Transforming Medicine with Synthetic Immunity

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Co-Founder, Tmunity Therapeutics

President Elect, International Society for Cell and Gene Therapy

@BLLPHD

TMUNITY™

Penn
University of Pennsylvania

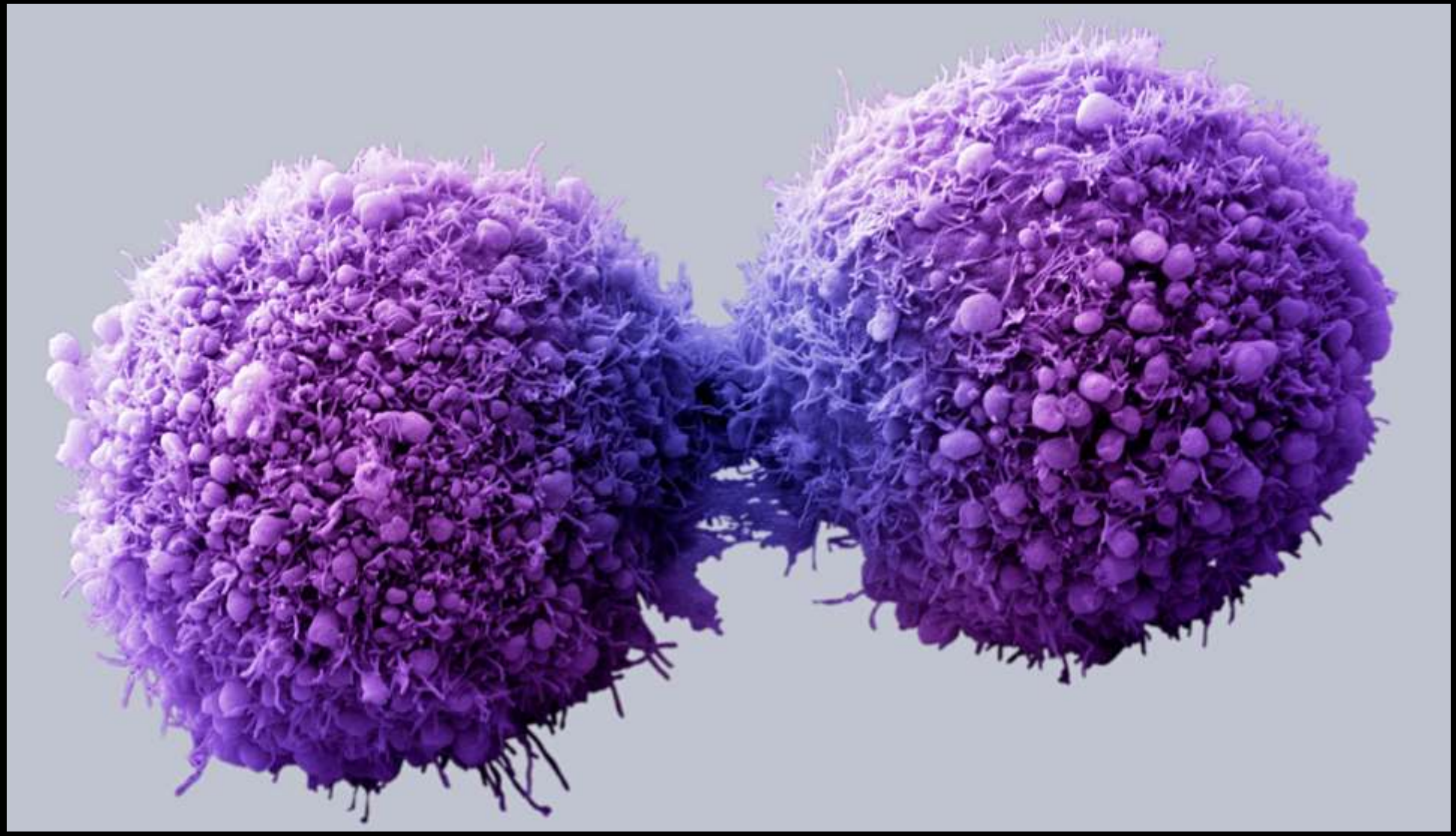
International Society
ISCT
Cell & Gene Therapy

Conflict of Interest Statement

- Declaration of financial interest due to intellectual property and patents in the field of cell and gene therapy.
- University of Pennsylvania Alliance with Novartis
- Consultant for CRC Oncology, Cure Genetics, Novartis
- Scientific Advisory Board for Avectas, Brammer Bio, Incysus, Vycellix
- Co-Founder and equity Tmunity Therapeutics
- Conflict of interest is managed in accordance with University of Pennsylvania policy and oversight

Cancer Therapy

Problem 1: The enemy is ourselves



Cancer Immunotherapy Problem 2: Cancer-Specific Immune Cells are very rare, if present at all

"**. . . we have only seen our monster more clearly and described his scales and fangs in new ways - ways that reveal a cancer cell to be . . . a distorted version of our normal selves.**"

Harold Varmus 1989

Cancers That "Succeed" Have Evolved Mechanisms of Tumor Immune Evasion

Hide

Suppress

Escape

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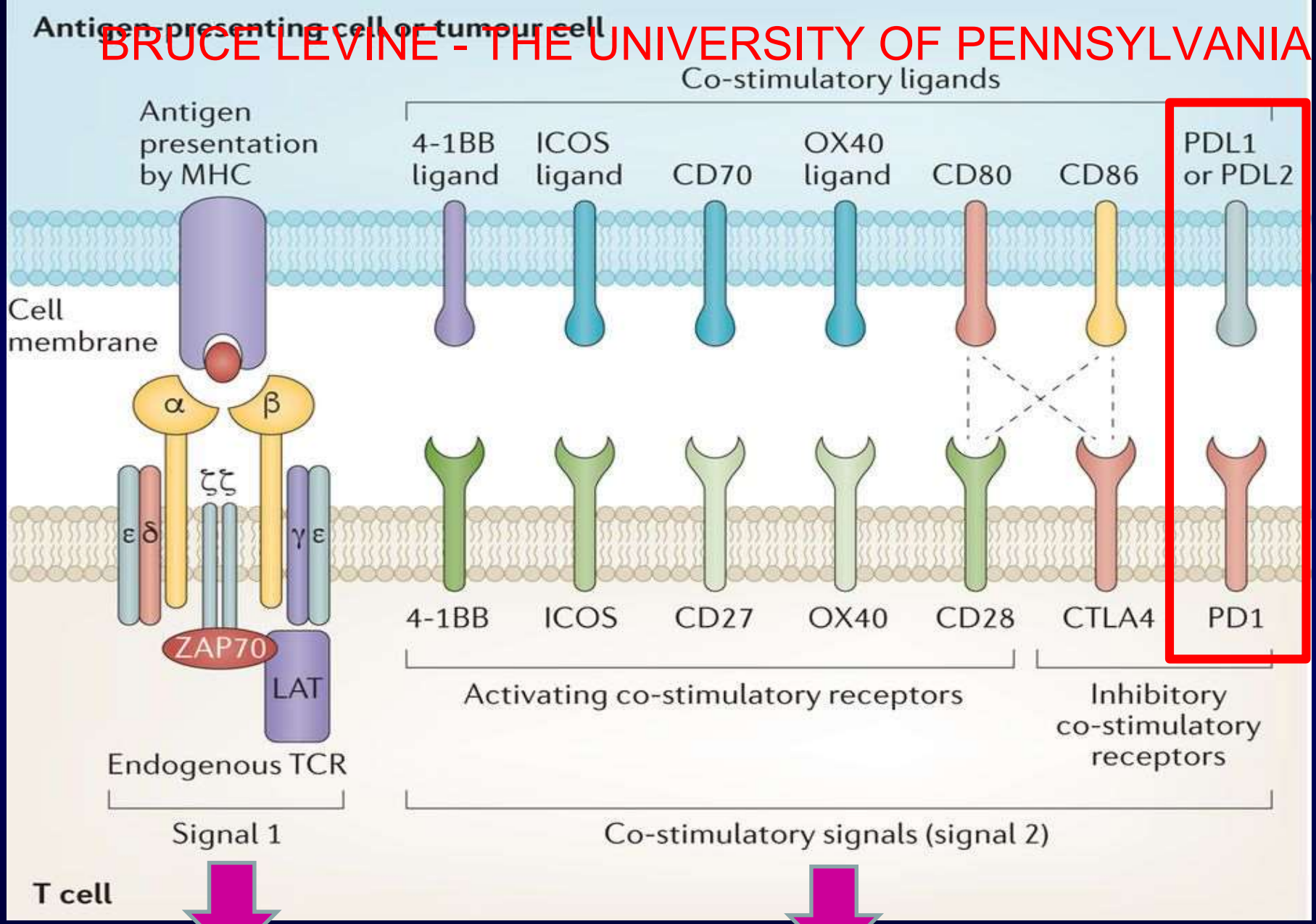
T Cell Activation and Inhibition Overview in 2 minutes



Tumors

Recognition

Controls

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October 1, 2018

Nobel Prize in Physiology or Medicine 2018

The Nobel Assembly at Karolinska Institutet has decided to award
the 2018 Nobel Prize in Physiology or Medicine jointly to

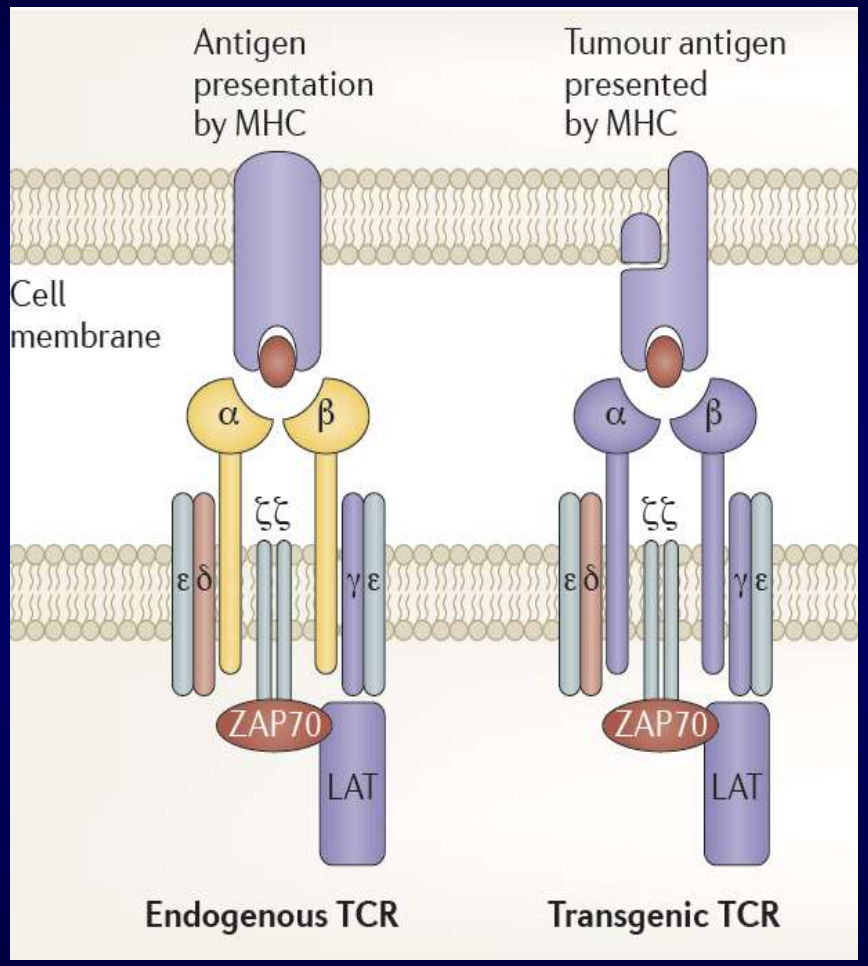
James P. Allison
Tasuku Honjo

for their discovery of cancer therapy by inhibition of negative immune regulation

Brakes and Accelerators Control T Cells Like Those in a CAR

Action Phase	Drive	Stop	Action Mode
Parking [Activation]	Ignition [CD28]	Parking Brake [CTLA4]	ON/OFF [Drastic]
Driving [Attack]	Accelerator [ICOS]	Brake [PD-1]	~100km/hr [Mild]

Overcoming the Scarcity of Tumor Specific Immunity and Tumor Suppression: Creation of Re-directed T cells

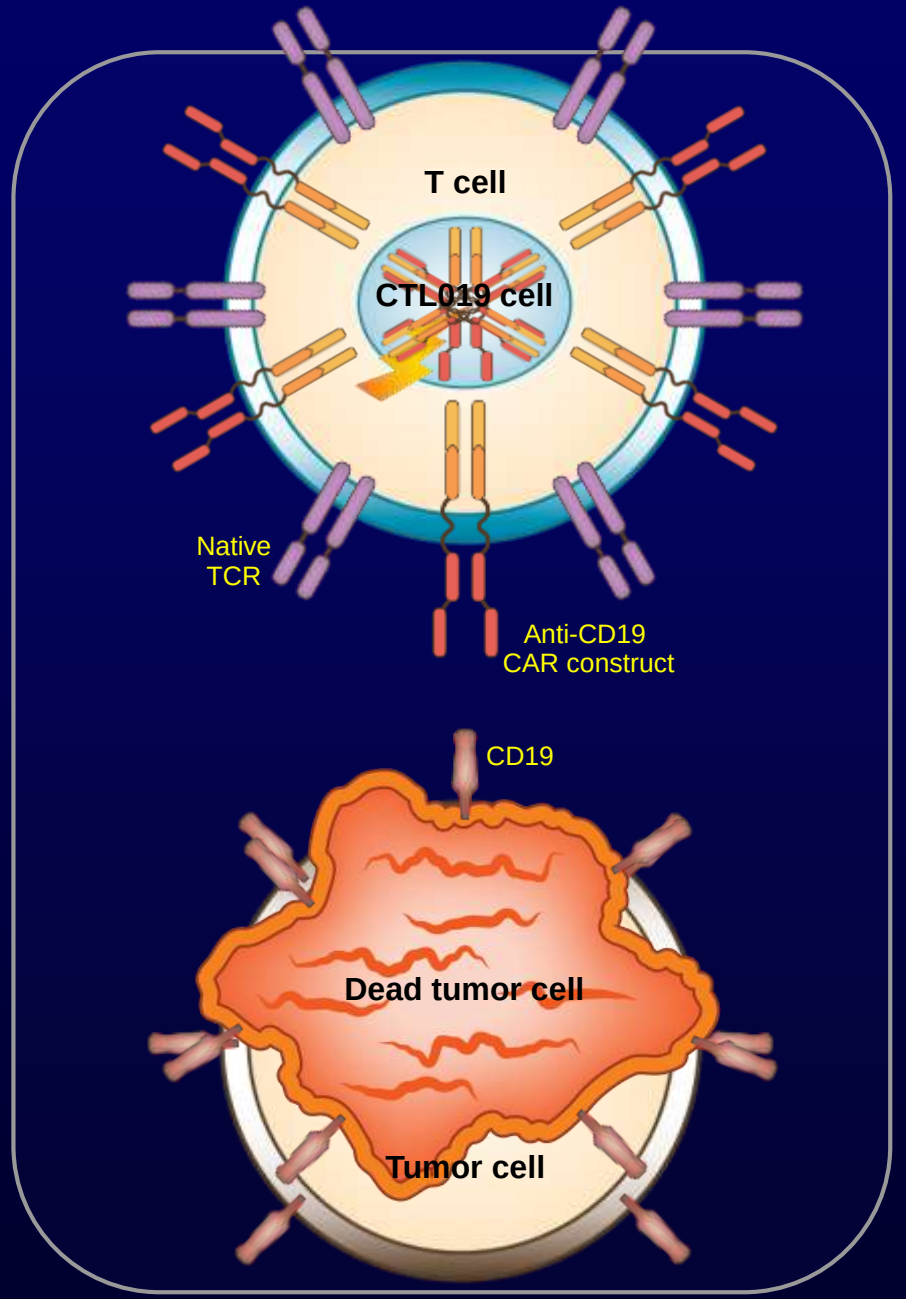


-intracellular Ags
-MHC dependent

Fesnak, June, Levine; Nature Reviews Cancer; Aug, 2016

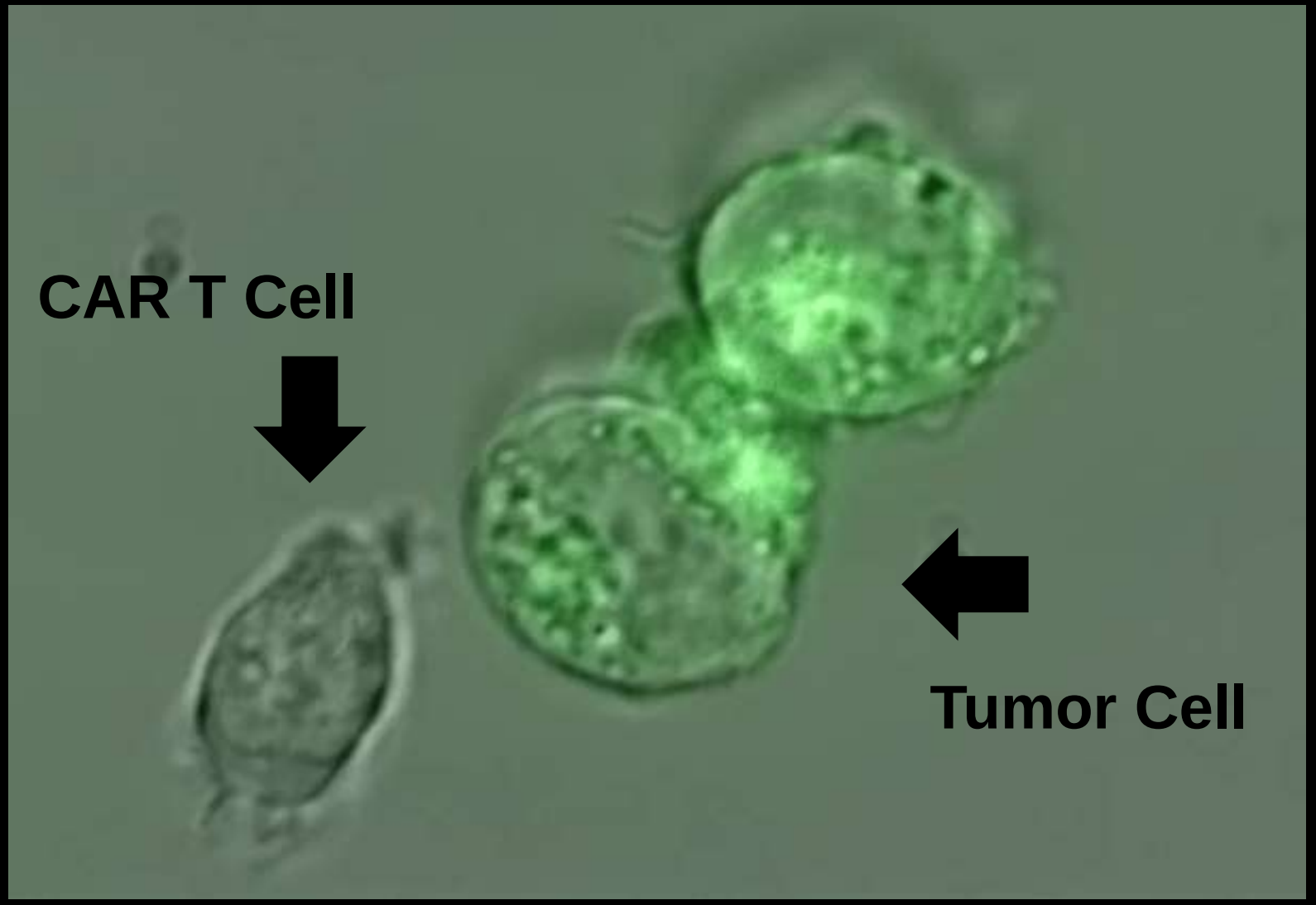
Targeting CD19+ Blood Cancers with CAR-Modified T cells

- CARs combine an antigen recognition domain of antibody with intracellular signaling domains into a single chimeric protein
- Gene transfer (lentiviral vector) to stably express CAR on T cells confers novel antigen specificity

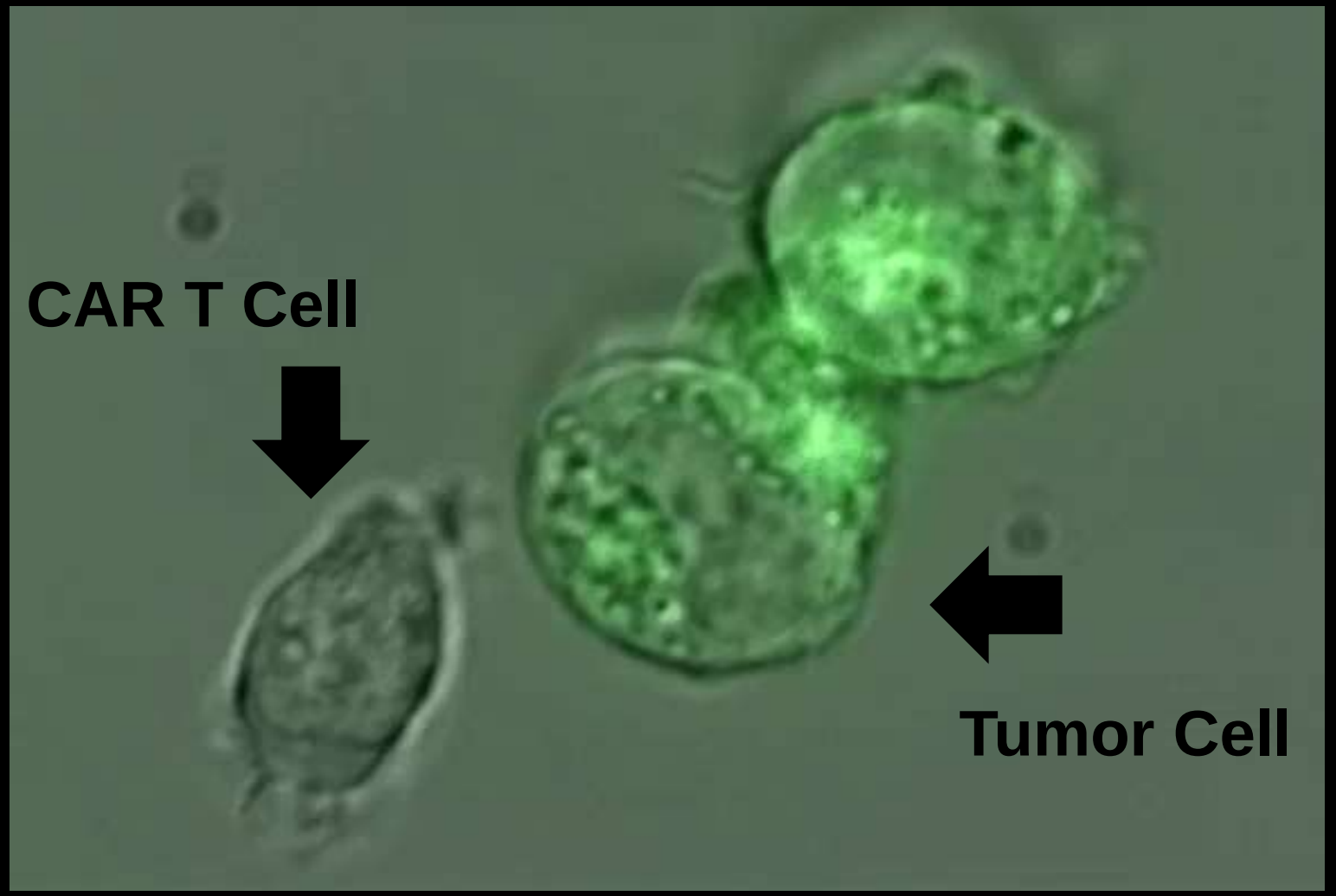


CAR, chimeric antigen receptor
TCR, T-cell receptor.

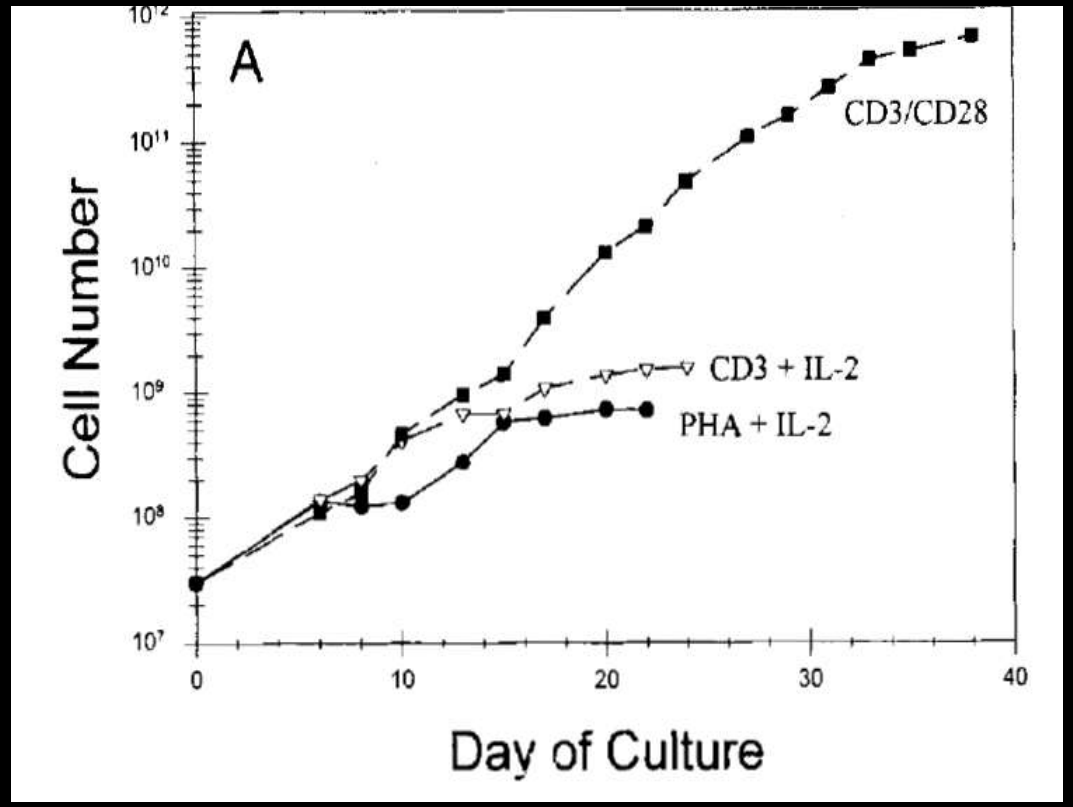
Engineered Immunity: Chimeric Antigen Receptor (CAR) T Cells To Kill Cancer

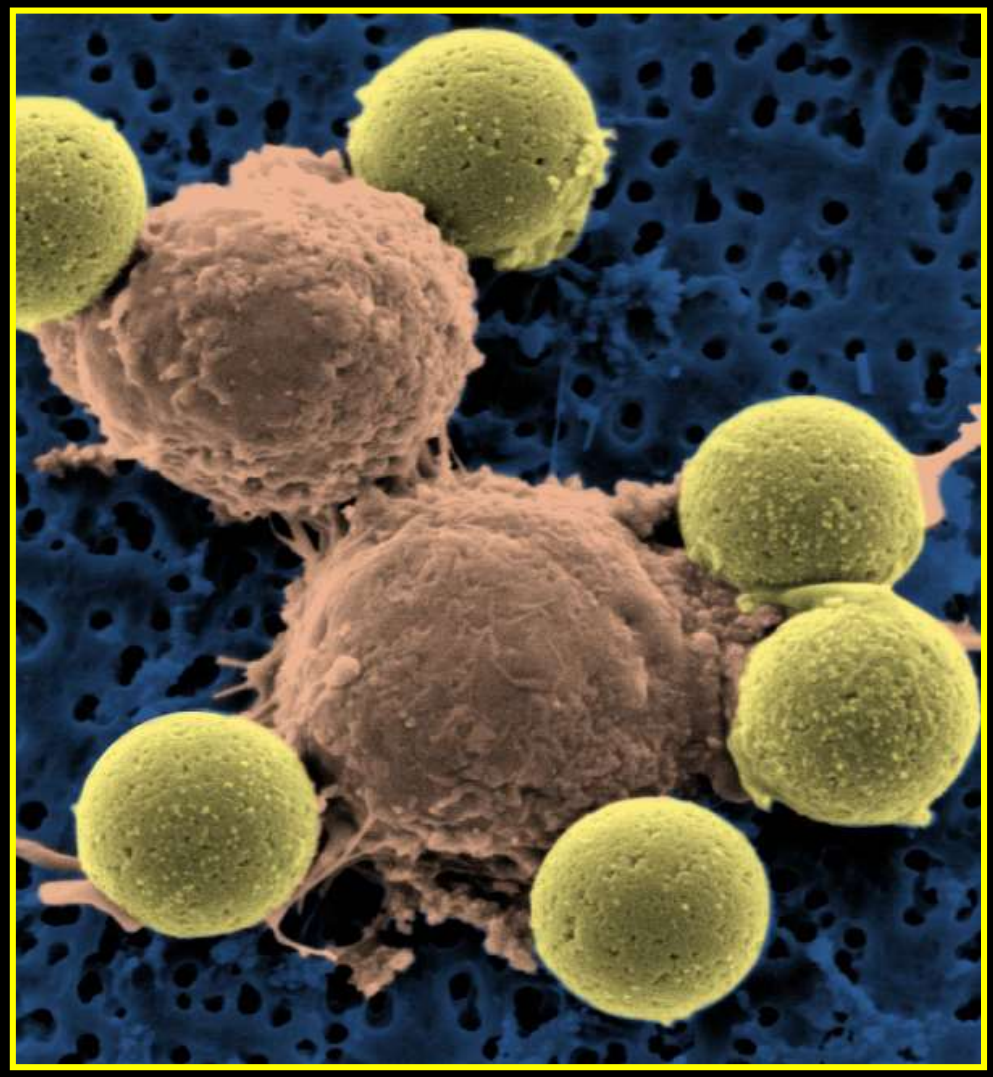


Engineered Immunity: Chimeric Antigen Receptor (CAR) T Cells To Kill Cancer



Synthetic Biology:
Improved ex vivo T Cell Culture System for Adoptive Immunotherapy
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

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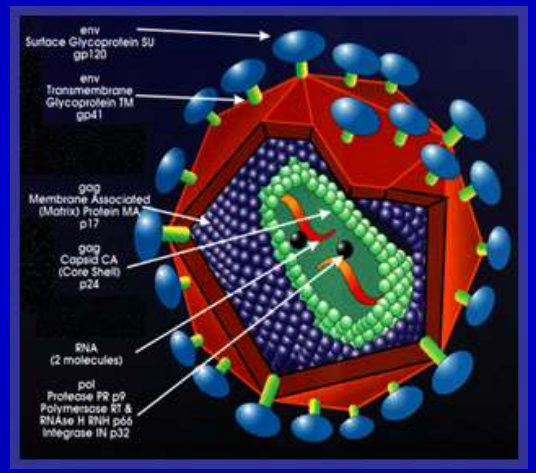
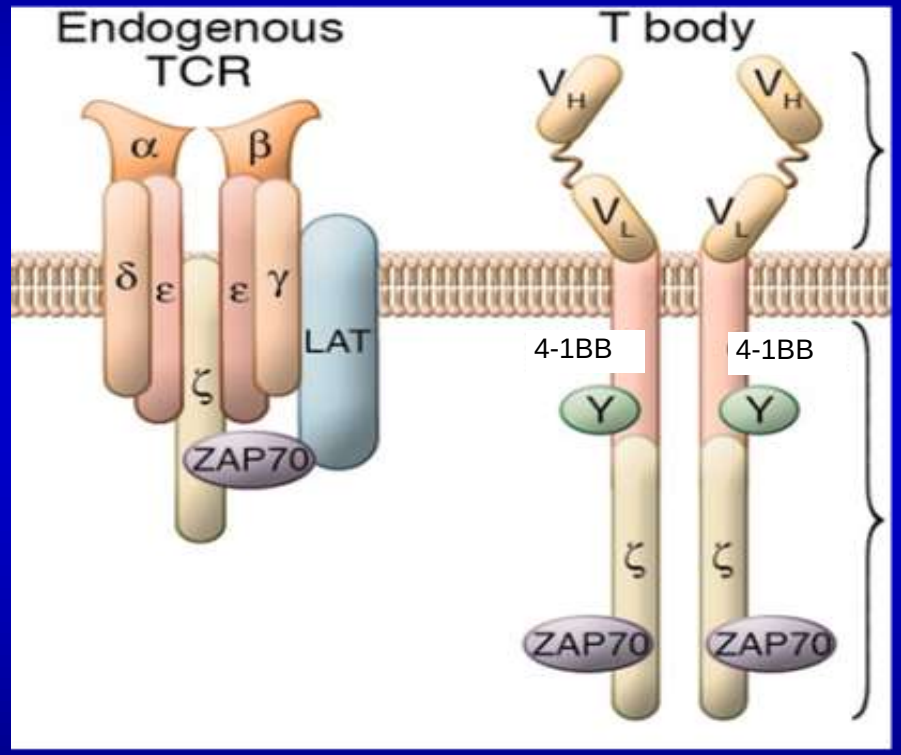
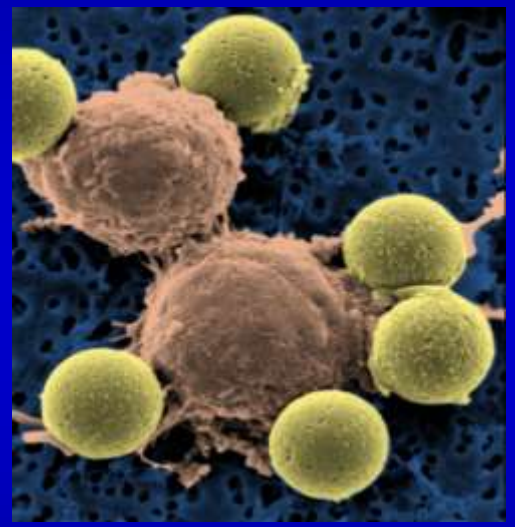
T Cell 360° Flyby

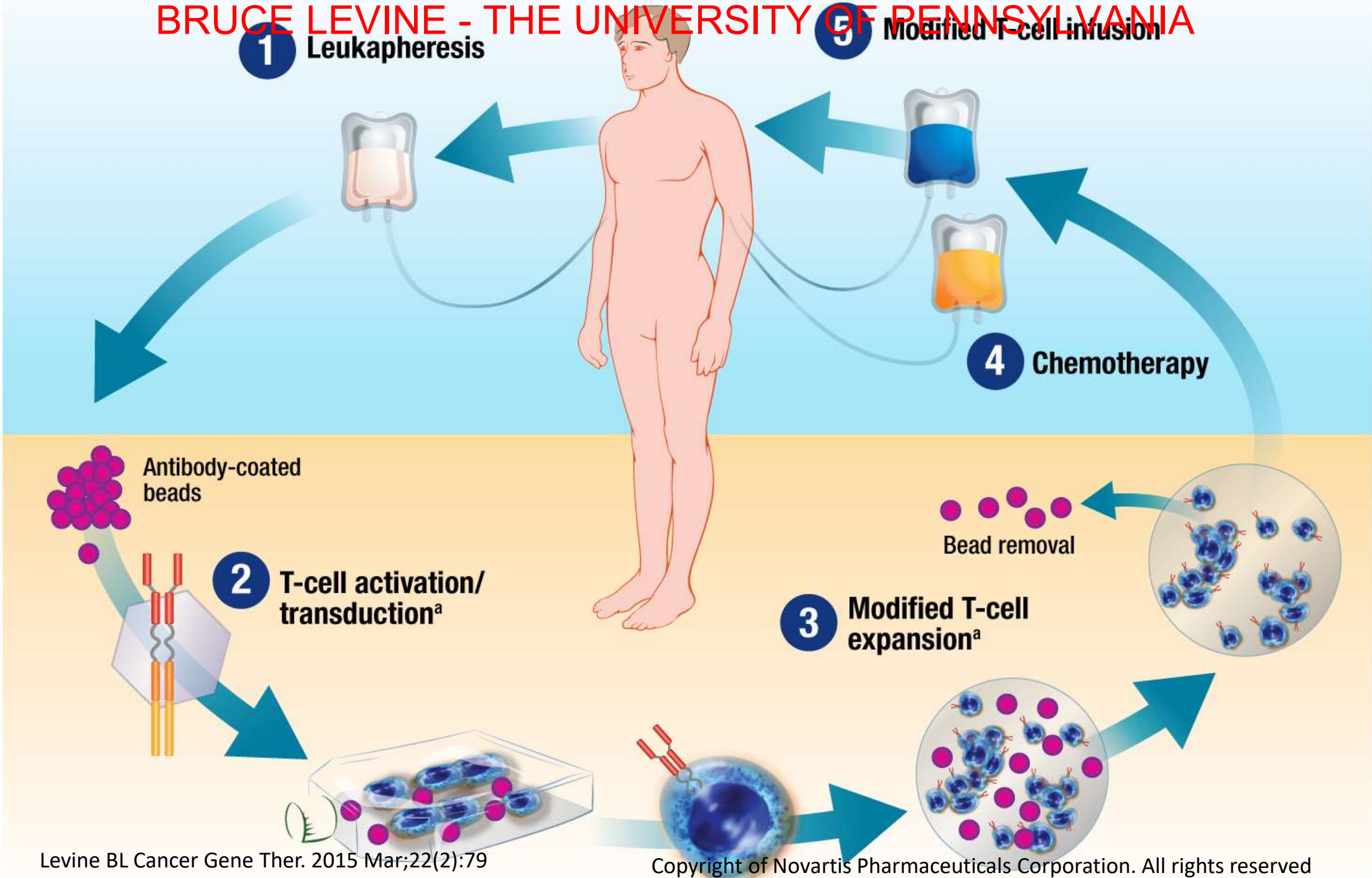
Three Technologies for Generating Engineered Cancer Immunity







- Lentiviral vector to deliver construct
- CD3-ζ and 4-1BB signaling domains
- Anti-CD3/anti-CD28 mAb coated bead stimulation



Levine BL Cancer Gene Ther. 2015 Mar;22(2):79

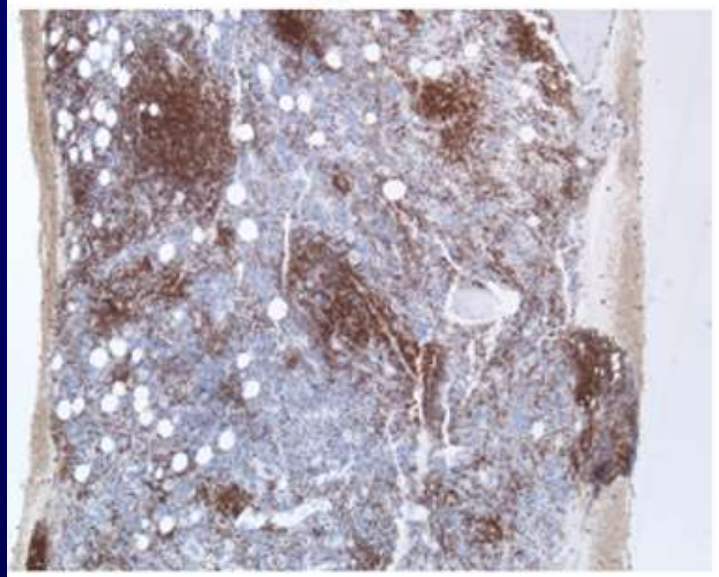
A Different Type of Drug

- Targeted
- Programmed
- Dividing
- Raw Material (Patient) Variability

How to set Critical Quality Attributes?

August, 2010

Before CAR T Cells



Pt #1

2.9 (1.3)

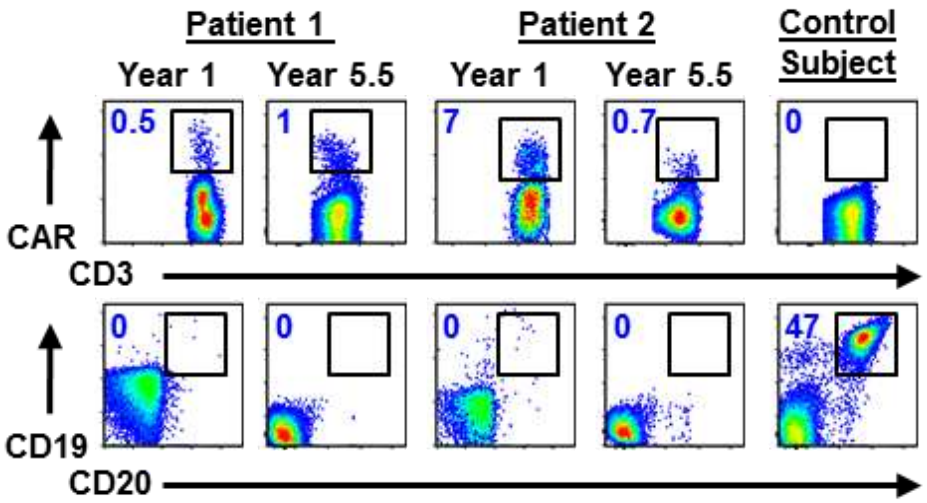
Pt#2

5.5 (2.5)

Pt #3

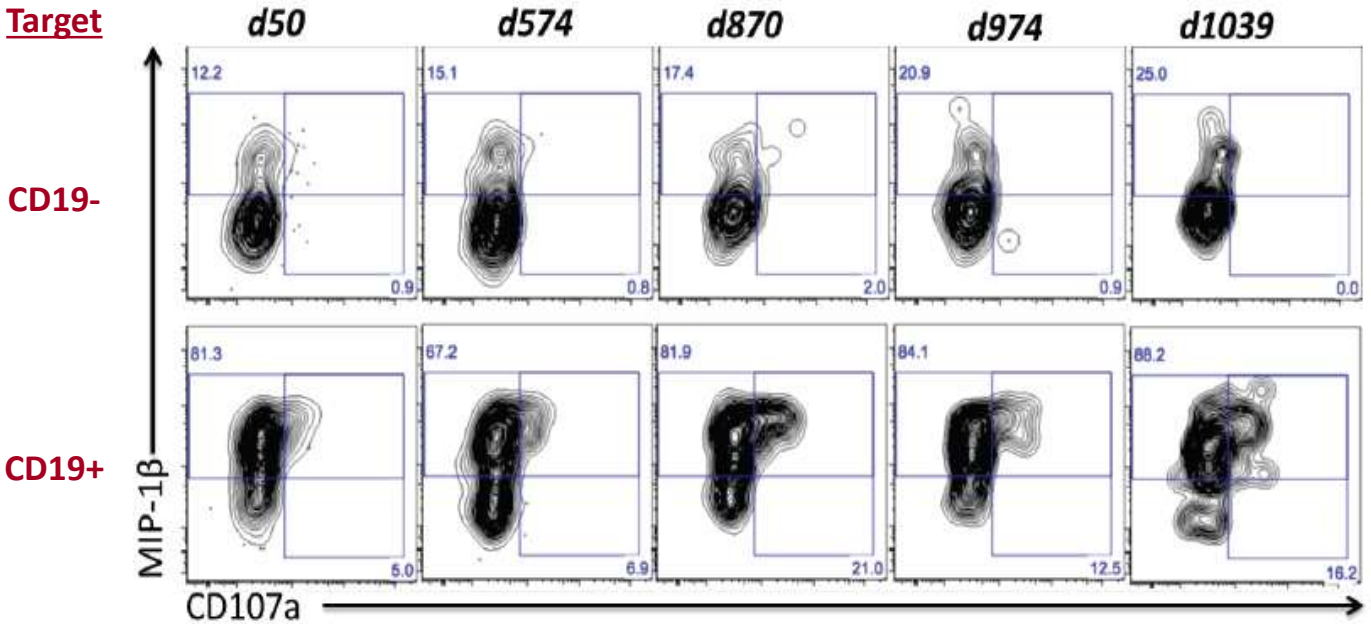
7.7 (3.5)

Long-term Persistent CTL019 Cells Remain Functional



- CRs endure beyond ***8 years*** and these patients still possess detectable CTL019 cells in the peripheral blood
- Ongoing B cell aplasia was seen, demonstrating that the persisting CAR T cells remained functional *in vivo*

Fraietta, Lacey et al., Melenhorst, Nat Med. 2018 May;24(5):563-571



- PBMC re-isolated from patient 2. Cells expressing CAR identified with anti-idiotype mAb
- Stimulated for 6 hours with CD19+ or control tumor cells. Cytokine induction and degranulation measured

Porter, D.L. et al. Sci Transl Med, 2015. 7(303); 303ra139.

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August, 2010

October, 2017

CAR T Cells
Moving to Acute Lymphoid Leukemia

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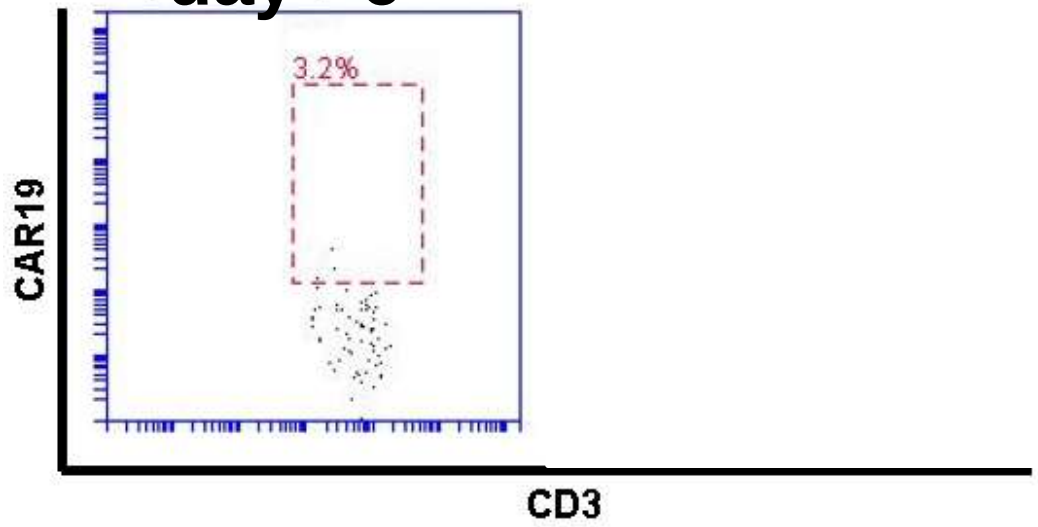
Rapid Induction of Remission in Pediatric Acute Lymphoblastic Leukemia

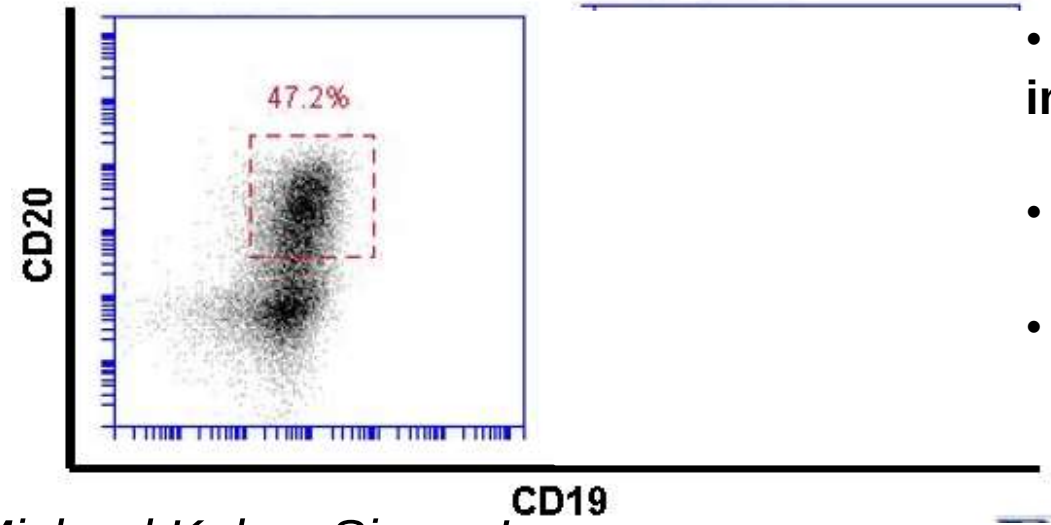
day +6

T Cells



Bone Marrow

B Cells (tumor)



- Deep remission induced in 23 days
- Status: CR (2+)
- MRD <0.01% cells

Stephan Grupp, Michael Kalos, Simon Lacey

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From Boutique

To Global

25 Site 11 Country 4 Continent Global Biologistics

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

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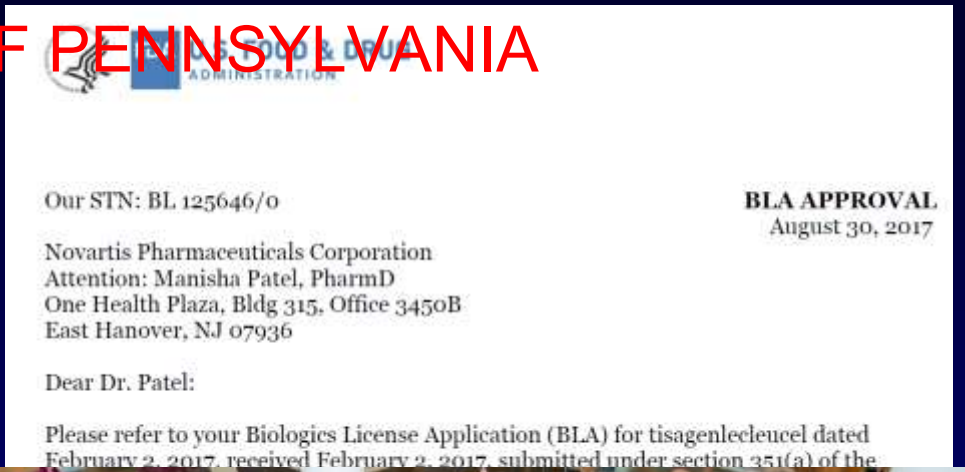
CART19
CTL019
Tisagenlecleucel
Kymriah™


Our STN: BL 125646/0

BLA APPROVAL
August 30, 2017

Novartis Pharmaceuticals Corporation
Attention: Manisha Patel, PharmD
One Health Plaza, Bldg 315, Office 3450B
East Hanover, NJ 07936

Dear Dr. Patel:

Please refer to your Biologics License Application (BLA) for tisagenlecleucel dated February 2, 2017, received February 2, 2017, submitted under section 351(a) of the

FDA News Release

FDA approves novel gene therapy to treat patients with a rare form of inherited vision loss

Luxturna is the first gene therapy approved in the U.S. to target a disease caused by mutations in a specific gene

Two FDA Approved Gene Therapies Developed at Penn and the Children's Hospital of Philadelphia

The Leukemia & Lymphoma Society
Fighting Blood Cancers

ACGT National grants for cell and gene therapy cancer research
ALLIANCE FOR CANCER GENE THERAPY

Penn
University of Pennsylvania

NOVARTIS

The Children's Hospital of Philadelphia

Spark THERAPEUTICS

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KYMRIAH®
(tisagenlecleucel) Suspension for IV infusion

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SCIENCE MEDICINES HEALTH

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- Japanese envoy urges concerted pressure on N.Korea
- Researchers test drug for treating ALS

Japan 10 hours ago

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The Sydney Morning Herald

EXCLUSIVE NATIONAL CANCER

'Revolutionary' cancer drug using genetically modified cells approved

By Esther Han
December 19, 2018 — 12.00am

A revolutionary cancer therapy that supercharges a patient's immune cells to hunt and destroy cancer cells has been approved for use in Australia, ushering in a new era in medicine.

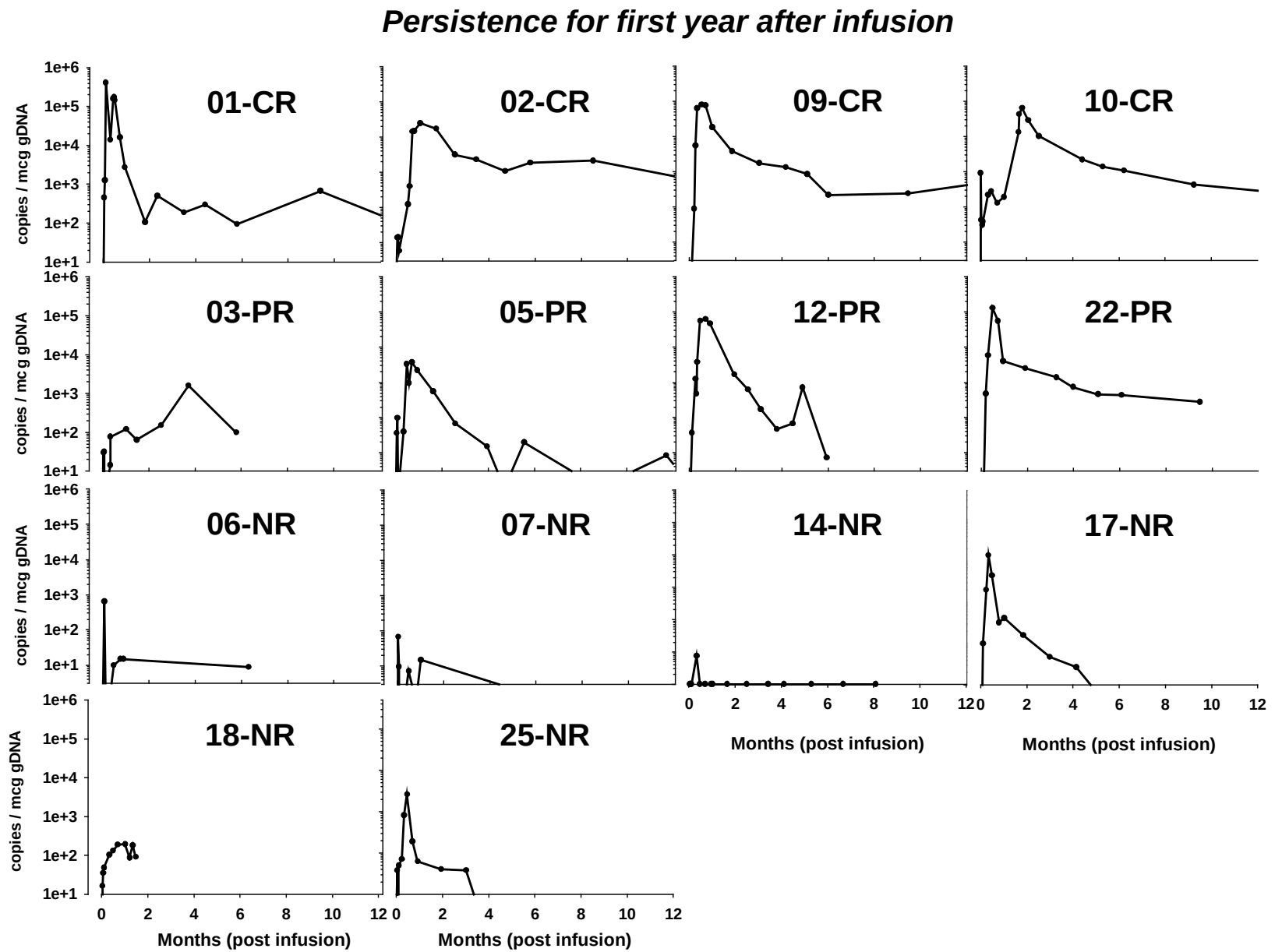
Desperate patients with aggressive blood cancers who have not responded to conventional treatments have been heading overseas to receive a shot of the "custom-made" drug and

A Different Type of Drug

- Targeted
- Programmed
- Dividing
- Raw Material (Patient) Variability

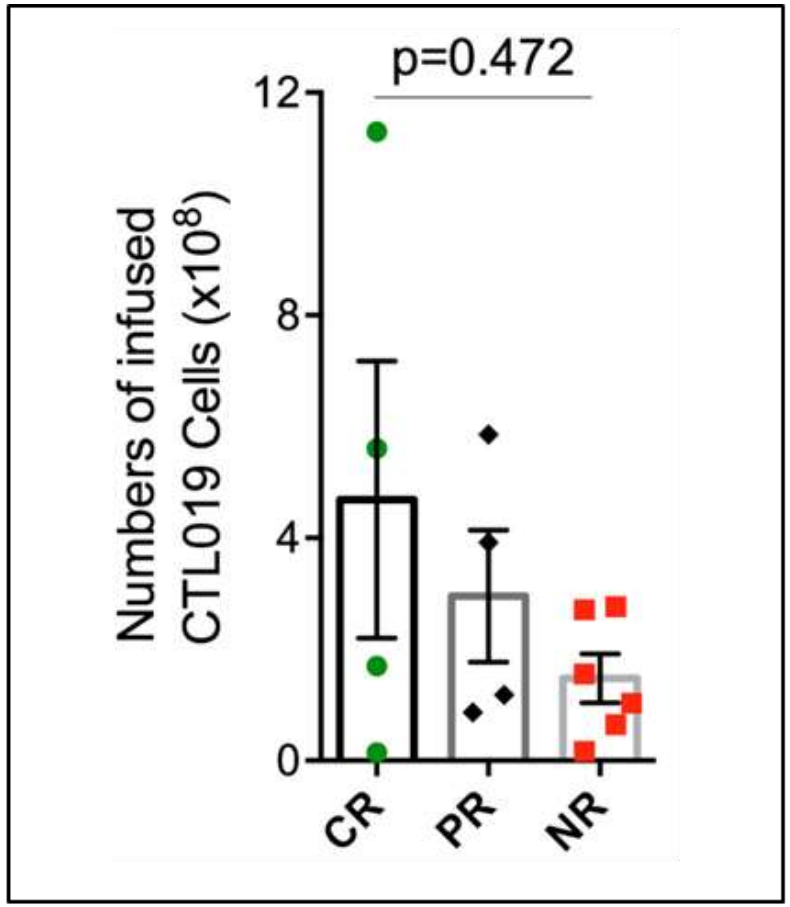
How to set Critical Quality Attributes?

Long term persistence of CTL019 in CLL patients with correlation to clinical response



For a Dividing Drug - Quality Counts More Than Dose!

CTL019 Therapy in R/R Chronic Lymphoid Leukemia

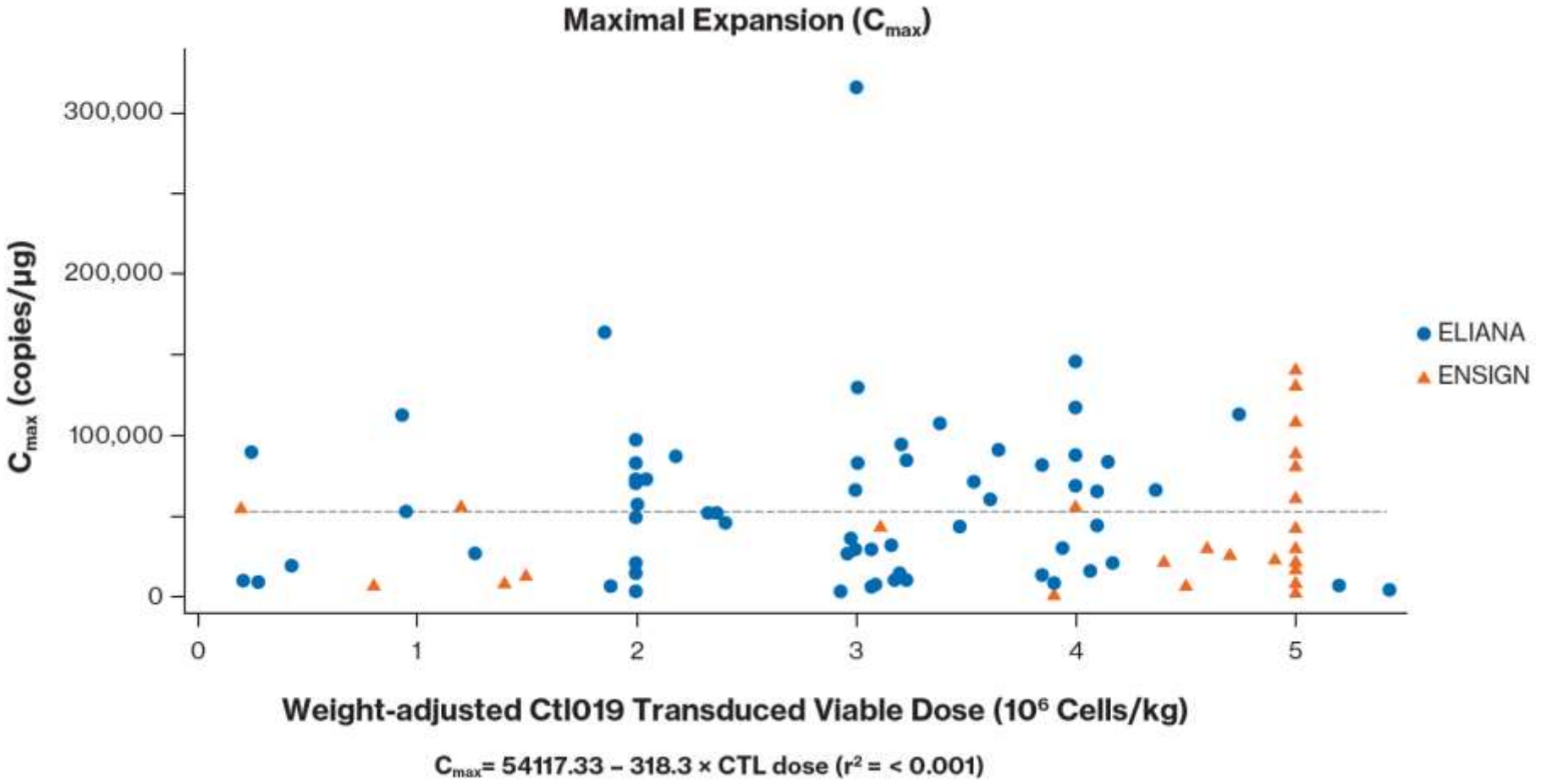


- No statistical difference in the numbers of CTL019 cells infused per patient and clinical outcome of therapy (Exact's Unpaired Mann-Whitney statistical test).

Porter D. L. *et al.*, Science TM (2015)

Tisagenlecleucel Expansion and Dose

- Across a wide range of doses, in vivo expansion and dose are independent



- **Product transduction efficiency, cell viability and total T cells do not impact expansion and persistence**

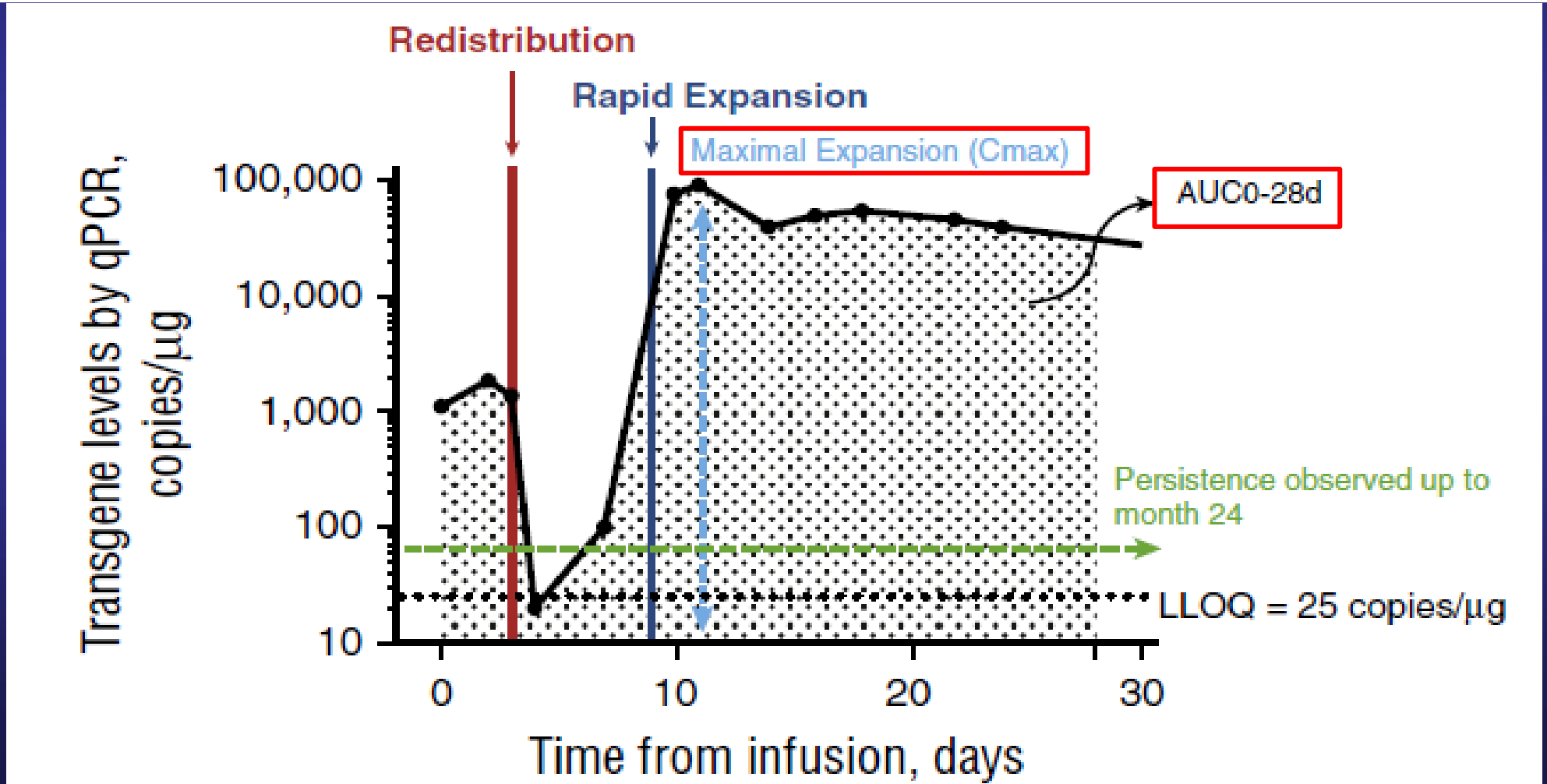
Data pooled from ELIANA AND ENSIGN.

Karen Thudium Mueller, et al. SOHO 2017

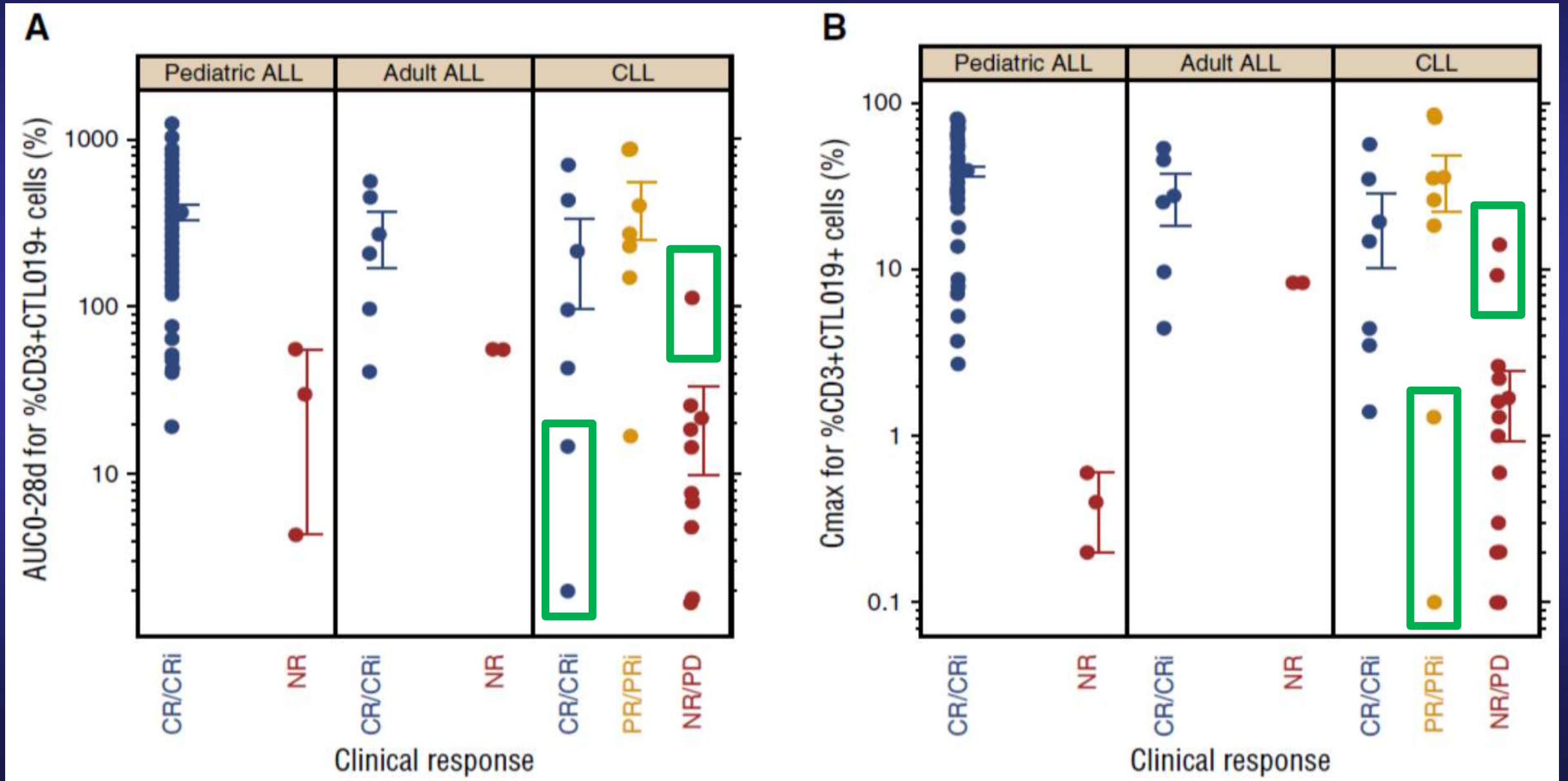
Cellular kinetics of CTL019 in relapsed/refractory B-cell acute lymphoblastic leukemia and chronic lymphocytic leukemia

Karen Thudium Mueller,[1] Shannon L. Maude,[2,3] David L. Porter,[3] Noelle Frey,[3] Patricia Wood,[1] Xia Han,[1] Edward Waldron,[1] Abhijit Chakraborty,[1] Rakesh Awasthi,[1] Bruce L. Levine,[3] J. Joseph Melenhorst,[3] Stephan A. Grupp,[2,3] Carl H. June,[3] and Simon F. Lacey[3]

BLOOD, 23 NOVEMBER 2017 • VOLUME 130, NUMBER 21



Relationship between exposure and expansion of CTL019 cells and response category in pediatric B-ALL, adult ALL, and CLL.



Engineering an Unsafe Target Into a Safe Target

CD33: Target for AML Therapy

- **CD33 is an established target in acute myeloid leukemia**
  - Antibody-drug conjugates (e.g. Gemtuzumab ozogamicin)
  - Bi-specific T cell engagers (e.g. AMG 330)
- **CD33 may not be essential for the hematopoietic system**
- **But, CD33 is present on HSC's**

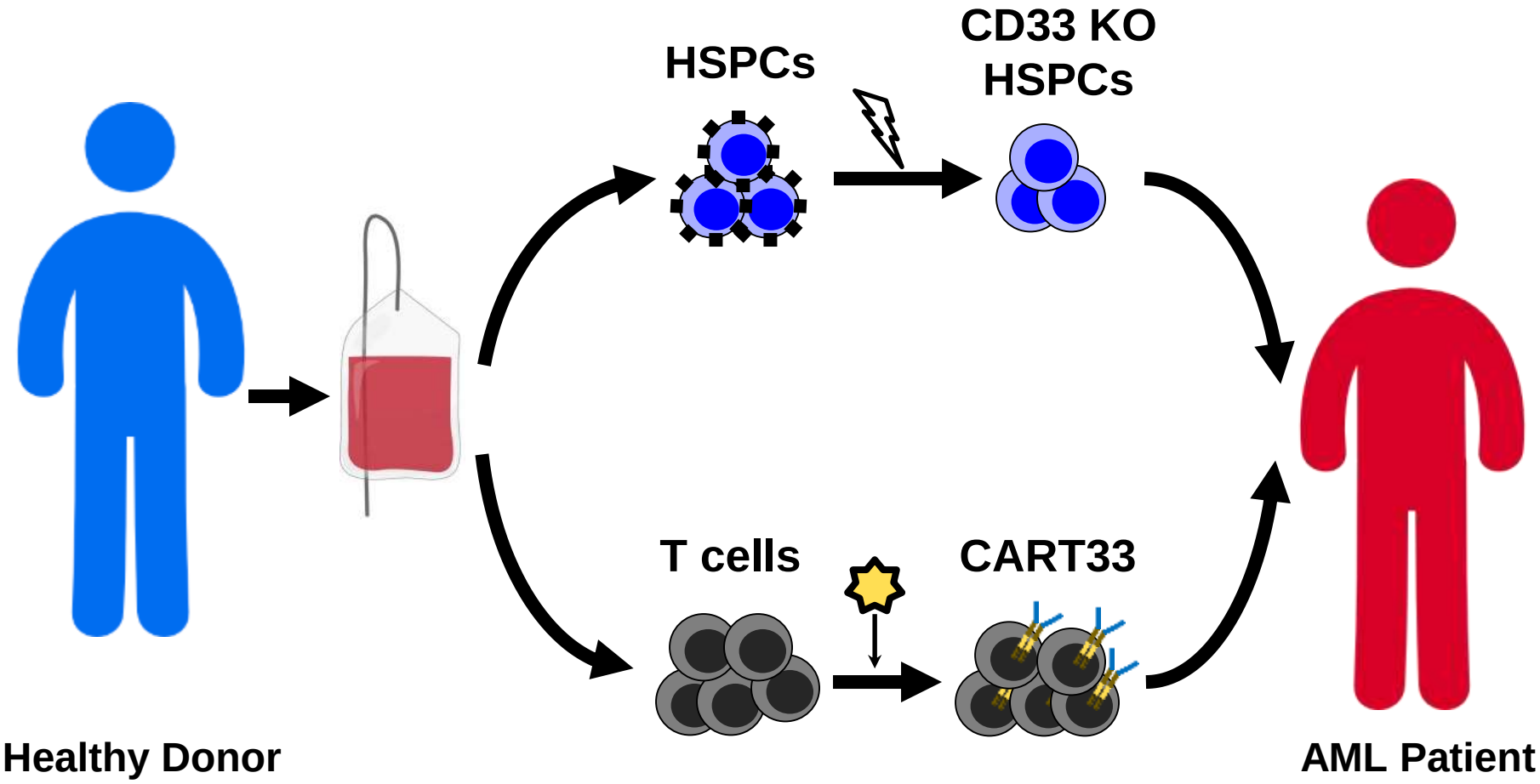
Pre-Clinical Studies

- **CD33 can be removed from HSPCs without impairing hematopoiesis**
- **CD33 KO HSPCs are resistant to CD33-targeted therapy**
- **CD33 KO myeloid cells retain functional properties**

Miriam Y. Kim, Saad S. Kenderian, Daniel Schreeder, Michael Klichinsky, Miroslaw Kozlowski, Olga Shestova, Marco Ruella, Saar Gill

Penn Medicine
Center for Cellular Immunotherapies

CRISPR Rescued Immunity For CD33 Targeted CART's in AML



Saar Gill and Colleagues

Penn Medicine
Center for Cellular Immunotherapies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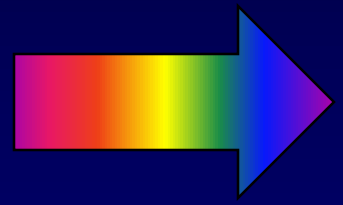
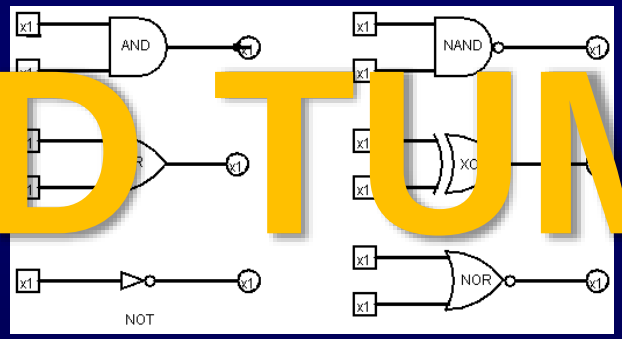
Infectious Diseases
???
Lung
Leukemia
Mesothelioma
Ovarian
Pancreatic
Myeloma
Breast
Lymphoma
Glioblastoma
Prostate
Melanoma
Sarcoma
Organ Transplant
Tolerance
Autoimmune Diseases

Synthetic Biology: The Advanced CAR Toolbox

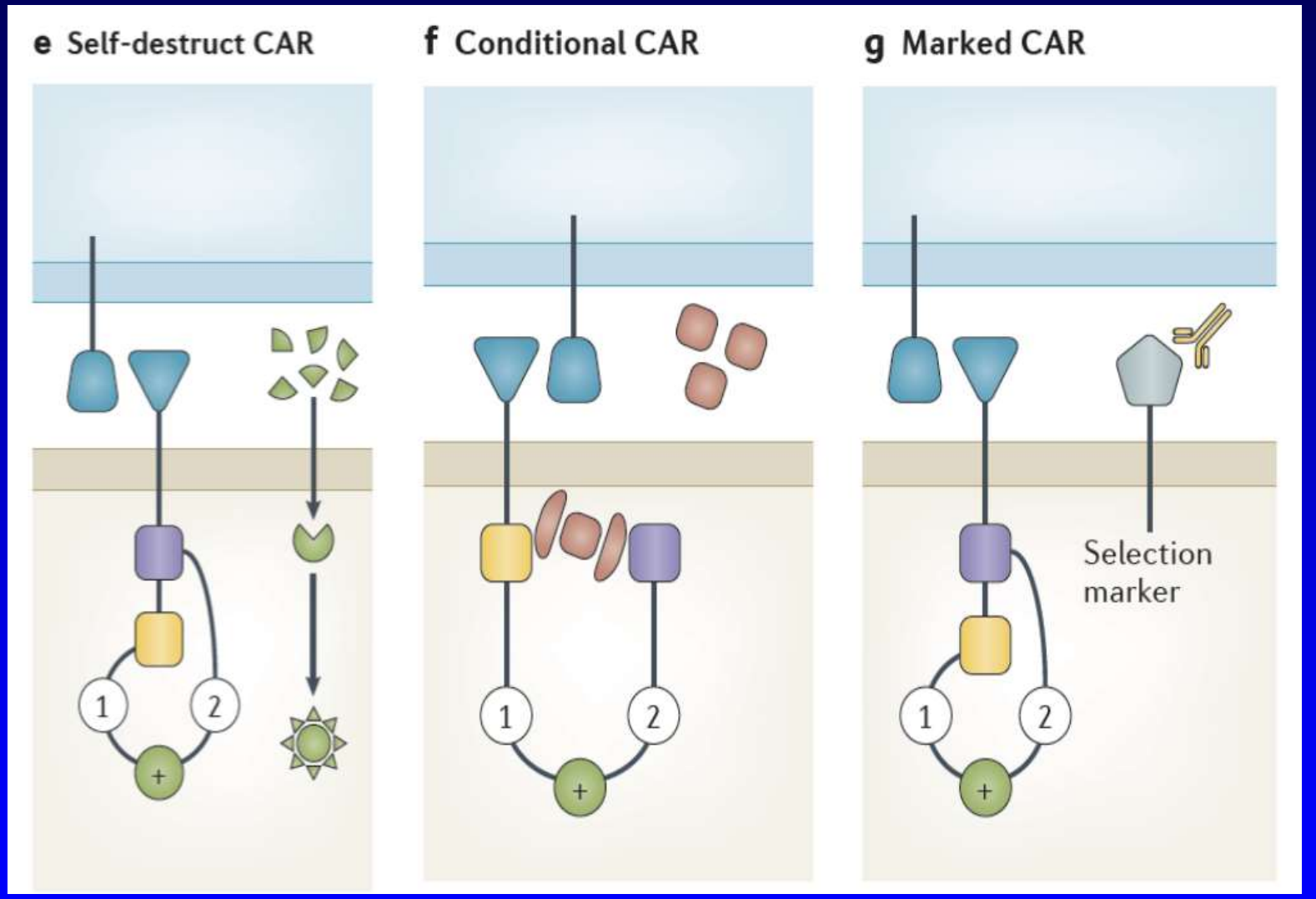


SOLID TUMORS



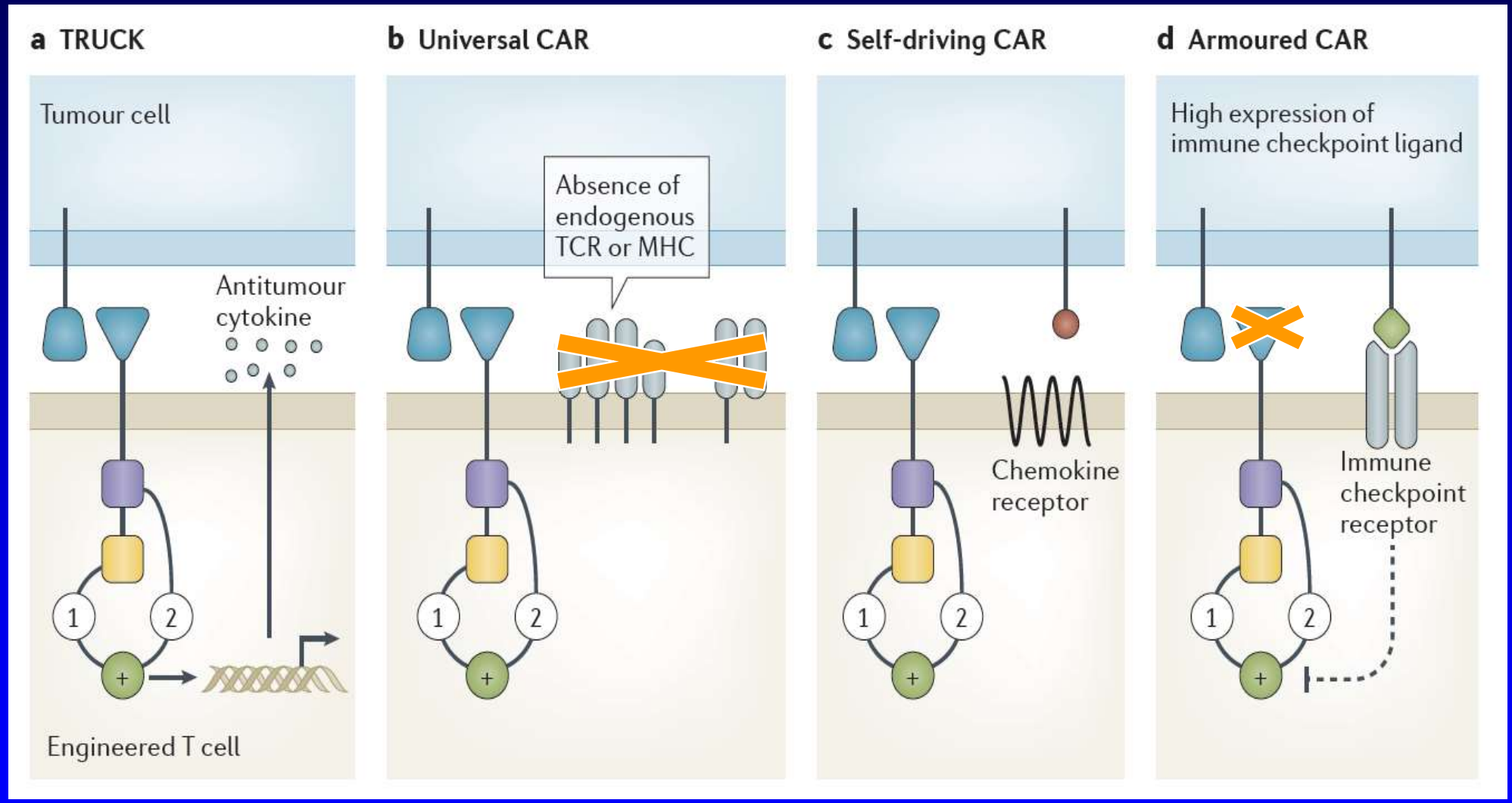
- Logic Gated Boolean CAR's- "And", "Or", Not
- Checkpoint Resistant CAR's
- Safety Switches
- Conditional/Stealth CAR's

Overcoming the Scarcity of Tumor Specific Immunity and Tumor Suppression: 10 New Models of CAR's



Fesnak, June, Levine; Nature Reviews Cancer; Aug, 2016

Overcoming the Scarcity of Tumor Specific Immunity and Tumor Suppression: 10 New Models of CAR's



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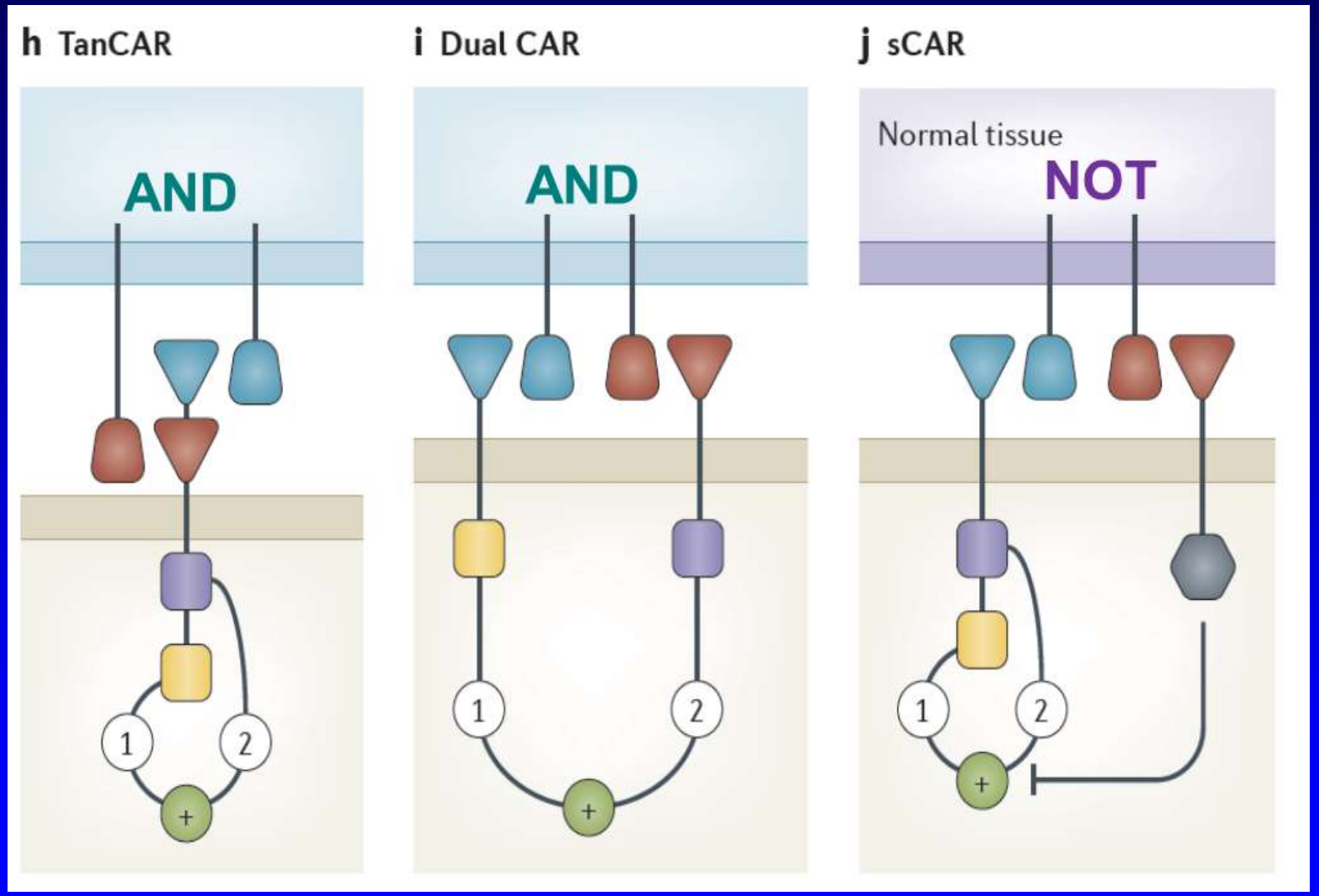
Overcoming the Scarcity of Tumor Specific Immunity and Tumor Suppression: 10 New Models of CAR's



Fesnak, June, Levine; Nature Reviews Cancer; Aug, 2016

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A Triple Shot of Engineered Immunity

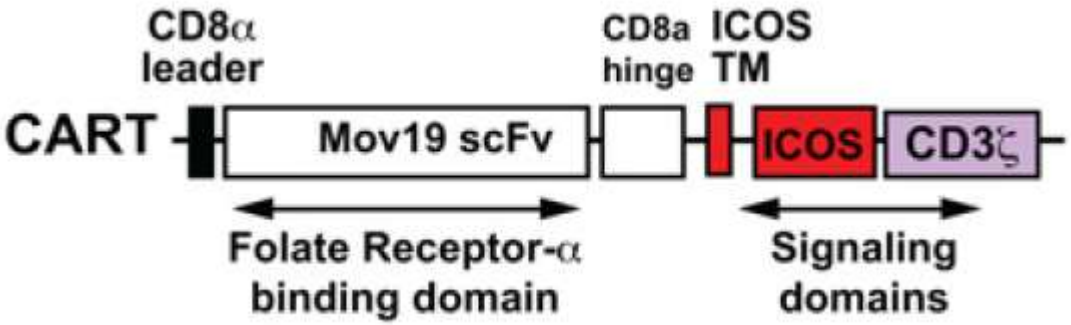
Published OnlineFirst March 27, 2018; DOI: 10.1158/2326-6066.CIR-17-0314

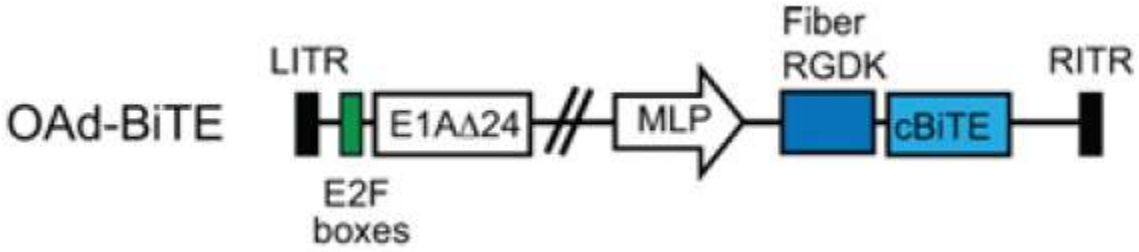
Research Article

Cancer Immunology Research

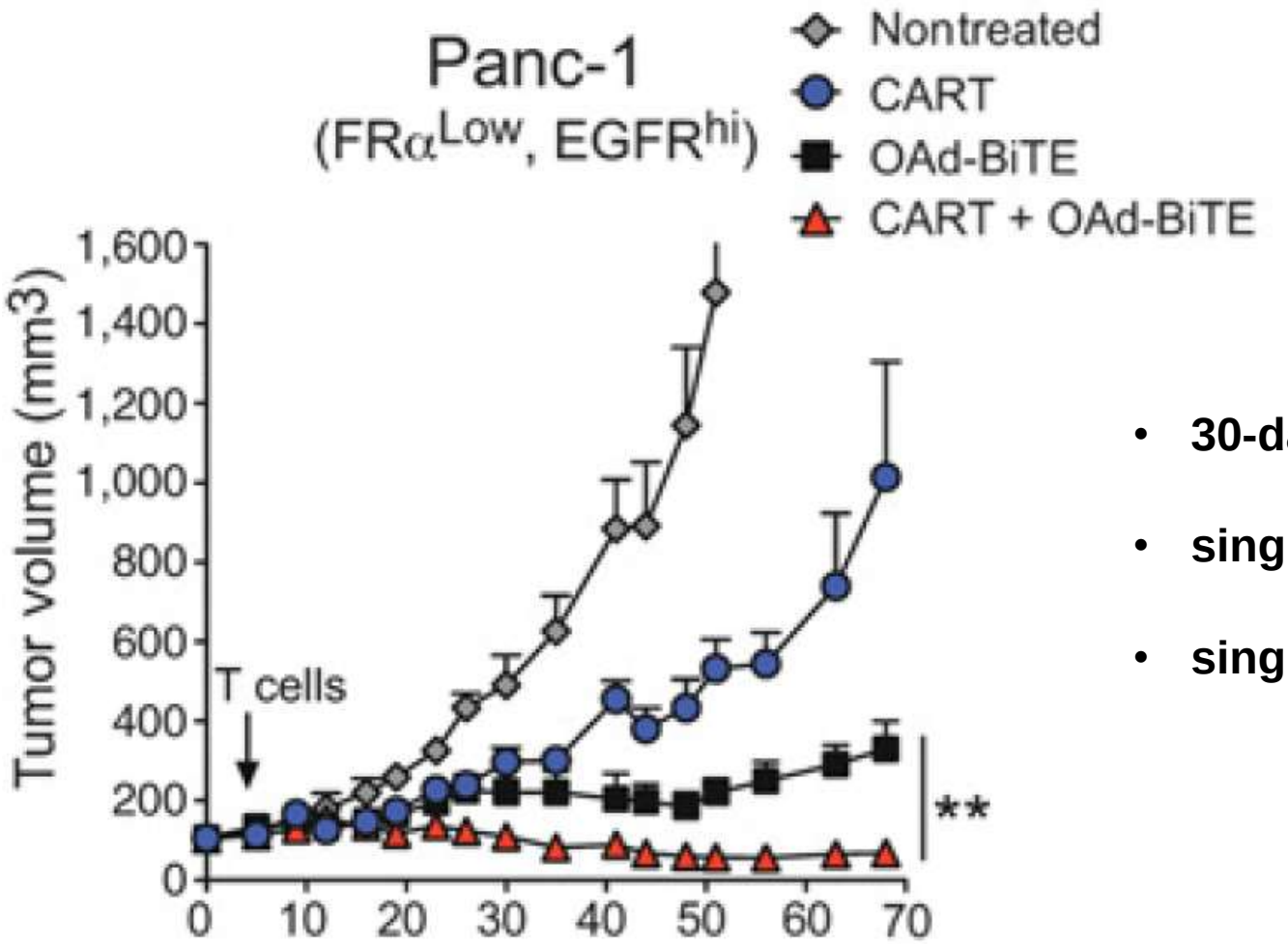
Improving CART-Cell Therapy of Solid Tumors with Oncolytic Virus–Driven Production of a Bispecific T-cell Engager

Anna Wing[1], Carlos Alberto Fajardo[2], Avery D. Posey Jr[1], Carolyn Shaw[1], Tong Da[1], Regina M. Young[1], Ramon Alemany[2], Carl H. June[1], and Sonia Guedan[1]





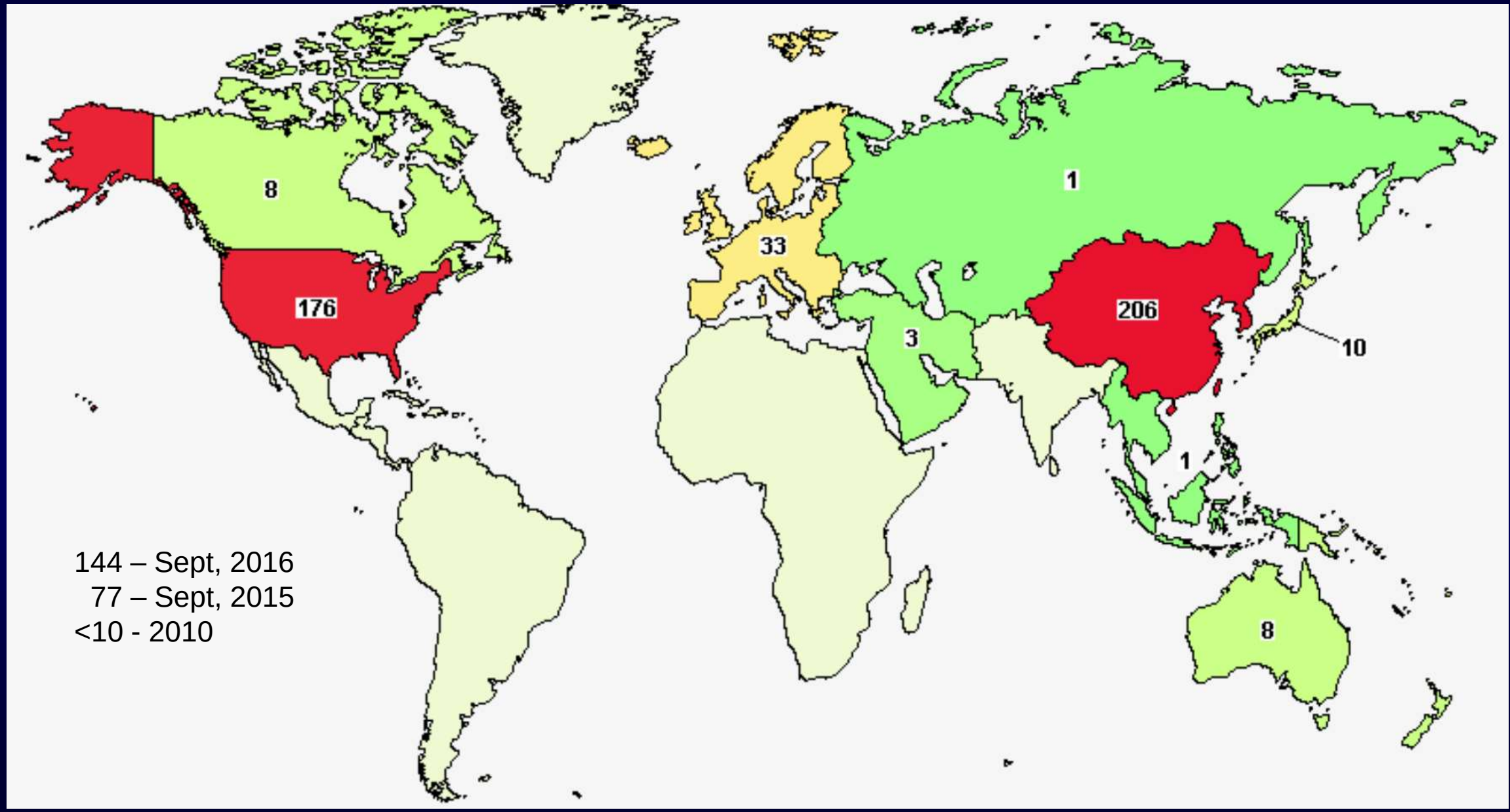
Combining CAR T and BiTEs: Synergism with OAd-BiTE



- **30-day established Panc-1 tumors**
- **single dose of OAd-BiTE (EGFR-targeted)**
- **single dose of FR-CART cells 3 days later**

Wing et al. Improving CART-Cell Therapy of Solid Tumors with Oncolytic Virus-Driven Production of a Bispecific T-cell Engager. *Cancer Immunol Res.* 2018;6(5):605-16.

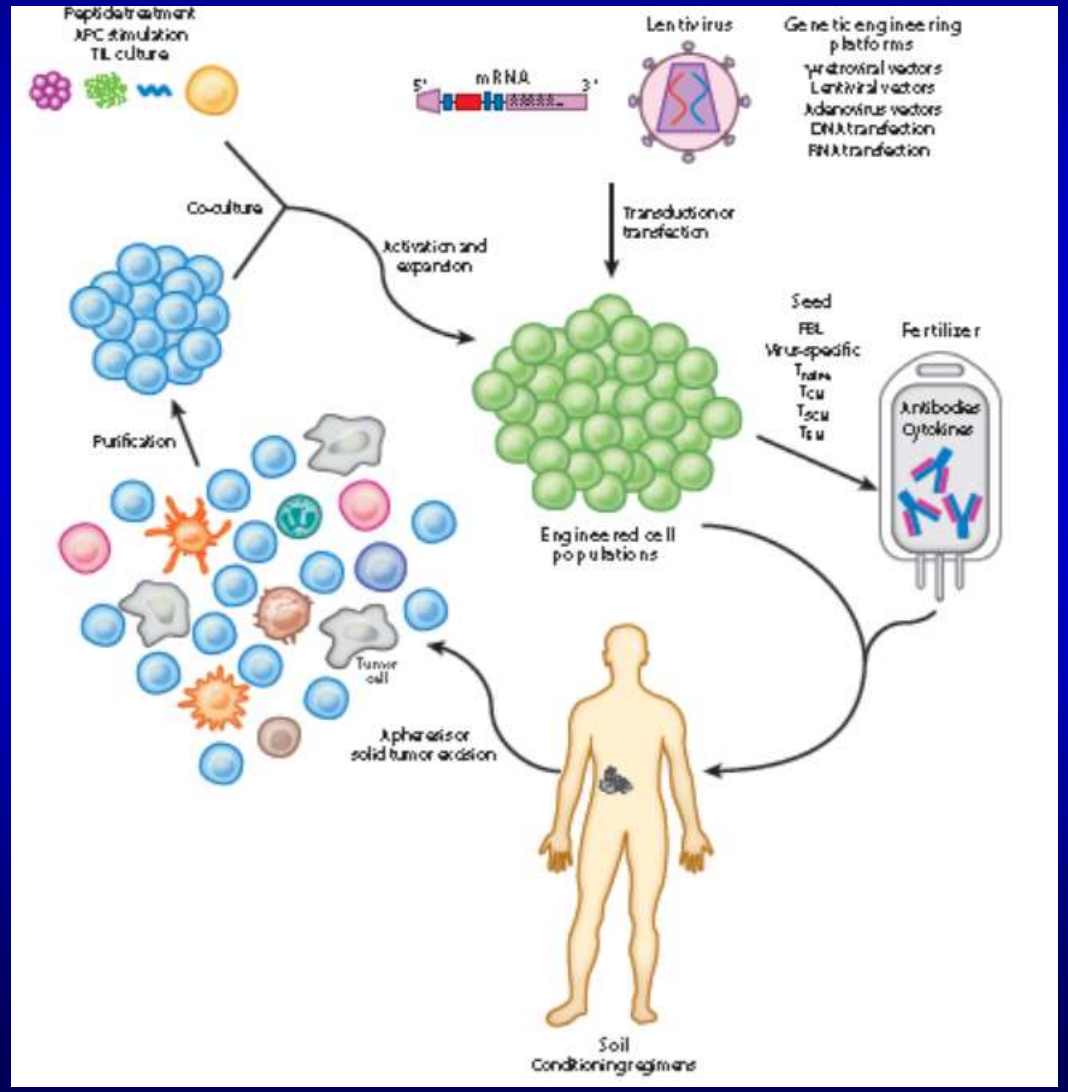
Clinicaltrials.gov search "chimeric antigen receptor"
October 15, 2019 yields 419 trials



CARs: The Make and Model is Important!

Variables:

- host conditioning
- cell subtype
- CAR design: scFv, signaling modules
- vector (retro, lenti)
- dose



Maus et al.
Ann Rev Immunol
32:189-225, 2014

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

- Securing Supply Chain – hundreds of complex components
- Reducing COGS and Labor
- Recruiting, Training, Retaining Technologists/Engineers
- Near Term Outscaling, Mid to Long Term Automation
- Increasing Consistency, Comparability, managing challenging cases
- Rapid and Modified Release Test Development
- Clinical Site Onboarding
- Near Term Clinical Trial/Post-Approval Allocation Ethics
- Enhancing potency & specificity, especially for solid tumors

Separating Hope from Hype

Tomorrow's treatments today—that's the promise of a growing number of companies offering cell therapies untested in rigorous clinical trials. Some experts say the claims must be challenged

Selling the Stem Cell Dream

IF YOU SUFFER FROM AN INCURABLE neurological disease such as multiple sclerosis (MS), Parkinson's, amyotrophic lateral sclerosis (ALS), or Huntington's disease, a clinic in the Netherlands says it may be able to help you. inject them. Almost all have Web sites to advertise the promise of the new therapies, often with hopeful case reports. The sites help recruit patients with what regular medicine cannot provide: a hope of recovery.

The result, Weissman fears, may be that stem cell research—already under criticism for its use trying to find out more, too, although they say it can be impossible to get even basic facts about the treatments.

Martin Enserink www.sciencemag.org SCIENCE VOL 313 14 JULY

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HEALTH

F.D.A. Cracks Down on 'Unscrupulous' Stem Cell Clinics

By SHEILA KAPLAN and DENISE GRADY AUG. 28, 2017

Dr. Mark Berman, of the Cell Surgical Network, in 2014 at his practice in Beverly Hills, Calif. Dr. Berman is a founder of the California Stem Cell Treatment Centers, where patients received an unapproved stem cell treatment made with the help of a smallpox vaccine and other ingredients. Raquel Maria Dillon/Associated Press

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June 3, 2019

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF FLORIDA

Case No. 0:18-cv-61047-UU

UNITED STATES OF AMERICA,

Plaintiff,

v.

US STEM CELL CLINIC, LLC, *et al.*,

Defendants.

_____/

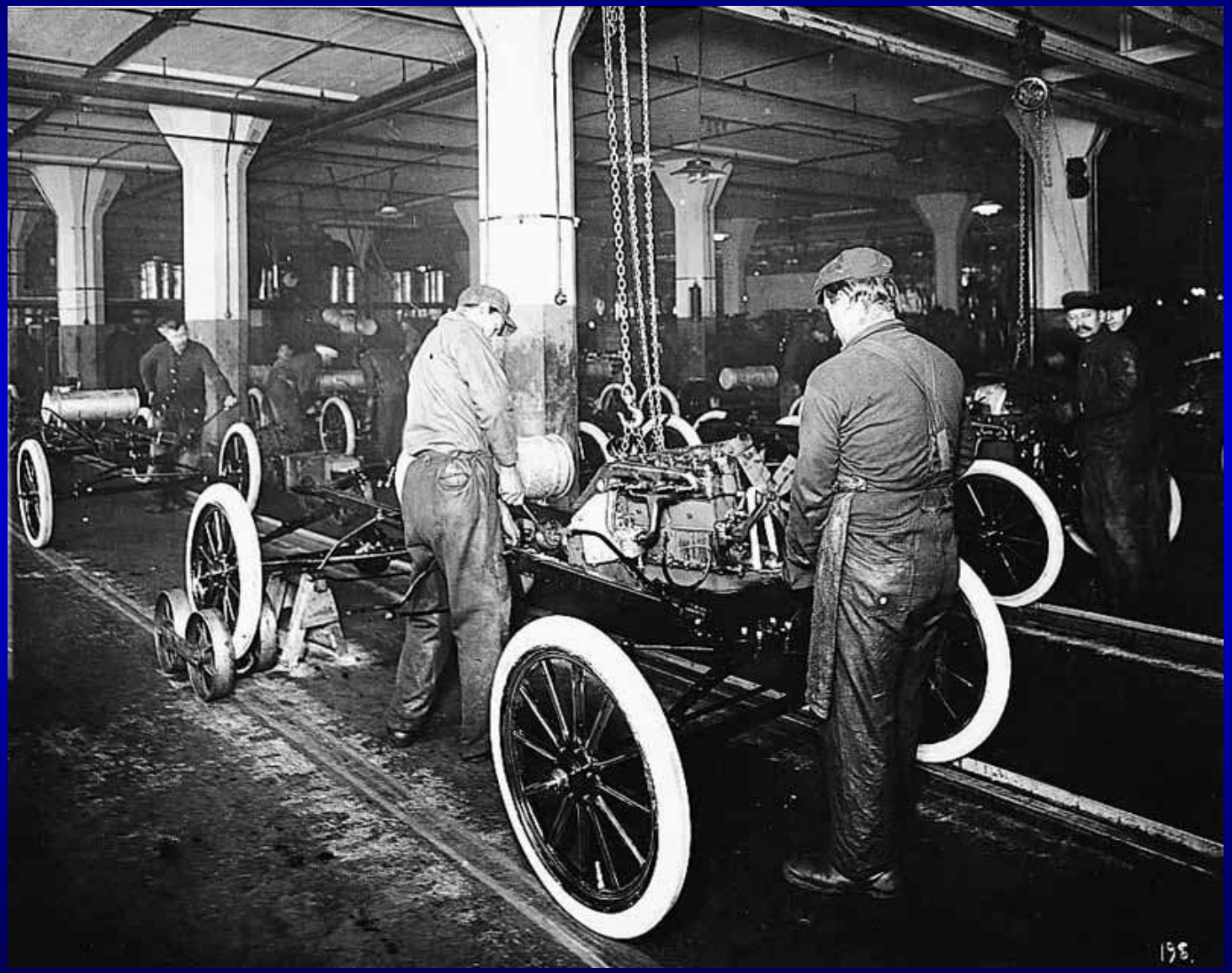
ORDER ON MOTIONS FOR SUMMARY JUDGMENT

Threats

- Bad actors coopting new technology terms
- Insufficient enforcement, “ethics dumping”
- Public confusion on new technology
- Moore’s Law in Biology
- Regulations and Guidances written in large part for small molecules and biologics
- Drug Industry and many regulators educated in the era of small molecules and biologics

Penn Medicine
Center for Cellular Immunotherapies

Building An Ecosystem for Advanced Cell and Gene Therapies



- Education & Training at all levels
- Academic – Industry Collaboration
- Regulatory Framework & Standards
- Affordability

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It Takes A Village

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ACKNOWLEDGEMENTS

Study Participants

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