# UNITED STATES
# SECURITIES AND EXCHANGE COMMISSION
**Washington, D.C. 20549**

## FORM 8-K

**CURRENT REPORT**
**PURSUANT TO SECTION 13 OR 15(d) OF THE**
**SECURITIES EXCHANGE ACT OF 1934**

**Date of report (Date of earliest event reported): June 9, 2016**

# ZIOPHARM Oncology, Inc.
**(Exact Name of Registrant as Specified in Charter)**

| **Delaware** | **001-33038** | **84-1475642** |
|---|---|---|
| **(State or Other Jurisdiction of Incorporation)** | **(Commission File Number)** | **(IRS Employer Identification No.)** |

**One First Avenue, Parris Building 34, Navy Yard Plaza**
**Boston, Massachusetts** **02129**
**(Address of Principal Executive Offices)** **(Zip Code)**

**(617) 259-1970**
**(Registrant's Telephone Number, including Area Code)**

**Not applicable**
**(Former Name or Former Address, if Changed Since Last Report)**

Check the appropriate box below if the Form 8-K is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425).

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12).

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b)).

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c)).

**Item 7.01 Regulation FD Disclosure**

On June 9, 2016, ZIOPHARM Oncology, Inc., or the Company, will present the attached presentation at the Jefferies 2016 Healthcare Conference in New York, New York.

A copy of the above referenced presentation is furnished as Exhibit 99.1 to this Current Report on Form 8-K. This information, including the information contained in the presentation furnished as Exhibit 99.1, shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, and is not incorporated by reference into any of the Company's filings, whether made before or after the date hereof, regardless of any general incorporation language in any such filing.

**Item 9.01 Financial Statements and Exhibits**

(d) Exhibits

| Exhibit No. | Description |
|---|---|
| 99.1 | Presentation of the Company dated June 9, 2016 |

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

ZIOPHARM Oncology, Inc.

By: /s/ Kevin G. Lafond
Name: Kevin G. Lafond
Title: Vice President Finance, Chief Accounting Officer
and Treasurer

Date: June 9, 2016

**INDEX OF EXHIBITS**

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Exhibit 99.1

# ZIOPHARM Oncology

## Jefferies 2016 Healthcare Conference

June 2016

ZIOPHARM Oncology

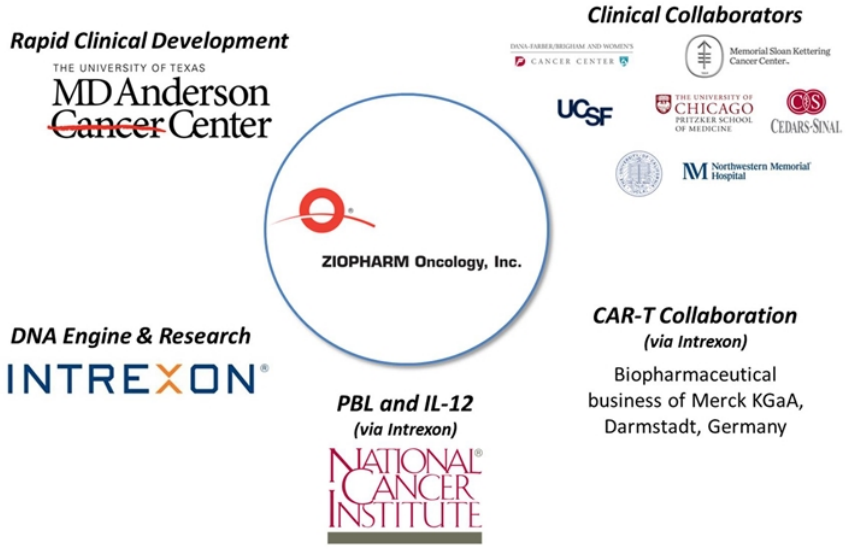
# Forward-looking statements

ZIOPHARM Oncology

*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 pre-clinical 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, 2015, and our Quarterly Report on Form 10-Q for the quarter ended March 31, 2016. 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.*

# Partnerships to implement multiple immunotherapies

ZIOPHARM Oncology




Well capitalized with cash and equivalents of $124.8M at Q1 16, providing resources to fund operations into Q4 2017

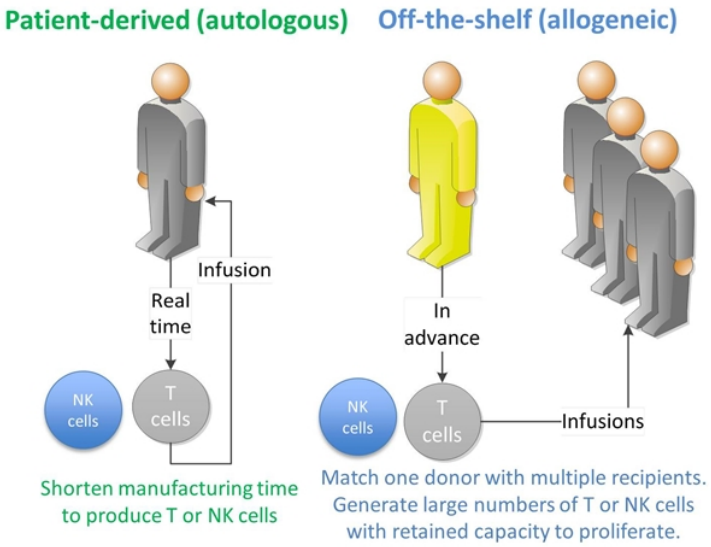
***Laurence Cooper, MD, PhD***

- Named CEO in May 2015
- Developed *Sleeping Beauty* technology in-licensed by ZIOP/XON in Jan 2015
- Previously, Professor of Pediatric Oncology at MD Anderson Cancer Center (MDACC) where he led the bone marrow transplant program and developed significant expertise in immunotherapy

# Bio-engineering and bio-processing to execute tumor cells

ZIOPHARM Oncology

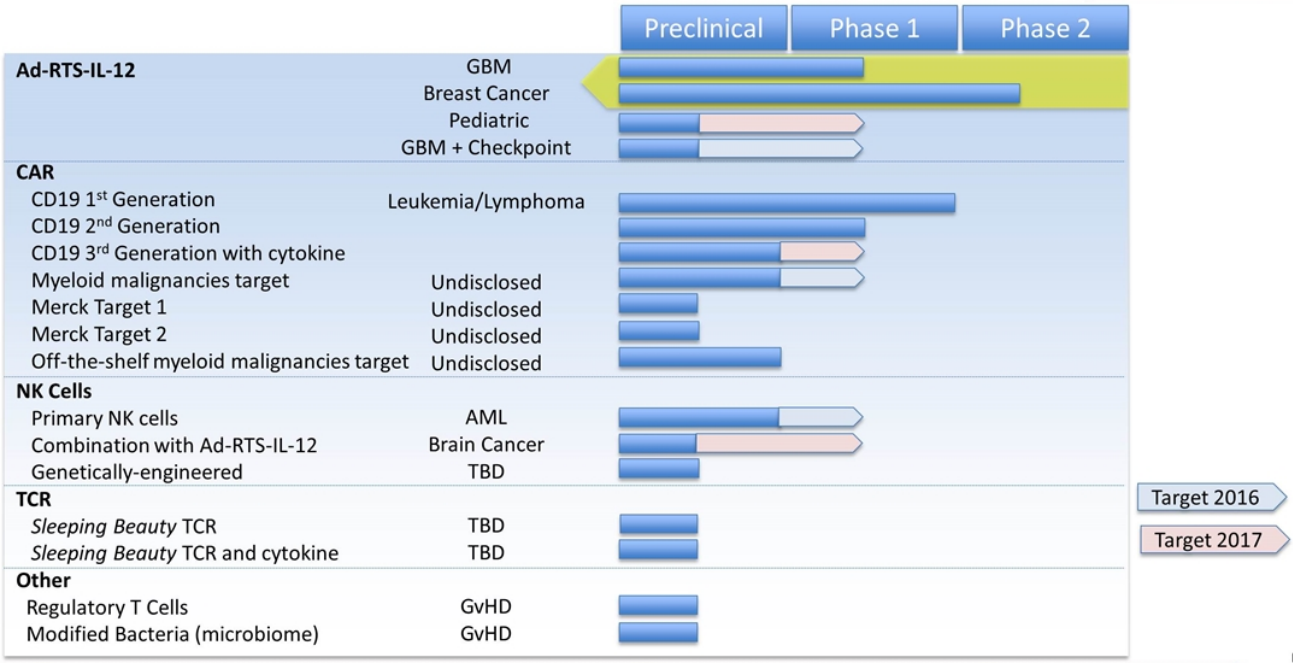
- Technologies
  - CARs, TCRs, Cytokines, RTS, non-viral gene transfer, T cells, NK cells
- Combinations
  - Cytokine & CAR, Cytokine & Checkpoint Inhibitor
- Implementing manufacturing processes for both autologous and allogeneic settings
- Targeting hematologic malignancies and solid tumors
- Continued optimization of manufacturing process to improve performance
- Leveraging manufacturing through the MDACC and CMOs




Molecular Therapy (2016); doi:10.1038/mt.2016.106.

# Addressing unmet medical needs: pipeline

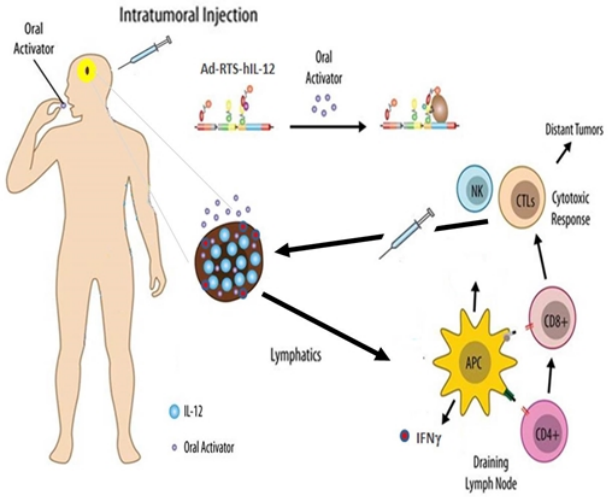
ZIOPHARM Oncology



# Controlled intra-tumor delivery of IL-12
# Ad-RTS-IL-12 + veledimex

ZIOPHARM Oncology

Ad injected intratumorally → Oral ligand activates gene switch → Localized production of IL-12 → T-cell activation to tumor-associated antigens → Influx of CD8+ T cells and reduction in CD4+ Tregs



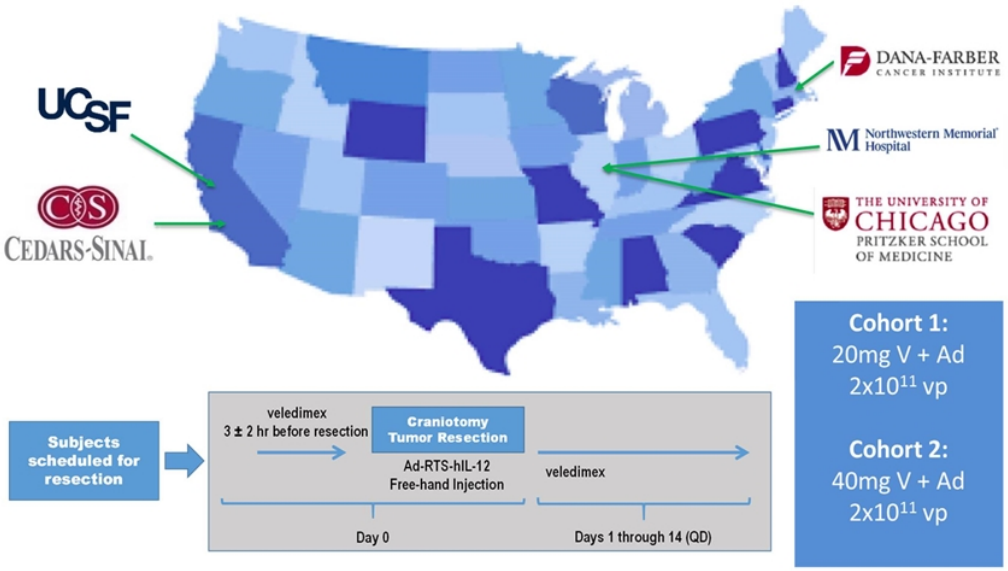

## IL-12

- Pro-inflammatory cytokine can reverse immune escape mechanisms and improve the function of tumor-fighting T cells
- Ad-RTS-IL-12 + veledimex (V, oral ligand) explores local treatment strategy under the control of the RheoSwitch Therapeutic System® (RTS®) gene switch to modulate the IL-12 therapeutic window
- Expression of functional IL-12 in human subjects by direct intratumoral injection of Ad-RTS-hIL-12 + veledimex generates downstream IFN-γ and elevation of IL-10 and IP-10
- We have previously demonstrated that intratumoral administration of Ad-RTS-IL-12 results in targeted tumor cytotoxicity and the induction of systemic T cell memory
- As of May 31st, we have safely treated 60 patients

# A study of Ad-RTS-hIL-12 with veledimex in subjects with glioblastoma or malignant glioma

ZIOPHARM Oncology

- GBM affects approximately 74,000 people worldwide each year
- Recurrent GBM has one of the lowest 3-year survival rates: 3%, among all cancers.
- For multiple recurrence, median overall survival (OS) is of 6 to 7 months
- OS in patients that have failed temozolomide and bevacizumab, or equivalent salvage chemotherapy, is approximately 3-5 months





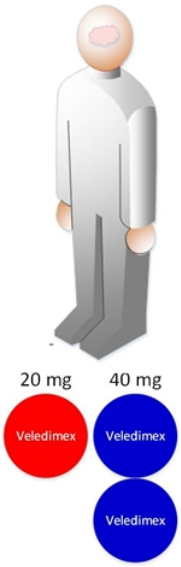


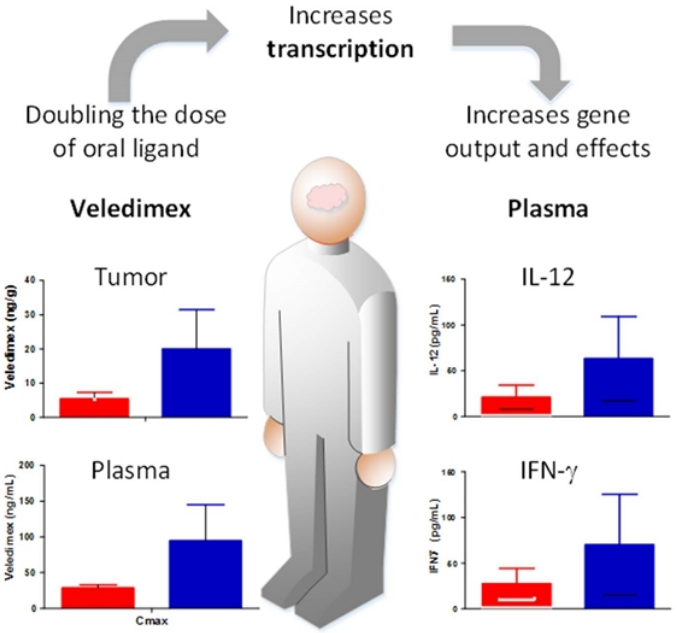
**Cohort 1:**
20mg V + Ad
$2x10^{11}$ vp

**Cohort 2:**
40mg V + Ad
$2x10^{11}$ vp

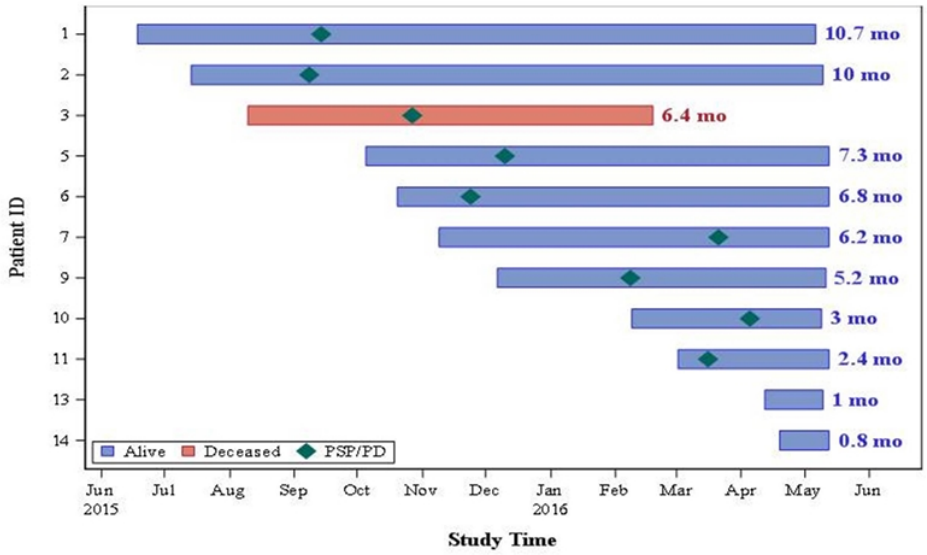
Clinicaltrials.gov: NCT02026271.

# RTS® switch responds to the dose of veledimex in patients with recurrent GBM



# Early data suggests benefit with a favorable trend in overall survival




- Too early to determine pseudoprogression versus progression
  - All pseudoprogression / progression are assumed to trigger PD for PFS analysis
  - Clinical benefit including long term survival and tumor regression, can occur after initial disease progression or after the appearance of new lesions in iRANO*
- Median OS has not been reached; median follow-up is 6.2 months with 10 out of 11 alive
- Data as of May 2016

*Okada, H., M. Weller, et al. (2015). "Immunotherapy response assessment in neuro-oncology: a report of the RANO working group." Lancet 16: 534-542.

# Safety summary from GBM study to date (N = 11)

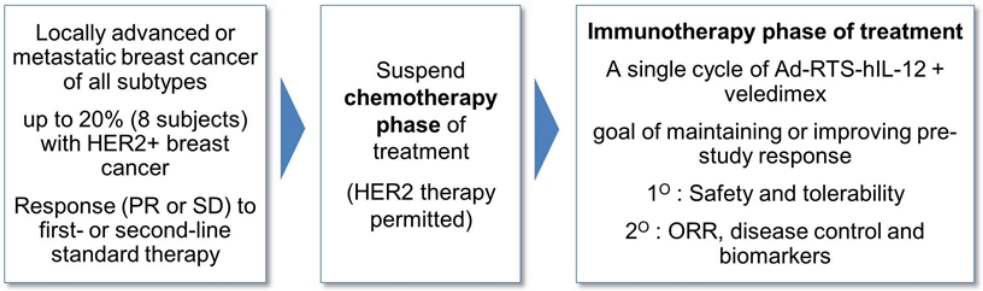
ZIOPHARM Oncology

- Overall Ad-RTS-hIL12 + veledimex was well tolerated
- Neurotoxicities were manageable and reversible
- All serious adverse events (SAEs) and Grade 3 related toxicities were found to be rapidly reversible upon discontinuation of veledimex
- Common related adverse events (most Grade 1 and 2) include headache, fever, nausea / vomiting, WBC /leukocyte count decreased, platelet count decreased, and LFTs increased
- Four subjects had related SAEs
  - One had a headache, nausea, vomiting, leukopenia, neutropenia, thrombocytopenia
  - One had aseptic meningitis
  - One had mild cytokine release syndrome
  - One had platelet count decreased and ALT increased
- Enrollment and dose escalation ongoing

# A study of Ad-RTS-hIL-12 with veledimex in subjects with breast cancer

ZIOPHARM Oncology

**Phase 1b/2 study to examine the safety, tolerability and preliminary efficacy of one cycle of Ad-RTS-hIL-12 with veledimex following achievement of stable disease (SD) or partial response (PR) on standard first or second-line chemotherapy in breast cancer subjects**

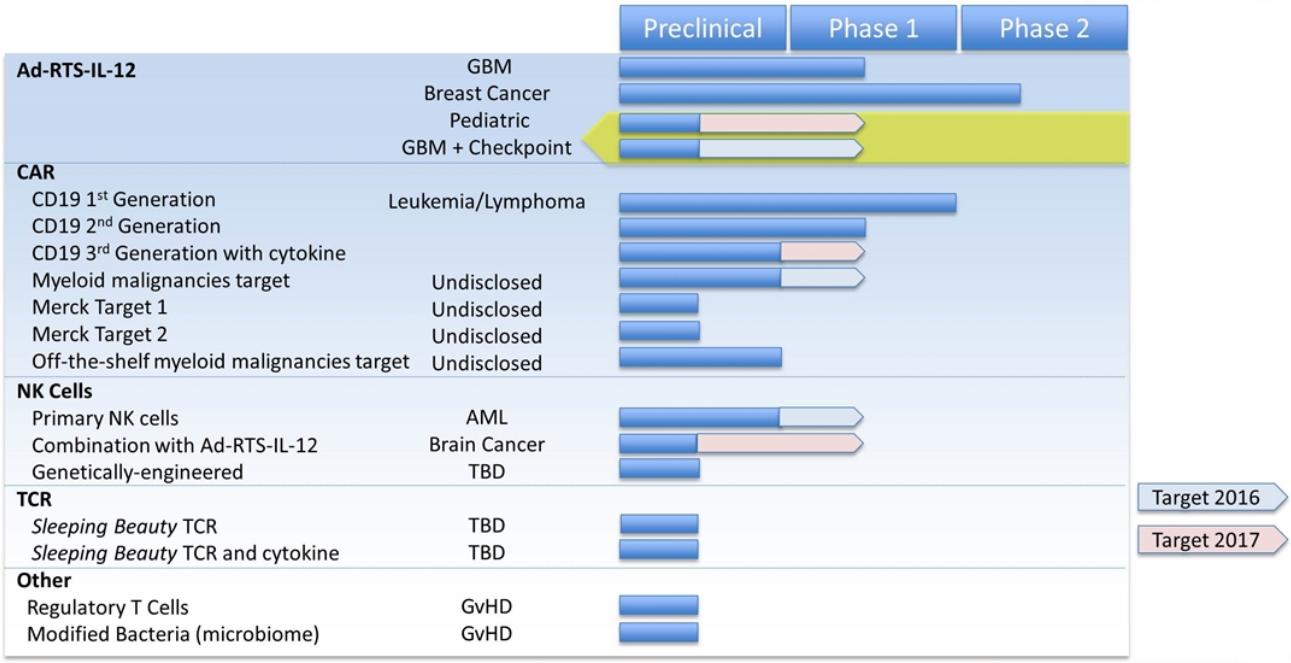



- Patient accrual: 9 subjects have been enrolled (8 $HER2^{neg}$ disease and 1 $HER2^{+}$ disease)
- Biomarker analyses underway
- "On-target toxicities" as expected and promptly reversible upon stopping veledimex
- Data as of May 2016

Clinicaltrials.gov: NCT02423902.

# Addressing unmet medical needs: pipeline

ZIOPHARM Oncology



# Next steps for Ad-RTS-IL-12

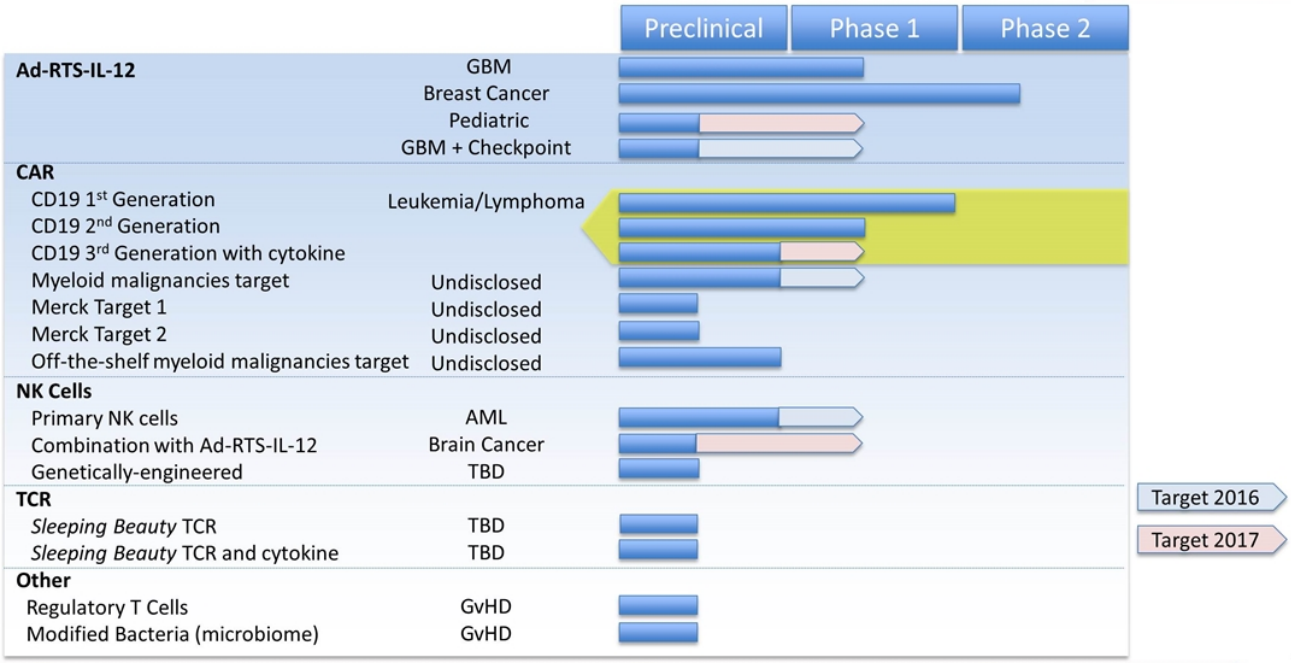
ZIOPHARM Oncology

- Pediatric program
  - Target refractory brain tumors in children
    - Pre-clinical data at Society for Neuro Oncology Annual Meeting (November 2016)

- Combination program
  - Combining Ad-RTS-hIL-12 with immune checkpoint inhibitors
    - American Society of Cell and Gene Therapy oral presentation May 2016
    - Survival of mice treated with adenovirus-delivered IL-12 and anti-PD-1 therapy was superior to either treatment alone, with a combination demonstrating 100% survival
    - Initiate combination study of Ad-RTS-hIL-12 with anti PD-1

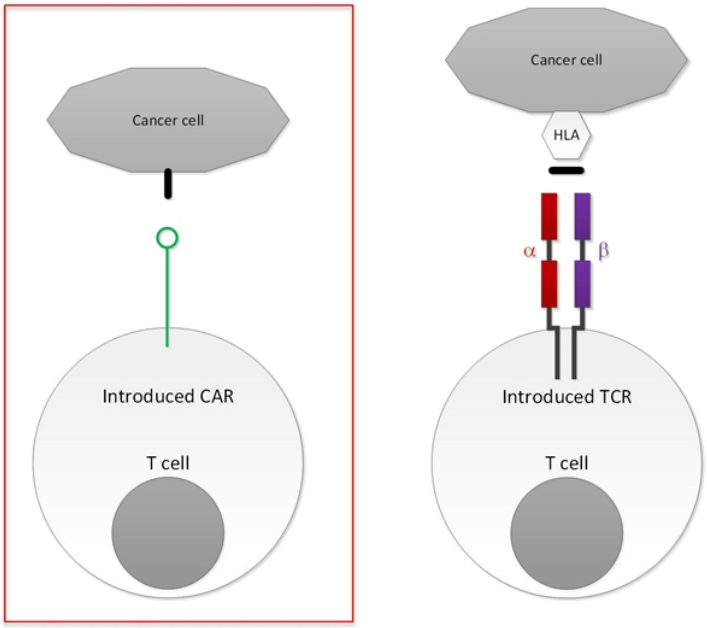
# Addressing unmet medical needs: pipeline

ZIOPHARM Oncology



# Targeting tumor antigens with CARs and TCRs

ZIOPHARM Oncology



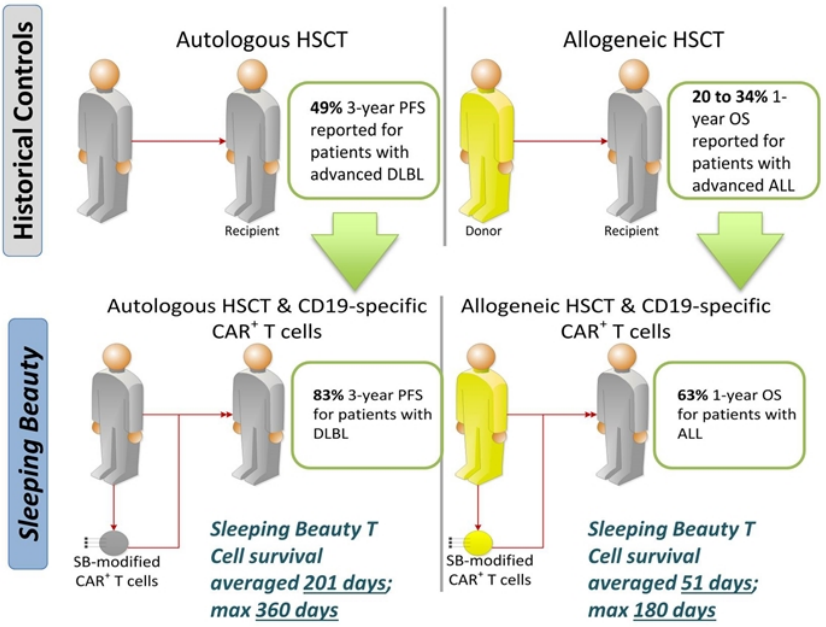
# *Sleeping Beauty*: First-in-human study using non-viral gene transfer

ZIOPHARM Oncology

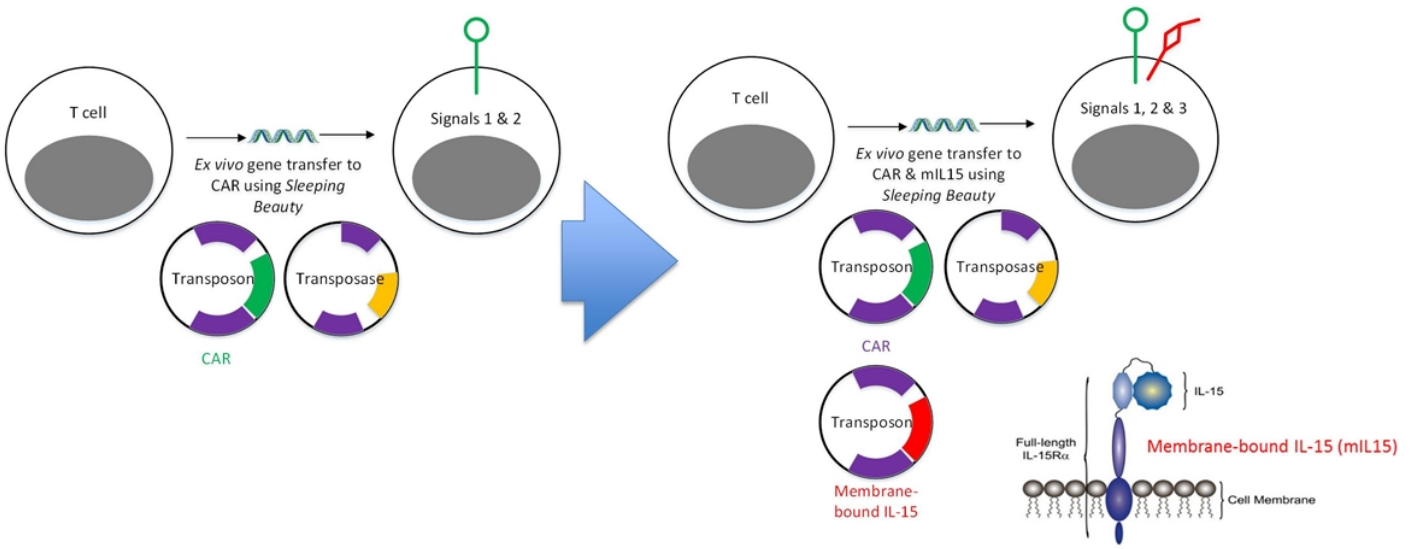
**Long-term follow-up data from 1st generation *Sleeping Beauty* platform** in two trials infusing CAR+ T cells *after* hematopoietic stem-cell transplantation (HSCT)

- Showed favorable PFS and OS trends in both autologous and allogeneic cohorts
- Non-viral *Sleeping Beauty* T-cell survival compared favorably versus viral approaches
- 2nd generation *Sleeping Beauty* trial underway

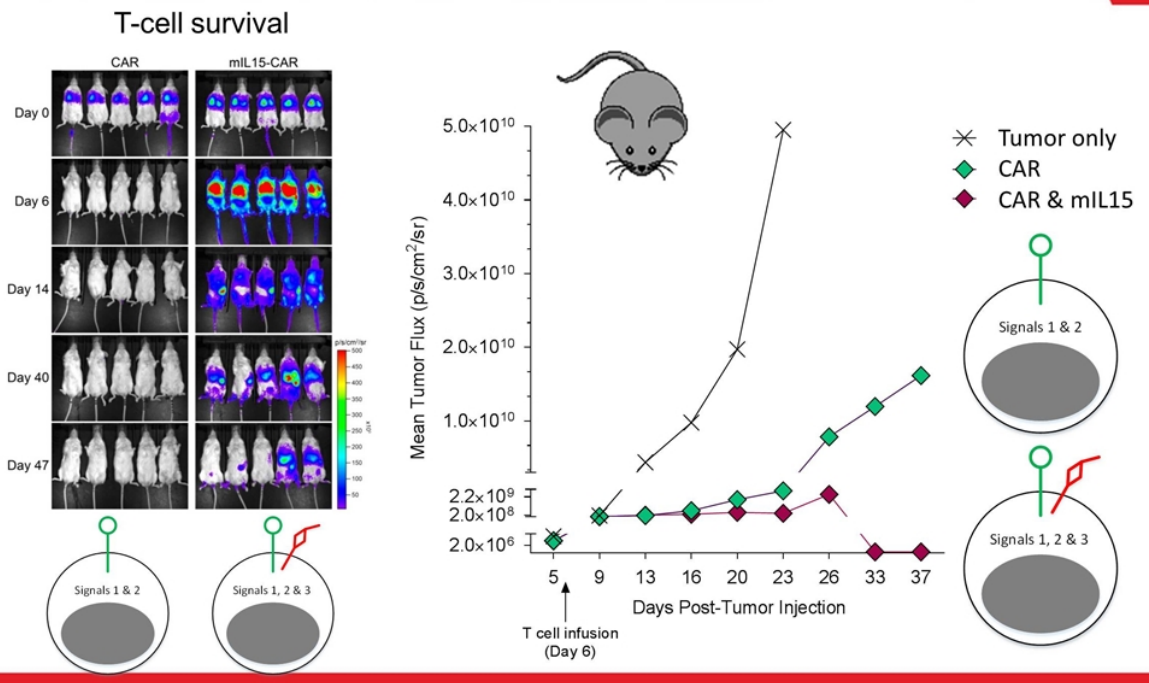
Accepted for publication JCI



# Improving CAR+ T cells by co-signaling through IL-15 receptor



# Improving CAR+ T cells by co-signaling through IL-15 receptor



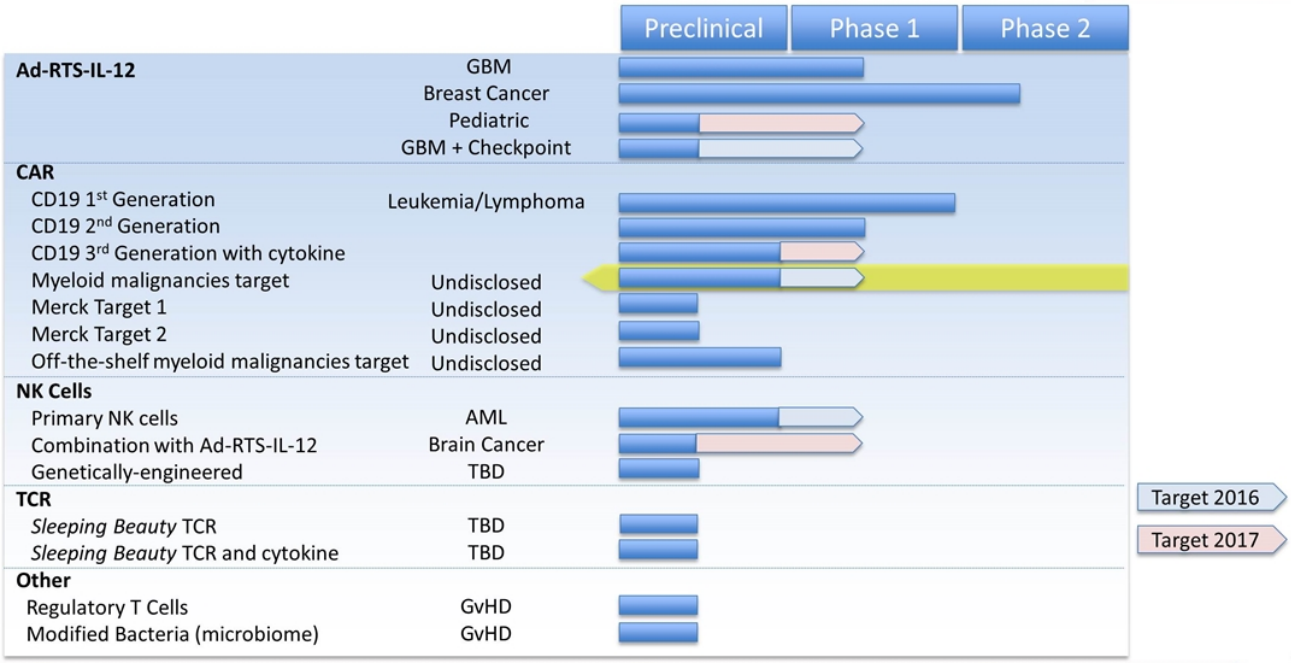
# Reducing manufacturing time to generate CAR+ T cells using the *Sleeping Beauty* (SB) system

ZIOPHARM Oncology

- American Society of Cell and Gene Therapy oral presentation (May 2016)
  - Fundamental to advancing SB platform, and any modified cell-based therapy, into a broadly deployed treatment option is a streamlined, simplified, and shortened manufacturing process, with a reduction in the associated cost
  - Decreasing the time the SB-modified CD19-specfic T cells were in culture to 14 days improved the anti-tumor effect, providing support for ZIOPHARM's efforts to address the challenges of cost and time of bioprocessing cell therapies

# Addressing unmet medical needs: pipeline

ZIOPHARM Oncology

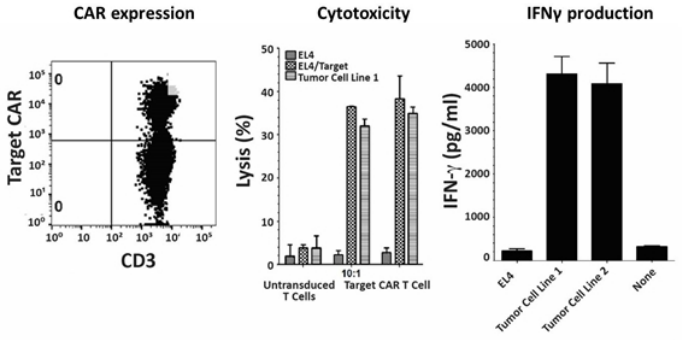


# CAR+ T-cell platform to target myeloid malignancies

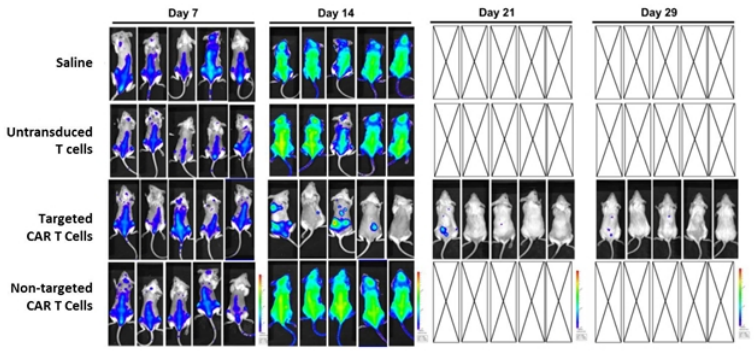
ZIOPHARM Oncology

- Immunotherapy of tumors with unmet needs outside of the crowded viral CAR T treatment landscape for CD19+ malignancies

- Rapidly advancing a CAR T target for myeloid malignancies:
  - Encouraging pre-clinical data including CAR expression, cytotoxicity, and IFN-γ production
  - Clinical trial is planned for 2016

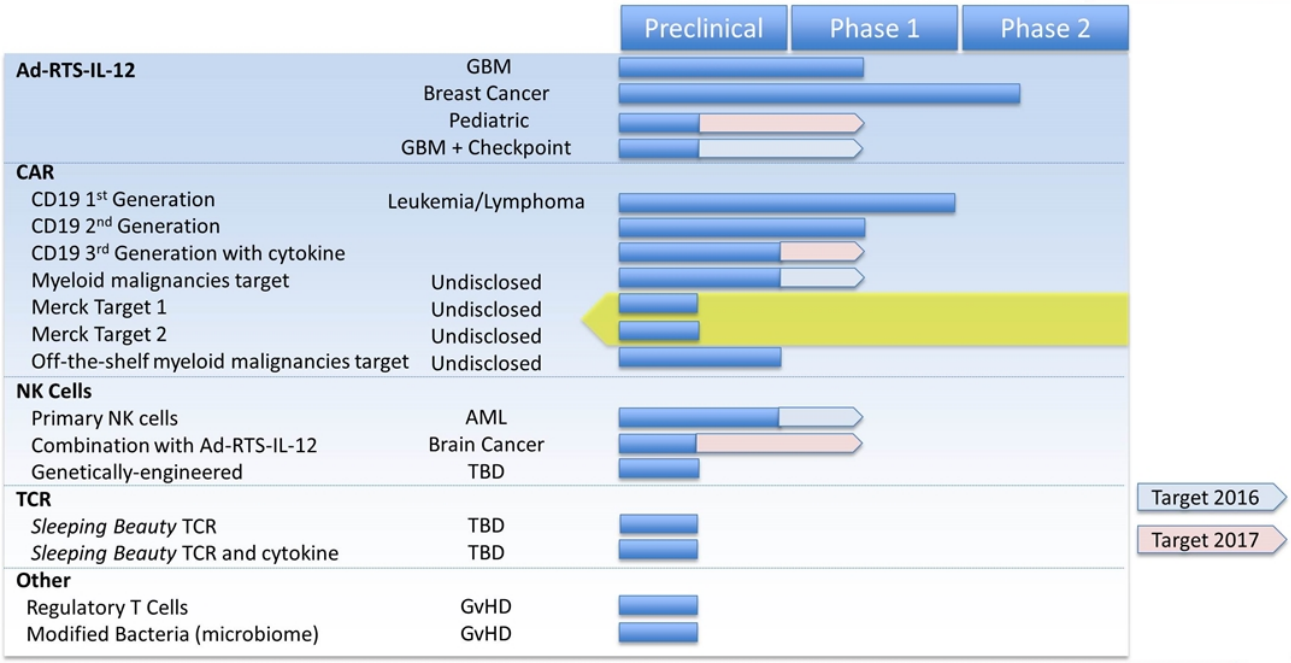



***In vivo* model for myeloid malignancies CAR-T target**



# Addressing unmet medical needs: pipeline

ZIOPHARM Oncology



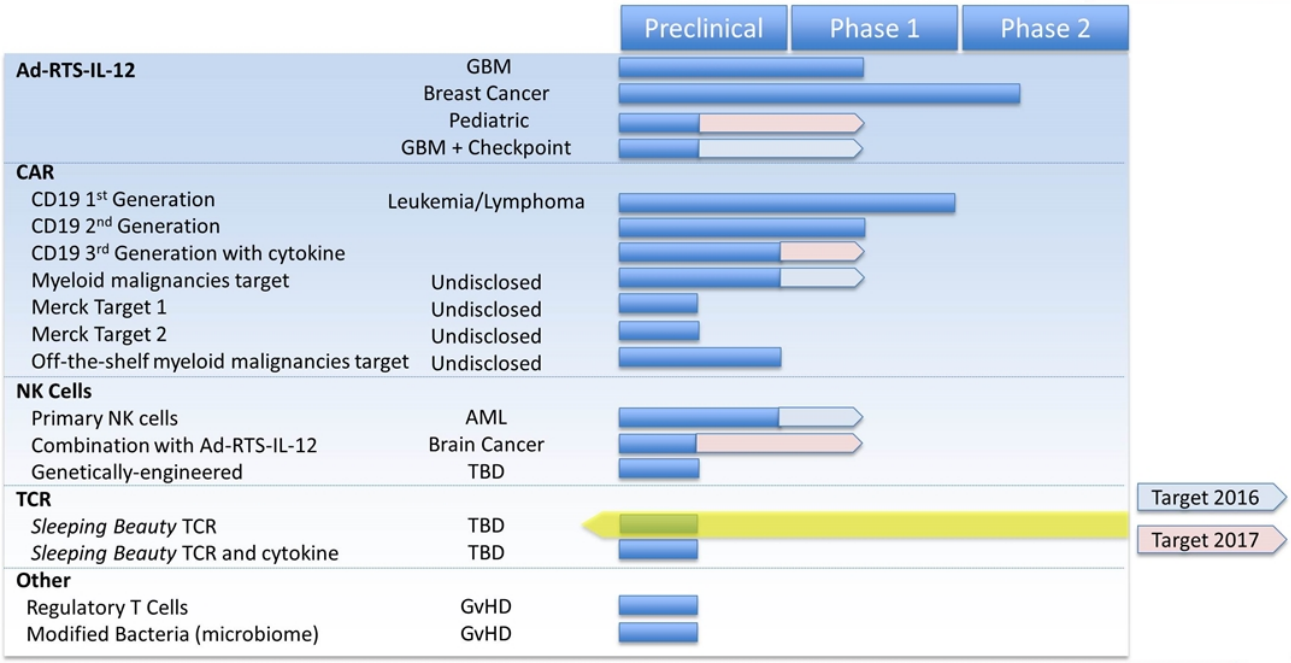
# Intrexon/Merck KGaA, Darmstadt, Germany in CAR-T

ZIOPHARM Oncology

- Exclusive agreement to develop and commercialize CAR-T cancer therapies
- 2 novel CAR T targets nominated
- Merck KGaA, Darmstadt, Germany to lead IND filing and pre-IND interactions, clinical development and commercialization
- Intrexon and ZIOPHARM retain ability to explore targets independently, granting Merck KGaA opt-in rights during clinical development
- Economics divided evenly between ZIOPHARM and Intrexon
  - $413 million per product in milestones
  - Tiered royalties up to lower-double digits on net sales

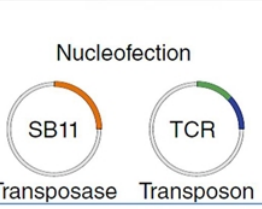
# Addressing unmet medical needs: pipeline

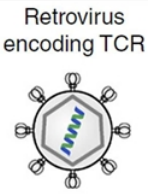
ZIOPHARM Oncology



# *Sleeping Beauty* (SB): Non-viral approach key for targeting intracellular antigens by TCRs

ZIOPHARM Oncology

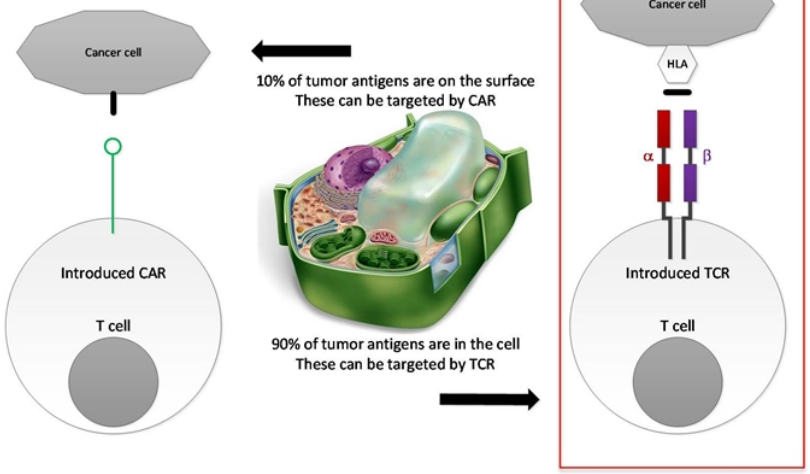


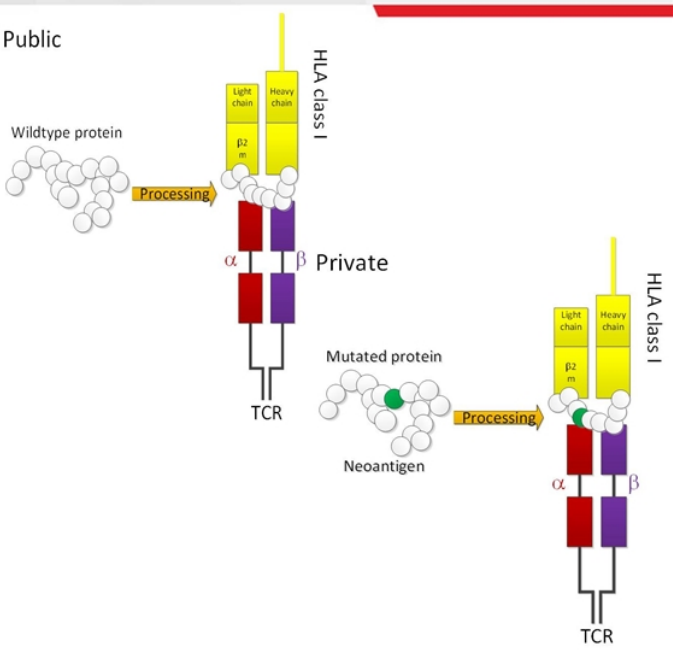




| Non-viral *Sleeping Beauty* | Viral delivery |
|---|---|
| Target tumor antigens via multiple TCRs | Limited appeal for targeting multiple intracellular antigens via TCRs |
| Cost-effective approach | High cost approach |
| Rapid manufacture | Labor intensive, slow manufacture |
| Express multiple genes by combining DNA plasmids | Packaging limits the cargo load |
| Customizable, able to swap in different receptors | Challenging to customize |

# Targeting intracellular antigens: The key to implementing T-cell therapy for solid tumors

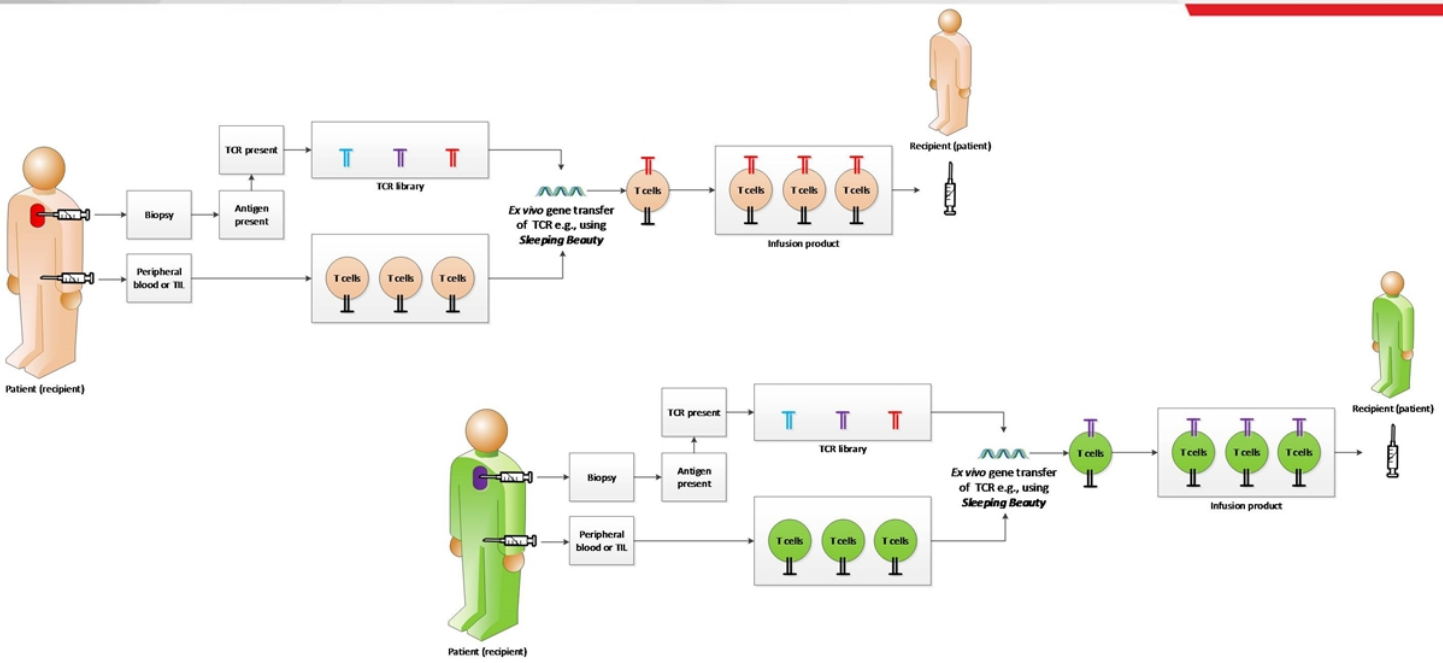
ZIOPHARM Oncology



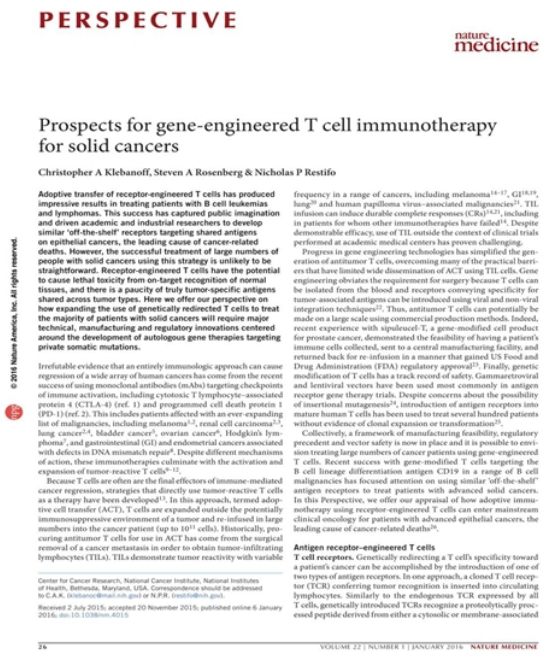
# Targeting “shared” intracellular tumor antigens using a library of TCRs

ZIOPHARM Oncology



# Targeting “private” intracellular tumor antigens (neoantigens)

ZIOPHARM Oncology



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[3,4], 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 cells**

**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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- *“Clinical evidence supports the hypothesis that immunogenic products of somatic mutations unique to each patient’s cancer—so-called neoantigens—are the relevant targets for successful immunotherapies”*
- *“Success for cell-based immunotherapies may come from the arduous task of targeting the unique set of mutations that cause each patient’s cancer”*
- *“Presently, use of the Sleeping Beauty (SB) transposon / transposase system has advanced farthest in clinical development"*

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

# Targeting neoantigens deploying personalized TCR-modified T cells

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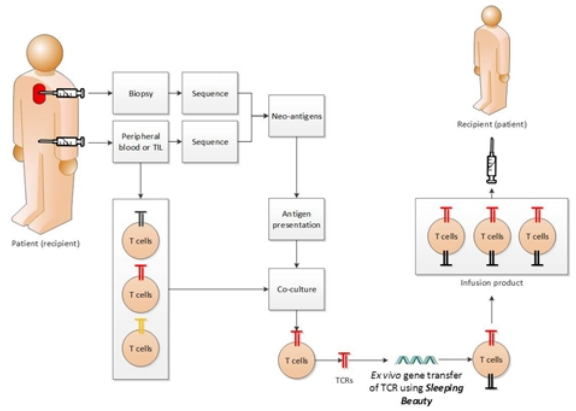
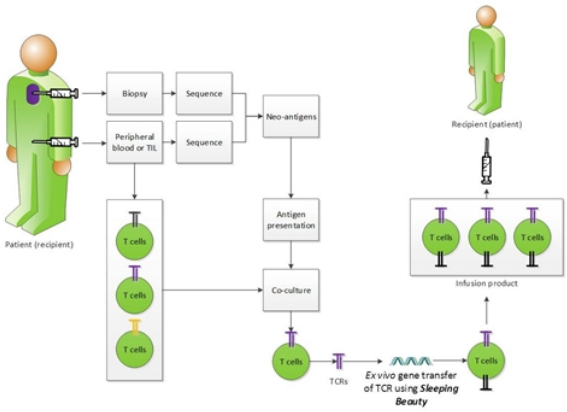
- Tumor antigen is not known before the patient arrives
- Tumor and normal cells are interrogated to determine the neoantigen
- TCRs against known tumor antigen are prepared in real time
- TCR expressed in autologous T cells using SB platform



# Neoantigen-specific TCRs expressed using SB system to target solid tumors

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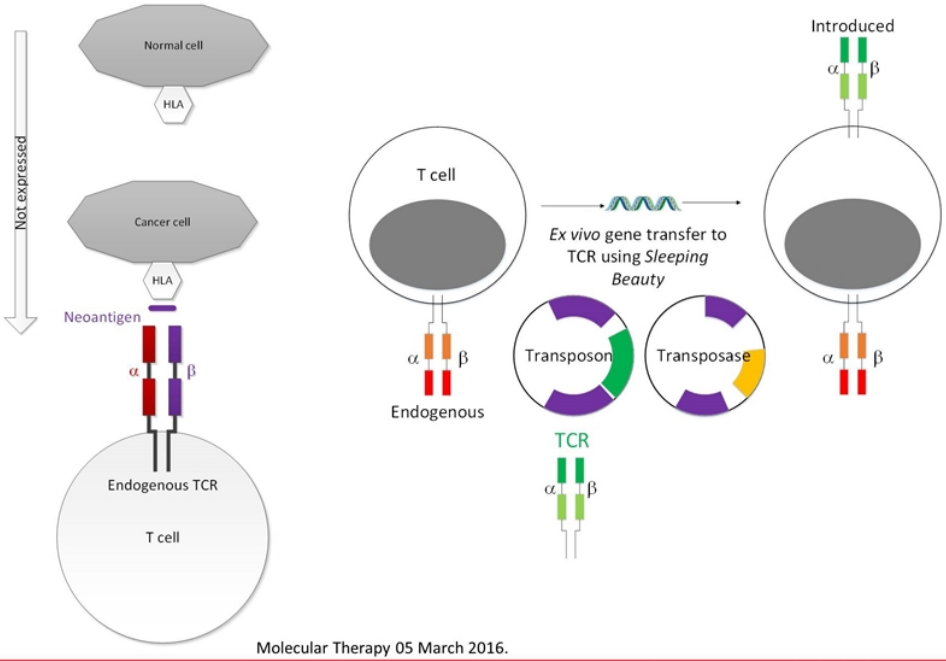


Molecular Therapy 05 March 2016.



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]

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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*-restriced neoantigens AHNAK$^{S2373F}$ or ERBB2IP$^{E285K}$ or the *HLA-DQB*0601*-restricted neoantigen ERBB2IP$^{E285K}$ 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.

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### 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.[4,5] Retrospective analysis of these infused T cells revealed that TIL recognized patient-specific, somatic, non-synonymous mutations expressed by tumors.[6–8] Prospective administration of TIL specifically reactive with ERBB2IP$^{E285K}$ 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.[9,10] Most cancers have tumor-derived mutations which could serve as neoantigens for T cells.[11,12] 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 mutanome, which can be problematic if the tumor/mutation-specific TIL are infrequent or in late/terminal differentiation stages with limited *in vivo* expansion capacity.[13–15] 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.

Genetic 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.[16,17] *Sleeping Beauty* transposition was originally developed from fish undergoing their evolutionary maturation and has been adapted for genetic transfer into human cells.[18,19] 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

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# Addressing unmet medical needs: pipeline

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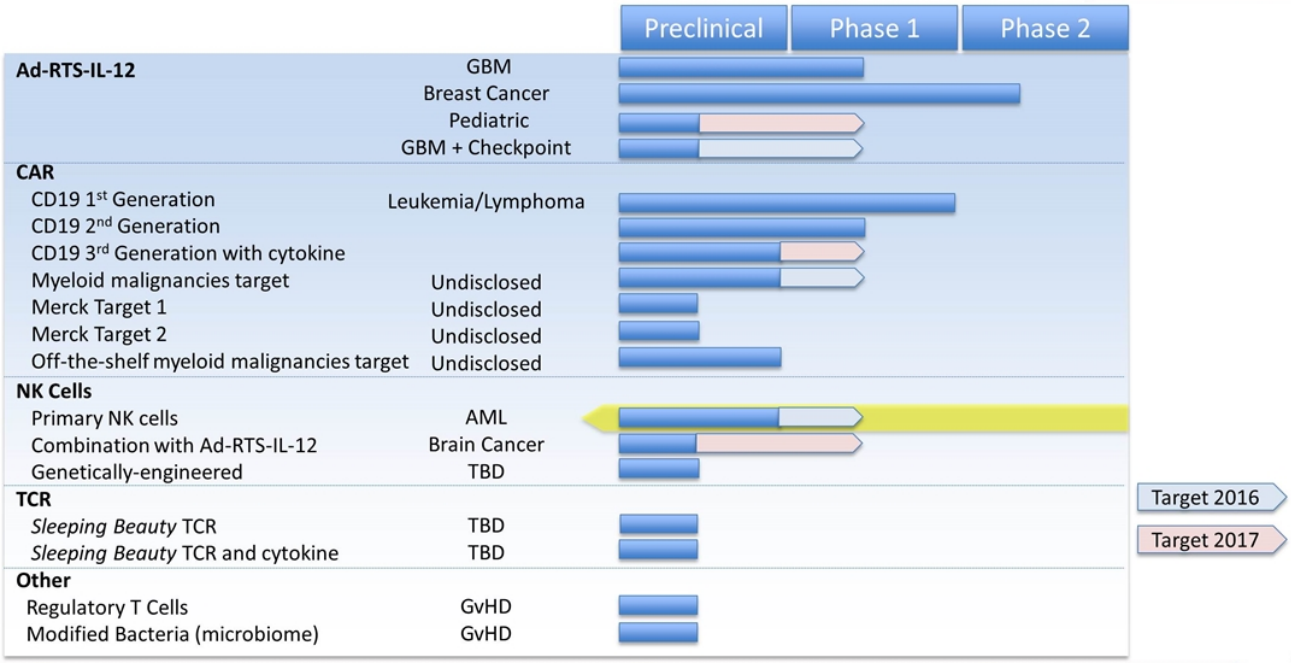

# Natural Killer Cells: Beyond CAR+ T cells

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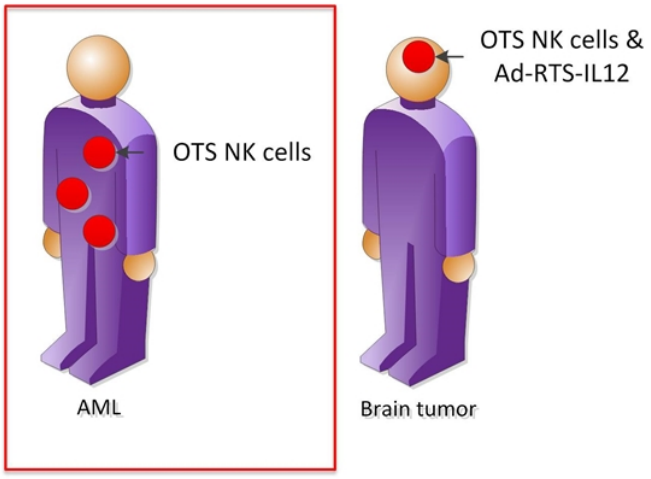
## Natural killer (NK) cells

- Target tumors such as AML so do not require CAR
  - Killing is independent of a specific (known) target antigen
- Do not have T-cell receptor (TCR), so do not require genetic editing to eliminate TCR
  - May be used as an off-the-shelf therapeutic
- Cytokines, *e.g.,* IL-12 are "fuel" for NK cells
- Build on promising proof-of-principle trials ongoing at MDACC infusing autologous and allogeneic NK cells
  - Manufactured using designer feeder cells to generate large numbers

***Launching Phase 1 trials of off-the-shelf NK cells for AML and brain tumors in 2016 & 2017***



# Addressing unmet medical needs: pipeline

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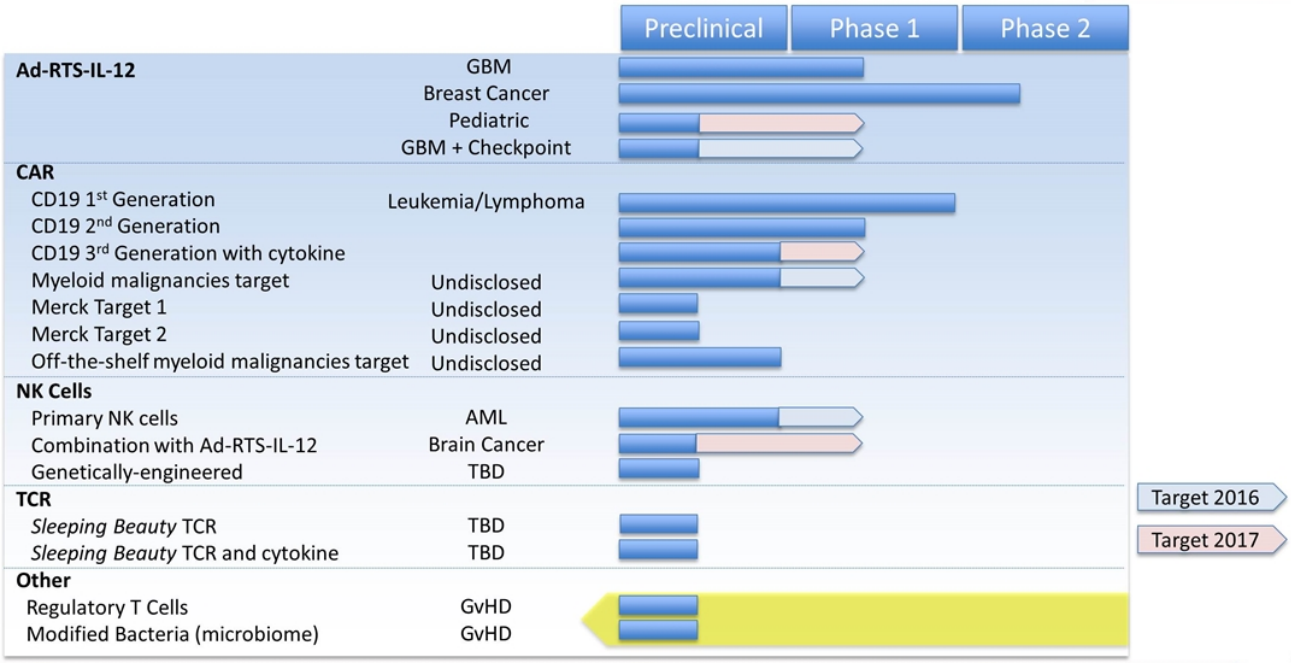
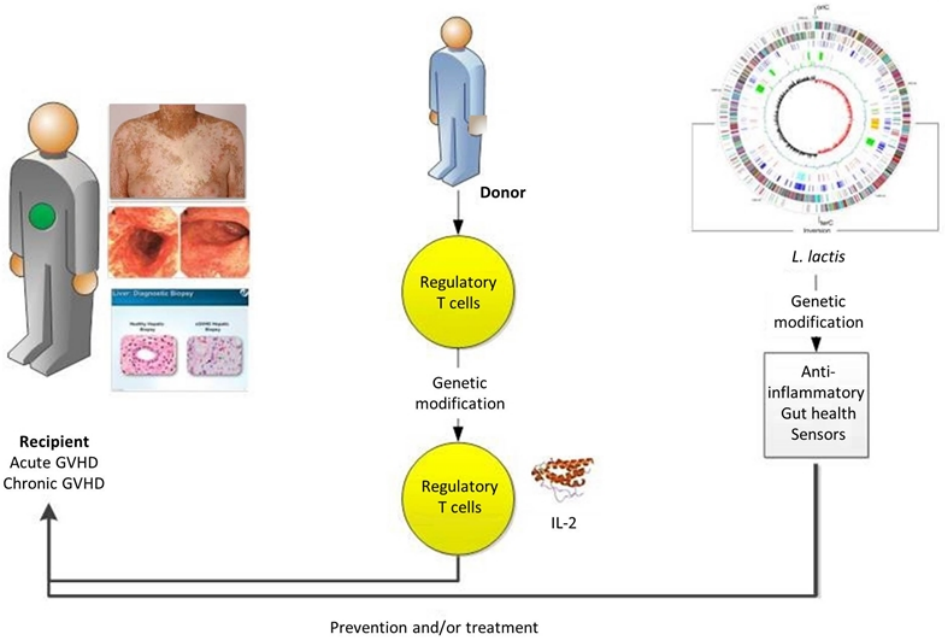


# Regulatory T cells and manipulating the microbiome for graft-versus-host-disease (GvHD)



# Multiple immunotherapies and combination immunotherapies are needed and being administered

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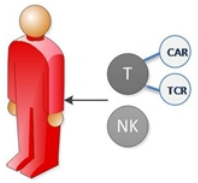
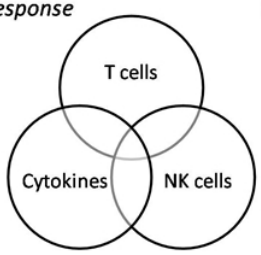
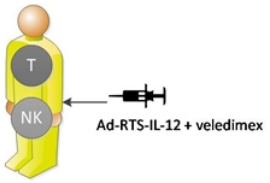
***Current Clinical Approaches leading to combination immunotherapy***

*Administer modified immune cells to provide effective anti-tumor response*




*Administer IL-12 via controlled gene therapy to bolster endogenous immune response*




- We stand alone in our ability to control the delivery of IL-12
- We stand alone in being able to harness non-viral DNA as a method to genetically control T cells
- We are launching multiple immunotherapy trials
  - Trial initiated with 2nd generation CD19 CAR-T utilizing non-viral *Sleeping Beauty* platform
  - Three new trials in 2016: Combination immunotherapy, viral CAR-T, and NK cells
- We are combining different elements of the immune system (*e.g.*, Ad-RTS-IL-12 and CPI)
- We have an ecosystem to efficiently develop and test new ideas in the clinic
- We have an expanding and unique platform to control the immune system

# ZIOPHARM Oncology

Jefferies 2016 Healthcare Conference
June 2016

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