Transitioning Engineered T Cells From Discovery to Manufacturing to Regulatory Approval

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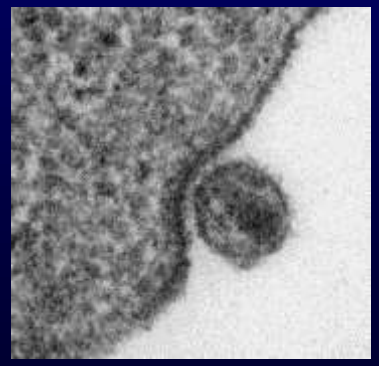
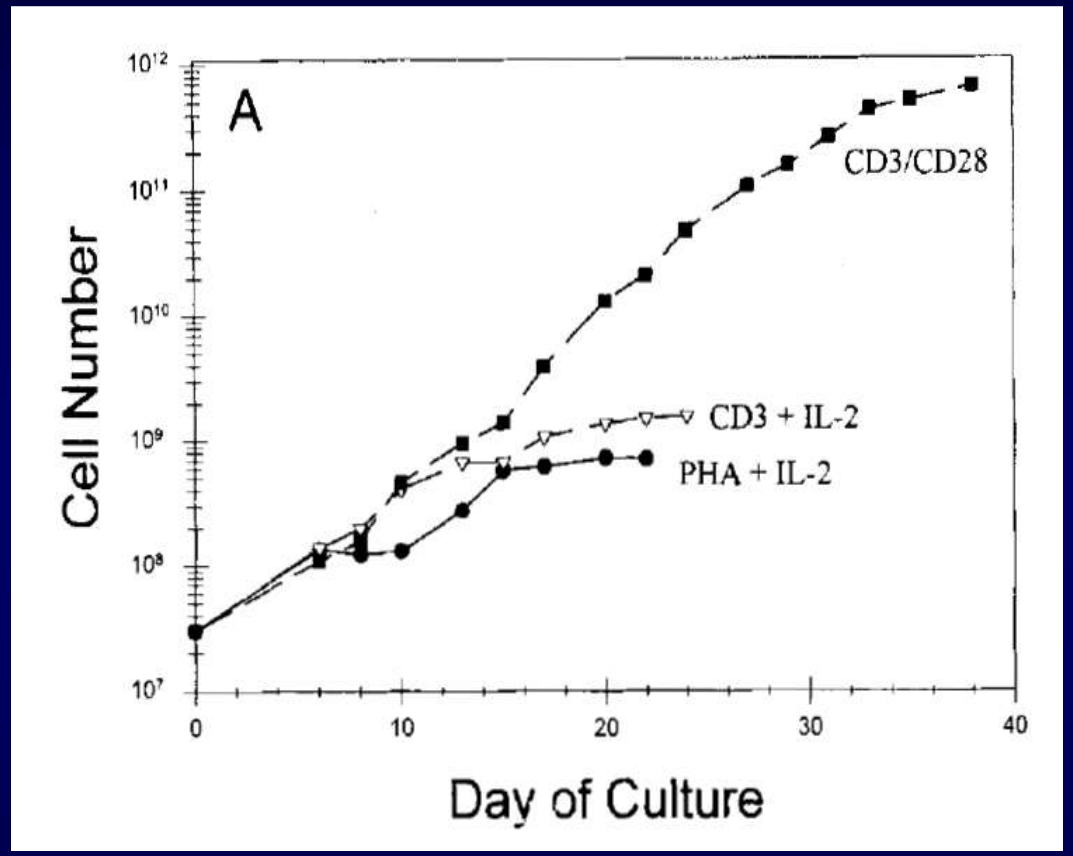
Conflict of Interest Statement

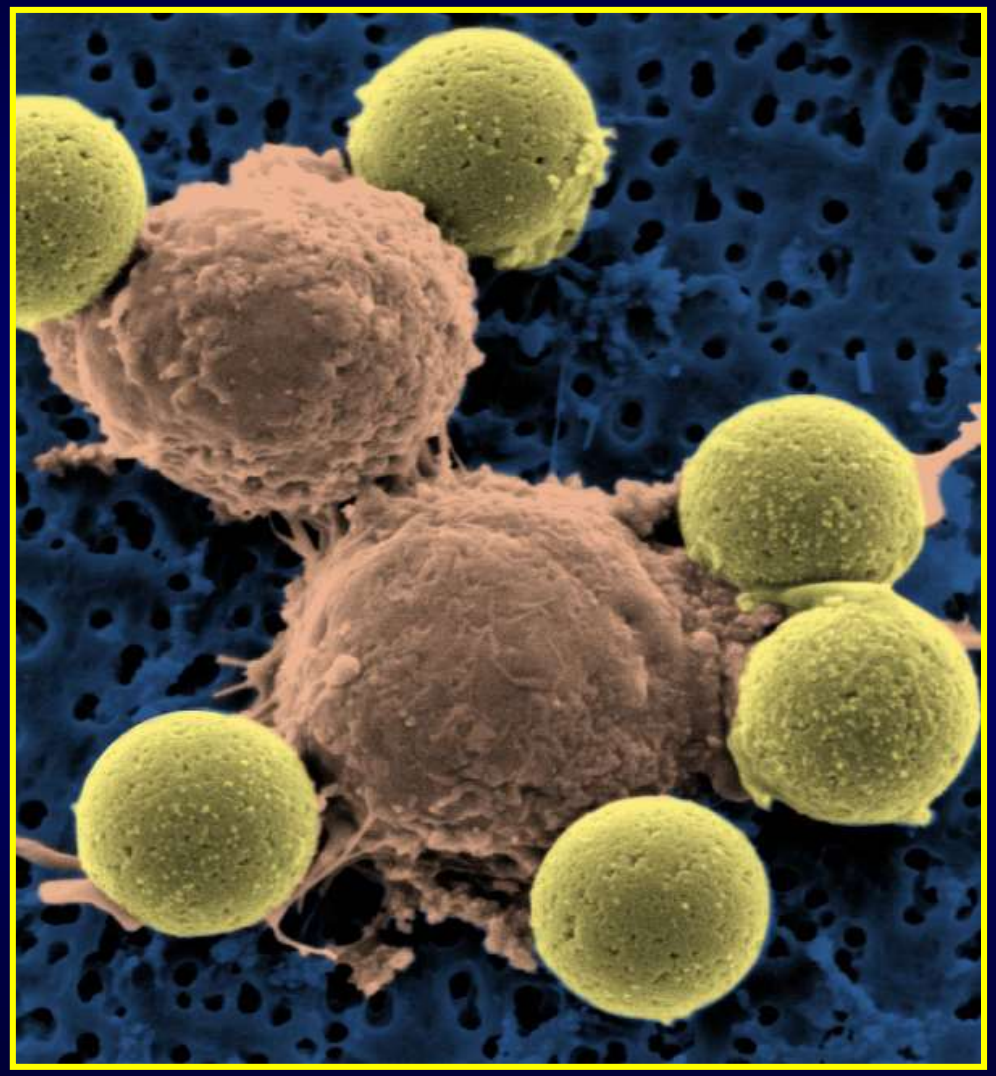
- Declaration of financial interest due to intellectual property and patents in the field of cell and gene therapy.
- Univ. Penn. Alliance with Novartis
- Consultant for GE Healthcare
- Consultant for Brammer Bio
- Founder Tmunity Therapeutics
- Conflict of interest is managed in accordance with University of Pennsylvania policy and oversight

The Fall of a Wall, Navy Research Priorities, and HIV Led to the First Cellular Gene Therapy BLA Accepted by the FDA



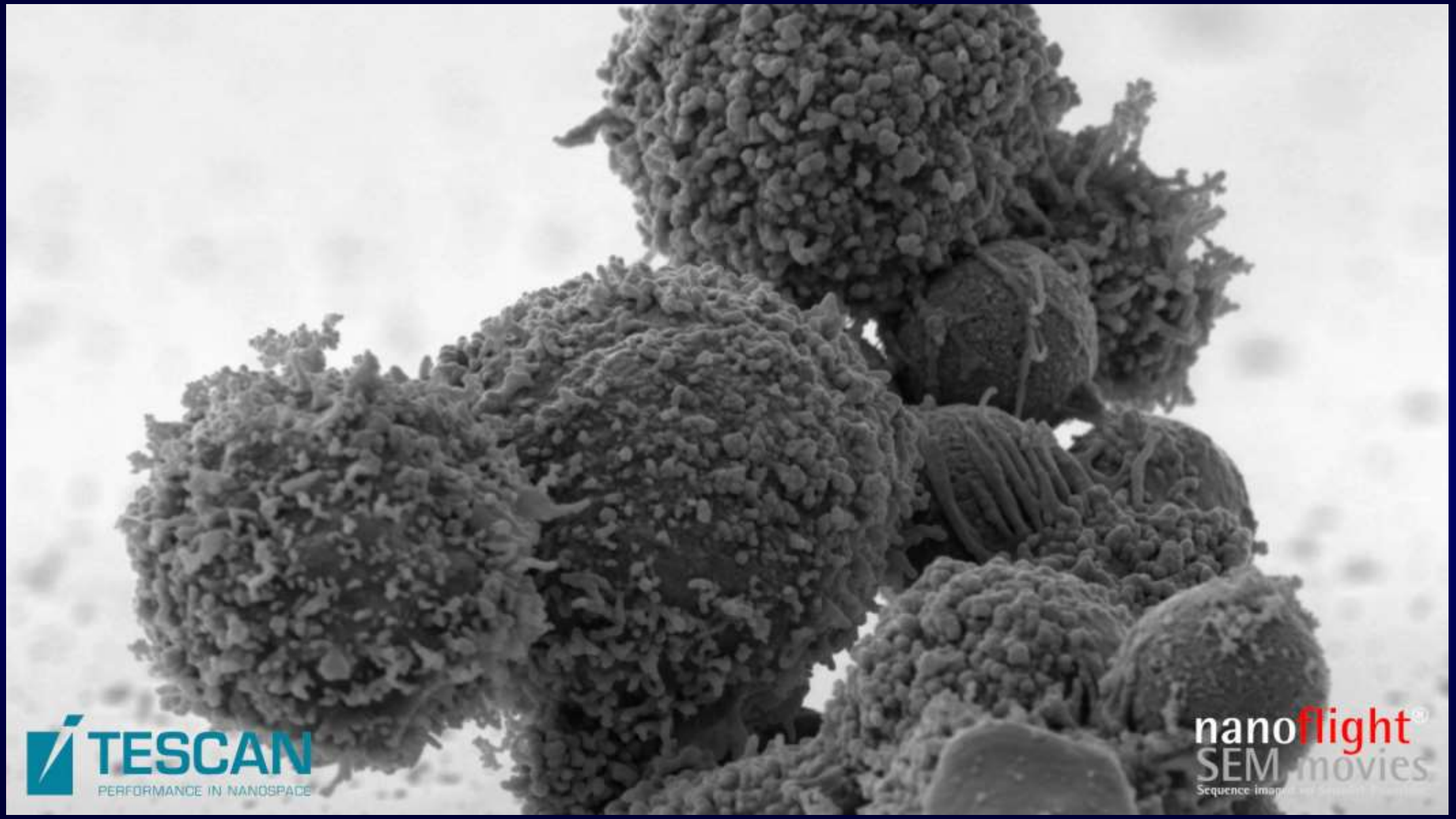
Goal: Improved T Cell Culture System for Adoptive Immunotherapy
Result: 10-100X Improved Growth and Function





J Immunol 1997; 159: 5921
Science 1997; 276: 273
Immunol. Rev. 1997; 160: 43
Mol. Ther. 2004; 9; 902
Exp. Opin. Biol. Ther. 2008; 8: 475

T Cells Embrace Enhanced Stimulation



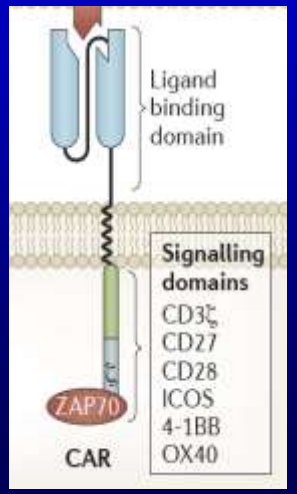
Electron Microscopy Resource Laboratory, University of Pennsylvania and (c) Scientific Photography - Stefan Diller, Wuerzburg, Germany www.nanoflight.info

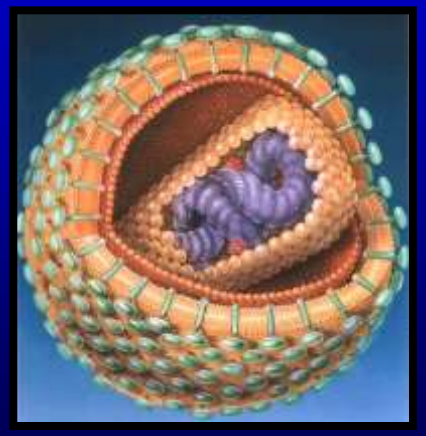
If we could design T cells for the treatment of disease, they would be:

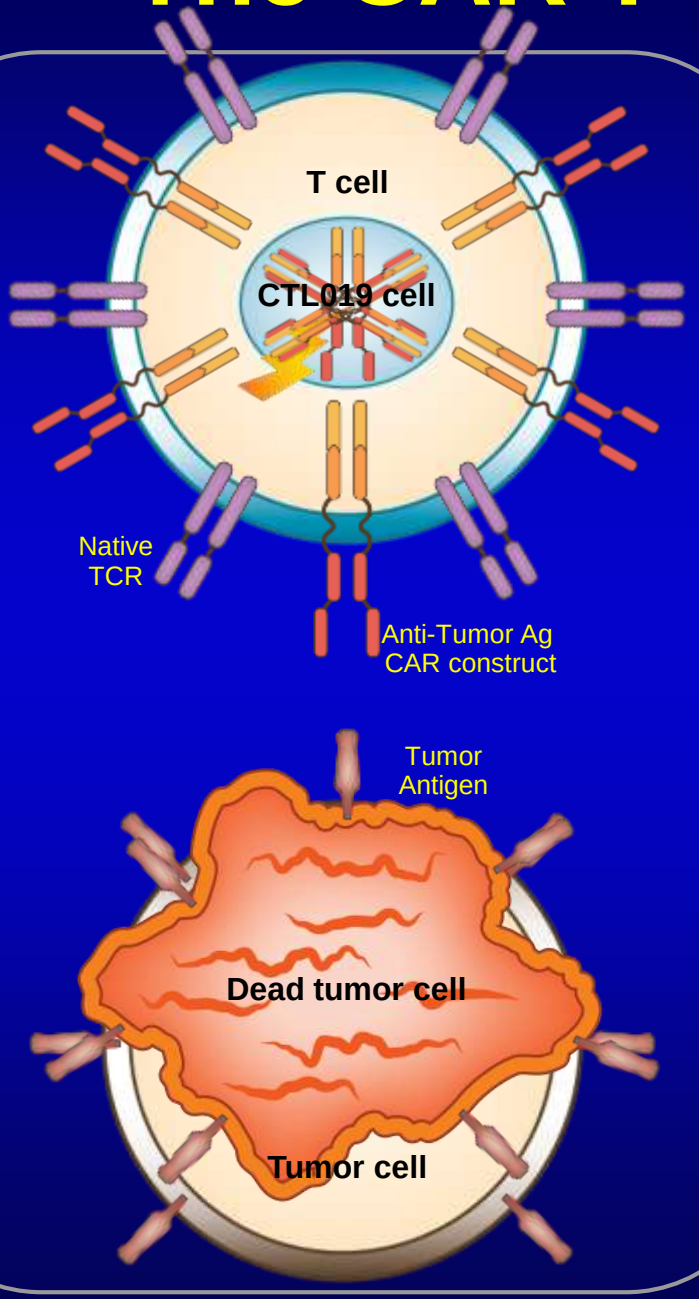
- Be Numerous (Effector to Target Ratio)
- Potent
- Be Persistent
- Have a Good Memory

But, in HIV and Cancer →

The Chimera + The Trojan Horse = The CAR T

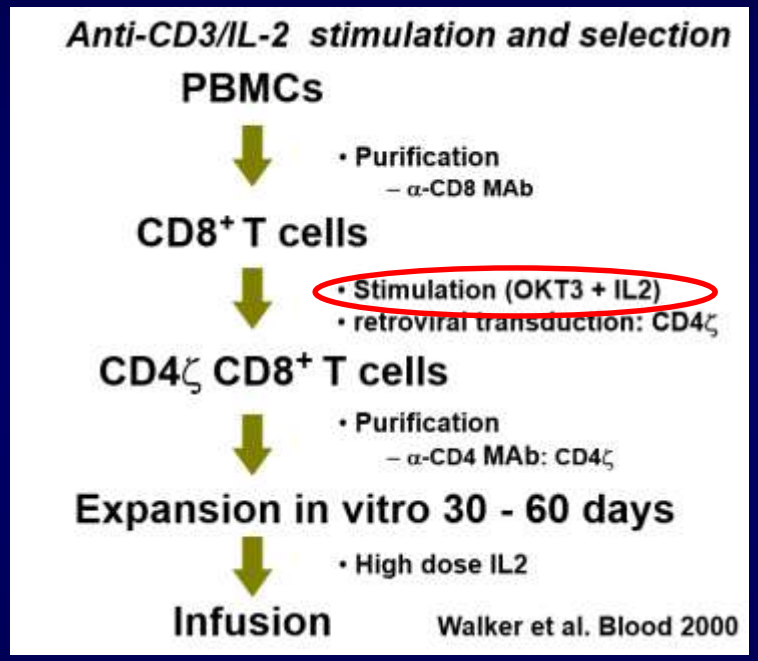




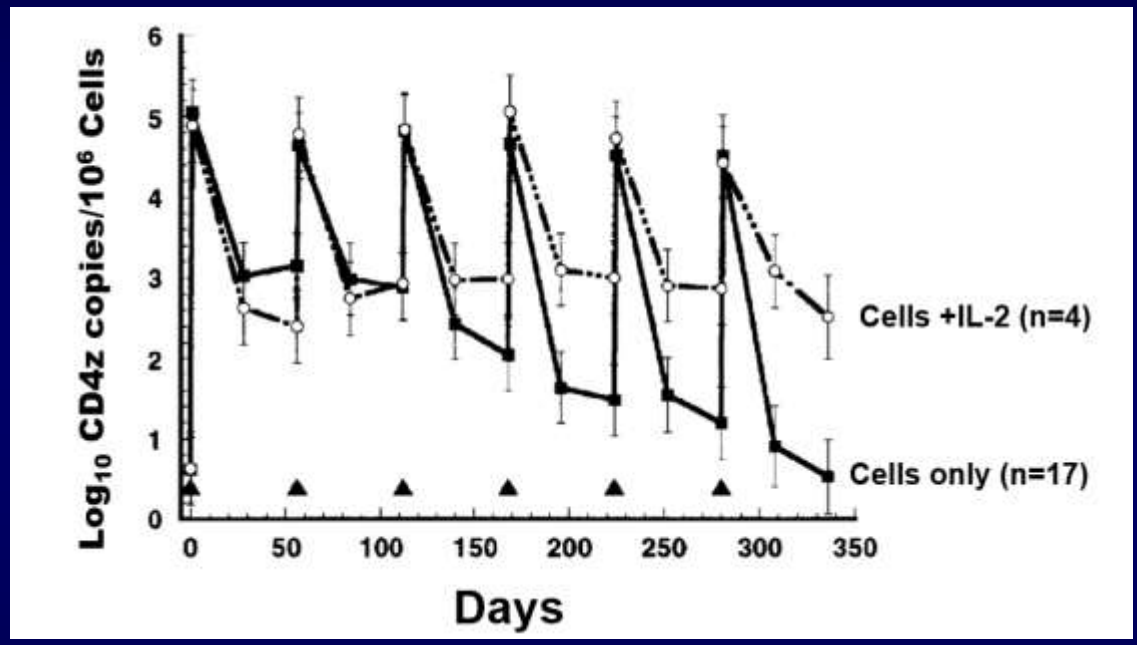


First CAR Clinical Trial (Was in HIV!)

CELL GENESYS



Persistence of CD4z-modified CD8 CAR T Cells in Blood



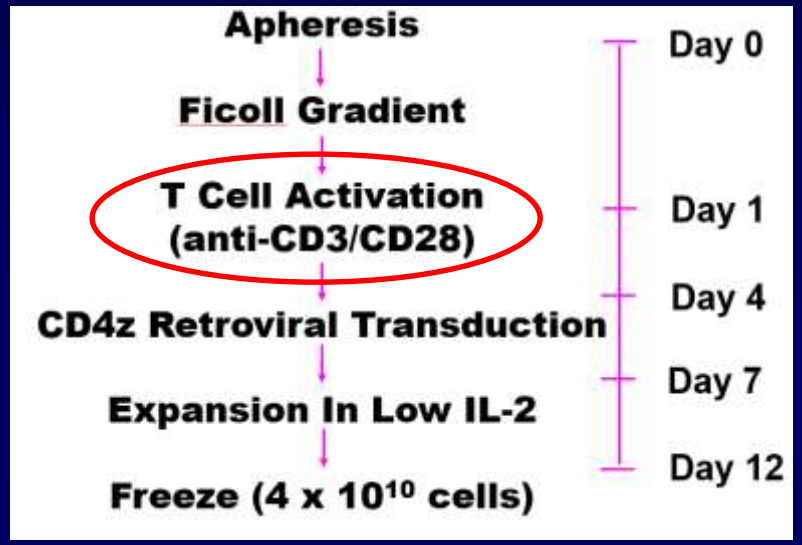
Long-term in vivo survival of receptor-modified syngeneic T cells in patients with human immunodeficiency virus infection

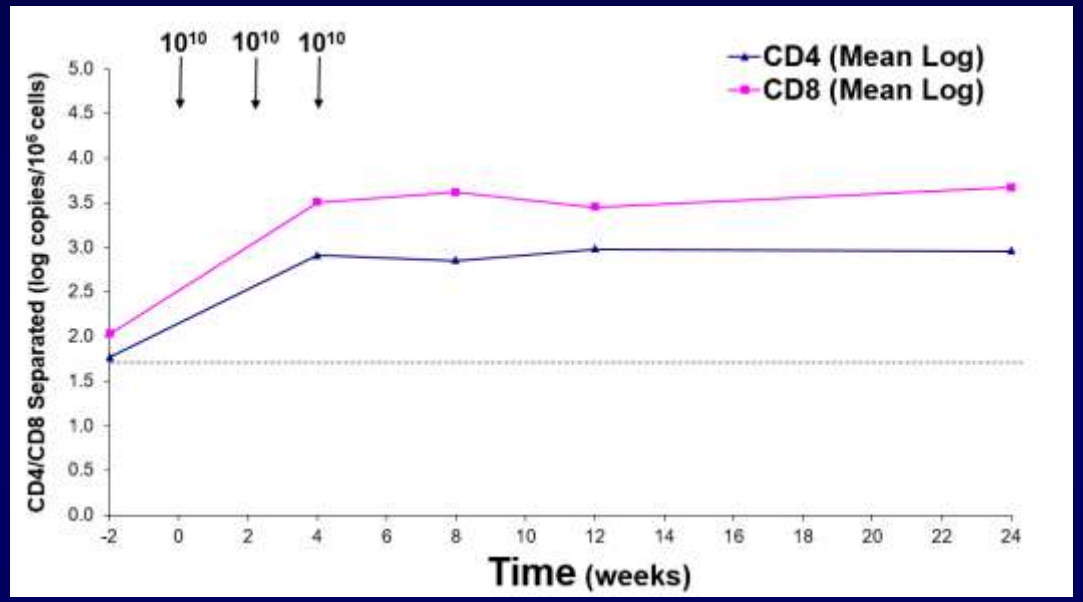
Robert E. Walker, Christine M. Bechtel, Ven Natarajan, Michael Baseler, Kristen M. Hege, Julia A. Metcalf, Randy Stevens, Allison Hazen, R. Michael Blaese, Clara C. Chen, Susan F. Leitman, Jolie Palensky, Janet Wittes, Richard T. Davey Jr, Judith Falloon, Michael A. Polis, Joseph A. Kovacs, David F. Broad, Bruce L. Levine, Margo R. Roberts, Henry Masur, and H. Clifford Lane

BLOOD, 15 JULY 2000 VOLUME 96, NUMBER 2

Improved Persistence of CD4z-modified CD8 CAR T Cells in Blood

Second Generation Trial Manufacturing





Prolonged survival and tissue trafficking following adoptive transfer of CD4ζ gene-modified autologous CD4$^+$ and CD8$^+$ T cells in human immunodeficiency virus–infected subjects

Ronald T. Mitsuyasu, Peter A. Anton, Steven G. Deeks, David T. Scadden, Elizabeth Connick, Matthew T. Downs, Andreas Bakker, Margo R. Roberts, Carl H. June, Sayeh Jalali, Andy A. Lin, Rukmini Pennathur-Das, and Kristen M. Hege

BLOOD, 1 AUGUST 2000 • VOLUME 96, NUMBER 3

CELL GENESYS

Translation of Targeted Gene Editing to Humans (circa 2004)

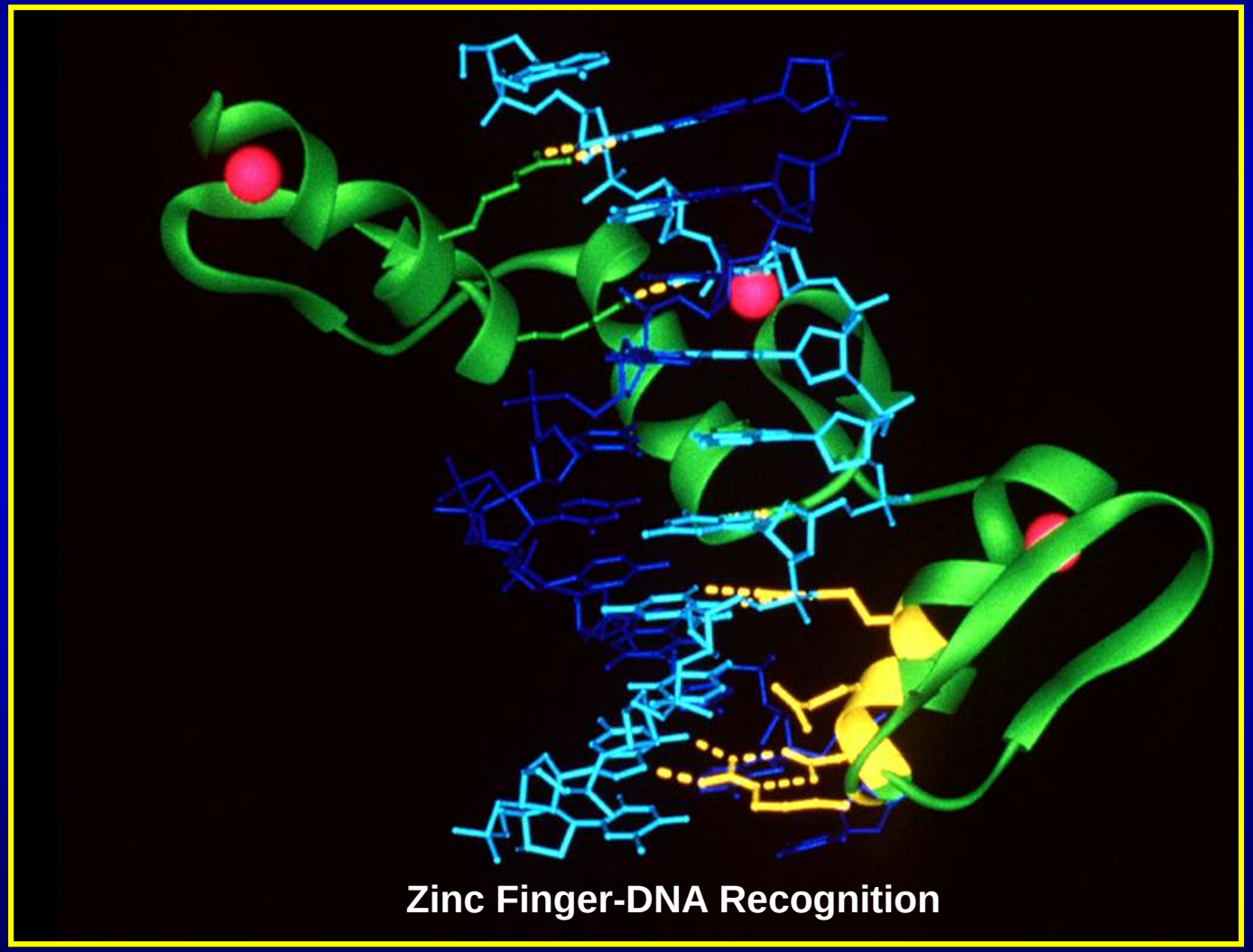
What are Zinc Finger Proteins?

-specific DNA binding proteins, e.g transcription factors and other regulatory proteins

Dale Ando, MD

CELL GENESYS

SANGHMD

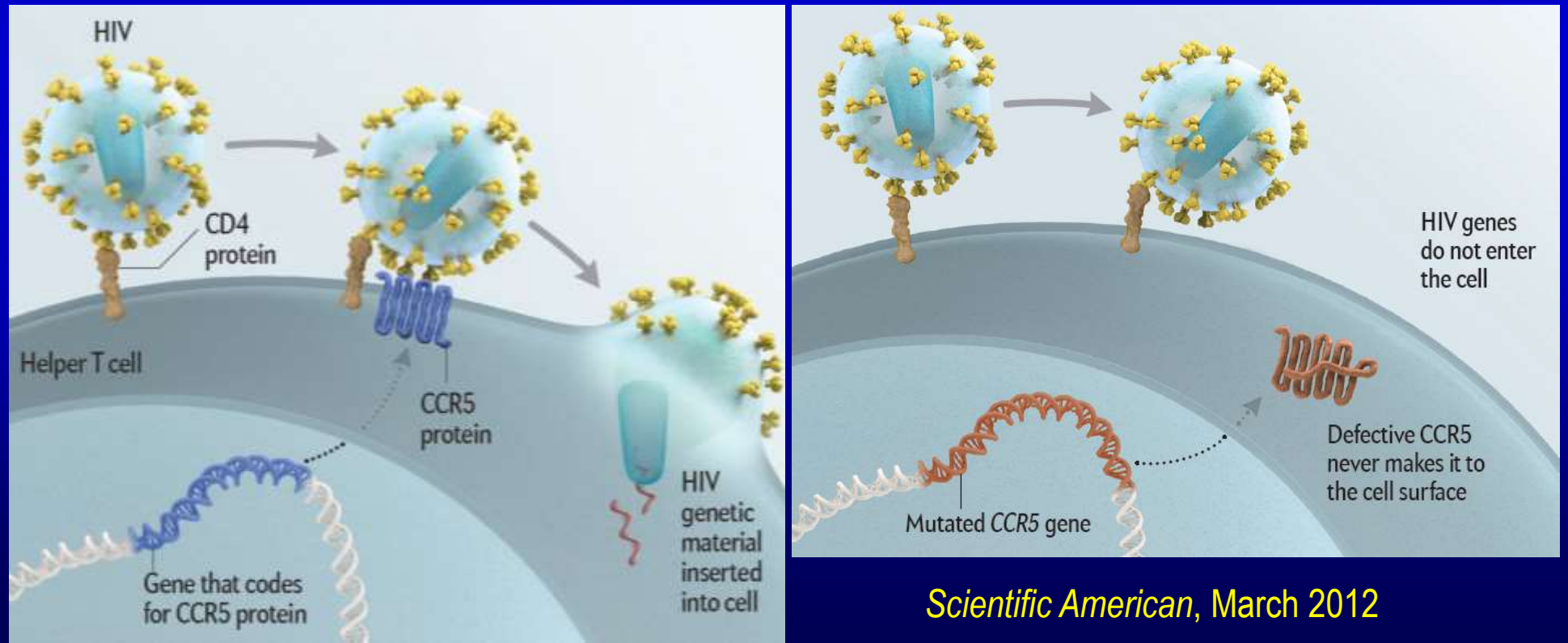


Zinc Finger-DNA Recognition

Paveltich and Pabo. *Science* **252:**809 (1991)

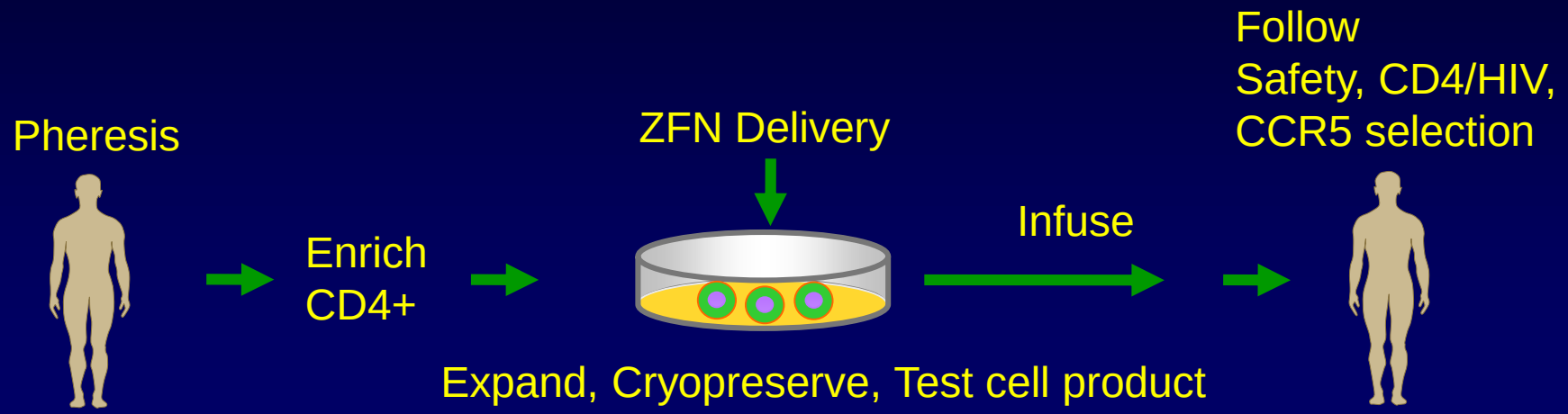
Why Target CCR5 in HIV?

- HIV (R5 virus) targets CD4 T-cells by binding to CCR5, one of the major co-receptors for HIV entry
- CCR5 delta-32 mutation produces a nonfunctional protein
  - Homozygotes are resistant to HIV infection
  - Heterozygotes have slower disease progression



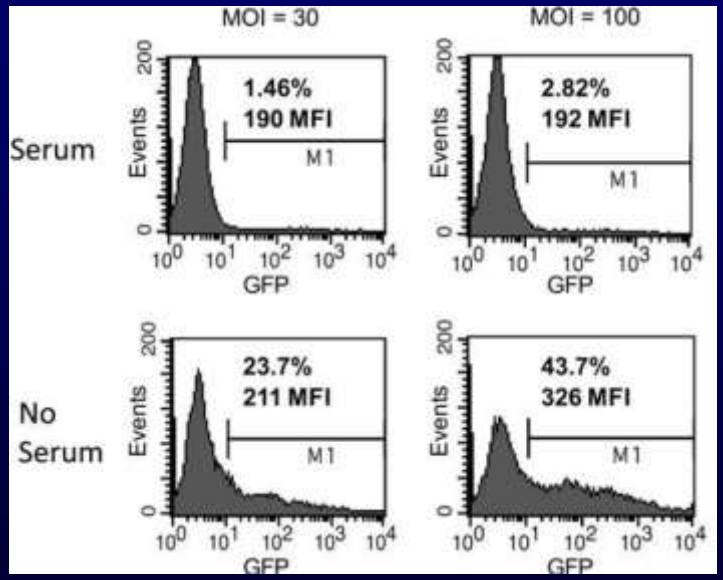
Scientific American, March 2012

What unique challenges have you faced as you prepared your product for clinical application?



Clinicaltrials.gov NCT00842634

- Research Lab Process 1: electroporation of plasmid DNA
  -feasible but toxic, low cell yield, viability
- Research Lab Process 2: adenovirus transduction
  -very efficient in research media, bombs in clinical media
- Clinical Process 1: serum free during adenovirus transduction
  -very efficient



Maier et al., Hum Gene Ther 2013: 24(3):245

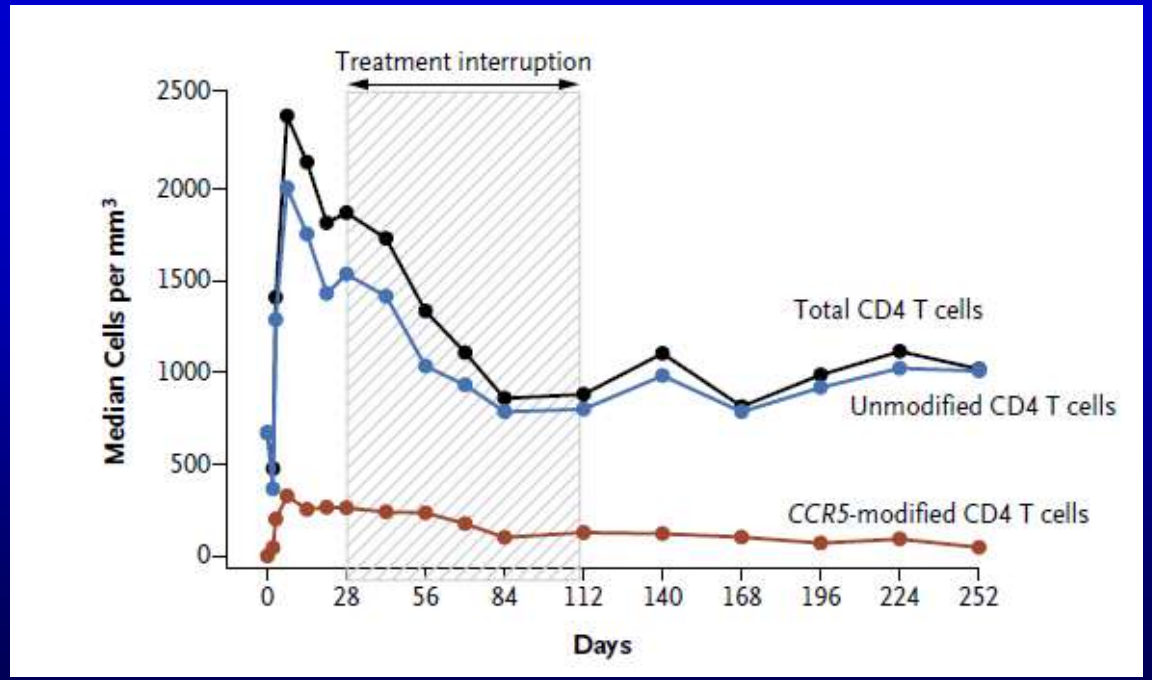
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 6, 2014 VOL. 370 NO. 10

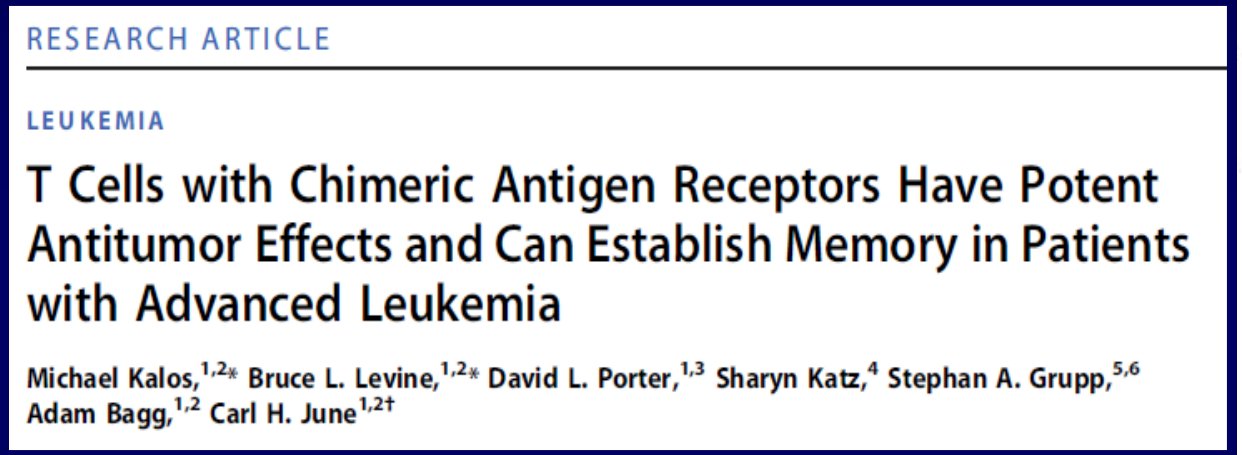
Gene Editing of *CCR5* in Autologous CD4 T Cells of Persons Infected with HIV

Pablo Tebas, M.D., David Stein, M.D., Winson W. Tang, M.D., Ian Frank, M.D., Shelley Q. Wang, M.D., Gary Lee, Ph.D., S. Kaye Spratt, Ph.D., Richard T. Surosky, Ph.D., Martin A. Giedlin, Ph.D., Geoff Nichol, M.D., Michael C. Holmes, Ph.D., Philip D. Gregory, Ph.D., Dale G. Ando, M.D., Michael Kalos, Ph.D., Ronald G. Collman, M.D., Gwendolyn Binder-Scholl, Ph.D., Gabriela Plesa, M.D., Ph.D., Wei-Ting Hwang, Ph.D., Bruce L. Levine, Ph.D., and Carl H. June, M.D.

- Engraft, expand, and persist (>1 yr) in circulation
- CCR5-modified CD4 T cells detected in gut mucosa, demonstrating homing and persistence
- Survival advantage of CCR5-modified cells during ARV treatment interruption



2004- present: Clinical Translation of HIV CAR's in 1990's Informs Cancer CAR's

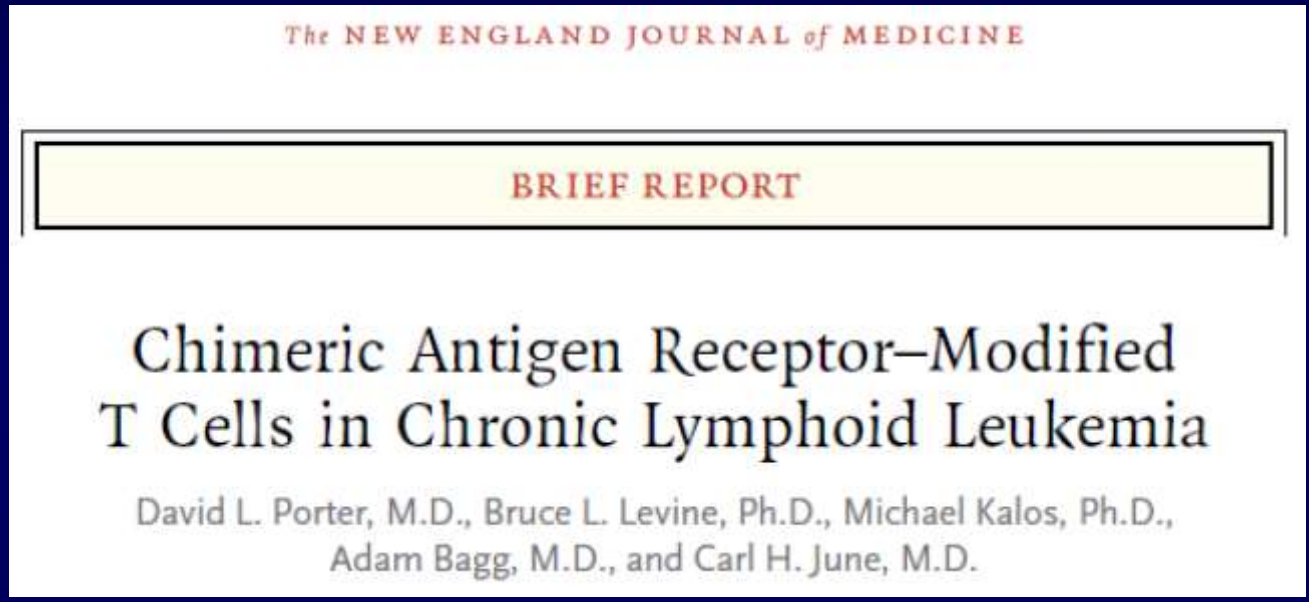


RESEARCH ARTICLE

LEUKEMIA

T Cells with Chimeric Antigen Receptors Have Potent Antitumor Effects and Can Establish Memory in Patients with Advanced Leukemia

Michael Kalos,[1,2]* Bruce L. Levine,[1,2]* David L. Porter,[1,3] Sharyn Katz,[4] Stephan A. Grupp,[5,6] Adam Bagg,[1,2] Carl H. June[1,2]†



The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Chimeric Antigen Receptor–Modified T Cells in Chronic Lymphoid Leukemia

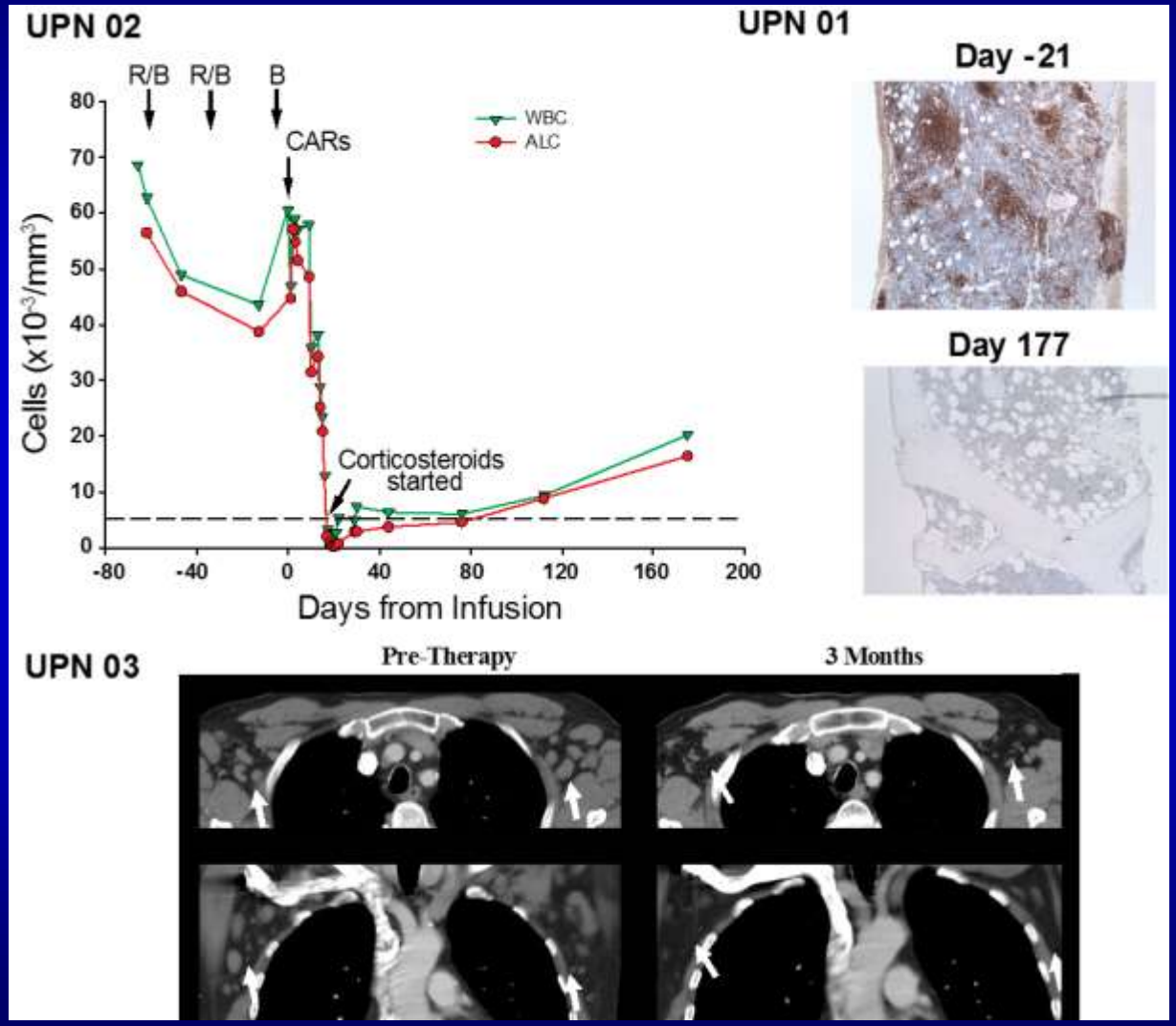
David L. Porter, M.D., Bruce L. Levine, Ph.D., Michael Kalos, Ph.D., Adam Bagg, M.D., and Carl H. June, M.D.

2010 CLL trial

Advanced, chemotherapy-resistant CLL, 2 of 3 patients had p53-deficient CLL

1 Partial & 2 Complete Responses in Relapsed/Refractory CLL

(3.5)



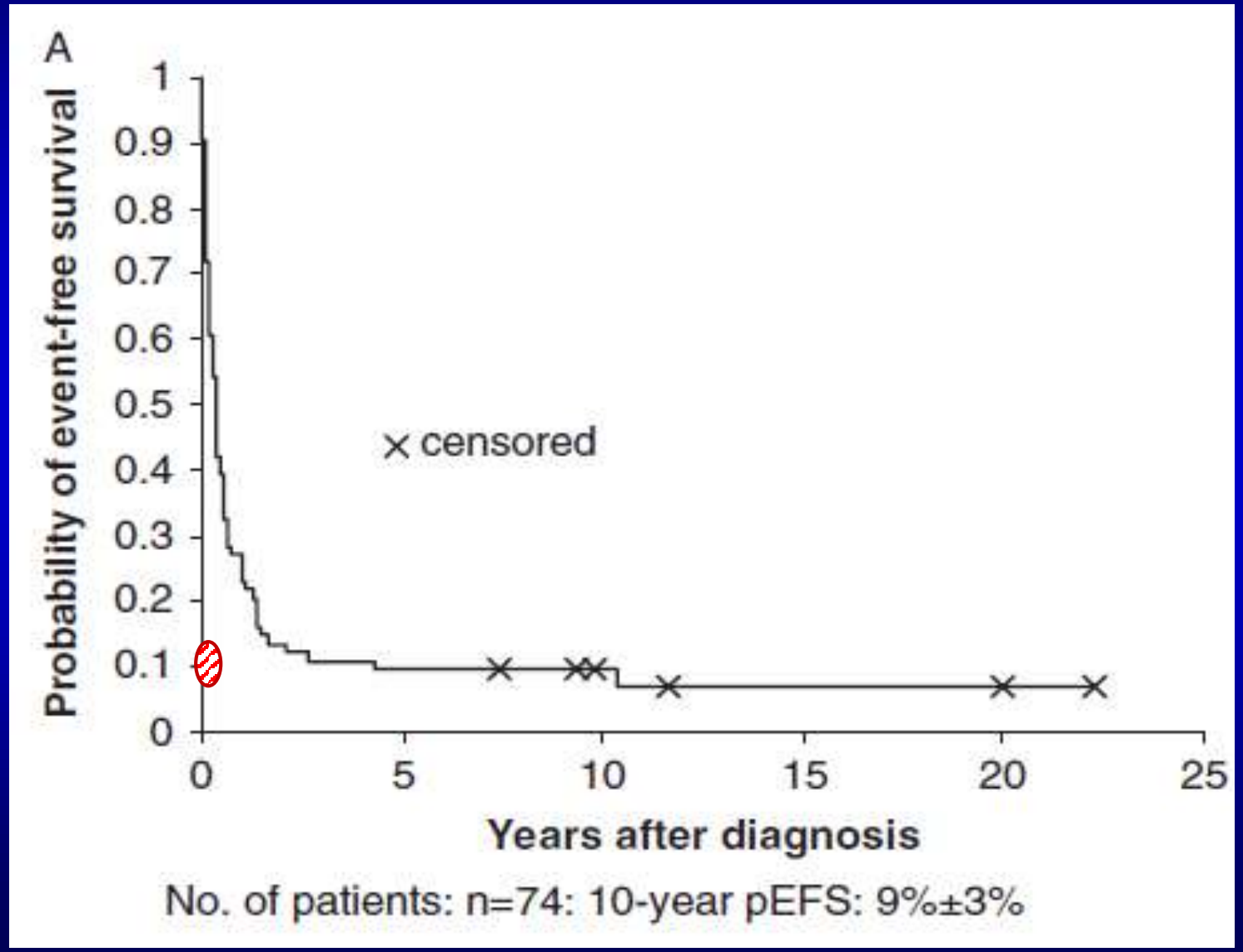
(2.5)

(1.3)

Porter, et al., N Engl J Med 365:725, 2011
Kalos, et al., Sci Transl Med 3(95):95ra73, 2011

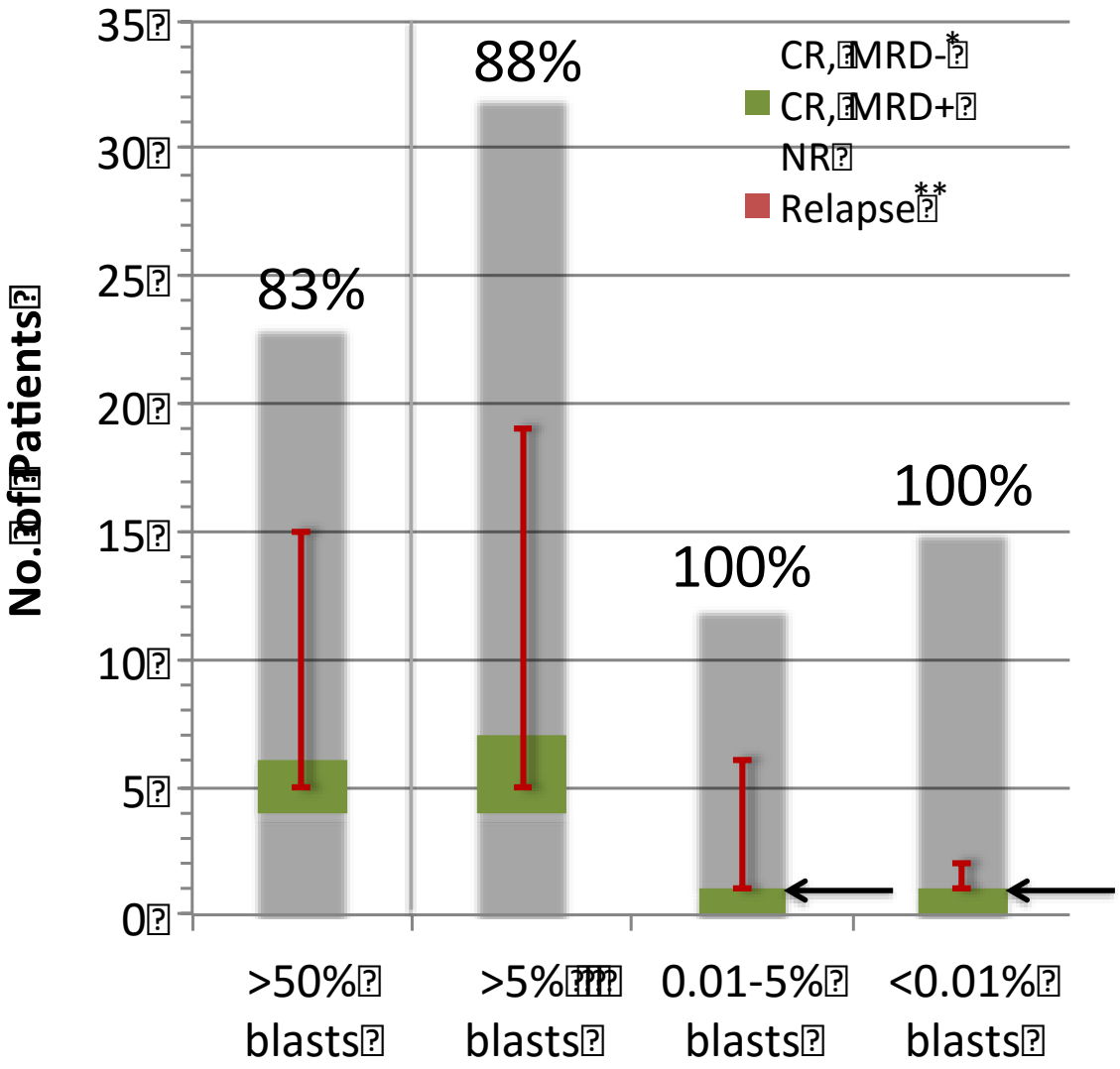
(Baseline total body tumor burden in kg)

Dismal Outcomes for 2nd Relapse ALL



Resimuller et al. JPHO 2013

CART19 in Ped ALL: Response similar at high and low disease burdens



Abbreviations: BM, bone marrow; CR, complete response, MRD, minimal residual disease; NR, no response

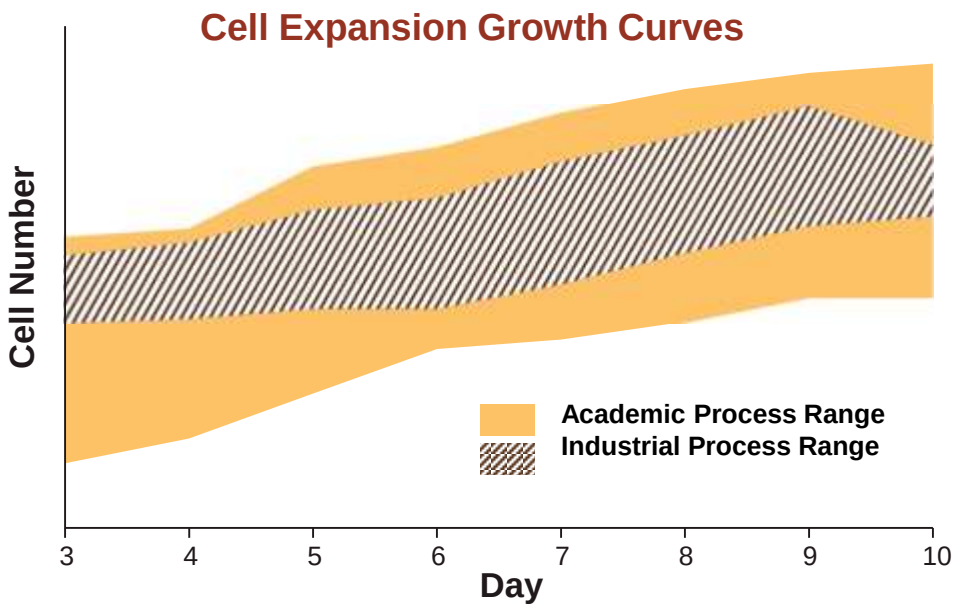
Patient population

- ≥ 2nd relapse or refractory
- Majority refractory to multiple prior therapies

* <0.01% MRD by flow cytometry
** ⅓ CD19+, ⅔ CD19-

MRD- by 3 months without further therapy

Successful Technology Transfer of CAR T Cell Processing from Academia to Industry Enabled Scale-Up to Support Global Clinical Trials



- **Further enhancement in control and consistency of the process**
  - Closing of process steps
  - Some manual processes replaced with automation solutions
- **Analytics - validation and implementation of more robust and/or faster methods**
  - New quantitation method for expression of CTL019 transgene
  - Rapid mycoplasma testing

Final product control through Analytical Specifications

Specifications

Product Release Tests

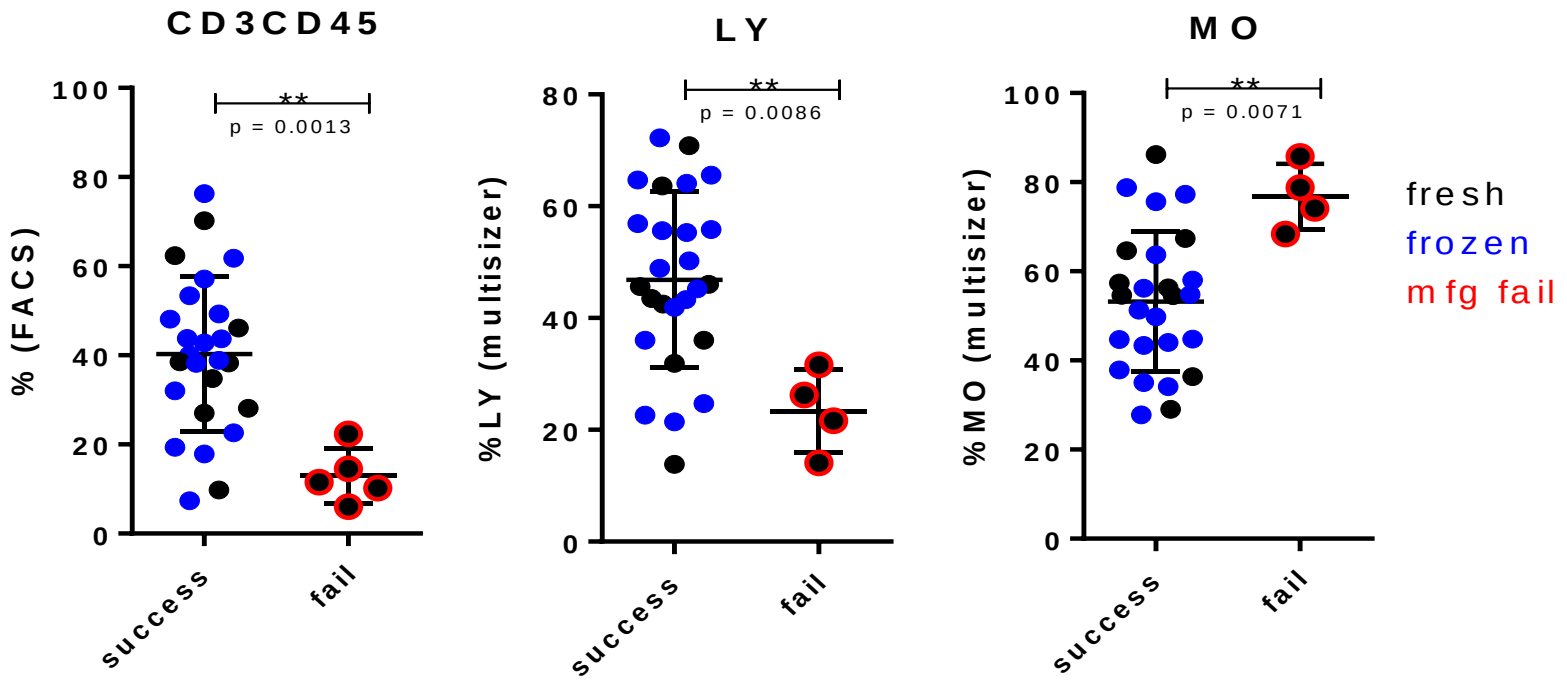
Identity	Purity	Impurities	Potency	Safety
-Appearance -Vector integration	-%T Cells (Flow) -Cell viability -Transduction efficiency	-Residual beads -B cells -Vector residuals	-CAR expression -Cytokine production	-Sterility -Endotoxin -Mycoplasma -RCL / vector residuals

Release specifications (and in-process controls) ensure:

- ✓ Consistency of manufacturing
- ✓ Adherence to Health Authority requirements
- ✓ Appropriate safety profile
- ✓ Desired product CQAs

What challenges do you face when defining source cell populations?

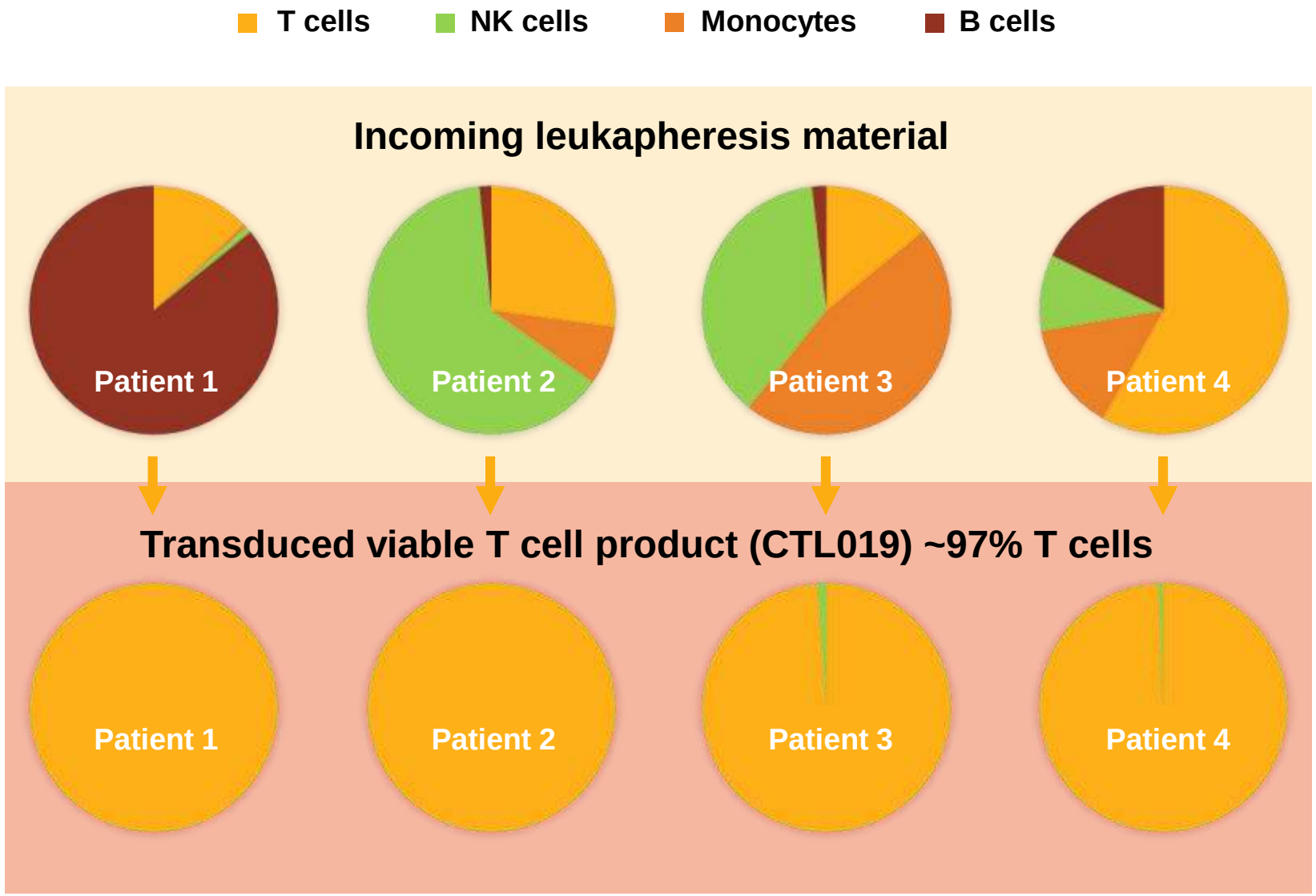
High variability of (patient derived) raw material



Apheresis products that resulted in failed MFG runs due to poor growth had significantly lower %CD3/45+ (via FACS) and %LY (via Multisizer) and significantly higher %MO (via Multisizer).

Solution: Conditional manufacturing pathways

Consistent CTL019 T-cell product from individual patient material



CGT Analytical Development

NOVARTIS

Determine Efficacy and Safety of CTL019 in Pediatric Patients with Relapsed and Refractory B-cell ALL (ELIANA)

Country	Institution
USA*	The Childrens Hospital of Phil
	Cincinnati Childrens Hospital
	University of Wisconsin Hospit
	University of Michigan
	University of Utah Clinical Tr
	University of Minnesota
	Childrens Mercy Hospital
	Stanford University Medical Ce
	Duke Unversity Medical Center
	Childrens Healthcare of Atlant
	Childrens Medical Center of Da
	Oregon Health & Science Univer
	Childrens Hospital Los Angeles

Country	Institution
Canada	CHU Hopital Ste. Justine
	The Hospital for Sick Children
Japan	National Cancer Center Hospital
	Kyoto University Hospital
Germany	Universitaetsklinikum Frankfur
Italy	Az.Ospedaliera San Gerardo Uni
France	Hopital Robert Debre
	Hopital Saint Louis
Spain	HOSPITAL SANT JOAN DE DEU
Belgium	UZ Gent
Austria	St. Anna Kinderspital
Norway	Oslo Universitetssykehus (University Hospital, Oslo)
Australia	Royal Childrens Hospital VIC

NOVARTIS

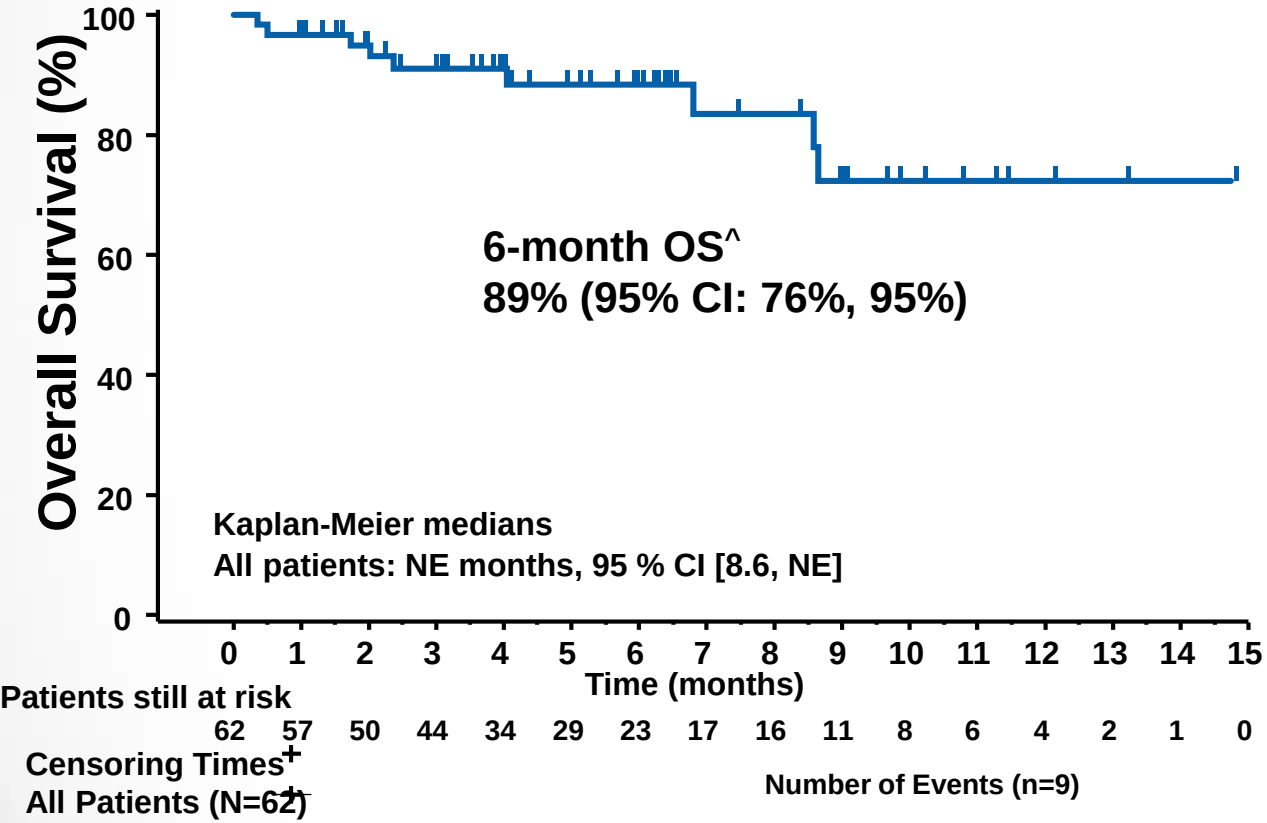
Clinicaltrials.gov NCT02435849

Closed to enrollment

25 Site 11 Country 4 Continent Global Biologistics

- **Scheduling**
- **Collection**
- **Shipping – cold chain management**
- **Manufacturing – supply chain management**
- **Testing**
- **Shipping – cold chain management**
- **Administration**

ELIANA: CTL019 Phase II global trial in Ped ALL



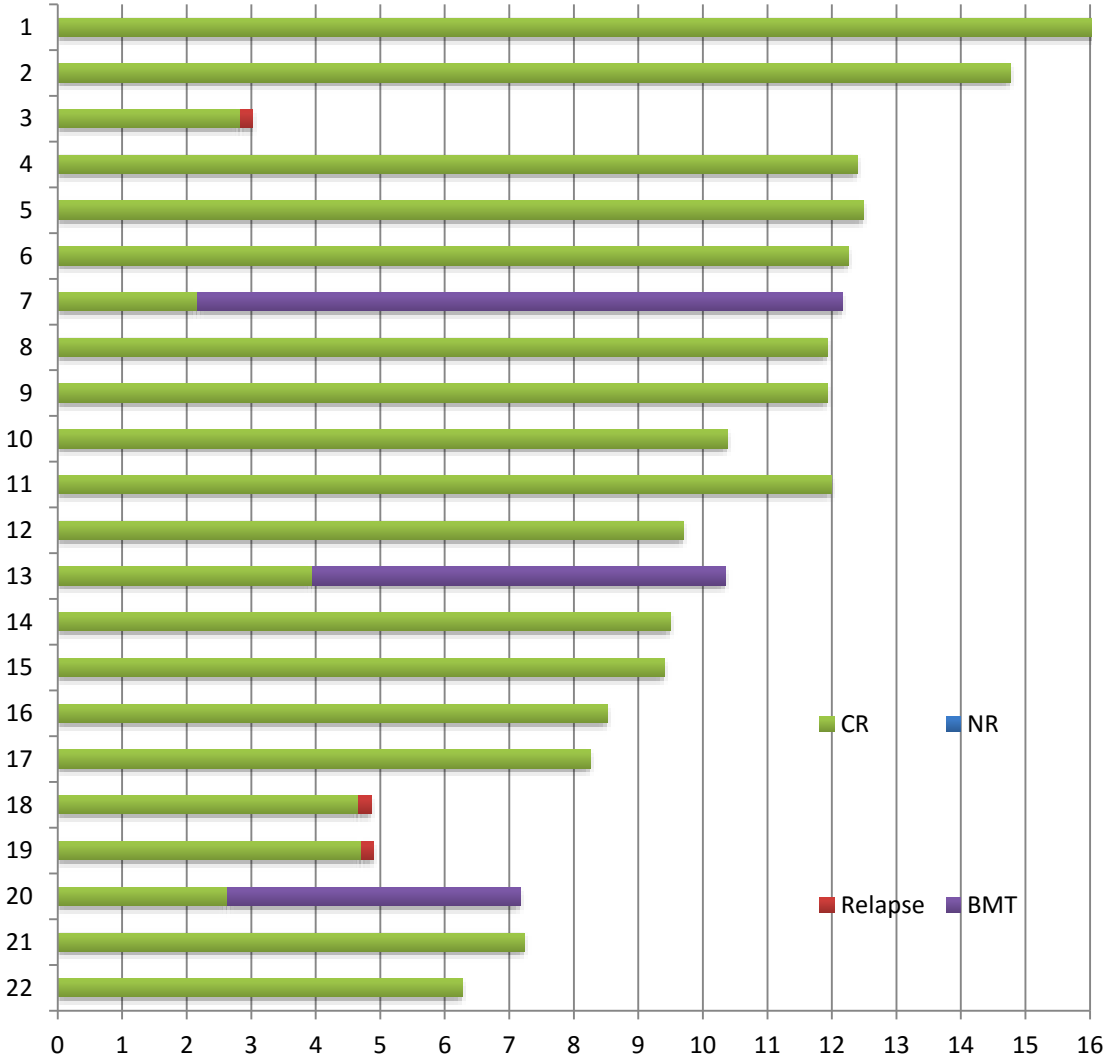
^Full analysis set
All patients infused with CTL019 were included. Time is relative to CTL019 infusion

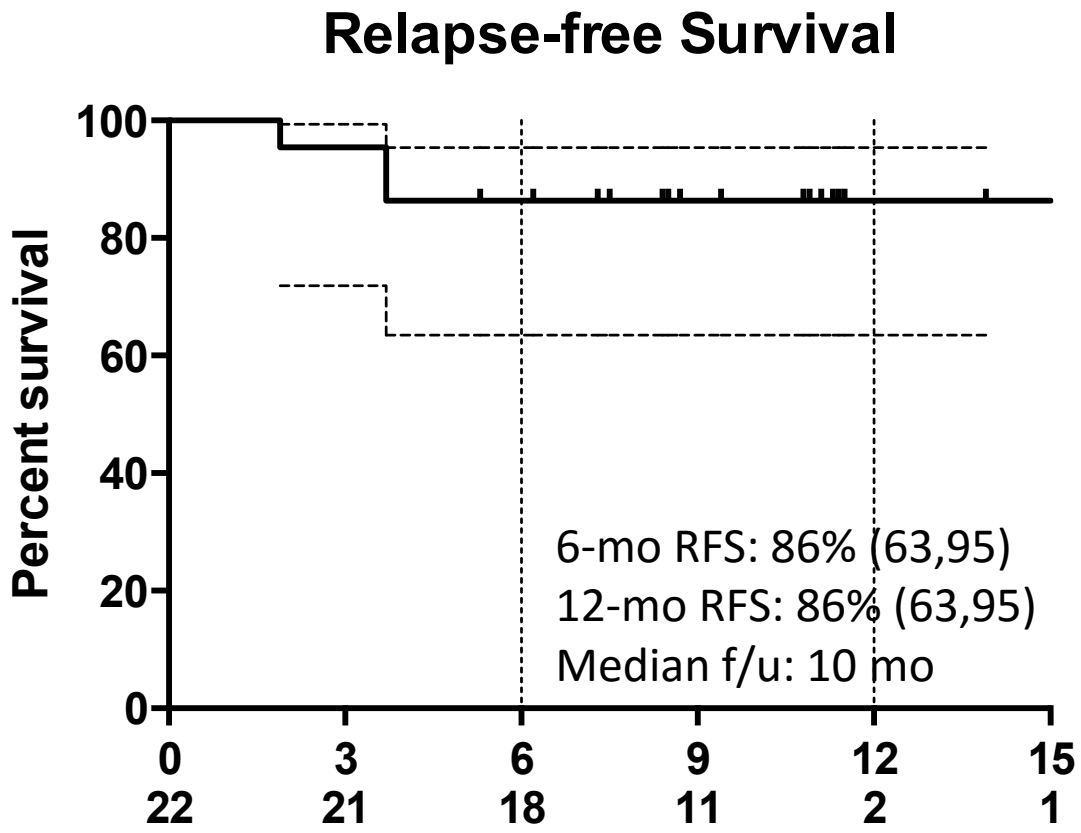
Overall remission rate (CR+CRi) within 3 mos	**82 (41/50)**
Best overall response (BOR)	
CR	**68**
CRi	**14**

- Novartis announced PedALL BLA accepted by FDA 3/29/17
- Granted Priority Review (FDA goal – 6 months)
- FDA ODAC Ad Comm 7/12/17
- PDUFA Date – not yet announced
- Filings for DLBCL in US and EU later in 2017

Humanized CART19 (CTL119) Response Rate

CAR-naïve cohort: 22/22 CR (100%)





Presented at ISCT 2017
http://dx.doi.org/10.1016/j.jcyt.2017.02.011

Shannon Maude
Stephan Grupp

Single Arm, Open-Label, Multi-Center, Phase II Study of Efficacy and Safety of CTL019 in Adult DLBCL Patients (JULIET)

US sites

- Emory Winship Cancer Institute
- University of Chicago
- University of Kansas
- University of Michigan
- University of Minnesota
- Duke University
- Ohio State James Cancer Hospital
- Oregon Health Sciences University
- MD Anderson Cancer Center

Ex- US
(Canada, Japan, EU)

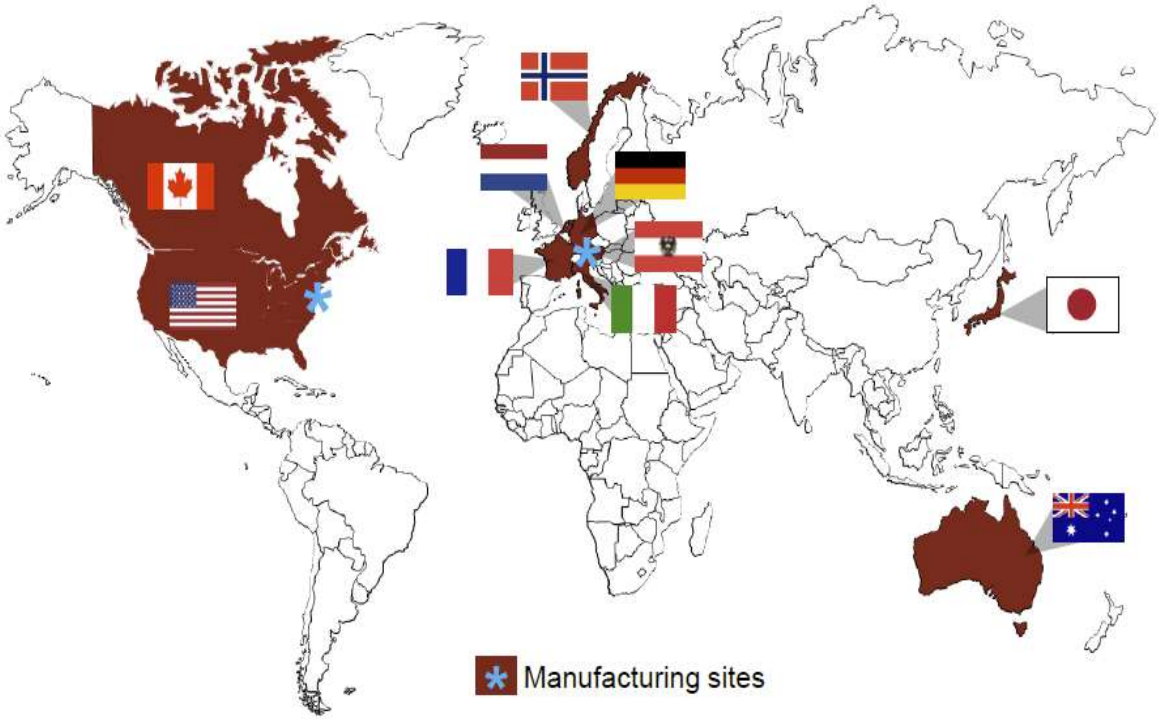
- Montreal
- Sapporo
- Oslo

Clinicaltrials.gov NCT02445248

NOVARTIS

Single Arm, Open-Label, Multi-Center, Phase II Study of Efficacy and Safety of CTL019 in Adult DLBCL Patients (JULIET)

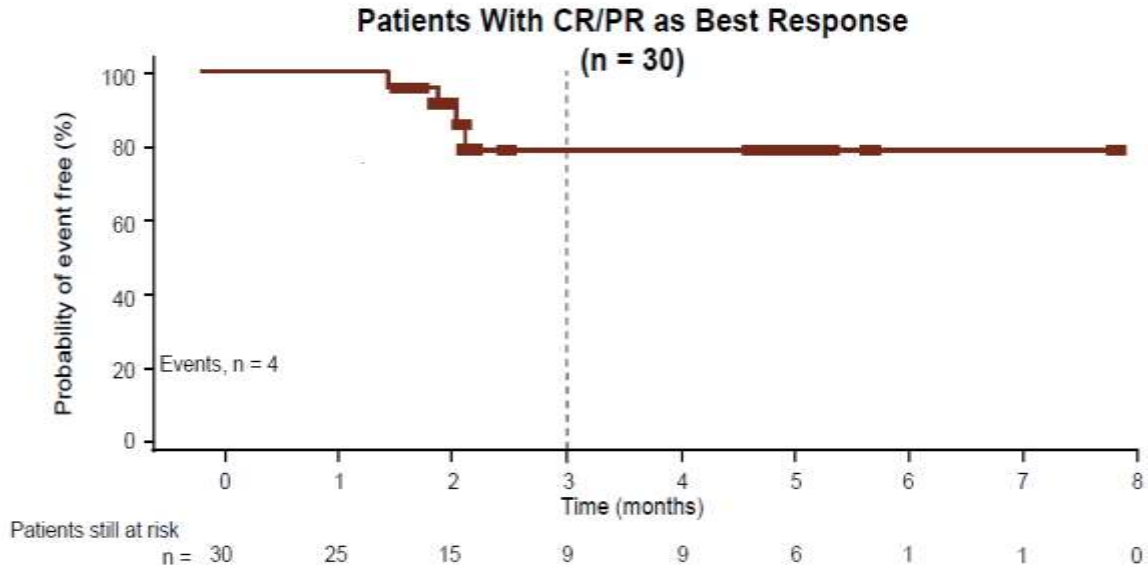
- 27 sites in 10 countries across North America, Europe, Australia, and Asia



Primary Endpoint Was Met

Response Rate	Patients (N = 51)[a]	
Best overall response (CR + PR)	**59%**	*P* < .0001[b] (95% CI, 44-72)
CR	**43%**	
PR	16%	
SD	12%	
PD	24%	

Duration of Response: 79% Relapse-free at 6 Months



- All responses at 3 months were ongoing at the time of cut-off
  - No responding patients went on to SCT
- Median DOR and OS not reached

(Some) Lessons Learned in Developing First in Human Clinical Trials

- Cells from healthy humans are not the same as cells from patients with advanced disease
- Demand your research laboratories begin working with clinical grade materials and methods early
- Currently, variable cell material requires human judgement and intervention
- More human intervention = opportunity for deviations = more training required
- A few very well studied patients can radically accelerate clinical development
- An academic scientist can learn to speak Novartian

(Some) Critical Path Issues for Commercialization and Wider Patient Access

- Securing Supply Chain – hundreds of complex components
  - Serum free media with comparable growth/potency
- Reducing COGS and Labor
  - Viral vector → electroporation/nanoparticle delivery
- Increasing Consistency, Comparability, managing challenging cases
- Rapid and Modified Release Test Development
  - Bacterial, Fungal, Mycoplasma
  - RCR, RCL testing of vector lots
- Recruiting, Training, Retaining Skilled Technologists/Engineers
- Near Term Clinical Trial/Post-Approval Allocation Ethics
  - AZT, Imatinib, Zmapp (Ebola)
- Near Term Outscaling, Mid to Long Term Automation