Ziopharm ONCOLOGY

The Next Generation of Immunotherapy Platforms

36th Annual J.P. Morgan Healthcare Conference

January 2018

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 the progress, timing and results of preclinical and clinical trials involving the Company's drug candidates, and the progress of the Company's research and development programs. All of such statements are subject to certain risks and uncertainties, many of which are difficult to predict and generally beyond the control of the Company, that could cause actual results to differ materially from those expressed in, or implied by, the forward-looking statements. These risks and uncertainties include, but are not limited to: whether chimeric antigen receptor T cell (CAR^+ T) approaches, Ad-RTS-IL-12, TCR and NK cell-based therapies, or any of our other therapeutic candidates will advance further in the preclinical or clinical trials process and whether and when, if at all, they will receive final approval from the U.S. Food and Drug Administration or equivalent foreign regulatory agencies and for which indications; whether chimeric antigen receptor T cell (CAR^+ T) approaches, Ad-RTS-IL-12, TCR and NK cell-based therapies, and our other therapeutic products will be successfully marketed if approved; the strength and enforceability of our intellectual property rights; competition from other pharmaceutical and biotechnology companies; and the other risk factors contained in our periodic and interim SEC reports filed from time to time with the Securities and Exchange Commission, including but not limited to, our Annual Report on Form 10-K for the fiscal year ended December 31, 2016 and our Quarterly Report on Form 10-Q for the quarter ended September 30, 2017. Readers are cautioned not to place undue reliance on these forward-looking statements that speak only as of the date hereof, 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.

Two Distinct Platforms, Multiple Opportunities

Control of IL-12

Weaponize existing immune system

- IL-12: master regulator of immune system
- RheoSwitch® controls local dosing
- Immune checkpoint inhibitor combination with nivolumab
- Multiple cancer indications beginning with GBM

Sleeping Beauty

Implement new immune system

- Most clinically advanced non-viral platform
- Point-of-care (P-O-C): fraction of cost in a fraction of the time
- Scalable

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Two Platforms Drive Next Generation Immunotherapy

	Target		Indication	Preclinical	Phase 1	Phase 2	Pivotal
Controlled IL-12	**Ad-RTS-hIL-12**	Multicenter	GBM				
			GBM & OPDIVO® (nivolumab)				
			GBM Stereotactic Treatment				
			Pediatric Brain Tumor				
Sleeping Beauty	**CAR**	CD19 2nd Gen shortened manufacture	Leukemia/Lymphoma				
		CD19 3rd Gen CAR with mbIL15 (P-O-C)	Leukemia/Lymphoma				
		CD33	AML				
		Merck Targets	Undisclosed				
		P-O-C	Hematologic				
	TCR	*Sleeping Beauty* neoantigen	Solid tumors				
		Sleeping Beauty neoantigen and cytokine	TBD				
	NK cells	Genetically engineered	TBD				

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

Merck KGaA Darmstadt · Germany

NIH NATIONAL CANCER INSTITUTE

P-O-C = Point-of-Care

Initiated Planned

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CONTROLLED IL-12

First Market: A New Paradigm for Recurrent Glioblastoma

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Glioblastoma: Global Opportunity for Controlled IL-12

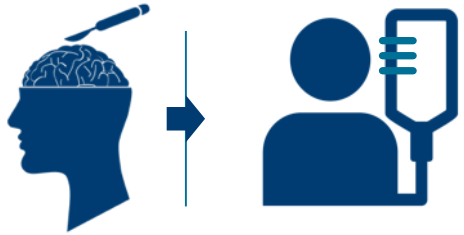
~70,000
new cases world wide each year

12,390[1]
new cases in the U.S. each year

14,576[2]
new cases in Europe each year

Frontline Therapy

- Surgery



- Radiation
- Chemotherapy (temozolomide)

Recurrence = 90%
US – 11,151[1]
EU – 13,118[2]

Recurrent GBM
Average time to death remains **5 to 8 months**

1. http://www.abta.org/about-us/news/brain-tumor-statistics/
2. GlobalData information, June 2016

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Multicenter Phase 1 Study Evaluates Ad-RTS-hIL-12 Plus Veledimex in Patients with Recurrent Glioblastoma

Ad-RTS-hIL-12

A replication-incompetent adenoviral vector administered via a single injection into the tumor and engineered to express and control hIL-12, a powerful cytokine that stimulates an immune anti-tumor response.

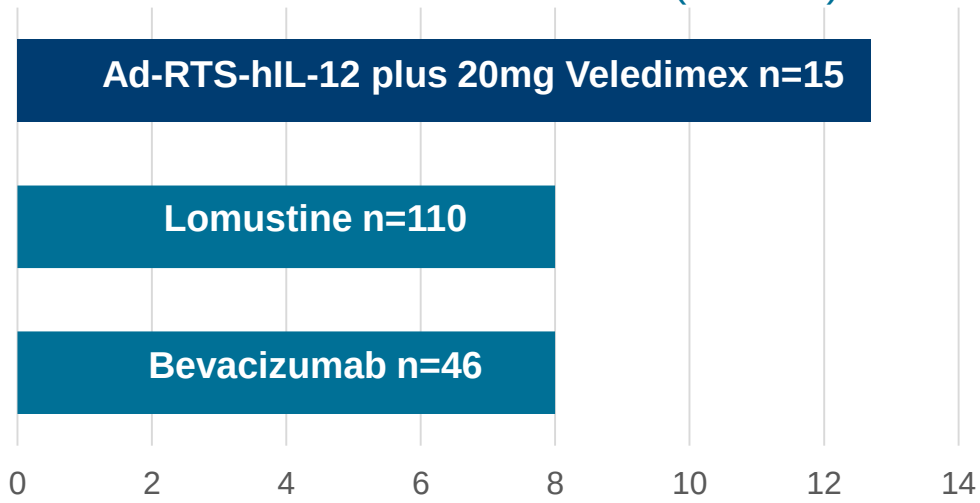
Patients scheduled for SOC resection/craniotomy

Veledimex 3±2 hrs before resection → Craniotomy with Ad-RTS-hIL-12 free-hand injection → Veledimex

Day 0

Days 1 to 14 QD and follow up

Median Overall Survival (months)



Ad-RTS-hIL-12 + v data as of October 18, 2017; Data for lomustine and bevacizumab from randomized phase 2 study (BELOB).

Phase 3 randomized control trial to initiate this year

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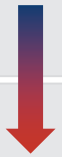
Why Do Patients Benefit?

Tumors Cold



Tumors Hot

Ad-RTS-hIL-12

1. IL-12 generated from replication-incompetent adenovirus delivered to GBM
2. Patient takes oral pill to produce IL-12 from tumor
3. IL-12 signals T cells to GBM for sustained anti-tumor activity

The Evidence*:

- **MRI evidence:** Tumors **shrinking** after IL-12 immune therapy
- **New emerging biomarker:** Ratio of killer-to-suppressor T cells correlates with **survival**
- **Low-dose steroids:** Improved **survival** likely by maintaining IL-12 immune response; 100%** survival (n=4)
- **Biopsy data:** IL-12 recruits T cells into GBM to make "cold" tumor site "**hot**" for long periods of time

** "A Phase 1 study of Ad-RTS-hIL-12 + veledimex in adult recurrent glioblastoma," presented at 2017 Society of Neuro-Oncology by Antonio Chiocca, M.D., Ph.D., Brigham and Women's / Dana-Farber Cancer Center*

*** As of October 2018*

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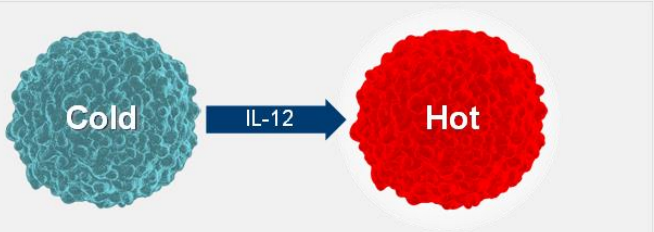
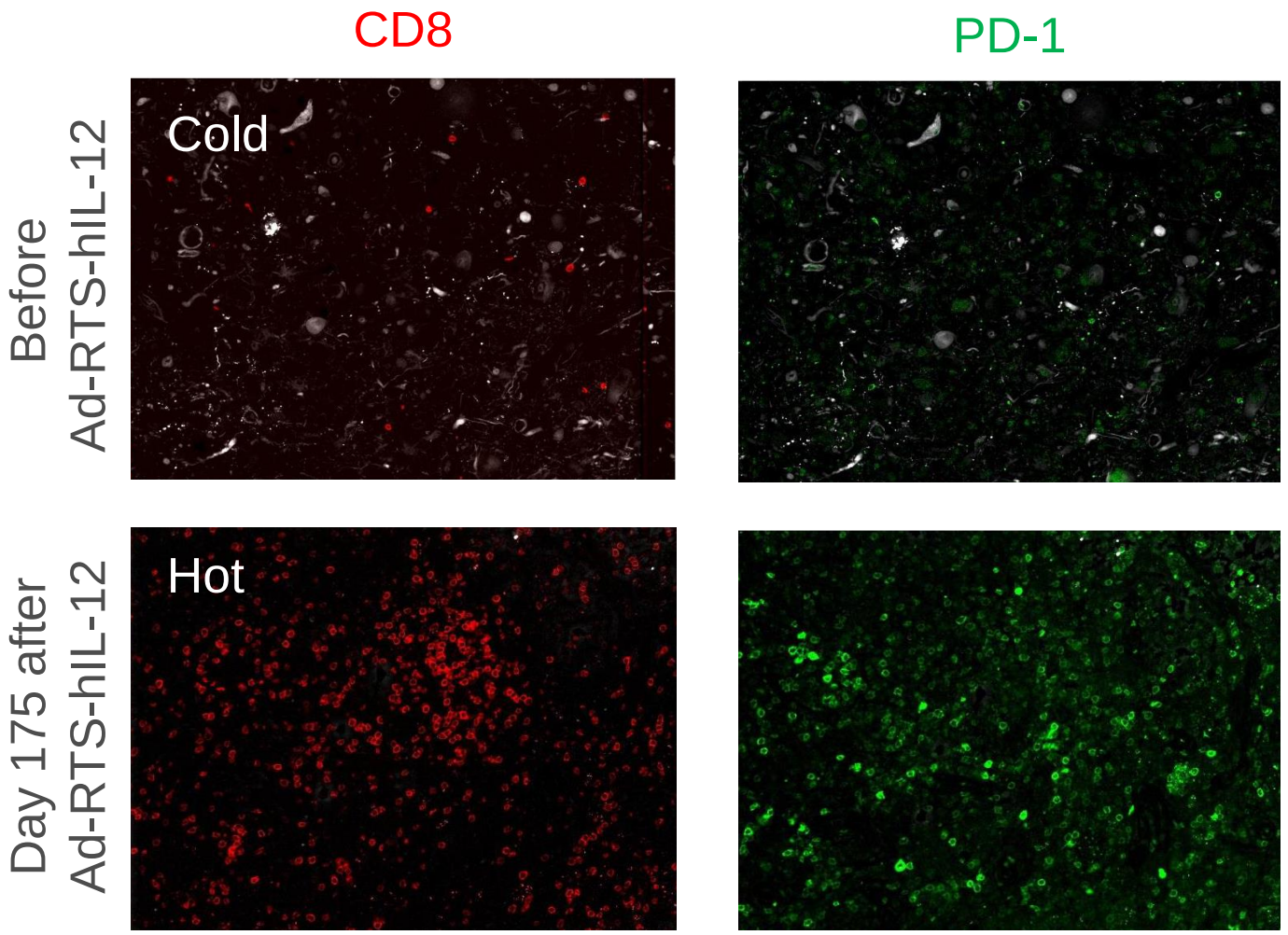
Biopsies Show New Influx of Killer T cells (CD8$^+$), Upregulation of PD-1



3/3 Subjects	IFNγ: Mean ± SEM (pg/g)	
	Serum (pg/mL)	Tumor (pg/g)
Baseline	0.0 ± 0.0	4.2 ± 2.6
Days 130-175	0.0 ± 0.0	226 ± 138

Biopsies at four-plus months after IL-12 activation by veledimex reveal new infiltrates of T cells active in 3 of 3 patients



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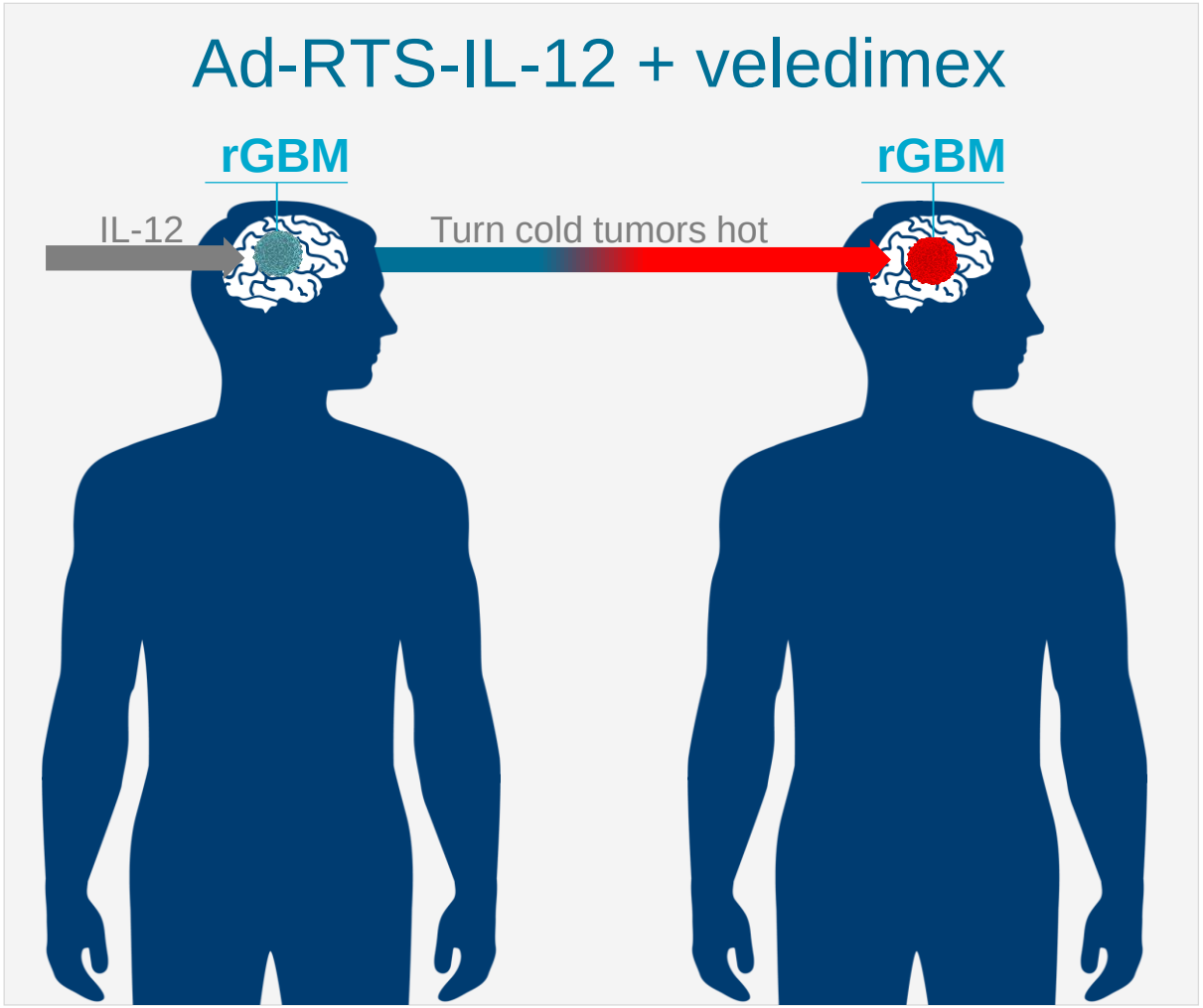
Rationale for Combination Therapy for rGBM

- Tumors **remain** HOT months after IL-12 therapy
- T-cells **traffic** deep into tumor
- **Reassuring** safety profile



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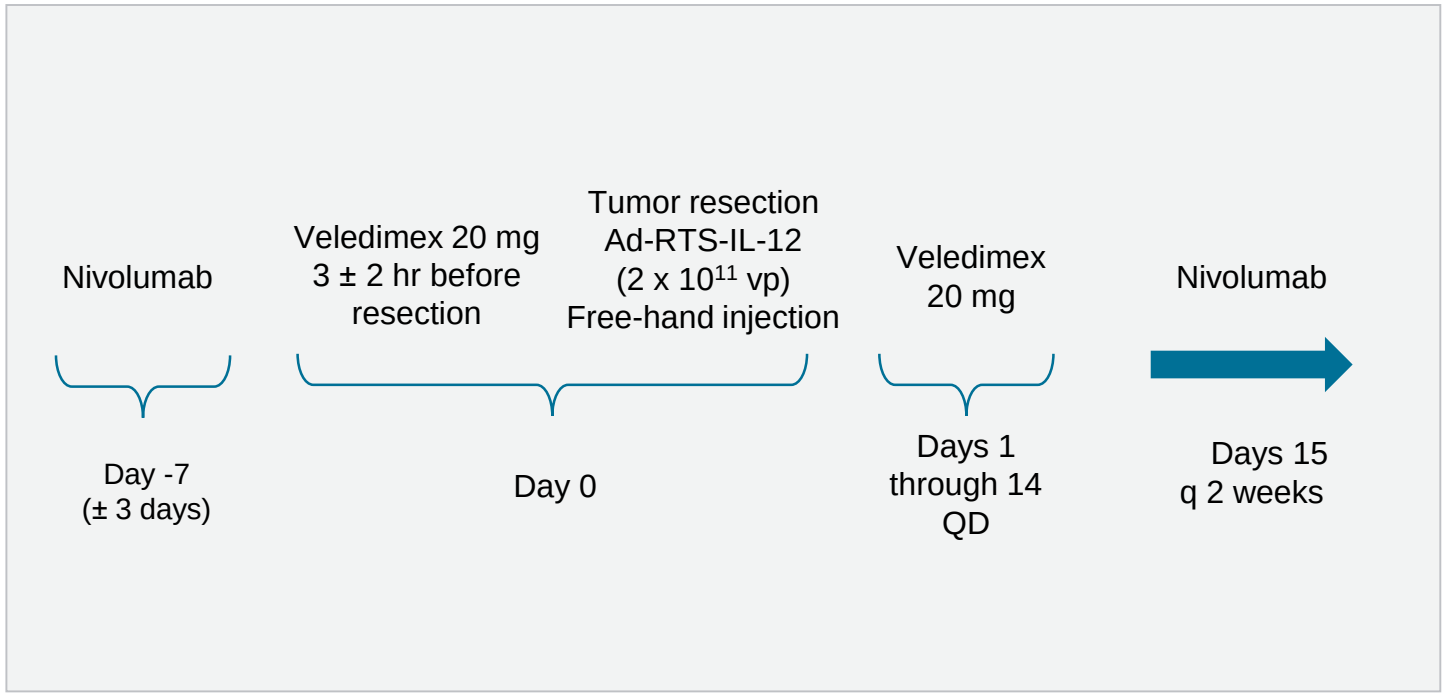
Phase 1 Trial Initiated to Evaluate Ad-RTS-hIL-12 plus Veledimex in Combination with OPDIVO® (nivolumab) to Treat Patients with rGBM

- Compelling data demonstrating that IL-12 can remodel the tumor microenvironment
- Sustained influx of $CD8^+$ T cells expressing PD-1
- Combining IL-12 with anti-PD-1 may yield even better anti-tumor responses

Up to 18 Patients

ELIGIBILITY

- Recurrent or progressive GBM
- Scheduled for resection
- Not previously treated with inhibitors of immune-checkpoint pathways



Primary objective:
Safety and tolerability

Secondary:
Optimal dose
Overall survival

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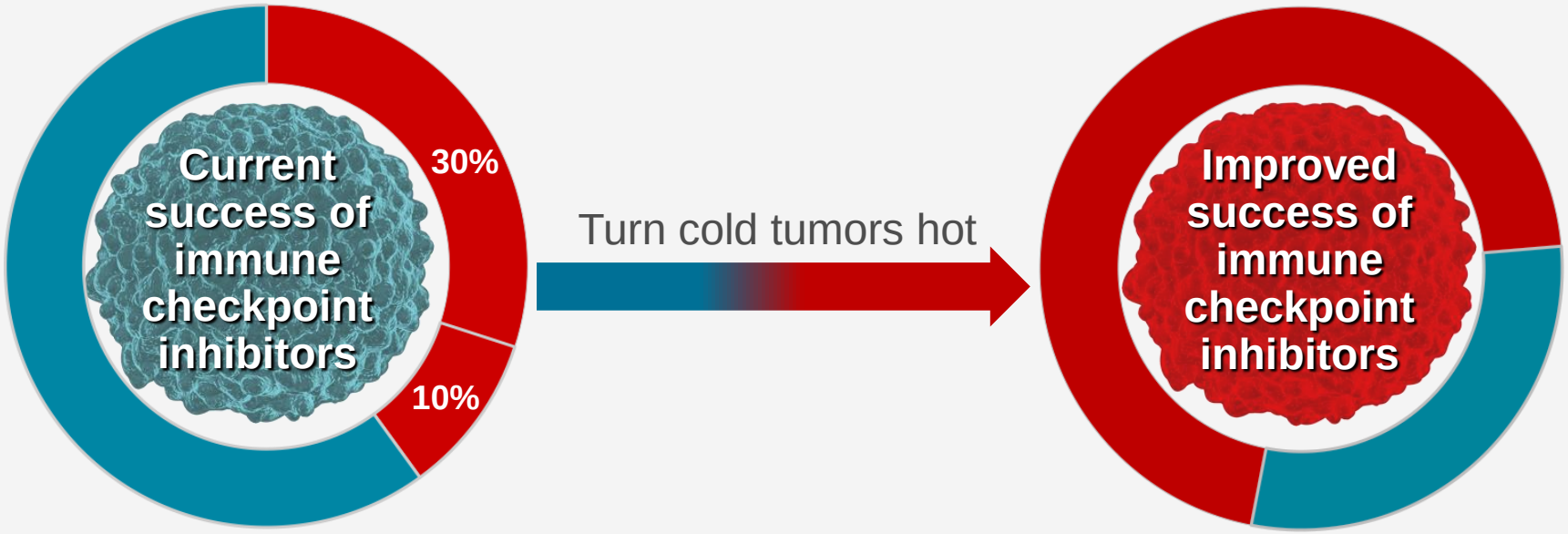
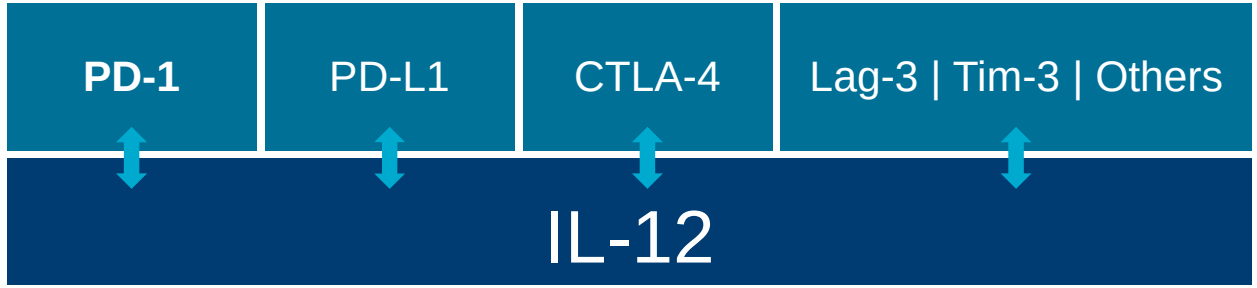
IL-12 Platform can Combine with Immune Checkpoint Inhibitors Across Oncology



Broad potential



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SLEEPING BEAUTY
A New Paradigm for Adoptive Cell Therapy

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Two Platforms Drive Next Generation Immunotherapy

	Target		Indication	Preclinical	Phase 1	Phase 2	Pivotal
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Sleeping Beauty	**CAR**	CD19 2nd Gen shortened manufacture	Leukemia/Lymphoma			THE UNIVERSITY OF TEXAS MD Anderson Cancer Center Making Cancer History®	
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		Sleeping Beauty neoantigen and cytokine	TBD				
	NK cells	Genetically engineered	TBD				

P-O-C = Point-of-Care

Initiated Planned

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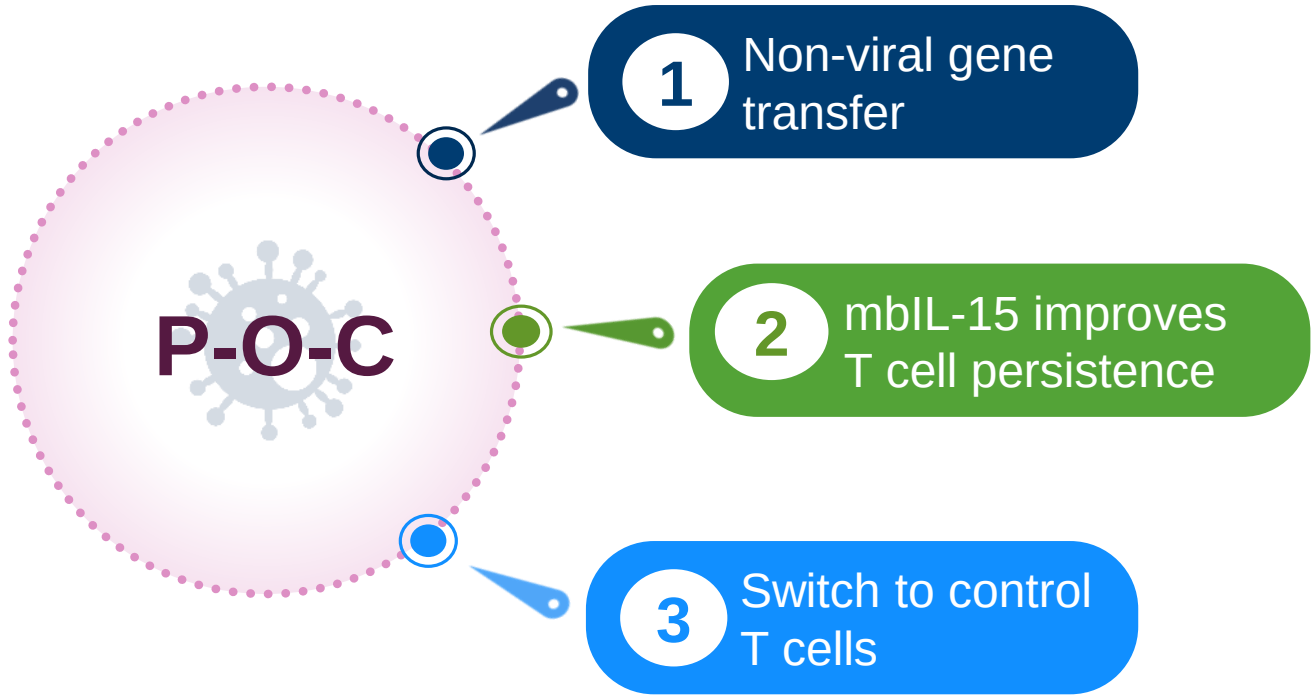
ZIOP's Vision – Scalable, Lower Cost, High-throughput Platform



Sleeping Beauty under P-O-C

- Very rapid manufacture
- Scalable process
- Avoids use of virus
- Removes need to grow T cells outside the body
- Reduces costs

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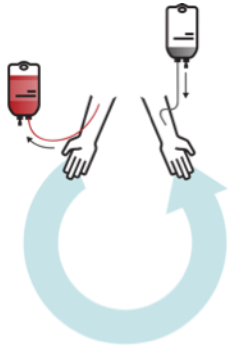
Eliminate the Complexity – P-O-C Trial to be Initiated 2018

<2 days

1. Apheresis (blood draw)

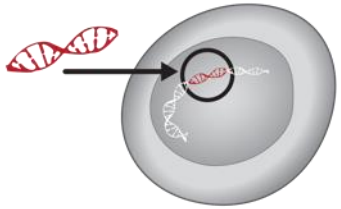


Resting (quiescent) T cells

2. Isolate, genetically modify T cells with electroporation

No *ex vivo* propagation

Sleeping Beauty



1. CAR Target
2. mbIL15 for T-cell survival benefit after infusion
3. HER1t for kill switch

3. Infuse CAR^{+} T cells for *in vivo* expansion

4. Control

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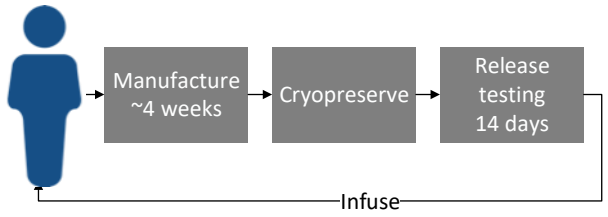
First Point-of-Care – CD19-Specific CAR$^+$ T cells

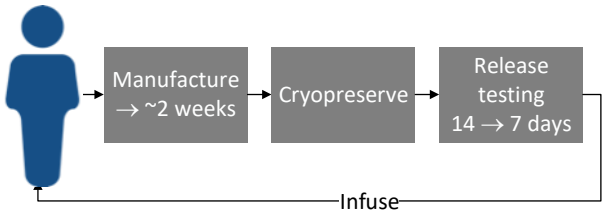
Implementing P-O-C 1, 2, 3

1st generation complete: CAR$^+$ T cells



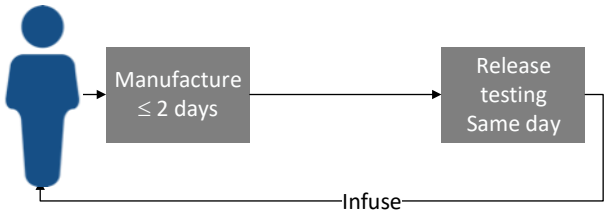
- Demonstrated *Sleeping Beauty* (SB) genetically modifies T cells safely
- ASH 2017: Long-term survival data and T-cell persistence

2nd generation ongoing: CAR$^+$ T cells



- Shorten manufacturing and release testing of SB-modified CAR$^+$ T cells
- ASH 2017: Interim safety, anti-tumor response, T-cell persistence

3rd generation 2018: CAR$^+$mbIL15$^+$Switch$^+$ T cells



- Rapid (<2 days) manufacturing
- Eliminate need to activate, propagate T cells *ex vivo*
- ASH 2017: CAR$^+$ T cells with mbIL15 expand *in vivo* in mice

FIRST-IN-CLASS NON-VIRAL APPROACH

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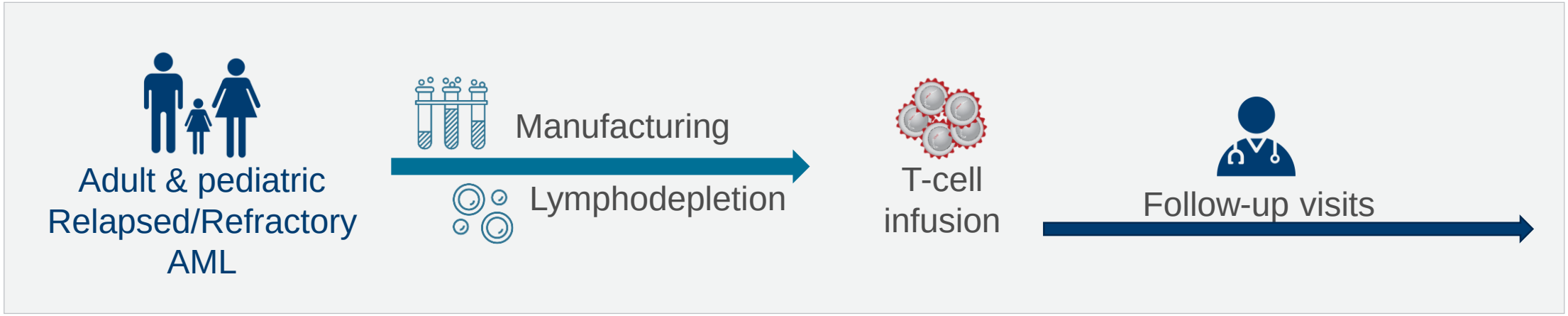
CAR+ T Cells Targeting CD33 on AML

- Trial open at MD Anderson Cancer Center to establish CD33 as a target for CAR+ T cells
- Technology employs lentivirus and kill switch
- Enrollment underway



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NCI Progressing *Sleeping Beauty* to Target Neoantigens in Solid Tumors with TCRs

2018

Preclinical Data ✓ — **CRADA** ✓ — **Clinical Protocol** ✓ — **Validation** ☐ — **Clinical** ☐

original article

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]

Neoantigens unique to each patient's tumor can be recognized by autologous T cells through their T-cell receptor (TCR) but the low frequency and/or terminal differentiation of mutation-specific T cells in tumors can limit their utility as adoptive T-cell therapies. Transfer of TCR genes into younger T cells from peripheral blood with a high proliferative potential could obviate this problem. We generated a rapid, cost-effective strategy to genetically engineer cancer patient T cells with TCRs using the clinical *Sleeping Beauty* transposon/transposase system. Patient-specific TCRs reactive against *HLA-A*0201*-restricted neoantigens AHNAK[mut] or ERBB2[IP,mut] or the *HLA-DQB1*0601*-restricted neoantigen ERBB2IP[mut] were assembled with murine constant chains and cloned into *Sleeping Beauty* transposons. Patient peripheral blood lymphocytes were coelectroporated with SB11 transposase and *Sleeping Beauty* transposon, and transposed T cells were enriched by sorting on murine TCRβ (mTCRβ) expression. Rapid expansion of mTCRβ[+] T cells with irradiated allogeneic peripheral blood lymphocytes feeders, OKT3, interleukin-2 (IL-2), IL-15, and IL-21 resulted in a preponderance of effector (CD27[-]CD45RA[+]) and less-differentiated (CD27[+]CD45RA[+]) T cells. Transposed T cells specifically mounted a polyfunctional response against cognate mutated neoantigens and tumor cell lines. Thus, *Sleeping Beauty* transposition of mutation-specific TCRs can facilitate the use of personalized T-cell therapy targeting unique neoantigens.

INTRODUCTION

Mutation-specific T cells likely play a key role in mediating long-term tumor regressions in adoptive T-cell therapy using tumor-infiltrating lymphocytes (TIL)[1–3] In melanoma, ~20% of the patients treated with TIL and interleukin-2 (IL-2) following a non-myeloablative conditioning regimen achieved durable, complete regression of metastatic disease.[4] Retrospective analysis of these infused T cells revealed that TIL recognized patient-specific, somatic, non-synonymous mutations expressed by tumors.[5–7] Prospective administration of TIL specifically reactive with ERBB2IP[mut] neoantigen resulted in a durable regression of metastatic cholangiocarcinoma indicating that mutation-specific T cells could be used as a treatment for common epithelial cancers.[8,9] Most cancers have tumor-derived mutations which could serve as neoantigens for T cells.[5,10] Therefore, highly tumor-specific T-cell treatments could be potentially generated for any patient with T cells that recognize tumor mutations.

However, the direct use of TIL with desired antigen specificity is not always feasible. Our current method relies on screening multiple independently grown TIL microcultures for reactivity against the patient melanoma, which can be problematic if the tumor/mutation-specific TIL are infrequent or in late/terminal differentiation stages with limited in vivo expansion capacity.[11–13] Alternatively, T-cell receptors (TCRs) from these patient's TIL could be transferred into autologous peripheral blood T cells with a younger phenotype and administered as treatment. This strategy would also allow for a more direct way to test the hypothesis that T cells recognizing somatic mutations can mediate objective tumor regressions.

Generic transfer of patient-specific TCRs will likely require a rapid, flexible, safe, and cost-effective approach. The *Sleeping Beauty* transposon/transposase system is a candidate for this application because it uses DNA plasmids, which are inexpensive to manufacture and easy to manipulate.[14–17] *Sleeping Beauty* transposition was originally developed from fish undergoing their evolutionary maturation and has been adapted for genetic transfer into human cells.[18–20] Cotransfer of two *Sleeping Beauty* DNA plasmids leads to stable transgene expression. The *Sleeping Beauty* transposase plasmid transiently expresses transposase enzyme that digests the second plasmid, the *Sleeping Beauty* transposon, at inverted/direct repeats and ligates the transposon cassette containing the gene of interest, i.e., TCR, into TA dinucleotide repeats within the genome.

Sleeping Beauty plasmids have been approved for use in clinical trials evaluating the ability of T cells modified with chimeric

Correspondence: Steven A Rosenberg, Surgery Branch, National Cancer Institute, 10 Center Drive MSC 1201, CRC Room 3-3940, Bethesda, Maryland 20892, USA. E-mail: sarnoth.gov

JANUARY 2017 - ZIOPHARM and Intrexon Announce CRADA with National Cancer Institute (NCI) Utilizing Sleeping Beauty System to Generate T cells Targeting Neoantigens

NATIONAL CANCER INSTITUTE

Completed

Preparations underway for process validation

"We have used the *Sleeping Beauty* platform to generate neoantigen-specific T cells and look forward to initiating a clinical trial infusing these genetically modified T cells to target solid tumors," **said Steven A. Rosenberg, M.D., Ph.D.,** Chief of the Surgery Branch at the NCI's Center for Cancer Research, who is leading this research. "The *Sleeping Beauty* system is able to target the unique mutations that give rise to a patient's malignancy."

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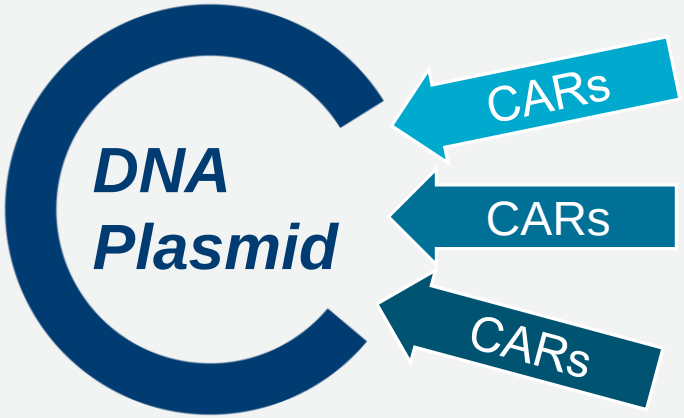
Sleeping Beauty Platform's Versatility, Multiple Targets

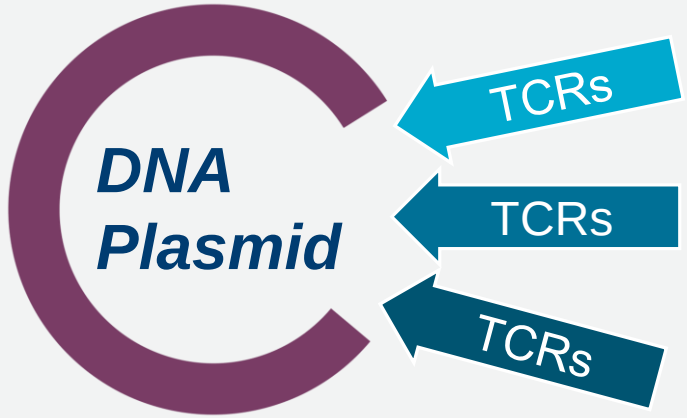


CD19

CD33

Merck KGaA: two targets

Plus others…..



Neoantigens

Sleeping Beauty reprograms T cells to target the personalized neoantigens within solid tumors

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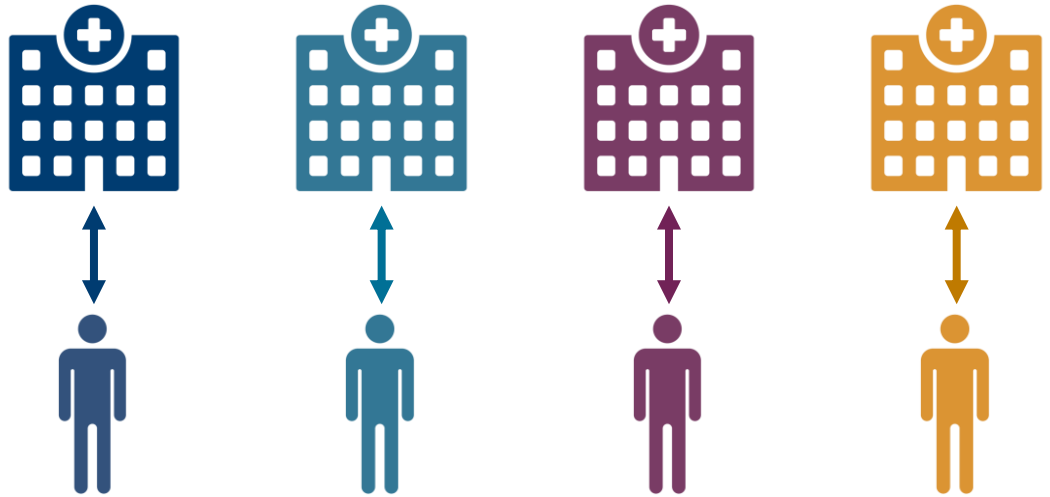
Changing the Paradigm for Manufacturing Genetically Modified T Cells

Centralized Manufacturing

Centralized production is necessary due to the use of viral-based gene transfer which is tied to the need for *ex vivo* numeric expansion

Hospital-based Manufacturing



Distributed production, *e.g.*, in blood banks, envisioned under point-of-care is now possible using non-viral-based gene transfer and undertaking *in vivo* numeric expansion

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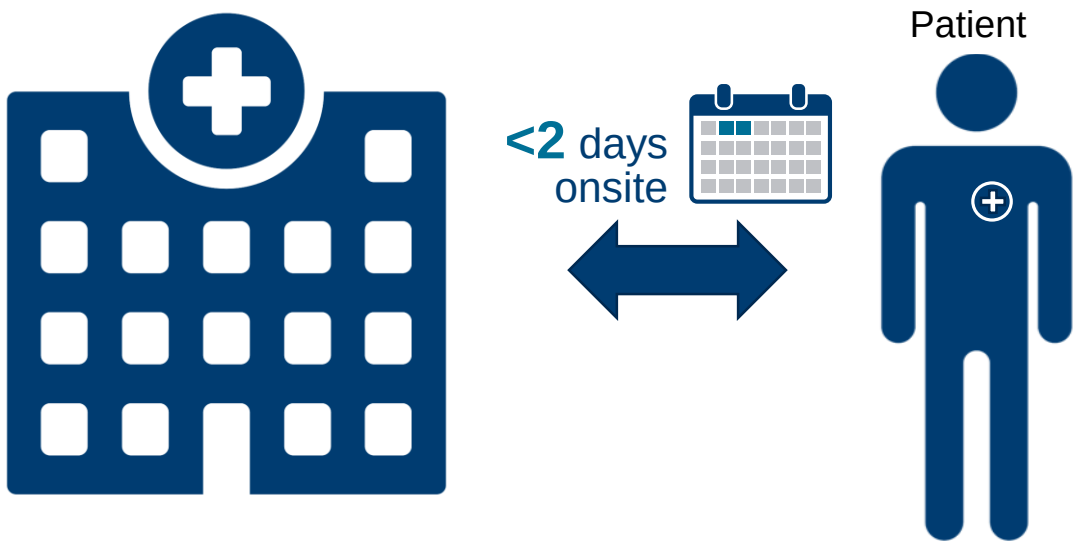
Rolling out Point-of-Care at Hospitals – First Hospital Signed Up



First Hospital Signed Up

- Hospital system holds exclusive regional license
- **Intrexon** and **Ziopharm** receive licensing fees, royalties

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The Year Ahead

Ziopharm ONCOLOGY

Two Platforms with Multiple Milestones in 2018

Controlled IL-12 with RTS®

Off to a great start

- Combination trial with nivolumab
- Stereotactic adult & pediatric trials

To be initiated

- Pivotal, randomized control trial

Sleeping Beauty

Off to a great start

- 2nd Gen. Phase 1 CAR+ CD19
- Trial evaluating CD33 as a target

To be initiated

- P-O-C Phase 1 targeting CD19
- Phase 1 w/ Merck KGaA CAR+ T cells
- NCI: File IND for Phase 1 study of SB-modified TCRs to target neoantigens

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Financial Update as of Sept. 30, 2017

Condensed Consolidated Balance Sheet

Cash, cash equivalents and short term investments	$84.4M
At MD Anderson Cancer Center from prepayment for programs to be conducted by the Company	$29.4M

Current resources will be sufficient to fund planned operations into the fourth quarter of 2018

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January 2018