Advances in Cellular Therapies for Cancer

CAR T cell Therapy

Mohamed Abou-el-Enein, MD, PhD, MSPH
Executive Director, USC/CHLA Cell Therapy Program
Director, USC/CHLA cGMP Facility
Associate Professor of Clinical Medicine (Oncology), Pediatrics, and Stem Cell Biology & Regenerative Medicine

August 25, 2024

California Cancer Consortium Conference

USC University of Southern California

Children's Hospital LOS ANGELES

Agenda

- Introduction to CAR T Cell Therapy and Its Clinical Applications
- Key Challenges in CAR T Cell Therapy Development
  - ❑ Safety: Addressing Second Primary Malignancies
  - ❑ Scalability: Enhancing Production and Accessibility
- Innovative Solutions and Current Developments
- Efficacy in Solid Tumors: Breaking Barriers

USC University of Southern California

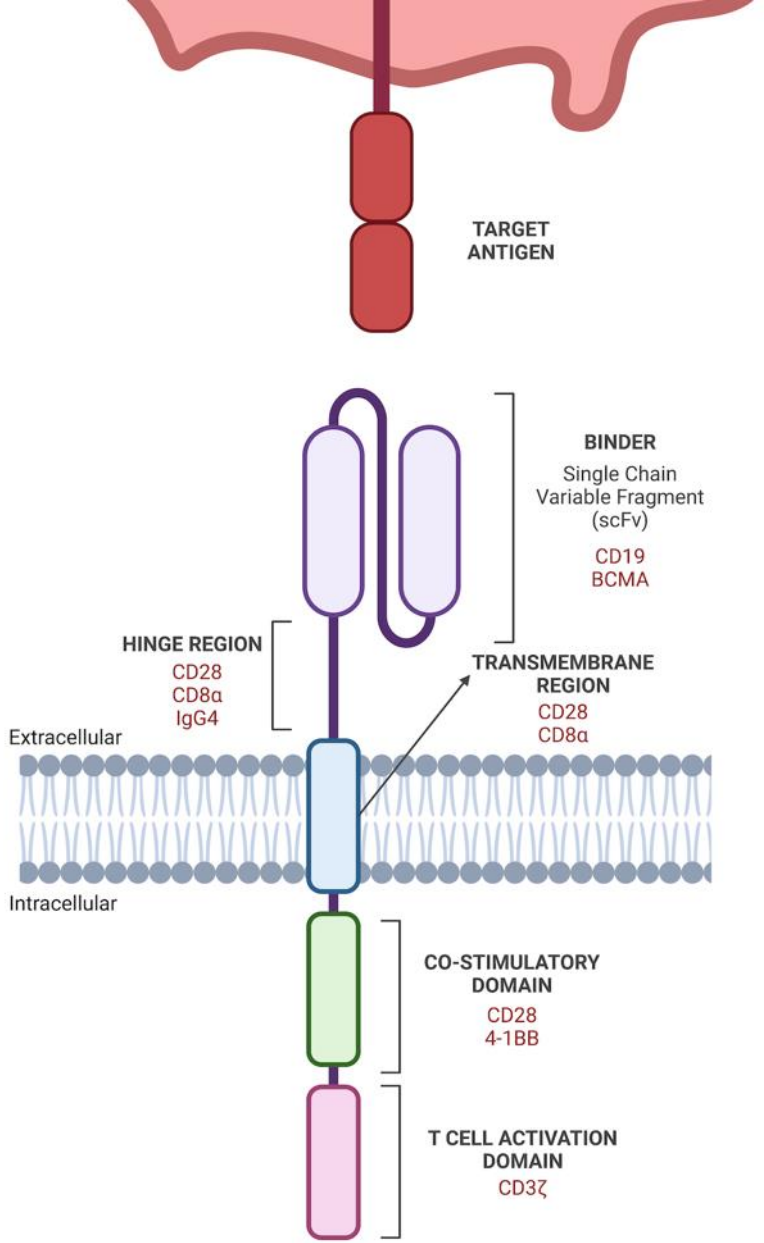
Children's Hospital LOS ANGELES

Principles of CAR T cells

- **CAR T cells:** Personalized immunotherapy using patient's own T cells, genetically engineered to target specific tumor antigens for cancer treatment.

- **Chimeric Antigen Receptor (CAR) Structure:**

  - **Binder**: Ensures antigen recognition, specificity, and affinity
  - **Hinge region**: Provides flexibility and maintains optimal distance to the target
  - **Transmembrane Region**: Contributes to receptor stability and function
  - **Co-stimulatory Domain**: Augments T cell function, metabolism, and persistence
  - **T cell activation domain**: Facilitates downstream T cell activation and functional responses



Second Generation CAR Structure

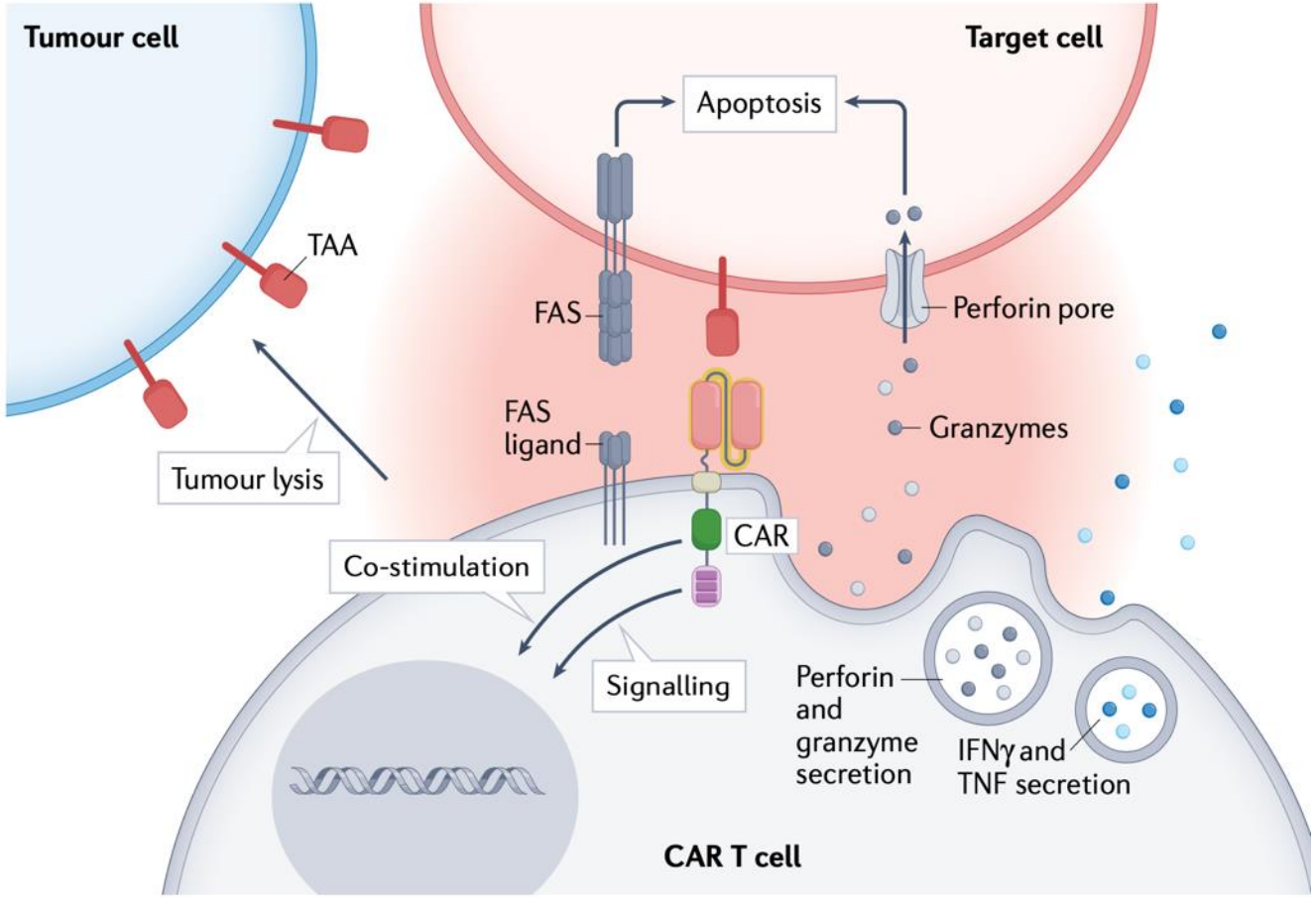
USC University of Southern California

Children's Hospital LOS ANGELES

Principles of CAR T cells

- **CAR T Cell Killing Mechanism:**
  - Recognize Tumor-Associated Antigen (TAA)
  - Form Immune Synapse with Target Cell
  - Release Cytotoxic Granules
  - Induce Target Cell Apoptosis
  - Trigger Cytokine Release & Immune Activation

- **Main target**: **CD19**, specifically expressed on B-cells
- Remarkable success in hematological B-cell malignancies as a **third line** of treatment in **Lymphoma** and **Leukemia**
- Recently approved CAR T-cells targeting **BCMA for Multiple Myeloma**



Flugel et al. Nat. Rev. Clin. Oncol. 2022

USC University of Southern California

Children's Hospital LOS ANGELES

FDA Approved CAR T cells in Hematological Malignancies

2017	tisagenlecleucel	Acute lymphoblastic leukemia (ALL) (B-cell precursor) Large B-cell lymphoma (LBCL) Follicular lymphoma (FL)
	axicabtagene ciloleucel	Large B-cell lymphoma (LBCL) Follicular lymphoma (FL)
2020	brexucabtagene autoleucel	Mantle cell lymphoma Acute lymphoblastic leukemia (ALL) (B-cell precursor)
2021	lisocabtagene maraleucel	Large B-cell lymphoma (LBCL) Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL)
	idecabtagene vicleucel	Multiple Myeloma (MM)
2022	ciltacabtagene autoleucel	Multiple Myeloma (MM)

USC University of Southern California

Children's Hospital LOS ANGELES

Approval restricted to patient populations and treatment line

CAR T Cells in Lymphoma: Pivotal Trials

Product	Disease	Trial	Line of treatment	Trial Phase	Overall Response	Event Free Survival	CRS	Neuro-toxicity	Reference
Tisa-cel	LBCL	JULIET (2018)	3rd	Phase II	52% (CR 40%)	NR	22%	12%	Schuster et al., 2019
		BELINDA (Primary endpoint unmet)	2nd	Phase III Kymriah vs SC	38.3% vs 53.8%	=3m	61.3%	10.3%	Bishop et al., 2022
	FL	ELARA (2022)	3rd	Phase II	86.2% (CR 69.1%)	NR	48.5%	4.1%	Fowler et al. 2022
Axi-cel	LBCL	ZUMA-1 (2017)	3rd	Phase II	82% (CR 54%)	5.7m	93%	64%	Neelapu et al., 2017
		ZUMA-7 (2022)	2nd	Phase III Yescarta vs SC	83% (CR 65%) vs 50% (CR 32%)	8.3m vs 2m	92%	60%	Locke et al., 2022
		ZUMA-12 (Primary endpoint met)	1st	Phase II	CR 78%	73% at 12m	100%	73%	Neelapu et al., 2022
	FL	ZUMA-5 (2021)	3rd	Phase II	91% (CR 60%)	NR	88%	81%	Jacobson et al., 2021

USC University of Southern California

Children's Hospital LOS ANGELES

LBCL; large B-cell lymphoma,
FL; follicular lymphoma

CAR T Cells in Lymphoma: Pivotal Trials

Product	Disease	Trial	Line of treatment	Trial Phase	Overall Remission	Event Free survival	CRS	Neuro-toxicity	Reference
Brexu-cel	MCL	ZUMA-2 (2020)	2nd	Phase II	85% (59% CR)	NR	91%	63%	Wang et al., 2020
Liso-cel	LBCL	TRANSCEND NHL 001 (2021)	3rd	Phase I	73% (CR 53%)	NR	42%	30%	Abramson et al. 2020
		TRANSFORM 2022 (Primary endpoint met)	2nd	Phase III Breyanzi vs SC	CR 66% vs CR 39%	10.1m vs 2.3m	49%	12%	Kamdar et al. 2022

USC University of Southern California

Children's Hospital LOS ANGELES

LBCL; large B-cell lymphoma,
MCL; Mantle Cell Lymphoma

CAR T Cells in Leukemia: Pivotal Trials

Product	Disease	Trial	Line of Treatment	Trial Phase	Overall Remission	Event Free Survival	CRS	Neuro-toxicity	Reference
Tisa-cel	ALL (Pediatric and young adults)	ELIANA (2017)	3rd	Phase I-II	82.5% (CR 63% + CRi 19%)	73%	77%	40%	Maude et al., 2018
Brexu-cel	ALL (Adults)	ZUMA -3 (2021)	3rd	Phase II	56% CR	NR	92%	87%	Shah et al. 2021
Liso-cel	CLL and SLL	TRANSCEND CLL004 (2023)	3rd	Phase I-II	18% CR	NR	9%	18%	Siddiqi et al. 2023

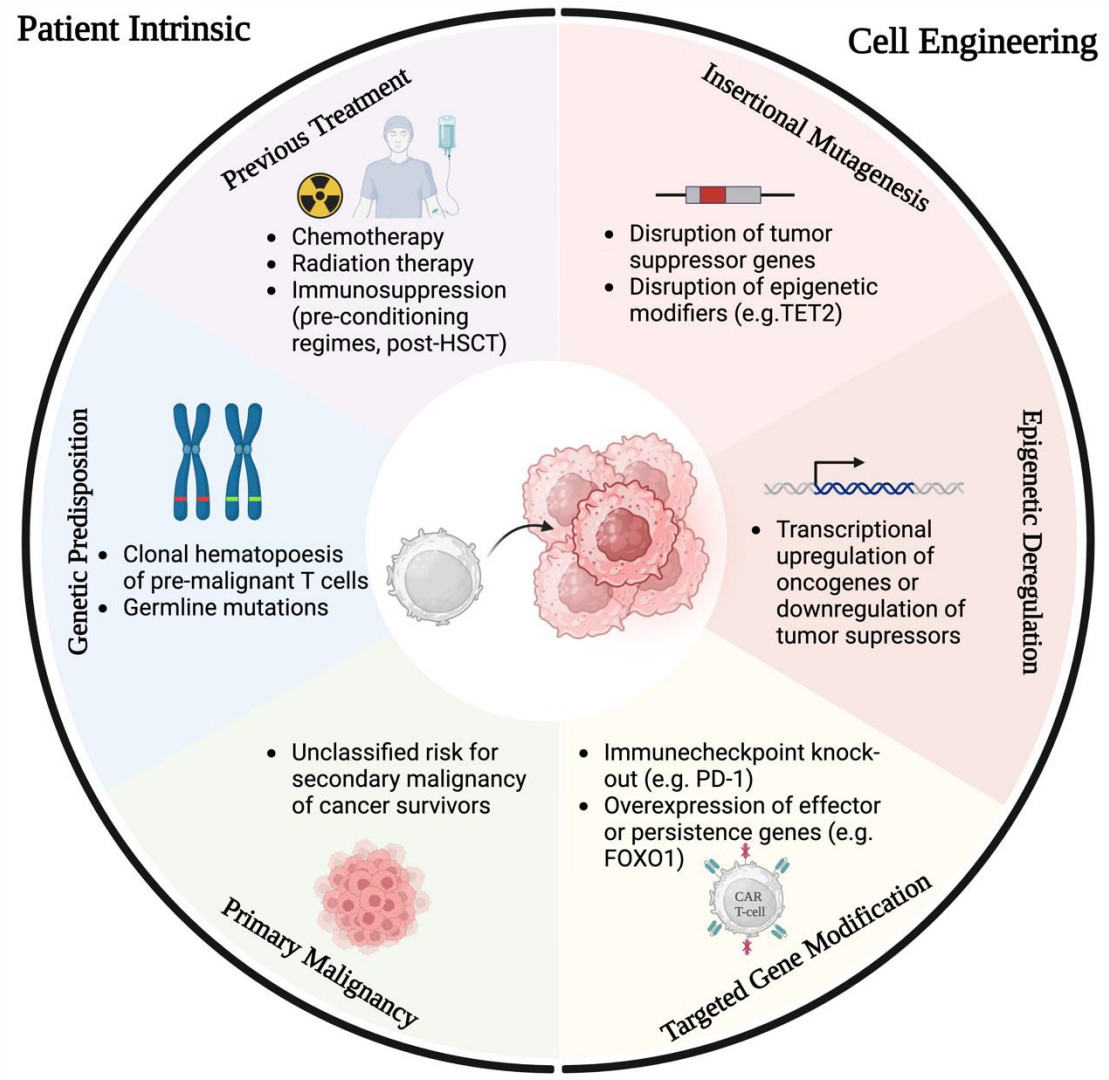
USC University of Southern California

Children's Hospital LOS ANGELES

B-ALL; B-cell acute lymphoblastic leukemia,
CLL; Chronic Lymphocytic Leukaemia
SLL: Small Lymphocytic Lymphoma

Key Challenges: CAR+ T-cell Second Primary Malignancies

- **Nov 2023: 22 cases of secondary T-cell malignancies** following CAR T-cell therapy
- **Potential cause:** Combination of *pre-existing and CAR T-cell genetic engineering derived* genetic and epigenetic alterations (e.g. use of viral vectors).
- *Not all of these cases have been definitively linked to CAR T cell treatment.*
- **Mitigation:** Requires multifaceted strategies, including patient education, stringent genomic monitoring, and continued regulatory oversight and surveillance.
- **Solution:** Next-generation CARs with enhanced targeting and safety features.



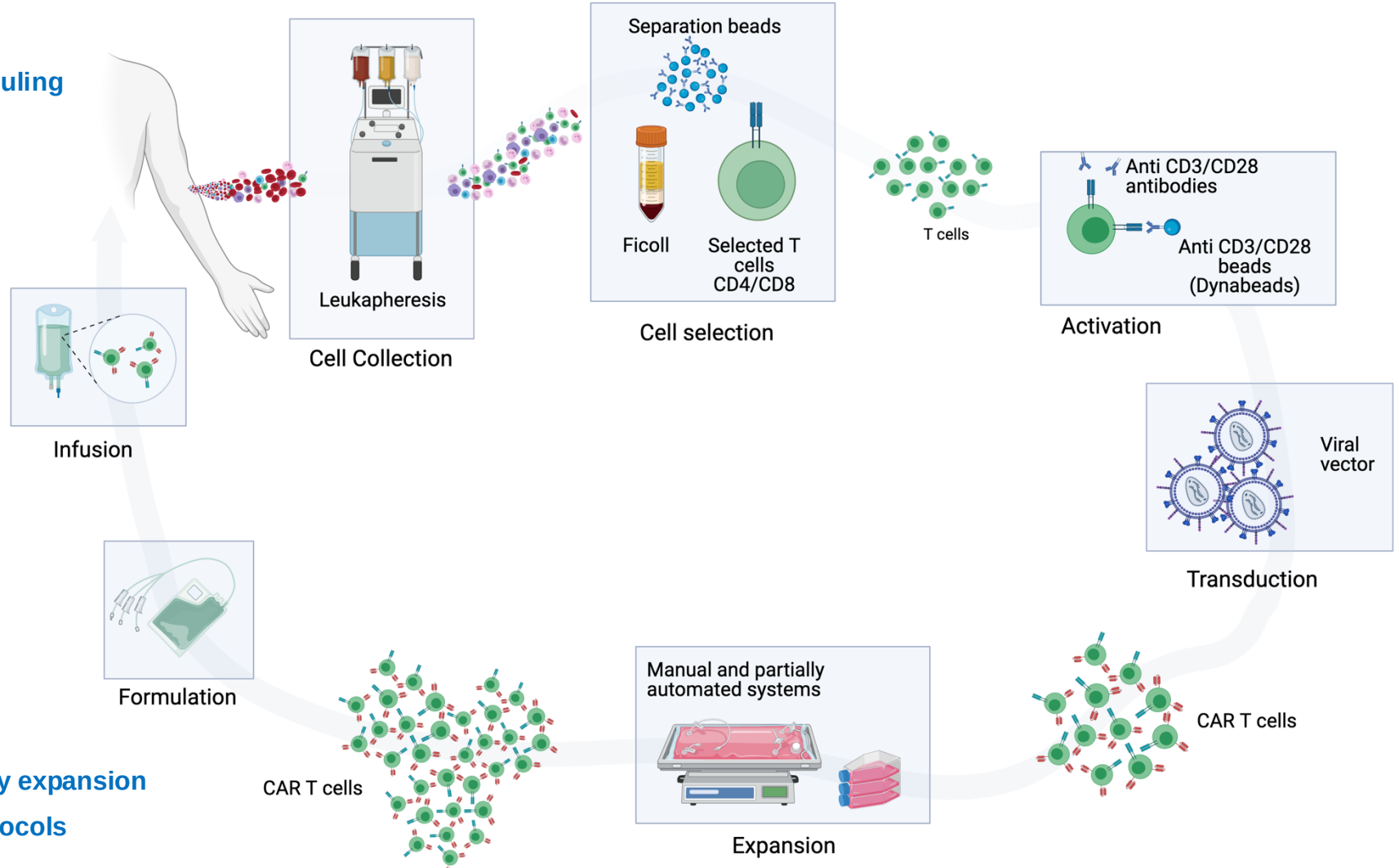
Abou-el-Enein et. al. (2024), Blood Cancer Discov

USC University of Southern California

Children's Hospital LOS ANGELES

Key Challenges: Scaling CAR T Cell Manufacturing

(1) Patient scheduling and cell fitness limitations



(2) Viral vector manufacturing, testing and supply constrains

(3) Manual or bulky systems

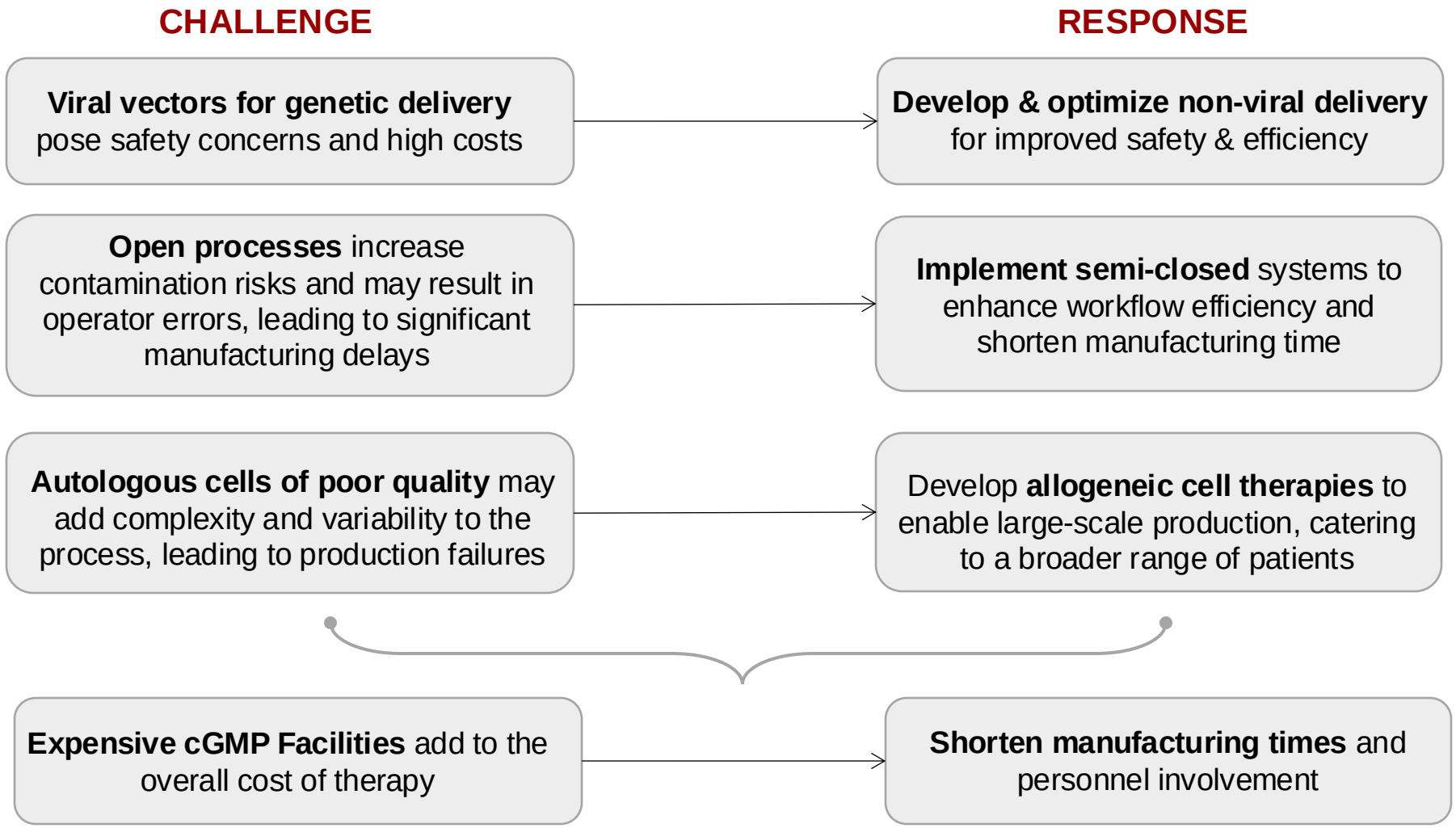
(4) Lengthy expansion protocols

USC University of Southern California

Children's Hospital LOS ANGELES

Abou-el-Enein et. al. (2021), Blood Cancer Discov (Adapted)

Innovative Solutions and Current Developments

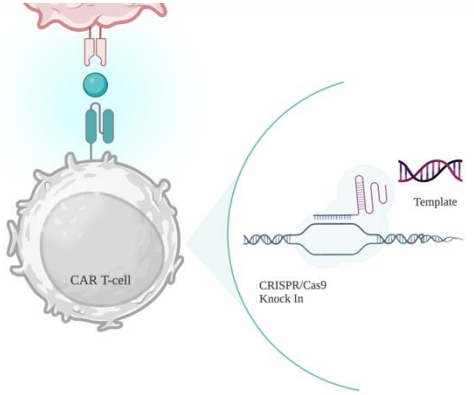


USC University of Southern California

Children's Hospital LOS ANGELES

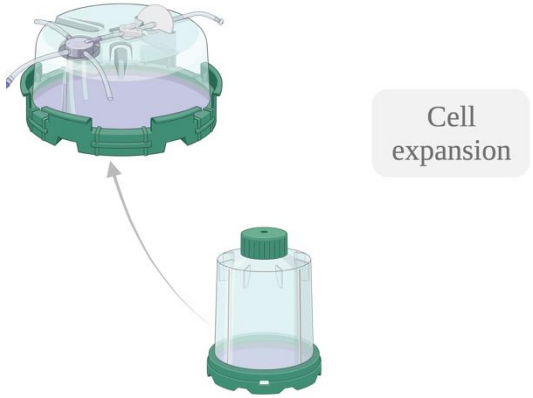
Innovative Solutions and Current Developments

Non - Viral



- Low Immunogenicity
- Low cost
- Scalable
- Enable multiplex editing

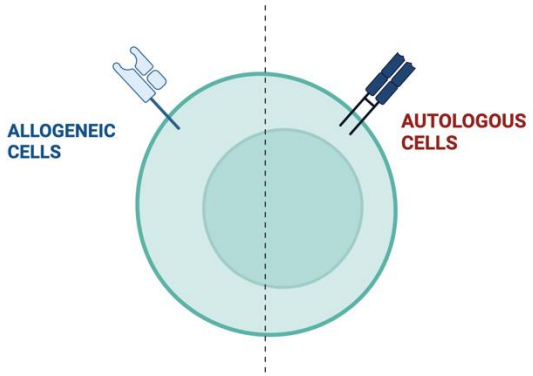
Semi-closed



G-Rex

- Adaptable semi-closed system
- Scalable
- Requires less space
- Achieve better yield

Allogeneic

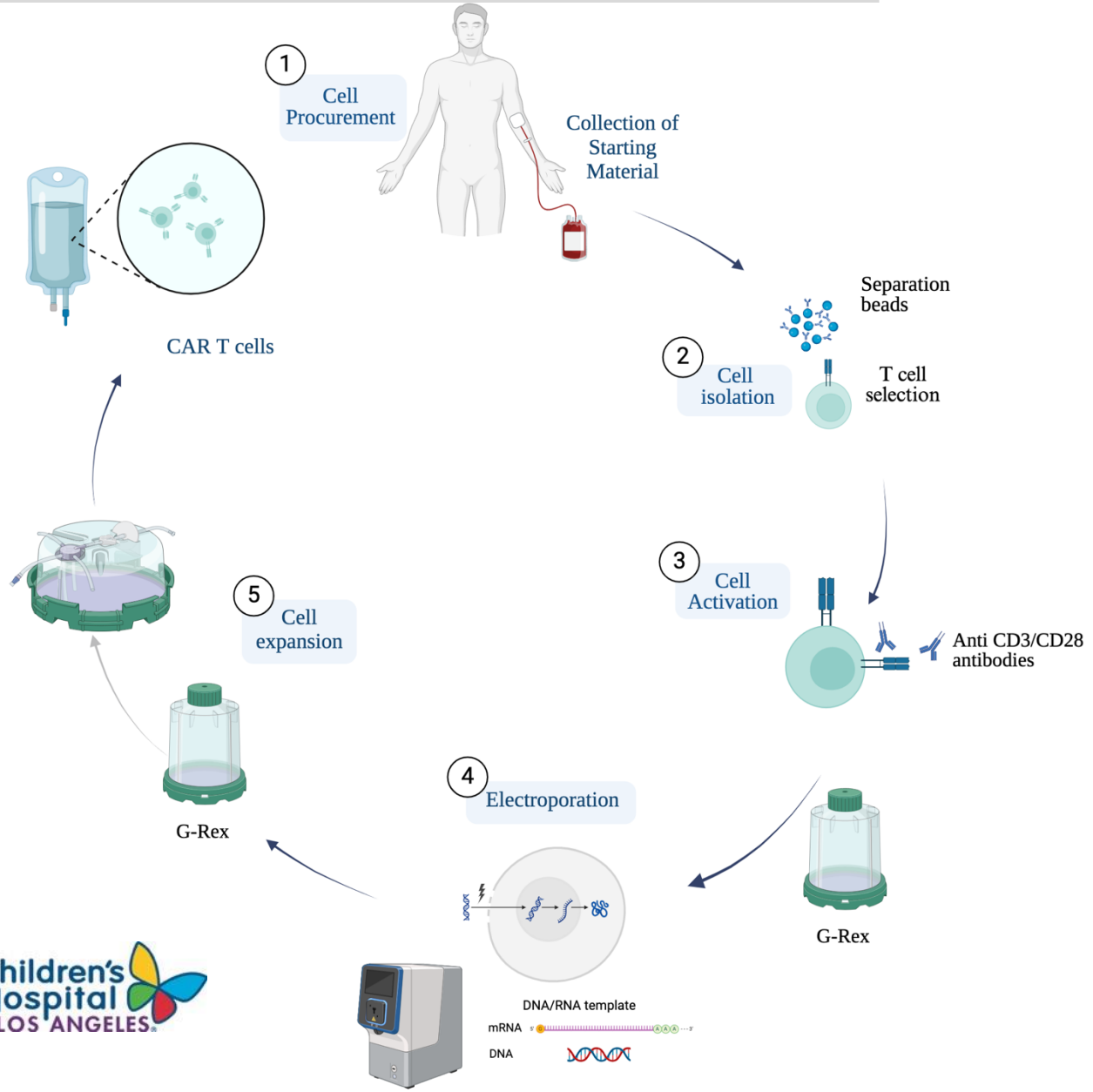


- Originate from healthy donor
- Available on demand
- Need to overcome alloreactivity and risk of GvHD

USC University of Southern California

Children's Hospital LOS ANGELES

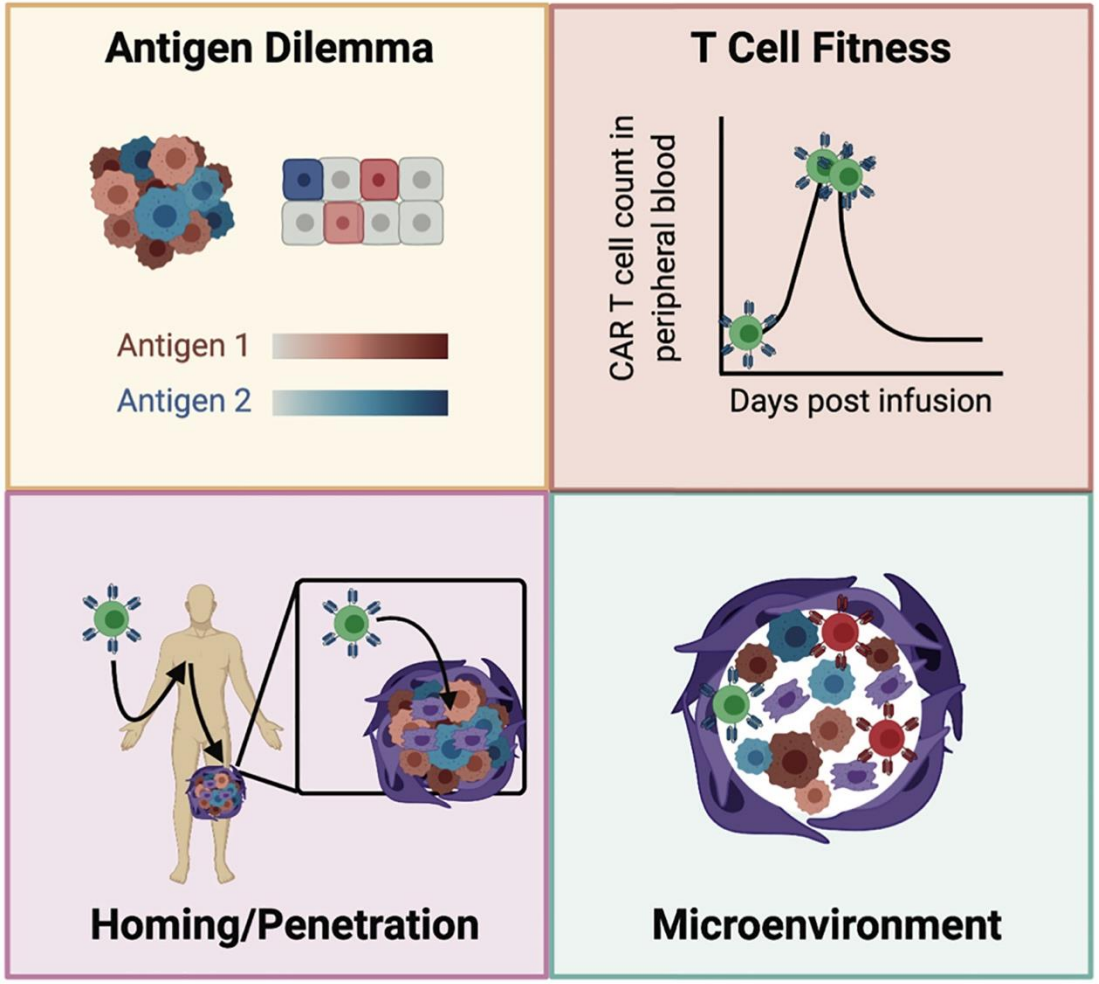
Innovative Solutions and Current Developments



USC University of Southern California

Children's Hospital LOS ANGELES

Limited Efficacy in Solid Tumors



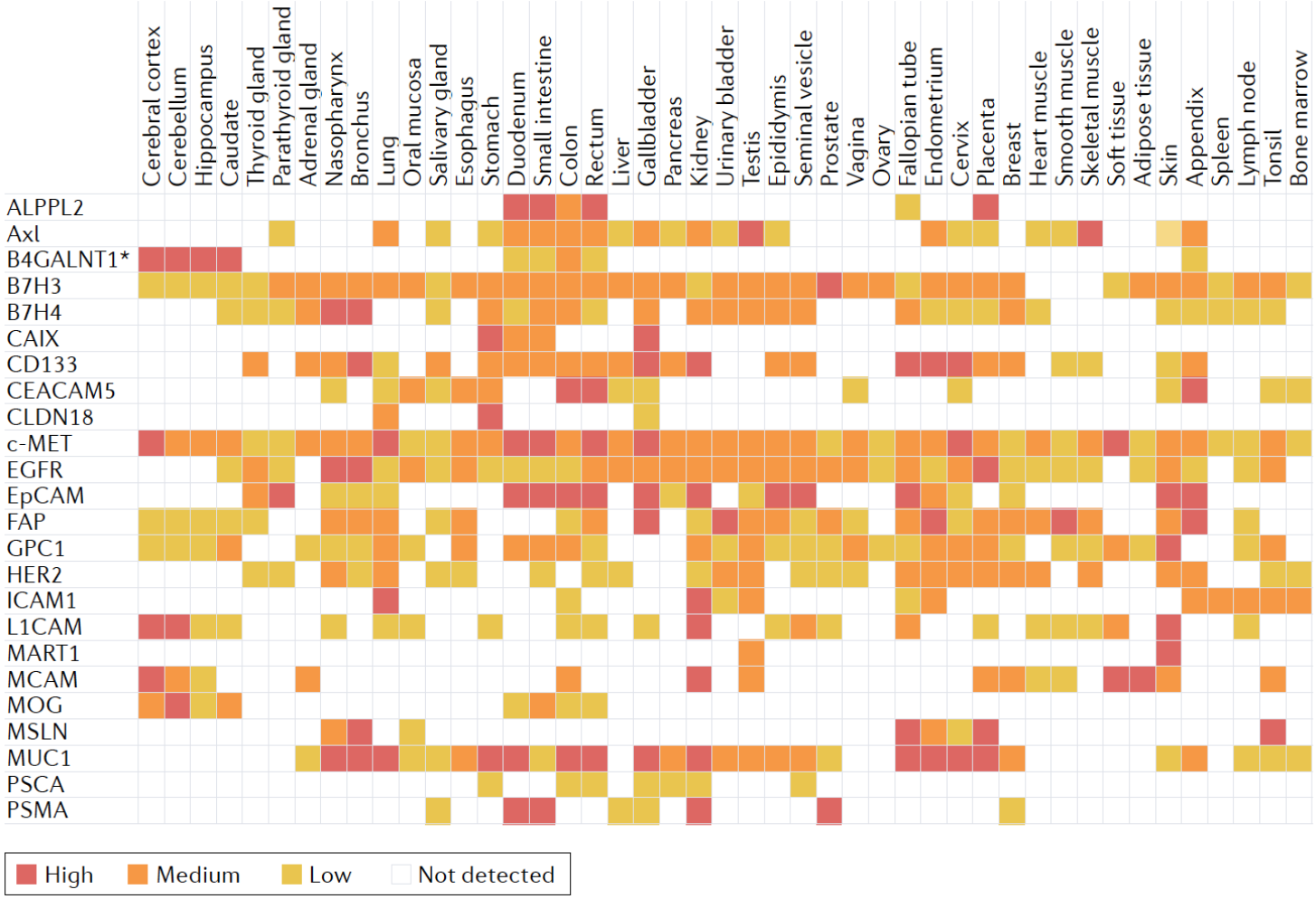
USC University of Southern California

Children's Hospital LOS ANGELES

Wagner et al. Mol. Ther. 2020

Limited Efficacy in Solid Tumors

- Lack of specific tumor antigen → Target expression in healthy tissue
- Risk of healthy tissue destruction **(OTOT)**
- **Risk:** Reduced safety and efficacy
- **Current efforts:** CAR T cells with enhanced specificity; dual-targeting CARs, logic-gated CARs, or affinity-tuned CARs.



Flugel et al. Nat. Rev. Clin. Oncol. 2022

Promise of CAR T in Solid Tumors

ORIGINAL ARTICLE | BRIEF REPORT

Intraventricular CARv3-TEAM-E T Cells in Recurrent Glioblastoma

Authors: Bryan D. Choi, M.D., Ph.D., Elizabeth R. Gerstner, M.D., Matthew J. Frigault, M.D., Mark B. Leick, M.D., Christopher W. Mount, M.D., Ph.D., Leonora Balaj, Ph.D., Sarah Nikiforow, M.D., Ph.D., Bob S. Carter, M.D., Ph.D., William T. Curry, M.D., Kathleen Gallagher, Ph.D., and Marcela V. Maus, M.D., Ph.D. Author Info & Affiliations

Published March 13, 2024 | N Engl J Med 2024;390:1290-1298 | DOI: 10.1056/NEJMoa2314390 | VOL. 390 NO. 14

Target: *EGFR*

USC University of Southern California

Children's Hospital LOS ANGELES

Article

GD2-CAR T cell therapy for H3K27M-mutated diffuse midline gliomas

https://doi.org/10.1038/s41586-022-04489-4

Received: 2 August 2021

Accepted: 28 January 2022

Published online: 7 February 2022

Open access

Check for updates

Robbie G. Majzner[1,2,3,13], Sneha Ramakrishna[1,2,13], Kristen W. Yeom[4], Shabnum Patel[1], Harshini Chinnasamy[1], Liora M. Schultz[1,2], Rebecca M. Richards[1,2], Li Jiang[5], Valentin Barsan[1,2], Rebecca Mancusi[6], Anna C. Geraghty[6], Zinaida Good[1,3,7], Aaron Y. Mochizuki[6], Shawn M. Gillespie[6], Angus Martin Shaw Toland[8], Jasia Mahdi[6], Agnes Reschke[1,2], Esther H. Nie[6], Isabelle J. Chau[6], Maria Caterina Rotiroti[2], Christopher W. Mount[6], Christina Baggott[1], Sharon Mavroukakis[1], Emily Egeler[1], Jennifer Moon[1], Courtney Erickson[1], Sean Green[2], Michael Kunicki[1,2], Michelle Fujimoto[1,2], Zach Ehlinger[2], Warren Reynolds[2], Sreevidya Kurra[2], Katherine E. Warren[5], Snehit Prabhu[1], Hannes Vogel[8], Lindsey Rasmussen[9], Timothy T. Cornell[9], Sonia Partap[6], Paul G. Fisher[6], Cynthia J. Campen[6], Mariella G. Filbin[5], Gerald Grant[10], Bita Sahaf[1,2], Kara L. Davis[1,2], Steven A. Feldman[1], Crystal L. Mackall[1,2,3,11,14] ✉ & Michelle Monje[1,2,6,8,10,12,14] ✉

Acknowledgments

USC/CHLA Cell Therapy Center

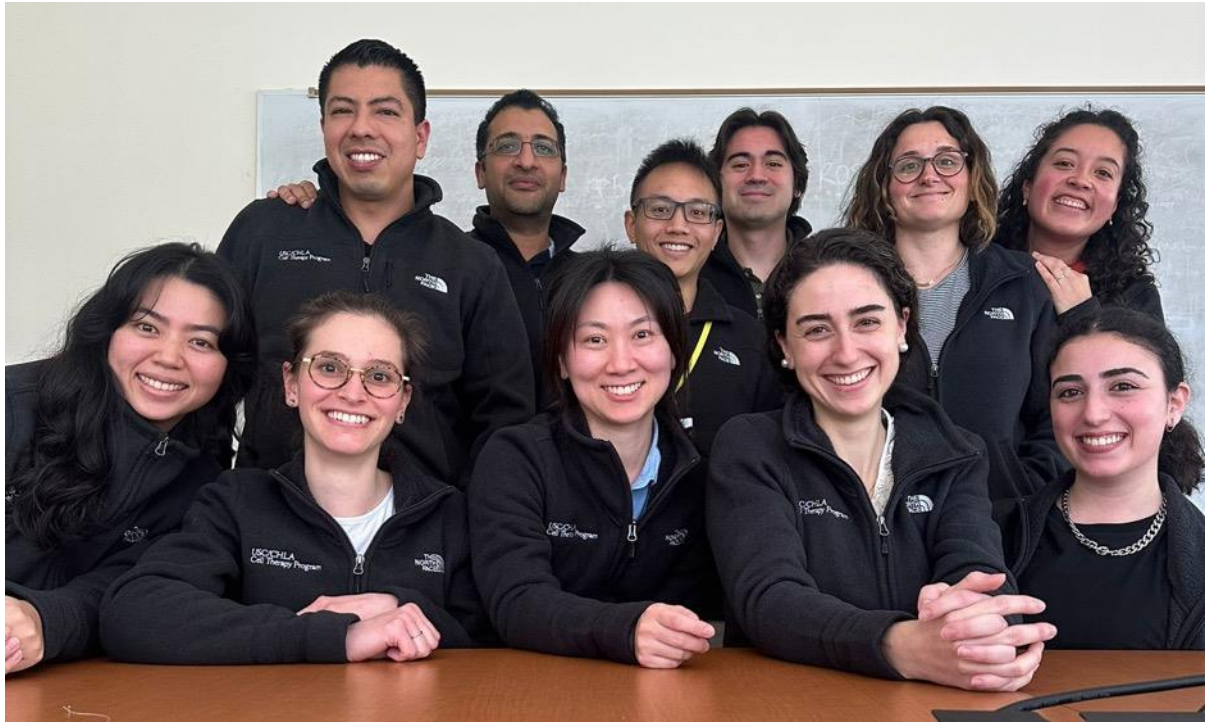
Alix Vaissie
Amaia Cadinanos-Garai
Xia Wu
Michael Woo
Vivian Quach
Jackson Lange
Ivan Segovia
Chiara Baraldi
Nanor Deirbadrossian
Christian Flugel
Anson Cheung
Cristina Fernandez
James Choung

Alpha Clinic

Thomas Buchanan
Allan Wayne
Juliane Glaeser
Elia Plascencia
Cort Brinkerhoff

Norris Comprehensive Cancer Center

Caryn Lerman
Steven Grossman
Heinz-Josef Lenz
Christopher Loertscher



USC/CHLA Cell Therapy Program

USC University of Southern California

Keck School of Medicine of USC

Children's Hospital Los Angeles

Advances in Cellular Therapies for Cancer

CAR T cell Therapy

Thank you!

Dr. Mohamed Abou-el-Enein
mabouele@usc.edu

Follow us on LinkedIn & Twitter: USC/CHLA Cell Therapy Program

USC University of Southern California

Children's Hospital LOS ANGELES