Ziopharm ONCOLOGY

# Welcome and Agenda

R&D Day – Cell Therapy Focus
March 11, 2021

Adam D. Levy, PhD, MBA
Executive Vice President, Investor Relations and Corporate Communications

# Forward Looking Statements

The presentations included in this virtual R&D Day contain certain forward-looking information about Ziopharm Oncology, Inc. that is intended to be covered by the safe harbor for "forward-looking statements" provided by the Private Securities Litigation Reform Act of 1995, as amended. Forward-looking statements are statements that are not historical facts, and in some cases can be identified by terms such as "may," "will," "could," "expects," "plans," "anticipates," and "believes." These statements include, but are not limited to, statements regarding the Company's business and strategic plans, the availability of cash resources, the progress and timing of the development of Ziopharm's research and development programs, including the design of its clinical trials and the timing for the initiation and completion, and the data readouts for, its clinical trials, and the anticipated benefits and market size of Ziopharm's products. Although Ziopharm's management team believes the expectations reflected in such forward-looking statements are reasonable, investors are cautioned that forward-looking information and statements are subject to various risks and uncertainties, many of which are difficult to predict and generally beyond the control of Ziopharm, that could cause actual results and developments to differ materially from those expressed in, or implied or projected by, the forward-looking information and statements. These risks and uncertainties include among other things, changes in our operating plans that may impact our cash expenditures; the uncertainties inherent in research and development, future clinical data and analysis, including whether any of Ziopharm's product candidates will advance further in the preclinical research or clinical trial process, including receiving or maintaining clearance from the U.S. Food and Drug Administration or equivalent foreign regulatory agencies to conduct clinical trials and whether and when, if at all, they will receive final approval from the U.S. FDA or equivalent foreign regulatory agencies and for which indication; the strength and enforceability of Ziopharm's intellectual property rights; competition from other pharmaceutical and biotechnology companies as well as risk factors discussed or identified in the public filings with the Securities and Exchange Commission made by Ziopharm, including those risks and uncertainties listed in Ziopharm's annual report on Form 10-K for the year ended December 31, 2020 filed by Ziopharm with the Securities and Exchange Commission. Readers are cautioned not to place undue reliance on these forward-looking statements that speak only as of the date of the presentation, and we do not undertake any obligation to revise and disseminate forward-looking statements to reflect events or circumstances after the date hereof, or to reflect the occurrence of or non-occurrence of any events.

# Additional Matters

**Industry and Market Data**

Certain industry and market data included in the presentations included in this virtual R&D Day were obtained from independent third-party surveys, market research, publicly available information, reports of governmental agencies and industry publications and surveys. All of management's estimates are based upon management's review of independent third-party surveys and industry publications prepared by a number of sources and other publicly available information. All of the market data used in these presentations involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. Ziopharm's management believes that the information from these industry publications and surveys is reliable. The industry in which we operate is subject to a high degree of uncertainty and risk due to a variety of factors, including those described in "Risk Factors." These and other factors could cause results to differ materially from those expressed in the estimates made by the independent parties and by Ziopharm.

**Views of Key Opinion Leaders**

This R&D day includes presentations by Dr. Steven Rosenberg, Chief of Surgery at the National Cancer Institute; Dr. Carl June, Chair of the Ziopharm Scientific Advisory Board and Director of the Center for Cellular Immunotherapies and Director of Translational Research in the Abramson Cancer Center of the University of Pennsylvania; Dr. Scott Kopetz, Colorectal Cancer Physician Scientist, NCI Colon Task Force Chair, Professor, and Deputy Chair at The University of Texas, MD Anderson Cancer Center; and Dr. Perry Hackett, Center for Genome Engineering, Dept. of Genetics, Cell Biology & Development, University of Minnesota. The views expressed in such presentations represent each individual's personal views and may not reflect the views or expectations of Ziopharm's management. Ziopharm expressly disclaims liability for such views to the maximum extent permissible by law.

# Context

- **Visionary Legacy Now with Suite of Cellular Immunotherapies in Clinical Development**
- **Executing with Disciplined Capital Allocation Aligned with our Priorities**
- **Incorporating a Stronger Shareholder Voice, Helping to Optimize Approach**
- **Management Team and Board Aligned in Commitment to Patients and Shareholders**

# Objectives

- **Share the View and Outlook from Management and the Board**
- **Highlight our Science and Clinical Programs and Progress**
- **Hear from a world-class set of KOLs**
- **Address your concerns and questions**

# Today's Speakers

**Heidi Hagen**
*Interim Chief Executive Officer*

**James Huang**
*Executive Chairman of the Board*

**Laurence Cooper, M.D., Ph.D.**
*Company Advisor*

**Drew Deniger, Ph.D.**
*VP, Immunology*

**Raffaele Baffa, M.D., Ph.D.**
*Chief Medical Officer*

**Adam Levy, Ph.D., MBA**
*EVP, Investor Relations and Corporate Communications*

**Perry Hackett, Ph.D.**
*Professor at University of Minnesota in the Department of Genetics, Cell Biology and development; Co-founder of the Center for Genome Engineering*

**Steven Rosenberg, M.D., Ph.D.**
*Chief of Surgery Branch, NCI*

**Scott Kopetz, M.D., Ph.D.**
*Colorectal Cancer Physician Scientist, NCI Colon Task Force Chair, Professor, and Deputy Chair*

**Carl June, M.D.**
*Director of the Center for Cellular Immunotherapies at the University of Pennsylvania Perelman School of Medicine*

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# Today's Agenda

*Cell Therapy Focus*

| Approx. Time | Topic | Speaker |
|---|---|---|
| 5 minutes | Welcome | Dr. Adam Levy |
| 15 minutes | Company Overview and Strategy | Ms. Heidi Hagen |
| 10 minutes | Executive Chairman's View and Program Update on CAR-T in Greater China | Mr. James Huang |
| 15 minutes | Ziopharm Approach, Portfolio Status and Prioritization | Dr. Raffaele Baffa |
| 5 minutes | Perspectives on Transposon Based Gene Transfer | Dr. Perry Hackett |
| 15 minutes | Ziopharm Science: the Right Target, the Right Cells, the Right System | Dr. Laurence Cooper |
| 20 minutes | Targeting neoantigens for the Treatment of Solid Epithelial Cancers | Dr. Steven Rosenberg |
| 10 minutes | T-Cell Therapy Application in Colorectal Cancer | Dr. Scott Kopetz |
| 20 minutes | Current Challenges and Future Directions in Cell Therapy | Dr. Carl June |
| 15 minutes | Program Update: Ziopharm TCR-T Program | Dr. Drew Deniger |
| 20 - 30 minutes | Q&A | Ziopharm Team |
| | Closing Remarks | Ms. Heidi Hagen |

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# Company Overview and Strategy

R&D Day
March 11, 2021
Heidi Hagen, Interim CEO of Ziopharm

# My Perspectives as Interim CEO

Ziopharm has **truly differentiated science and technology** in the cell therapy space – and technology is often the value driver in cell therapy

Laurence has left us a **legacy of scientific excellence** and passion for patients in need

Couldn't be happier James is involved and to **partner with him as our Executive Chairman**

James and I agree **we are at a key inflection point** in our journey

Board is committed to **identifying a world-class CEO**; I am excited to lead the organization through the transition

# Welcome to our R&D Day – Focusing on Suite of Cellular Therapies

Evolved strategy and disciplined capital allocation

## Mission

We develop innovative T cell-based therapies for the treatment of hematological and solid tumor cancers

## Ziopharm Oncology Today

## Long-Term Vision

Distinctive commercial and clinical portfolio of immunotherapies transforming patient lives, supported by a growing body of compelling data

Well positioned with distinctive platforms in clinic

# 2021 is Already off to a Fantastic Start

- FDA Clearance of Library TCR-T Phase 1/2 Trial
- Cell Therapy Labs and Infrastructure Buildout (Houston) Completed
- Completion of Board Refreshment Process
- R&D Day

*Near-term future*

- Licensing of Additional TCRs Underway, Continuing to Expand the Platform
- *Expected in March / April* Patient Dosing in Taiwan for Autologous CD-19 RPM CAR-T Trial

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# Leadership in Place to Drive Our Future

## Board of Directors


Chris Bowden


Kevin Buchi


Heidi Hagen


James Huang


Robert Postma


Mary Thistle


Jaime Vieser


Holger Weis

## Management


Raffaele Baffa


Jill Buck


Ellee De Groot


Lynn Ferrucci


Robert Hadfield


Heidi Hagen


Adam Levy

## Scientific Advisory Board


Adi Barzel


Gavin Dunn


Carl June


Matthew Porteus


Kole Roybal

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# Recent Recognition for Two Members of our Distinctive Scientific Ecosystem

Dr. Steven Rosenberg
Key Research Partner on TCR Work

Dr. Carl June
Chair of Ziopharm SAB

DAN DAVID PRIZE
2021 Laureates

# 2021 is a Key Inflection Point for the Company

**2015 – 2018**

Cell Therapy Research Initiated Under Partner Dependent Model

**Pre 2015**

Exploration of Small Molecules and Gene Therapy

**Inflection Point** 2021

**Q4 2018 – 2020**

**Cell Therapy and IL-12 Focus**

- Pursuing an independent strategy
- Establishing capabilities
- Initiating trials in prioritized areas

Foundational TCR-T IND for library therapy

Expect to treat first TCR-T and additional CAR-T patients

Strategic prioritization and capital allocation

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# We Have the Core Technology and Infrastructure to be Leaders in Cell Therapy

01 Pioneers in non-viral (transposon) gene transfer

02 Cytokine biology expertise

03 Eden BioCell advancing CAR-T in Asia

04 Cleared IND for Library TCR-T clinical phase I/II

05 Leadership and innovation in T-cell immunobiology

06 Establishing infrastructure and capabilities for clinical programs

07 Strong SAB and established partnership network bring external strength

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# 2021 is a Year of Disciplined Strategic Focus

Strategy entails transparent prioritization and directed capital allocation

## Strategic Filters

01 Our distinct **capabilities**

02 Balance of de-risked **feasibility and innovation**

03 Direct line of sight to **patient data and unmet need**

04 Assessment of resource and **capital constraints**

## Strategic Positioning


TCR-T Programs: Advance clinical program for library as top internal priority (and expand/refine library); plan for personalized / next gen program(s); leverage NCI where possible

CD19 CAR-T Programs: Cost effectively advance program to generate clinical data. Evaluate partnership opportunities for future development and commercialization. Evaluate cross-over potential of CAR-T technology to the TCR program

Controlled IL-12 Program: Seek partner(s) that can optimize the potential of the asset for patients and monetize / return value to Ziopharm shareholders

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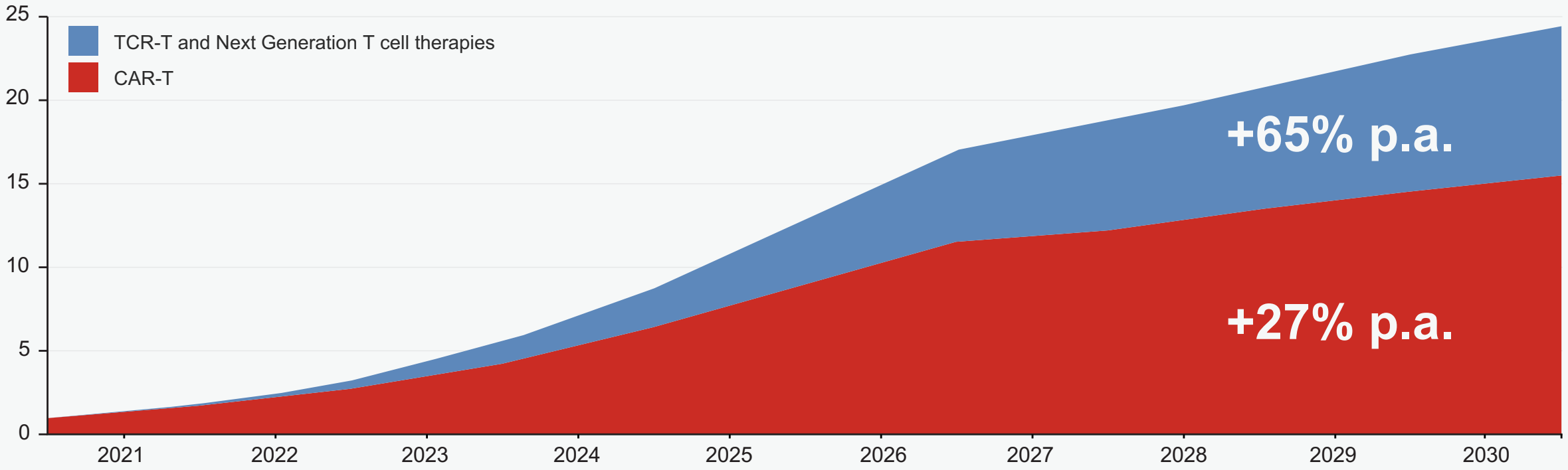
# Expectation Of Continued Cell Therapy Market Growth, With Disproportionate Growth In TCR-T

Market forecast for CAR-T and other cell therapies, $ billions

**$Billions**




Next Generation (non-CAR-T) cell therapies are forecasted to make up
**~40% of the cell therapy market by 2030,** despite lack of currently approved therapies

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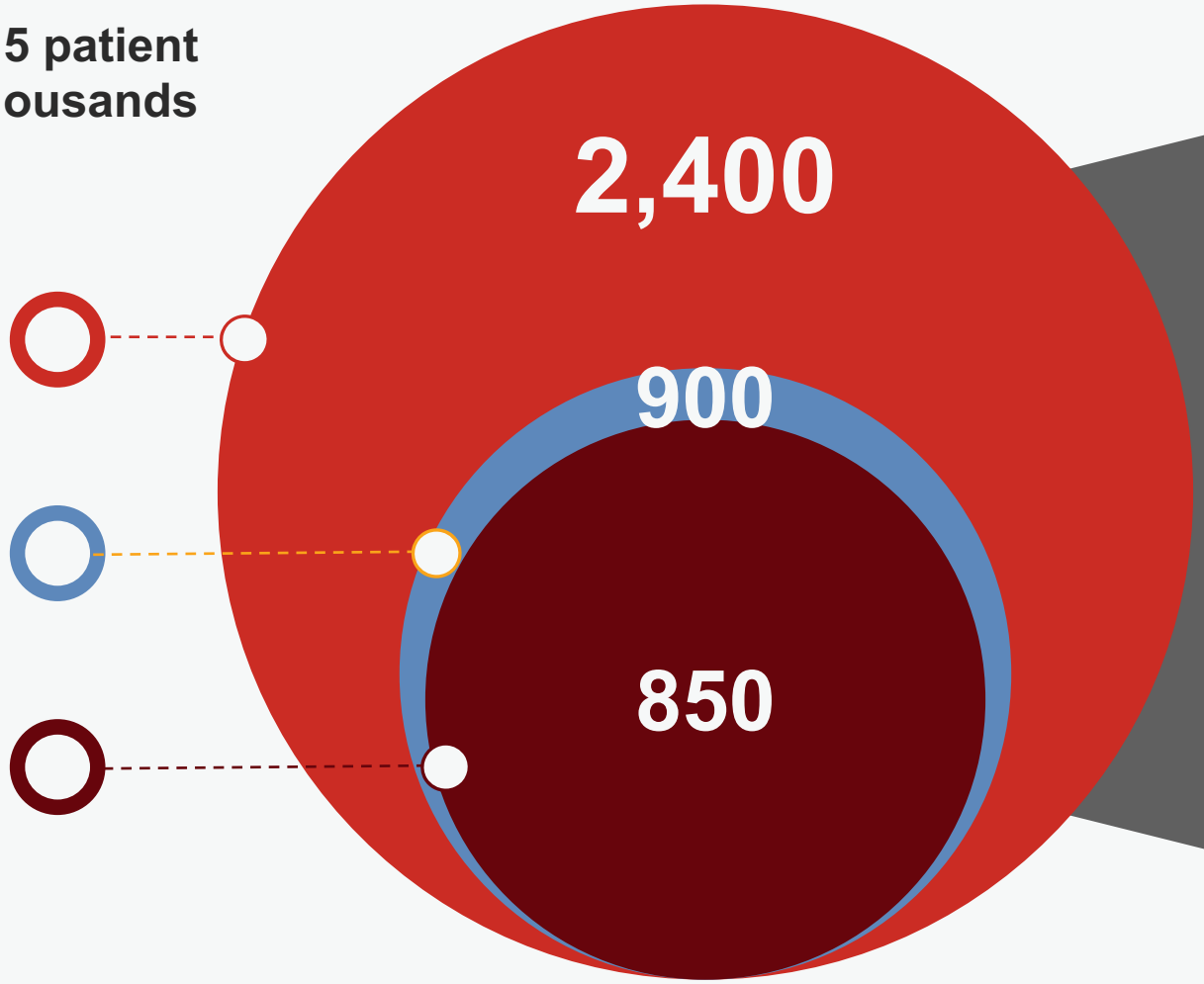
Source: Adapted from Evaluate Pharma; Next generation T cell engineering includes TCR-T, TIL, NK and other emerging T-cell modifications

# Over The Next 5-10 Years, The Addressable Patient Pool For Cell Therapies Is Expected To Grow Substantially

**Estimated US & EU5 patient population, thousands**




5-10 years
**Solid Tumor**

1-5 years
**MM, CLL, FL**

Today
**ALL DLBCL**

**Successive waves of innovation will open additional patient pools**

In the next 5-10 years, new indications, new manufacturing techniques, and new cell sources will open up new patient pools for TCR-T cell therapy, especially for solid tumors

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# CD19 CAR Rapid Personalized Manufacturing (RPM) – Clinical Programs

A solution to cost and complexity of commercial CAR-T today with one continuous program

## Phase 1 Trial Initiated To Evaluate Allogeneic CD19 CAR-T

- Investigational treatment for patients with $CD19^+$ leukemias and lymphomas who have relapsed after allogeneic bone marrow transplantation
- Strategic purpose to validate Ziopharm's RPM technology, potential commercial opportunity
- Infuse as soon as day after gene transfer
- Trial to be conducted at MD Anderson; Initiation announced in July 2020

## Ziopharm & Eden BioCell pursuing autologous CD19 CAR-T

- 50-50 joint venture with TriArm Therapeutics
- Taiwan: Eden BioCell IND cleared in Q4 2020 for Phase 1 trial
- Mainland China: Infusion of several patients with encouraging data

TriArm™ THERAPEUTICS

Eden BioCell

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# Allocating Capital in a Disciplined Manner and Based on Strategy

## Financial Snapshot

**$115.1 million in cash and cash equivalents** as of 12/31/20

**$8.1 million** at MD Anderson from **prepayment for programs to be conducted by the Company** as of 12/31/20

Sufficient to fund planned operations and **execute our strategy into late second quarter of 2022**

Seeking avenues to **slow cash burn and identify sources of non-dilutive capital** enabled by clear strategic focus

## Capital Allocation Priorities

01 TCR-T program advancement with initial focus on ZIOP library clinical study

- Continued buildout of operational capabilities (Houston)
- Operationalizing clinical program
- Hunting for additional TCRs

02 CAR-T resourcing to demonstrate initial clinical benefit of RPM

Support Eden Biocell Asia clinical program (CD19)

03 We expect to reduce the amount of capital allocated to our Controlled IL-12 program in 2021 and to continue to explore partnerships to support further development

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# Perspectives on Ziopharm and Update on our Efforts in Asia

James Huang, Executive Chairman

March 11, 2021

R&D Day

- **RPM SB CD19 mbIL15 CAR+T**
- **The First in Human Trial: Initial Observations**

# We have a Real Opportunity to Build the Oncology Company of the Future

**Positive view informed by experience**

Perspective from the point of view of numerous investments in biotech during 20+ years as an entrepreneur and founder

**Strategic evolution underway**

Evolving to a cell therapy clinical stage enterprise driving value with line of site to key milestones and ultimately commercialization

**Next 6-12 months are pivotal**

We will always be led by the science and a drive to create and return value for investors, while developing potentially transformative therapies for patients in need

# CAR-T Therapies for Hematological Malignancies – Meeting the Challenge and Addressing the Opportunity

*The **Opportunity***

- Revenues for approved CAR-T therapies broke through $1 billion for the first time in 2020
- Estimates that this market will grow to ~$2.4 billion in 2024, but these estimates have come down as analysts are increasingly concerned with limitations
  - Prior estimates of $3.5 billion indicate a larger opportunity and need exists

*The **Challenges** Current Technologies and Players Face*

- Immune-related toxicity (CRS and neurotoxicity)
- Lengthy manufacturing time of 16-21 days
- Expensive ($370,000+ USD)
- Antigen escape vulnerable (16-75%)
- Requires toxic lymphodepletion

*We believe our approach, leveraging our Sleeping Beauty gene transfer system, and the RPM approach utilizing mbIL15, both of which have demonstrated proof-of-concept, offers us the potential opportunity to address many of the challenges in this already established and growing market*

*Our work in Asia is a critical component in our exploration of this opportunity*

Statistics and Estimates source: Mizuho Equity Research

# Eden BioCell - Ziopharm's Foothold in Asia

## Ziopharm's Asia Strategy

- Access to the world's most populous region
- Dynamic and growing economy
- Nimble development of biotechnology and biopharmaceutical industry
- Favorable environment (Government regulation, capital investment, high quality talent)
- Vast unmet medical needs (# of patients, lack of high quality SOC, various indications w/o treatments)
- Competitive cost of technology/product development

## Eden BioCell

- 50-50 Joint venture between Ziopharm and TriArm Therapeutics Inc.
- Co-development of *Sleeping Beauty* RPM CD19 mbIL15 CAR T cell for B cell malignancies
- Joint governance model
- Local team with strong expertise and extensive experience in US biotech landscape

# Eden BioCell JV Built on an Economically Favorable Model with Significant Potential for Long-Term Value Creation

- Successful Technology Transfer and Future Process Development
  - Transfer of manufacturing production process and assay development
  - Developing approaches for further process improvement through scientific studies
    - Ziopharm with full rights to apply learnings and improvements elsewhere and in other CAR-T programs
- Regulatory milestones
  - Multiple and multichannel interactions with regulatory agencies and local hospitals
  - Formal clearance for phase 1 clinical trial in Taiwan; First patient expected to be dosed March / April 2021
  - On-going investigator initiated clinical trials (IIT) in several centers of China
- Foundation for future
  - A team of experienced and talented professionals
  - A GMP compliance facility in Shanghai to support Phase 1 clinical trials of cell and gene therapies
  - Co-development of new technologies and products

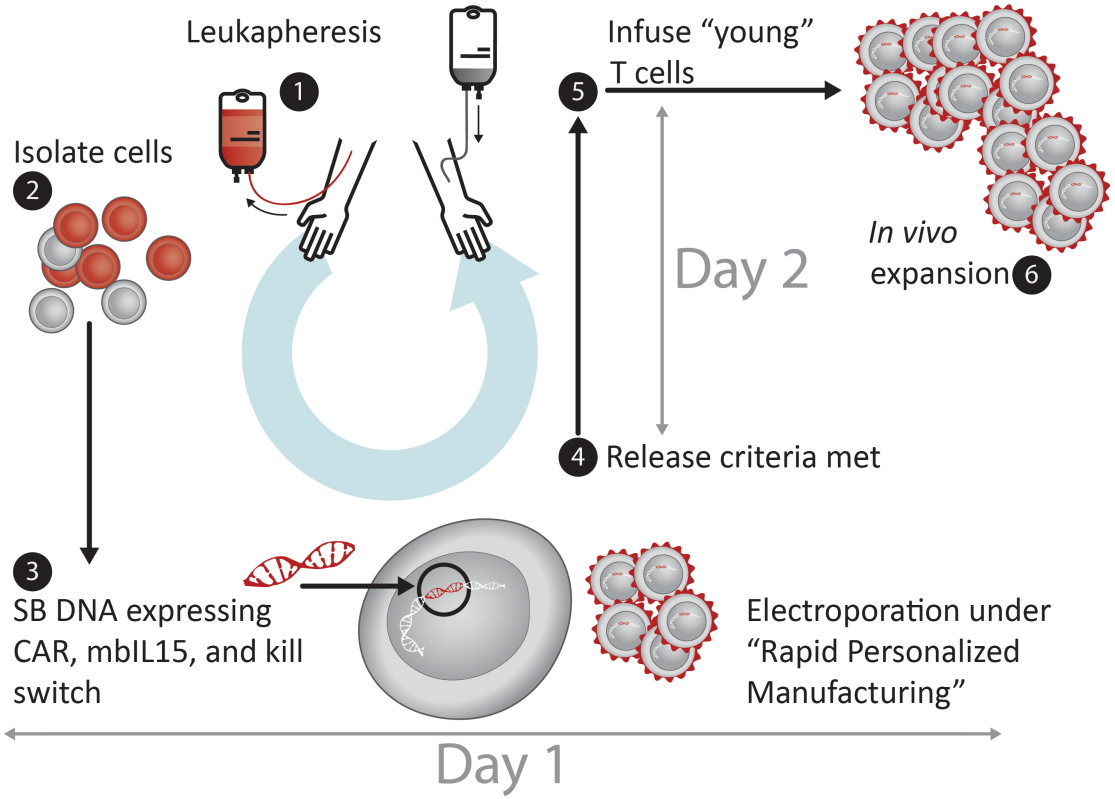
# GMP Compliance Manufacturing, IND, IIT & Phase I in Asia

- TriArm GMP Manufacture Facility in Shanghai Certified.
- More Than Two Dozen Pilot Manufacturing Runs Conducted
- GMP Compliance QA & QC Systems Established.
- Phase I Site (National Taiwan Univ Hospital) Evaluated and Contract Signed.
- CROs for Assay and Clinical Study Contracted.
- IND Approved by Taiwan FDA on December 18th, 2020.
- Patients for IIT Enrolled & Dosed in Asia.
- Phase I Study in Taiwan Initiated with First Patient Expected to be Dosed in March/April 2021.




# CAR-T Innovation: Rapid Personalized Manufacturing (RPM)

## Addressing Cost And Complexity Limiting The Commercialization Of Existing CAR-T




- Uses *Sleeping Beauty* non-viral system
- Local, very rapid, simplified, scalable manufacturing
- Genetic modification of resting T cells with CAR and membrane-bound IL-15 (mbIL15) to preserve "young" state
- mbIL15 may avoid lymphodepletion
- Administering low numbers of T cells to expand in the body may avoid cytokine release syndrome
- Rapid manufacture: Can be infused day after gene transfer without the need to *ex vivo* expand cells

# First in Human Treatment – Early Observations

Compassionate Use
Investigator Initiated






| Female | Male | Male | Male | Male | Male |
|---|---|---|---|---|---|
| 52 years old | 49 years old | 62 years old | 55 years old | 56 years old | 57 years old |
| FL | MCL | DLBCL | ALL | DLBCL | DLBCL |
| Two prior lines of therapy | Four prior lines of therapy | Seven prior lines of therapy | Two prior lines of therapy | Three prior lines of therapy | Three prior lines of therapy |
| Treated in Jul-2020 | Treated in Aug-2020 | Treated in Aug-2020 | Treated in Sep-2020 | Treated in Dec-2020 | Treated in Dec-2020 |
| Appears well tolerated<br>No serious CRS | Appears well tolerated<br>No serious CRS | Appears well tolerated<br>No serious CRS | Appears well tolerated<br>No serious CRS | Appears well tolerated<br>No serious CRS | Appears well tolerated<br>No serious CRS |

***Compassionate use and investigator initiated trials are conducted by the sites, without active clinical oversight by Eden BioCell or TriArm. Data received from the sites is limited, does not undergo customary quality control procedures and may not be representative of the results seen in future clinical trials; observations as of March 1, 2021.***

# Other Observations and Next Steps

- Eden BioCell successfully executed technology transfer of the manufacturing process
  - The fact that tech transfer occurred between Houston and Shanghai and Taipei speaks to the robustness of the process and the vision of distributed production
- RPM SB CD19 CAR-T products have been manufactured for IIT/CU for 6 subjects
- RPM SB CD19 CAR-T appears well tolerated and robust in vivo expansion of infused cells has been observed*
- Clinical efficacy, including one confirmed CR and other PRs which investigators continue to monitor, was observed*
- RPM may work without lymphodepletion.
  - Lymphodepletion is needed by other approaches including autologous CAR-T to “free up” endogenous cytokine to help infused T cells persist and allogeneic CAR-T (“off-the-shelf”) to prevent rejection
- Formal phase 1 clinical study is underway in Taiwan
  - Initial data expected in H2 of 2021; data to be generated throughout year and into 2022
  - Data from trials in Asia can be brought back to Ziopharm for “rest-of-world” partnerships
- Eden BioCell continues to lead development of RPM CD19 CAR-T in Asia for Ziopharm and poised to carry out new technology and product development in partnership with Ziopharm

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R&D Day
March 11, 2021
Raffaele Baffa, MD, PhD
CMO of Ziopharm

# Why I Joined Ziopharm

**Strong track record of pharma experience and achievements at AstraZeneca, Sanofi, Pfizer, and Servier**

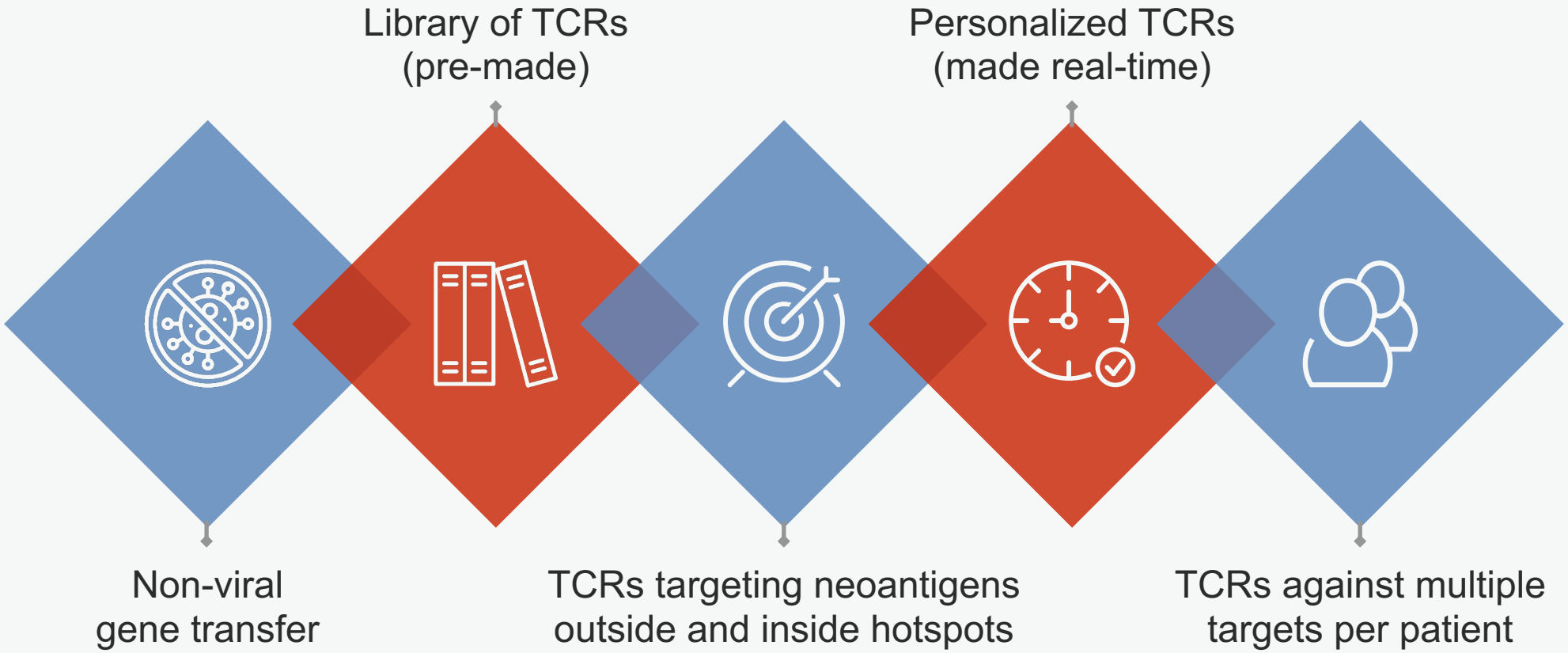
## Innovative technology

- Non-viral transposon/transposase T-cell engineering (Sleeping Beauty)
  - Potentially enables many more patients to benefit, under a transformational, economically scalable model
  - Allows for patients who could not otherwise be treated to be treated
  - System applicable in hematological malignancies and solid tumors
  - Biology suggests safer profile than other transposon/transposase systems in terms of insertional mutagenesis

## Precision medicine

- We are in the era of precision medicine in oncology. This medical model involves identifying the molecular lesions that are present in a tumor and then selecting the treatments that specifically target these lesions.
  - Exponentially increases the probability of response
  - Especially important in solid tumors given the tissue heterogeneity between the primary tumor and secondary metastases.
- These targeted therapies tailored to a specific patient will allow for faster time to approval and broad use of this exciting technology
- Combining broadly scalable technology with individualized treatment provides the vision; the achievements we have made to date reflects strong progress over last two years

# Competitive Advantage:
# Differentiated Positioning in Solid Tumors




**Ziopharm's complementary and unique suite of technologies**

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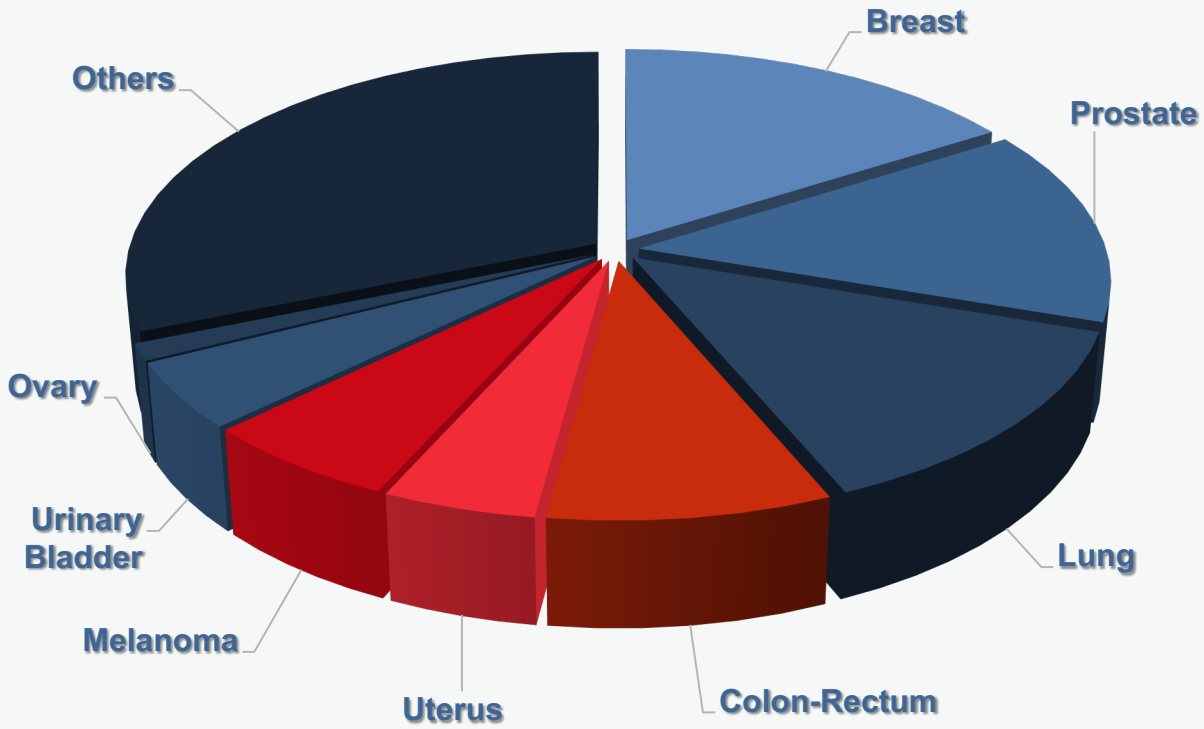
# Estimated New Cancer Cases and Deaths, United States, 2021




## US Statistics

01 **1,898,160** new cancer cases

02 **1,755,510** solid tumors

03 **142,650** leukemias/lymphomas

04 **608,570** cancer death

05 **564,190** cancer death for solid tumors

06 **44,380** cancer death for leukemias and lymphomas

**4,804** patients are diagnosed every day with a type of solid cancer

**1,548** patients die every day from a solid cancer

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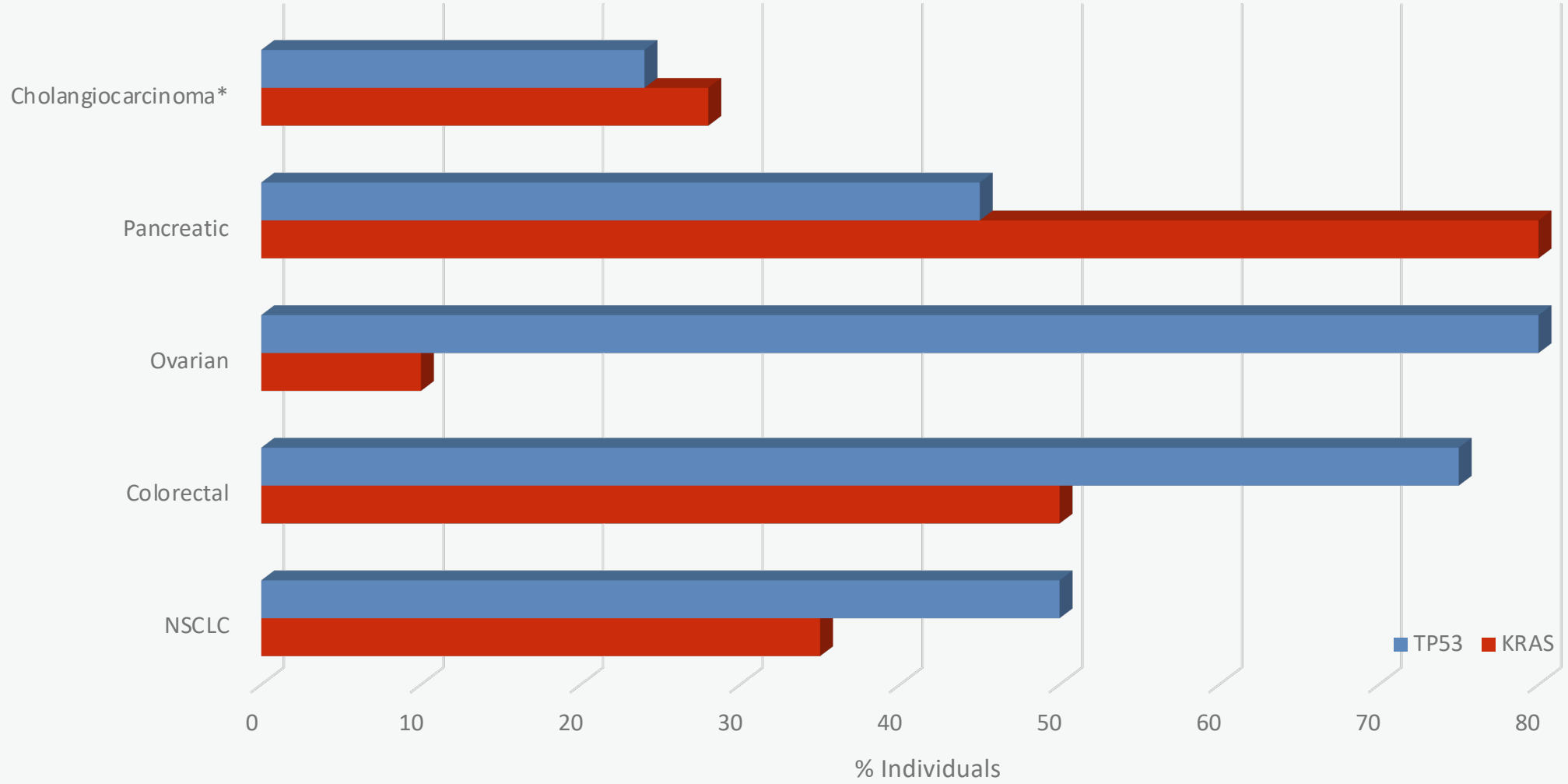
Ca: A Cancer Journal for Clinicians; vol. 71 (1): 7-33
http://cancerstatisticscenter.cancer.org/

# *KRAS* and *TP53* are most commonly mutated genes in epithelial cancers

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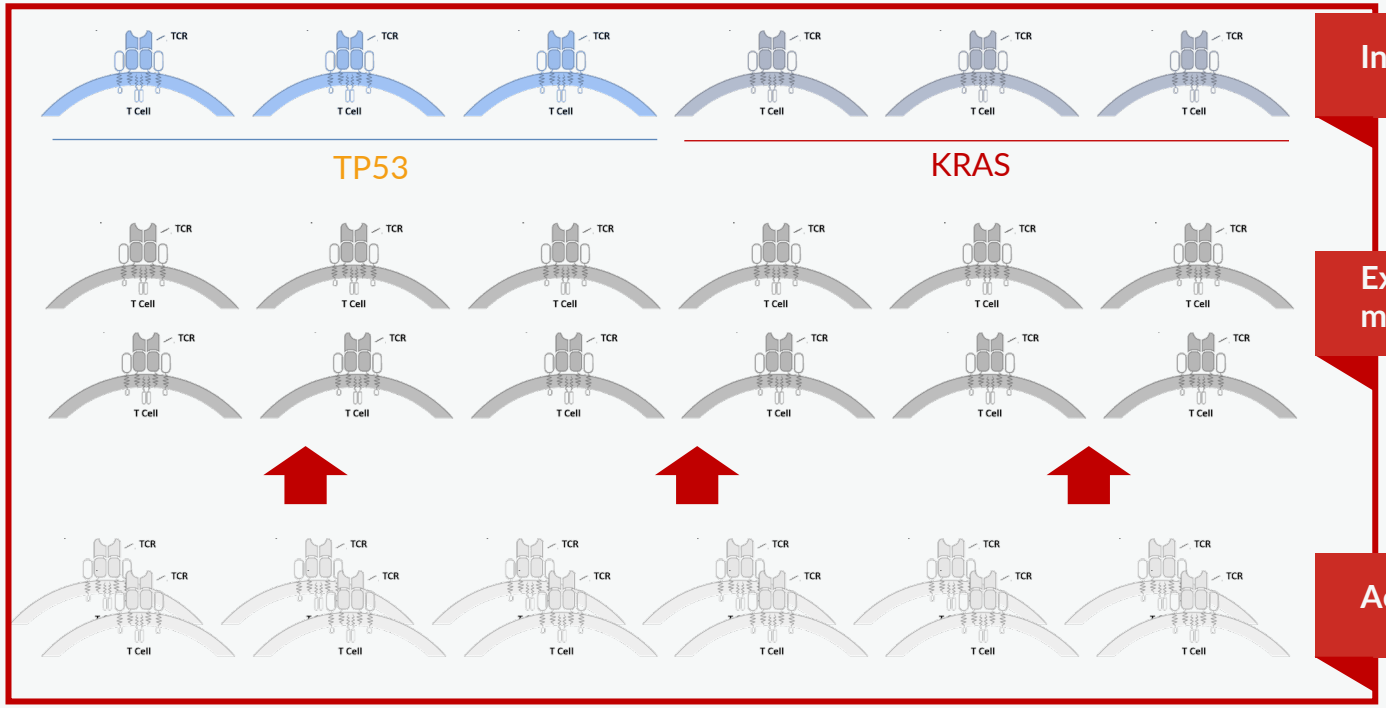
Cancer Res May 1 2017 (77) (9) 2464-2475; *World J Gastrointest Oncol*. 2017;9(7):268-280; *Surgery*. 1998;124:143–150; *Cancers (Basel)*. 2017;9(5):42
* Intrahepatic and extrahepatic combined

# TCR-Based Immunotherapies Can Potentially Address Significant Patient Need Across Broad Range of Solid Tumors

## Expanding Off-the-Shelf TCR Library – Q1 2021 IND Cleared




**Initially, six unique TCR/HLA TCRs in cleared IND**

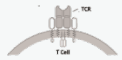
- Candidate TCRs through ongoing vetting process
- **3 each against *TP53* and *KRAS* hotspots**
- Tumor types: Lung, Cholangiocarcinoma, Pancreas, Colorectal, Ovarian

**Existing library includes 30+ TCRs, targeting 18 unique mutation/HLA combinations (*KRAS*, *TP53*, *EGFR*)**

- **Covers ~5-6% of epithelial cancers***
- **Translates to ~85-100K new potential patients annually in US (based on incidence of 1.7M per year)**
- **Potential** to bring on additional TCRs through one or more IND amendments

**Active Research and Partnerships to Grow TCR Library**

## Personalized TCR-T Approach – Increased Complexity and Broader Applicability



Potential to treat half or more of the ~1.7-1.8M annual (US) new cases of cancer

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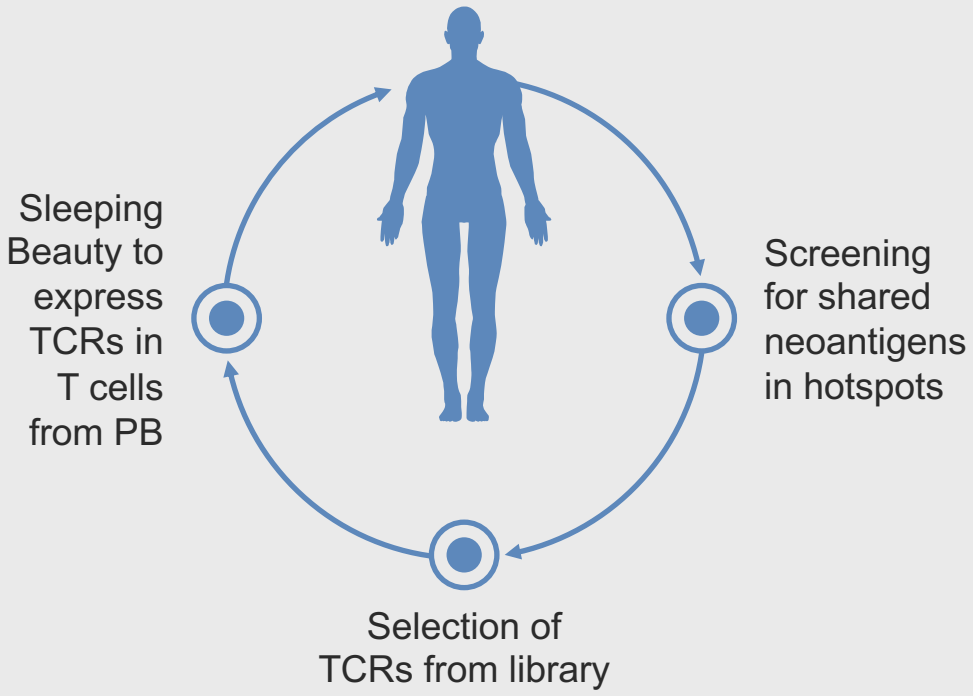
*COSMIC mutation database (https://cancer.sanger.ac.uk/cosmic) and allele frequency data (www.allelefrequencies.net)

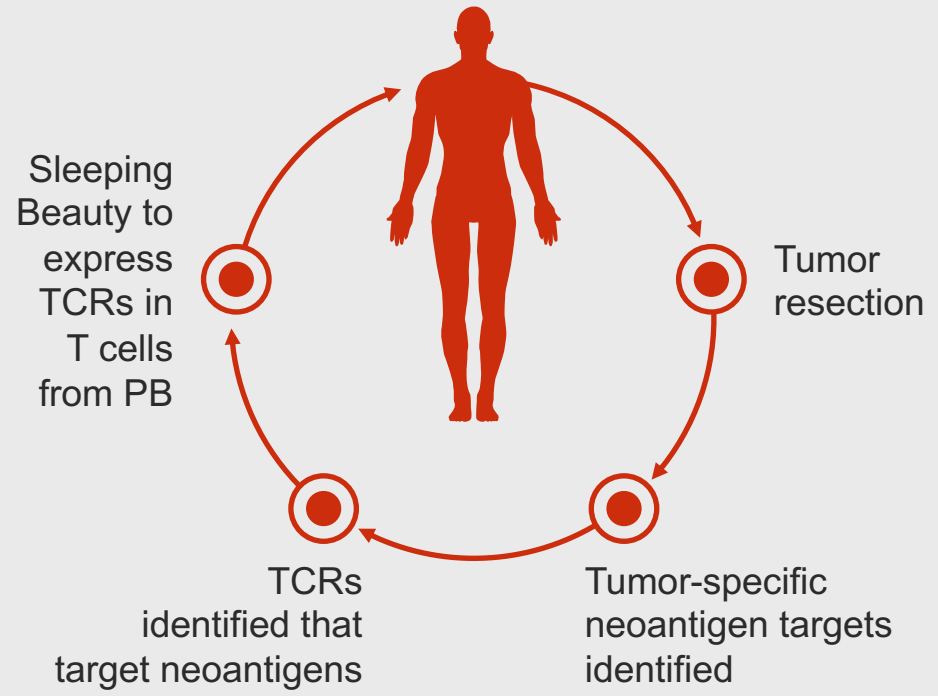
# Two Options To Treat All Patients With A Solid Tumor

## Library TCR-T Process




**Active Ziopharm IND for phase 1/2 trial (Autologous T-cells)**

## Personalized TCR-T Process




**NCI phase 2 trial (Autologous T-cells)**

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# 2021/2022 Clinical Milestones

| H1 2021 | H2 2021 | 2022 |
| --- | --- | --- |
| ✓ **Library TCR-T Program**<br>Ph 1/2 IND Clearance | **Library TCR-T Program**<br>Ph 1/2 Patient Initiation | **Library TCR-T Program**<br>Ph 1 Initial Data Readout |
| **CD19 CAR-T RPM Autologous (Taiwan)**<br>Ph 1 Patient Initiation | **CD19 CAR-T RPM Autologous (Taiwan)**<br>Preliminary Ph 1 data | **Next Gen or Personalized TCR-T Program**<br>Ph 1 IND Clearance |
| **IL-12**<br>Data Updates | | **CD19 CAR-T RPM**<br>Ph 1 Data Readout(s) |
| **CD19 CAR-T RPM Allogeneic (US)**<br>Ph 1 Patient Initiation/Update | **Personalized TCR-T Program (NCI)**<br>Ph 2 Patient Initiation | **Personalized TCR-T Program (NCI)**<br>Ph 2 Data |

NCI clinical operations are not under control of Ziopharm; delays have been communicated based on matters unrelated to Ziopharm

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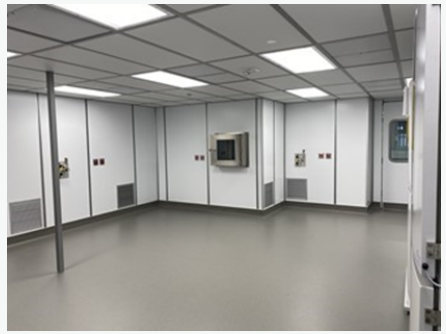
# Growth of Ziopharm's Laboratory and Manufacturing Capabilities



## Houston R&D Laboratory Completed In 2020

01 Infrastructure and hiring of talented personnel enabled experimentation for company sponsored TCR-T IND

02 Established processes in-house for

- Neoantigen identification
- TCR hunting and screening
- TCR-T manufacturing process development

## In-house Cell Therapy GMP Manufacturing Planned

01 Clinical production unit (CPU) on track to be operational by end of 2021

02 Will provide control over clinical manufacturing and facilitate translation of future process improvements

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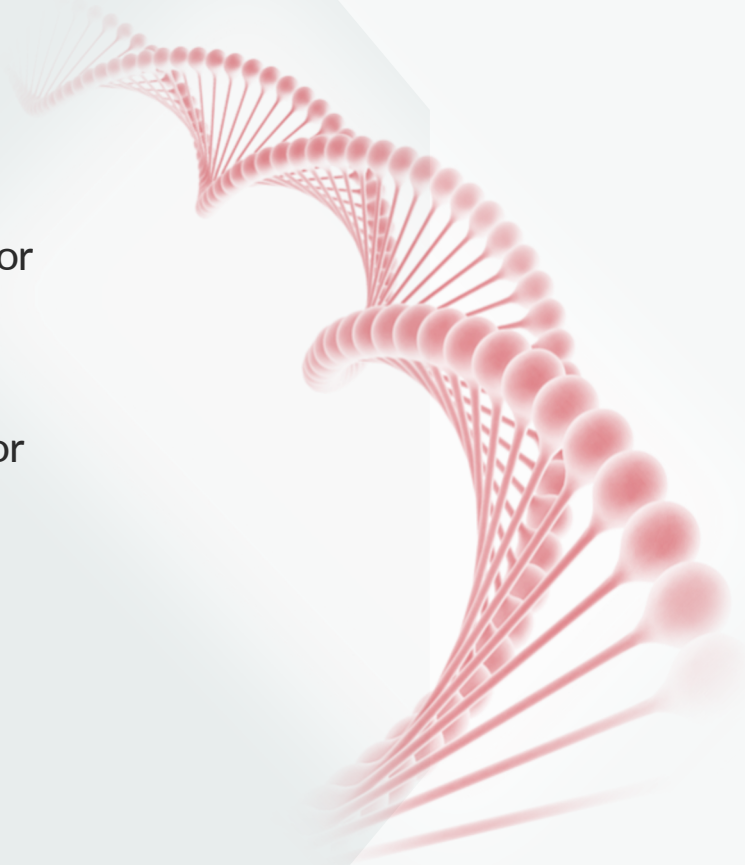
# Summary

- The Library TCR-T program is underway, and we expect clinical data to be available early next year.
- We plan to augment the current TCR library in the FDA cleared IND, allowing for broader patient inclusion.
- In house manufacturing capabilities coming online 4th quarter 2021, allowing for increased patient recruitment. In 2022 additional capacity will be added.
- Next generation or personalized program TCR-T IND expected in 2022.
- Autologous RPM CD19 CAR-T program underway in Asia.



# The Sleeping Beauty Transposon System


## Perry B. Hackett

**Center for Genome Engineering**
**Dept. of Genetics, Cell Biology & Development**
**University of Minnesota**

*Discovery Genomics / Immusoft*
*Recombinetics*
*NovoClade*

# The Sleeping Beauty Transposon System – A Minnesota Fish Story

## 1995 Engineer faster growing fish without using viral vectors

Walleye season on Mille Lacs faces early shutdown

Unprecedented action would be huge blow to struggling resorts



By Doug Smith Star Tribune | JULY 22, 2015 — 8:42AM

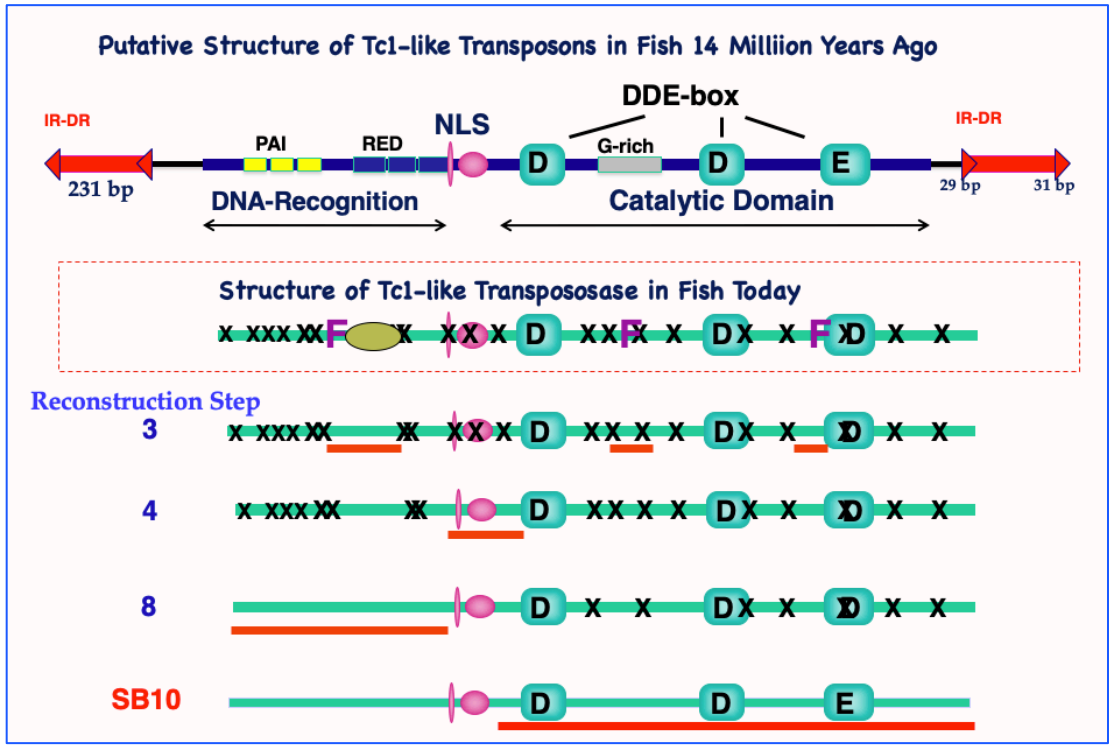


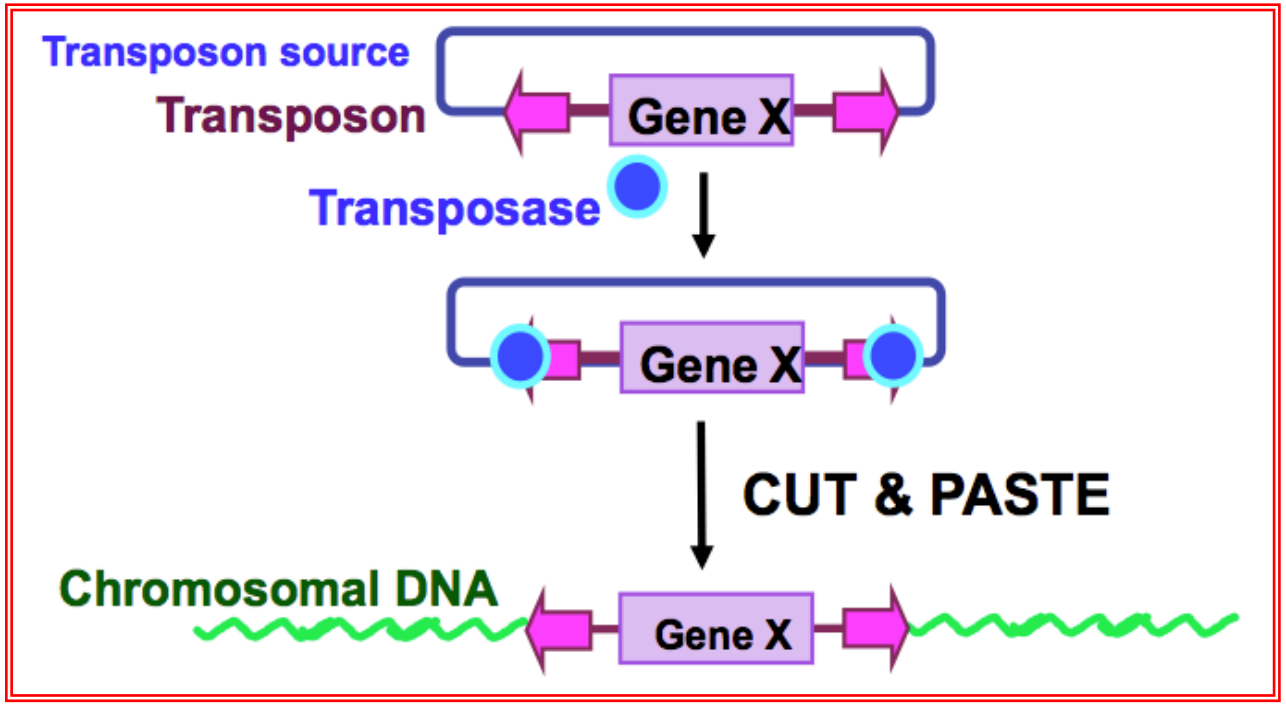
CARLOS GONZALEZ, STAR TRIBUNE

Cell, Vol. 91, 501–510, November 14, 1997, Copyright ©1997 by Cell Press

**Molecular Reconstruction of *Sleeping Beauty*, a *Tc1*-like Transposon from Fish, and Its Transposition in Human Cells**

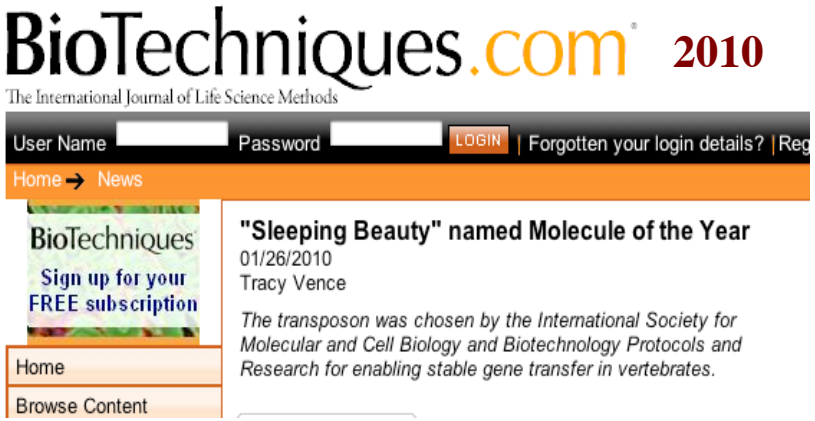
Zoltan Ivics
Zsuzsanna Izsvak

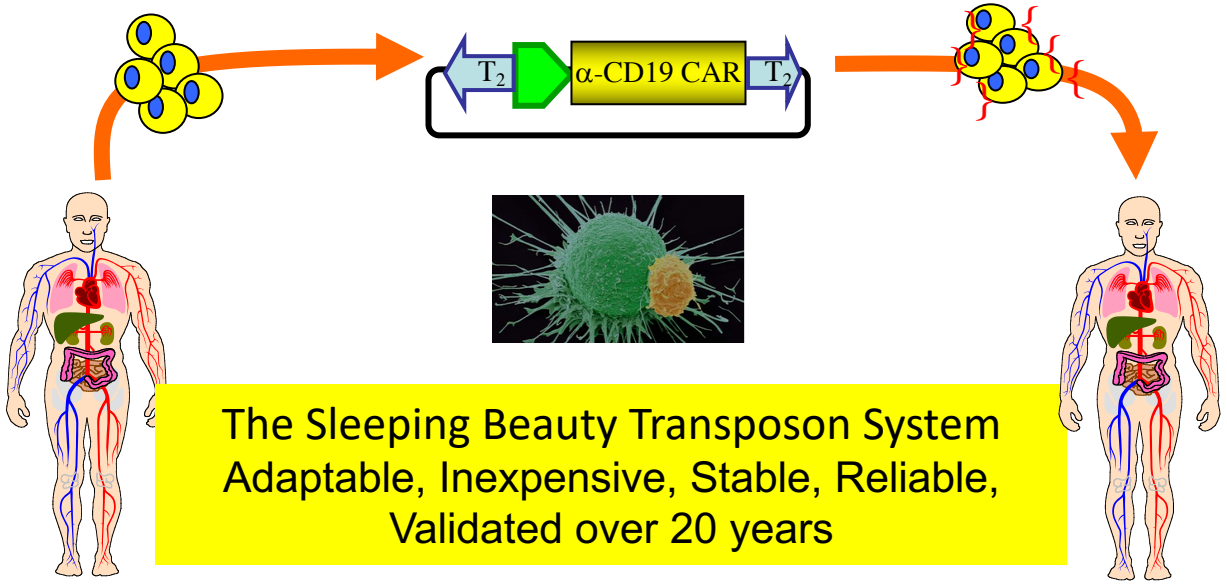


# CAR T Cell Therapy using Sleeping Beauty Transposons

Laurence Cooper, PhD, MD


The Sleeping Beauty Transposon System
Adaptable, Inexpensive, Stable, Reliable,
Validated over 20 years

***Sleeping Beauty* transposons *(vs. viruses)***

Are not immunogenic

Don't target genes & promoters

Don't replicate in host cells

Nimble

Reliably isolated & purified

Can be stored indefinitely and shipped

*=> can economically treat large populations*

Ziopharm
ONCOLOGY

# The Right System, the Right Cells and the Right Targets: Ziopharm Science

R&D Day
March 11, 2021
Laurence Cooper, PhD, MD
Scientific Advisor

# Dr. Laurence Cooper

## Reflections and Introduction

- Pediatric Oncologist, and noted Expert in immunotherapy and Stem-Cell Transplantation
- Visionary Leader who transitioned Ziopharm to a new scientific path
- Ushered in non-viral gene transfer for T-cell therapy: Brought *Sleeping Beauty* to the clinic in both TCR-T and CAR-T settings
- Developed and brought membrane-bound IL-15 to the clinic
- Redirected specificity of T cells to neoantigens for Library TCR-T and Personalized TCR-T
- Simplified manufacturing with next-day infusion and release of CAR-T

# Scientific Foundation Drives Ziopharm Value and Outlook

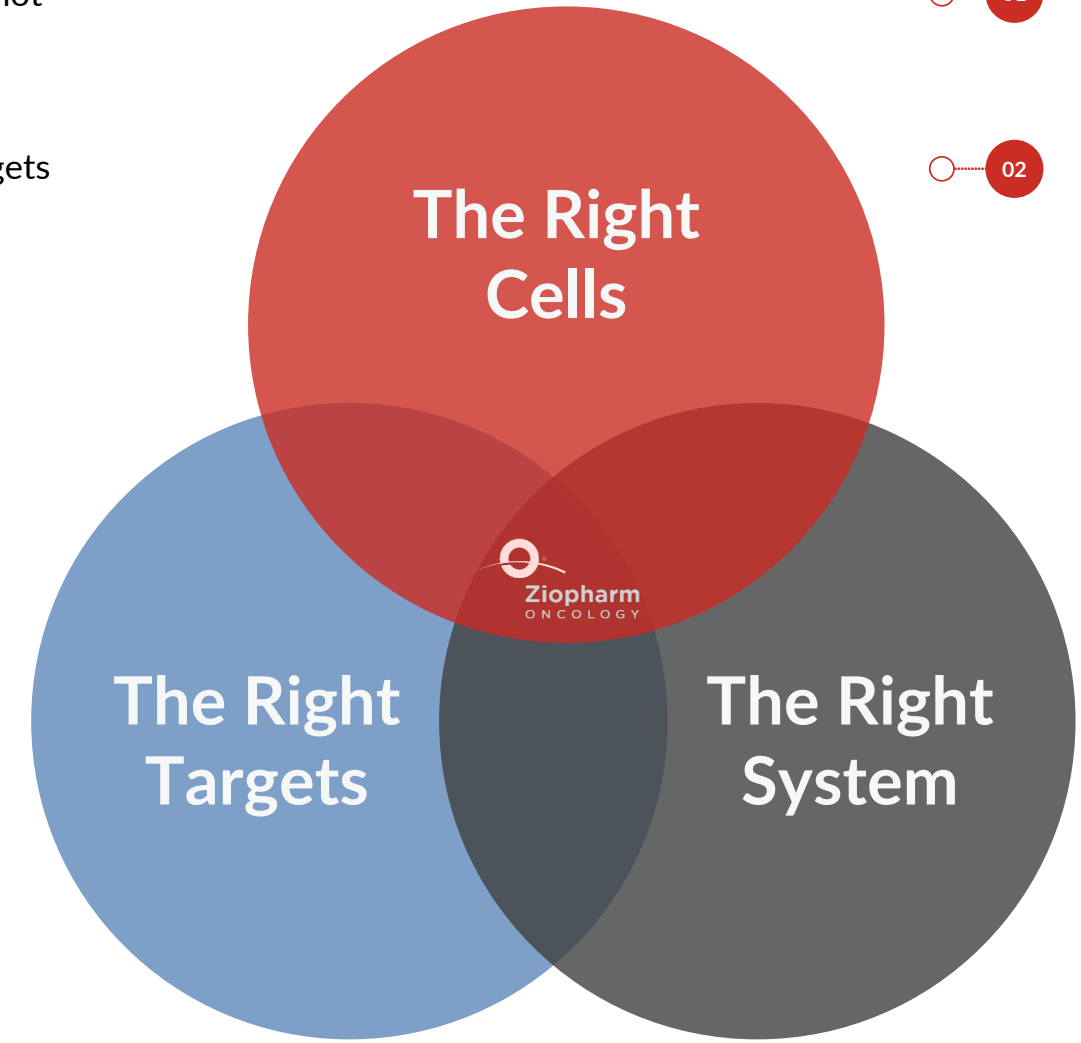
01 Germline or public antigens are not present in the vast majority of epithelial cancers

02 Neoantigens are the desired targets as they arise from foundational genetic mutations in cancer

03 **Ziopharm** TCRs target shared neoantigens in hotspots and neoantigens unique to patients

04 **Ziopharm** addresses heterogeneity of antigen expression between patients and within tumors

05 **Ziopharm** has exclusive rights to a growing set of library hotspot-specific TCRs for products engineered by transposon-mediated gene transfer, and has a cleared IND for phase I/II clinical work




01 **Ziopharm** immuno-biology is based on the use of "young" peripheral blood T cells

02 Exhausted T cells isolated from tumor (TILs) have limited efficacy for most solid tumors

01 Viral gene transfer is costly, cumbersome and complex

02 **Ziopharm** gene transfer utilizes the best-in-class non-viral *Sleeping Beauty* transposon system

Ziopharm ONCOLOGY

*Top Minds in Industry Agree*

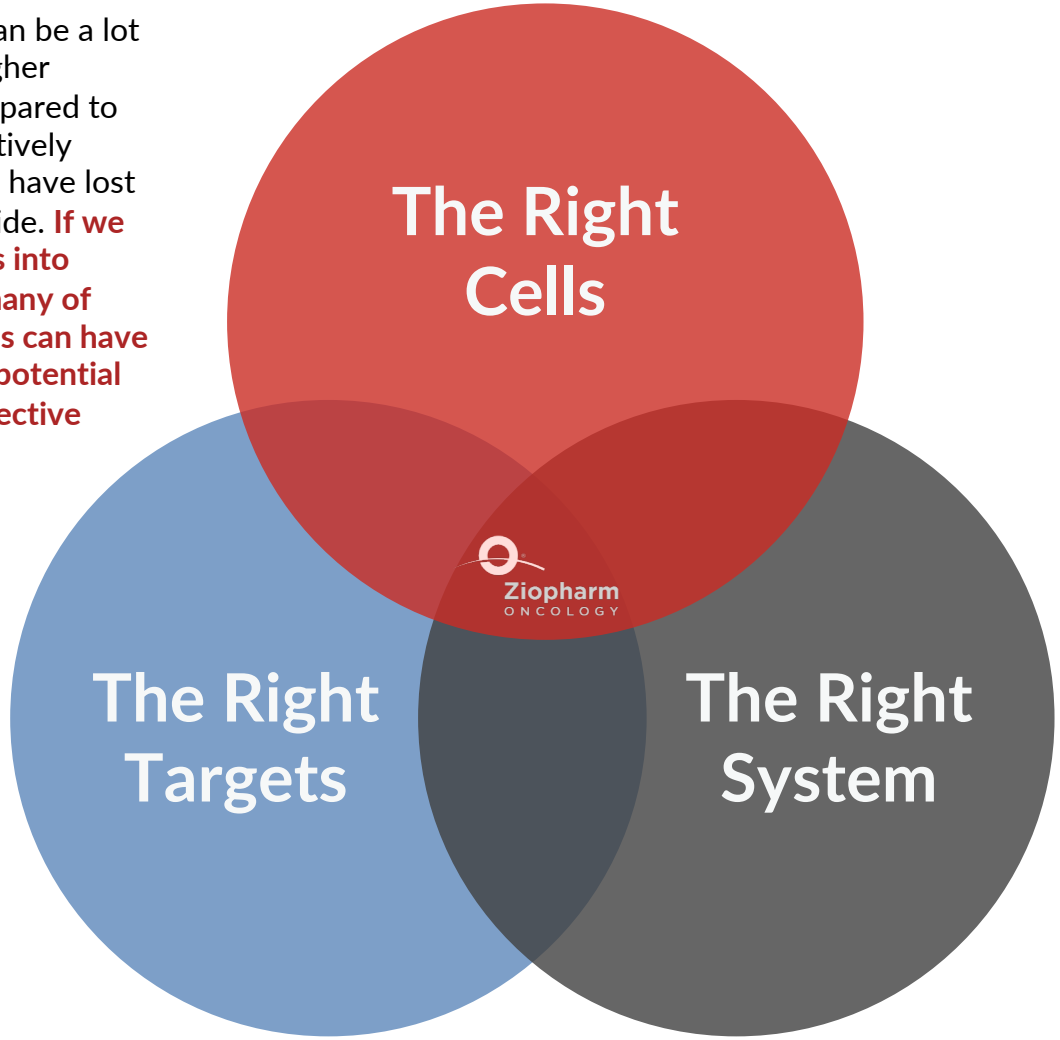
# Scientific Foundation Drives Ziopharm Value and Outlook

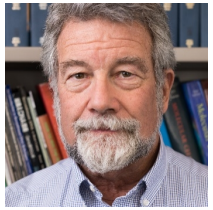
Dr. Steven Rosenberg

"Peripheral lymphocytes can be a lot more active and have a higher proliferative potential compared to TILs that have been repetitively stimulated in a patient and have lost some of their ability to divide. **If we could put these TCR genes into peripheral lymphocytes, many of whom are naïve, these cells can have an explosive proliferative potential and could offer a more effective treatment.**"

Dr. Robert Schreiber

"Tumor-specific neoantigens can also function as **optimal targets of cancer immunotherapy against established tumors.**"



Dr. Perry Hackett

"The *Sleeping Beauty* Transposon System has matched the results of the viral studies, and there are reasons to believe that ***Sleeping Beauty* may be preferable—not only for price and availability, but also for potential effects.**"

Ziopharm ONCOLOGY

Sources: AACR Interview with Dr. Rosenberg https://www.aacr.org/blog/2018/11/19/3944-2-til-therapy/; University of Minnesota Interview with Dr. Hackett https://research.umn.edu/inquiry/post/fight-against-cancer-sleeping-beauty-awakens; Advances in Immunology Chapter Two - The Role of Neoantigens in Naturally Occurring and Therapeutically Induced Immune Responses to Cancer https://www.sciencedirect.com/science/article/pii/S0065277616300013

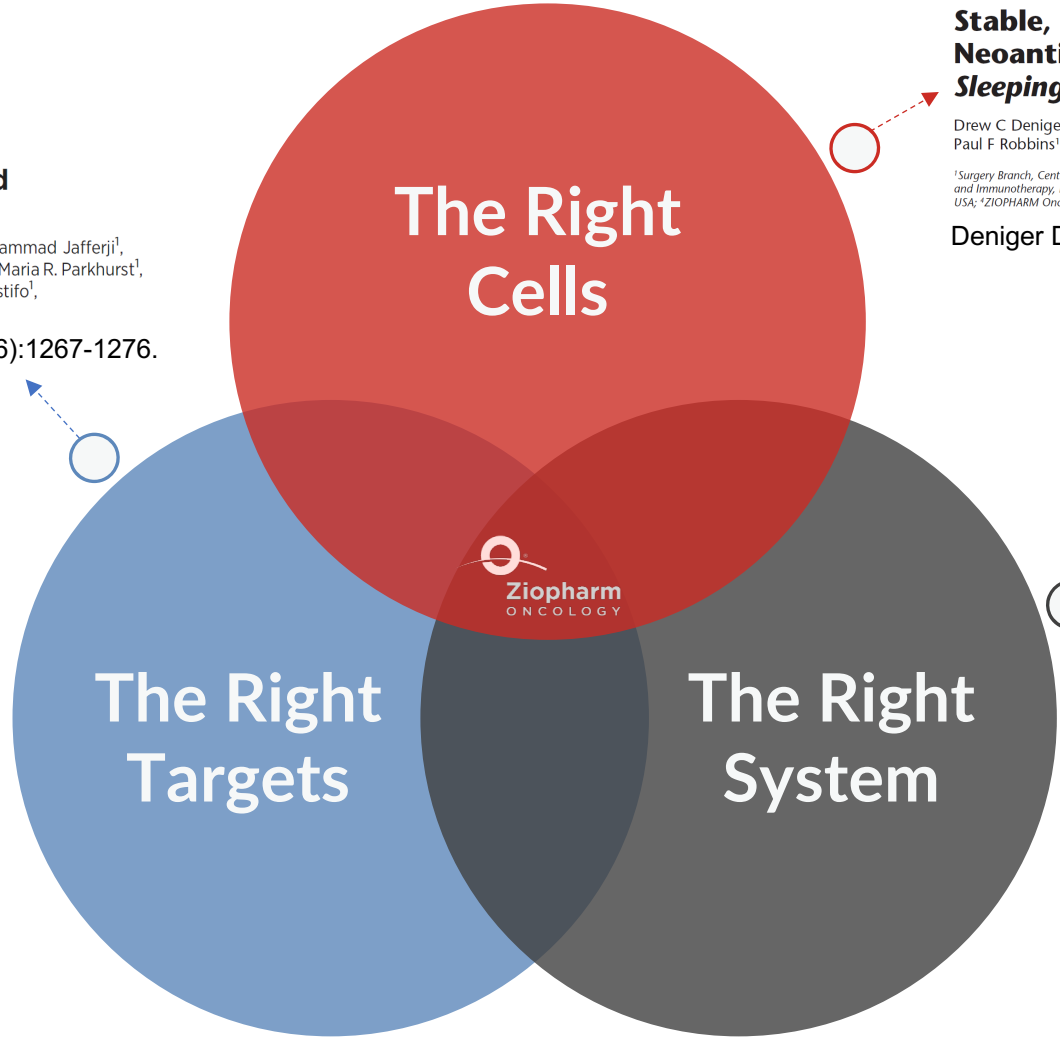
*Published Research Validates*

# Scientific Foundation Drives Ziopharm Value and Outlook

**Antigen Experienced T Cells from Peripheral Blood Recognize p53 Neoantigens**

Parisa Malekzadeh[1], Rami Yossef[1], Gal Cafri[1], Biman C. Paria[1], Frank J. Lowery[1], Mohammad Jafferji[1], Meghan L. Good[1], Abraham Sachs[1], Amy R. Copeland[1], Sanghyun P. Kim[1], Scott Kivitz[1], Maria R. Parkhurst[1], Paul F. Robbins[1], Satyajit Ray[1], Liqiang Xi[2], Mark Raffeld[2], Zhiya Yu[1], Nicholas P. Restifo[1], Robert P.T. Somerville[1], Steven A. Rosenberg[1], and Drew C. Deniger[1]

Malekzadeh P *et al.* Clin Cancer Res. 2020 Mar 15;26(6):1267-1276.




**Stable, Nonviral Expression of Mutated Tumor Neoantigen-specific T-cell Receptors Using the *Sleeping Beauty* Transposon/Transposase System**

Drew C Deniger[1], Anna Pasetto[1], Eric Tran[1], Maria R Parkhurst[1], Cyrille J Cohen[2], Paul F Robbins[1], Laurence JN Cooper[3,4] and Steven A Rosenberg[1]

[1]Surgery Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA; [2]Tumor Immunology and Immunotherapy, Bar-Ilan University, Ramat Gan, Israel; [3]Division of Pediatrics, University of Texas M.D. Anderson Cancer Center, Houston, Texas, USA; [4]ZIOPHARM Oncology, Inc., Boston, Massachusetts, USA

Deniger DC et al. Mol Ther. 2016 Jun;24(6):1078-1089.

The Journal of Clinical Investigation CLINICAL MEDICINE

**Phase I trials using *Sleeping Beauty* to generate CD19-specific CAR T cells**

Partow Kebriaei,[1] Harjeet Singh,[2] M. Helen Huls,[2] Matthew J. Figliola,[2] Roland Bassett,[3] Simon Olivares,[2] Bipulendu Jena,[2] Margaret J. Dawson,[2] Pappanaicken R. Kumaresan,[2] Shihuang Su,[2] Sourindra Maiti,[2] Jianliang Dai,[3] Branden Moriarity,[4] Marie-Andrée Forget,[2,5] Vladimir Senyukov,[2] Aaron Orozco,[2] Tingting Liu,[1] Jessica McCarty,[1] Rineka N. Jackson,[2] Judy S. Moyes,[2] Gabriela Rondon,[1] Muzaffar Qazilbash,[1] Stefan Ciurea,[1] Amin Alousi,[1] Yago Nieto,[1] Katy Rezvani,[1] David Marin,[1] Uday Popat,[1] Chitra Hosing,[1] Elizabeth J. Shpall,[1] Hagop Kantarjian,[6] Michael Keating,[6] William Wierda,[6] Kim Anh Do,[3] David A. Largaespada,[4] Dean A. Lee,[2,7] Perry B. Hackett,[4] Richard E. Champlin,[1] and Laurence J.N. Cooper[2,7]

Kebriaei P et al. J Clin Invest. 2016 Sep 1;126(9):3363-76.

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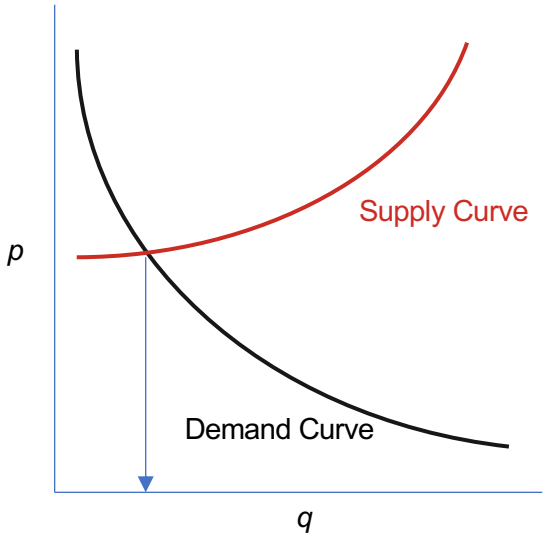
# Scientific Innovation Drives Economics Along Demand Curve

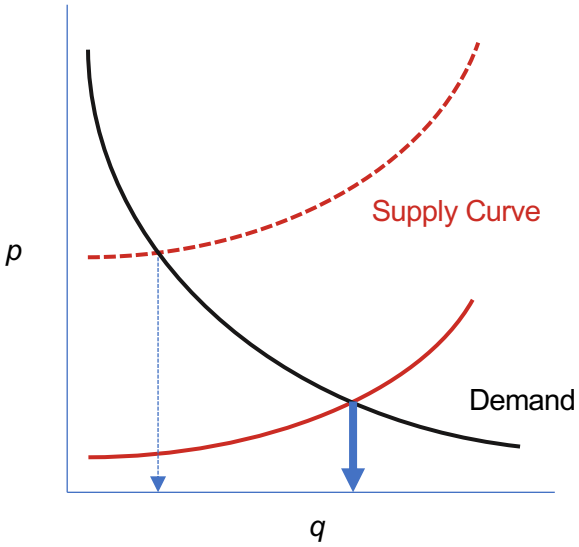
Small, unprofitable market driven by high costs, requiring companies to charge high prices, limiting access




1983: DynaTac 8000X cost $10,500 in today's dollars
Cell Phone Revenue for Motorola in 1985 ~$200M

1985: "Despite the glamour in mobile phones, Motorola has lost money in it."

Large, profitable market driven by companies' ability to price lower based on technology enabled cost, manufacturing and scalability improvements




2021: iPhone 12 Mini costs $700, a 90%+ decrease in price
2020 Apple iPhone Revenues $138B in a market that still supports highly profitable economics for tech leaders

- *When technologies emerge, **the cost and lack of scalability often limits usage**; today, approved CAR-T cell therapy is the DynaTac 8000X*
- *When technologies succeed in lowering costs, you get today's cell phone market, in which >5 billion own mobile devices and **highly profitable innovator companies like Apple and Samsung dominate revenues**, growth and market cap*
- *We believe Sleeping Beauty is a technological key for potentially **unleashing cell therapy for a dramatically larger market***

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https://www.govtech.com/archive/Mobile-Phones-Looking-Back-40-Years.html
https://www.nytimes.com/1985/08/20/business/motorola-s-fast-growth-path.html
https://www.sec.gov/Archives/edgar/data/1510580/000156459016013699/kite-10k_20151231.htm

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Making Cancer History®

# Overview of clinical needs in GI cancers

*Scott Kopetz, MD, PhD*
*Deputy Chair, GI Medical Oncology*

# Survival has been improving for GI cancers with improved therapies….


## … but treatment resistance with targeted therapy and chemotherapy is universal

# Most patients exhaust standard of care therapies, and need novel approaches.

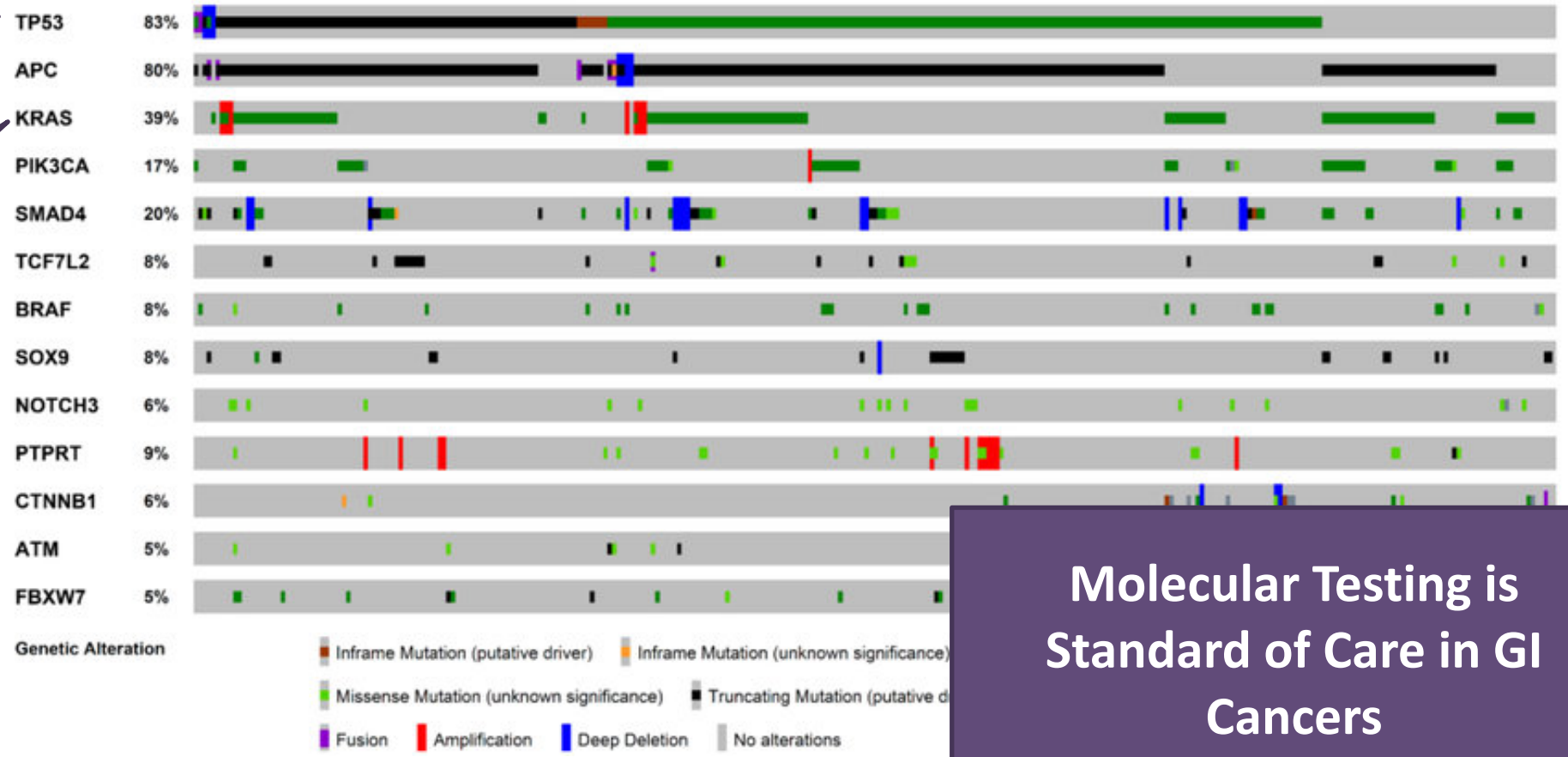
| Anti-EGFRs | Anti-VEGFs | TKI | Immunotherapy | Chemotherapy |
|---|---|---|---|---|
| Cetuximab | Bevacizumab | Regorafenib | Pembrolizumab | FOLFIRI |
| Panitumumab | Aflibercept | Encorafenib | Nivolumab ± Ipilimumab | FOLFOX |
| | Ramucirumab | | | Taxanes |
| | | | | Gemcitabine |
| | | | | Trifluridine/tipiracil |

**T-cell therapy represents a promising approach for this unmet need.**

# TP53 and KRAS are frequently mutated in GI Cancers

83% TP53 mutations

39% KRAS mutations




**Molecular Testing is Standard of Care in GI Cancers**

# TCR-Based Immunotherapies Can Potentially Address Significant Patient Need for Patients with GI Cancers

Hotspot mutations, particularly in KRAS and TP53, are common in GI cancers

| | Estimated frequency of patients that have match to Ziopharm's TCR Library* | | |
|---|---|---|---|
| | Colorectal | Pancreatic | Cholangiocarcinoma |
| Initial 6 TCRs | 5% | 13% | 4% |
| Full library, targeting 18 unique mutation/HLA combos | 11% | 29% | 8% |

**Estimates based on COSMIC mutation database (https://cancer.sanger.ac.uk/cosmic) and allele frequency data (www.allelefrequencies.net)*


# MD Anderson Cancer Center is an Ideal Partner

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

# Quick Facts about MD Anderson:

148.7 K
PATIENTS

1.5 M
OUTPATIENT VISITS

$902.3 M
SPENT ON RESEARCH

$5.4 B
OPERATING BUDGET

MD Anderson is

#1

in cancer care

BEST HOSPITALS U.S.News & WORLD REPORT NATIONAL CANCER 2019-20

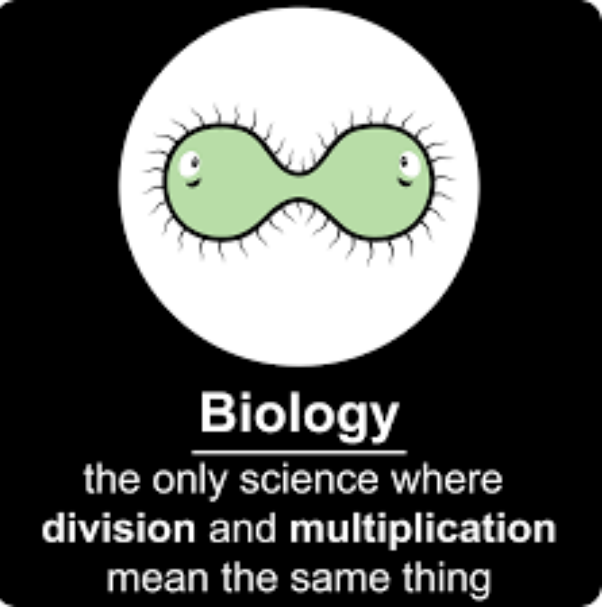
1.4 K
CLINICAL TRIALS

7 K
TRAINEES

21.7 K
EMPLOYEES

2.1 K
VOLUNTEERS

# Thank you




# Current Challenges and Future Directions in Cell Therapy

**Carl June**

**ZIOPHARM VIRTUAL R&D DAY**

March 11, 2021

PARKER INSTITUTE
*for* CANCER IMMUNOTHERAPY

Penn Medicine
Center for Cellular Immunotherapies

# Conflict of Interest Statement

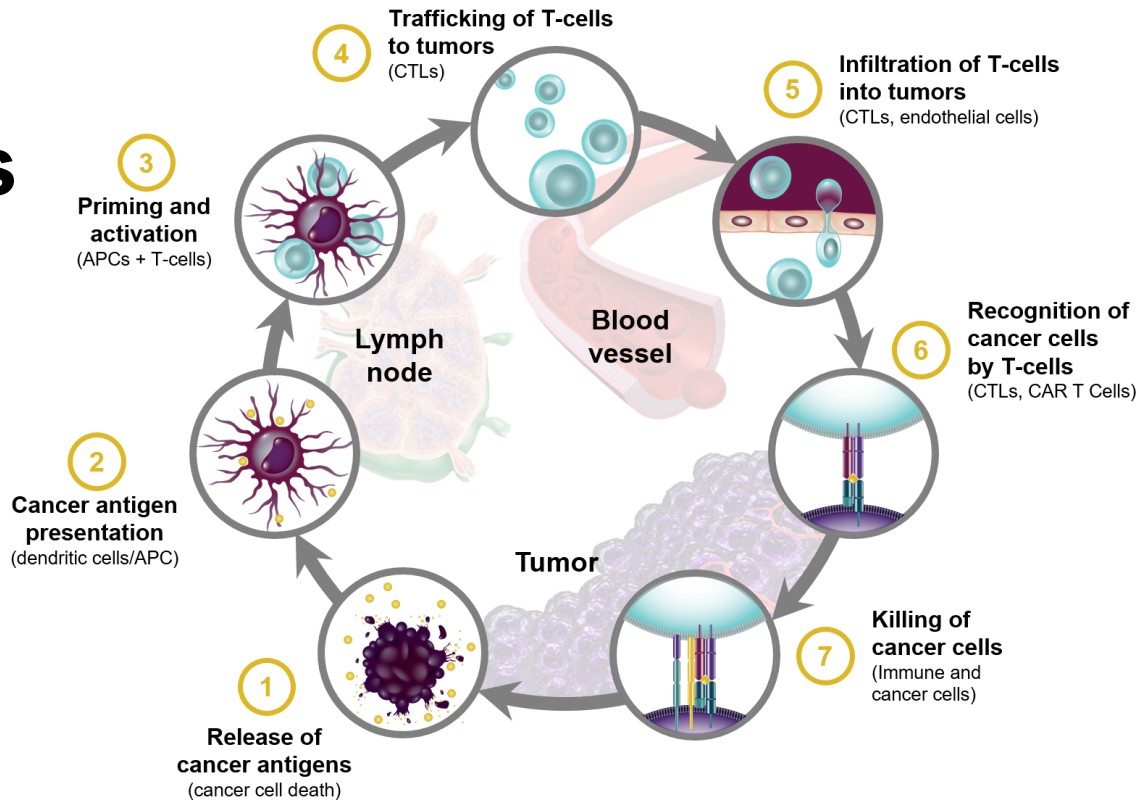
Declaration of financial interest due to intellectual property and patents in the field of cell and gene therapy:

- Royalties and IPR: Novartis
- Scientific Advisory Board for Celldex, Cabaletta, Carisma, Kiadis, Viracta, WIRB-Copernicus Group, and Ziopharm
- Scientific Founder and equity: Tmunity Therapeutics, DeCart Therapeutics

Conflict of interest is managed in accordance with The University of Pennsylvania policies and oversight

# Issues and challenges: Towards the next generation therapies with engineered T Cells

- CAR T cells for blood cancer
- Challenges with solid tumors
- Non-viral engineered T cells




Lim WA, and June CH. The Principles of Engineering Immune Cells to Treat Cancer. *Cell.* 2017;168(4):724-40.

Chimeric

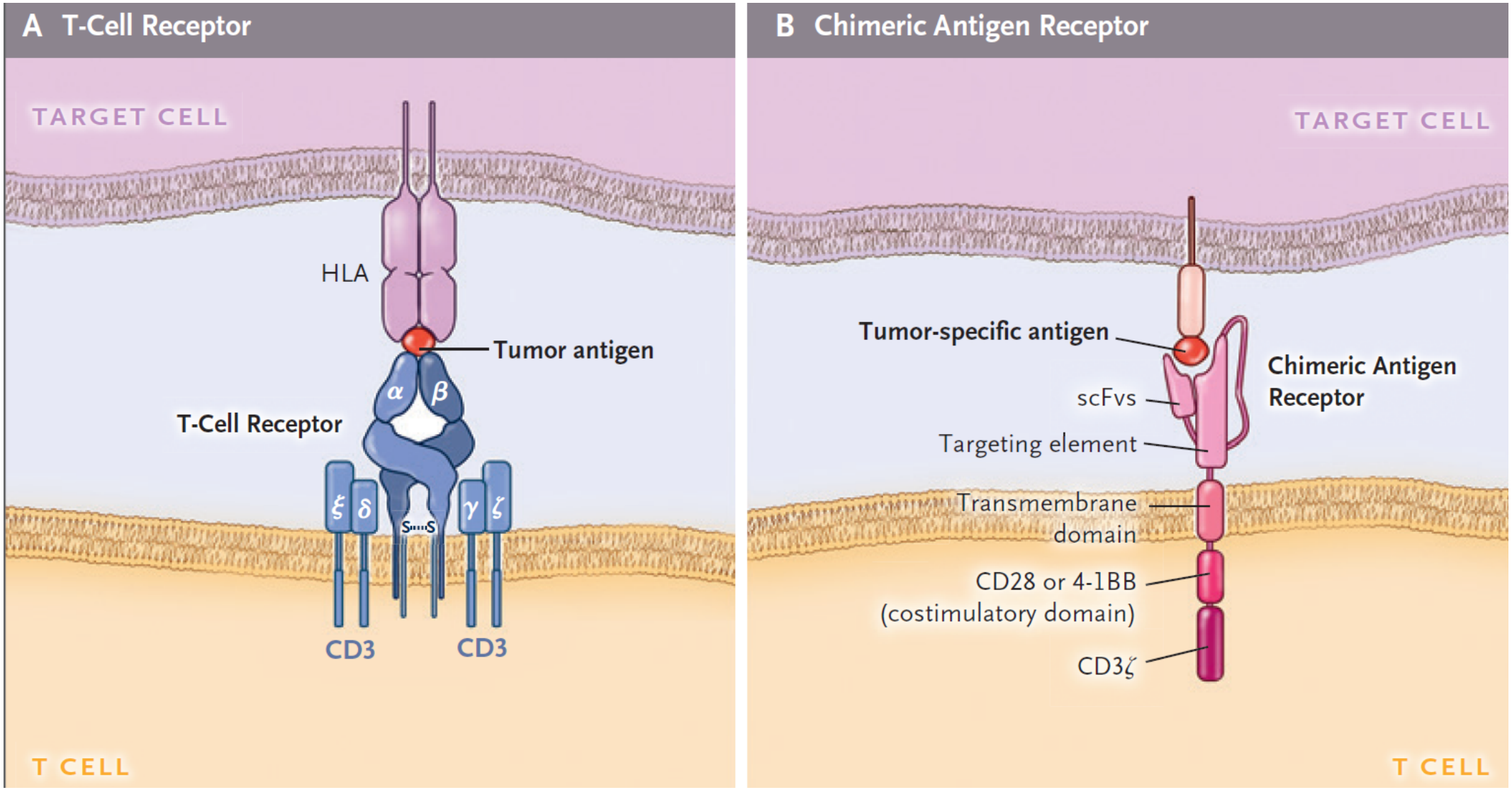
Antigen

Receptor

T Cells

CAR T Cells

# Engineered T Cells: CAR T and TCR T




June and Sadelain, NEJM 2018

# CD19 CAR T at the University of Pennsylvania

## CT019 (tisagenlecleucel): Kymriah™ FDA approval August 30,2017

The NEW ENGLAND JOURNAL of MEDICINE

July 31, 2010
1st CART19 Infusion

The New York Times

Porter, 2011
Grupp, 2013
Maude, 2014
Garfall, 2015
Schuster, 2017
Maude, 2018

# First Adult Patient: chemo refractory leukemia

- Our first patients treated with leukemia remain in remission >10 years at Penn after a single infusion of CAR T
- Cure of refractory leukemia and lymphoma has become routine!
- The CAR T cells persist and remain functional 10 years after infusion in the initial patients treated
- No unexpected long-term toxicities from CAR T
- Engineered CAR T cells can guard against remission by tumor immunosurveillance
- The first “living drug”

**August 2010**

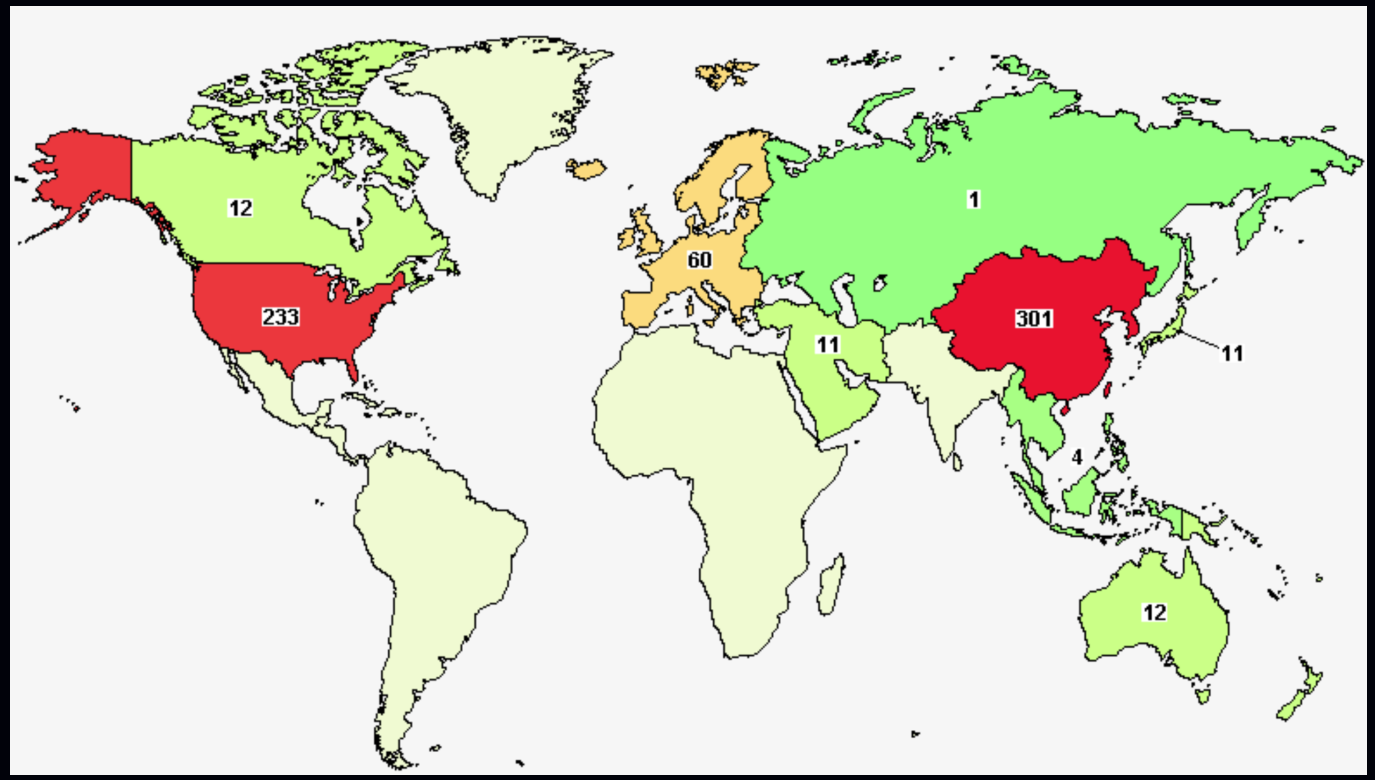
**August 2020**

# First Pediatric Patient: chemo refractory leukemia

- Emily Whitehead: first pediatric leukemia patient treated in 2012
- Severe cytokine release syndrome: rescued with tocilizumab
- She is currently a straight A student in high school living a normal life


Emily Whitehead at the White House in 2015

# CAR T Cells Are Now World Wide




- CAR T Cell trials started in the US in 2006
- There are now more than 600 CAR T trials
- Most CAR T cell trials are now in China!

Colors indicate the number of studies with locations in that region.

Least — Most

Labels give the exact number of studies.

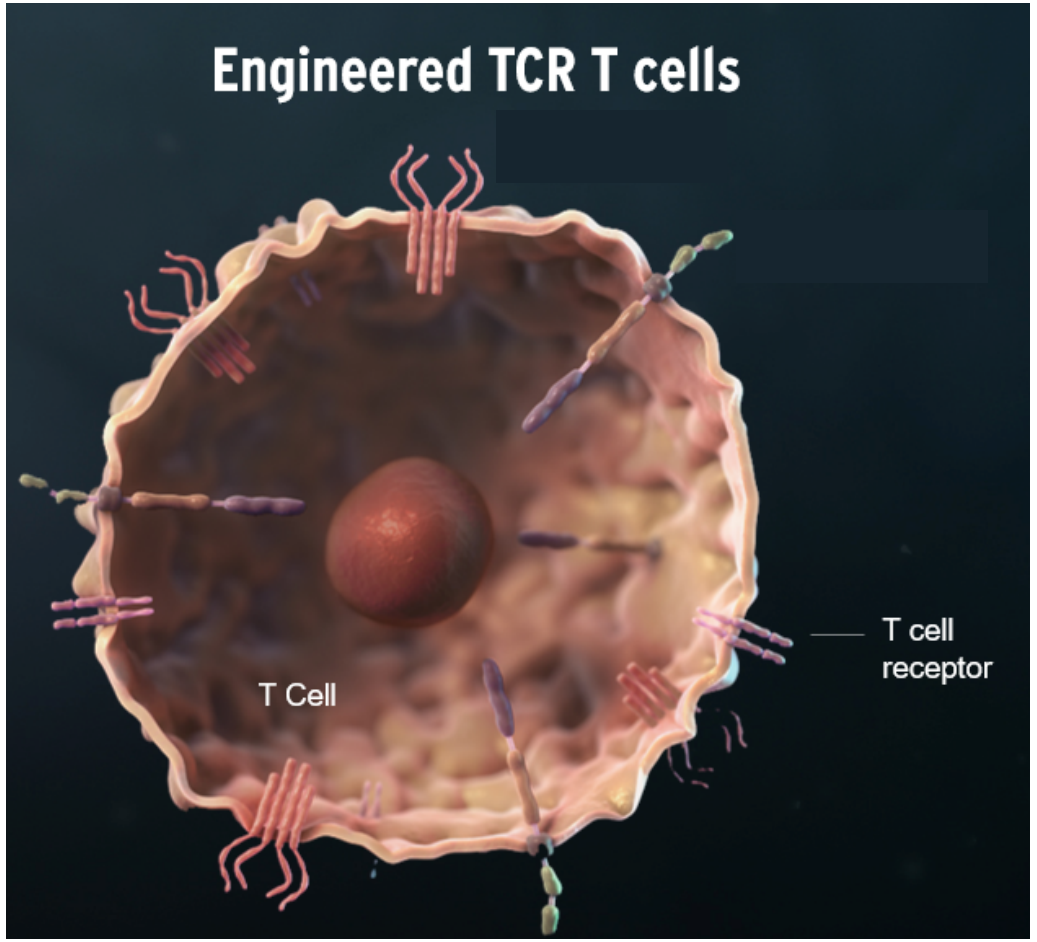
Clinical trials.gov search term “chimeric antigen receptor”
633 trials listed as of February, 2020

# Issues, challenges and solutions for solid tumors

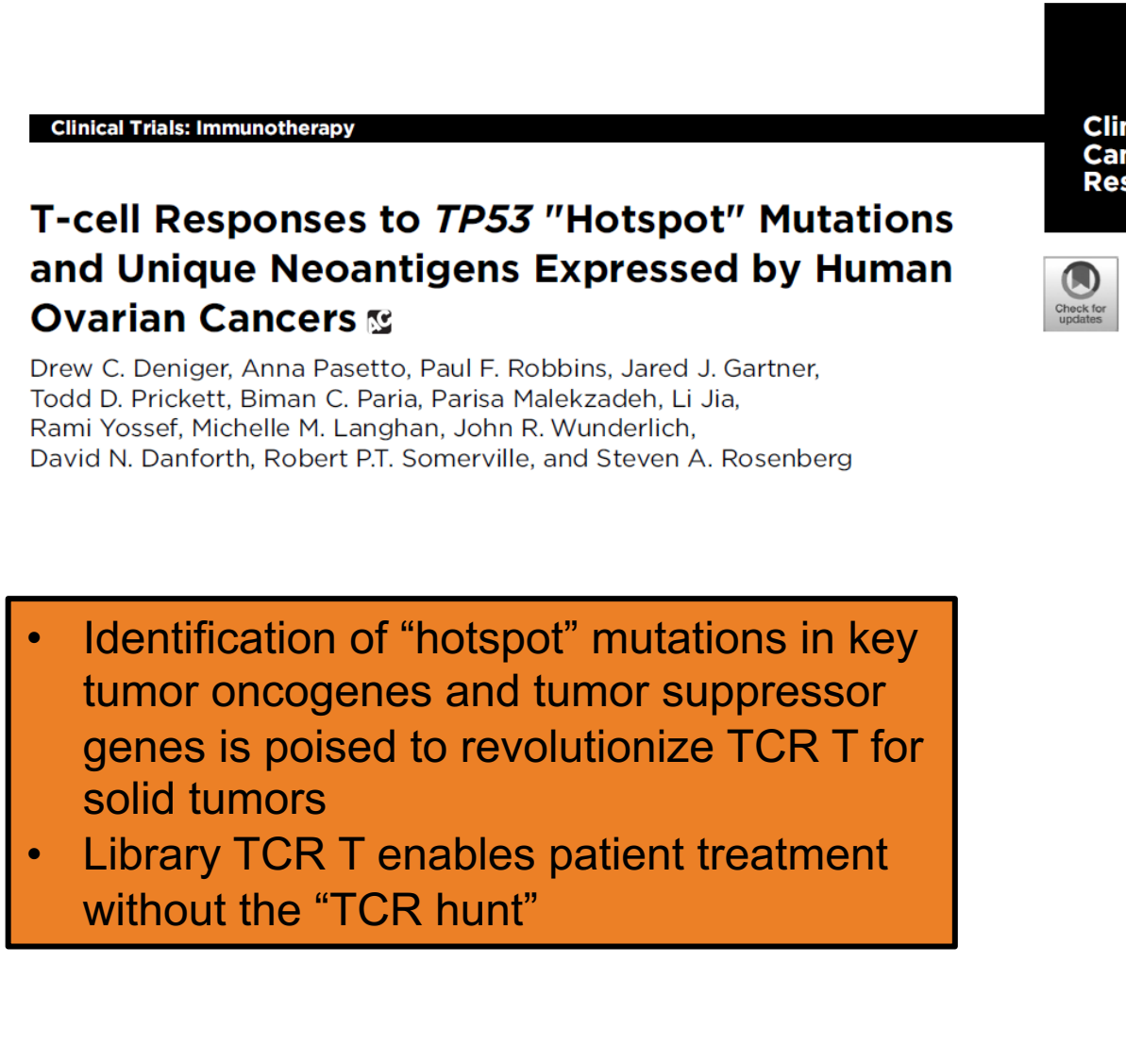
- Lack of ideal CAR targets for solid tumors
- TCR T cells can cure some patients with solid tumors:
  => Lessons from TIL at NCI
- Solutions at hand:

=> TCRs targeting “hot spot” mutations

=> TCRs targeting neoantigens



# Targeting “hotspot” mutations in solid tumors has the potential to revolutionize TCR T Cell Therapy

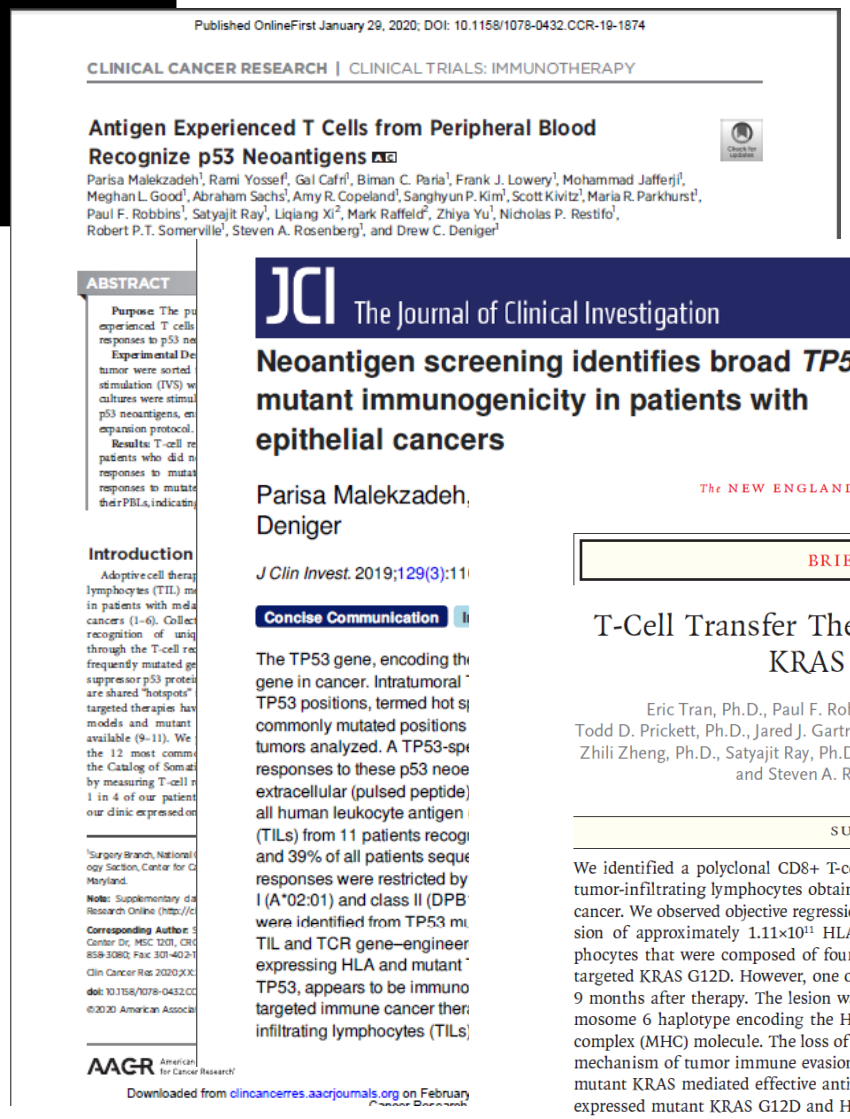

Clinical Trials: Immunotherapy

Clinical Cancer Research

## T-cell Responses to *TP53* "Hotspot" Mutations and Unique Neoantigens Expressed by Human Ovarian Cancers

Drew C. Deniger, Anna Pasetto, Paul F. Robbins, Jared J. Gartner, Todd D. Prickett, Biman C. Paria, Parisa Malekzadeh, Li Jia, Rami Yossef, Michelle M. Langhan, John R. Wunderlich, David N. Danforth, Robert P.T. Somerville, and Steven A. Rosenberg

Check for updates


Published OnlineFirst January 29, 2020; DOI: 10.1158/1078-0432.CCR-19-1874

CLINICAL CANCER RESEARCH | CLINICAL TRIALS: IMMUNOTHERAPY

Antigen Experienced T Cells from Peripheral Blood Recognize p53 Neoantigens

Parisa Malekzadeh, Rami Yossef, Gal Cafri, Biman C. Paria, Frank J. Lowery, Mohammad Jafferji, Meghan L. Good, Abraham Sachs, Amy R. Copeland, Sanghyun P. Kim, Scott Kivitz, Maria R. Parkhurst, Paul F. Robbins, Satyajit Ray, Liqiang Xi, Mark Raffeld, Zhiya Yu, Nicholas P. Restifo, Robert P.T. Somerville, Steven A. Rosenberg, and Drew C. Deniger

ABSTRACT

Introduction

AACR

Downloaded from clincancerres.aacrjournals.org on February


JCI The Journal of Clinical Investigation

Neoantigen screening identifies broad *TP53* mutant immunogenicity in patients with epithelial cancers

Parisa Malekzadeh, Deniger

*J Clin Invest.* 2019;129(3):11

Concise Communication

The TP53 gene, encoding th gene in cancer. Intratumoral TP53 positions, termed hot s commonly mutated positions tumors analyzed. A TP53-sp responses to these p53 neoe extracellular (pulsed peptide) all human leukocyte antigen (TILs) from 11 patients recog and 39% of all patients seque responses were restricted by I (A*02:01) and class II (DPB were identified from TP53 m TIL and TCR gene–engineer expressing HLA and mutant TP53, appears to be immuno targeted immune cancer ther infiltrating lymphocytes (TILs)


The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

T-Cell Transfer Therapy Targeting Mutant KRAS in Cancer

Eric Tran, Ph.D., Paul F. Robbins, Ph.D., Yong-Chen Lu, Ph.D., Todd D. Prickett, Ph.D., Jared J. Gartner, M.Sc., Li Jia, M.Sc., Anna Pasetto, Ph.D., Zhili Zheng, Ph.D., Satyajit Ray, Ph.D., Eric M. Groh, M.D., Isaac R. Kriley, M.D., and Steven A. Rosenberg, M.D., Ph.D.

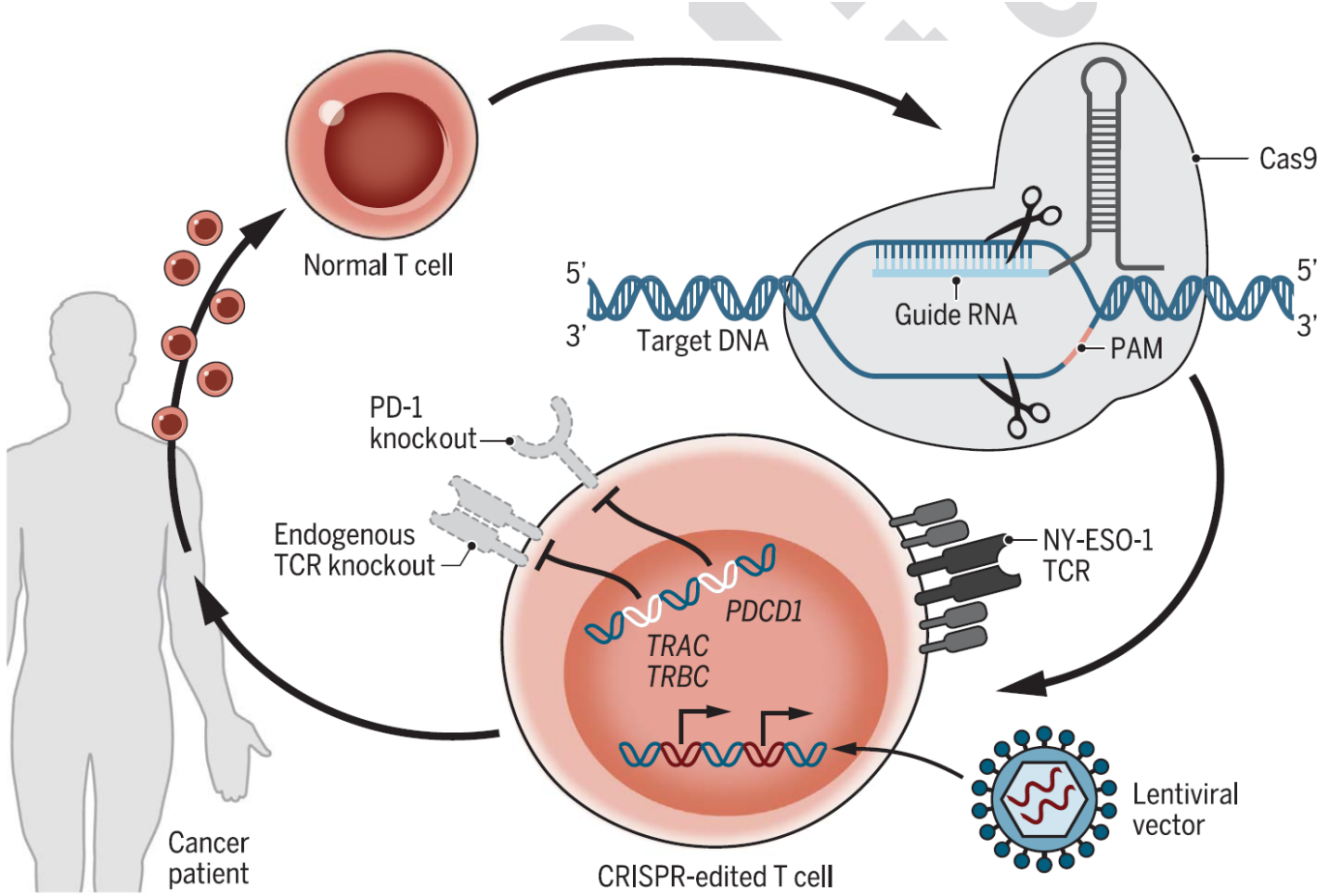
SUMMARY

We identified a polyclonal CD8+ T-cell response against mutant KRAS G12D in tumor-infiltrating lymphocytes obtained from a patient with metastatic colorectal cancer. We observed objective regression of all seven lung metastases after the infusion of approximately $1.11\times10^{11}$ HLA-C*08:02–restricted tumor-infiltrating lymphocytes that were composed of four different T-cell clonotypes that specifically targeted KRAS G12D. However, one of these lesions had progressed on evaluation 9 months after therapy. The lesion was resected and found to have lost the chromosome 6 haplotype encoding the HLA-C*08:02 class I major histocompatibility complex (MHC) molecule. The loss of expression of this molecule provided a direct mechanism of tumor immune evasion. Thus, the infusion of CD8+ cells targeting mutant KRAS mediated effective antitumor immunotherapy against a cancer that expressed mutant KRAS G12D and HLA-C*08:02.

- Identification of “hotspot” mutations in key tumor oncogenes and tumor suppressor genes is poised to revolutionize TCR T for solid tumors
- Library TCR T enables patient treatment without the “TCR hunt”

# Combining Gene Editing with TCR T and CAR T

- In solid tumors, the tumor microenvironment is toxic to T cells
- Genome editing has the potential to render T cells resistant to the toxic effects of the tumor
- Non-viral gene editing technologies have a high potential to improve T cell function



Science

RESEARCH ARTICLES

Cite as: E. A. Stadtmauer *et al.*, *Science* 10.1126/science.aba7365 (2020).

# CRISPR-engineered T cells in patients with refractory cancer

**Edward A. Stadtmauer,[1,2*†] Joseph A. Fraietta,[2,3,4,5*] Megan M. Davis,[5,6] Adam D. Cohen,[1,2] Kristy L. Weber,[2,7] Eric Lancaster,[8] Patricia A. Mangan,[1] Irina Kulikovskaya,[5] Minnal Gupta,[5] Fang Chen,[5] Lifeng Tian,[5] Vanessa E. Gonzalez,[5] Jun Xu,[5] In-young Jung,[4,5] J. Joseph Melenhorst,[3,5,6] Gabriela Plesa,[5] Joanne Shea,[5] Tina Matlawski,[5] Amanda Cervini,[5] Avery L. Gaymon,[5] Stephanie Desjardins,[5] Anne Lamontagne,[5] January Salas-Mckee,[5] Andrew Fesnak,[5,6] Donald L. Siegel,[5,6] Bruce L. Levine,[5,6] Julie K. Jadlowsky,[5] Regina M. Young,[5] Anne Chew,[5] Wei-Ting Hwang,[9] Elizabeth O. Hexner,[1,2] Beatriz M. Carreno,[3,5,6] Christopher L. Nobles,[4] Frederic D. Bushman,[4] Kevin R. Parker,[10] Yanyan Qi,[11] Ansuman T. Satpathy,[10,11] Howard Y. Chang,[10,12] Yangbing Zhao,[5,6] Simon F. Lacey,[5,6*] Carl H. June[2,3,5,6*†]**

# Translation of *Sleeping Beauty* transposition for CAR-T and TCR-T cell therapy

The Journal of Clinical Investigation

CLINICAL MEDICINE

## Phase I trials using *Sleeping Beauty* to generate CD19-specific CAR T cells

Partow Kebriaei,[1] Harjeet Singh,[2] M. Helen Huls,[2] Matthew J. Figliola,[2] Roland Bassett,[3] Simon Olivares,[2] Bipulendu Jena,[2] Margaret J. Dawson,[2] Pappanaicken R. Kumaresan,[2] Shihuang Su,[2] Sourindra Maiti,[2] Jianliang Dai,[3] Branden Moriarity,[4] Marie-Andrée Forget,[2,5] Vladimir Senyukov,[2] Aaron Orozco,[2] Tingting Liu,[1] Jessica McCarty,[1] Rineka N. Jackson,[2] Judy S. Moyes,[2] Gabriela Rondon,[1] Muzaffar Qazilbash,[1] Stefan Ciurea,[1] Amin Alousi,[1] Yago Nieto,[1] Katy Rezvani,[1] David Marin,[1] Uday Popat,[1] Chitra Hosing,[1] Elizabeth J. Shpall,[1] Hagop Kantarjian,[6] Michael Keating,[6] William Wierda,[6] Kim Anh Do,[3] David A. Largaespada,[4] Dean A. Lee,[2,7] Perry B. Hackett,[4] Richard E. Champlin,[1] and Laurence J.N. Cooper[2,7]

Kebriaei P et al. J Clin Invest. 2016 Sep 1;126(9):3363-76.

blood® Letters to *Blood*

TO THE EDITOR:

## Long-term outcomes of Sleeping Beauty–generated CD19-specific CAR T-cell therapy for relapsed-refractory B-cell lymphomas

S. A. Srour,[1] H. Singh,[2] J. McCarty,[1] E. de Groot,[3] H. Huls,[2] G. Rondon,[1] M. Qazilbash,[1] S. Ciurea,[1] G. Bardelli,[3] J. Buck,[3] A. Alousi,[1] Y. Nieto,[1] K. Rezvani,[1] D. Marin,[1] U. Popat,[1] C. Hosing,[1] E. J. Shpall,[1] W. G. Wierda,[4] H. Kantarjian,[4] R. E. Champlin,[1] L. J. Cooper,[3] and P. Kebriaei[1]

Srour SA et al. Blood. 2020 Mar 12;135(11):862-865.

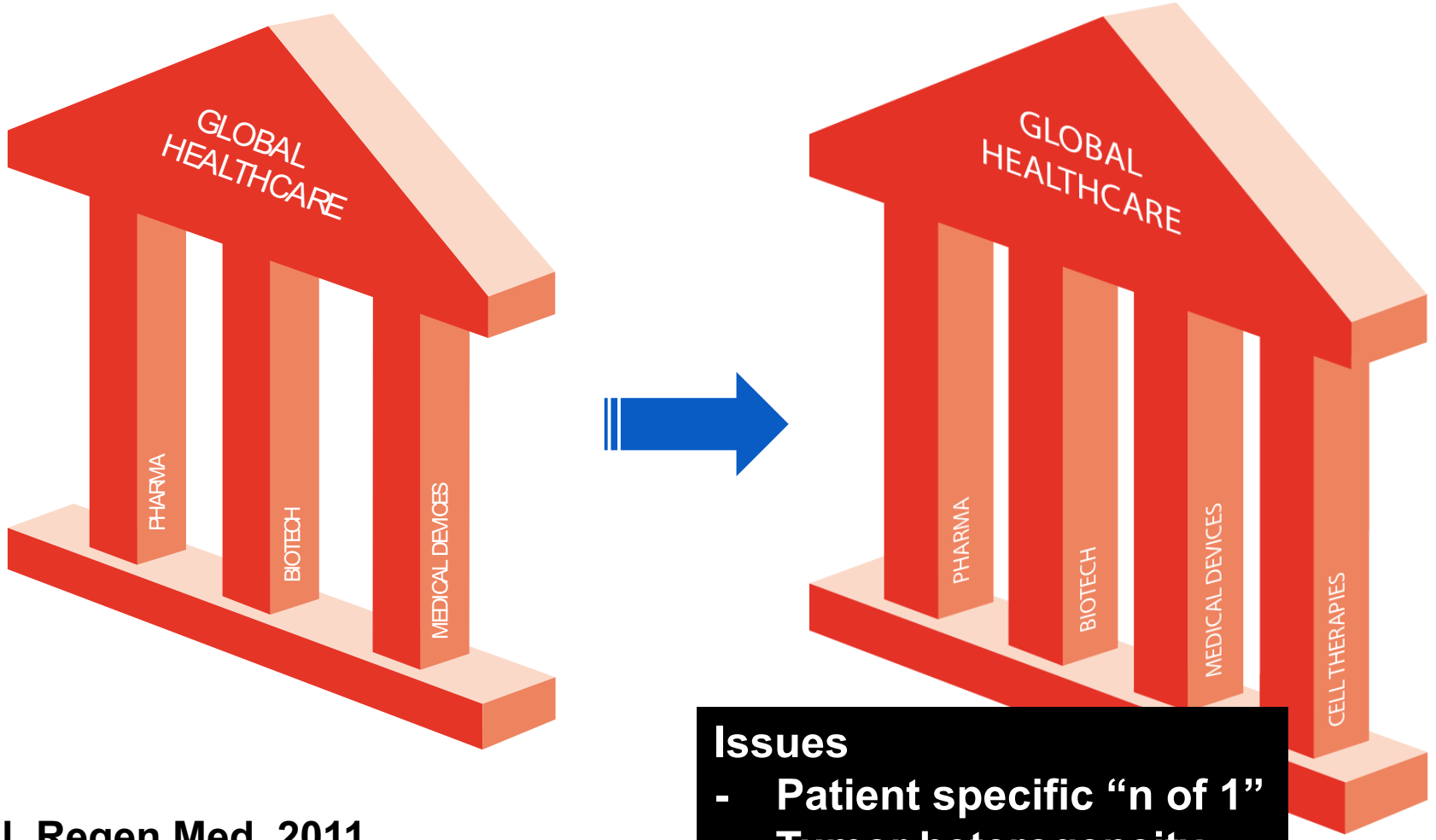
## Stable, Nonviral Expression of Mutated Tumor Neoantigen-specific T-cell Receptors Using the *Sleeping Beauty* Transposon/Transposase System

Drew C Deniger[1], Anna Pasetto[1], Eric Tran[1], Maria R Parkhurst[1], Cyrille J Cohen[2], Paul F Robbins[1], Laurence JN Cooper[3,4] and Steven A Rosenberg[1]

*[1]Surgery Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA; [2]Tumor Immunology and Immunotherapy, Bar-Ilan University, Ramat Gan, Israel; [3]Division of Pediatrics, University of Texas M.D. Anderson Cancer Center, Houston, Texas, USA; [4]ZIOPHARM Oncology, Inc., Boston, Massachusetts, USA*

Deniger DC et al. Mol Ther. 2016 Jun;24(6):1078-1089.

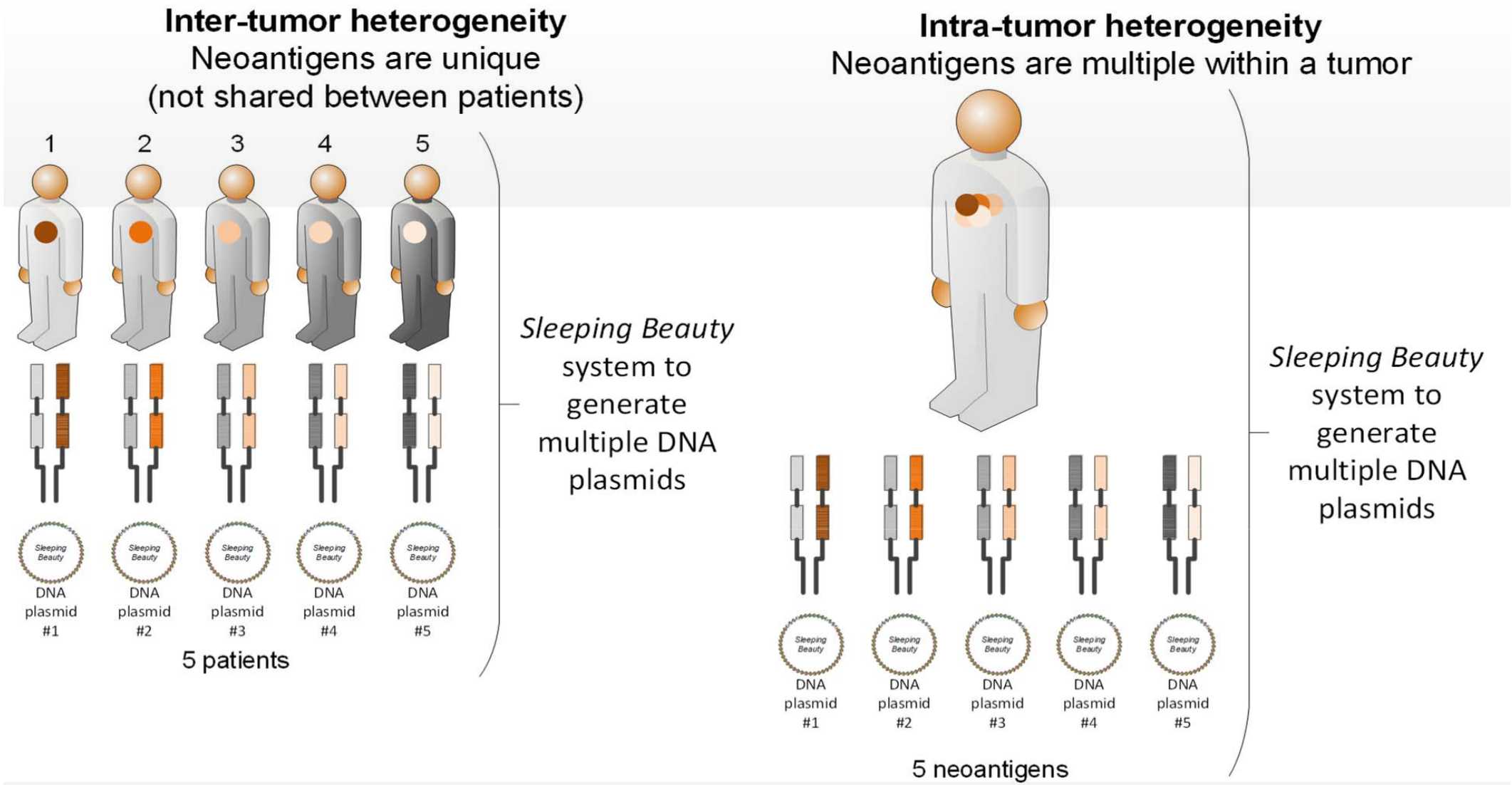
# Health Care Challenges
# Facing cell and gene therapy




**Issues**
- Patient specific “n of 1”
- Tumor heterogeneity
- Speed to patient

Chris Mason et al, Regen Med. 2011
Levine and June, Nature. 2013

# *Sleeping Beauty* Platform Facilitates Manufacture of Personalized TCR-T Therapy and Overcoming Challenges of Heterogeneity



# Universal TCR and CAR T Cells

***Off-the-shelf UCART and UTCRT cells from unrelated donors, cord blood or IPSC would be disruptive***

| | Patient Specific TCR and CAR T Cells | Off-the-Shelf TCR and CAR T Cells |
|---|---|---|
| **Cell Source** | Autologous T cells | Allogeneic cells |
| **# Patients** | One patient | Multiple patients |
| **Manufacturing** | Real time | Master cell bank |
| **Business model** | Point-of-Care | Standard Pharma: centralized |
| **Results** | Can cure leukemia! | Efficacy unknown<br>Disease control? |

**Qasim W, et al. Molecular remission of infant B-ALL after infusion of universal TALEN gene-edited CAR T cells. *Sci Transl Med.* 2017;9(374).**

# Summary: the road ahead

- **CAR T for blood cancers are becoming standard of care. Likely that all blood cancers will be treated with current and future versions of CAR T. Access and costs are an engineering problem that will be readily solved by industry investments.**

- **The treatment of solid tumors with TCR T cells is on the horizon. This is a scientific challenge that can be solved by:**
  - ⇒ **Library TCR T directed against shared hotspot mutations**
  - ⇒ **Personalized TCR T pipelines with advanced non-viral engineering, reducing vein to vein times to a practical process**

Ziopharm ONCOLOGY

# Program Update: Ziopharm TCR-T program

11-MAR-2021

# Ziopharm TCR-T cell therapy

- Patient T cells from peripheral blood (younger and healthier) are genetically modified with T-cell receptors (TCRs) to re-direct them to the tumor through recognition of neoantigens.

- Ziopharm uses non-viral *Sleeping Beauty* transposition to genetically modify the T cell, which is perfectly suited for our application, and is a key competitive advantage for the company.

- We will be treating patients with common epithelial cancers that kill hundreds of thousands of Americans every year (huge market).

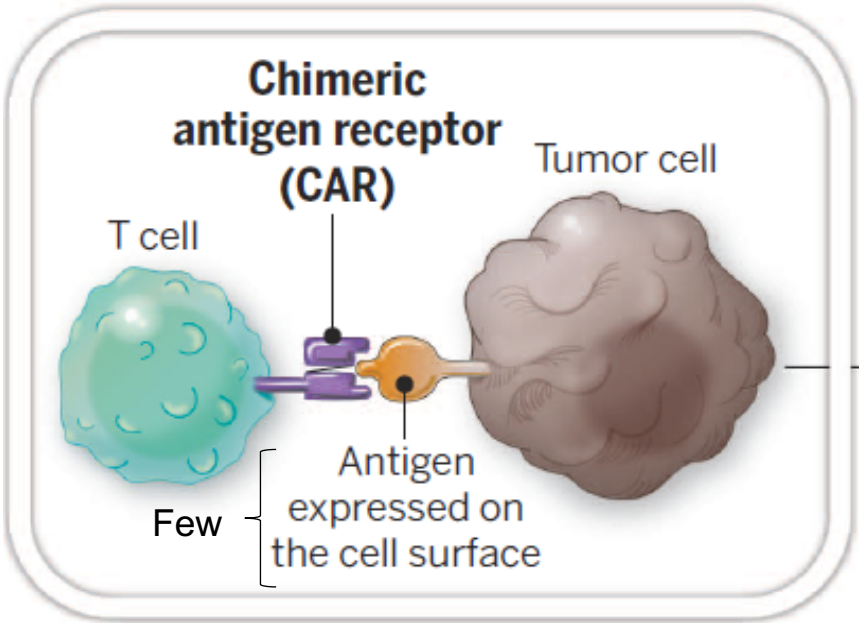


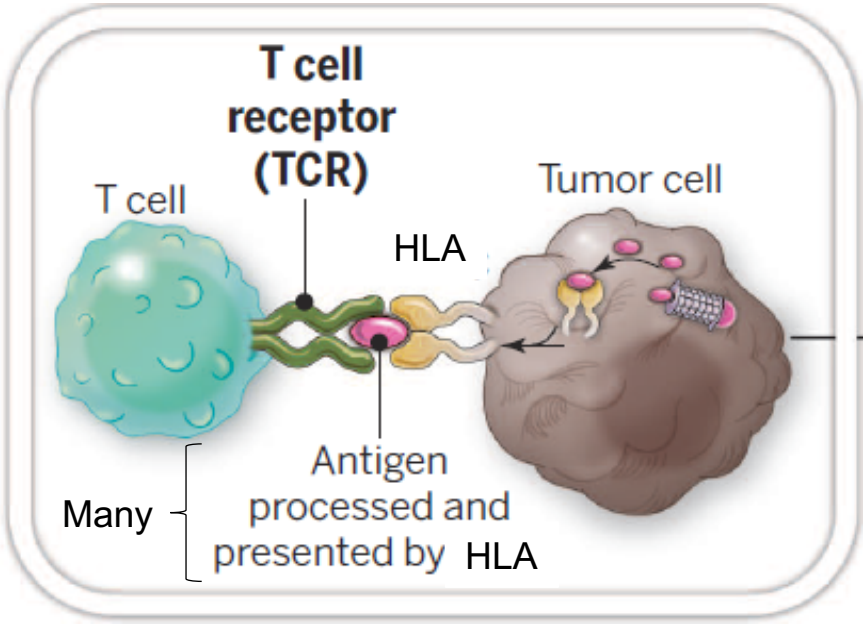
Ziopharm ONCOLOGY

# Adoptive cell therapy basics

- T cells have a natural role in killing damaged cells in the body, including cancer cells, and co-exist with tumor cells in solid cancers.
- T cells are a type of white blood cell, and intravenous transfusion of T cells can act as a living drug and eliminate established tumors.
- T cells can be used directly for cell therapy (TILs) or can be genetically modified to augment anti-tumor function (CAR-T and TCR-T cell therapy).

# TCR-T cell therapy has exceptionally larger targeting capacity relative to CAR-T cell therapy




Rosenberg SA and Restifo NP. Science. 2015 Apr 3;348(6230):62-8.



Ziopharm ONCOLOGY

# Neoantigens are the best of the potential solid cancer targets for TCR-T cell therapy

- Viral antigens: HPV, EBV, etc. Only in few cancer types.
- Germline antigens: MART, gp100, NY-ESO-1, MAGE, PRAME, etc. Present on normal tissues, irregularly expressed in tumor cells, and only relevant for few patients.
- Neoantigens: could arise from any somatic (non-inherited) mutation. Completely tumor-specific, either unique to patient or shared in unrelated people, and are potentially applicable to all cancer patients.

# Somatic mutations are the blueprint for pan-cancer therapy

- Genomic instability is a hallmark of cancer. Genetic mutations arising from this instability are largely unique to the patient, but a subset of mutations are shared in “hotspots” of critical cancer genes.

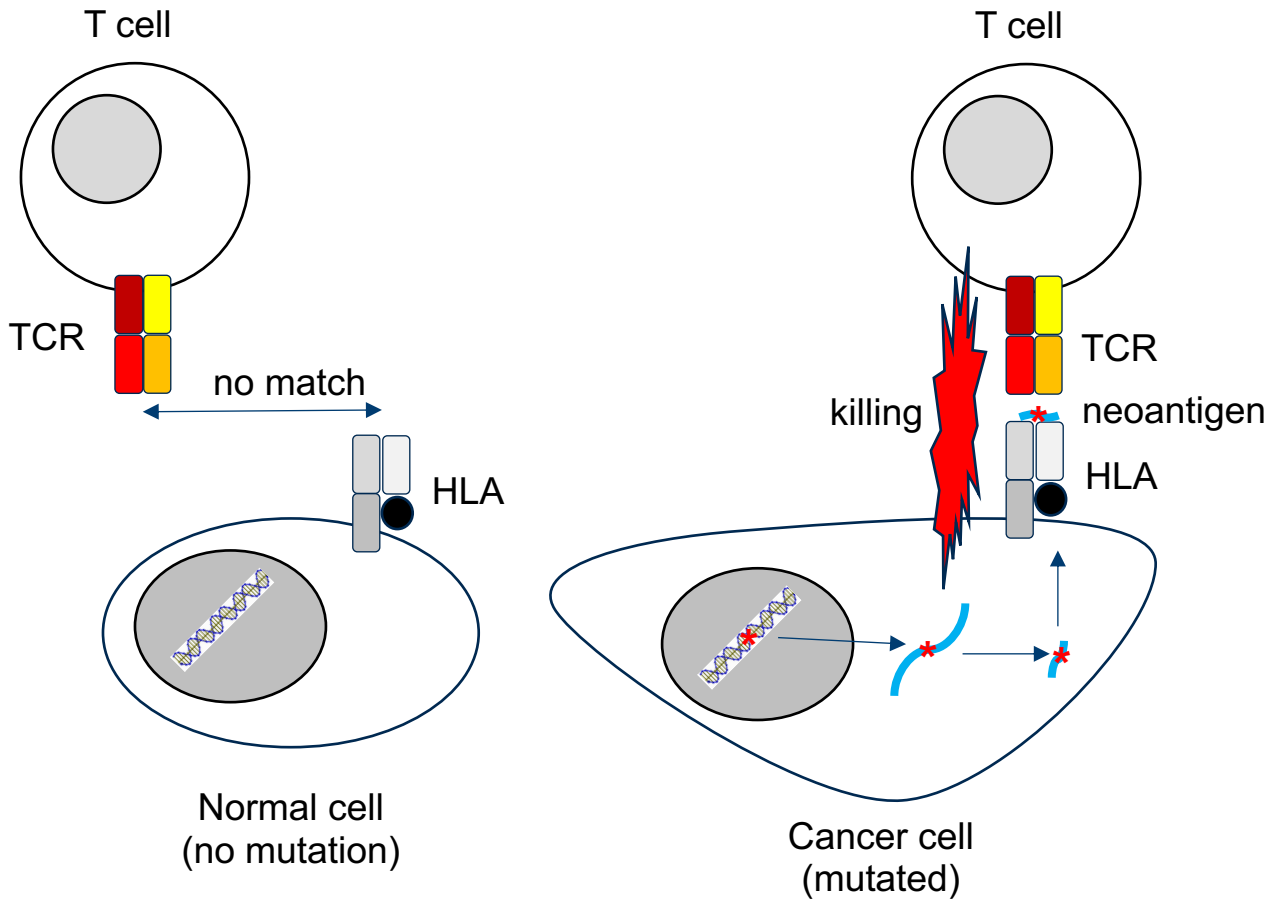
- Some somatic genetic mutations will be transcribed, translated, processed and presented on the cancer cell surface generating a “neoantigen” which is not in the normal cells.

- T cells, through their TCR, recognize neoantigens and can kill the cancer cell with mutation.



Ziopharm ONCOLOGY

# Presentation of neoantigens to T cells leads to exquisite tumor-specificity of TCR-T cells






Ziopharm ONCOLOGY

# Most epithelial cancer patients have TILs which recognize at least one autologous neoantigen

nature medicine

## Mining exomic sequencing data to identify mutated antigens recognized by adoptively transferred tumor-reactive T cells

Paul F Robbins[1], Yong-Chen Lu[1], Mona El-Gamil[1], Yong F Li[1], Colin Gross[1], Jared Gartner[2], Jimmy C Lin[3], Jamie K Teer[4,5], Paul Cliften[3], Eric Tycksen[3], Yardena Samuels[2,5] & Steven A Rosenberg[1]

Robbins PF *et al.* Nat Med. 2013 Jun;19(6):747-52.

CANCER IMMUNOTHERAPY

## Immunogenicity of somatic mutations in human gastrointestinal cancers

Eric Tran, Mojgan Ahmadzadeh, Yong-Chen Lu, Alena Gros, Simon Turcotte,* Paul F. Robbins, Jared J. Gartner, Zhili Zheng, Yong F. Li, Satyajit Ray, John R. Wunderlich, Robert P. Somerville, Steven A. Rosenberg†

Tran E *et al.* Science. 2015 Dec 11;350(6266):1387-90.

## Unique Neoantigens Arise from Somatic Mutations in Patients with Gastrointestinal Cancers

Maria R. Parkhurst[1], Paul F. Robbins[1], Eric Tran[2], Todd D. Prickett[1], Jared J. Gartner[1], Li Jia[1], Gabriel Ivey[1], Yong F. Li[1], Mona El-Gamil[1], Almin Lalani[1], Jessica S. Crystal[1], Abraham Sachs[1], Eric Groh[1], Satyajit Ray[1], Lien T. Ngo[1], Scott Kivitz[1], Anna Pasetto[1], Rami Yossef[1], Frank J. Lowery[1], Stephanie L. Goff[1], Winifred Lo[1], Gal Cafri[1], Drew C. Deniger[1], Parisa Malekzadeh[1], Mojgan Ahmadzadeh[1], John R. Wunderlich[1], Robert P.T. Somerville[1], and Steven A. Rosenberg[1]

Parkhurst MR *et al.* Cancer Discov. 2019 Aug;9(8):1022-1035.

## Tumor infiltrating lymphocytes (TIL) therapy in metastatic melanoma: boosting of neoantigen-specific T cell reactivity and long-term follow-up

Joost H van den Berg ,[1] Bianca Heemskerk,[2] Nienke van Rooij,[2] Raquel Gomez-Eerland,[2] Samira Michels,[2] Maaike van Zon,[1] Renate de Boer,[1] Noor A M Bakker,[1] Annelies Jorritsma-Smit,[2] Marit M van Buuren,[2] Pia Kvistborg,[2] Hergen Spits,[3,4] Remko Schotte,[3] Henk Mallo,[5] Matthias Karger,[5] Joris A van der Hage,[6] Michel W J M Wouters,[7,8] Loes M Pronk,[9] Marnix H Geukes Foppen,[5] Christian U Blank,[10] Jos H Beijnen,[11,12] Bastiaan Nuijen,[11] Ton N Schumacher,[2,13] John B A G Haanen[2]

van den Berg JH et al. J Immunother Cancer 2020 Aug;8(2):e000848.

Clinical Trials: Immunotherapy

Clinical Cancer Research

## T-cell Responses to *TP53* "Hotspot" Mutations and Unique Neoantigens Expressed by Human Ovarian Cancers

Drew C. Deniger, Anna Pasetto, Paul F. Robbins, Jared J. Gartner, Todd D. Prickett, Biman C. Paria, Parisa Malekzadeh, Li Jia, Rami Yossef, Michelle M. Langhan, John R. Wunderlich, David N. Danforth, Robert P.T. Somerville, and Steven A. Rosenberg

Deniger DC *et al.* Clin Cancer Res. 2018 Nov 15;24(22):5562-5573.

The Journal of Immunology

## Identification of Neoantigen-Reactive Tumor-Infiltrating Lymphocytes in Primary Bladder Cancer

Vid Leko,*,† Lucas A. McDuffie,*,[1] Zhili Zheng,* Jared J. Gartner,* Todd D. Prickett,* Andrea B. Apolo,[‡] Piyush K. Agarwal,[§] Steven A. Rosenberg,* and Yong-Chen Lu*

Leko V *et al.* J Immunol. 2019 Jun 15;202(12):3458-3467.

## Detection of neoantigen-specific T cells following a personalized vaccine in a patient with glioblastoma

Tanner M. Johanns[a,b], Christopher A. Miller[c], Connor J. Liu[b,d], Richard J. Perrin[e], Diane Bender[b], Dale K. Kobayashi[b], Jian L. Campian[a], Michael R. Chicoine[d], Ralph G. Dacey[d], Jiayi Huang[f], Edward F. Fritsch[g], William E. Gillanders[b,h], Maxim N. Artyomov[b,e], Elaine R. Mardis[i], Robert D. Schreiber[b,e], and Gavin P. Dunn[b,d]

Johanns TM et al. Oncoimmunology. 2019 Jan 25;8(4):e1561106.

ARTICLE

DOI: 10.1038/s41467-018-03301-0 OPEN

## Sensitive and frequent identification of high avidity neo-epitope specific CD8+ T cells in immunotherapy-naive ovarian cancer

Sara Bobisse[1], Raphael Genolet[1], Annalisa Roberti[2], Janos L. Tanyi[2], Julien Racle[1,3], Brian J. Stevenson[3], Christian Iseli[3], Alexandra Michel[1], Marie-Aude Le Bitoux[1], Philippe Guillaume[1], Julien Schmidt[1], Valentina Bianchi[1], Denarda Dangaj[1], Craig Fenwick[4], Laurent Derré[5], Ioannis Xenarios[3], Olivier Michielin[1,3], Pedro Romero[1], Dimitri S. Monos[6], Vincent Zoete[1,3], David Gfeller[1,3], Lana E. Kandalaft[1,2], George Coukos[1] & Alexandre Harari[1]

Bobisse S *et al.* Nat Commun. 2018 Mar 15;9(1):1092.

## Landscape of immunogenic tumor antigens in successful immunotherapy of virally induced epithelial cancer

Sanja Stevanović,[1]* Anna Pasetto,[2] Sarah R. Helman,[1] Jared J. Gartner,[2] Todd D. Prickett,[2] Bryan Howie,[3] Harlan S. Robins,[3,4] Paul F. Robbins,[2] Christopher A. Klebanoff,[5,6] Steven A. Rosenberg,[2] Christian S. Hinrichs[1]*

Stevanović S *et al.* Science 2017 Apr 14;356(6334):200-205.



Ziopharm ONCOLOGY

# Shared "hotspot" mutations in *KRAS* and *TP53* genes are immunogenic and can be used for off-the-shelf TCR-T cells

The Journal of Clinical Investigation CLINICAL MEDICINE

## mRNA vaccine–induced neoantigen-specific T cell immunity in patients with gastrointestinal cancer

Gal Cafri,[1,2] Jared J. Gartner,[1] Tal Zaks,[3] Kristen Hopson,[3] Noam Levin,[1] Biman C. Paria,[1] Maria R. Parkhurst,[1] Rami Yossef,[1] Frank J. Lowery,[1] Mohammad S. Jafferji,[1] Todd D. Prickett,[1] Stephanie L. Goff,[1] Christine T. McGowan,[1] Samantha Seitter,[1] Mackenzie L. Shindorf,[1] Anup Parikh,[1] Praveen D. Chatani,[1] Paul F. Robbins,[1] and Steven A. Rosenberg[1]

[1]Surgery Branch, National Cancer Institute (NCI), NIH, Bethesda, Maryland, USA. [2]Sheba Medical Center, Ramat Gan, Israel. [3]Moderna Inc., Cambridge, Massachusetts, USA.

Cafri G *et al.* J Clin Invest. 2020 Nov 2;130(11):5976-5988.

ARTICLE

https://doi.org/10.1038/s41467-019-08304-z OPEN

## Memory T cells targeting oncogenic mutations detected in peripheral blood of epithelial cancer patients

Gal Cafri[1], Rami Yossef[1], Anna Pasetto[1], Drew C. Deniger[1], Yong-Chen Lu[1], Maria Parkhurst[1], Jared J. Gartner[1], Li Jia[1], Satyajit Ray[1], Lien T. Ngo[1], Mohammad Jafferji[1], Abraham Sachs[1], Todd Prickett[1], Paul F. Robbins[1] & Steven A. Rosenberg[1]

Cafri G *et al.* Nat Commun. 2019 Jan 25;10(1):449.

## Enhanced detection of neoantigen-reactive T cells targeting unique and shared oncogenes for personalized cancer immunotherapy

Rami Yossef,[1] Eric Tran,[1,2] Drew C. Deniger,[1] Alena Gros,[1,3] Anna Pasetto,[1] Maria R. Parkhurst,[1] Jared J. Gartner,[1] Todd D. Prickett,[1] Gal Cafri,[1] Paul F. Robbins,[1] and Steven A. Rosenberg[1]

Yossef R *et al.* J Clin Invest. 2019 Mar 1;129(3):1109-1114.

The Journal of Clinical Investigation CONCISE COMMUNICATION

## Neoantigen screening identifies broad *TP53* mutant immunogenicity in patients with epithelial cancers

Parisa Malekzadeh,[1] Anna Pasetto,[1] Paul F. Robbins,[1] Maria R. Parkhurst,[1] Biman C. Paria,[1] Li Jia,[1] Jared J. Gartner,[1] Victoria Hill,[1] Zhiya Yu,[1] Nicholas P. Restifo,[1] Abraham Sachs,[1] Eric Tran,[1,2] Winifred Lo,[1] Robert P.T. Somerville,[1] Steven A. Rosenberg,[1] and Drew C. Deniger[1]

[1]Surgery Branch, National Cancer Institute, Bethesda, Maryland, USA. [2]Earle A. Chiles Research Institute, Providence Cancer Institute, Portland, Oregon, USA.

Malekzadeh P *et al.* J Clin Invest. 2019 Mar 1;129(3):1109-1114.

Cancer Immunology Miniature

Cancer Immunology Research

## Immunologic Recognition of a Shared p53 Mutated Neoantigen in a Patient with Metastatic Colorectal Cancer

Winifred Lo[1,2], Maria Parkhurst[2], Paul F. Robbins[2], Eric Tran[3], Yong-Chen Lu[2], Li Jia[2], Jared J. Gartner[2], Anna Pasetto[2], Drew Deniger[2], Parisa Malekzadeh[2], Thomas E. Shelton[2], Todd Prickett[2], Satyajit Ray[2], Scott Kivitz[2], Biman C. Paria[2], Isaac Kriley[1,2], David S. Schrump[1], and Steven A. Rosenberg[2]

Lo W *et al.* Cancer Immunol Res. 2019 Apr;7(4):534-543.

## Antigen Experienced T Cells from Peripheral Blood Recognize p53 Neoantigens

Parisa Malekzadeh[1], Rami Yossef[1], Gal Cafri[1], Biman C. Paria[1], Frank J. Lowery[1], Mohammad Jafferji[1], Meghan L. Good[1], Abraham Sachs[1], Amy R. Copeland[1], Sanghyun P. Kim[1], Scott Kivitz[1], Maria R. Parkhurst[1], Paul F. Robbins[1], Satyajit Ray[1], Liqiang Xi[2], Mark Raffeld[2], Zhiya Yu[1], Nicholas P. Restifo[1], Robert P.T. Somerville[1], Steven A. Rosenberg[1], and Drew C. Deniger[1]

Malekzadeh P *et al.* Clin Cancer Res. 2020 Mar 15;26(6):1267-1276.



Ziopharm ONCOLOGY

# Neoantigen-reactive T cells (non-gene modified) resulted in objective regressions of metastatic epithelial cancers

Science AAAS

## Cancer Immunotherapy Based on Mutation-Specific CD4+ T Cells in a Patient with Epithelial Cancer

Eric Tran,[1] Simon Turcotte,[1]* Alena Gros,[1] Paul F. Robbins,[1] Yong-Chen Lu,[1] Mark E. Dudley,[1]† John R. Wunderlich,[1] Robert P. Somerville,[1] Katherine Hogan,[1] Christian S. Hinrichs,[1] Maria R. Parkhurst,[1] James C. Yang,[1] Steven A. Rosenberg[1]‡

Tran E *et al.* Science. 2014 May 9;344(6184):641-5.

**1 unique driver neoantigen from 26 total mutations**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE BRIEF REPORT

## T-Cell Transfer Therapy Targeting Mutant KRAS in Cancer

Eric Tran, Ph.D., Paul F. Robbins, Ph.D., Yong-Chen Lu, Ph.D., Todd D. Prickett, Ph.D., Jared J. Gartner, M.Sc., Li Jia, M.Sc., Anna Pasetto, Ph.D., Zhili Zheng, Ph.D., Satyajit Ray, Ph.D., Eric M. Groh, M.D., Isaac R. Kriley, M.D., and Steven A. Rosenberg, M.D., Ph.D.

Tran E *et al.* N Engl J Med. 2016 Dec 8;375(23):2255-2262

**Driver gene**

nature medicine

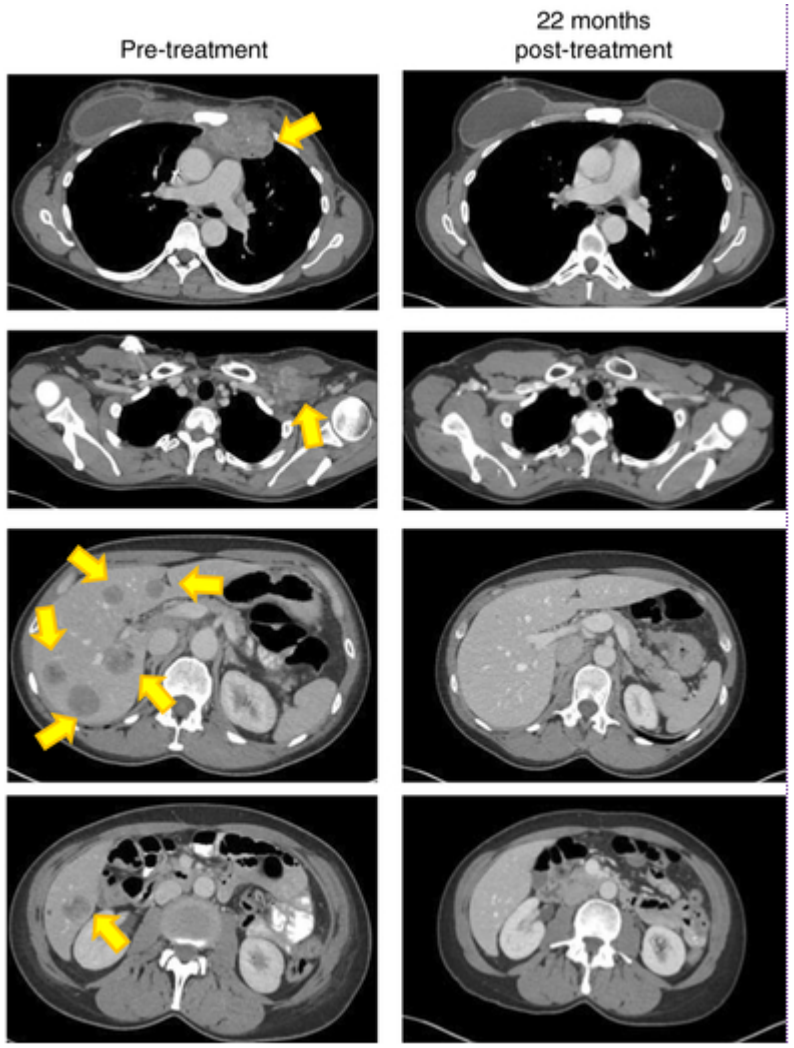
Letter | Published: 04 June 2018

## Immune recognition of somatic mutations leading to complete durable regression in metastatic breast cancer

Nikolaos Zacharakis, Harshini Chinnasamy, Mary Black, Hui Xu, Yong-Chen Lu, Zhili Zheng, Anna Pasetto, Michelle Langhan, Thomas Shelton, Todd Prickett, Jared Gartner, Li Jia, Katarzyna Trebska-McGowan, Robert P. Somerville, Paul F. Robbins, Steven A. Rosenberg ✉, Stephanie L. Goff & Steven A. Feldman

Zacharakis N *et al.* Nat Med. 2018 Jun;24(6):724-730.

**Multiple unique neoantigen specificities**






Ziopharm ONCOLOGY

# Application of neoantigen-specific TCR-T cell therapy

- Prior TCR-T cell therapy established that metastatic cancers can be effectively treated in some patients when targeting non-neoantigen targets, but the application was limited by target expression and cancer type.

- Non-gene modified adoptive cell therapy (TIL) resulted in objective clinical regressions in some patients but was ineffective for most people likely due to infrequent and/or terminal differentiation of neoantigen-specific T cells.

- The ability to translate a library or personalized neoantigen-specific TCR-T cell approach is complex and will likely require a rapid, mobile and cost-effective solution.

***Sleeping Beauty* transposition is an ideal candidate for this because it uses plasmid DNA, which is inexpensive to manufacture and allows for rapid personalization.**

# *Sleeping Beauty* transposition has been established for TCR-T cell and translated for CAR-T cell to the clinic

The Journal of Clinical Investigation

CLINICAL MEDICINE

## Phase I trials using *Sleeping Beauty* to generate CD19-specific CAR T cells

Partow Kebriaei,[1] Harjeet Singh,[2] M. Helen Huls,[2] Matthew J. Figliola,[2] Roland Bassett,[3] Simon Olivares,[2] Bipulendu Jena,[2] Margaret J. Dawson,[2] Pappanaicken R. Kumaresan,[2] Shihuang Su,[2] Sourindra Maiti,[2] Jianliang Dai,[3] Branden Moriarity,[4] Marie-Andrée Forget,[2,5] Vladimir Senyukov,[2] Aaron Orozco,[2] Tingting Liu,[1] Jessica McCarty,[1] Rineka N. Jackson,[2] Judy S. Moyes,[2] Gabriela Rondon,[1] Muzaffar Qazilbash,[1] Stefan Ciurea,[1] Amin Alousi,[1] Yago Nieto,[1] Katy Rezvani,[1] David Marin,[1] Uday Popat,[1] Chitra Hosing,[1] Elizabeth J. Shpall,[1] Hagop Kantarjian,[6] Michael Keating,[6] William Wierda,[6] Kim Anh Do,[3] David A. Largaespada,[4] Dean A. Lee,[2,7] Perry B. Hackett,[4] Richard E. Champlin,[1] and Laurence J.N. Cooper[2,7]

Kebriaei P et al. J Clin Invest. 2016 Sep 1;126(9):3363-76.

blood® Letters to *Blood*

TO THE EDITOR:

## Long-term outcomes of Sleeping Beauty–generated CD19-specific CAR T-cell therapy for relapsed-refractory B-cell lymphomas

S. A. Srour,[1] H. Singh,[2] J. McCarty,[1] E. de Groot,[3] H. Huls,[2] G. Rondon,[1] M. Qazilbash,[1] S. Ciurea,[1] G. Bardelli,[3] J. Buck,[3] A. Alousi,[1] Y. Nieto,[1] K. Rezvani,[1] D. Marin,[1] U. Popat,[1] C. Hosing,[1] E. J. Shpall,[1] W. G. Wierda,[4] H. Kantarjian,[4] R. E. Champlin,[1] L. J. Cooper,[3] and P. Kebriaei[1]

Srour SA et al. Blood. 2020 Mar 12;135(11):862-865.

## Stable, Nonviral Expression of Mutated Tumor Neoantigen-specific T-cell Receptors Using the *Sleeping Beauty* Transposon/Transposase System

Drew C Deniger[1], Anna Pasetto[1], Eric Tran[1], Maria R Parkhurst[1], Cyrille J Cohen[2], Paul F Robbins[1], Laurence JN Cooper[3,4] and Steven A Rosenberg[1]

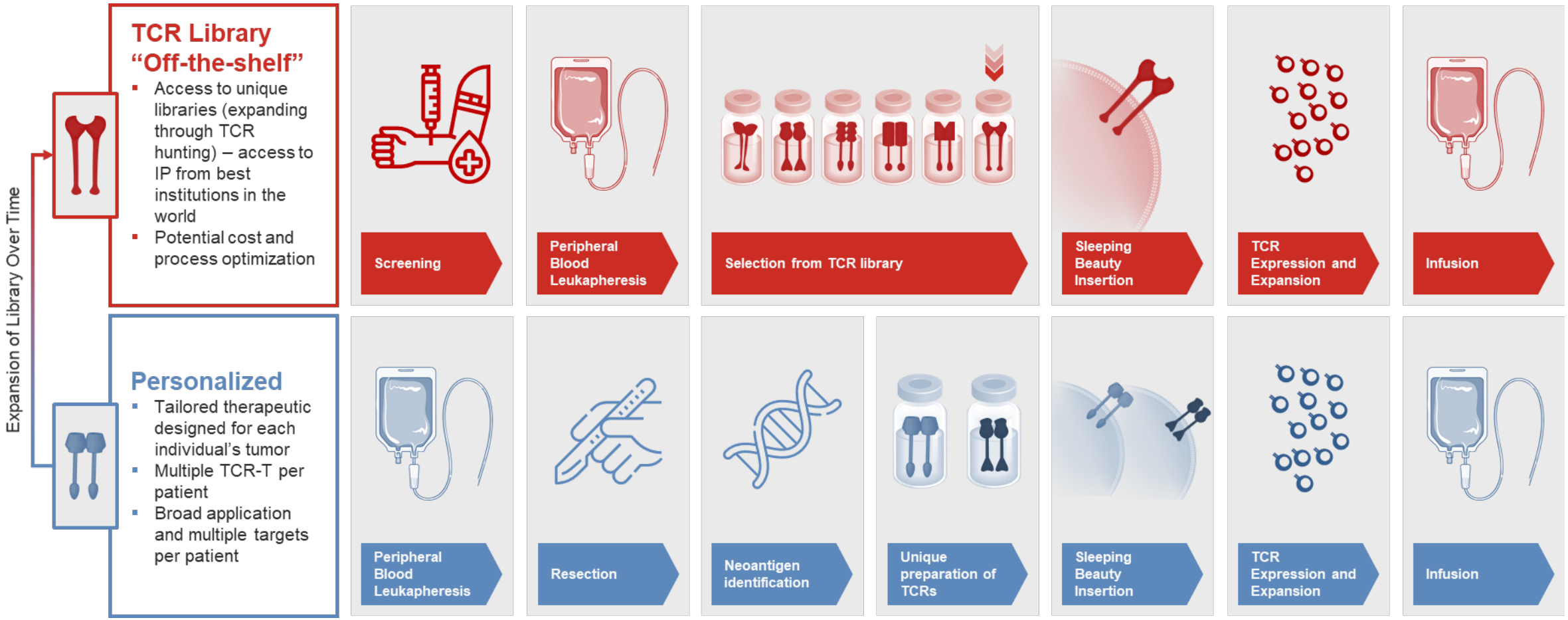
[1]*Surgery Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA;* [2]*Tumor Immunology and Immunotherapy, Bar-Ilan University, Ramat Gan, Israel;* [3]*Division of Pediatrics, University of Texas M.D. Anderson Cancer Center, Houston, Texas, USA;* [4]*ZIOPHARM Oncology, Inc., Boston, Massachusetts, USA*

Deniger DC et al. Mol Ther. 2016 Jun;24(6):1078-1089.



Ziopharm ONCOLOGY

# Two cutting-edge Ziopharm programs for TCR-T cell therapy in the treatment of epithelial cancers






Ziopharm ONCOLOGY

# Ziopharm personalized TCR-T cell therapy as a revolutionary platform to bring effective immunotherapy to all cancer patients

- We have an open IND at NCI (PI: Steven A. Rosenberg) evaluating personalized TCR-T cell therapy targeting neoantigens in common epithelial malignancies.

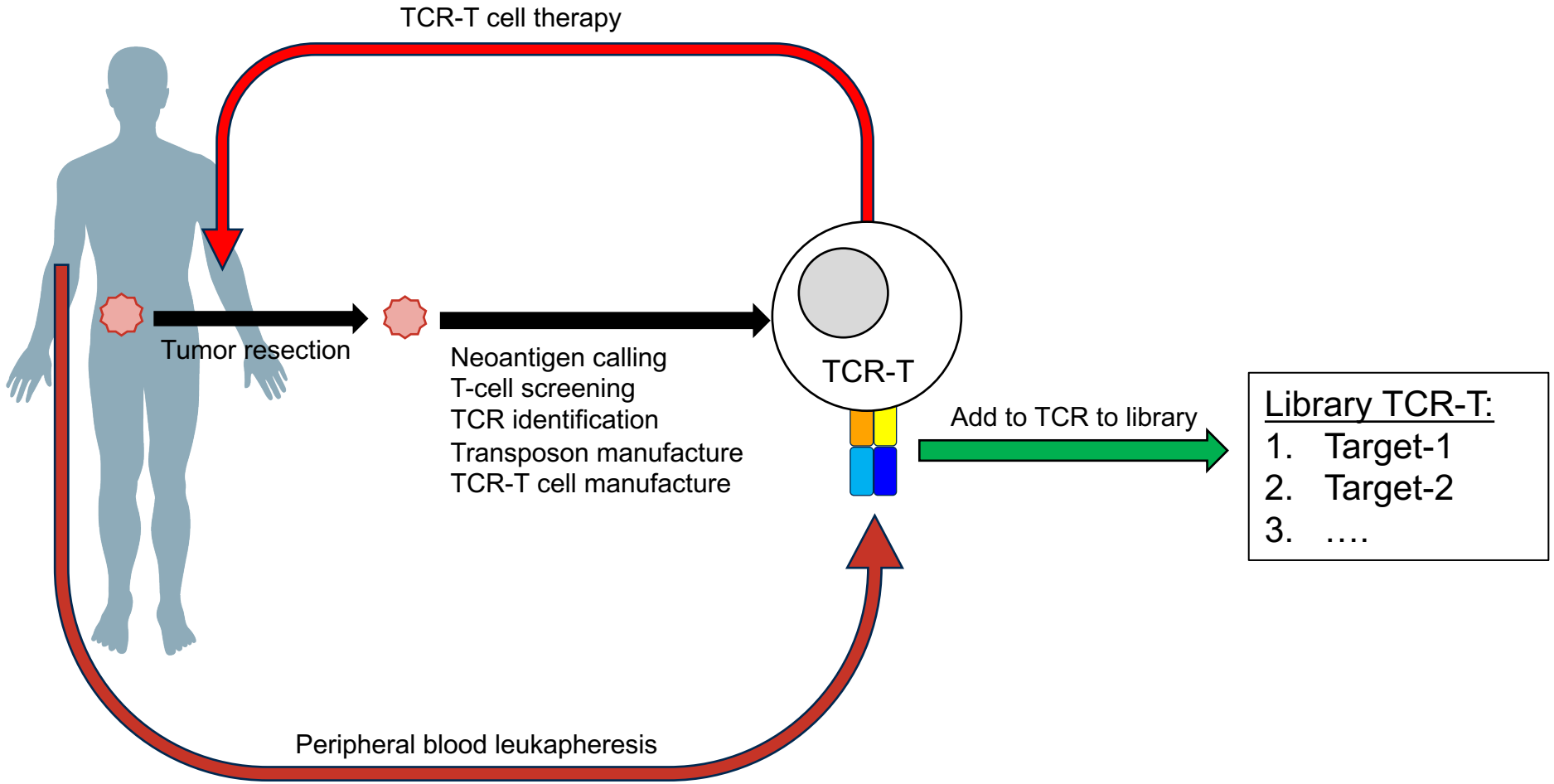
- The Ziopharm internal program is being developed in-house for commercial success, building upon the NCI platform.

- We have an active research protocol at MD Anderson Cancer Center to acquire patient samples for this program, which may feed into the clinical program as it comes online.



Ziopharm ONCOLOGY

# Ziopharm's personalized TCR-T cell program enables effective customized treatment for individual patients






Ziopharm ONCOLOGY

# Current status of Ziopharm's library TCR-T cell program

- Six TCRs representing unique "hotspot" neoantigen specificities have been cleared for clinical use and were prioritized based on ability to accrue patients by target frequency and quality of the TCR.

- Additional library TCRs in our portfolio are being vetted and will be added to the clinical pipeline following validation. More TCRs will be added over time.

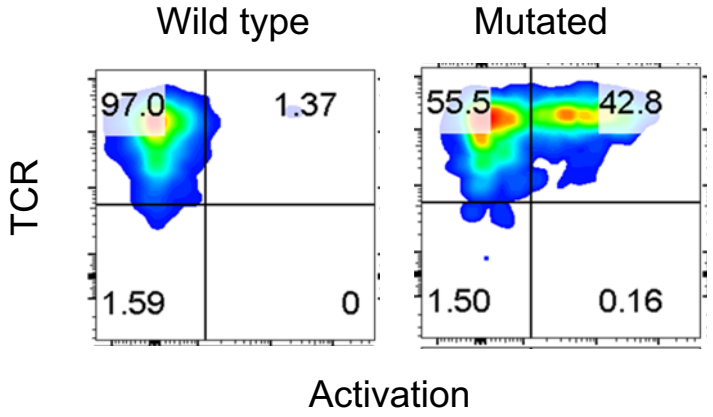
- A phase I/II clinical trial was given safe-to-proceed from the FDA to use library TCR-T cell therapy at MD Anderson Cancer Center for the treatment of common epithelial cancers (bile duct, colon, lung, ovary, pancreas).

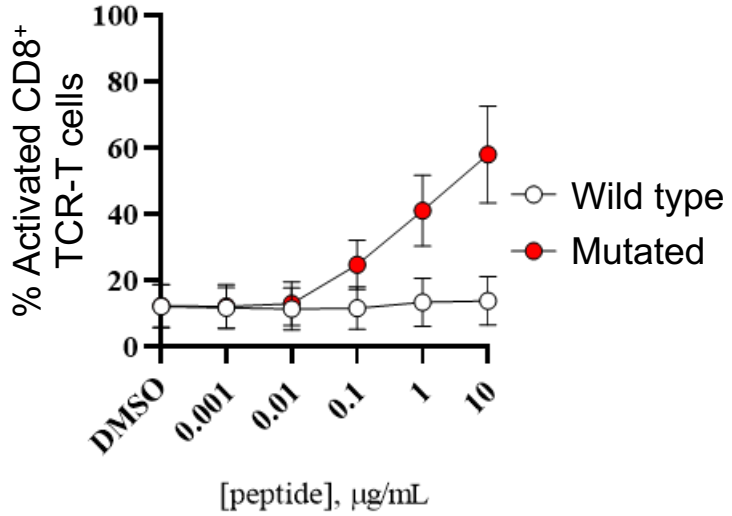
**Ziopharm is the first and currently only commercial group evaluating library TCR-T cells targeting shared "hotspot" neoantigens.**

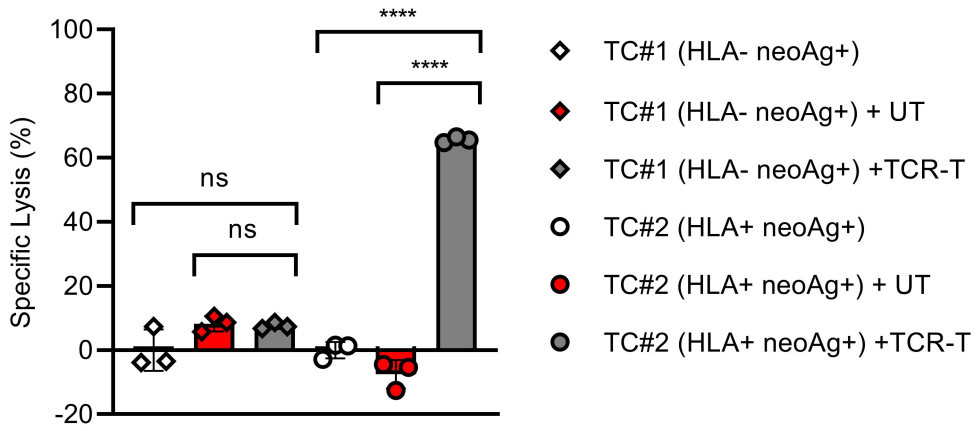


Ziopharm ONCOLOGY

# Ziopharm's *Sleeping Beauty* library TCR-T cells were neoantigen-specific and led to tumor cell lysis






Ziopharm ONCOLOGY

# Conclusions

- Neoantigens are the blueprint and “Achilles heel” for effective targeting of all cancers.
- TCR-T cell therapy is the answer to targeting neoantigens, which will require a rapid, flexible, cost-effective gene transfer platform, of which *Sleeping Beauty* transposition is the most advanced and commercially appealing.
- Ziopharm is the world leader of *Sleeping Beauty*-transposed TCR-T cell therapy and is positioned for clinical and commercial success treating solid tumors.



Ziopharm ONCOLOGY

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# Q&A