Jefferies 2019 Global Healthcare Conference

June 6, 2019

Forward Looking Statement

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Ziopharm Today…

Ziopharm Oncology is an **independent** immuno-oncology company focused on developing end-to-end cost-effective solutions using its **non-viral *Sleeping Beauty*** platform for TCR and CAR T-cell therapies and immune-stimulating gene therapy with Controlled interleukin 12 (IL-12)

Investment Highlights

- Clinical stage immuno-oncology company developing next generation cell and gene therapies
- *Sleeping Beauty* is the most-clinically advanced non-viral gene transfer technology
- Controlled IL-12 addresses solid tumors where target is unknown; Treated more than 160 patients across the two platforms
- All three programs in the clinic this year, with trials at NCI and MD Anderson Cancer Center
- Building on momentum established by new agreement for independence; restructured team, BOD, debt-free

Strong clinical partnerships

National Cancer Institute & Steven Rosenberg	REGENERON
Infusing TCR-T cells targeting solid tumor neoantigens with ***Sleeping Beauty*** technology	**Advancing Controlled IL-12** in combination with Libtayo for recurrent GBM
MD Anderson Cancer Center	Eden BioCell
Deploying ***Sleeping Beauty*** CD19-specific CAR-T for rapid personal manufacturing; expansion of activities underway	Expanding ***Sleeping Beauty*** CD19-specific CAR-T for rapid personal manufacturing into Greater China

Cancer Immunotherapy: Huge Market, but Major Issues Remain

1.7M

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

1.5M+ **solid tumors**[1]

174,250 **blood cancers**[1]

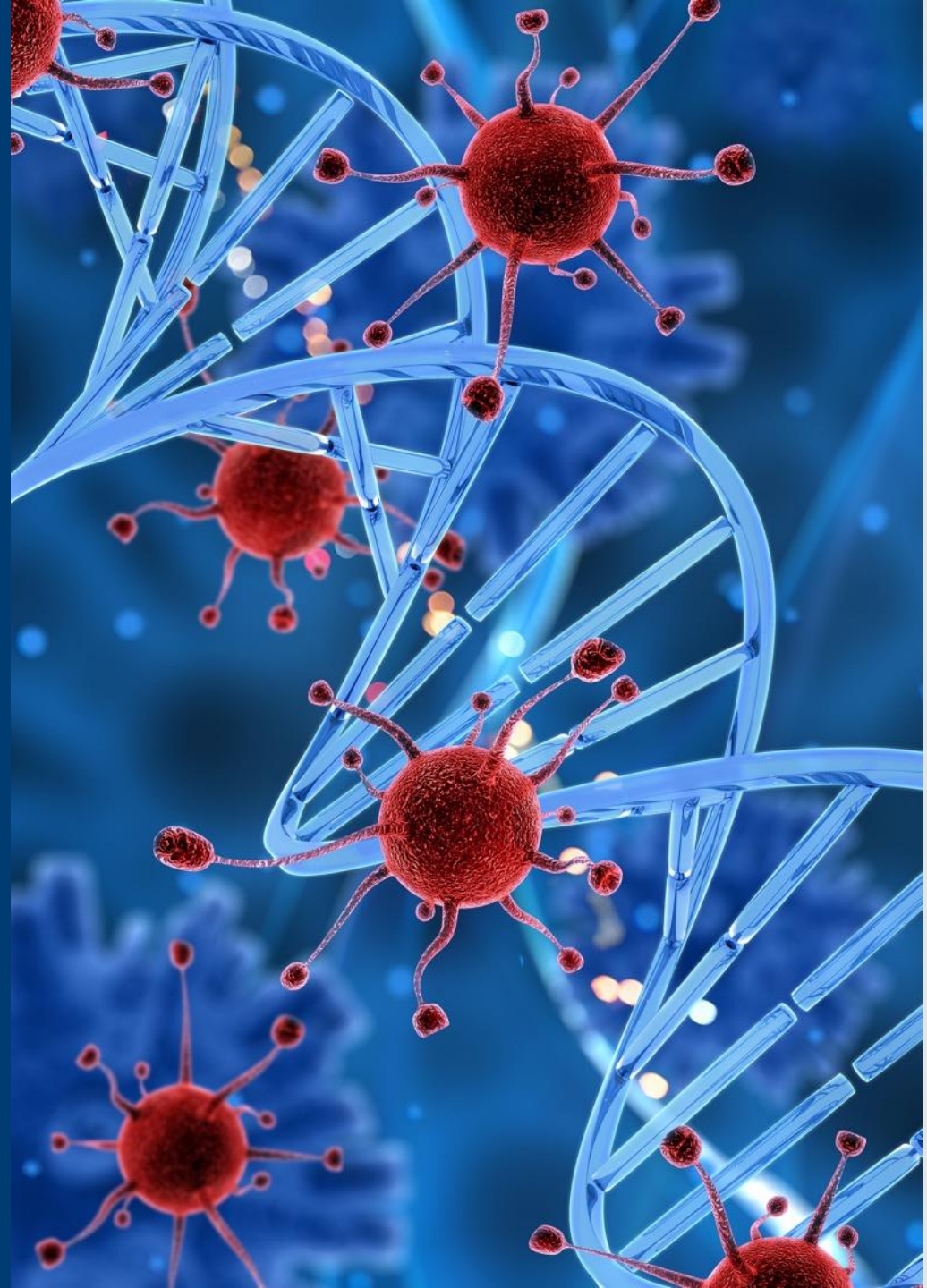
Current challenges

- **Viral TCR-T approach for solid tumors is not scalable**
  - Each patient likely requires multiple TCRs: with multiple T-cell gene transfer events
  - Manufacturing costs in hundreds of thousands of dollars per TCR via lentivirus[2]
  - Treating multiple patients with multiple TCRs quickly becomes daunting
- **Cost and complexity hamper CAR-T**
  - Viable business model remains elusive using viral modification of CAR-T
  - High cost and reimbursement dynamic is likely unsustainable
  - Reliance on centralized manufacturing adds logistical complexities
  - Significant time required to deliver to patients

1. 2018, Int'l Agency on Research for Cancer, *Cancer Facts & Figures*, 2018, American Cancer Society
2. Based on industry estimates for costs of GMP lentivirus

2019 in Review – Post ASCO

- Secured exclusive license from NCI to identify and use TCRs targeting neoantigens for cancer with *Sleeping Beauty* platform
- Extended with NCI the existing CRADA with Dr. Steven Rosenberg through January 2022
- Launching Eden BioCell JV for development of CAR-T in Greater China with $35 million committed from TriArm/Panacea
- Presented positive data from Controlled IL-12 platform at 2019 ASCO Annual Meeting
- Announced Fast Track Designation granted by FDA for Controlled IL-12 program for the treatment of rGBM in adults
- Commenced enrollment in third cohort of Controlled IL-12 combination substudy with OPDIVO®
- Completed enrollment in Controlled IL-12 Monotherapy Expansion Study with 36 patients enrolled in less than 6 months (11 more than target)



Sleeping Beauty
Solid Tumor Program – Leaders in clinical stage non-viral manufacturing of TCRs

Targeting Neoantigens: Years in Research, in Clinic Mid-Year

PERSPECTIVE

nature medicine

Prospects for gene-engineered T cell immunotherapy for solid cancers

Christopher A Klebanoff, Steven A Rosenberg & Nicholas P Restifo

Adoptive transfer of receptor-engineered T cells has produced impressive results in treating patients with B cell leukemias and lymphomas. This success has captured public imagination and driven academic and industrial researchers to develop similar 'off-the-shelf' receptors targeting shared antigens on epithelial cancers, the leading cause of cancer-related deaths. However, the successful treatment of large numbers of people with solid cancers using this strategy is unlikely to be straightforward. Receptor-engineered T cells have the potential to cause lethal toxicity from on-target recognition of normal tissues, and there is a paucity of truly tumor-specific antigens shared across tumor types. Here we offer our perspective on how expanding the use of genetically redirected T cells to treat the majority of patients with solid cancers will require major technical, manufacturing and regulatory innovations centered around the development of autologous gene therapies targeting private somatic mutations.

Irrefutable evidence that an entirely immunologic approach can cause regression of a wide array of human cancers has come from the recent success of using monoclonal antibodies (mAbs) targeting checkpoints of immune activation, including cytotoxic T lymphocyte–associated protein 4 (CTLA-4) (ref. 1) and programmed cell death protein 1 (PD-1) (ref. 2). This includes patients affected with an ever-expanding list of malignancies, including melanoma[1,2], renal cell carcinoma[2,3], lung cancer[2,4], bladder cancer[5], ovarian cancer[6], Hodgkin's lymphoma[7], and gastrointestinal (GI) and endometrial cancers associated with defects in DNA mismatch repair[8]. Despite different mechanisms of action, these immunotherapies culminate with the activation and expansion of tumor-reactive T cells[9–12].

Because T cells are often are the final effectors of immune-mediated cancer regression, strategies that directly use tumor-reactive T cells as a therapy have been developed[13]. In this approach, termed adoptive cell transfer (ACT), T cells are expanded outside the potentially immunosuppressive environment of a tumor and re-infused in large numbers into the cancer patient (up to 10^{11} cells). Historically, procuring antitumor T cells for use in ACT has come from the surgical removal of a cancer metastasis in order to obtain tumor-infiltrating lymphocytes (TILs). TILs demonstrate tumor reactivity with variable frequency in a range of cancers, including melanoma[14–17], GI[18,19], lung[20] and human papilloma virus–associated malignancies[21]. TIL infusion can induce durable complete responses (CRs)[14,21], including in patients for whom other immunotherapies have failed[14]. Despite demonstrable efficacy, use of TIL outside the context of clinical trials performed at academic medical centers has proven challenging.

Progress in gene engineering technologies has simplified the generation of antitumor T cells, overcoming many of the practical barriers that have limited wide dissemination of ACT using TIL cells. Gene engineering obviates the requirement for surgery because T cells can be isolated from the blood and receptors conveying specificity for tumor-associated antigens can be introduced using viral and non-viral integration techniques[22]. Thus, antitumor T cells can potentially be made on a large scale using commercial production methods. Indeed, recent experience with sipuleucel-T, a gene-modified cell product for prostate cancer, demonstrated the feasibility of having a patient's immune cells collected, sent to a central manufacturing facility, and returned back for re-infusion in a manner that gained US Food and Drug Administration (FDA) regulatory approval[23]. Finally, genetic modification of T cells has a track record of safety. Gammaretroviral and lentiviral vectors have been used most commonly in antigen receptor gene therapy trials. Despite concerns about the possibility of insertional mutagenesis[24], introduction of antigen receptors into mature human T cells has been used to treat several hundred patients without evidence of clonal expansion or transformation[25].

Collectively, a framework of manufacturing feasibility, regulatory precedent and vector safety is now in place and it is possible to envision treating large numbers of cancer patients using gene-engineered T cells. Recent success with gene-modified T cells targeting the B cell lineage differentiation antigen CD19 in a range of B cell malignancies has focused attention on using similar 'off-the-shelf' antigen receptors to treat patients with advanced solid cancers. In this Perspective, we offer our appraisal of how adoptive immunotherapy using receptor-engineered T cells can enter mainstream clinical oncology for patients with advanced epithelial cancers, the leading cause of cancer-related deaths[26].

Antigen receptor–engineered T cell receptors. Genetically redirecting a T cell's specificity toward a patient's cancer can be accomplished by the introduction of one of two types of antigen receptors. In one approach, a cloned T cell receptor (TCR) conferring tumor recognition is inserted into circulating lymphocytes. Similarly to the endogenous TCR expressed by all T cells, genetically introduced TCRs recognize a proteolytically processed peptide derived from either a cytosolic or membrane-associated

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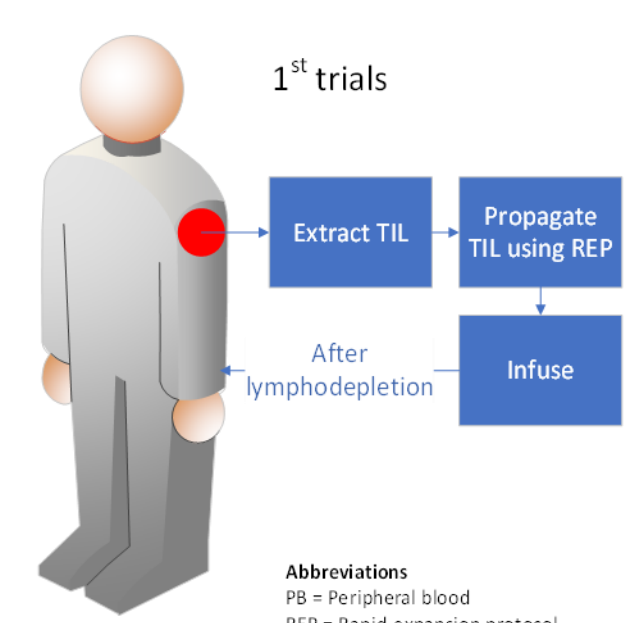
Received 2 July 2015; accepted 20 November 2015; published online 6 January 2016; doi:10.1038/nm.4015

> *"Success for cell-based immunotherapies may come from* ***the arduous task of targeting the unique set of mutations that cause each patient's cancer****"*

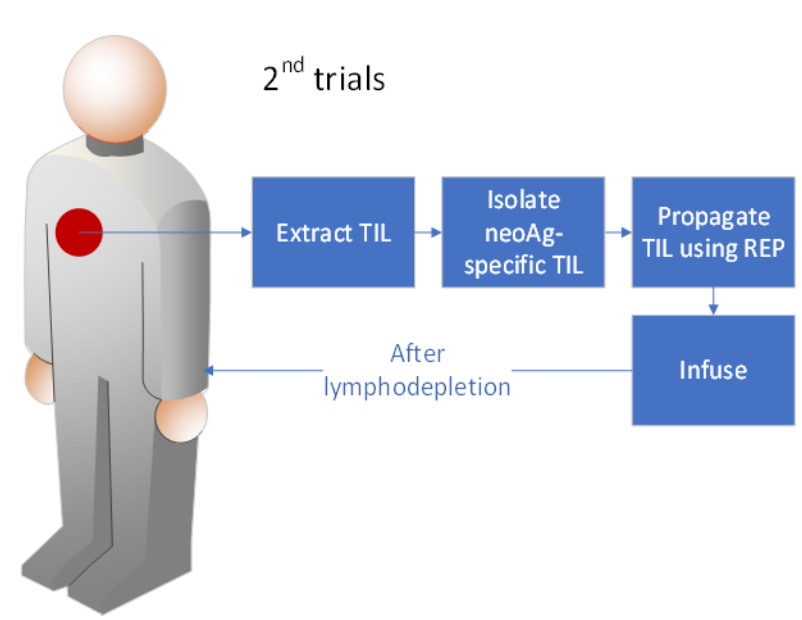
Nat Med. 2016 Jan 6;22(1):26-36
Science. 2015 Apr 3;348(6230):62-8
Science. 2015 Apr 3;348(6230):69-74

Ziopharm ONCOLOGY

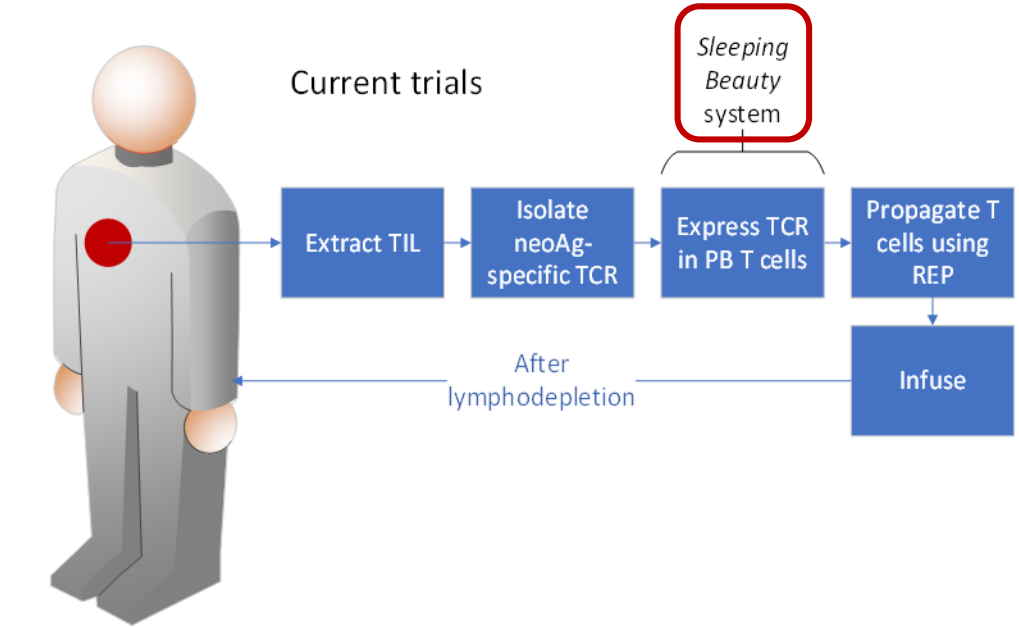
Evolution of Neoantigen-Specific T-cell Therapy at NCI



Anti-tumor effect due to:
- Lymphodepletion to improve T-cell persistence
- T cells recognizing neoantigens



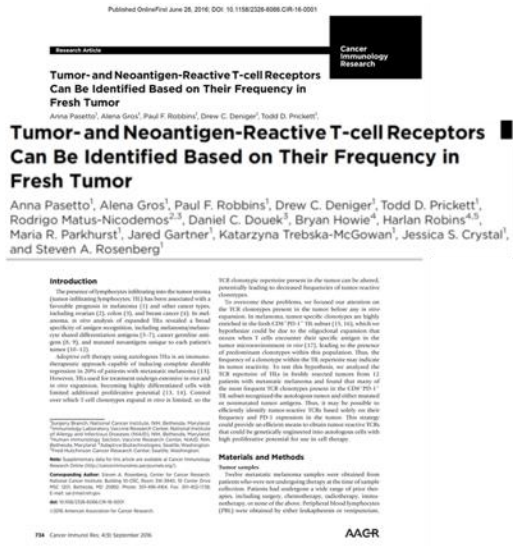
Anti-tumor effects are episodic due to:
- Ineffective (exhausted) T cells derived from TIL



Anti-tumor effect based on:
- Neoantigen-specific TCRs derived from TIL
- Redirected specificity of "young" T cells genetically modified to express neoantigen-specific TCR

Sleeping Beauty platform Expresses Neoantigen-Specific TCRs

Clinical Success: TCRs from Patients Transposed into Peripheral Blood T Cells with *Sleeping Beauty* Platform


Cancer Immunology Research

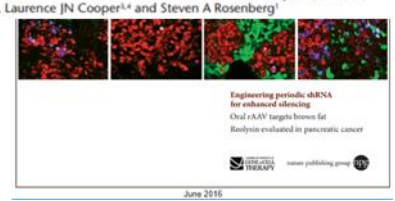
Tumor- and Neoantigen-Reactive T-cell Receptors Can Be Identified Based on Their Frequency in Fresh Tumor

Anna Pasetto[1], Alena Gros[1], Paul F. Robbins[1], Drew C. Deniger[1], Todd D. Prickett[1], Rodrigo Matus-Nicodemos[2,3], Daniel C. Douek[3], Bryan Howie[4], Harlan Robins[4,5], Maria R. Parkhurst[1], Jared Gartner[1], Katarzyna Trebska-McGowan[1], Jessica S. Crystal[1], and Steven A. Rosenberg[1]


Molecular Therapy

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]


Engineering periodic shRNA for enhanced silencing

Oral rAAV targets brown fat

Reolysin evaluated in pancreatic cancer

June 2016


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]


Clinical Cancer Research

Published OnlineFirst May 31, 2018; DOI: 10.1158/1078-0432.CCR-18-0573

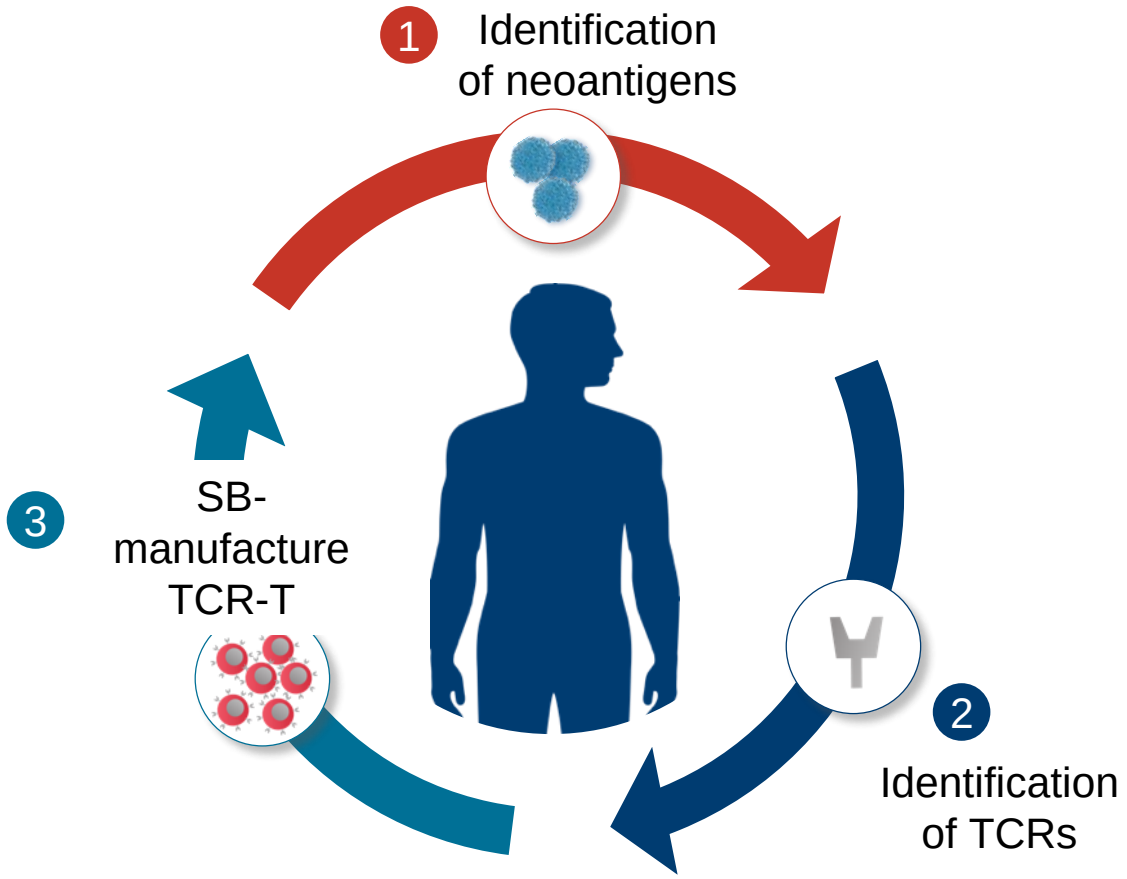
Clinical Trials: Immunotherapy

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

End-to-end Solution to Target Solid Tumors with T Cells Expressing Neoantigen-Specific TCRs

Current model for NCI collaboration



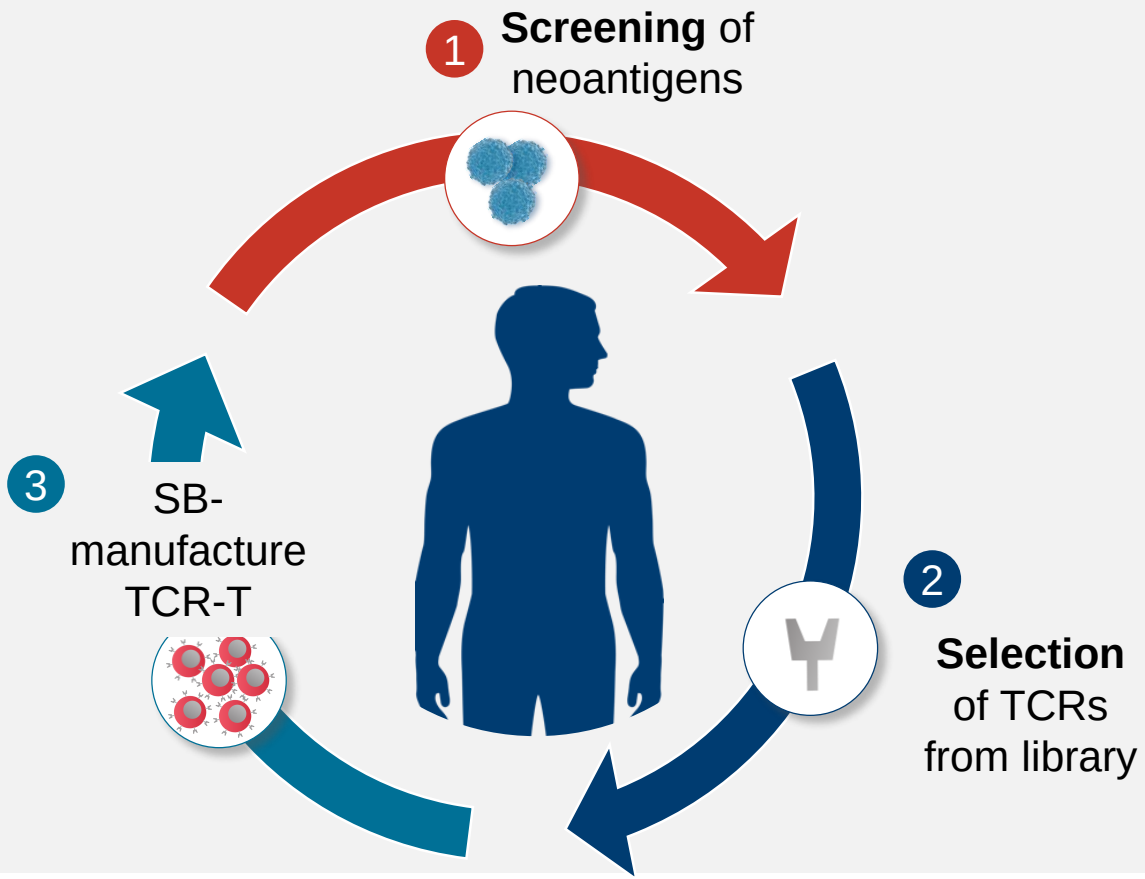
TCRs from, and for, the patient

Sleeping Beauty non-viral solution

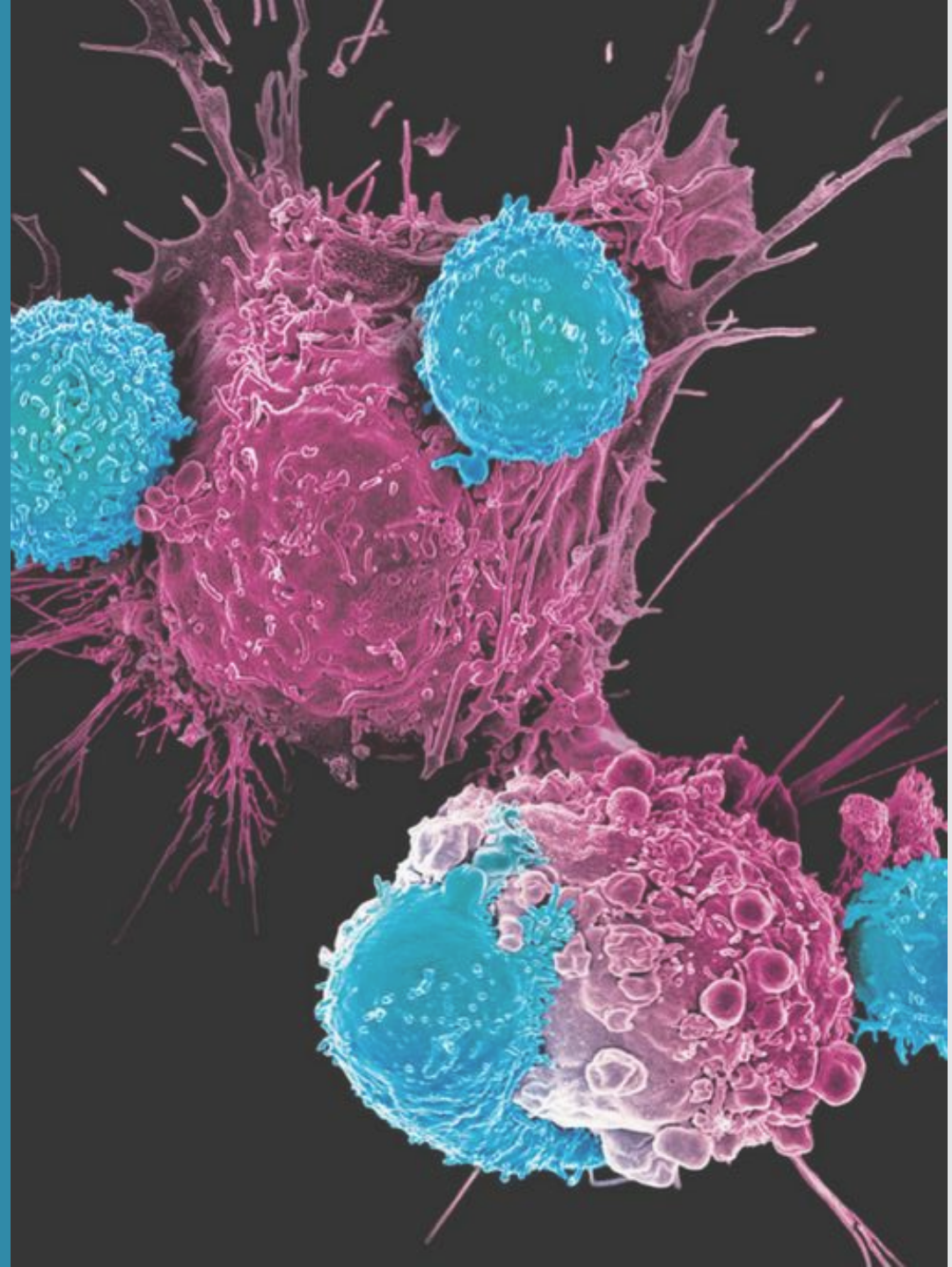
- Most-clinically advanced non-viral gene transfer technology
- Personalized TCR-T by expressing unique TCRs to target patient-specific neoantigens at scale to treat multiple patients
- Reduce costs by avoiding virus to manufacture TCR-T
- Produce multiple TCRs to meet demands of tumor target diversity within one patient to minimize relapse (antigen escape)
- Reaffirm timeline to enroll patients at NCI in mid-2019

Neoantigens Occurring in “Hotspots” are Attractive Targets

New license with NCI announced last week



- KRAS, with recent clinical data, reinforces that single-foundation mutation class gives rise to cancer
- KRAS is thus a druggable target family, ideally suited for TCRs
- Ziopharm licensed this class of targets, along with p53 and EGFR from Dr. Rosenberg / NCI in May 2019
- *Sleeping Beauty* enables targeting of KRAS and p53 and EGFR, and *variations of each*
- Fortifies Ziopharm’s lead in treating patients with non-viral manufacturing

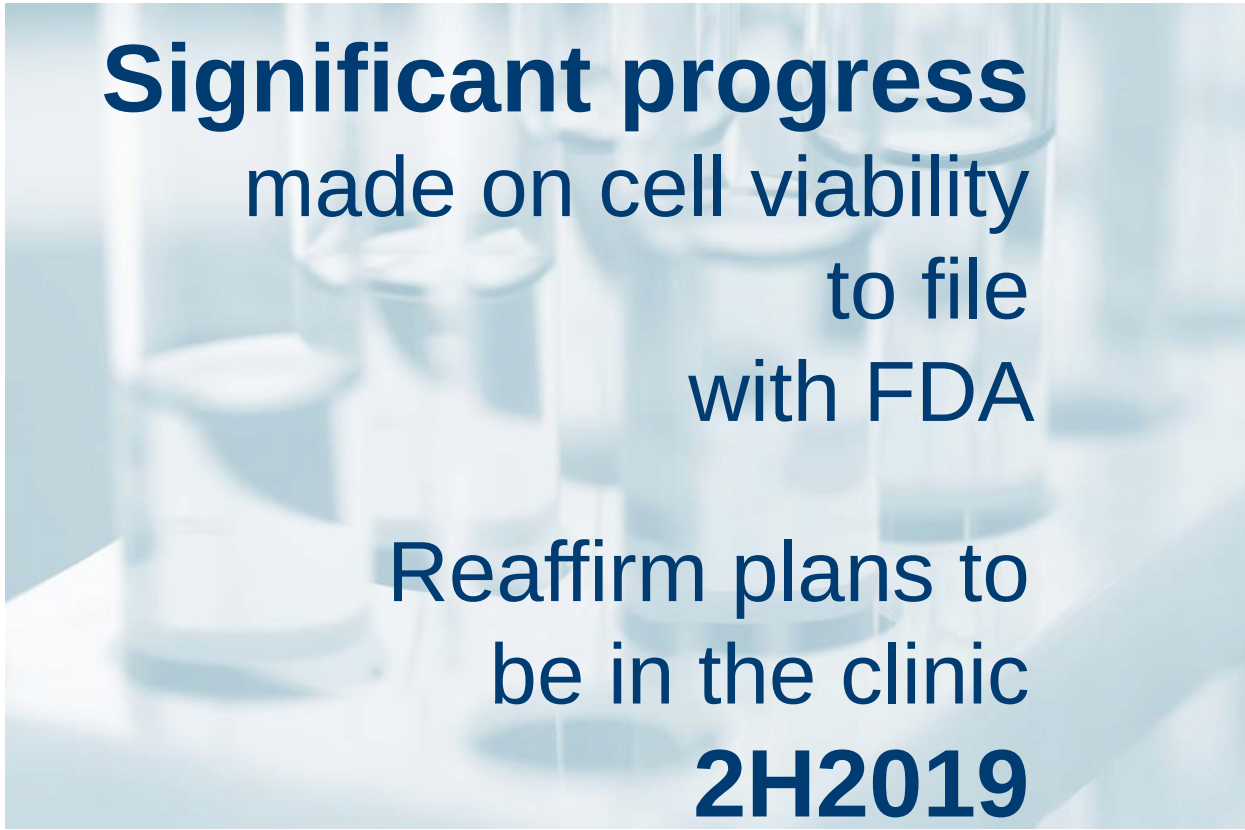


Sleeping Beauty

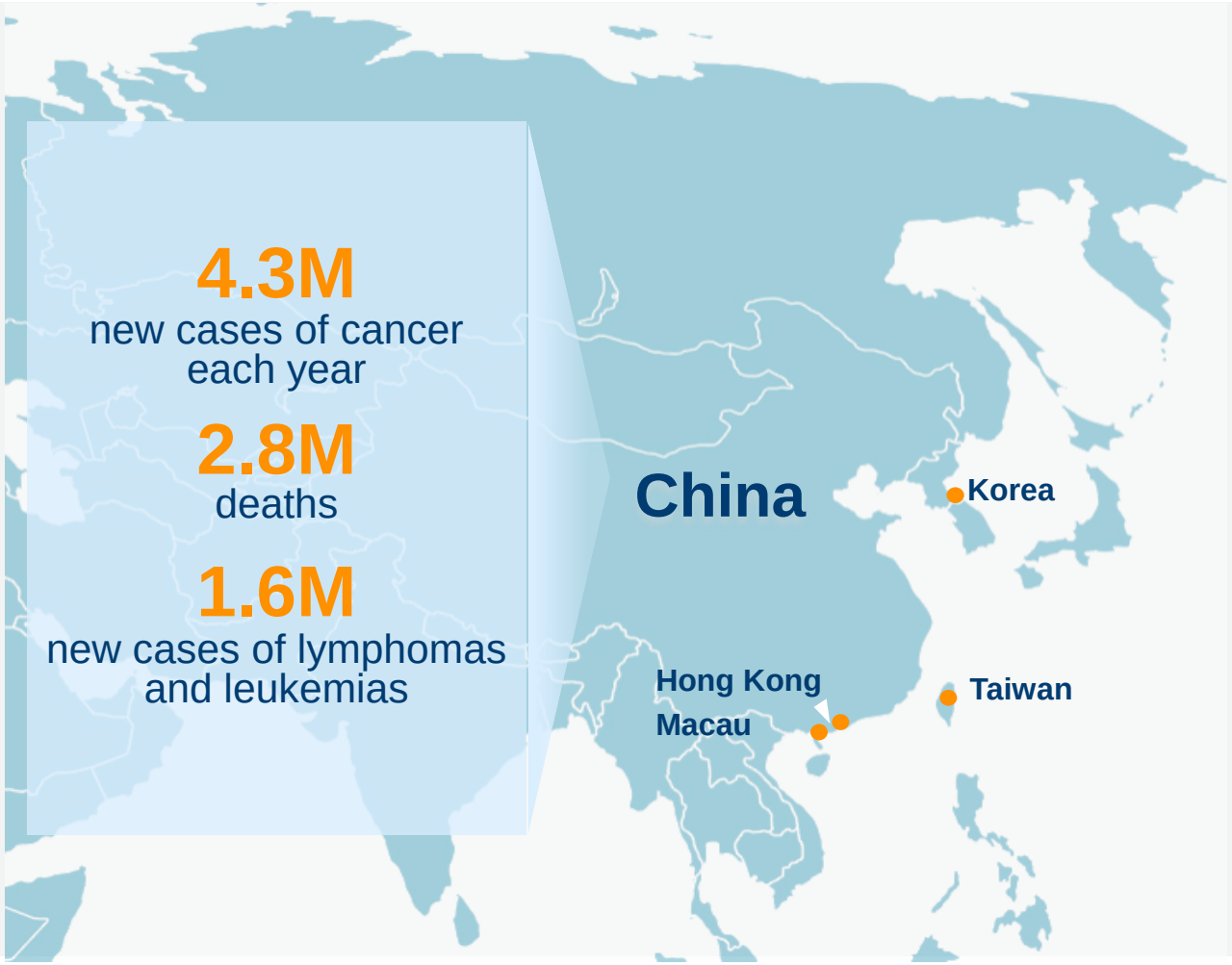
CAR-T CD19 – to reduce the time and cost of manufacture

Clinically Tested CAR-T Program

- Demonstrated *Sleeping Beauty* with CD19-specific CAR-T
- Lower cost, faster manufacturing required for commercial adoption
  - CD19 China: Fully-funded phase 1 with Eden BioCell
  - CD19 US: Fully-funded phase 1 at MD Anderson Cancer Center

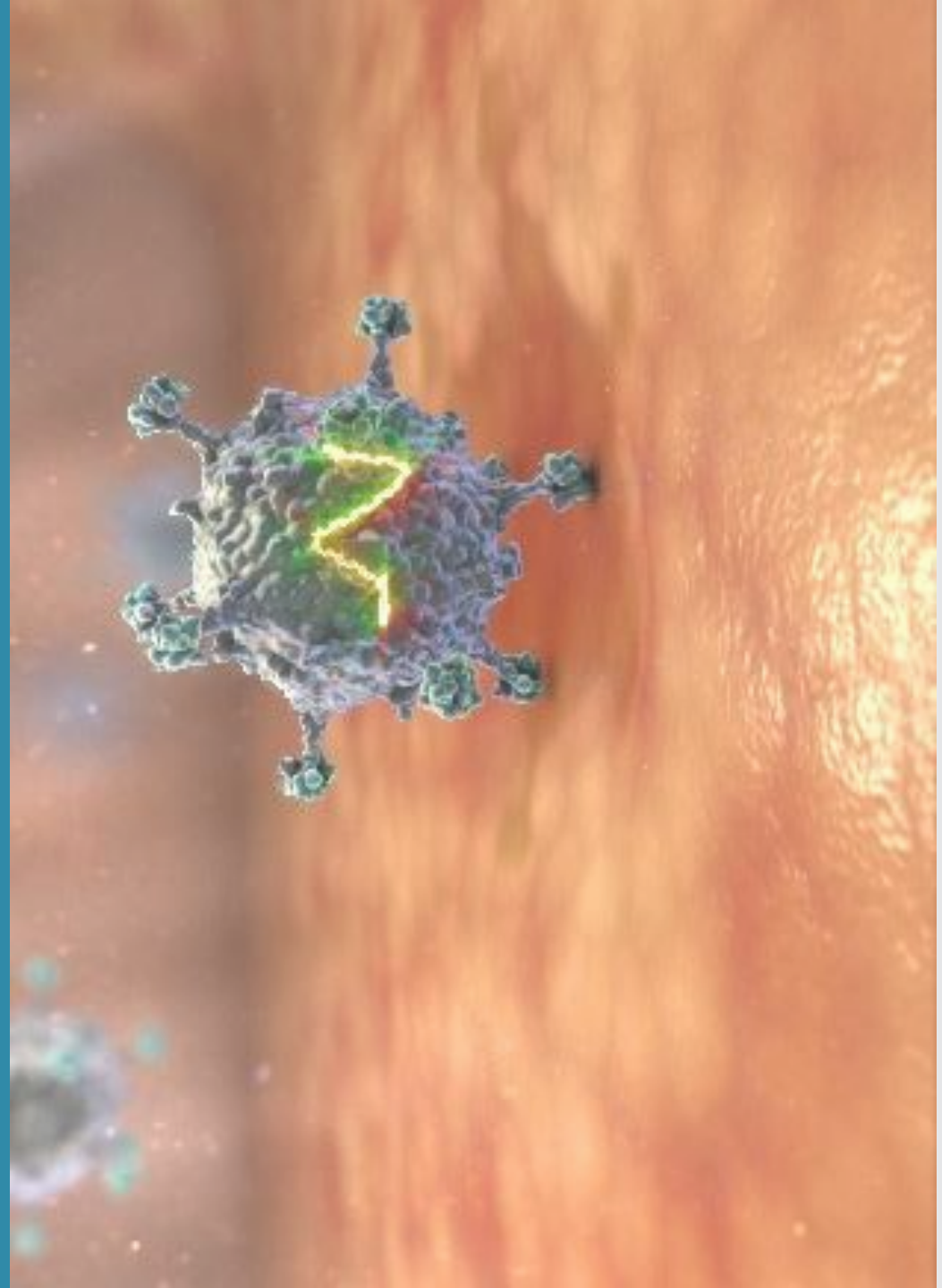


Eden BioCell to take CAR-T CD19 to Greater China



- To succeed in China, must have access to front-line hospitals, key regulatory bodies, clinicians, and state-of-the-art GMP facilities
- Greater China markets dwarf US, cost pressure more significant
- $35 million funding committed from TriArm Therapeutics; 50-50 joint venture
- Together, continuing to grow and staff with top-tier scientific research, clinical and regulatory experts, as well as significant laboratory and manufacturing know-how regarding T-cell therapies

"Cancer Statistics in China, 2015" Wanqing Chen, Ph.D., M.D., et al in CA Cancer J Clinical 2016; 66: 115-132



Controlled IL-12 Platform

First Opportunity for IL-12: Recurrent Glioblastoma is not Curable; A New Rational Approach is Needed

TARGETS ARE UNKNOWN

Current therapies don’t work

LOW SURVIVAL RATE

Historical overall survival is 6 to 9 months

IMMUNOTHERAPY BEST APPROACH

Immune system to fight the cancer

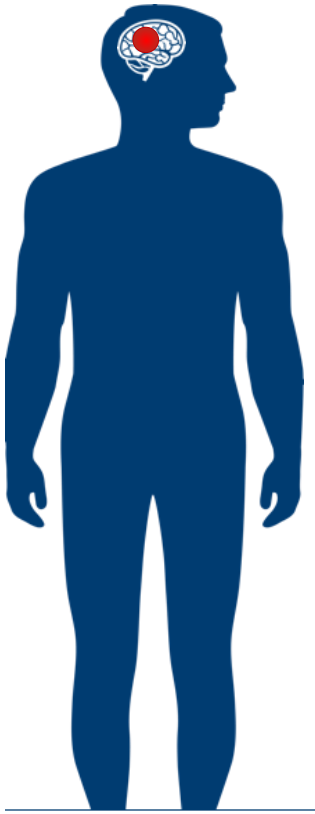
THE PROBLEM

Brain tumors exclude or weaken the immune system

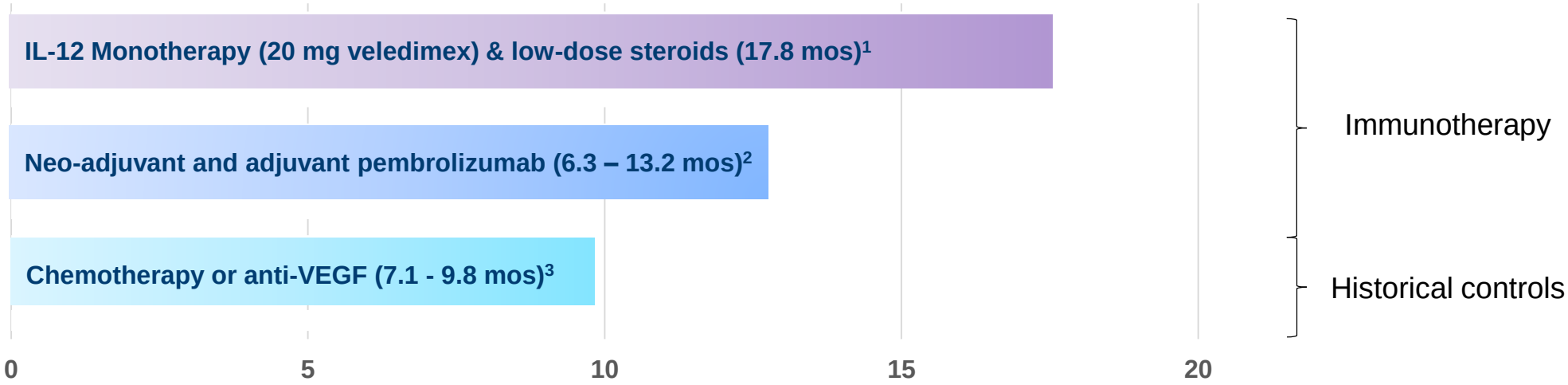
THE SOLUTION: IL-12 as a DRUG

Most powerful immuno-stimulant to recruit T cells

First Data: Encouraging Survival with Controlled IL-12 for rGBM



Median Overall Survival (months)



1. Subset of patients receiving less than 20mg dexamethasone after surgery, SNO2018 presentation entitled, “A Phase 1 study of Ad-RTS-hIL-12 + veledimex in adults with recurrent glioblastoma: Dose determination with updated overall survival”;

2. Cloughesy *et al.*, Nat Med. 2019 Feb 11. [Epub ahead of print]

3. Taal et al., Lancet Oncology, 2014, 15: 943–953; Brandes et al., Neuro Oncol. 2016 Sep;18:1304-12; Friedman et al., J Clin Oncol. 2009;27:4733–4740; Chamberlain et al., Journal of Neuro Oncology. 2010;96:259-269; Field et al., Neuro Oncol. 2015 Nov;17:1504-1513; Wick et al., J Clin Oncol. 2010 28: 1168-1174; Batchelor et al., J Clin Oncol 2013 31:3212-3218; Brandes AA et al., Neuro Oncol 2016;18, 1146-1156; Wick et al., N Engl J Med 2017;377:1954-63.

Additional resources: Zhao *et al.*, Nat Med. 2019 Feb 11. [Epub ahead of print]; Schalper *et al.*, Nat Med. 2019 Feb 11. [Epub ahead of print].

IL-12 Monotherapy with Low-dose Steroids Expanded Trial

Phase 1: Ad-RTS-hIL-12 plus 20mg of veledimex

- Expansion cohort of monotherapy and guidance for low dose (<20 mg) dexamethasone
- Enrollment exceeded target (expected n=25), with 36 patients enrolled in less than 6 months
  - Enthusiasm attributable to encouraging survival and tumor biopsy data
  - Over half of enrolled patients received low-dose steroids

Positive Clinical Data for Controlled IL-12 for the Treatment of Recurrent Glioblastoma presented at 2019 ASCO Annual Meeting

ASCO American Society of Clinical Oncology

Evaluation of Controlled IL-12 as Monotherapy	*Evaluation of Controlled IL-12 in Combination with a PD-1 Inhibitor*
• 75% patients received low-dose steroids • "Cytoindex", an emerging biomarker, showed immune activation consistent with results seen in the Main Study, which correlated with median overall survival • Mean follow up 3.7 months (1 to 7.5 mos.)	• 66% of patients in first two cohorts received low-dose steroids • Cytoindex improved compared with Ad+V as monotherapy • Mean follow up 4.5 months (0.4 to 10.1 mos.) • Study continues to enroll

Next Step: Controlled IL-12 in Combination with PD-1 Inhibitors for recurrent GBM

Biomarker-Driven Studies

Monotherapy resulted in upregulation of PD-1 in tumor microenvironment

Combination with OPDIVO

- **Phase 1** trial of Controlled IL-12 in combination PD-1 antibody OPDIVO® (nivolumab) to treat patients with rGBM
- Enrollment expected to be complete in 2Q2019

Collaboration with Regeneron Pharmaceuticals

- **Phase 2** trial of Controlled IL-12 in combination with PD-1 antibody Libtayo® (cemiplimab-rwlc) to treat patients with rGBM
- Enroll up to ~30 patients; primary endpoints are safety and efficacy
- Initiate first-half 2019

Ziopharm Building Momentum Through 2019

1Q2019	2Q2019	1H2019	Mid-2019	2H2019
Phase 1 Fully enrolled **Controlled IL-12** monotherapy expansion cohort ✓	**Phase 1** Fully enrolled **Controlled IL-12** in combination with OPDIVO	**Phase 2** trial for **Controlled IL-12** in combination with Libtayo to open	**Phase 1** First-in-human trial initiation NCI-led ***Sleeping Beauty*** TCR-T-cell trial targeting solid tumors	**Phase 1** Trial for ***Sleeping Beauty*** CD19-specific CAR-T third-generation trial with membrane-bound IL-15
Controlled IL-12 Platform			*Sleeping Beauty* Platform	


Thank you