



**Stanford**  
M E D I C I N E

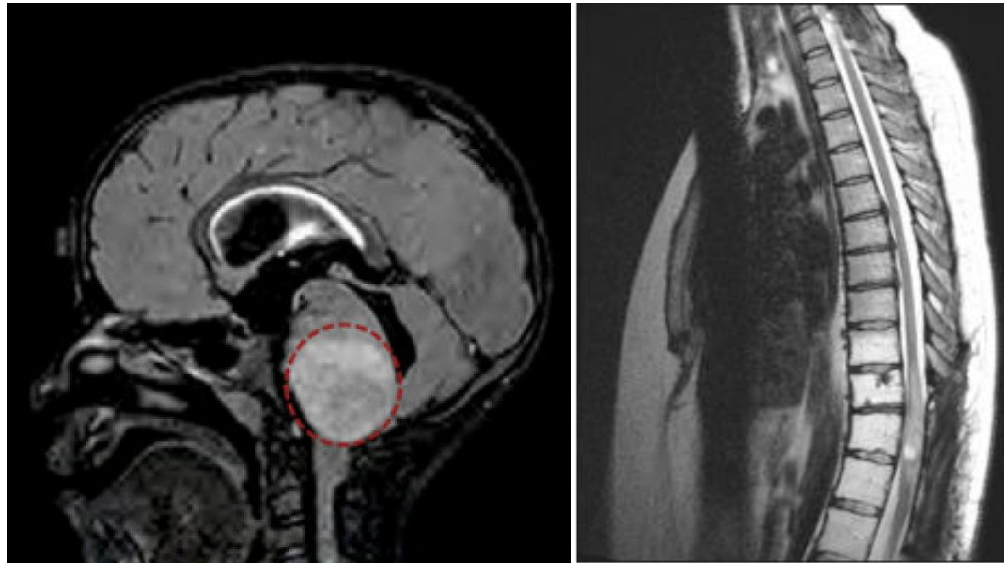
# GD2-CAR T Cells for Diffuse Midline Gliomas

CIRM Board Meeting  
January 2026

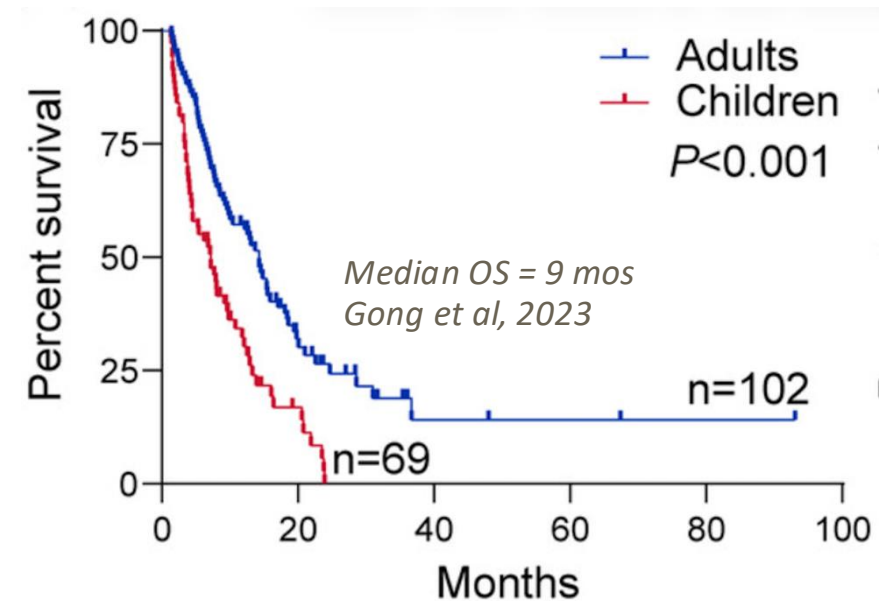
*Crystal L Mackall MD  
Ernest and Amelia Gallo Family Professor of Pediatrics and Medicine  
Director, Stanford Center for Cancer Cell Therapy  
Director, Parker Institute for Cancer Immunotherapy @ Stanford  
Stanford University*

# Diffuse Midline Gliomas: Universally Lethal Cancers With No Upfront Standard Therapy Options

Midline Cancers of the Brainstem and Spinal Cord

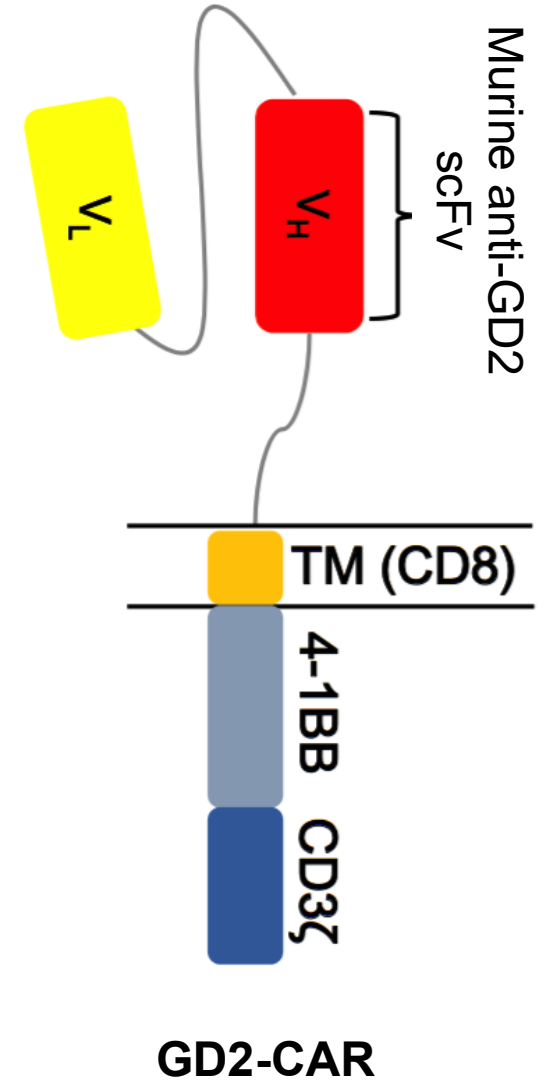
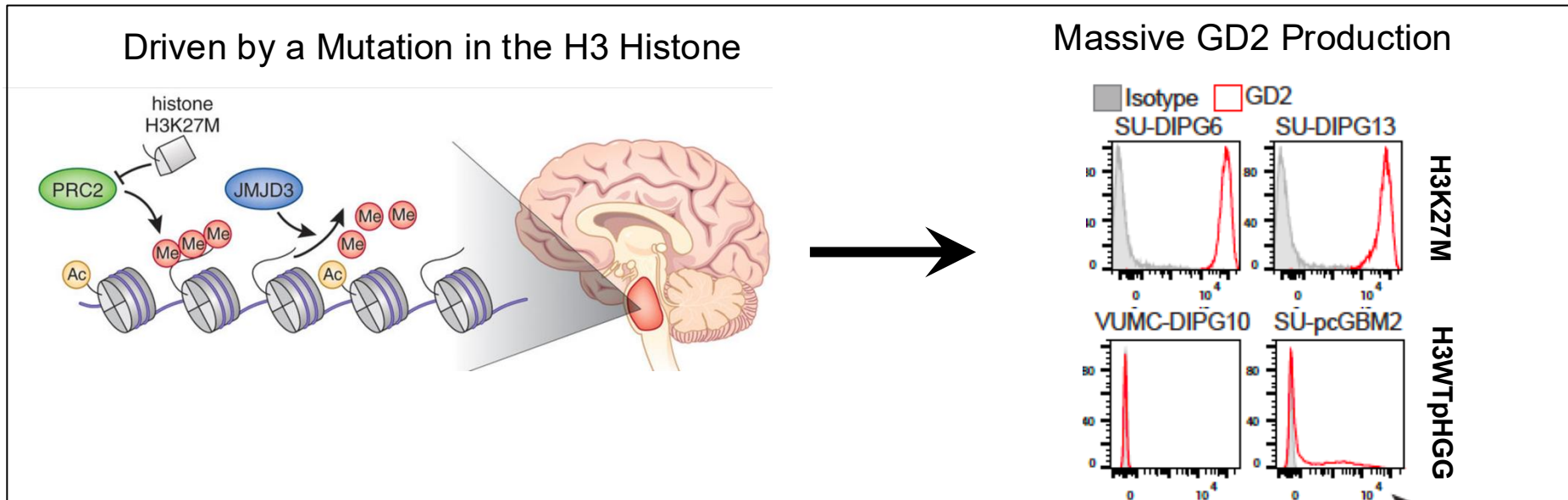


Lethal Despite Many Clinical Trials

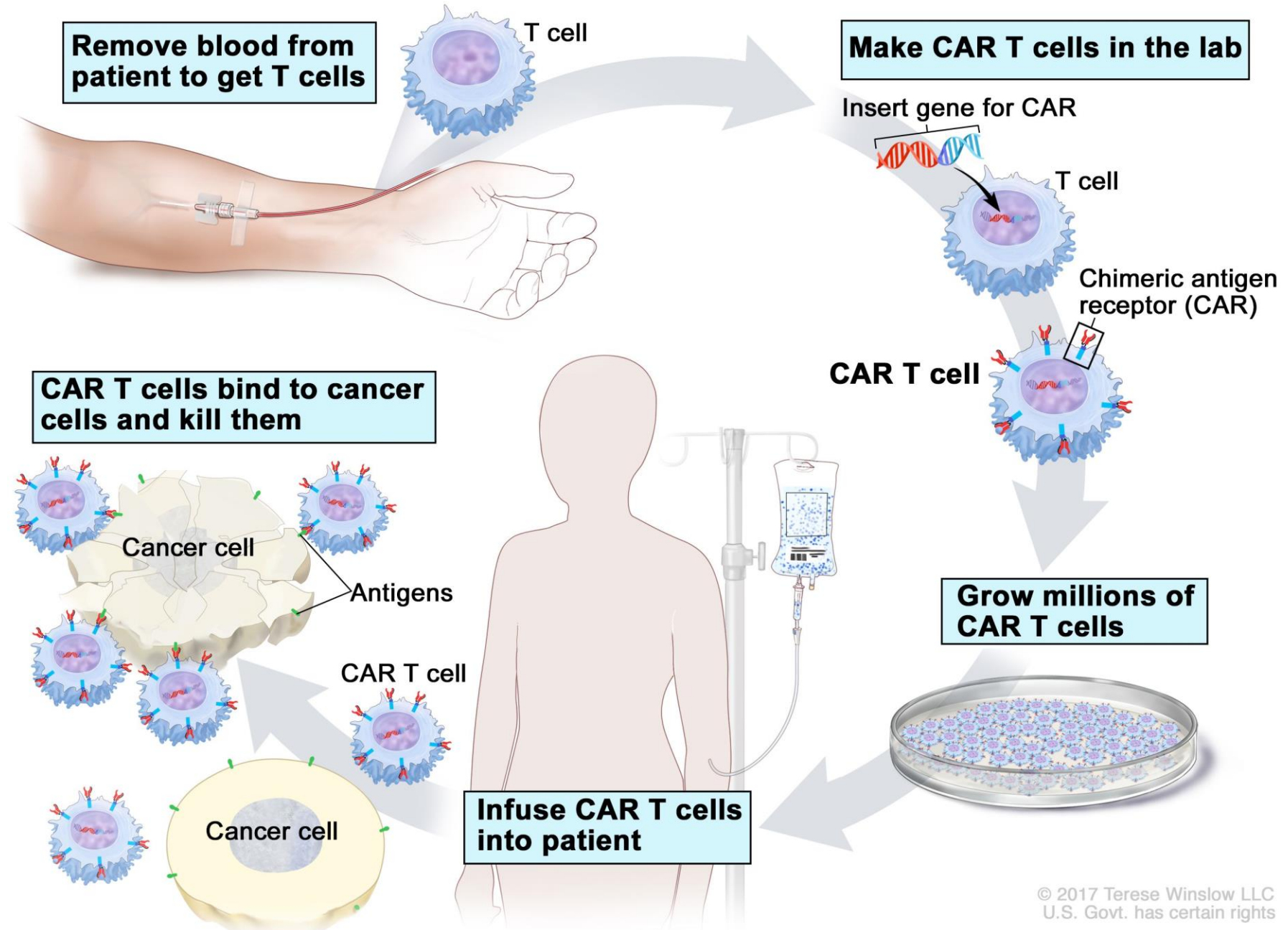


- Approximately 1000 patients/yr in the US, approximately 120 patients/yr in California
- Most common killer of children due to brain tumors.
- No standard frontline therapy except palliative radiation

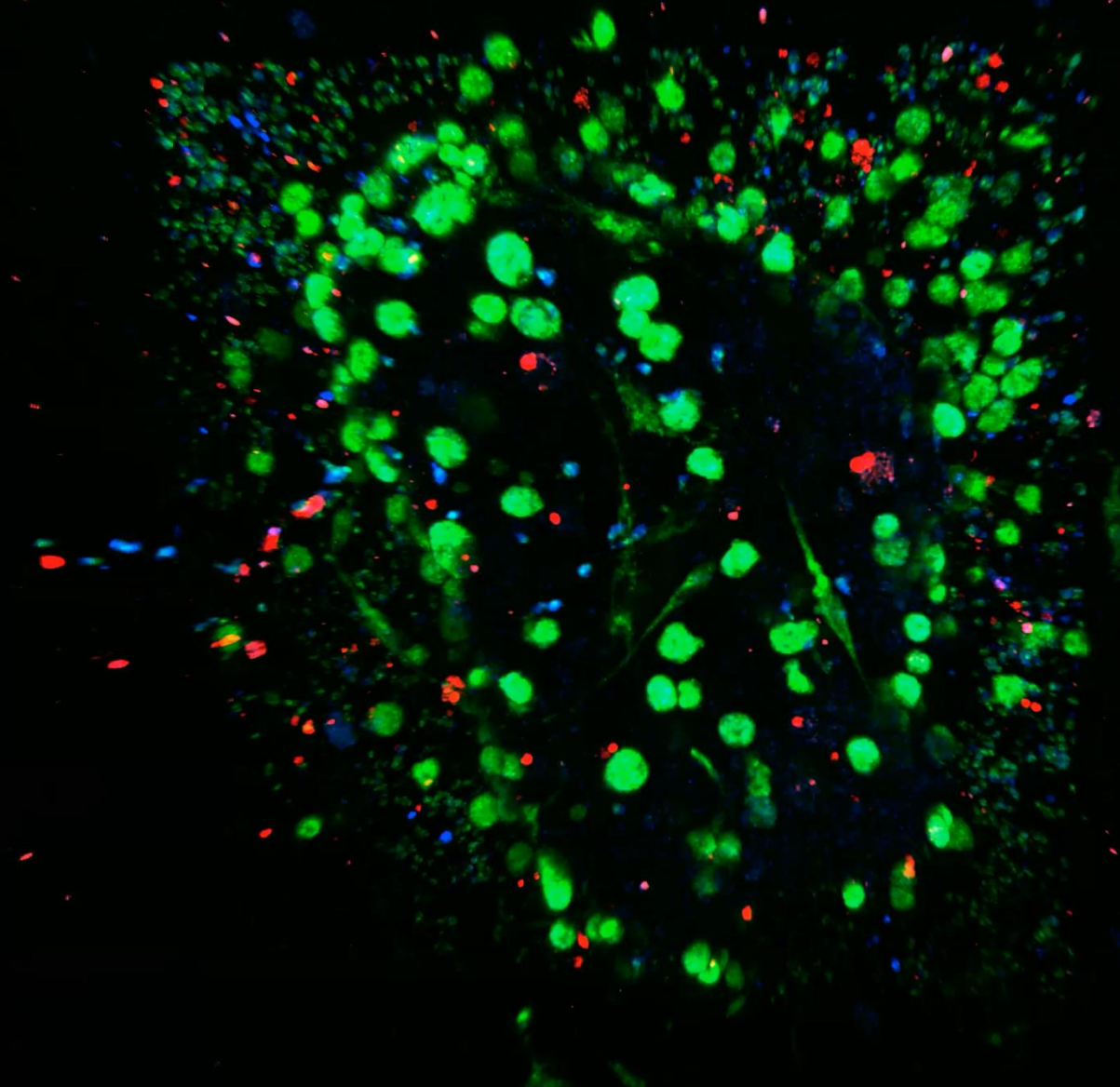
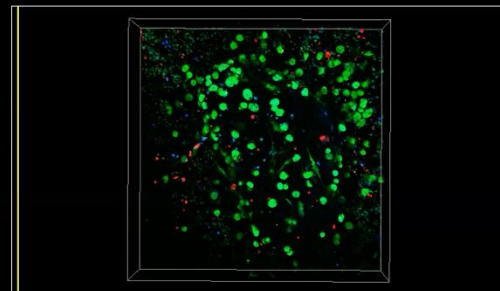
# We discovered that the genetic program that causes DMGs leads to massive production of GD2, a fatty sugar that can be targeted by Chimeric Antigen Receptors (CARs)



# CAR T-cell Therapy



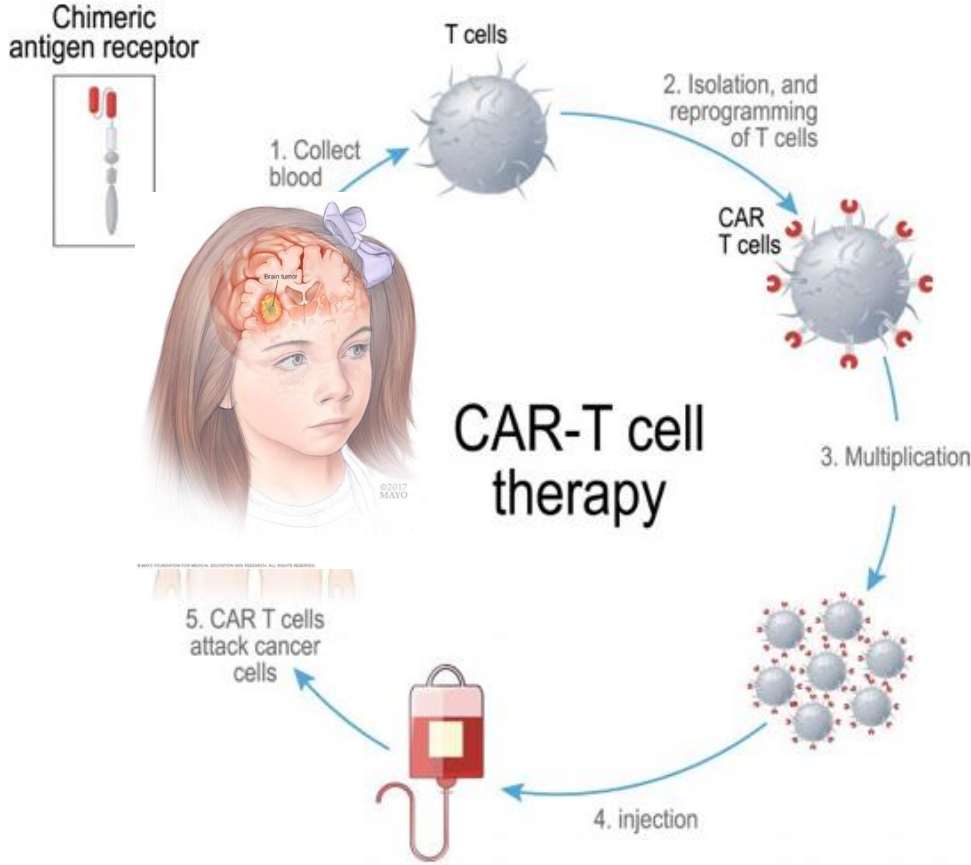
14-35 HOURS POST CAR T



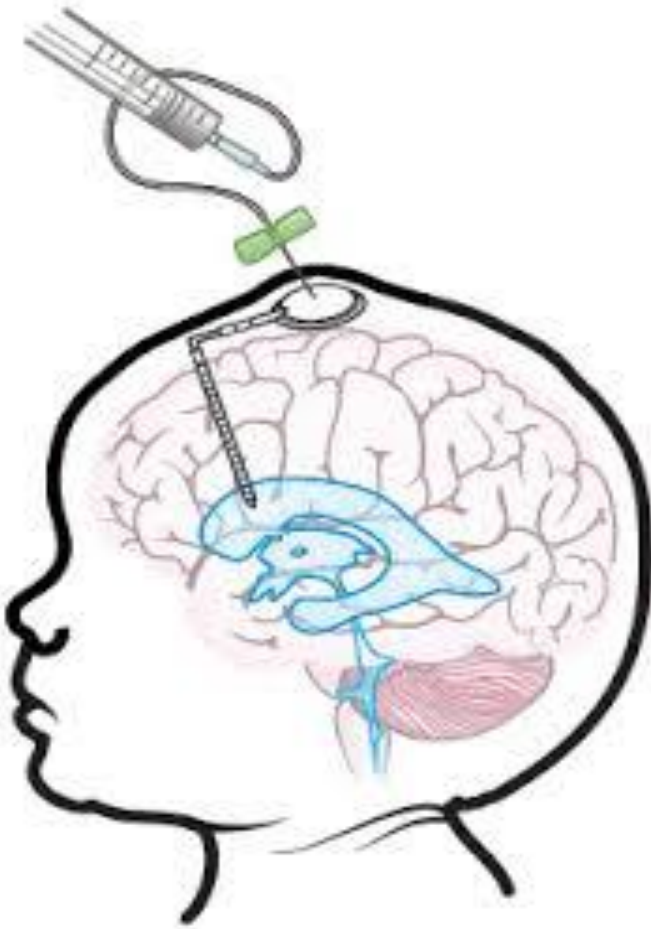
**Green = live tumor**  
**Red = dead cell**  
**Blue = CAR T cells**

# Opportunity: Systemic and/or Intracranial Delivery of GD2-CAR T Cells for a Lethal Pediatric Brain Tumor

## *Intravenous Delivery (IV)*

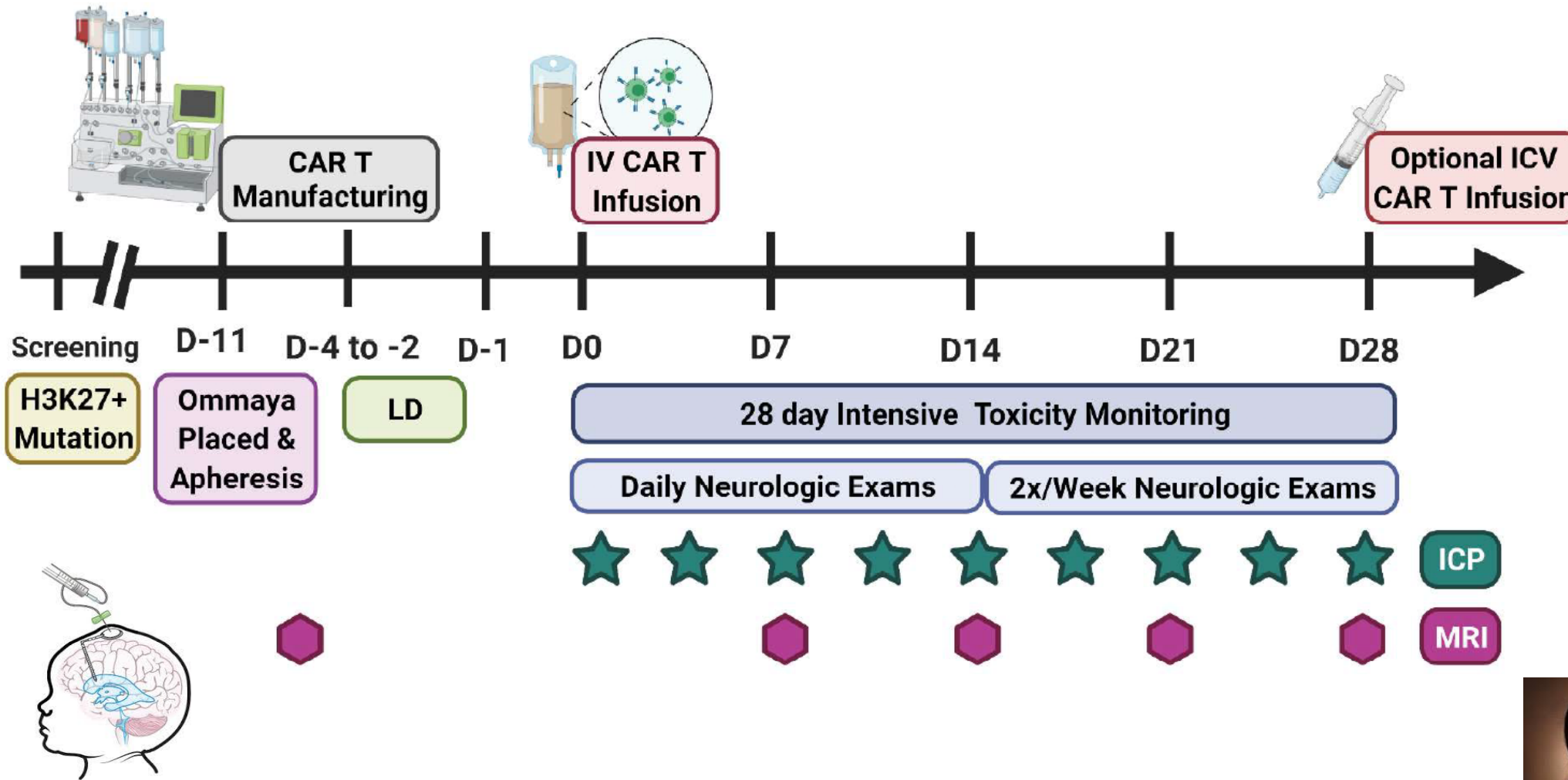


## *Delivery Into the CNS (ICV)*



# CLIN2-12595: CIRM Funded Phase 1 trial to assess feasibility and safety of GD2.41BB.z CAR T cells in H3K27M DMG

Arm A, Trial opened June 2020



Michelle Monje



Sneha Ramakrishna



Kun Wei Song



Robbie Majzner



Jasia Mahdi

# Pt. #3: Remarkable Clinical Response to ICV GD2-CART

Pre ICV GD2-CAR

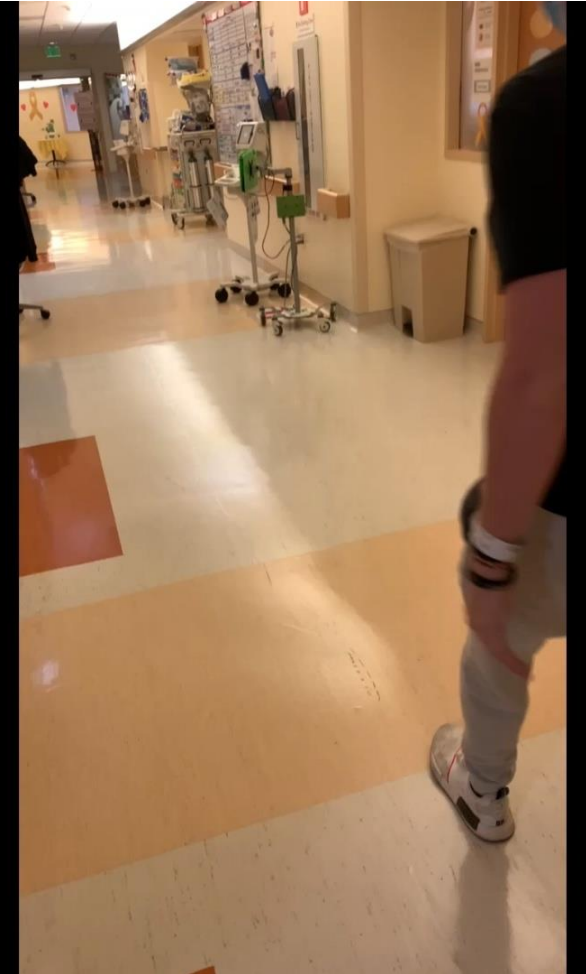
Post ICV GD2-CAR



Videos with  
patient's  
consent



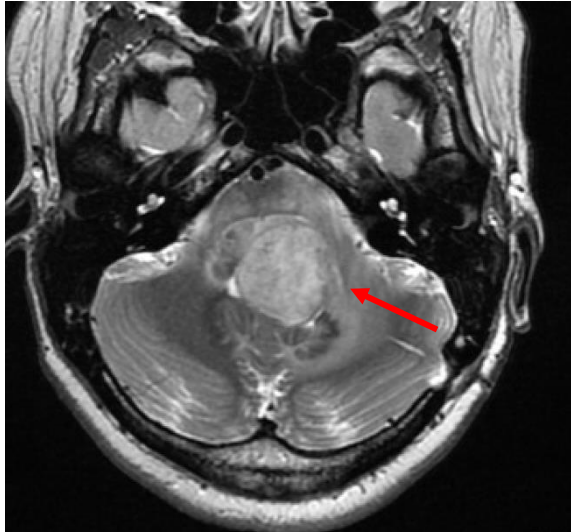
Pre ICV GD2-CAR



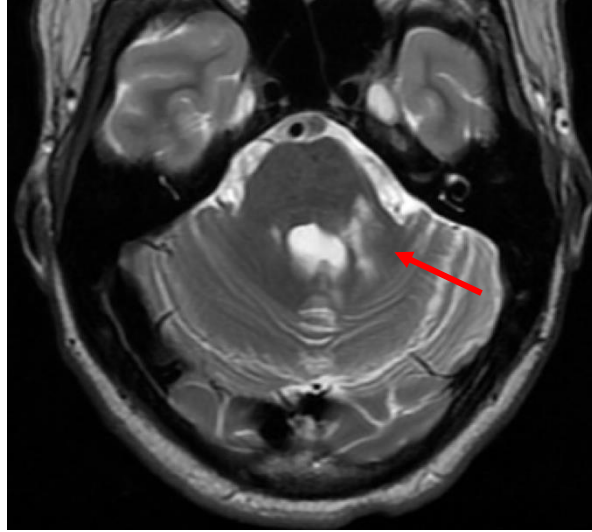
2 weeks post  
ICV GD2-CAR

# Pt. #10: 17-year-old male with DIPG achieved a CR over 6 infusions, response ongoing 5 years from diagnosis

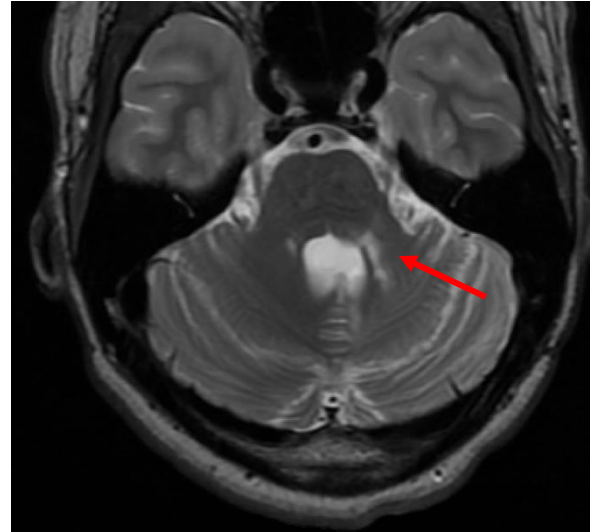
Baseline



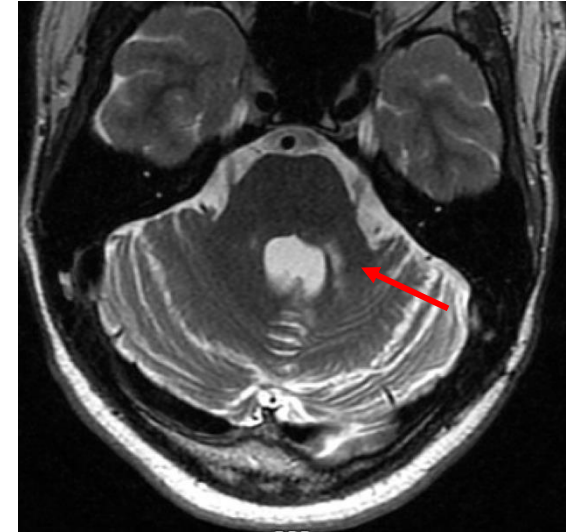
+3 months



+5 months



+8 months



## *Major clinical improvements:*

- *Wheelchair with any distance to independent walking*
- *Homebound at treatment entry in high school, in college and living independently, traveled Europe in summer 2024*

# Pt #10: Complete Radiographic Clearance Associated with Durable Clinical Benefit

Videos with patient's consent

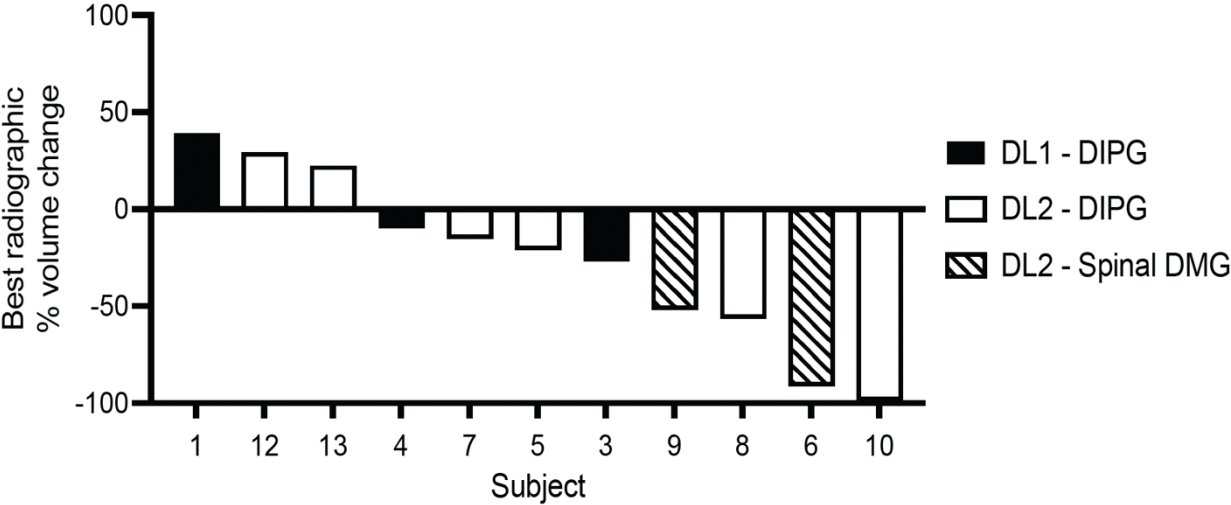


**One month after first infusion**

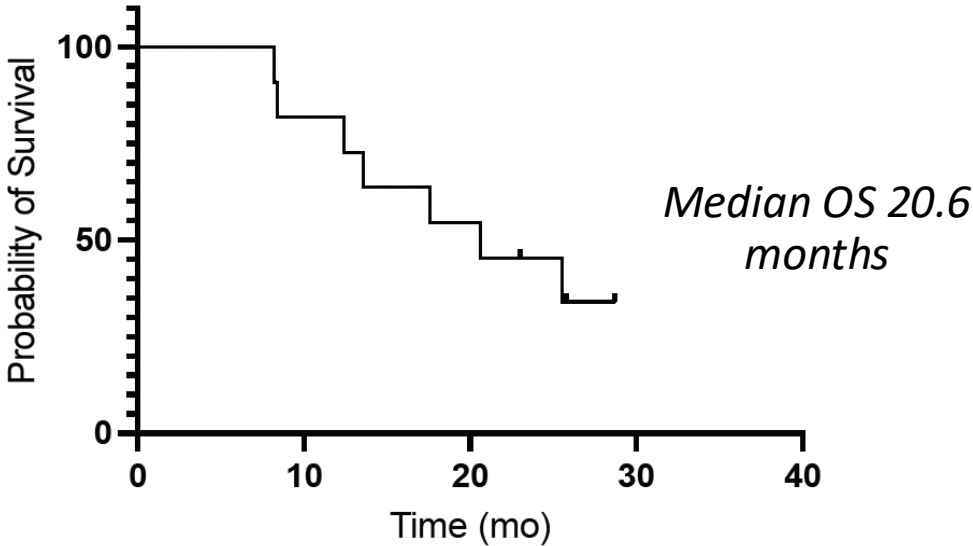


**8 months after first infusion**

# Arm A: IV followed by Sequential ICV Infusions of GD2-CAR For DMGs



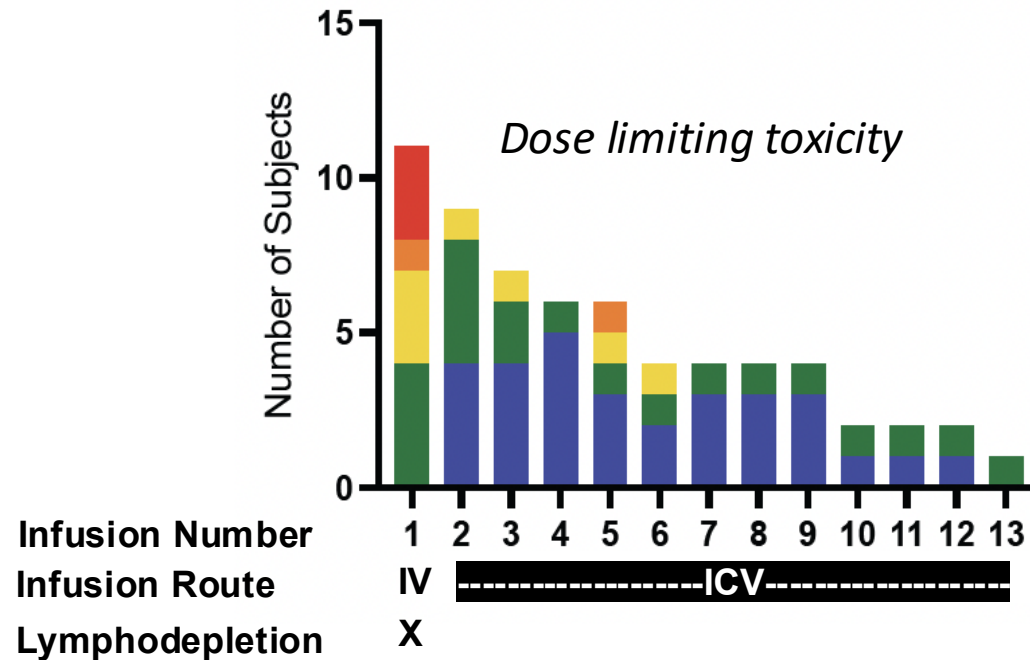
- 13 patients enrolled, 11 patients treated
- Substantial clinical benefit measured by neurologic improvement
- Significant numbers of patients had major tumor shrinkage
- Higher median overall survival compared to historical controls (20.6 months vs. 9-11 mos)



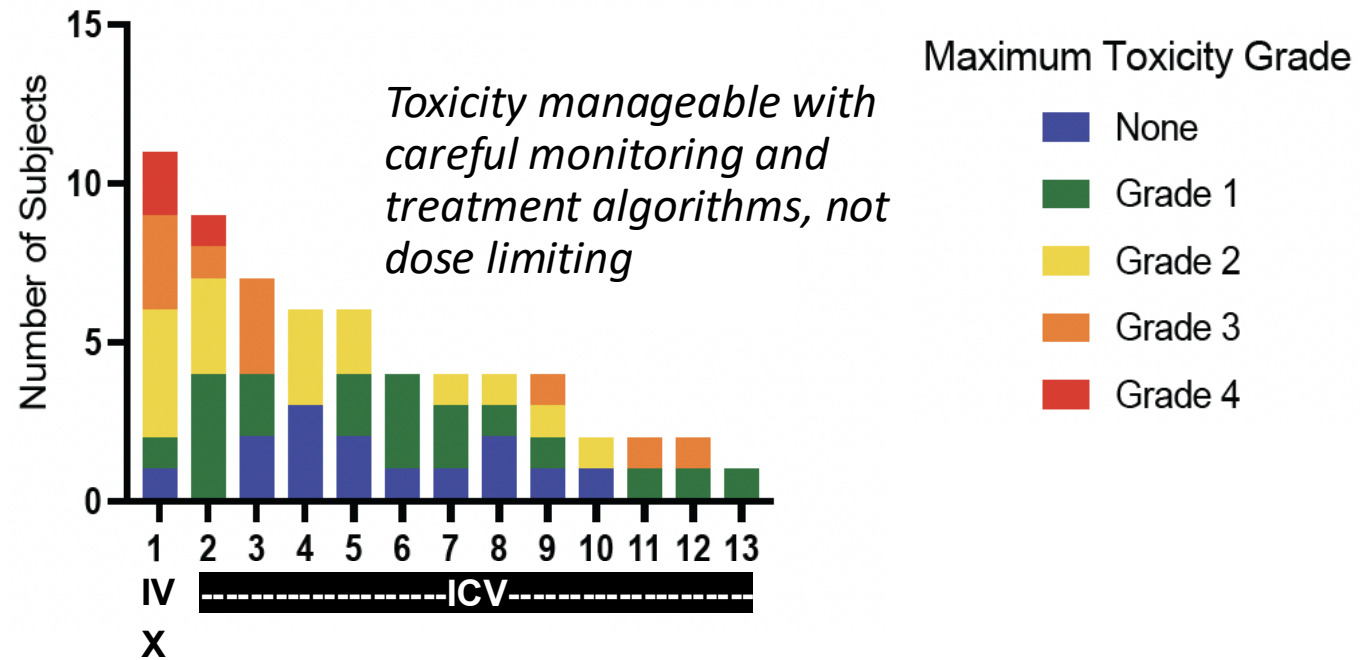
## Arm A Toxicity:

-IV infusion: Dose Limiting High-Grade Cytokine Release Syndrome

-ICV infusions: no Dose Limiting Toxicity



TIAN = Tumor Inflammation Associated Neurotoxicity

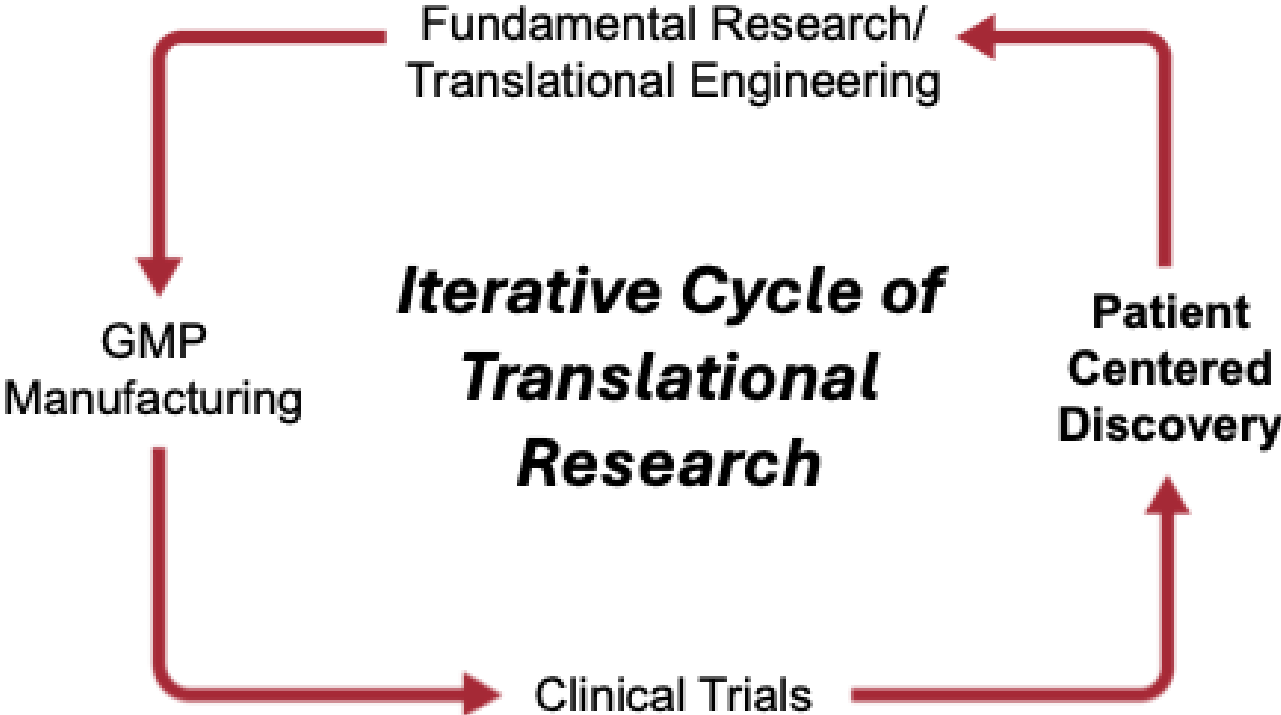


Majzner\*, Ramakrishna\*...Mackall^, Monje^ Nature, 2022

Monje....Mackall, Nature, 2024

Mahdi....Monje, Nature Med, 2023

# CIRM Funding Accelerates Progress by Enabling Patient Centered Discovery Research



*Why do some patients experience better outcomes than others?*

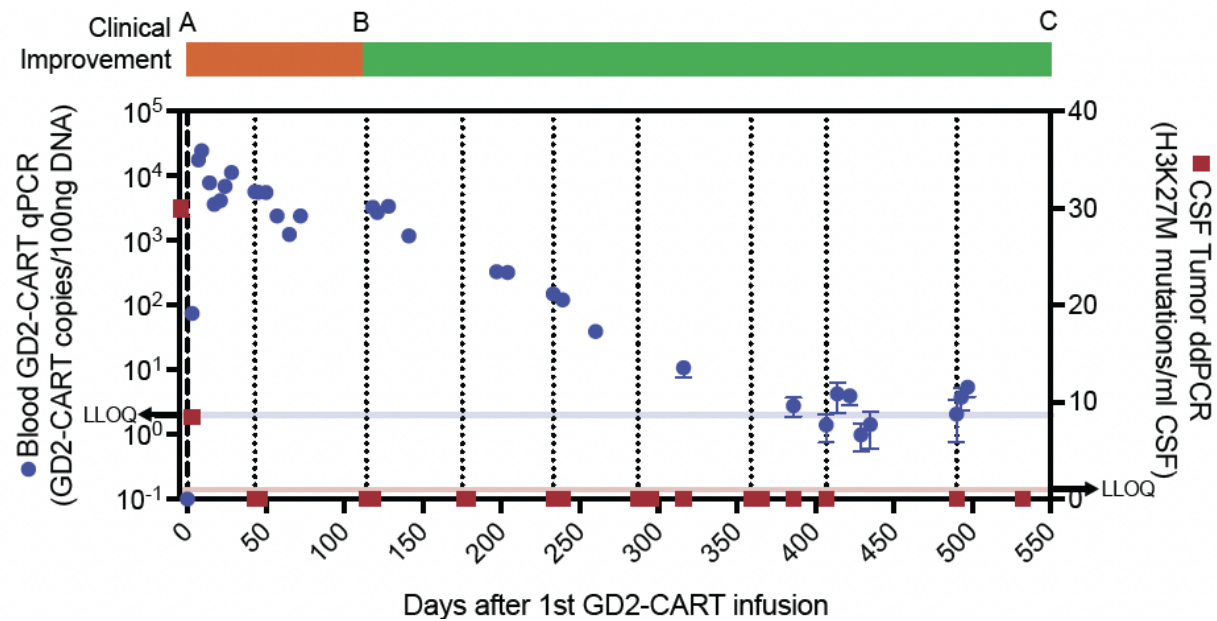
*How do the therapies fail?*

*What are the mechanisms of resistance?*

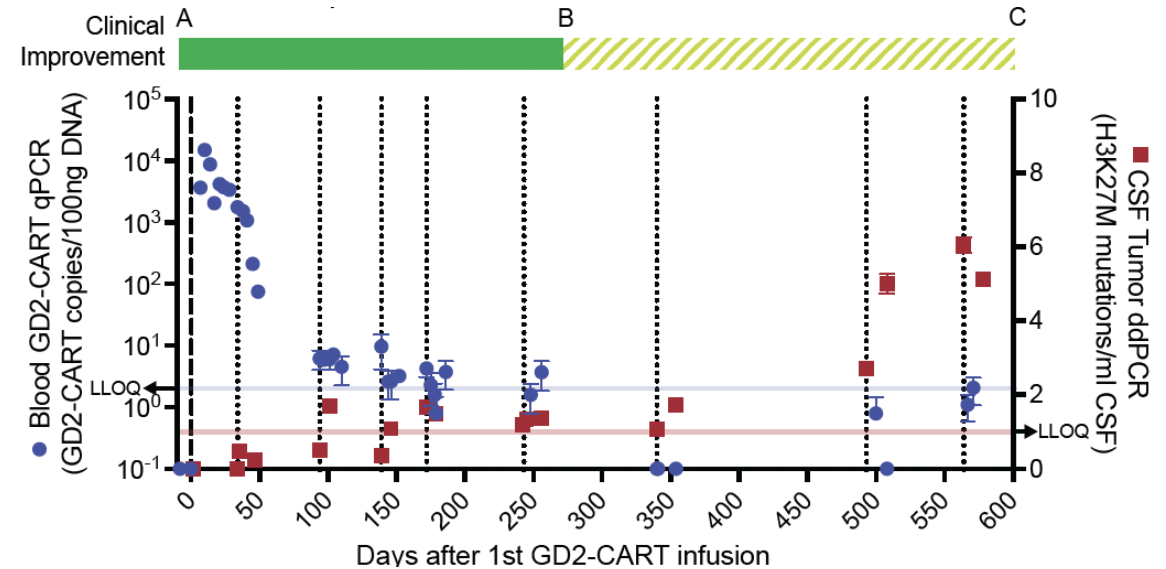
*What are the most important steps needed to improve the therapy?*

# Arm A: Durability of Response to GD2-CART Appears to Correlate with Durability of CAR T Cell Persistence?

Patient 10: Durable Complete Response & Durable Persistence



Patient 6: Near Complete Response Followed by Progression Temporally Associated with Loss of CAR T cells



- Clinical worsening
- Clinical improvement
- Mixed response

# Evolution of the Treatment Regimen to Diminish Toxicity Resulted in Diminished Efficacy

## Arm A (n=13)

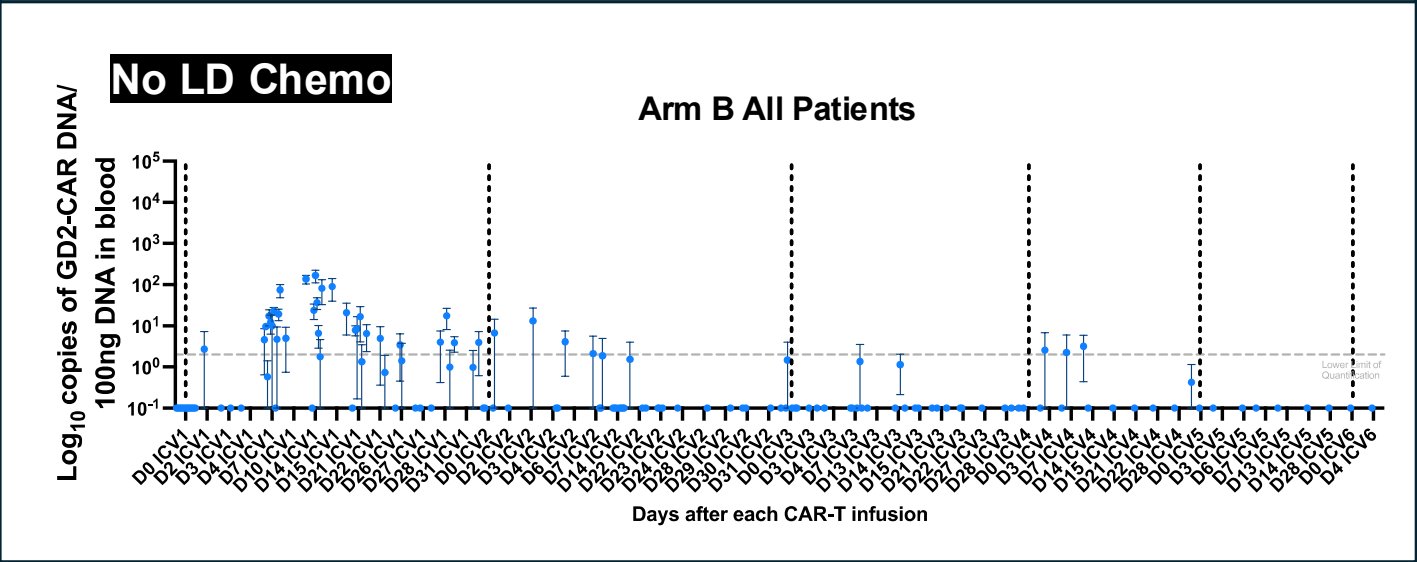
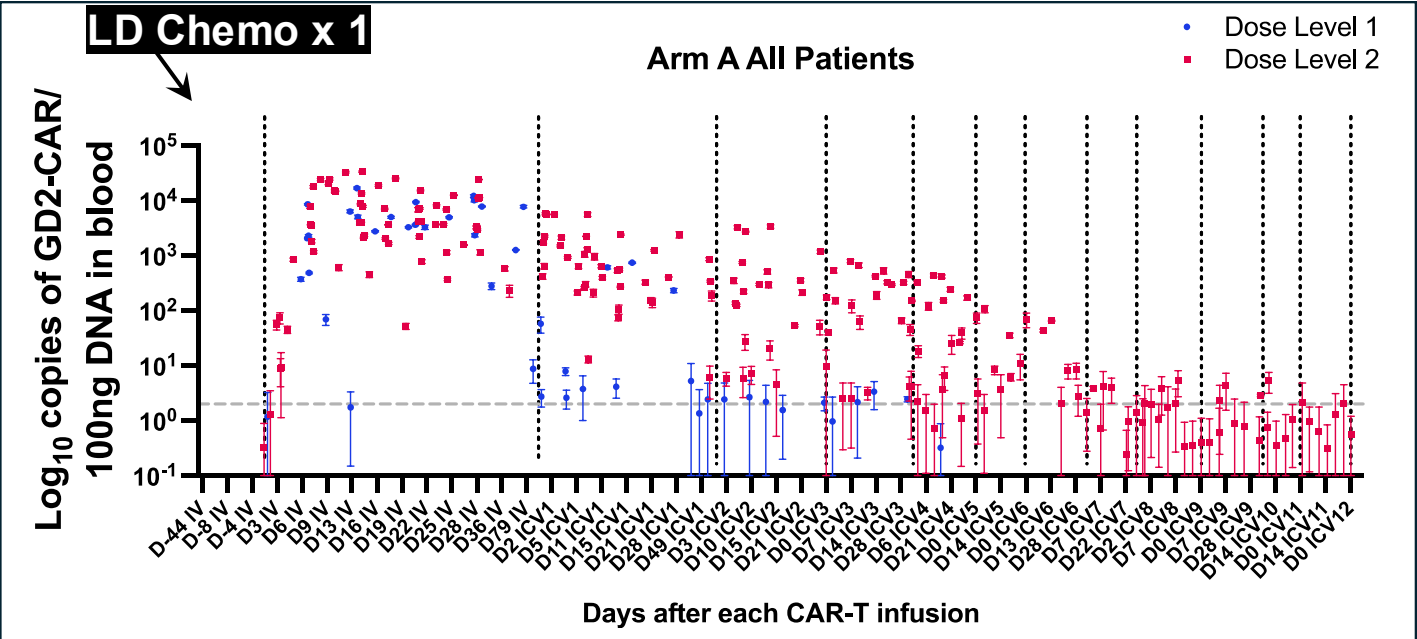
Regimen	Outcomes	Toxicity	Correlates
Lymphodepletion x 1 IV infusion x1 Sequential ICV	<b>OS 20.6 mos, Sustained clinical benefit</b>	<b>Dose limiting CRS</b>	Some patients with excellent persistence, ?better outcomes

*Based upon these results, we modified the protocol to open Arm B*

## Arm B (n=18)

Regimen	Outcomes	Toxicity	Correlates
No lymphodepletion Sequential ICV	<b>OS 14.8 mos, Transient clinical benefit</b>	Non-Dose limiting	Very poor CAR persistence

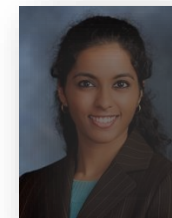
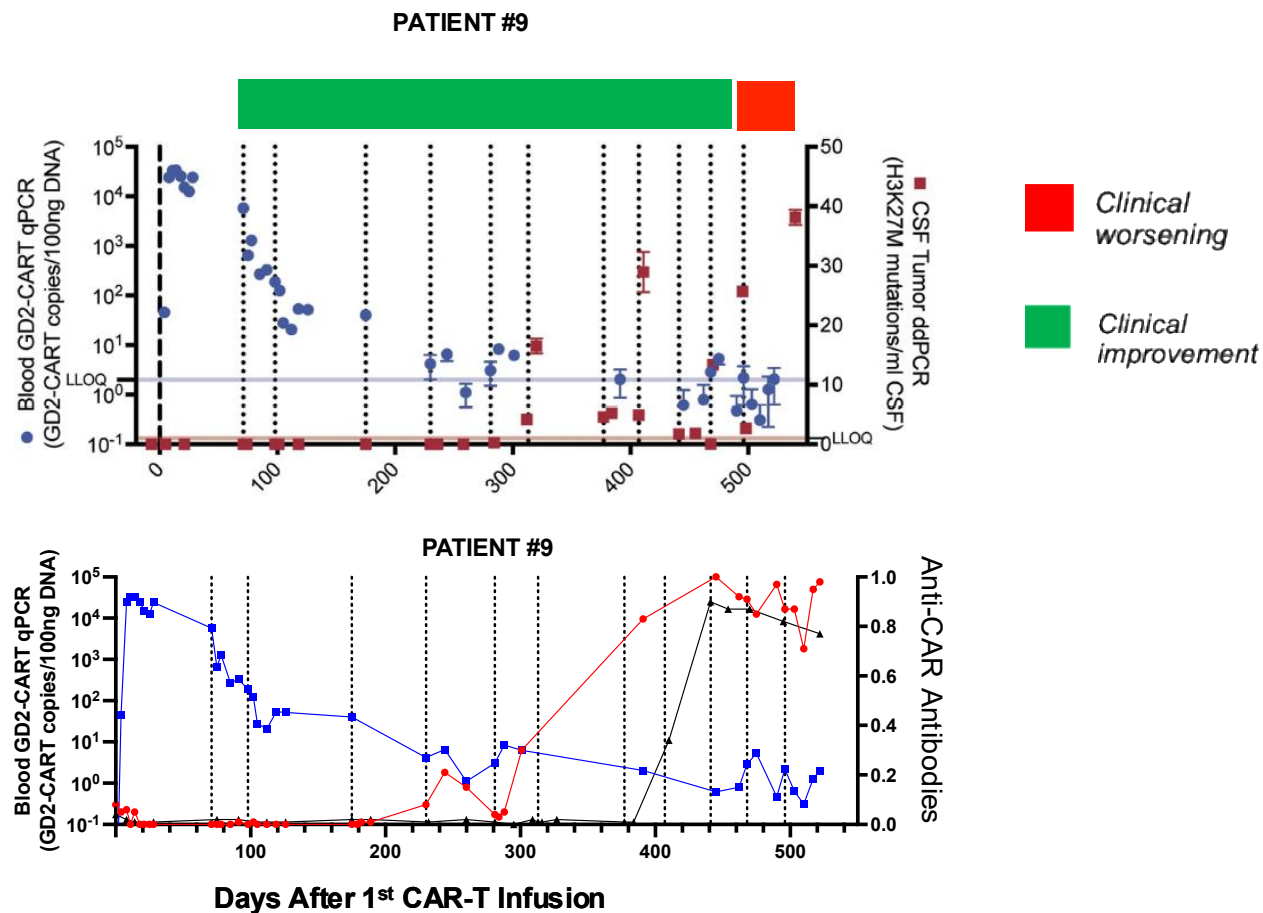
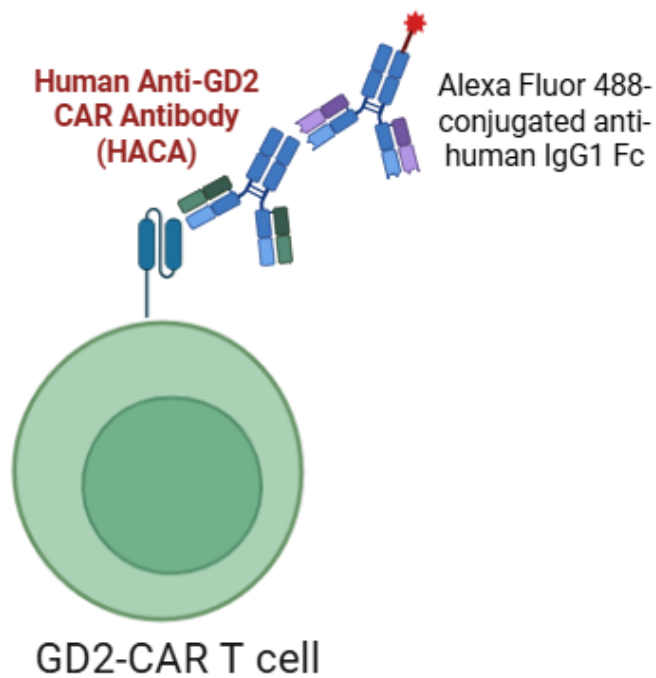
# GD2-CAR Persistence Much Greater on Arm A Than Arm B



# Anti-GD2-CAR Antibodies:

--Emerged in most patients on Arm A and temporally correlated with loss of GD2-CART persistence and tumor progression

--Emerged early on Arm B in all patients



Sneha Ramakrishna, MD



Bitu Saha PhD  
Director, CCSU

Nadya Iswari  
Ying-Wen Huang  
Zachary Ehlinger  
Chris Daghagh

*Hypothesis: Immune responses to the CAR T cells are limiting CAR persistence and preventing disease control. Lymphodepletion reduced these immune responses on Arm A.*

# Evolution of the Treatment Regimen Has Identified an Important Role for Lymphodepletion in Efficacy

Regimen	Outcomes	Toxicity	CAR Persistence	Anti-CAR immune responses
<b>Arm A (n=13)</b>				
<b>Lymphodepletion x 1</b> IV infusion x1 Sequential ICV	<b>Median OS 20.6 mos,</b> <b>Sustained benefit</b>	Dose limiting CRS	Greater persistence correlates with better outcomes	Many patients, occur late
<b>Arm B (n=18)</b>				
<b>No lymphodepletion</b> Sequential ICV	<b>Median OS 14.8 mos,</b> <b>Transient benefit</b>	Non-Dose limiting	Very poor CAR persistence	All patients, occur early
<b>Arm C (n=11)</b>				
<b>Sequential lymphodepletion</b> Sequential ICV	<b>Median OS not reached</b>	Non-Dose limiting	Better CAR persistence	Preliminary data shows lower levels but still present
<b>Arm D (now enrolling)</b>				
<b>Sequential lymphodepletion + rituximab,</b> Sequential ICV	<b>Too early</b>	Non-dose limiting thus far	Pending	Pending

# Current Status and Next Steps

- **CLIN2-12595** Demonstrated safety and significant clinical efficacy of GD2-CAR T cells for a universally lethal brain tumor for which no standard upfront therapies are available beyond palliative radiation.
  - Patients appear to be living longer and are experiencing better quality of life following GD2-CART
- We have learned that the target product profile requires sequential intracerebral infusions and sequential lymphodepleting chemotherapy, likely with rituximab (mirror Arm D).
- Based upon these promising results, this therapy has been designated an Regenerative Medicine Advanced Therapeutic by the US FDA.
- We have completed a Comprehensive RMAT Type B Meeting with the US FDA, which has provided critical details regarding steps necessary for pivotal testing:
  - Clinical manufacturing and controls
  - Primary and secondary endpoints
- Next steps
  - Completion of the current Phase I single institution trial funded by the CLIN2-12595
  - Conduct a (small) multisite Phase I to ensure reproducibility of results and train non-Stanford investigators regarding toxicity management
  - Launch multisite potentially pivotal single arm Phase II to demonstrate efficacy
  - File Biological License Application
- This success has emphasized a critical need for to bring active cell/gene therapies for market for rare diseases.

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# Enhancing pediatric access to cell and gene therapies

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Received: 5 January 2024


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Accepted: 30 April 2024






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 Check for updates

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

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# ACCESSforKIDS

A *not-for-profit 501c3* with a nested Public Benefit Corporation (B Corp) *for-profit subsidiary* designed to *bridge the pharma valley of death* and *expand access for children* by developing and commercializing *life-saving advanced medicines* for pediatric oncology indications

***Our approach will disrupt the typical cell therapy and not-for-profit landscapes to create a sustainable organization***



Mission-driven approach



Lean, virtual biotech



Subsidiary for-profit public benefit corp.



Low-cost IP acquisition



Development and commercialization cost reduction



De-risked asset portfolio

# CONTRIBUTORS



## Pediatric Cancer Cellular Therapy

- Sneha Ramakrishna
- Katie Ryan
- Kara Davis
- Liora Schultz
- Raya Saab
- Christina Baggott
- Michelle Fujimoto
- Michael Kunicki
- Robbie Majzner\*

## CCT

- Casey Carr
- Katie Kong
- Carol Sinoben

## Collaborators

- Sabine Heitzeneder
- Zina Good

## Neuro-Oncology

- Michelle Monje
- Kun-Wei Song
- Sonia Partap
- Cynthia Campen
- Barb Beebe
- Divya Madhav
- Katie Ryan
- Paul Fisher
- Jasia Mahdi\*

## Neurosurgery

- Neurosurgery NP and resident team
- Michael Lim
- Laura Prolo
- Kelly Mahaney
- May Casazza
- Diana Poon

## Stanford GMP Team

- Steve Feldman
- Ramya Tanuguntla
- Nikolaos Gkitsas

## LPCH Inpatient

- Team C
- PICU
- Countless nurses, physicians, pharmacists, and others...

## Monje Lab

- Chris Mount
- Anna Geraghty
- Pam Woo
- Daniel Zamler

## CCSU

- Bita Sahaf
- Nadya Iswari
- Ying-Wen Huang
- Chris Daghigh
- Sreevidya Kurra
- Jeffrey Waters
- Zach Ehlinger
- Fang Wu
- Anita Wong
- Moksha Desai
- Snehit Prabhu

## Regulatory Team

- Emily Egeler
- Fahn Bryant
- Monika Patel
- Sharon Mavroukakis

## Mackall Lab

- Elena Sotillo
- Yiyun Chen
- Vandon Duong
- Hima Abunathan
- Sean Yamada-Hunter
- Anne Marjin Kramer
- Naiara Martinez Velez
- Diren Usta
- Cindy Klein
- Aarti Malhotra
- Kevin Reynolds
- Maria Del Carmen Arenas
- Diane Cruz Manjarrez
- Nikoo Jafari
- Kelvin Mo
- Kylie Burdsall
- Adria Canellos Socias
- Alex Salter
- Jeremy Bjelajac
- Audre May
- William Wang
- Frank Lin
- Tara Murty
- Peng Xu
- Kaithlen Pacheco
- Patrick Quinn
- Naiara Martinez Velez
- Meena Malipotlolla
- Preeti Nehra
- Kristin Tsui

Our patients and families!

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