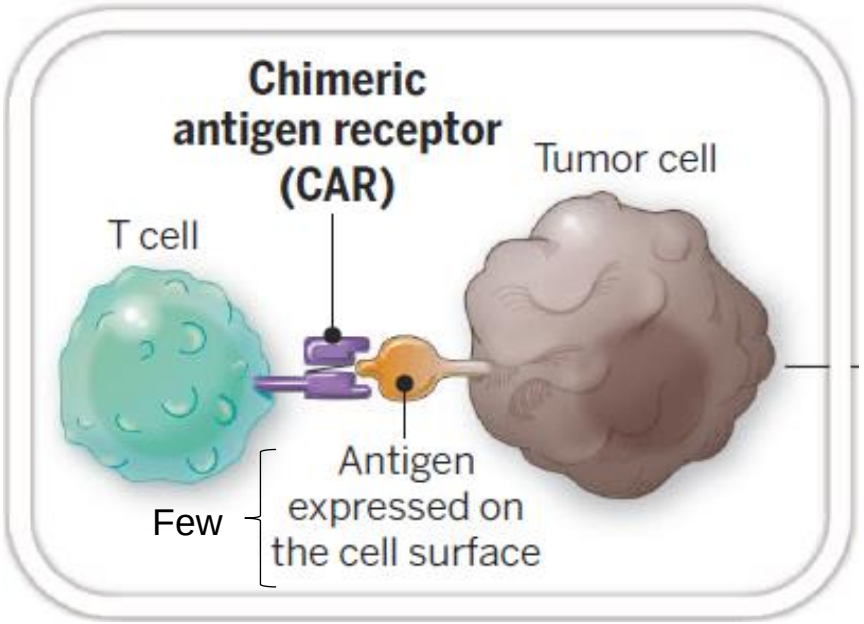
DNA Plasmids for the Genetic Engineering of Clinical-Grade T cells

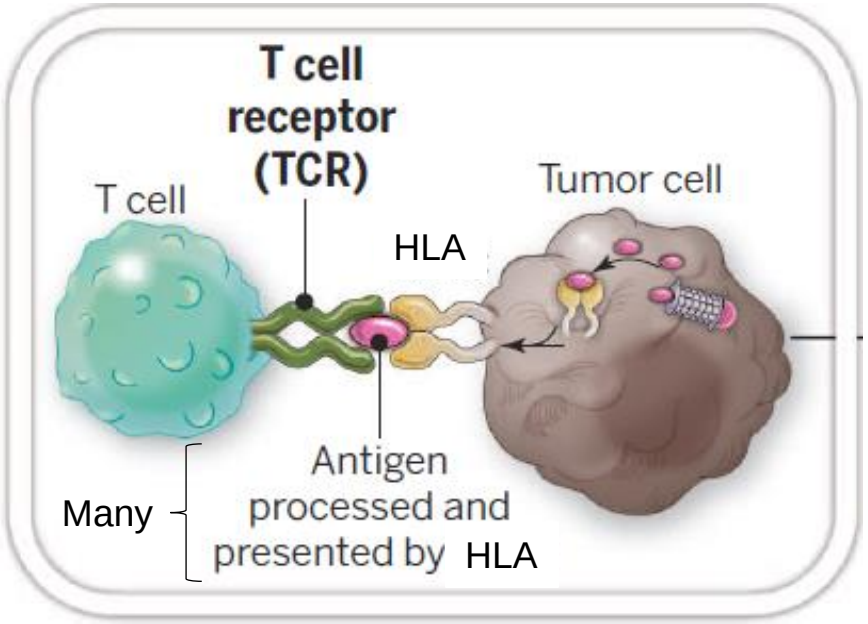
Laurence Cooper on behalf of Ziopharm Oncology
Aldevron Breakthrough Symposium

Forward Looking Statements

This presentation contains 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 our business and strategic plans, the availability of cash resources, the progress and timing of our research and development programs, including the anticipated dates for the FDA clearance, initiation, patient dosing and data readouts of our clinical trials, the potential market and treatment opportunity of our products, expectations regarding partnership opportunities for our programs and the number of patients in our clinical trials. 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 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.

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

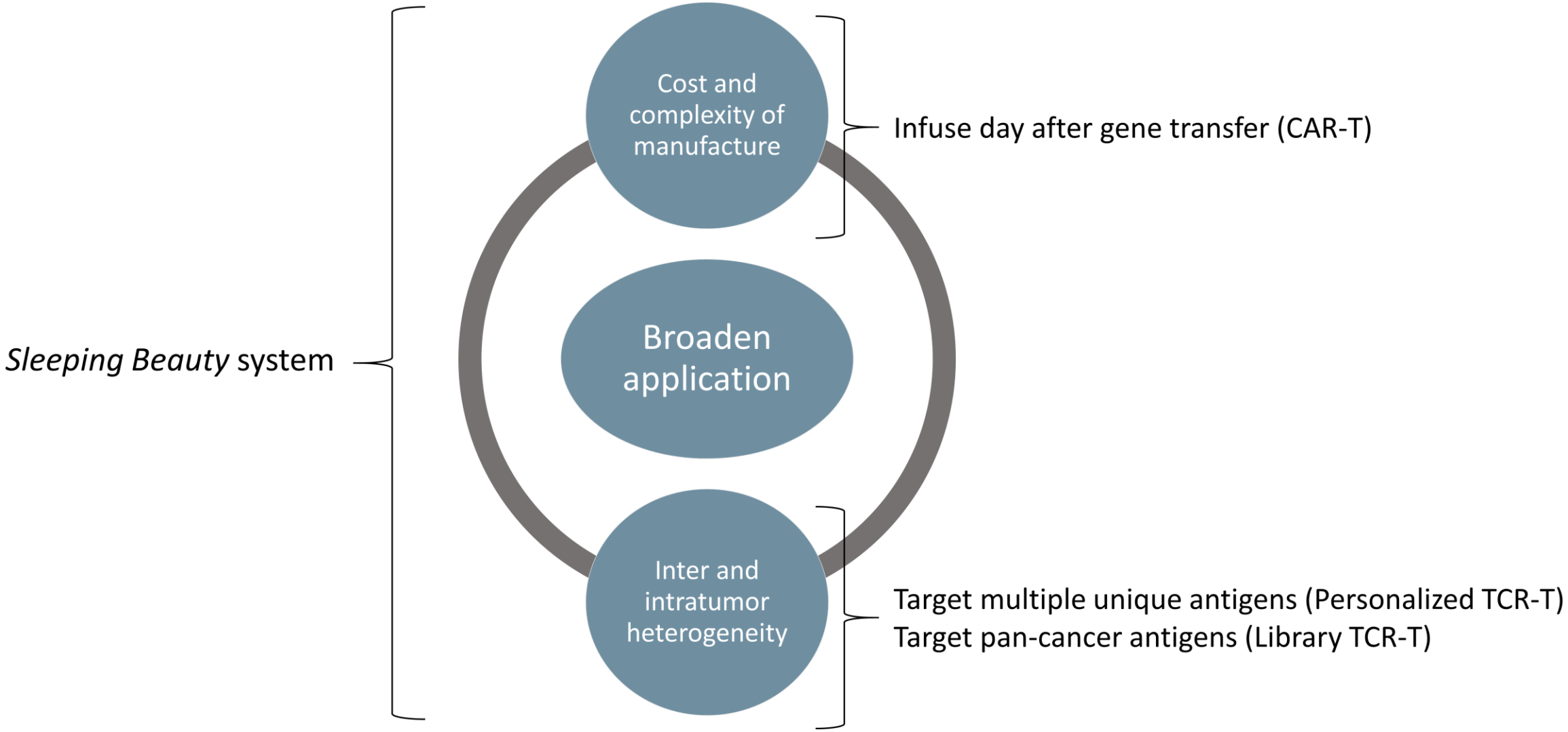




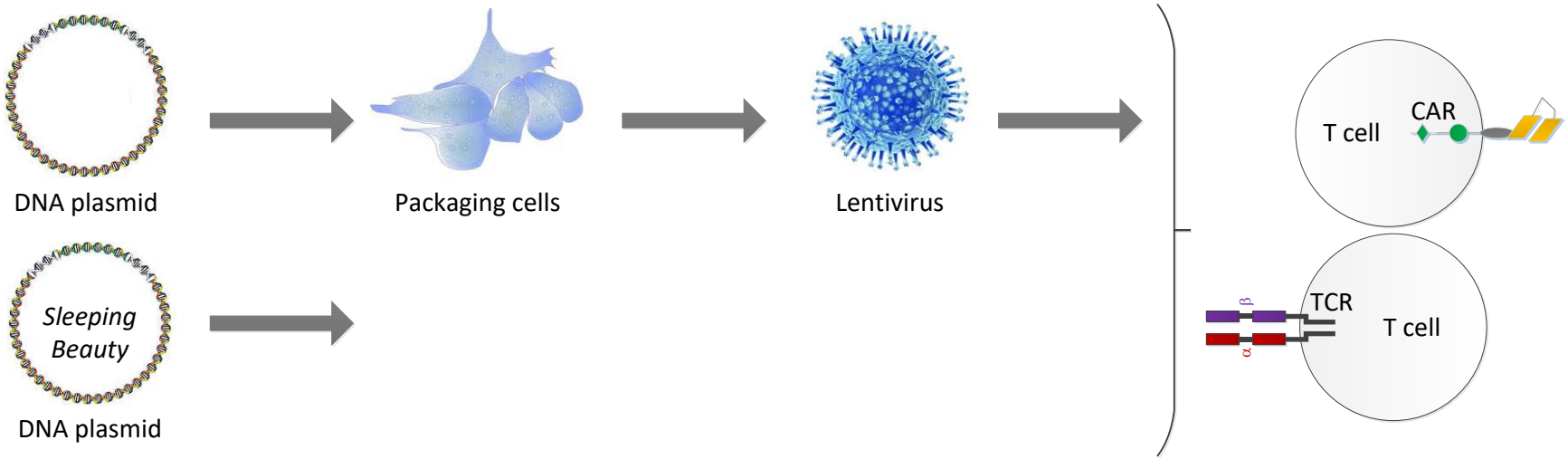
Rosenberg SA and Restifo NP. Science. 2015 Apr 3;348(6230):62-8.

Ziopharm ONCOLOGY

Addressing the Major Problems of Genetically Modified T Cells for Cancer



Non-Viral Gene Transfer Using *Sleeping Beauty*

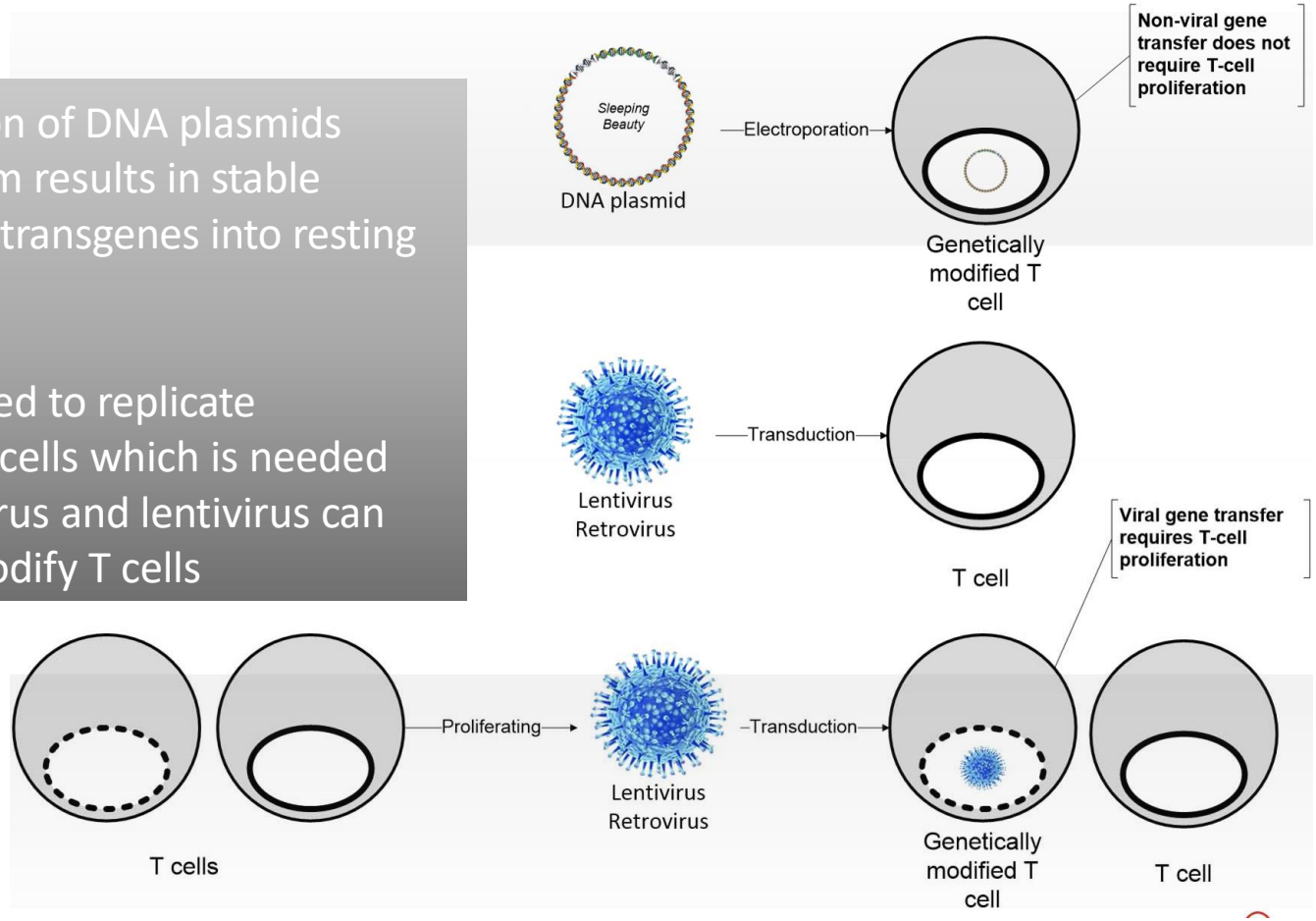


Non-viral gene transfer: *Sleeping Beauty*	Viral gene transfer: Retrovirus & Lentivirus
Cost effective	High cost
Rapid production	Labor intensive and slow production
Customizable (rapid exchange of immunoreceptors)	Challenging to customize
Target solid tumor intracellular neoantigens via multiple TCRs	Limited appeal for targeting multiple intracellular antigens via TCRs

SB allows genetic modification of quiescent T cells

Electroporation of DNA plasmids from SB system results in stable integration of transgenes into resting T cells

Avoids the need to replicate (propagate) T cells which is needed before retrovirus and lentivirus can genetically modify T cells



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]

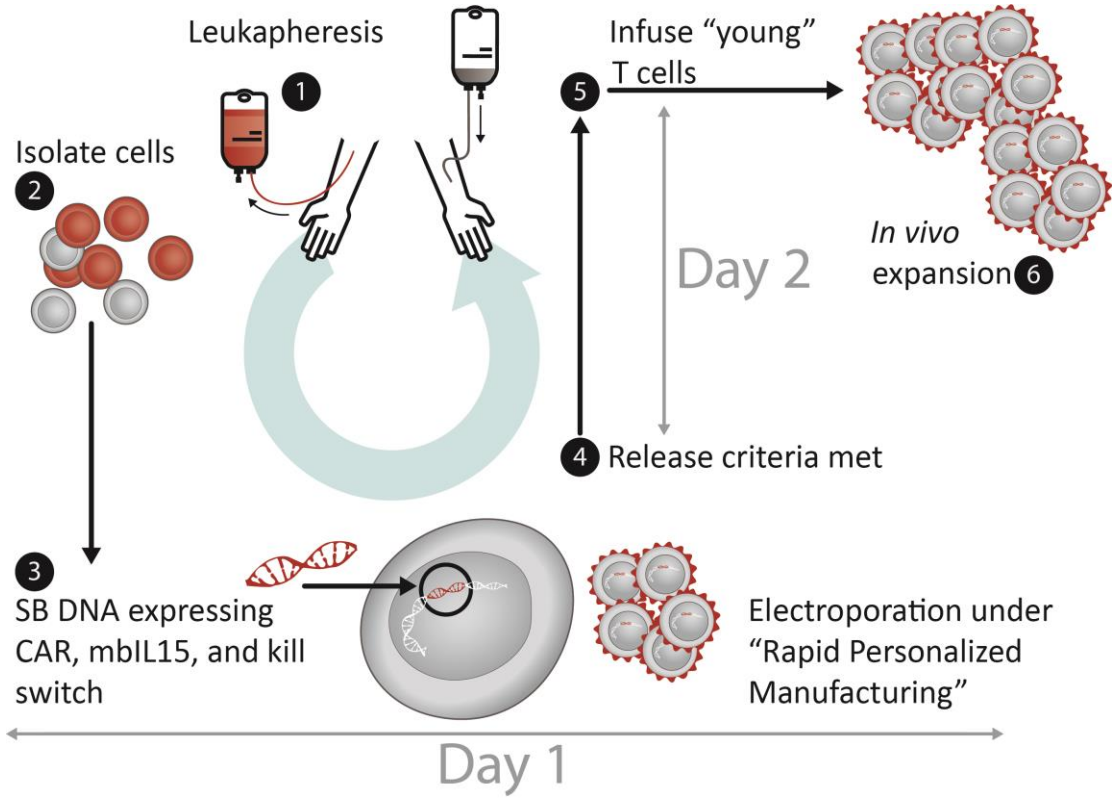
[1]Surgery Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA; [2]Tumor Immunology and Immunotherapy, Bar-Ilan University, Ramat Gan, Israel; [3]Division of Pediatrics, University of Texas M.D. Anderson Cancer Center, Houston, Texas,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

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

CAR-T Innovation: Rapid Personalized Manufacturing (RPM)

Treatment underway in Asia

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

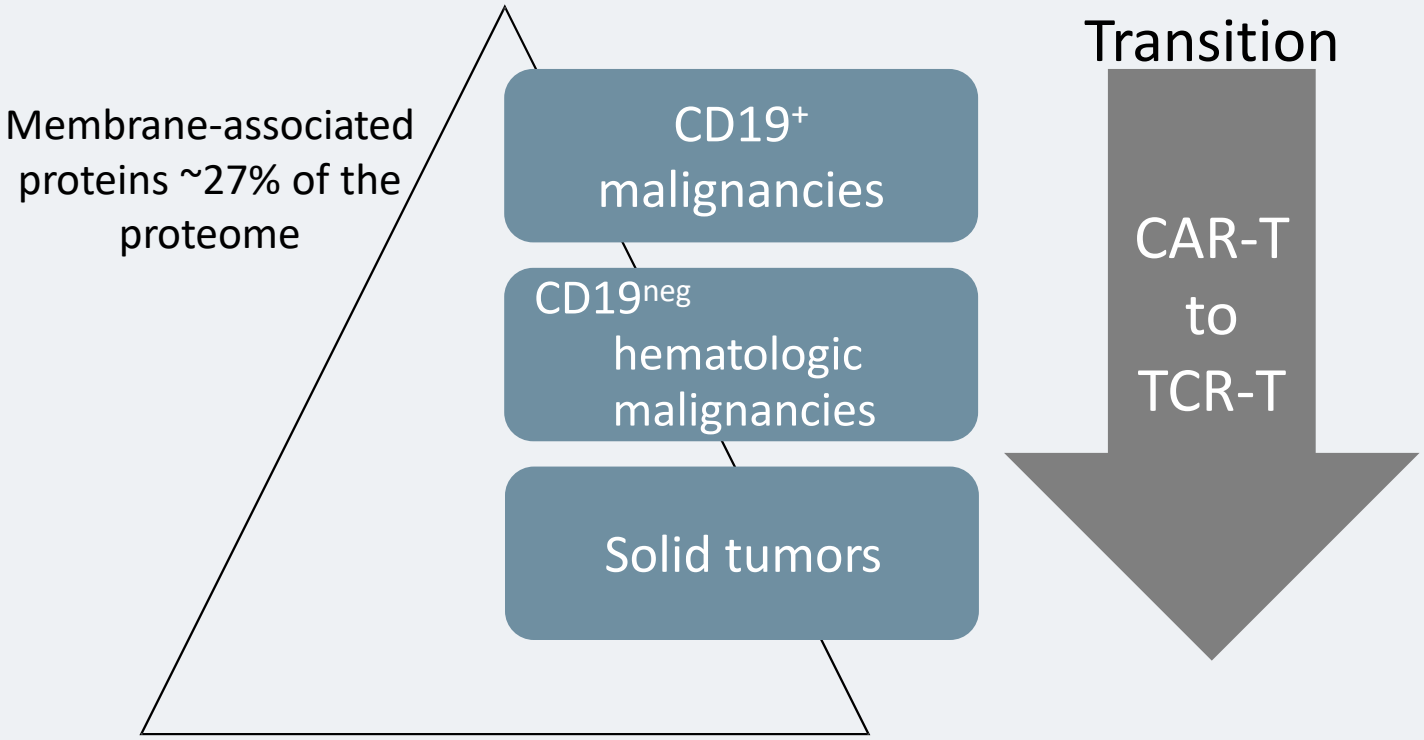
T-cell Immunotherapy for Cancer

1.7M
New cancer cases in the U.S.[1]

1.5M+
solid tumors[1]

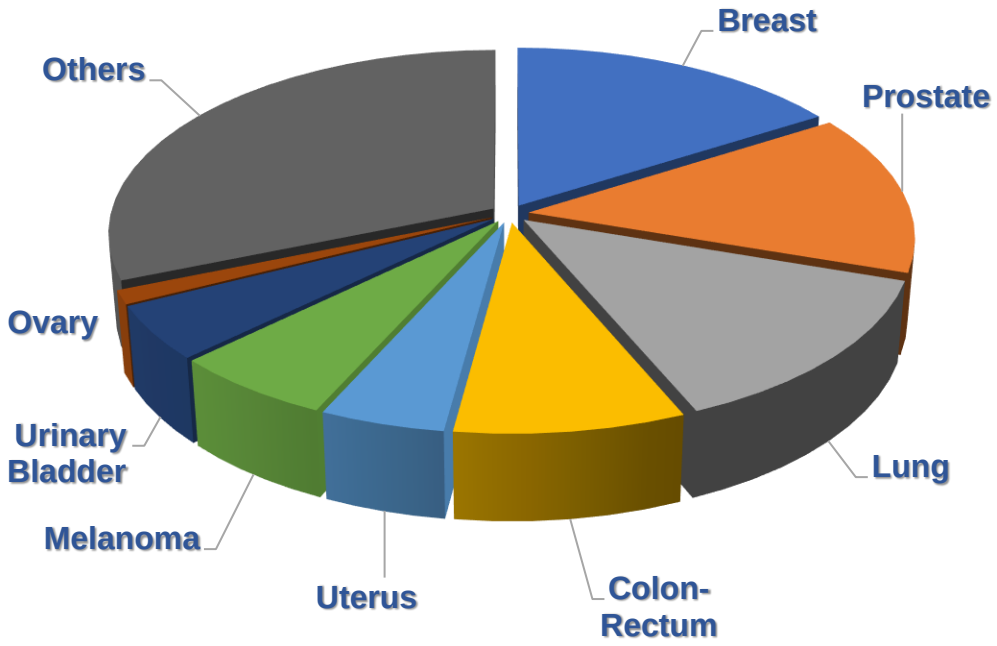
174,250
blood cancers[1]

1. 2018, Int'l Agency on Research for Cancer, *Cancer Facts & Figures*, 2018, American Cancer Society



Immunol Rev. 2019 Jul;290(1):127-147

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

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

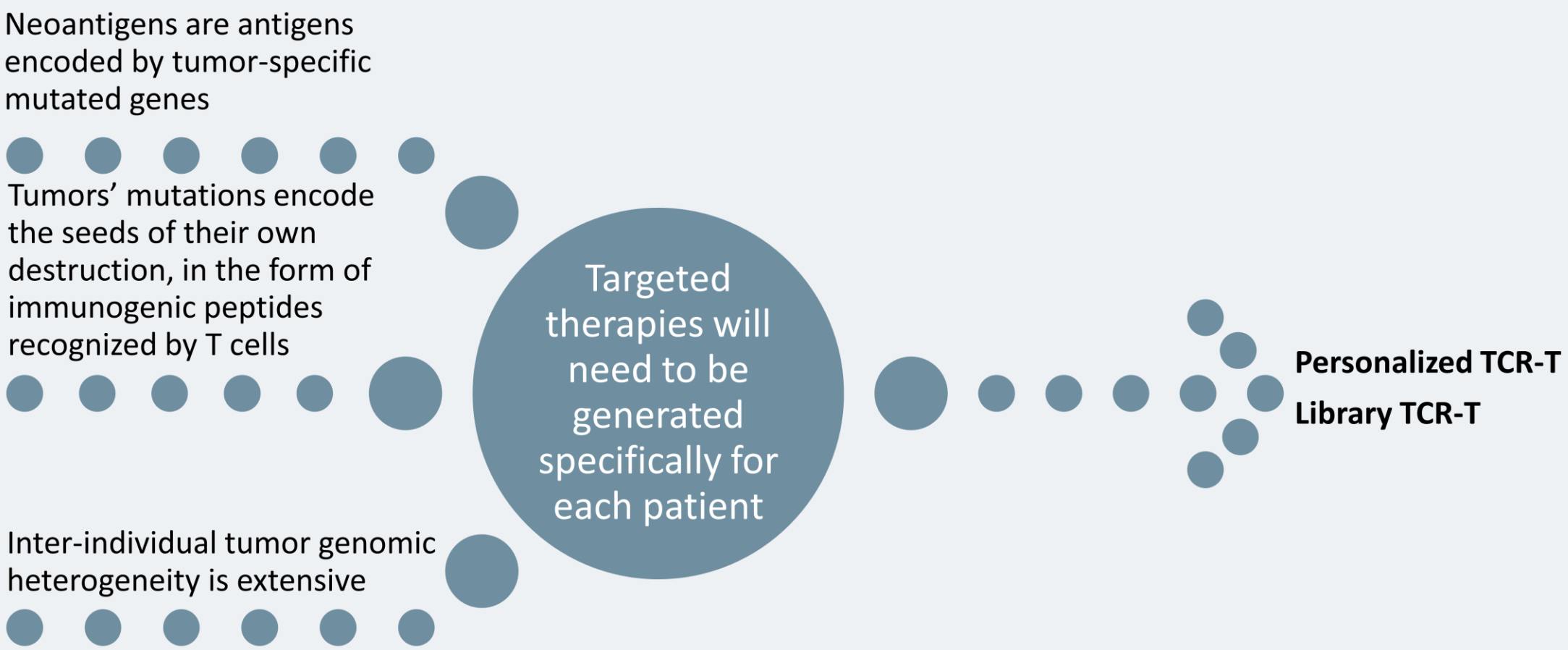
Somatic Mutations are the Blueprint for Pan-cancer Therapy

- 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

Targeting Neoantigens – the Achilles' Heel of Cancer



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

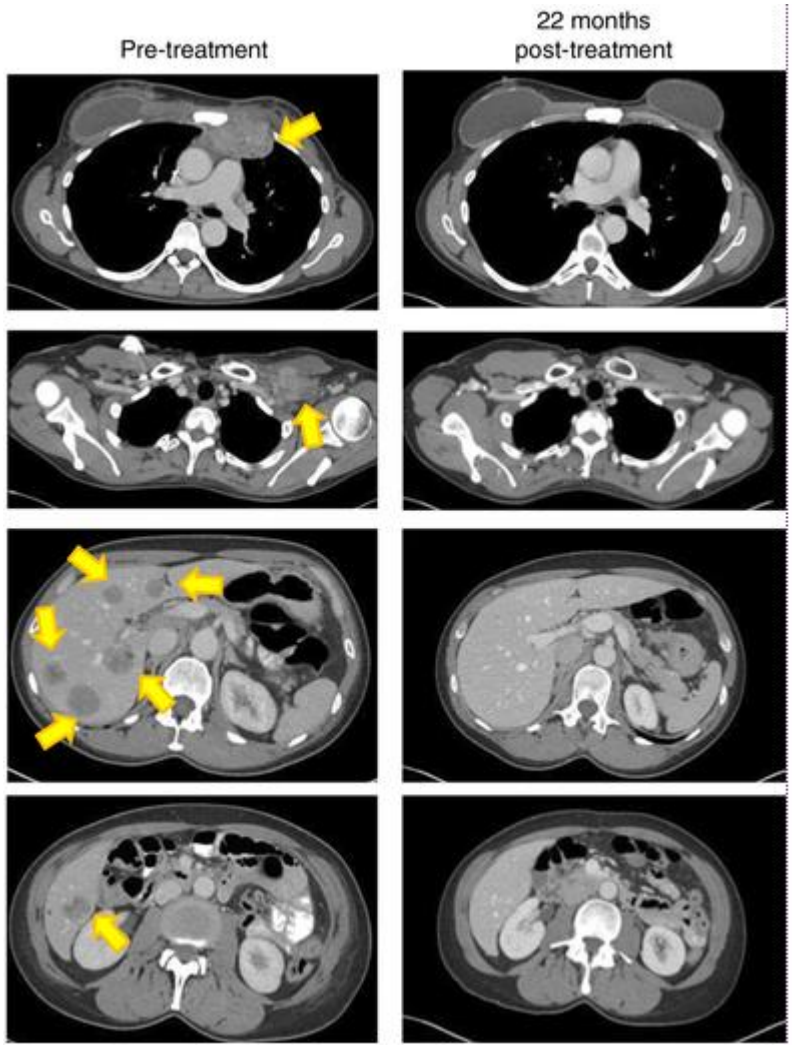
Letter | Published: 04 June 2018

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



Clinical Application of neoantigen-specific TCR-T cell Therapy

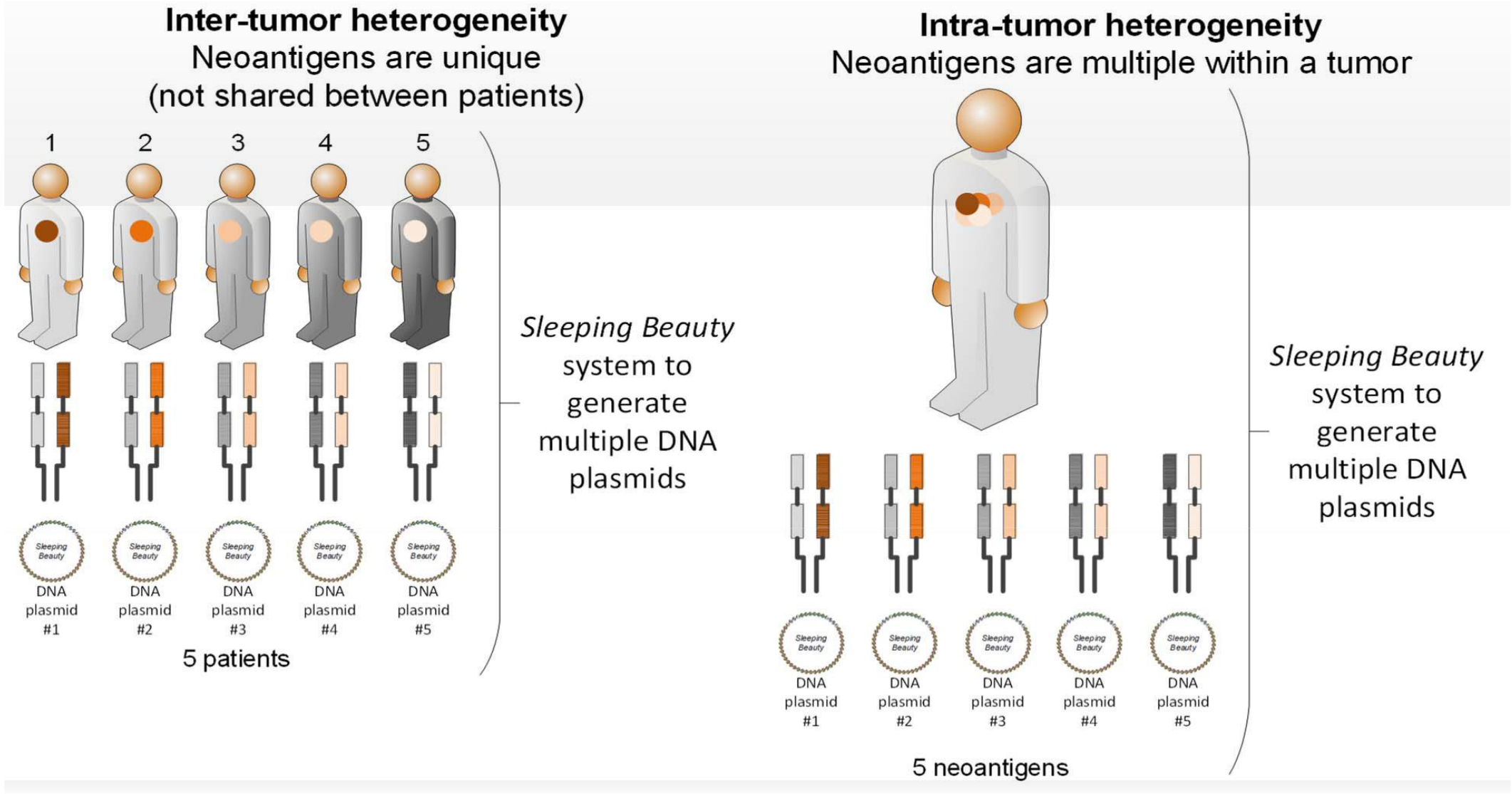
- Prior TCR-T cell therapy established that metastatic cancers can be effectively treated in some patients when targeting non-neoantigen targets, but the application was limited by target expression and cancer type.

- 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.

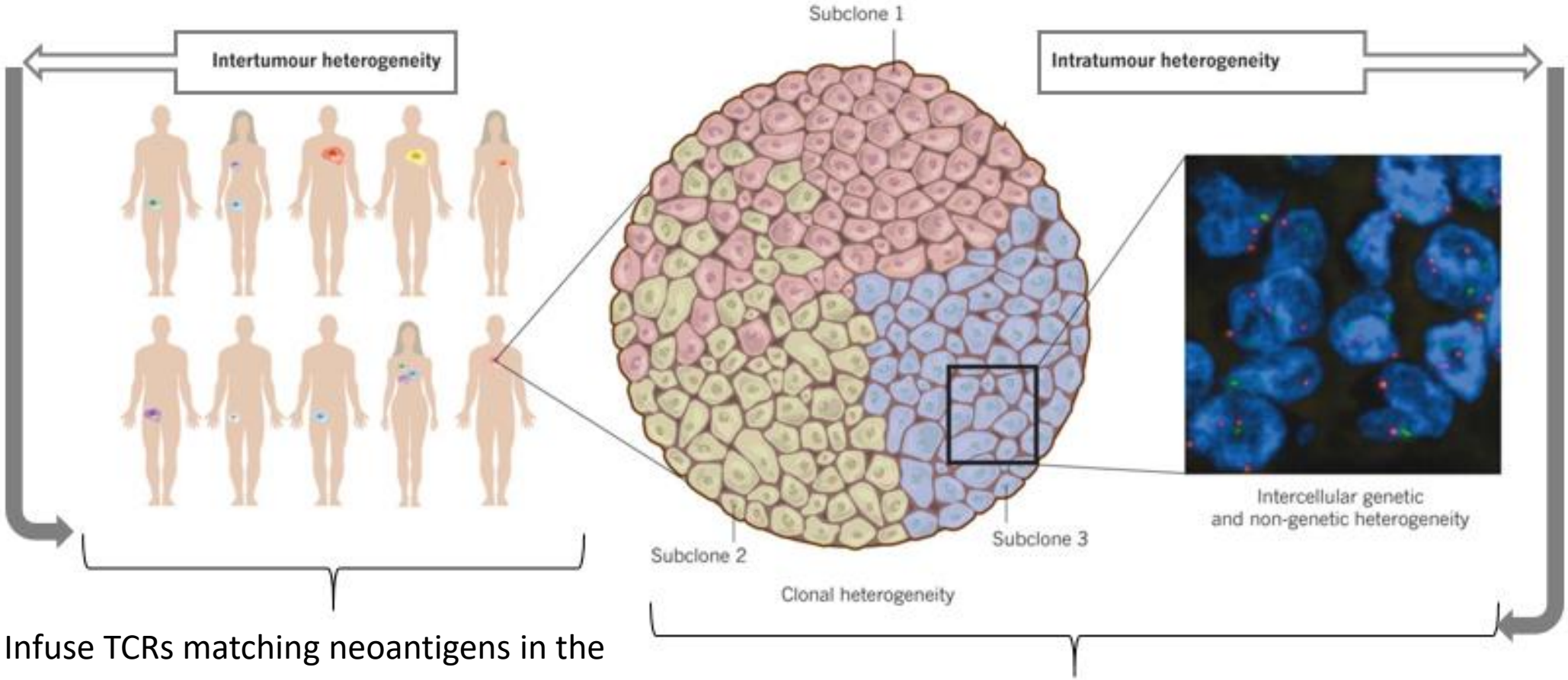
- The ability to translate a library or personalized neoantigen-specific TCR-T cell approach is complex and will likely require a rapid, mobile and cost-effective solution.

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-Modified T Cells to Overcome Heterogeneity



Successful T-cell Therapy Must Addressing Heterogeneity



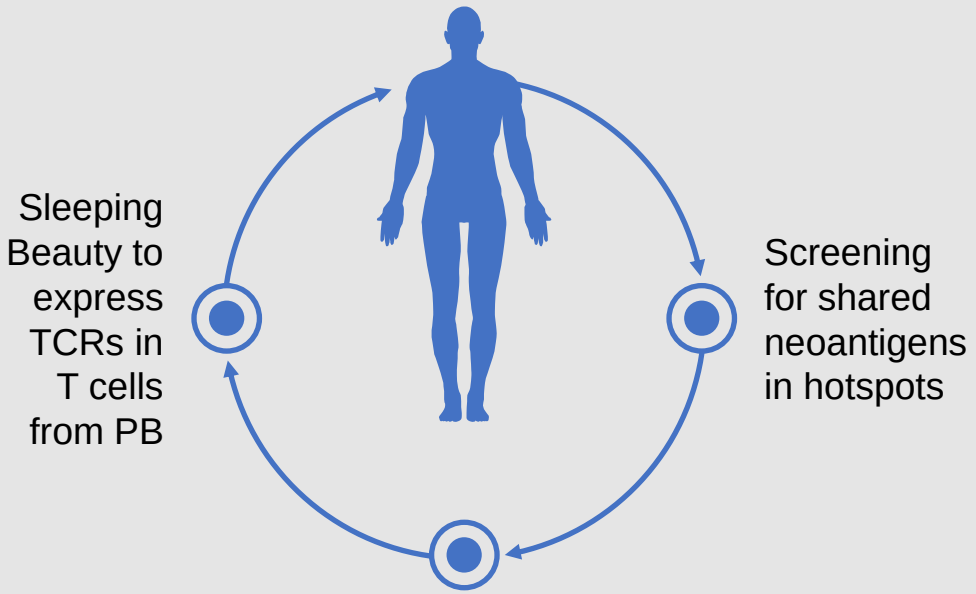
- Infuse TCRs matching neoantigens in the tumor
- Most TCRs are unique; “from and for the patient” (autologous TCRs)
- Some TCRs are shared (allogeneic TCRs)

- Infuse suite of TCR-T with multiple TCRs matching multiple neoantigens
- Infuse TCR-T with TCR against clonal neoantigens

Nature. 2013 Sep 19;501(7467):338-45

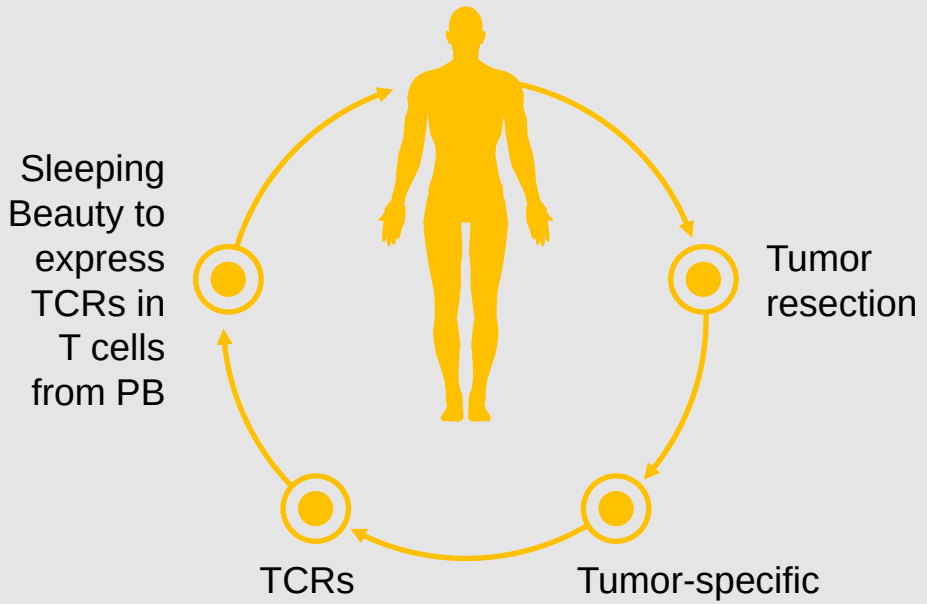
Two Options To Treat All Patients With A Solid Tumor

Library TCR-T Process



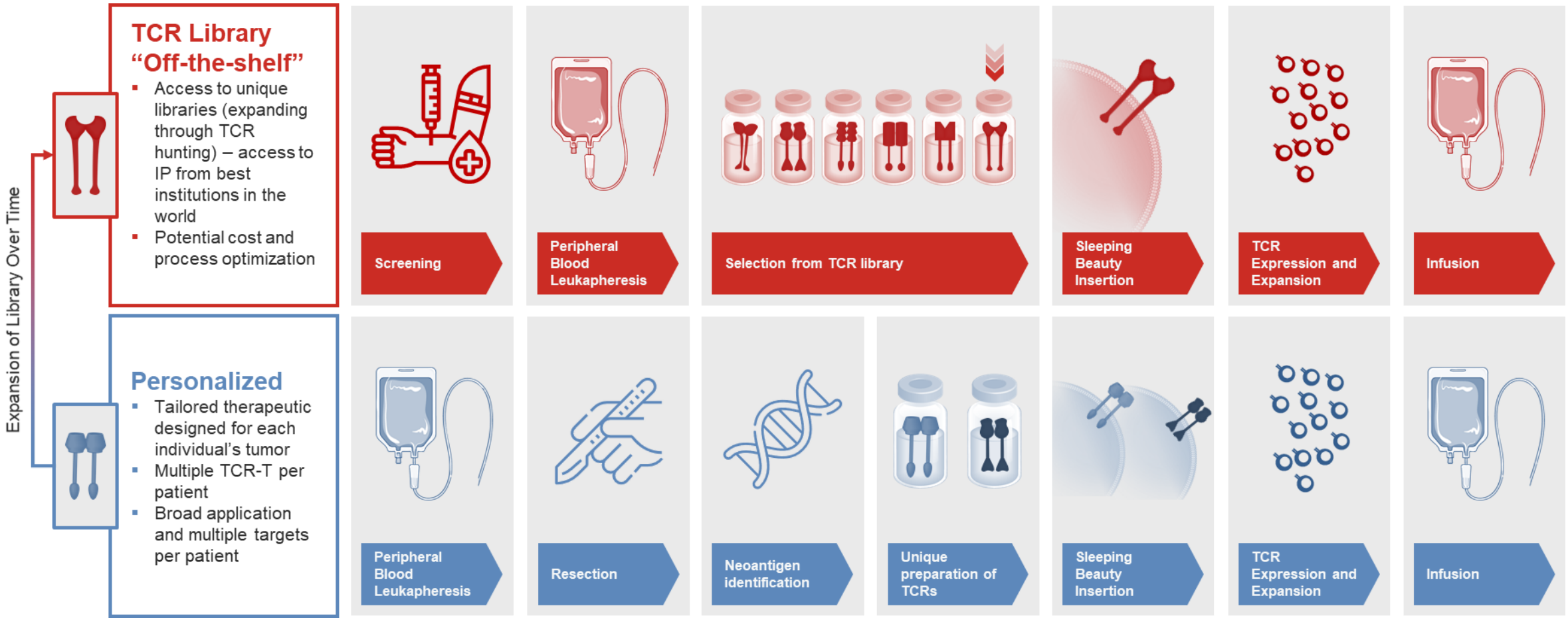
Active Ziopharm IND for phase 1/2 trial (Autologous T-cells)

Personalized TCR-T Process

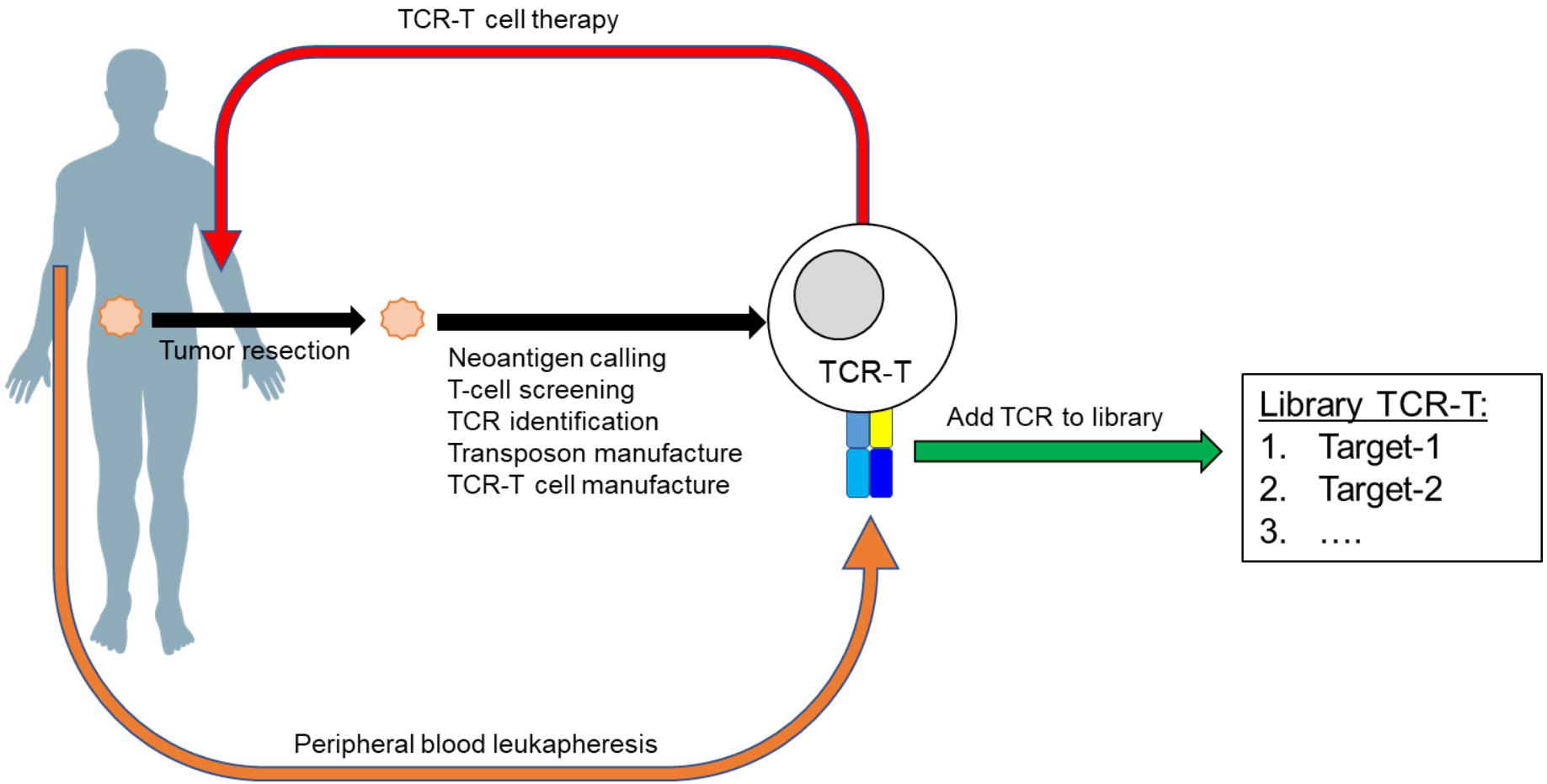


NCI phase 2 trial (Autologous T-cells)

Two TCR-T Cell Therapies for Treatment of Epithelial Cancers



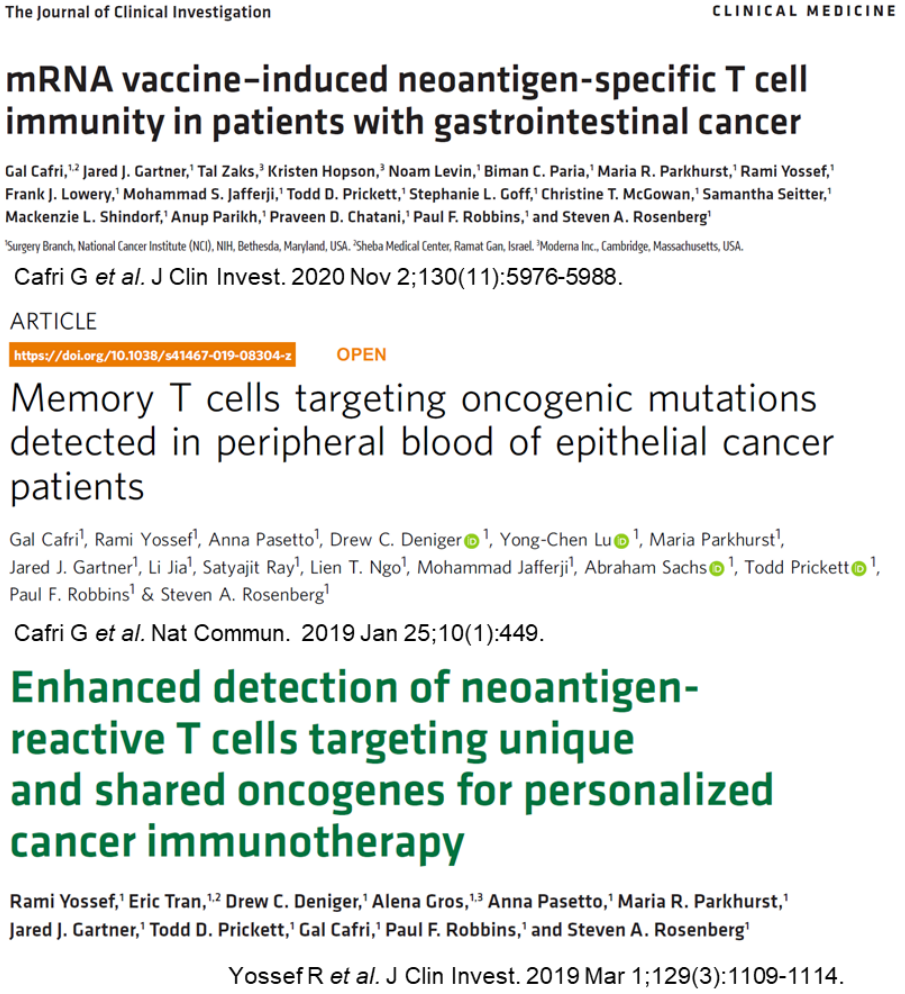
Personalized TCR-T Cell Program Enables Effective Customized Treatments for Many Individual Patients



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

Library TCR-T Cell Program Facilitates Treatments for Subset of Patients

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]

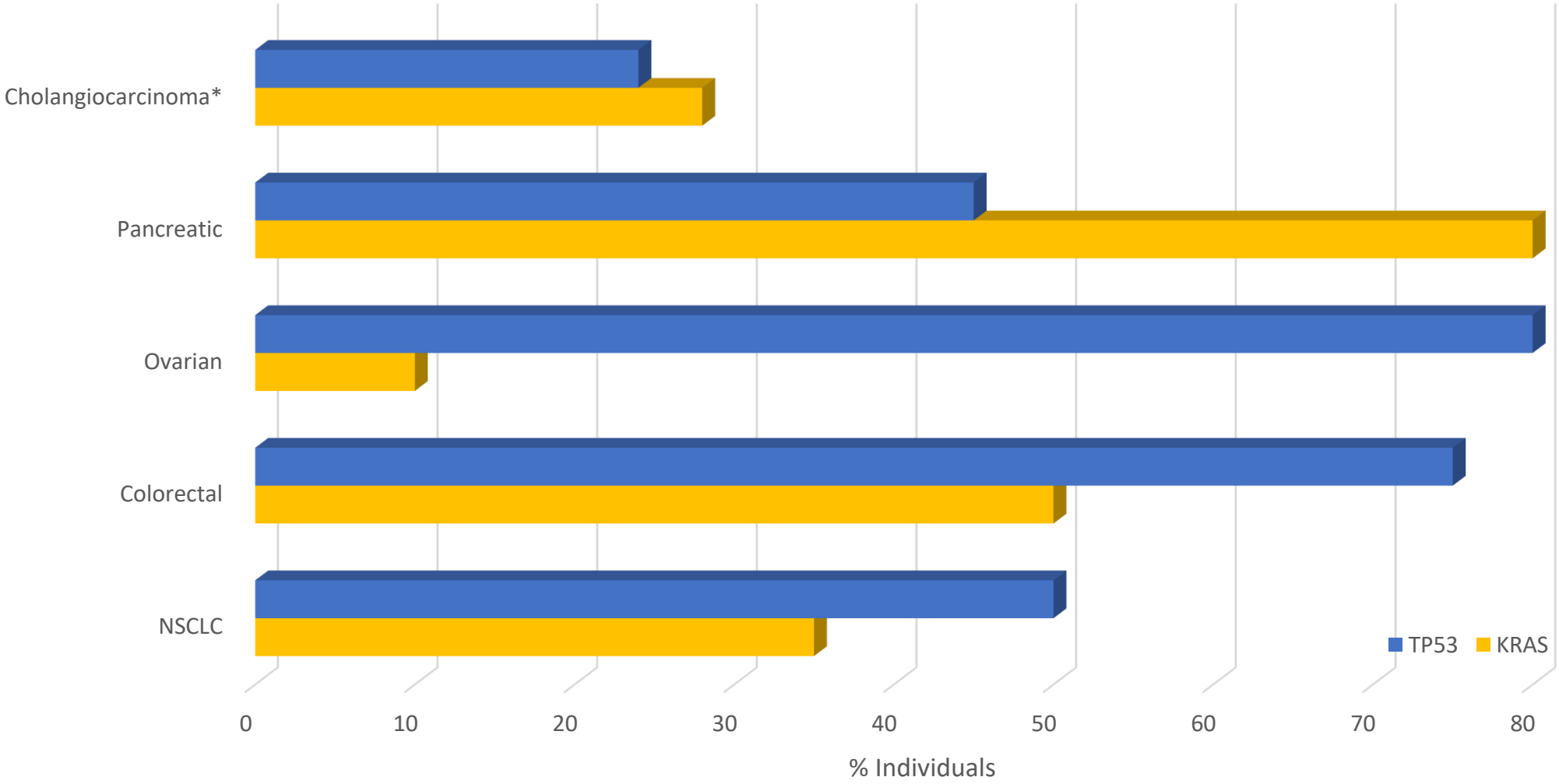
Lo W *et al.* Cancer Immunol Res. 2019 Apr;7(4):534-543.

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]

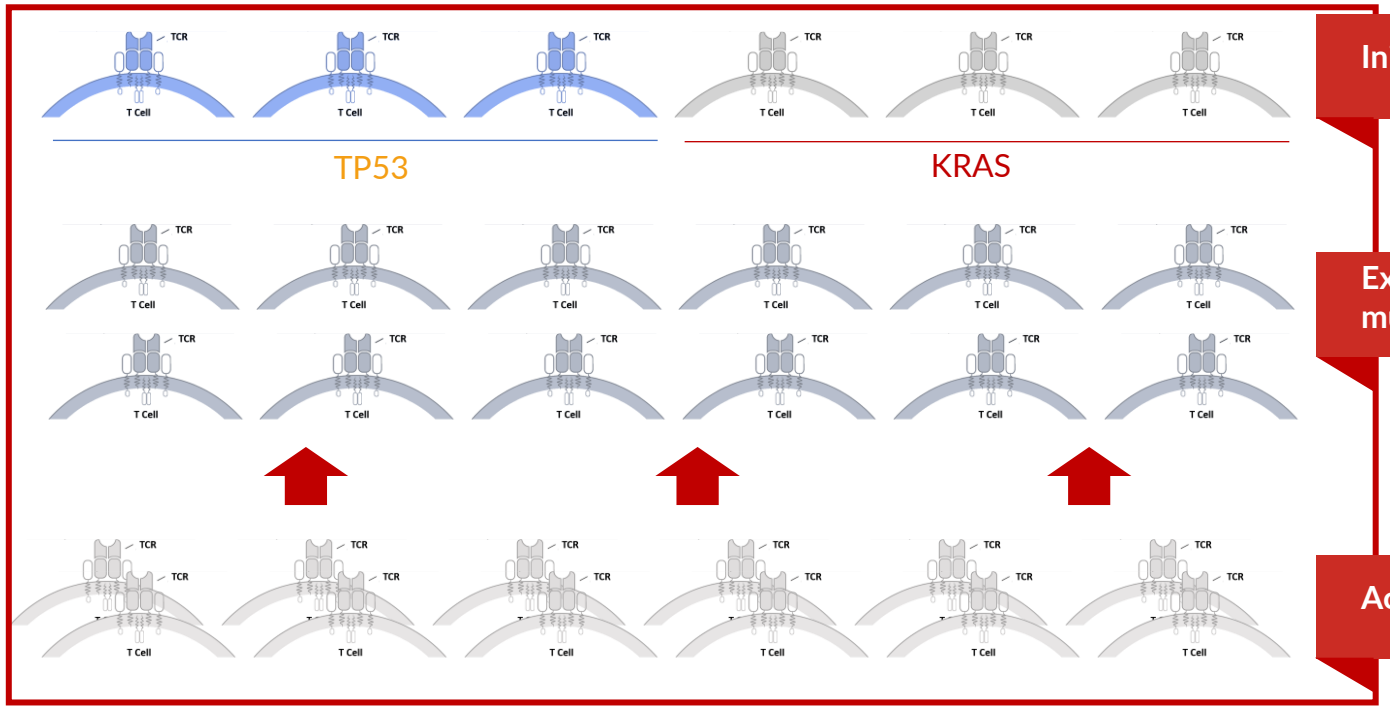
Malekzadeh P *et al.* Clin Cancer Res. 2020 Mar 15;26(6):1267-1276.

KRAS and *TP53* are Most Commonly Mutated Genes in Epithelial Cancers



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

Library TCR-T Can Potentially Address Need Across Broad Range of Solid Tumors



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*)

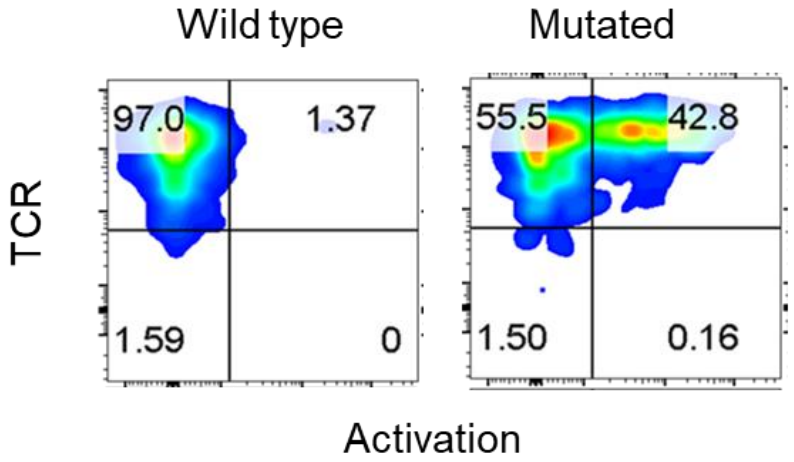
- **Covers ~5-6% of epithelial cancers***
- **Translates to ~85-100K new potential patients annually in US (based on incidence of 1.7M per year)**
- **Potential** to bring on additional TCRs through one or more IND amendments

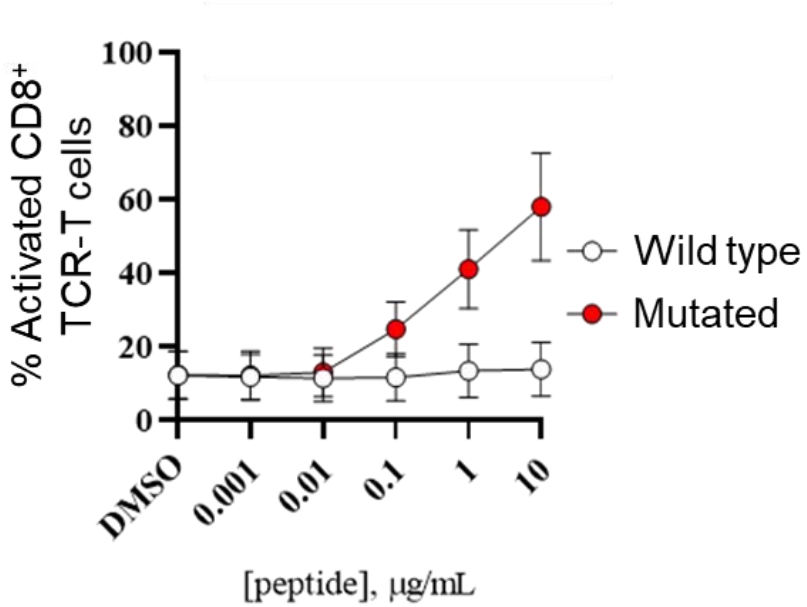
Active Research and Partnerships to Grow TCR Library

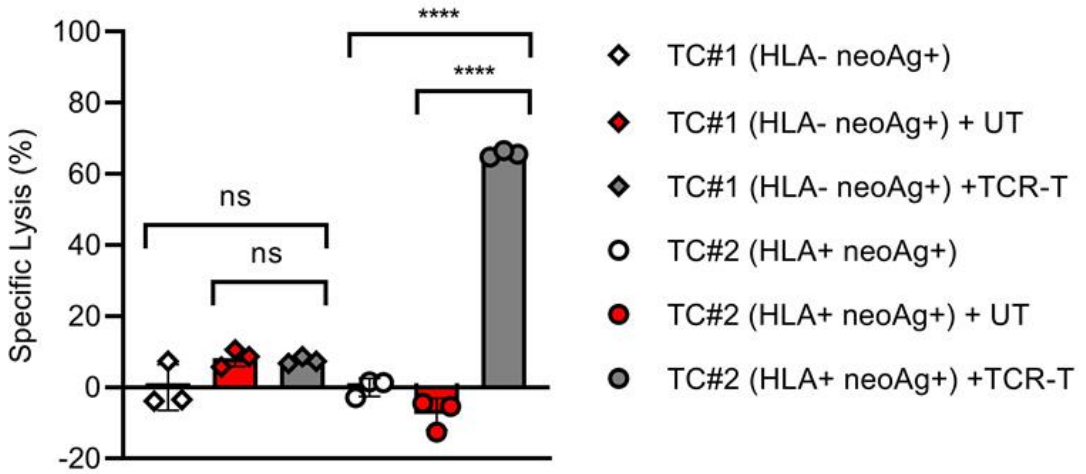
Expanding Off-the-Shelf TCR Library – Q1 2021 IND Cleared

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

Ziopharm's *Sleeping Beauty* Library TCR-T Cells Were Neoantigen-Specific and Led to Tumor Cell Lysis



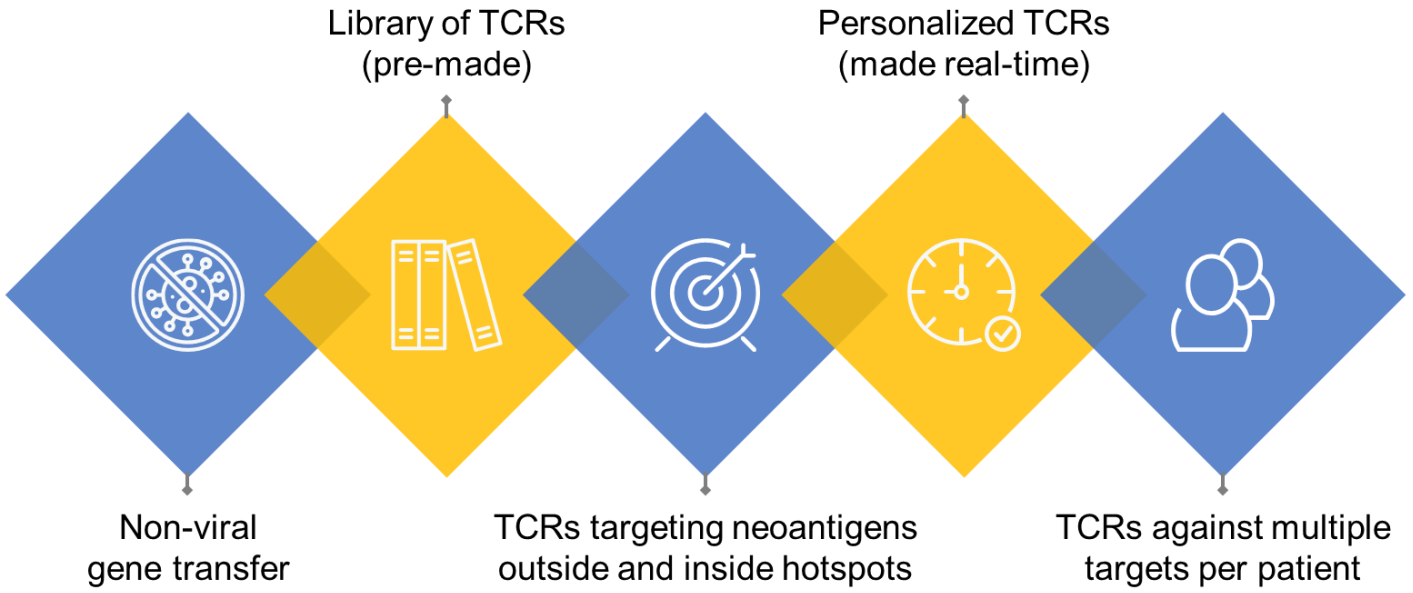




TCR-T for Solid Tumors

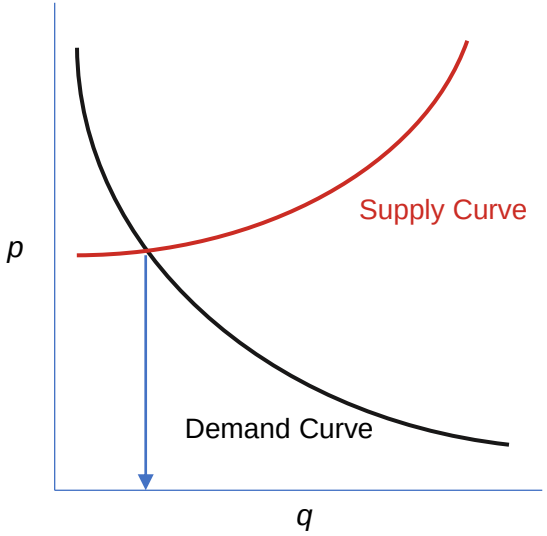
Ziopharm's complementary and unique suite of technologies

- 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.
- Expect to treat patients with common epithelial cancers that we estimate kill over 100,000 Americans every year.



Scientific Innovation Drives Economics Along Demand Curve

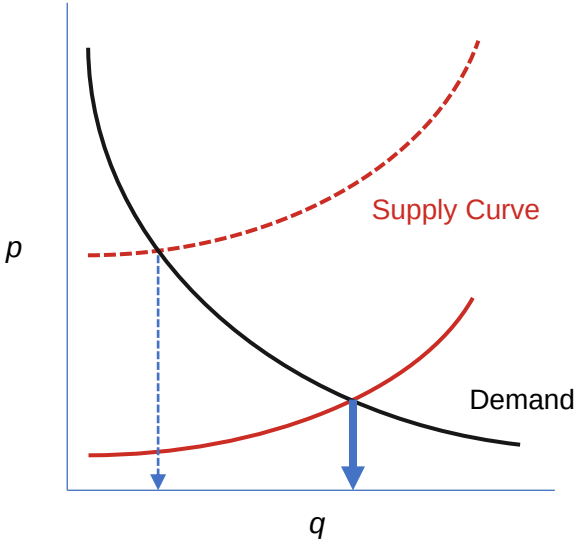
Small, unprofitable market driven by high costs, requiring companies to charge high prices, limiting access



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***

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

Summary: *Sleeping Beauty* System for TCR-T

- *Sleeping Beauty* system provides scale to express multiple TCRs targeting neoantigens and address inter-tumor and intra-tumor heterogeneity of neoantigens
- Trial to start at NCI targeting metastatic epithelial cancers with Personalized TCR-T
- Trial to start at MD Anderson targeting metastatic epithelial cancers with Library TCR-T