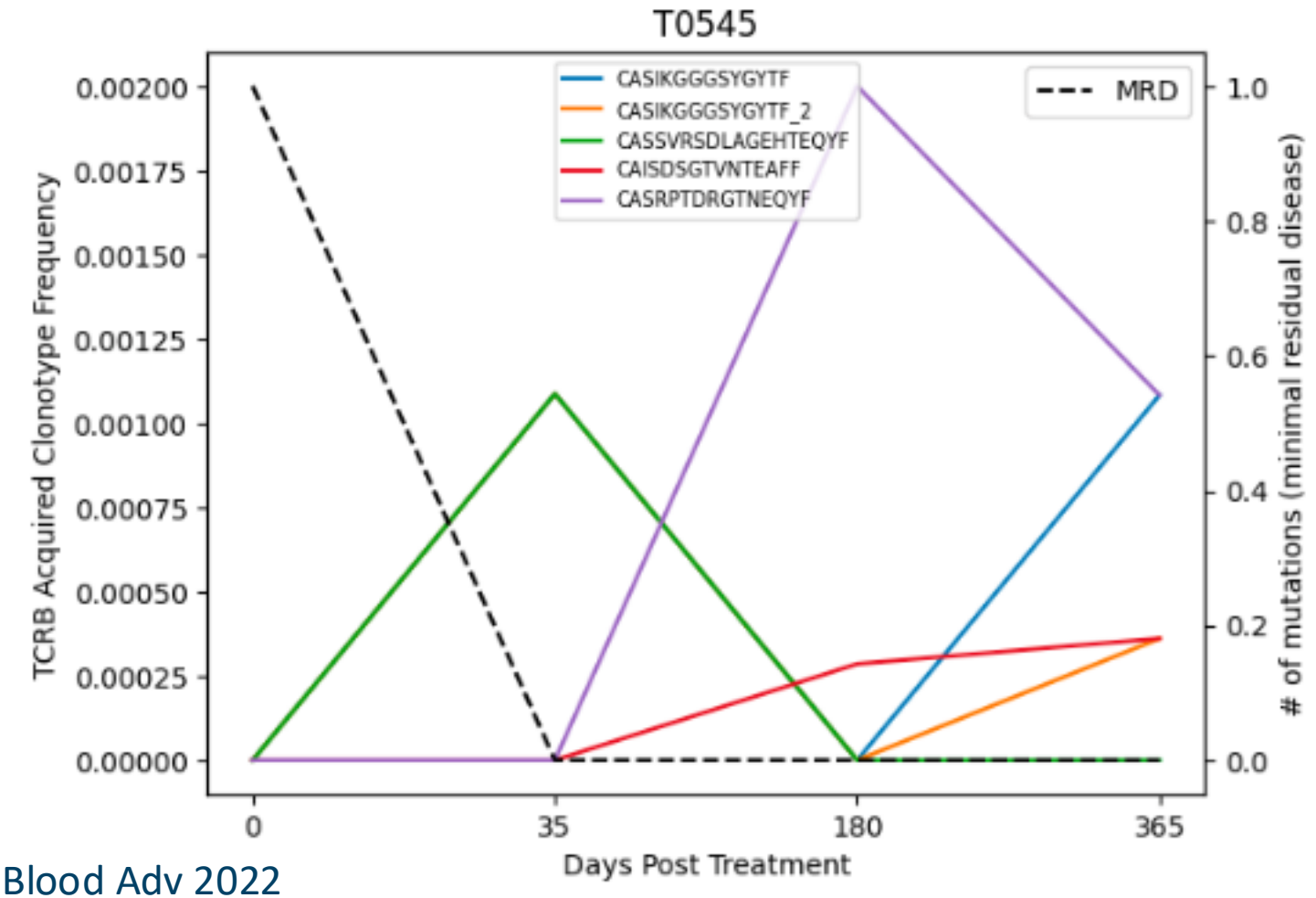
Expansion of unique TCR clonotypes correlates with MRD-level disease response



Kinoshita and Cooke – Blood Adv 2022

And Unpublished data
Keri Toner and Hannah Kinoshita

Summary- Antigen Specific T cells post BMT

- TAA-specific T cells are safe in patients with high-risk hematologic malignancies (leukemia and lymphoma) post transplant** ***(Naik et al, Blood 2022)***
  - Lower risk of GVHD compared to second BMT or DLI
  - No CRS or neurotoxicity seen in this cohort
- Persistence of T cell receptor clones is demonstrated in long term survivors
- More patients required to be enrolled on Phase II Arm to evaluate whether there is an impact on PFS post BMT* (no pharma interest ☹)
- Opportunity for Off the Shelf use in solid tumors? **(NCT05238792)**
- **Opportunity to combine with CAR-T**? (with VSTs ***Cruz et al, Blood 2013***)

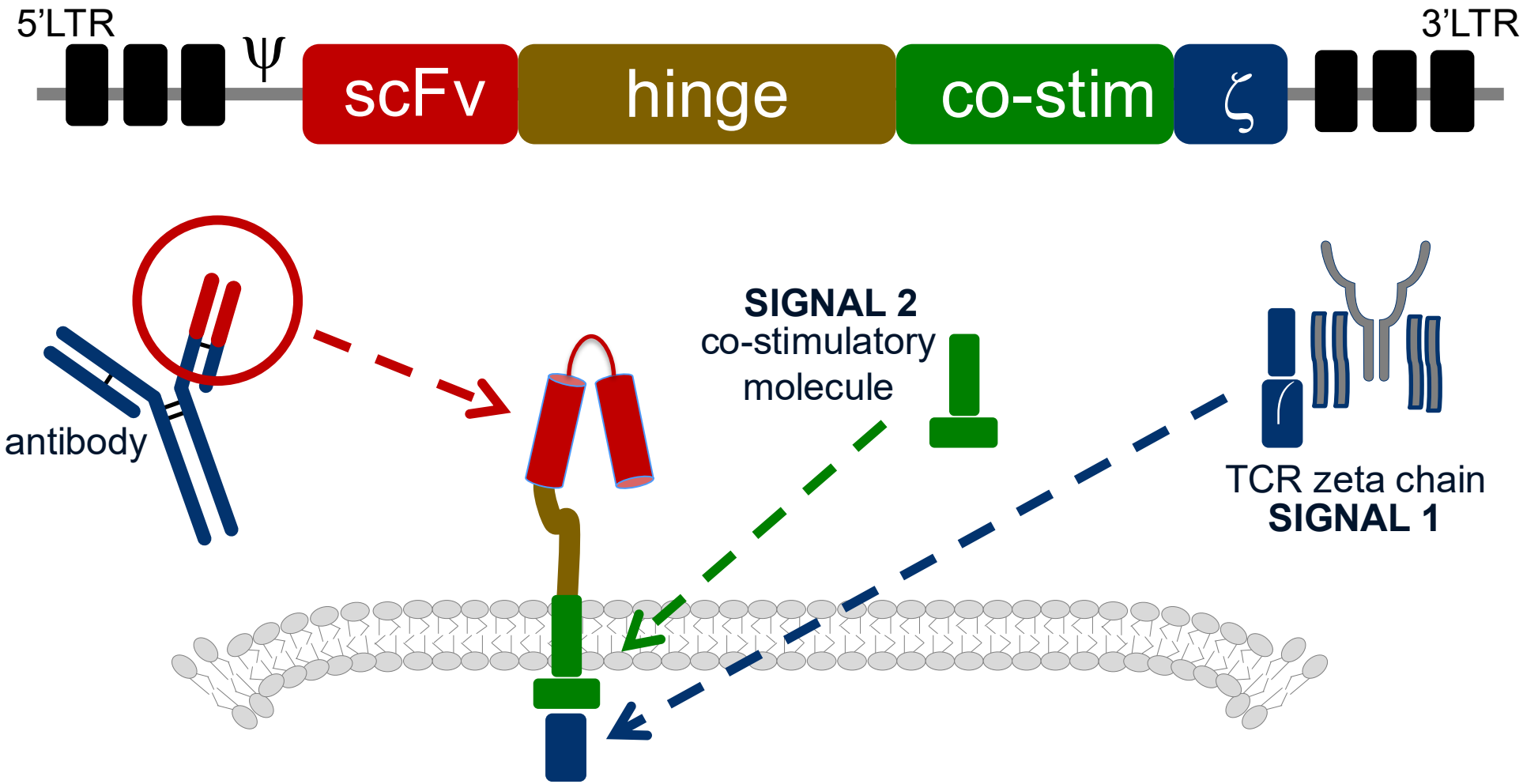
*Funded by: 1 P01 CA225618-01A1 and technology licensed to Mana Therapeutics
**Similar findings from BCM studies Naik et al, Blood 2022

Children's National GW

Chimeric Antigen Receptor (CAR) T cells

3: CAR T cells

Designing a Chimeric Antigen Receptor



Redirecting the Specificity of T Cells

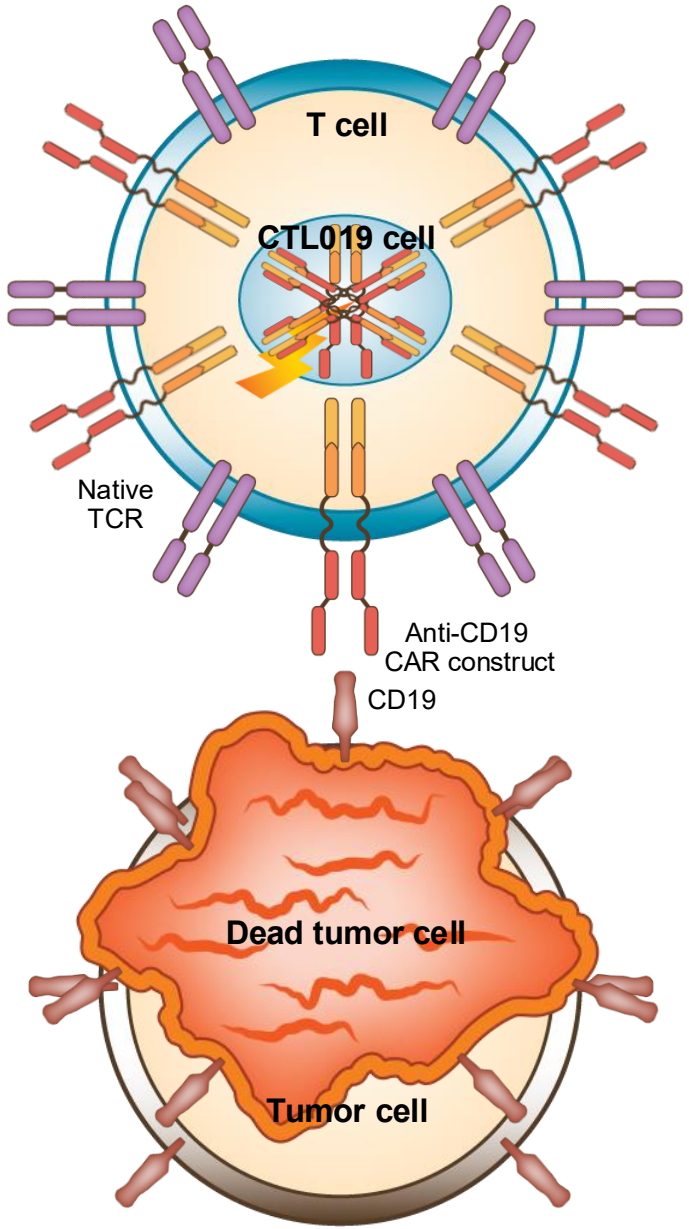
- Different transduction systems to get CARs into T cells:

→Retroviral transduction

→Lentiviral transduction

versus

→ non viral transduction (Sleeping Beauty)



Courtesy of David Porter- U Penn

Rapid Development of 19-CAR T- Starting with Pediatric B-ALL

Cooper/Jensen
First CD19. CAR T cell study (1st generation)

Dotti/Savoldo/Bollard
Reports of clinical success in pediatric B-ALL and adult NHL using CD19 CAR transduced VSTs

Lee/Fry/Mackall
Reports clinical results with CD28 2nd gen CAR first case report of clinical success in pediatric B-ALL w CD19 CAR

Maude/Grupp
Reports of clinical success in pediatric B-ALL using a 41BB 2nd gen CD19 CAR

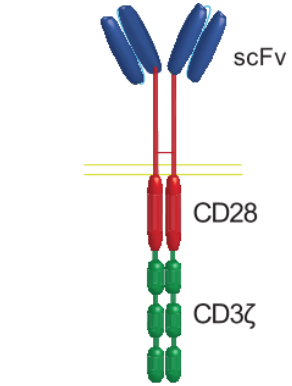
FDA approval of Tisagenlecleucil for use in children/young adults with r/r B-ALL

Maude
Reports ELIANA study in r/r B-ALL children/young adults. This is the first CAR T phase II study.

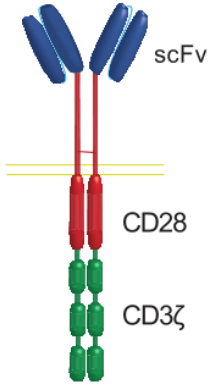
UK NICE
Approves reimbursement for Tisagenlecleucil

Original CD19 CARs

MSKCC CD28z CAR

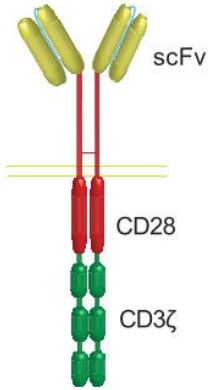


Juno *MSKCC*

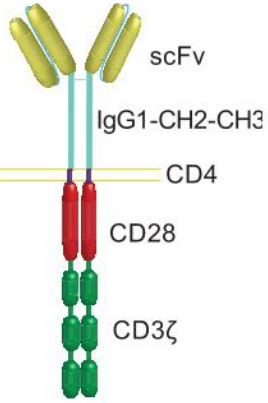


Axicabtagene Ciloleucel

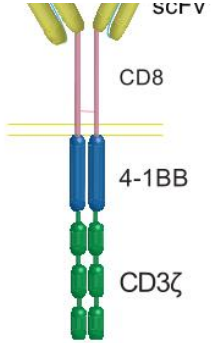
Kite/Gilead (*NCI*)



Bluebird Bio *Baylor*

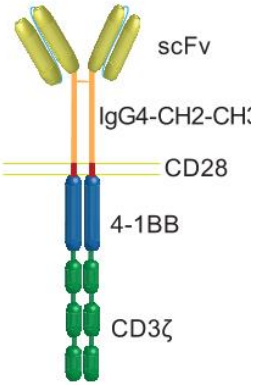


SJRH-4 4-1BB CAR



Lisocabtagene Maraleucel

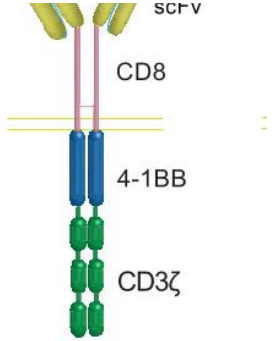
Juno (*FHCRC*)



Novartis

Tisagenlecleucel

CHOP + UPenn

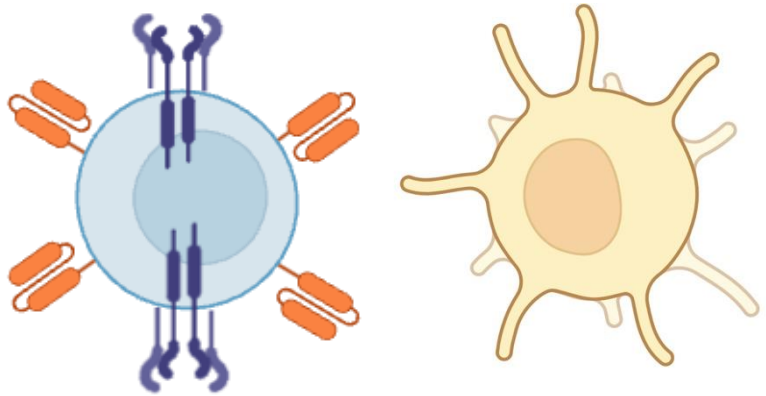


Courtesy of M Sadelain MSKCC

CAR T For Pediatric Blood Cancers- The Future?

Expanding to other CAR Targets:

- CD20
- CD22
- **CD30**
- CD33
- CD123
- **CD7**
- **CD5**
- Cancer Testis Antigen (PR1, SSX2, PRAME)
- B7H3
- GRP78



Combining CAR-T With TAA-T (IND31718)

Summary of CAR-T for Pediatric Blood Cancers

- Only 1 CD19-CAR-T cell product commercially available for children in the USA (for leukemia and not lymphomas)
- CD30 CAR T cells show promise in the Phase 2 setting – but not commercialized
- CD5 CAR-T cells (and CD7 CAR T cells) show promising in Phase 1 setting – ? Will be commercialized
- **CAR-T cells targeting pediatric AML – no "home run" yet**
- **Opportunities to Combine CAR-T with Antigen-specific T cells**

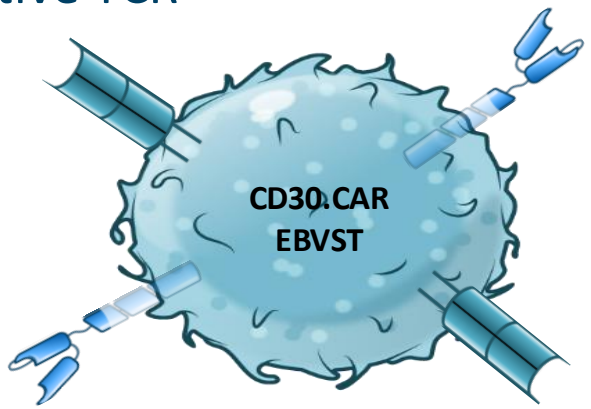
Chimeric Antigen Receptor (CAR) T cells

4: CAR T cells with Antigen specific T cells

EBV-specific T cells with CD30 CAR

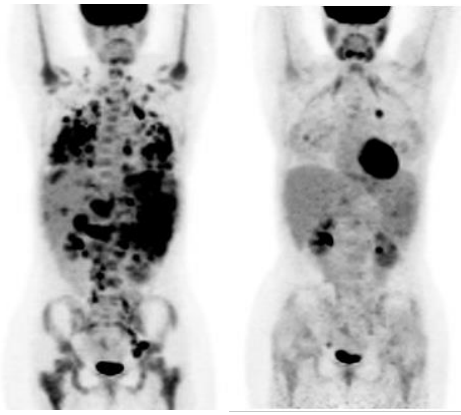
Native TCR

CD30 CAR



Pre

Week 12



Responses

- 11 of 14 patients with responses
  - 5 CR
  - 6 PR

Clio Rooney

David Quach

Carlos Ramos

Premal Lulla

Baylor College of Medicine

DAN L DUNCAN COMPREHENSIVE CANCER CENTER

Quach et al Blood 2023

CAR-T for Solid Tumors have NOT had a "home run" yet….

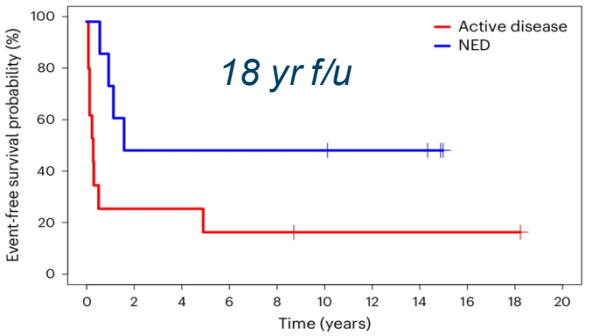
CAR T Cells Demonstrate Clinical Activity in Pediatric Cancers (But Are Not Being Developed by Biopharma)

CD30-CAR for Hodgkin Disease

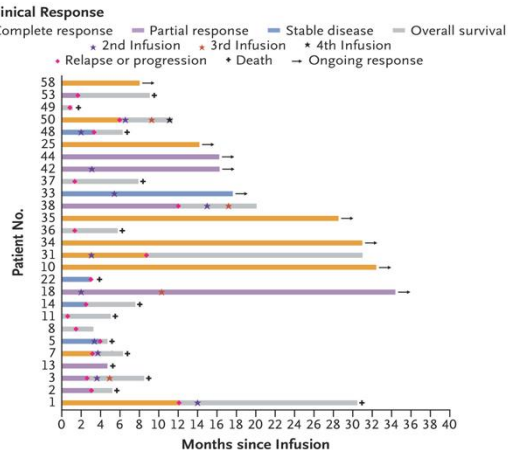
Response	All Patients (N = 37)	Benda (n = 5)	Benda-Flu (n = 15)	Cy-Flu (n = 17)
ORR				
CR + PR	23 (62)	0 (0)	12 (80)	11 (65)
Response rate				
CR	19 (51)	0 (0)	11 (73)	8 (47)
PR	4 (11)	0 (0)	1 (7)	3 (18)
SD	4 (11)	1 (20)	1 (7)	2 (11)
PD	10 (27)	4 (80)	2 (13)	4 (24)

Ramos, J Clin Oncol, 2020

GD2-CAR for Neuroblastoma

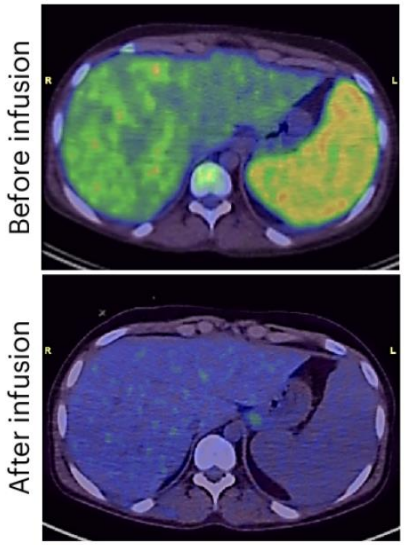


Li et al, Nat Med 2025



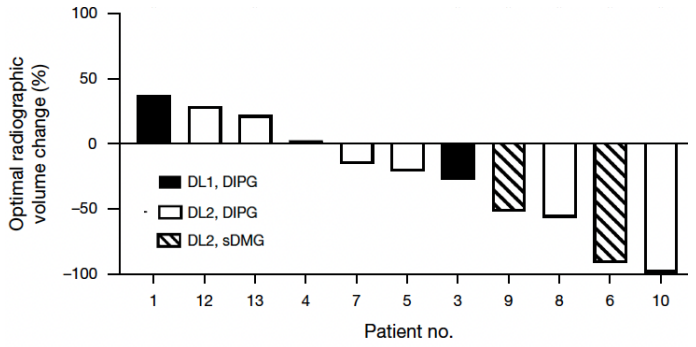
Del Bufalo, NEJM, 2023

CD7-CAR T for T-ALL



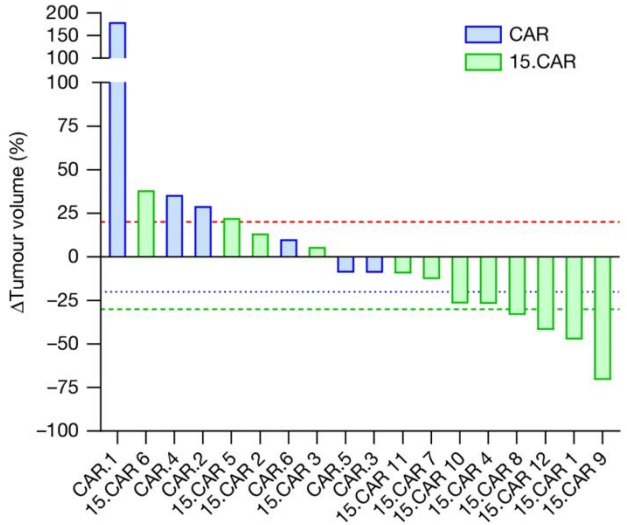
Oh, Nat Med, 2024

GD2-CAR for Diffuse Midline Gliomas



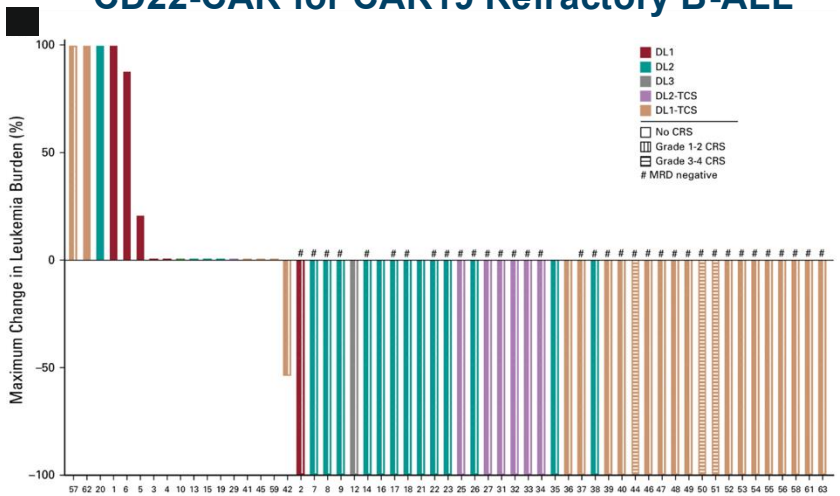
Monje et al, Nature 2022, 2024

GPC3.15-CAR for Solid Cancers



Steffin, Nature, 2025

CD22-CAR for CAR19 Refractory B-ALL



Fry Nat Med 2018, Shah J Clin Onc 2020

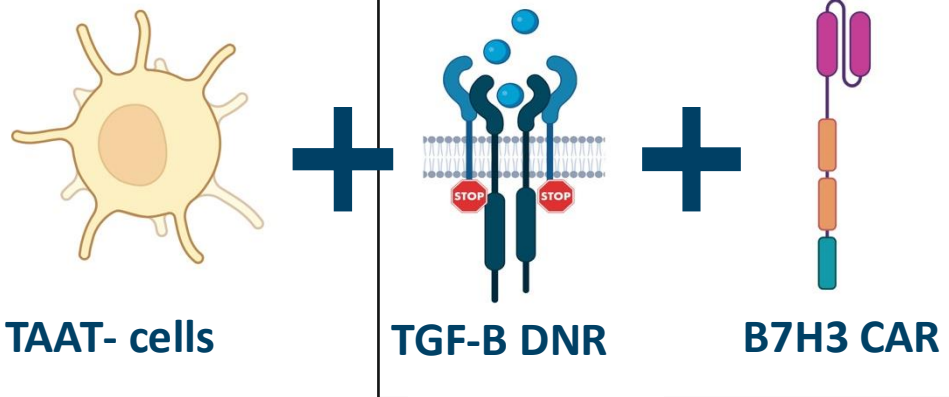
Enhancing T Cell Product Potency for Pediatric Solid Tumors

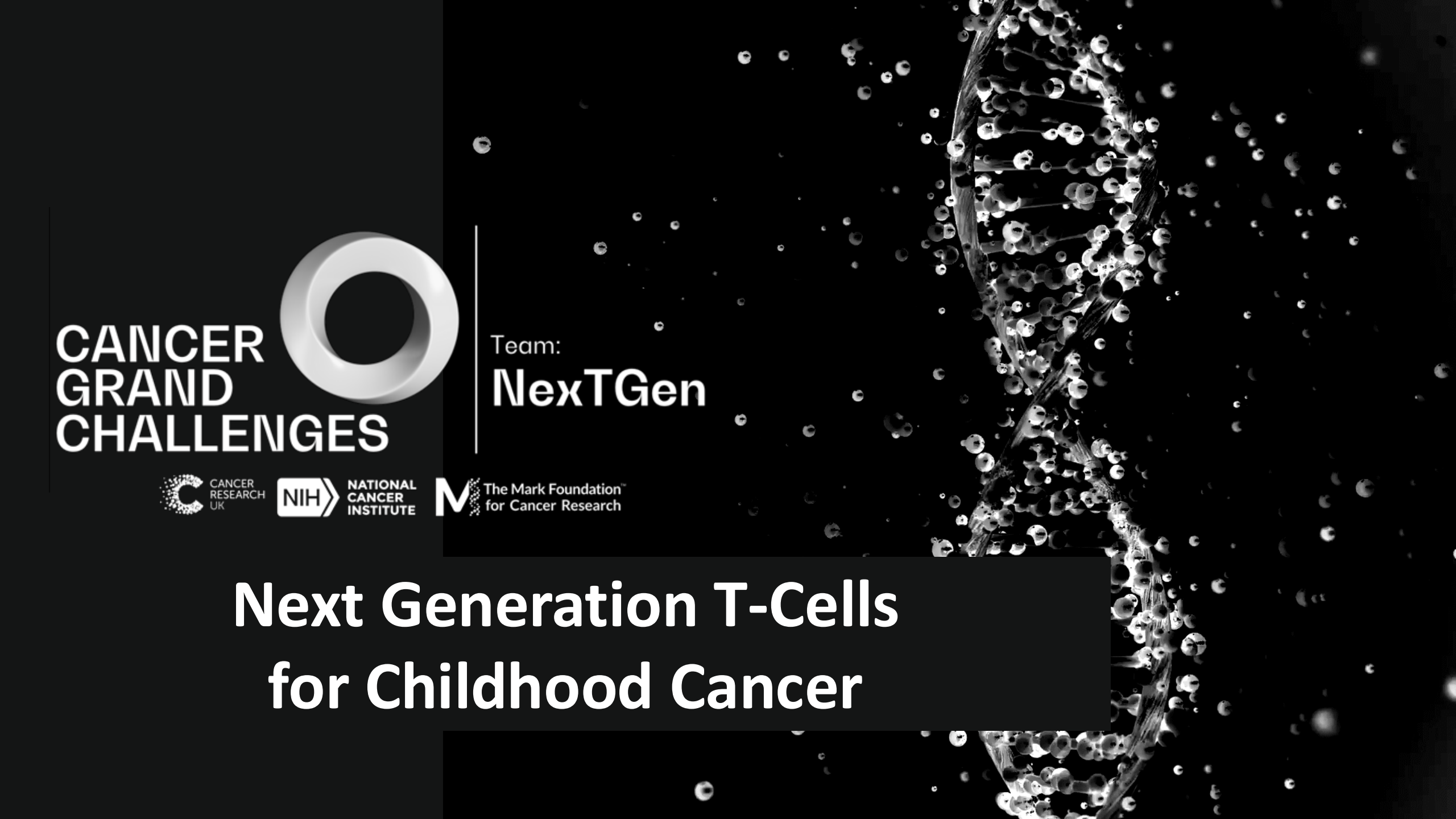
Despite the successes in Blood Cancers-

- Chimeric Antigen Receptor (CAR)-T cell therapies have **not yet** achieved definitive breakthrough in solid tumors.

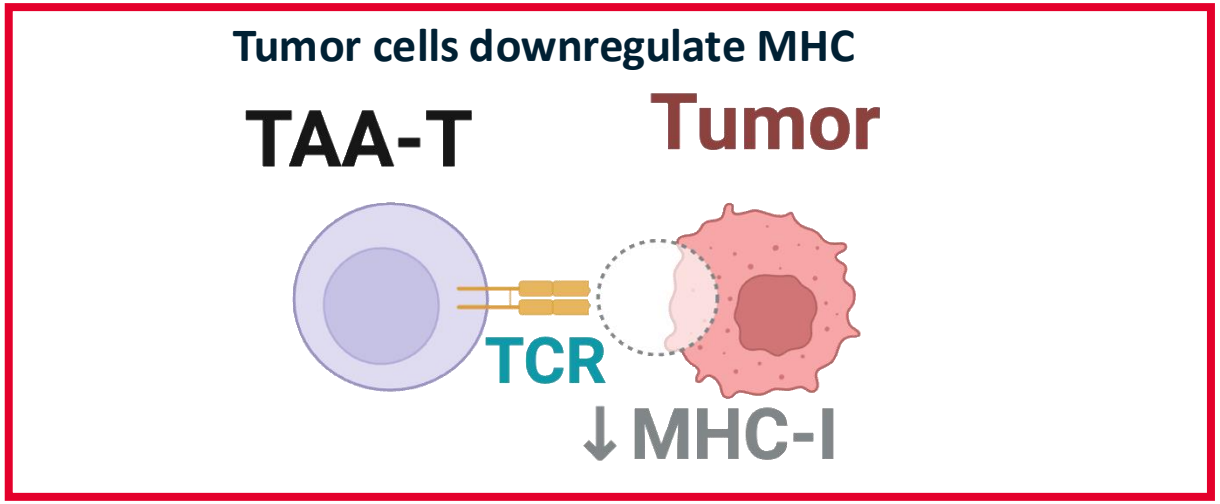
- Tumor Infiltrating Lymphocytes (TILs) containing tumor antigen specific T cells are FDA approved for melanoma

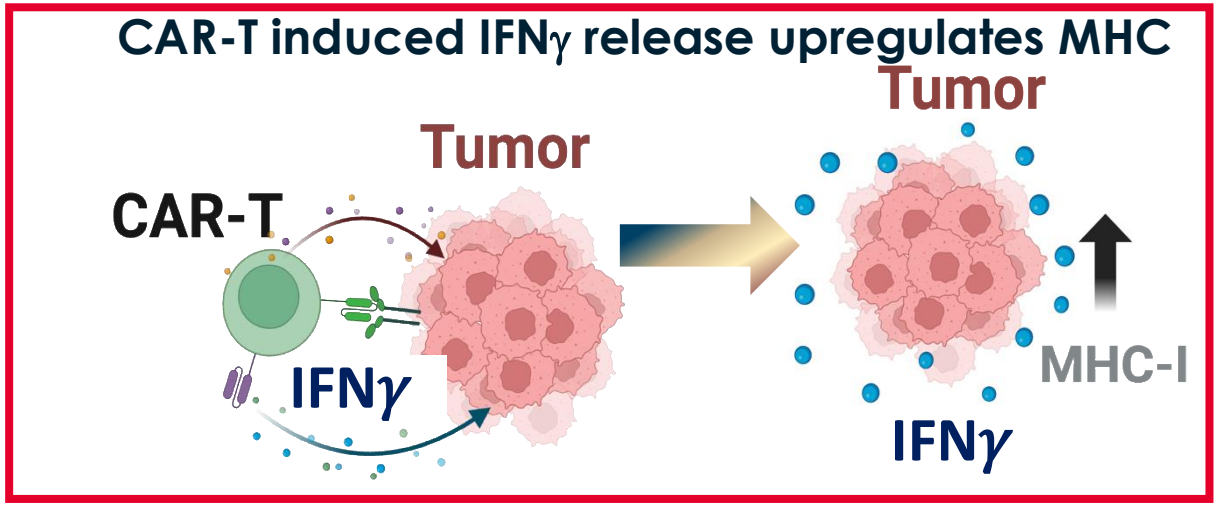
- ***Potential solution:***
  - Combine CAR-T with tumor antigen specific T cells (TAA-T)
  - Overcome the TGFβ rich immune suppressive tumor microenvironment

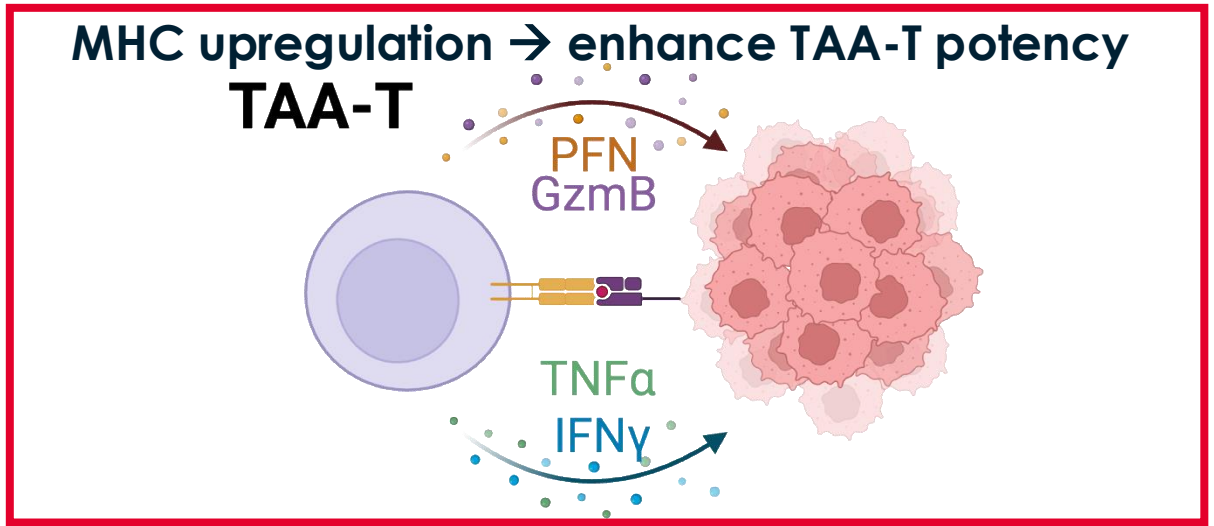



CANCER
GRAND
CHALLENGES
Team:
NexTGen
CANCER RESEARCH UK
NIH NATIONAL CANCER INSTITUTE
The Mark Foundation for Cancer Research
Next Generation T-Cells
for Childhood Cancer

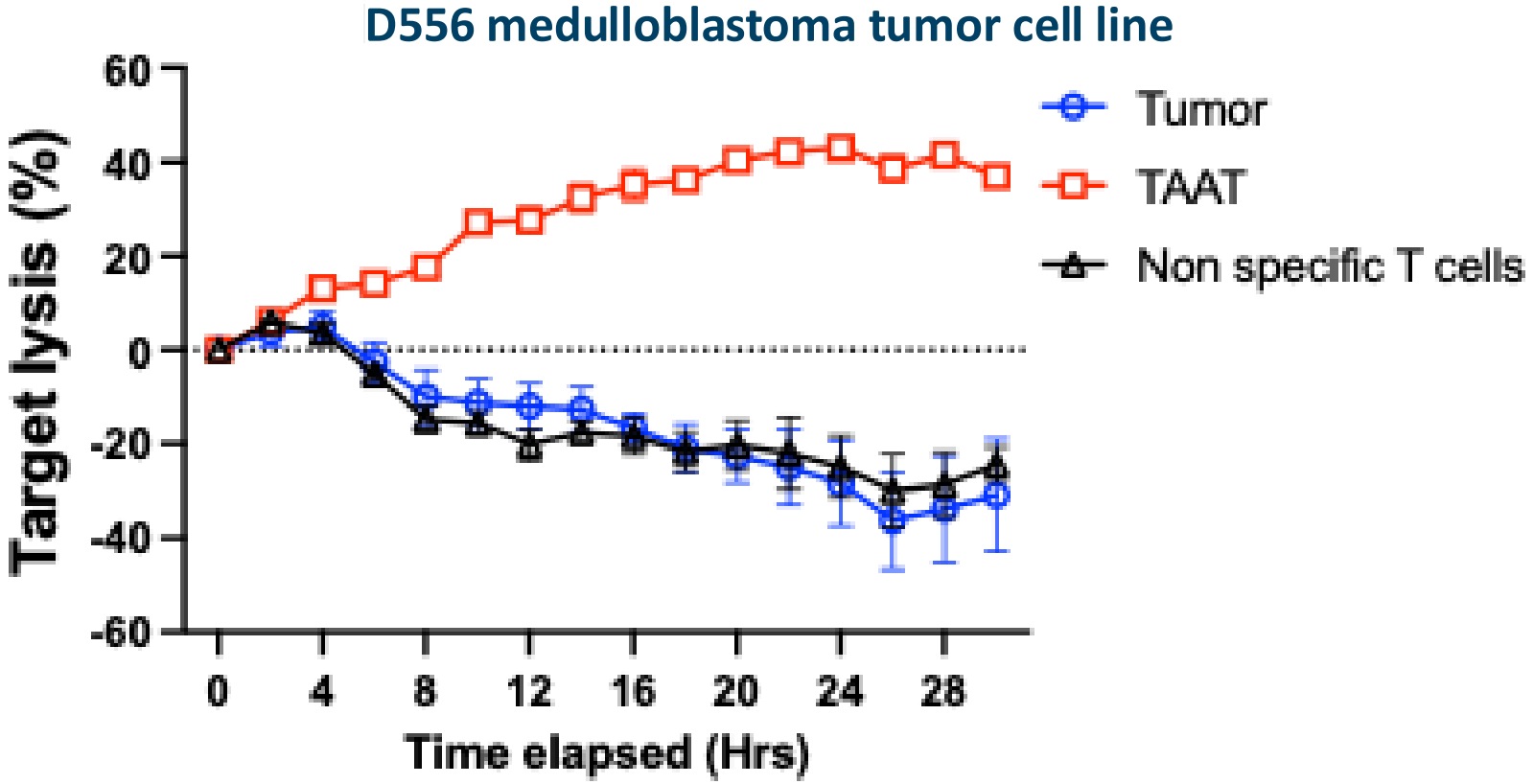
Proposed Mechanism of Action to Enhance the Potency of T cell therapies for Pediatric Solid Tumors

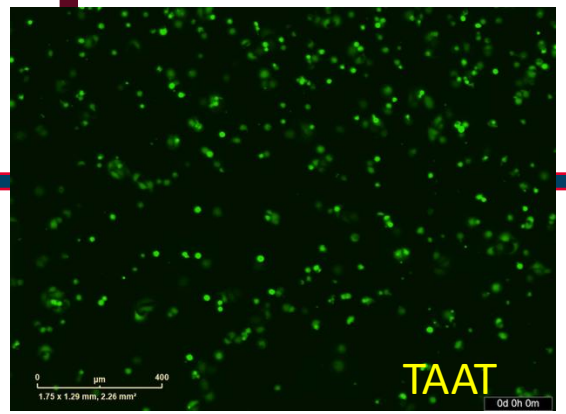


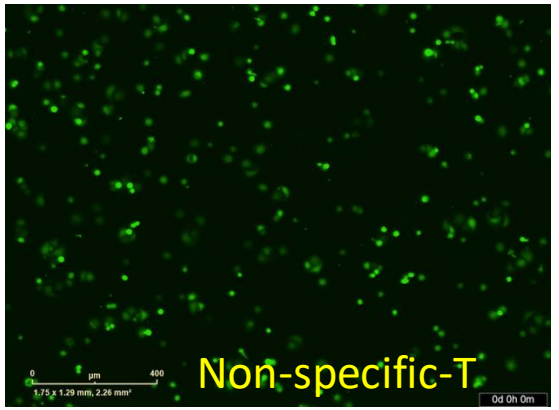


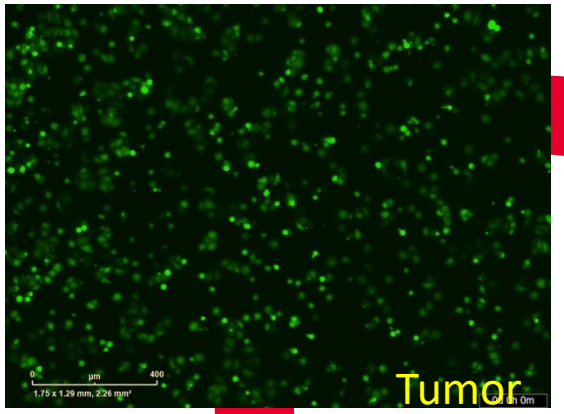


PRAME-specific TAA-T cells have potent anti-tumor activity in vitro









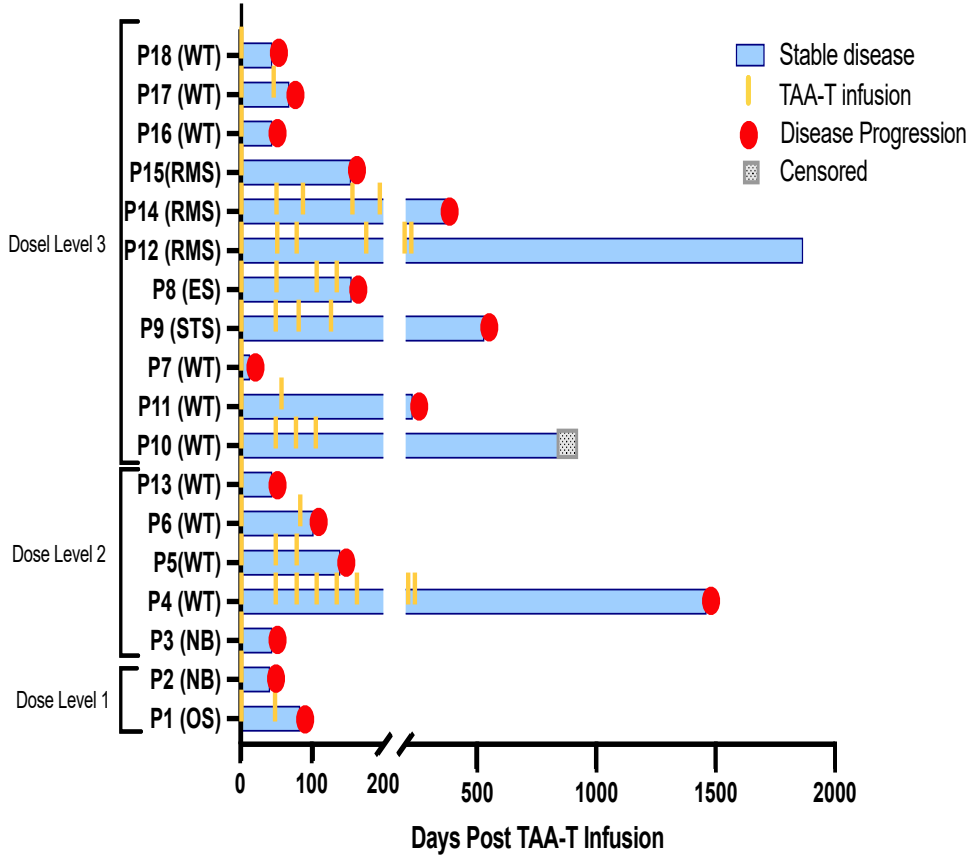
xCELLigence cytotox; Effector:Target ratio 2:1: Target D556

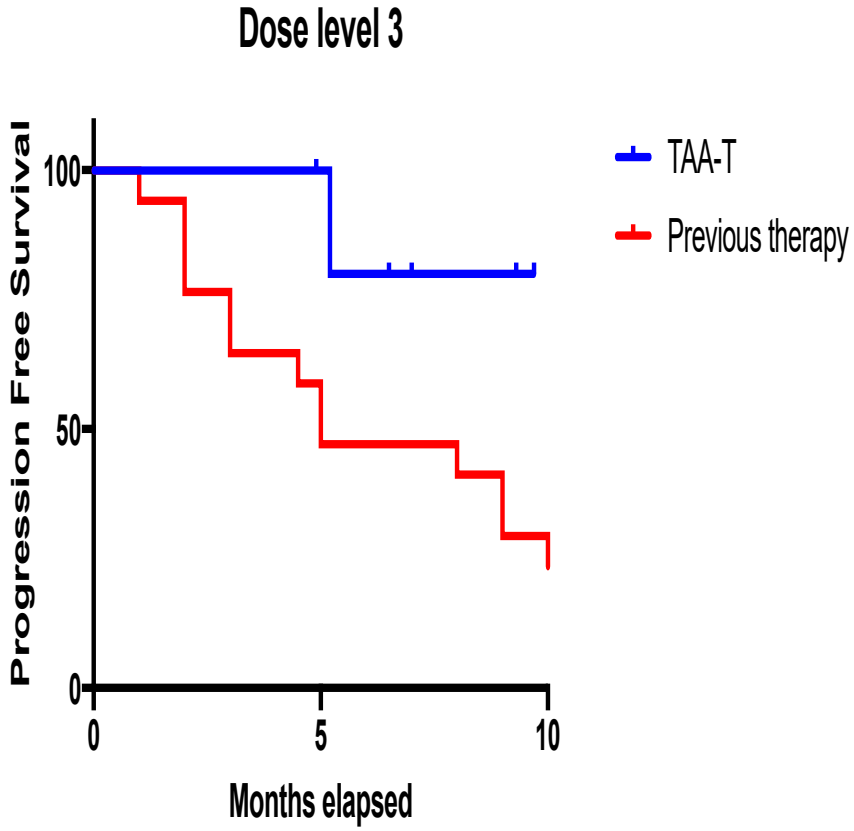
N=5

Representative examples out of 5 lines manufactured

Autologous TAA-T Targeting WT1, PRAME and Survivin for Solid Tumors: SAFE with prolonged progression free survival

- **Patients Safely Received Multiple Autologous TAA-T Infusions without Prescribed LD with Disease Stabilization (n >20)**





PI: Holly Meany, MD

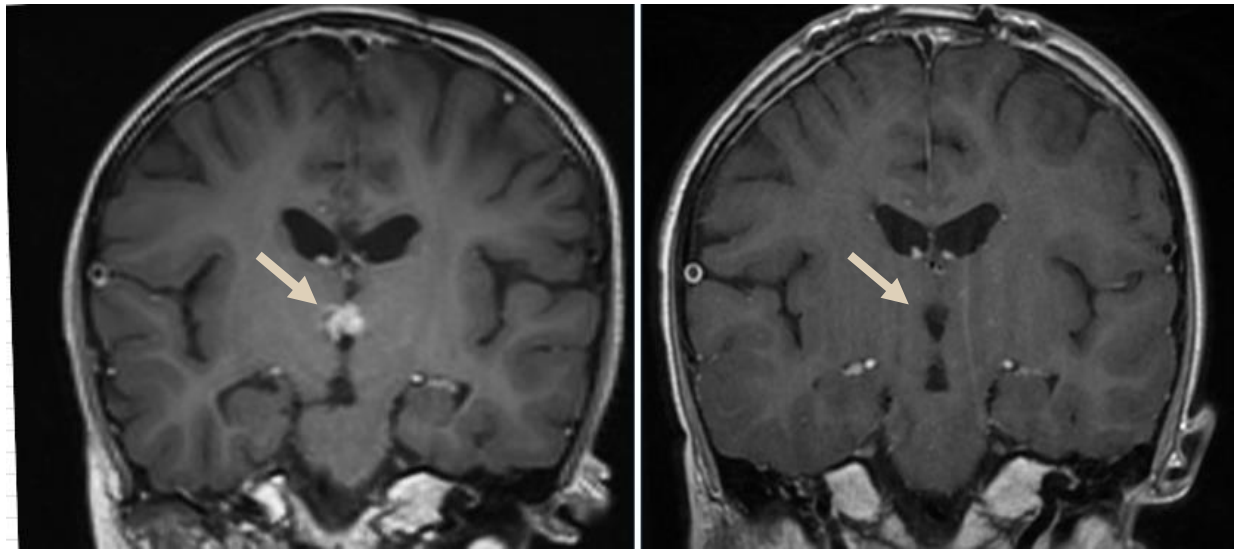
Amy Hont, MD

Hont…Bollard, Meany, JCO 2019 & unpublished update

Tumor Antigen Specific T (TAAT) Cells Have Also Been Used to Treat Pediatric Patients with R/R Brain Tumors

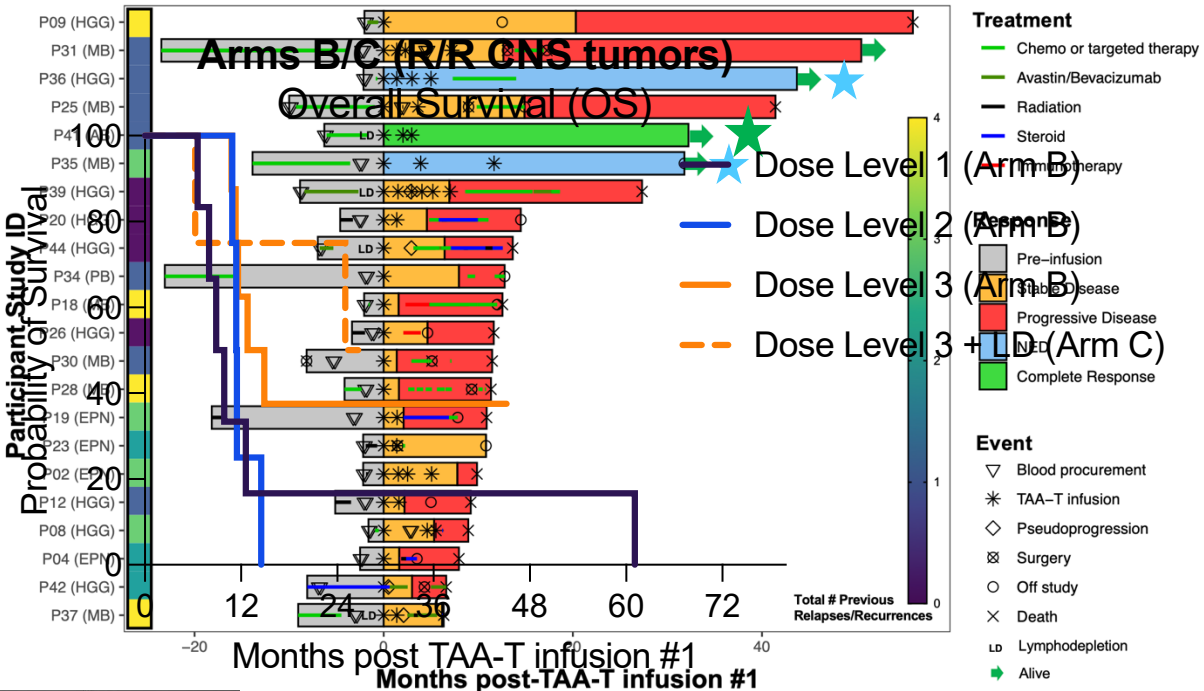
Pre-Infusion

Post Therapy Year 1



Complete remission post TAAT cell therapy

Gomez, Bollard, Hwang – Nature Medicine 2006
(n >30)



Enhancing TAA-T Cell Product Potency for Pediatric Solid Tumors and Brain Tumors

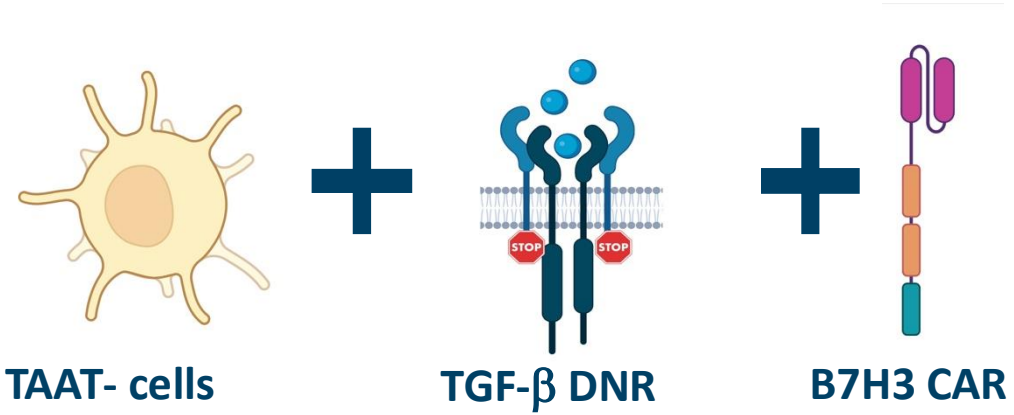
- Enhancing Specificity

Potential solution: Combining TAA-T with B7H3-CAR

- Overcoming Immunosuppressive TME: TGF-β in the TME has devastating effects on T cell function and proliferation

Potential solution: Gene-engineering strategies to resist TGF-β

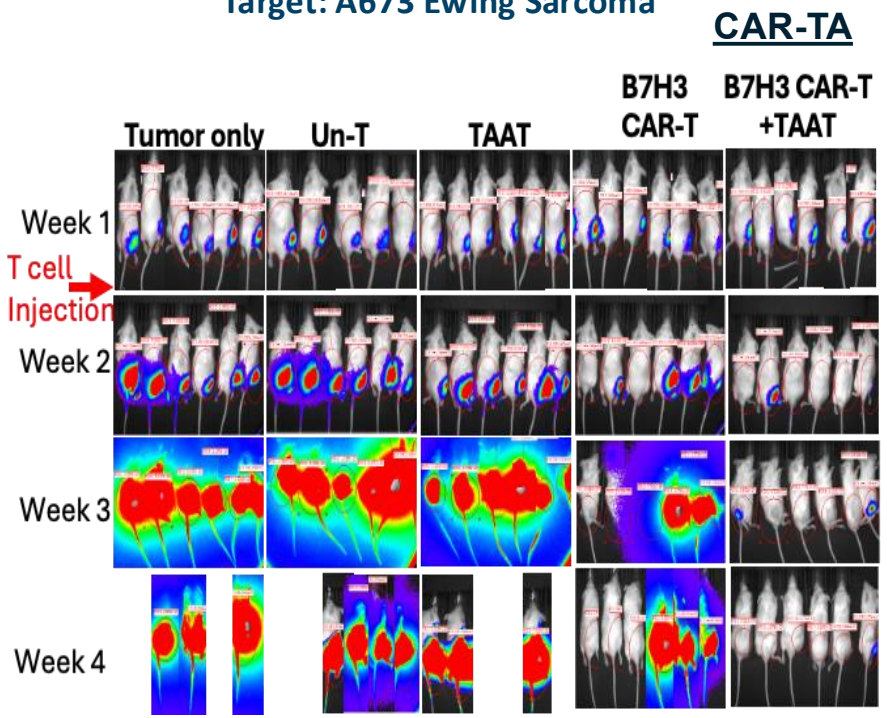
TGFBRII Dominant Negative TGF-β Receptor (DNR)

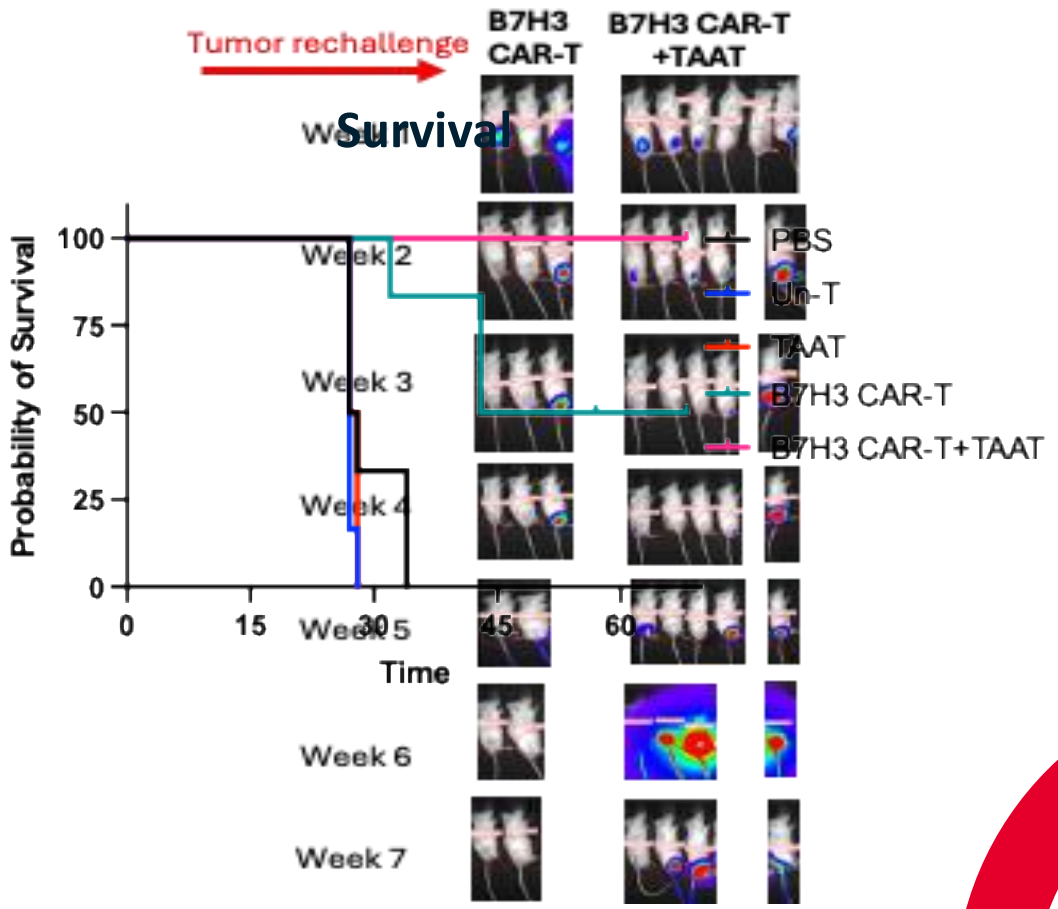


Kajal Chaudhry

Combination B7H3 CAR-T/ PRAME-specific TAA-T Product Elicits Enhanced Anti-tumor Activity *in vivo*

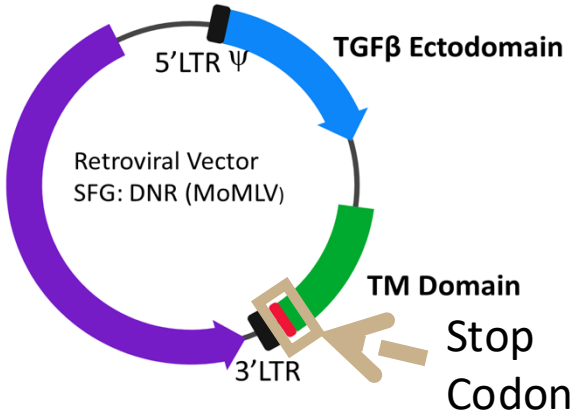
HLA-Matched tumor
Target: A673 Ewing Sarcoma

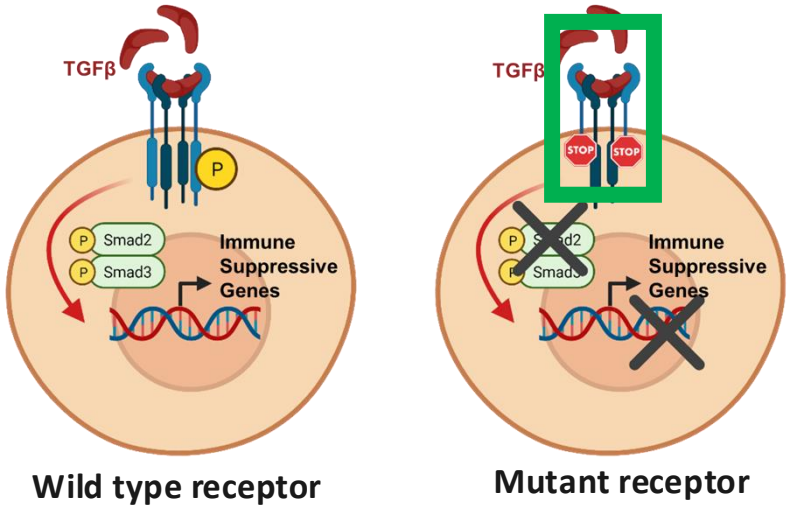




Unpublished Data

Adding a Dominant TGFb Receptor to CAR-T Product to Resist the Immune Suppressive TME



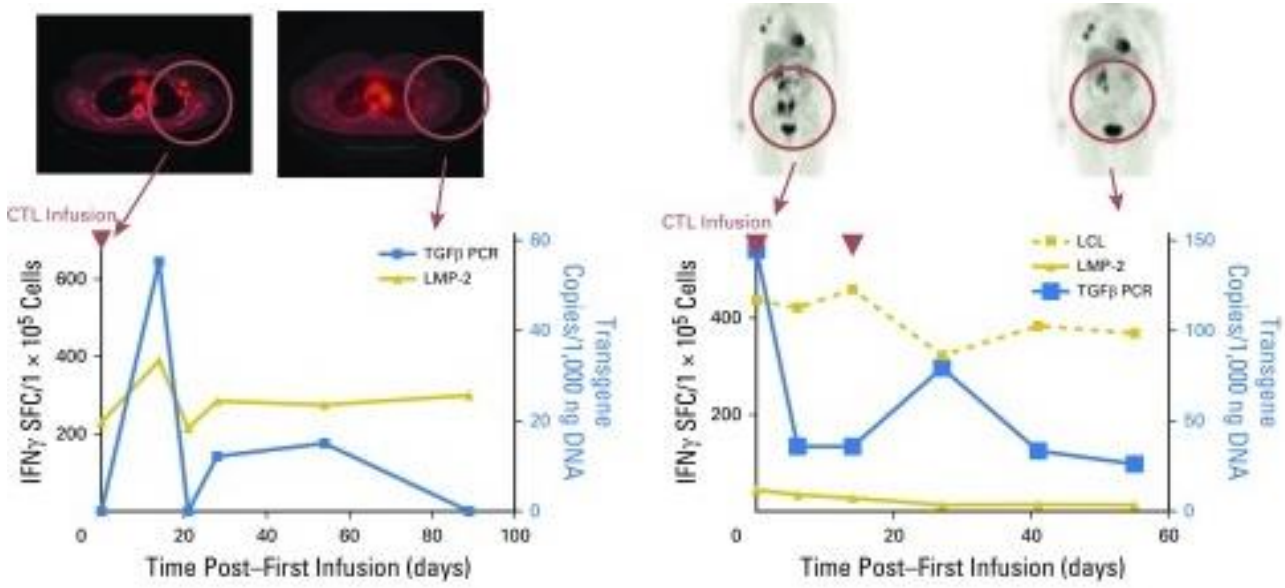


DNR-TAA-T are safe clinically and persist in vivo long term

2018 Jan 9;36(11):1128–1139. doi: 10.1200/JCO.2017.74.3179

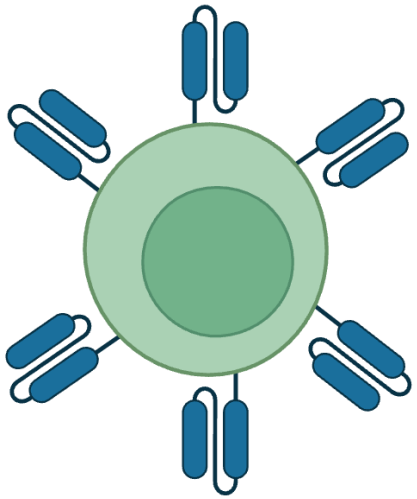
Tumor-Specific T-Cells Engineered to Overcome Tumor Immune Evasion Induce Clinical Responses in Patients With Relapsed Hodgkin Lymphoma

Catherine M Bollard [1,✉], Tamara Tripic [1], Conrad Russell Cruz [1], Gianpietro Dotti [1], Stephen Gottschalk [1], Vicky Torrano [1], Olga Dakhova [1], George Carrum [1], Carlos A Ramos [1], Hao Liu [1], Meng-Fen Wu [1], Andrea N Marcogliese [1], Cecilia Barese [1], Youli Zu [1], Daniel Y Lee [1], Owen O'Connor [1], Adrian P Gee [1], Malcolm K Brenner [1], Helen E Heslop [1], Cliona M Rooney [1]

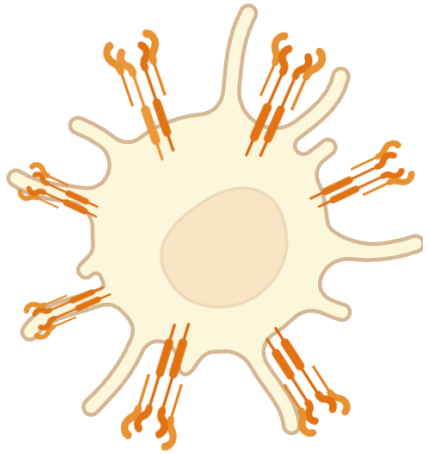


Bollard et al. Blood 2002 and Bollard et al, JCO 2018

CAR-TA manufacture for clinical use: B7H3 CAR-T cells with TGFβ DNR transduced TAAT cells



B7H3.28z CAR-T



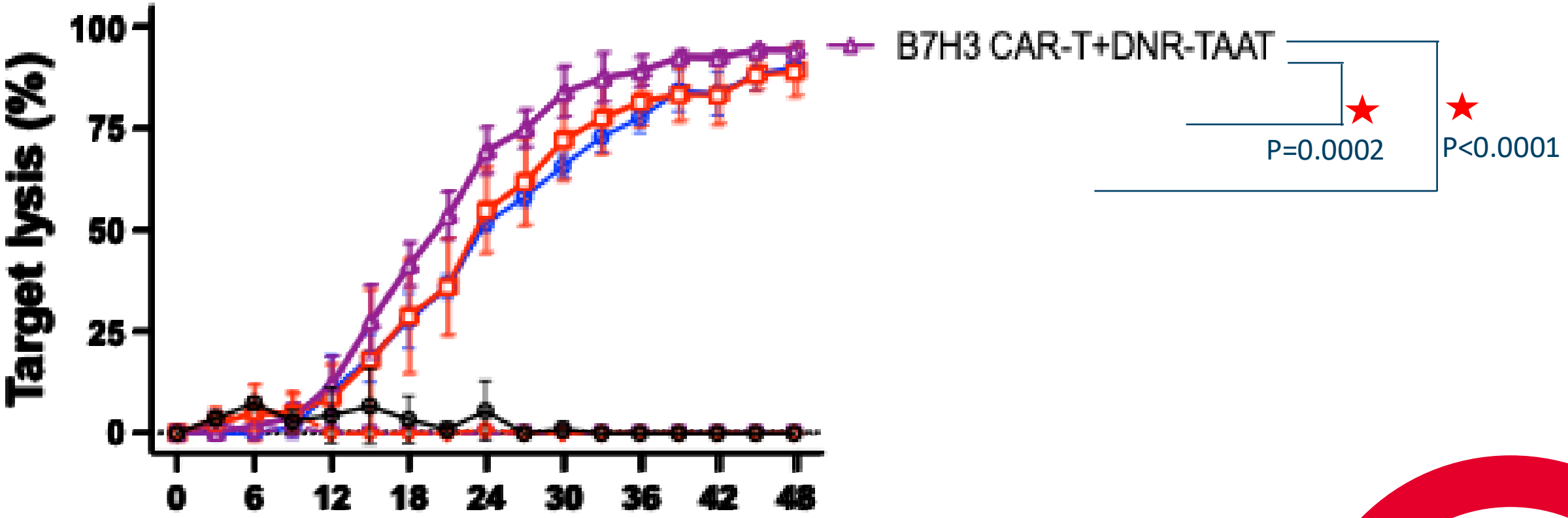
DNR-TAA-T cells
Targeting PRAME

GMP Team: Abeer Shibli, Emily Reynolds, Tavis Sparrer, Nana Yaa Gyaama Owusu-Tieku, **Chase Daniel McCann** and Patrick Hanley

ITC Team: Adriana Valenzue and **Anushree Datar**

CHILDREN'S NATIONAL HOSPITAL

CAR-TA Product Elicits Potent Killing of HLA-matched Tumors.

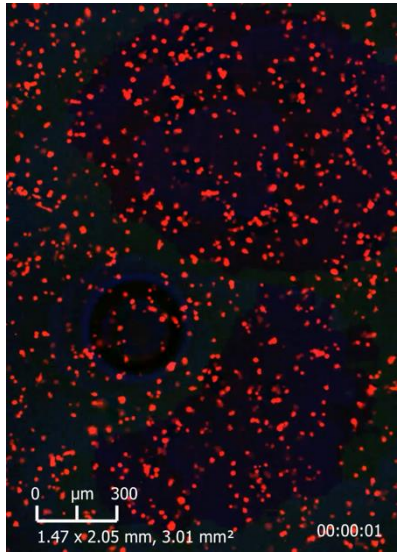


xCELLigence cytotox; E:T ratio: 1:5;
HLA-Matched tumor Target SUDIP-35

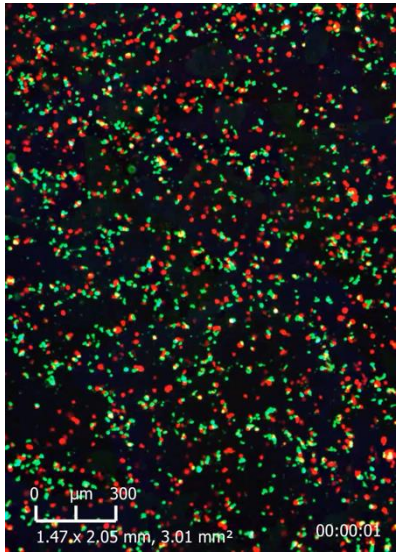
Unpublished Data

CAR-TA T cells Target and Kill A673 Ewing Sarcoma cells in vitro

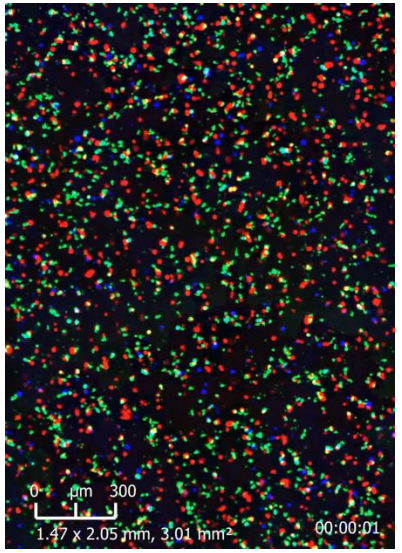
Tumor



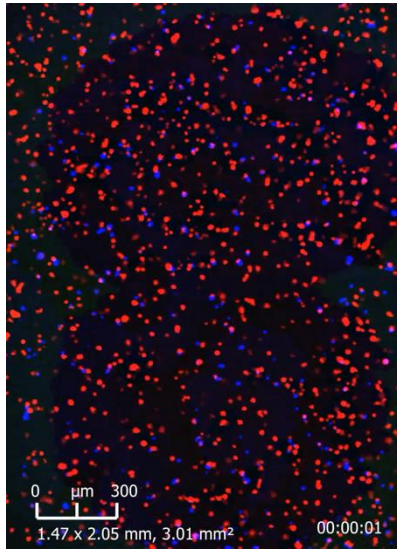
TAAT



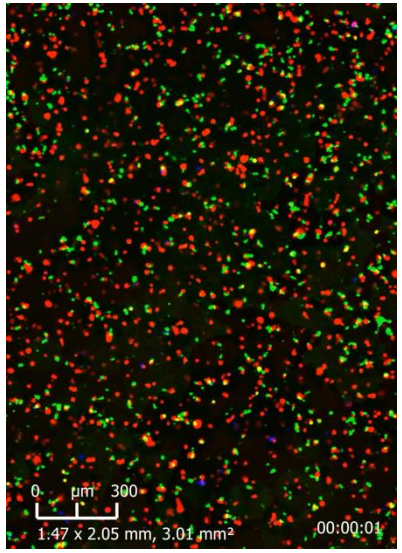
Un-T+TAAT



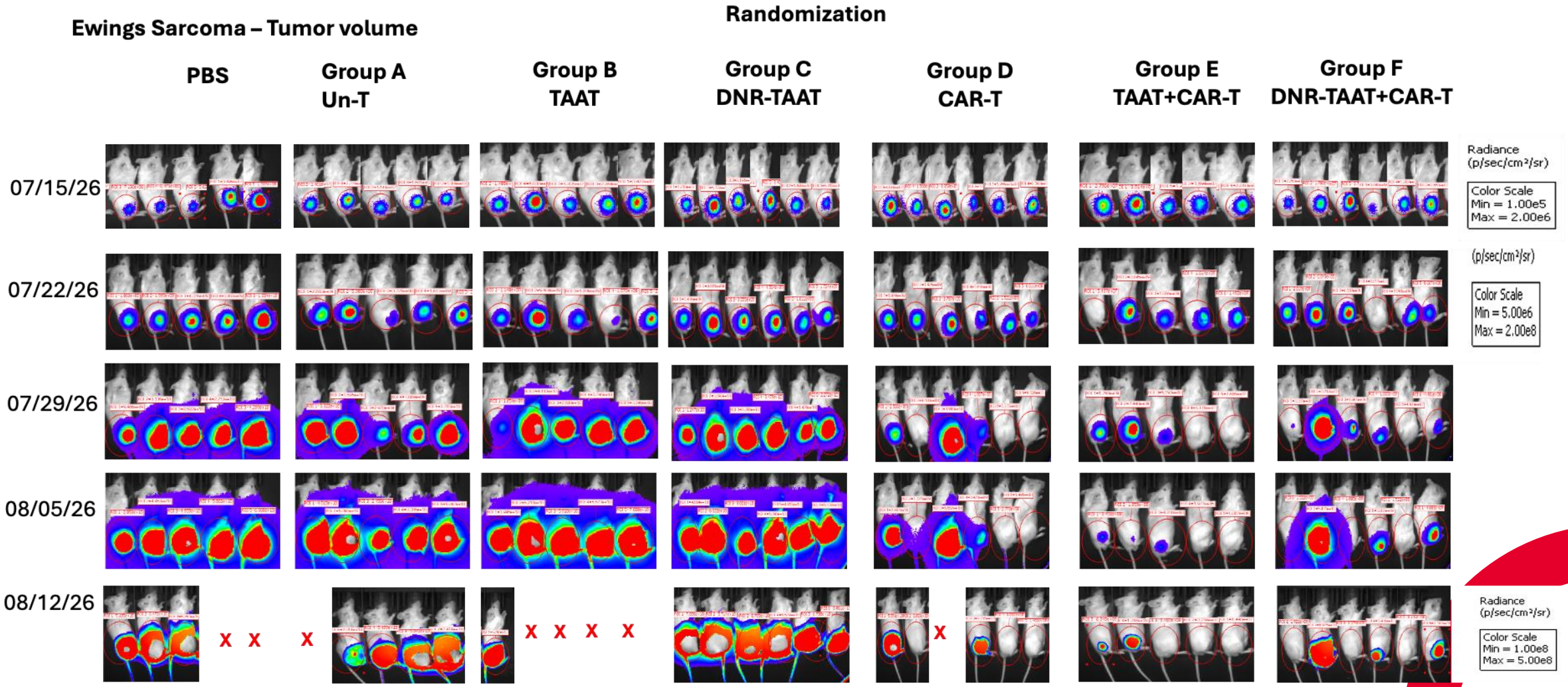
CAR-T cells



CAR-TA cells



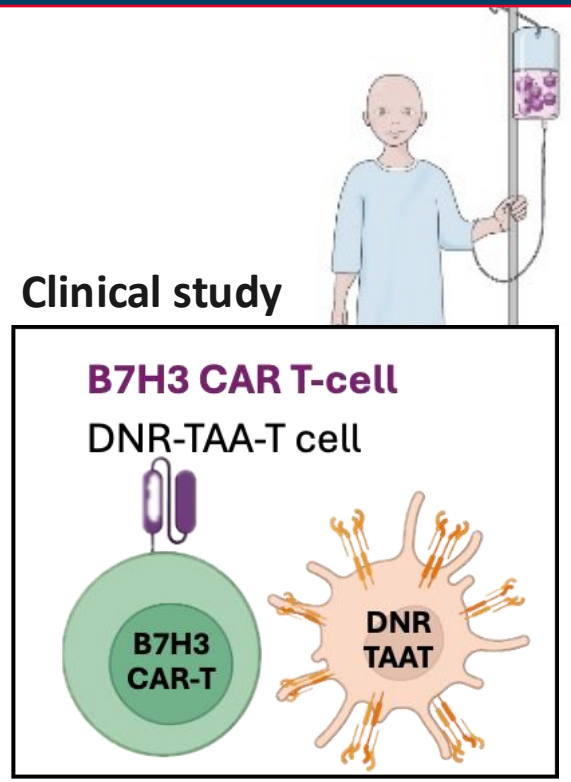
CAR-TA T cells Target and Kill A673 Ewing Sarcoma cells in vivo



Conclusions

The combined CAR-T and DNR-TAA-T CAR-TA approach demonstrates synergistic effects in vitro and in vivo.

- ✓Multiple antigen targeting
- ✓Protection against TGF-B-mediated immune suppression
- ✓Enhanced potency in preclinical models
- ✓**This product is now being evaluated clinically in the SABRE trial (IND31718)**



Children's National

Sustainability Beyond Phase I Studies for Adults and Children?

Cancers and other **rare diseases** are among the top 10 causes of death for children in the US, with an estimated **7,000 children lost** every year

Source: CDC; CA Cancer J Clin; ACS; NCBI; CureSearch; NCCS; SEER

CAR T Cell Therapies Have Demonstrated the Ability to Cure "Incurable" Pediatric Cancers

April 17, 2012

- Emily had B-ALL that was refractory to all standard therapies.
- She was the first child to receive CD19-CAR T cell therapy.
- She remains free of disease to this day.

The Remarkable Story of Emily Whitehead

16 FDA Approvals for Cell Therapies for Cancer

Only one cell therapy is approved for the treatment of children

YEAR	AGENT	INDICATION	TYPE	TARGET	Signaling Domain	AGE
2017	Tis-cel	R/R B-ALL	CAR	CD19	BB.z	≤ 26 years
2017	Axi-cel	3rd line LBCL	CAR	CD19	28.z	≥ 18 yrs
2019	Tis-cel	3rd line LBCL	CAR	CD19	BB.z	≥ 18 yrs
2020	Brex-cel	R/R Mantle Cell Lymphoma	CAR	CD19	28.z	≥ 18 yrs
2021	Axi-cel	R/R Follicular lymphoma	CAR	CD19	28.z	≥ 18 yrs
2021	Liso-cel	3rd line LBCL	CAR	CD19	BB.z	≥ 18 yrs
2021	Ide-cel	5th line Multiple Myeloma	CAR	BCMA	BB.z	≥ 18 yrs
2021	Brex-cel	R/R B-ALL	CAR	CD19	28.z	≥ 18 yrs
2022	Cilta-cel	5th line Multiple Myeloma	CAR	BCMA	BB.z	≥ 18 yrs
2022	Axi-cel	2nd line LBCL	CAR	CD19	28.z	≥ 18 yrs
2022	Liso-cel	2nd line LBCL	CAR	CD19	BB.z	≥ 18 yrs
2022	Tis-cel	R/R Follicular lymphoma	CAR	CD19	BB.z	≥ 18 yrs
2024	Liso-cel	CLL/SLL	CAR	CD19	BB.z	≥ 18 yrs
2024	Lifi-cel	Metastatic melanoma	Non-engineered	unknown	none	≥ 18 yrs
2024	Afami-cel	Metastatic synovial cell sarcoma	TCR	MAGE-A4	none	≥ 18 yrs
2024	Obecel	R/R B-ALL	CAR	CD19	BB.z	≥ 18 yrs

CHILI
ONCO
GROU

ACCESSforKIDS brings together cell therapy leaders and industry veterans to deliver life-saving treatments to children

A4K founders

Renowned scholars

Crystal Mackall, MD

Ernest and Amelia Gallo Family Professor

Stanford MEDICINE

- **Pioneered CAR T-cell therapy advancements** for rare pediatric brain indications
- **27-year tenure at NCI** as Chief of Pediatric Oncology and Head of the Immunology Section
- **Co-founded 3 biotech companies**: Lyell Immunopharma, CARGO Therapeutics and Link Cell Therapies

Catherine Bollard, MD

SVP & Chief Research Officer

Children's National

- Extensive expertise in virus-specific T cells and **stem cell and cord blood transplantation**
- Immediate Past President of the Foundation for the Accreditation of Cellular Therapy (FACT)
- **Scientific co-founder** of Catamaran Bio and Mana Therapeutics

Alan Wayne, MD

Pediatrician-in-Chief & SVP of Academic Affairs

Children's Hospital LOS ANGELES

- Instrumental in advancing **CAR T-cell therapy for pediatric hematologic malignancies**
- Medical Director of the **Therapeutic Advances in Childhood Leukemia & Lymphoma Consortium**

Helen Heslop, MD

Director, Center for Cell and Gene Therapy

Baylor College of Medicine

- Pioneered adoptive immunotherapy treatments for **Epstein-Barr virus-induced disease**
- Elected to the National Academy of Medicine and **former President of the American Society of Gene and Cell Therapy (ASGCT)**

Industry leaders

Sam Blackman, MD, PhD

Founder & Head of R&D

Day One BIOPHARMACEUTICALS

- Distinguished scholar and industry leader in pediatric oncology
- Led the early clinical development of **more than 10 novel pediatric cancer therapeutics**
- Expertise in **commercializing pediatric oncology assets** and bridging the industry "valley of death"

Surajit Sen

Partner, Head of US Life Sciences Strategy Practice

EY Parthenon

- 24 years of experience providing professional services across the Life Sciences industry
- Extensive experience in consulting Fortune 100 biopharmas and biotechs **across every aspect of the advanced therapeutics value chain**

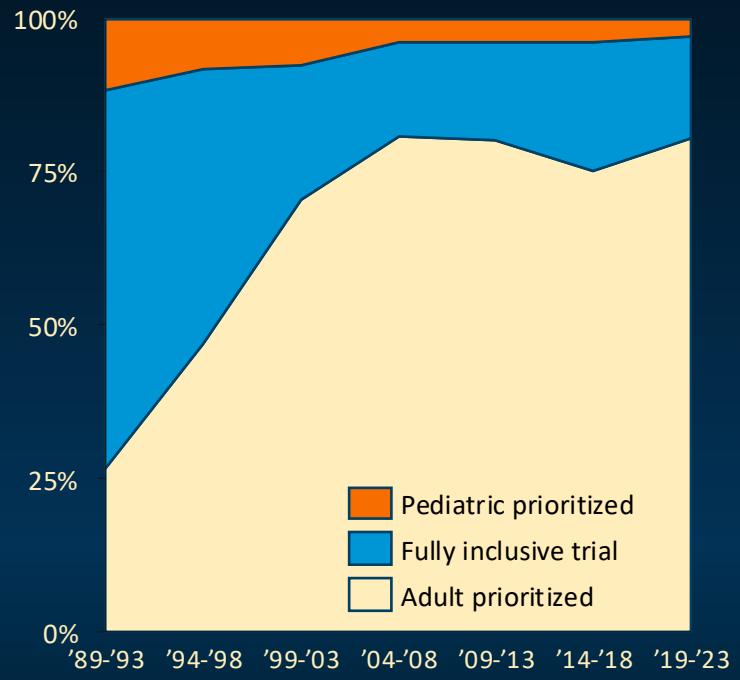
ACCESSFORKIDS

The *status quo* in pharmaceutical development has *failed* kids with cancer at *numerous points*

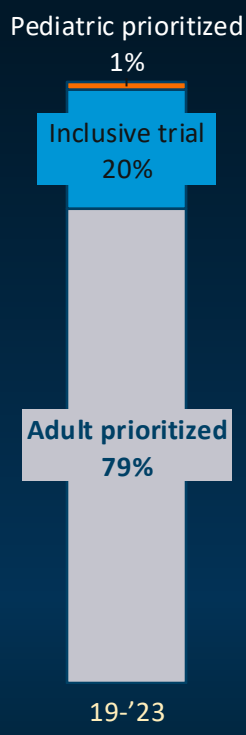
Therapies targeting pediatric cancers represent a small and diminishing portion of the development pipeline in oncology

Pediatric patients must endure toxicity of outdated drugs; advanced modalities could cure disease and reduce toxicity

***Oncology trial starts by age group**,'89-'23*



***Oncology drug approvals**,'19-'23*



Current pediatric oncology therapies (i.e., chemotherapy) show little efficacy and induce detrimental impacts on lifespan and quality of life

Advanced medicines like cell and gene therapies (CGTs) have the potential to dramatically improve outcomes in pediatric cancers—enhance efficacy, reduce toxicity, and improve quality of life

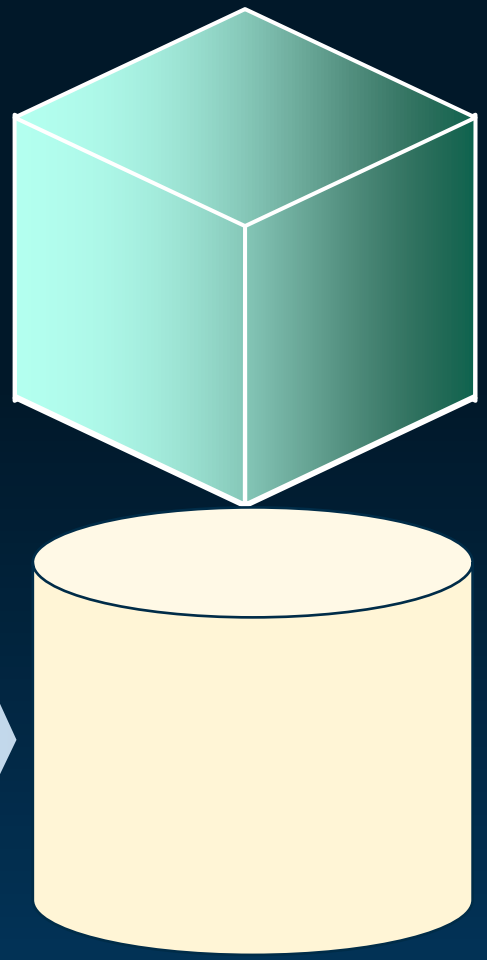
Less than 1% of all trials focus on pediatric CGTs

Source: Informa PharmaIntelligence; EJC Pediatric Oncology; FDA; Citeline Trialtrove

Incentive misalignment between Biopharma and Pediatric Cell and Gene Therapies

Biopharma

- Obligation to **maximize return on investment** for investors
- Development of therapeutics for **common diseases will be prioritized over rare diseases**
- **Cell and gene therapies are more expensive** to develop than other therapeutics, accentuating the difficulty of developing this therapeutic class for small markets
- **The instinct to increase price to offset small market size can help but is not a sustainable approach and risks diminishing access**[1]



Pediatric cancer

- #1 killer due to disease in children in high income countries
- **Cell and gene therapies are poised for major impact** against pediatric cancer
- **Extensive investment in basic research by the public sector** (NIH, DOD, etc.) driven remarkable advances to create more effective and less toxic treatments.
- Failure to deliver these therapies to market is a waste of public resources and opportunity cost to improve the health of children
- Pediatric cell and gene therapies are potentially transformative, they do not **provide sufficient return to merit biopharma investment**

1. Reduced access to CAR-T in black American children (Shah et al, Schultz et al)

Incentive Misalignment between Biopharma and Pediatric Cell and Gene Therapies means Untraditional Initiatives are Necessary to Fill in the Gap

nature medicine

Perspective

https://doi.org/10.1038/s41591-024-03035-1

Enhancing pediatric access to cell and gene therapies

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Crystal L. Mackall[1,2,3], Catherine M. Bollard[4], Nancy Goodman[5], Casey Carr[1], Rebecca Gardner[6], Rayne Rouce[7], Elena Sotillo[1], Rich Stoner[8], Fyodor D. Urnov[9], Alan S. Wayne[10], Julie Park[6] & Donald B. Kohn[11]

We propose a mission-driven biotech to drive development of cell therapies for pediatric cancer

1. Prioritize the development of advanced therapeutics for underserved pediatric patient populations

2. Organized and funded under a primarily mission-driven focus (versus profit maximization focus)

3. A mission-driven biotech can drive pediatric cell therapy development forward in the current industry paradigm if it reduce costs from a bloated clinical development and commercialization process

4. Newly commercialized advanced therapeutics have the potential for long-term curative impact and reduction of permanent treatment-related effects for pediatric populations

5. Long-term ambition and trajectory of the mission-driven biotech is to become financially self-sustaining, and reinvest revenues to develop additional therapies

ACCESSFORKIDS

Drug development valley of death

70+ cellular therapies with pediatric indications in the US have not progressed past phase 1 and have seen no further clinical development

Pre-clinical to early stage | Late stage of development | Commercial development

Summary/Conclusions- What have we learned?

- Virus specific T cells began in adults (CMV) and children (EBV) and have expanded even to the off the shelf setting in both populations
- Expanded antigen specific T cells to multiple viruses and then to tumor associated antigens in adults (AML) and children (solid tumors)
- No home run for CAR-T beyond B-cell ALL/NHL and Myeloma → Combination approaches may enhance potency of CAR-T cells - learn from pediatrics?
- Despite successes of cell therapies in the pediatric setting→**Incentive Misalignment between Biopharma and Pediatric Cell and Gene Therapies means Untraditional Initiatives are Necessary to Fill in the Gap**

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