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): **July 14, 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 July 14, 2016, ZIOPHARM Oncology, Inc., or the Company, will present the attached presentation at the American Society of Hematology Workshop on Genome Editing in Washington, DC.

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 July 14, 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.

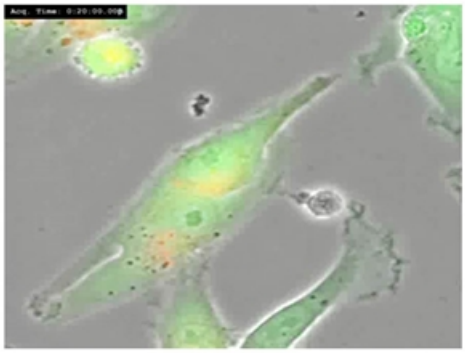
Date: July 14, 2016

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

INDEX OF EXHIBITS

Exhibit No.	Description
99.1	Presentation of the Company dated July 14, 2016

Exhibit 99.1



The "ins" and "outs" of Genetic Engineering of T cells for Human Applications

Laurence Cooper M.D., Ph.D.
ljncooper@ziopharm.com

ASH workshop 3:55 to 4:15 pm
July 14, 2016

ZIOPHARM Oncology, Inc.

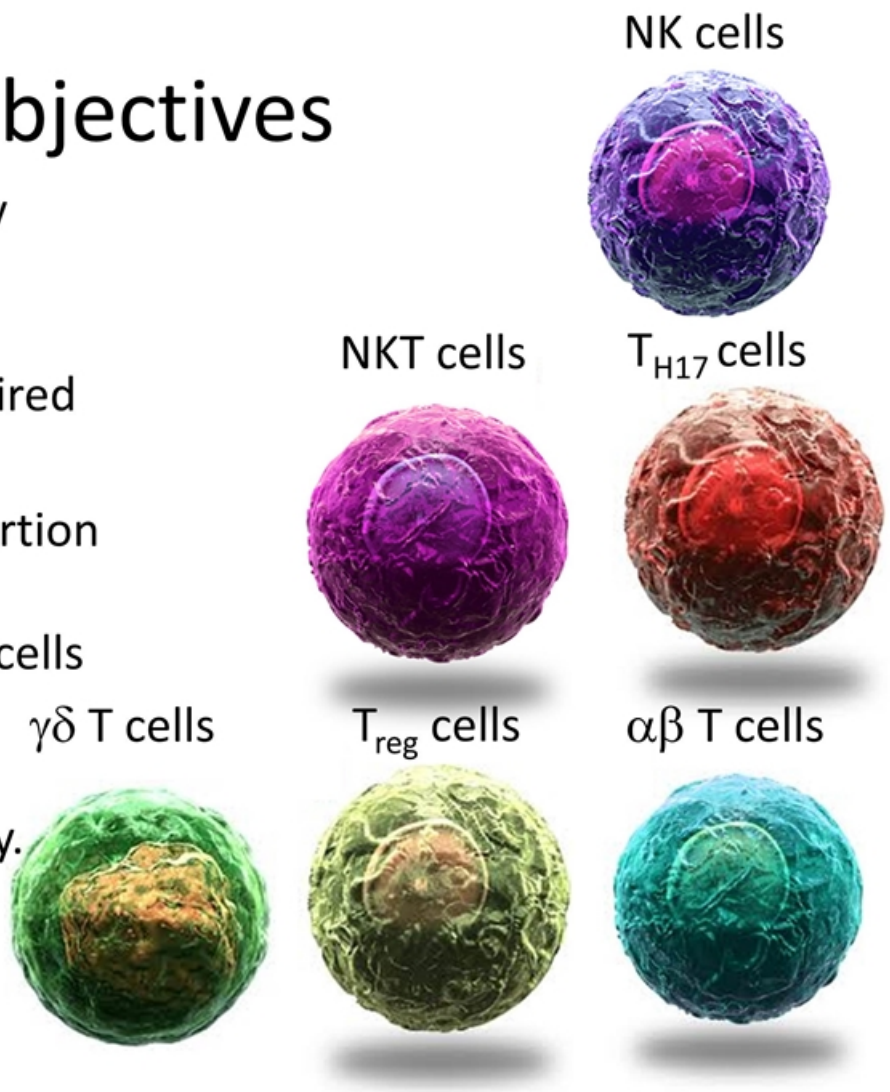
Forward-looking statements

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 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.*

Some of technology described was advanced through research conducted at the MD Anderson Cancer Center by Laurence J.N. Cooper, M.D., Ph.D. On May 7, 2015, Dr. Cooper was appointed as the Chief Executive Officer at ZIOPHARM. Dr. Cooper is now a Visiting Scientist at MD Anderson.

Objectives

1. T cells can be genetically modified to introduce desired transgenes and edited to remove undesired endogenous genes.
2. The combination of insertion and elimination can be harnessed to develop T cells with desired specificity, improve potency, and widen bioavailability.



T cells genetically engineered for human applications

- Oncology examples
  - T-cell receptor (TCR)
  - Chimeric antigen receptor (CAR)
- Non-oncology examples
  - CCR5 gene knockout for HIV^+ patients
  - ADA-SCID, other primary immune-deficiencies
  - Virus specific T-cells (often after HSCT)
  - T_{regs} for autoimmunity (*e.g.*, type 1 diabetes)
  - Chimeric autoantibody receptor (CAAR)

Exemplary mechanisms of gene insertion

- Viral
  - Retrovirus
  - Lentivirus
    - Non-integrating lentivirus ("episomal"), S/MAR attachment element
  - Adenovirus (non-integrating)
  - Adeno-associated virus (integration into AAVS1 safe harbor site)
- Non viral
  - DNA
    - *Sleeping Beauty* transposon
    - piggyBac transposon
  - mRNA

Targeted integration

Examples:

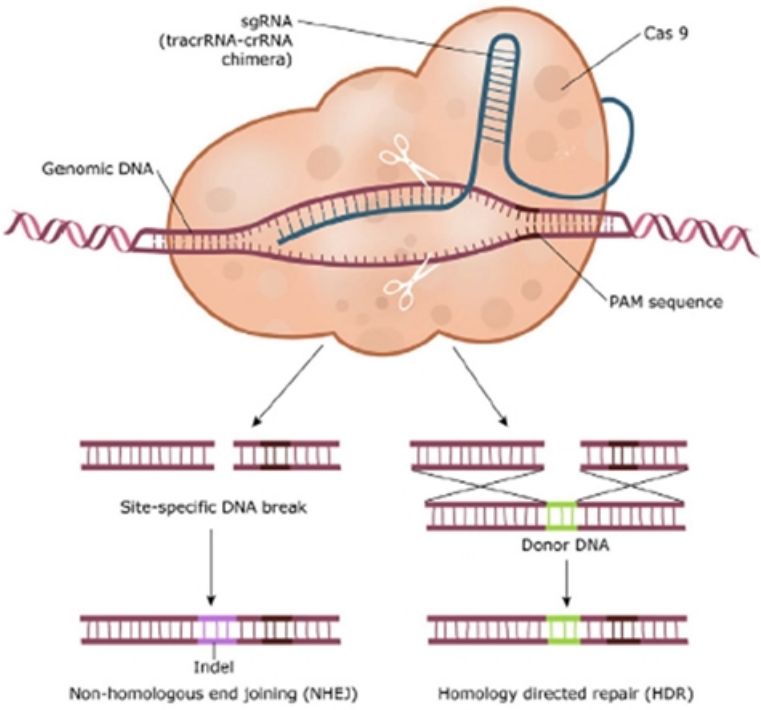
- Meganucleases
- Zinc Finger Nucleases
- TAL Effector Nucleases
- CRISPR/Cas9 nucleases
- Homologous recombination (and selection)

Note: “Nucleases” are often used as paired nickases

Mechanisms of gene elimination

Examples

- Zinc Finger Nucleases
- TAL Effector Nucleases
- CRISPR/Cas9 nucleases
- RNAi



On June 21, 2016, NIH RAC approved first-in-human CRISPR gene editing at UPENN

CRISPR Knockout: TCRα constant, TCRβ constant, PD-1

Integrate (lentivirus): NY-ESO-1 TCR

NIH RAC videocast https://videocast.nih.gov/PastEvents.asp?c=91

Exemplary CAR targets

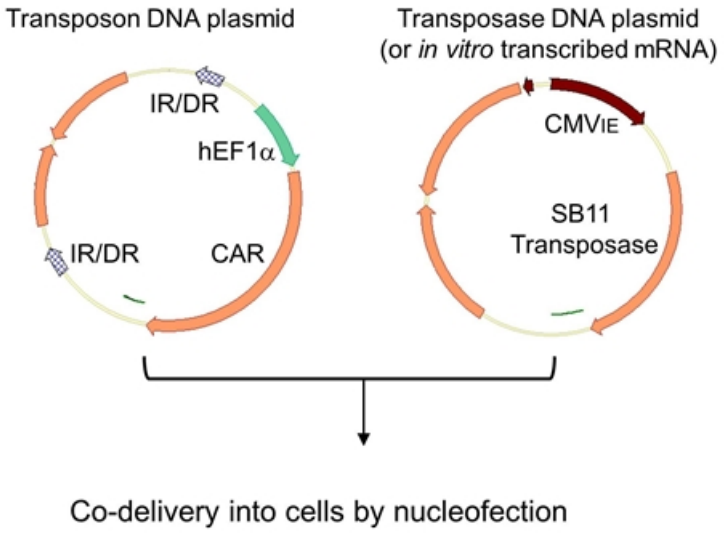
- Oncology
  - Hematologic malignancies
  - Solid tumors
- Non-oncology
  - Infectious disease
  - Auto-immunity

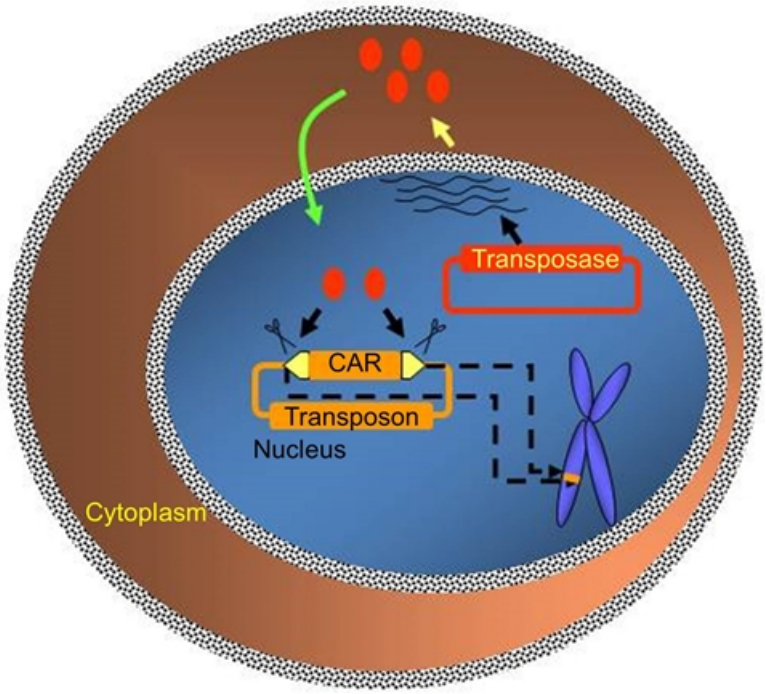
In clinical trials

Hematological	Solid tumors
CD19	B7H6 (using NKp30)
CD22	CD133
CD30	CD171 (L1-CAM)
CD33	CEA (CEACAM5)
CD123	EGFRvIII
CD138	EphA2
CD269 (BCMA)	ErbB1 (EGFR)
Kappa (IgKappa)	ErbB2 (Her2)
Lewis Y	FAP
MUC1	FRbeta (folate receptor)
	GD2
	GPC3 (liver cancer)
	IL-13Ralpha2
	Mesothelin
	MUC1
	MUC1 ("Tn-MUC1")
	MUC16
	PSMA

Infectious diseases	**Autoimmunity**
HCV E2 glycoprotein	Dsg3 (PV autoantigen)
HIV (using bnAbs)	
HIV (using CD4)	

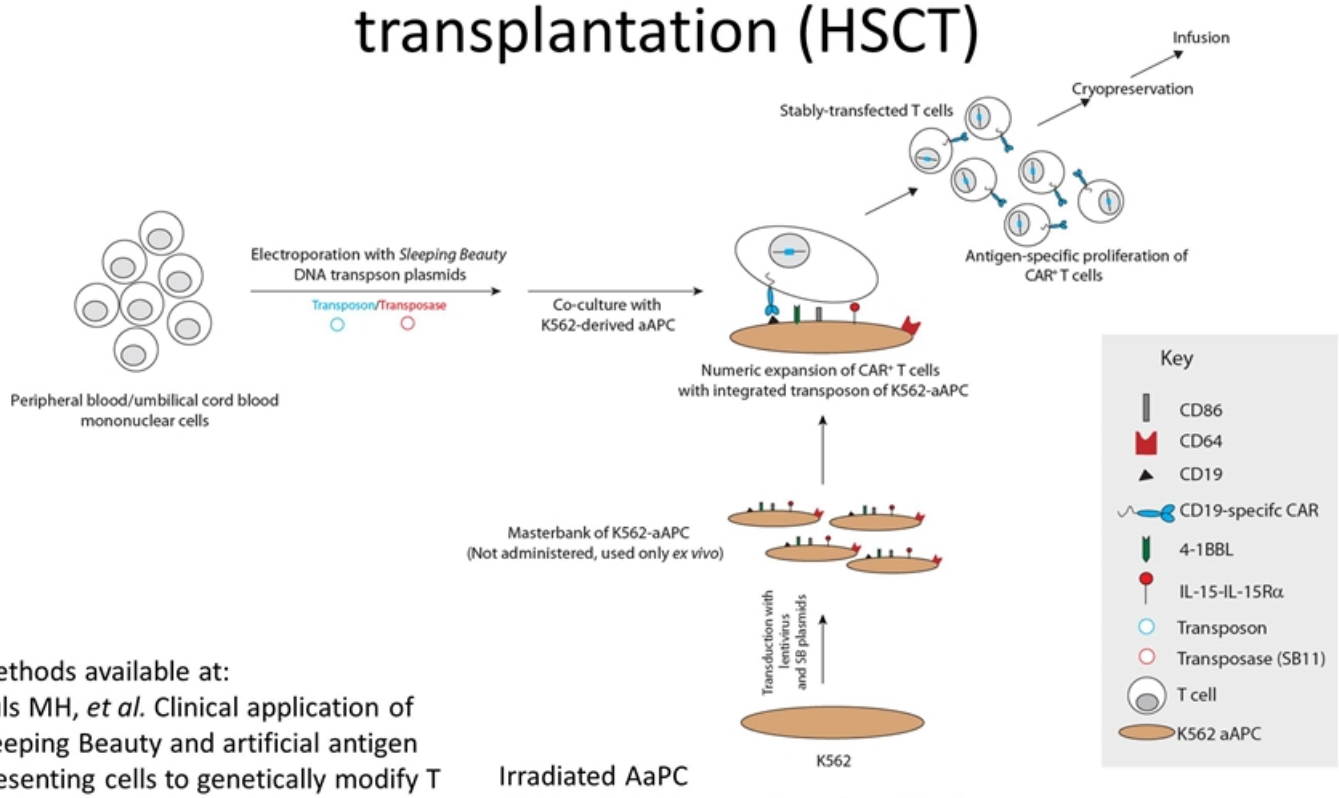
Sleeping Beauty (SB) system transposon/transposase for non-random integration





First-in-human application of SB system

CAR+ T cells infused after hematopoietic stem-cell transplantation (HSCT)



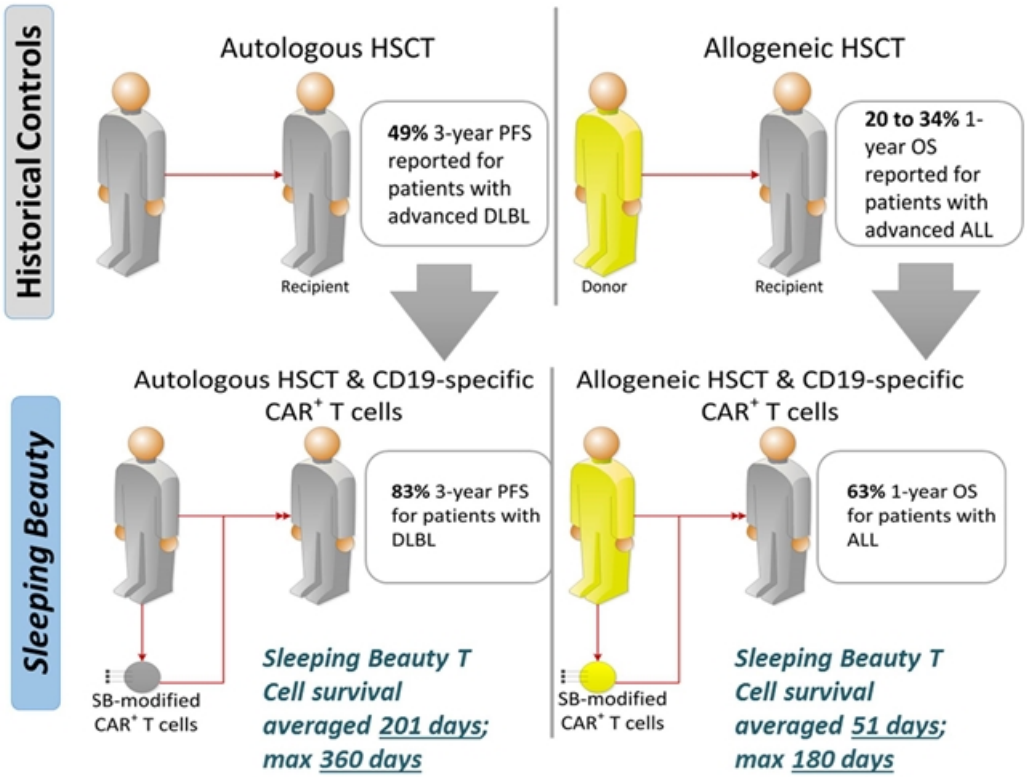
Methods available at:
Huls MH, *et al.* Clinical application of Sleeping Beauty and artificial antigen presenting cells to genetically modify T cells from peripheral and umbilical cord blood. J Vis Exp. 2013 Feb 1;(72):e50070.

Irradiated AaPC
Derived from K-562 cells and modified to co-express CD19, CD86, CD137L, membrane-bound IL-15 (and CD64)

Non-viral delivery: SB CAR$^+$ T-cell platform (first-in-human studies)

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

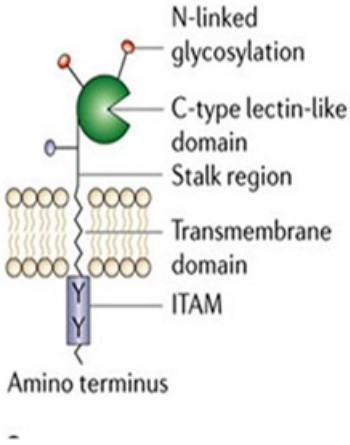


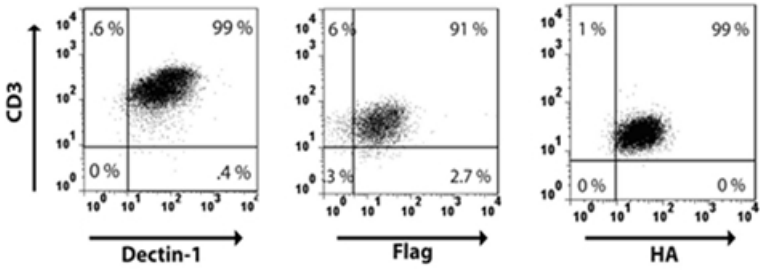
Data based on work/trial performed at MDACC

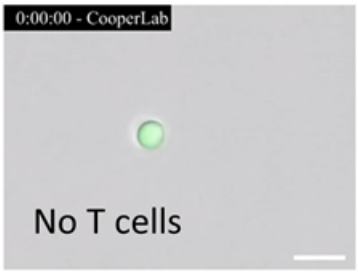
Reprogram T cells to target carbohydrate antigens

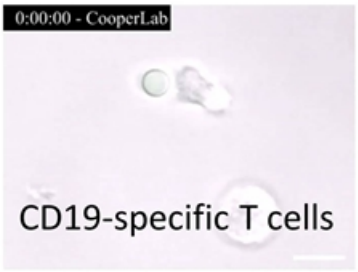
- Redirect T-cell specificity to target *Aspergillus*
  - Combine binding of pattern-recognition receptor from Dectin-1 with T-cell activation domains (CD28 & CD3-ζ)

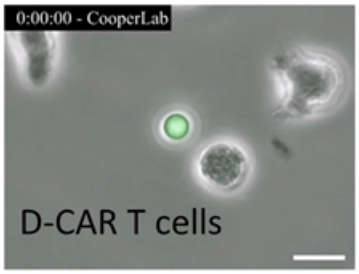
Proc Natl Acad Sci U S A. 2014 Jul 22;111(29):10660-5



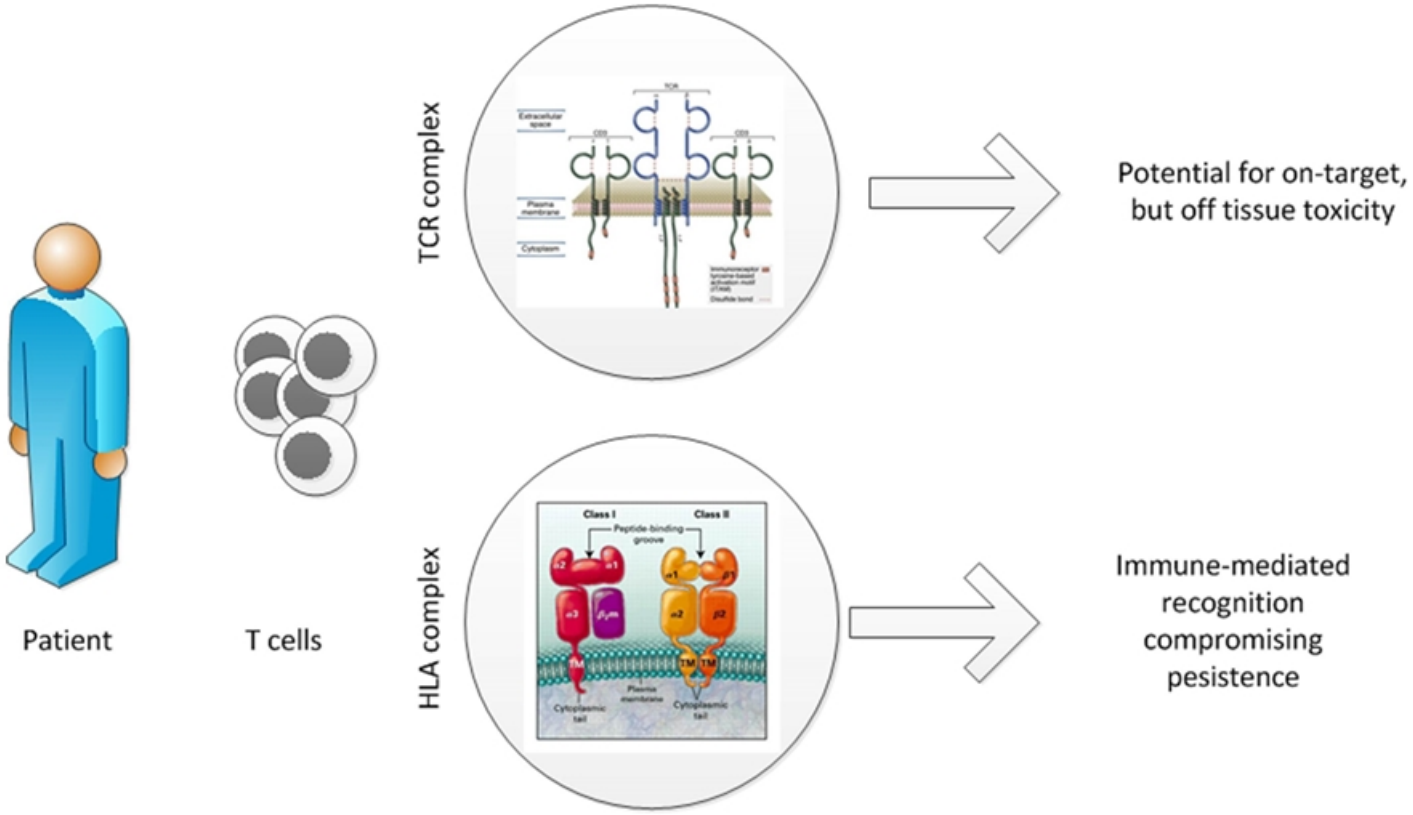








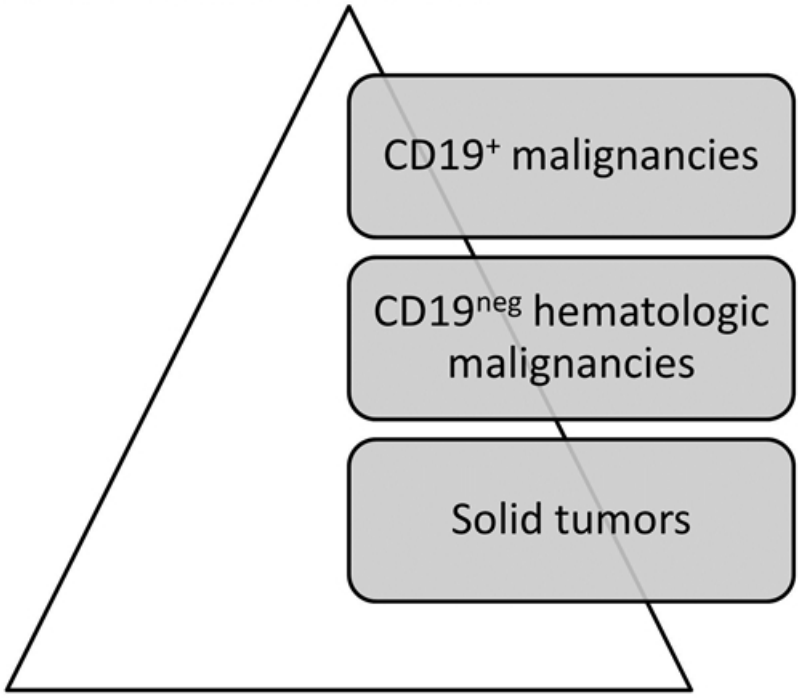
Genetic engineering of next-generation off-the-shelf (OTS) CAR+



Mol Ther. 2016 Jun 14. doi: 10.1038/mt.2016.106.

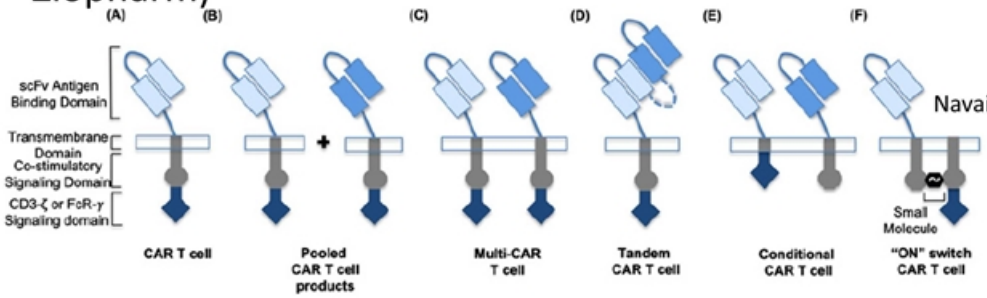
Challenges and opportunities

Serial and specific killing of tumor cells within tumor microenvironment

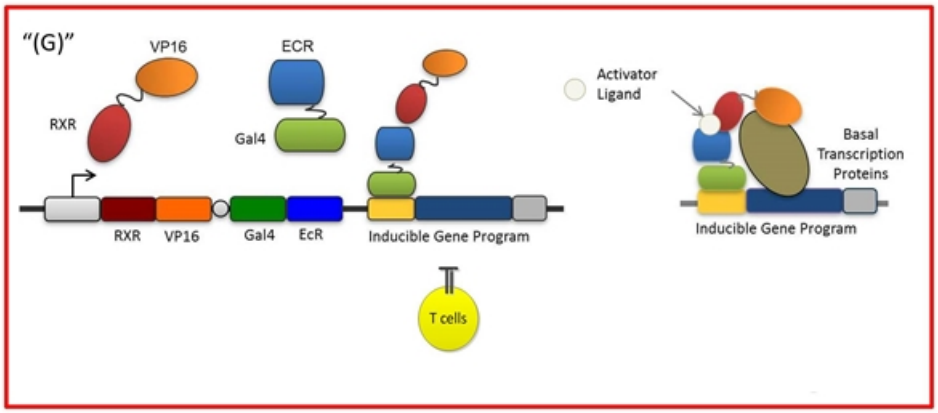


Exemplary Switches

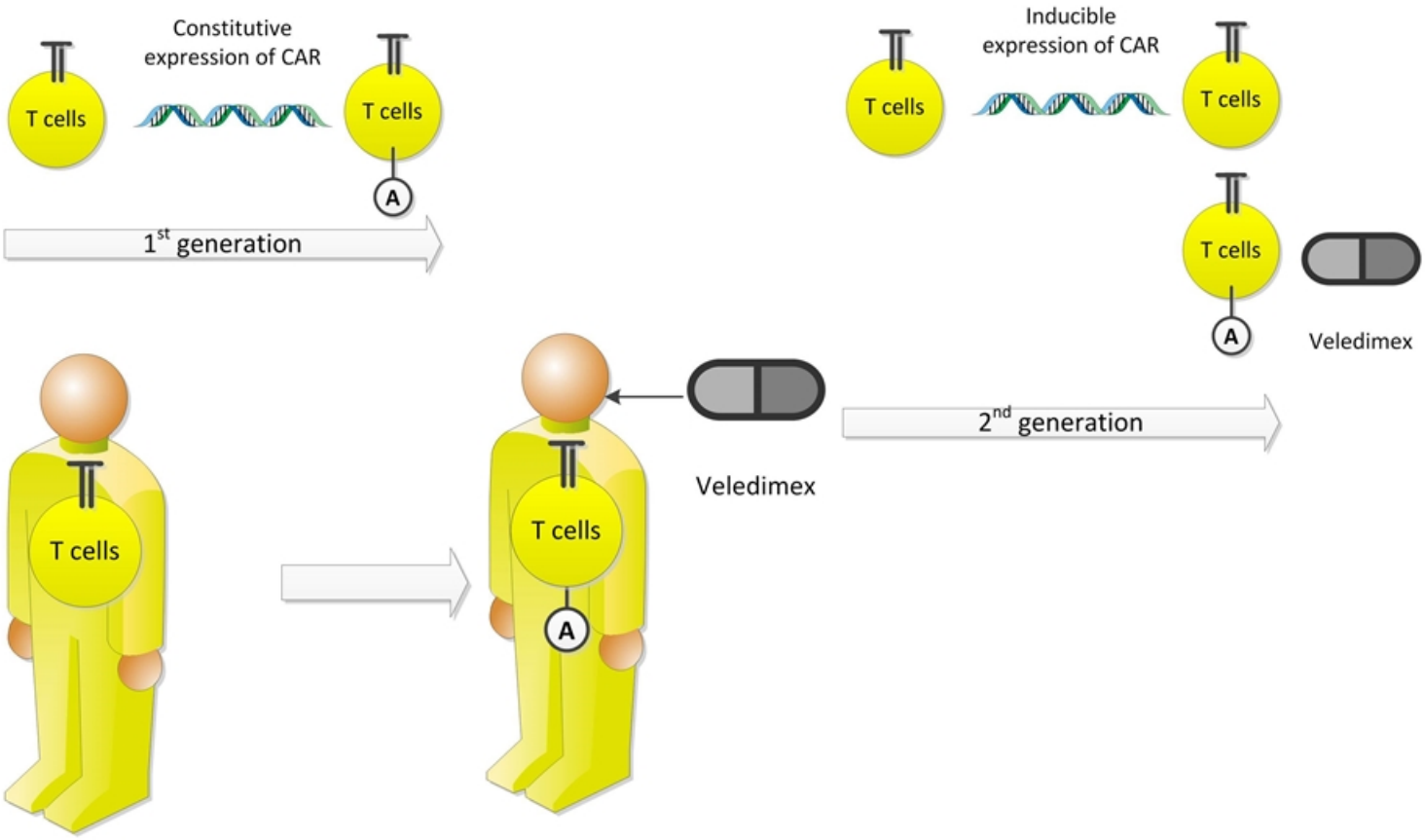
- iMyD88/CD40 (AP1903 dimerizer); Split CAR (AP21967 dimerizer); "Tandem", *e.g.*, CD19-OR-CD20 bispecific CAR (Zah 2016); "Switchable" (Ma 2016, Rodgers 2016); SynNOTCH (Roybal 2016); TetOn + tetracycline promoter ➔ CAR (Sakemura 2015 ASH 4424); RheoSwitch® + veledimex ➔ CAR (Intrexon / Ziopharm)



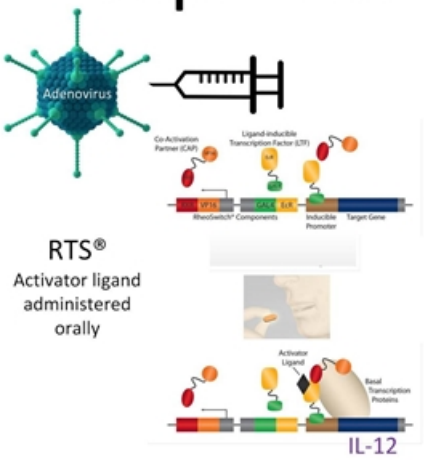
Navai, Ahmed 2016 Biochem Soc Trans 44: 391.

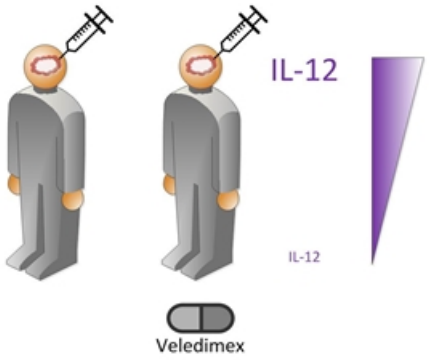


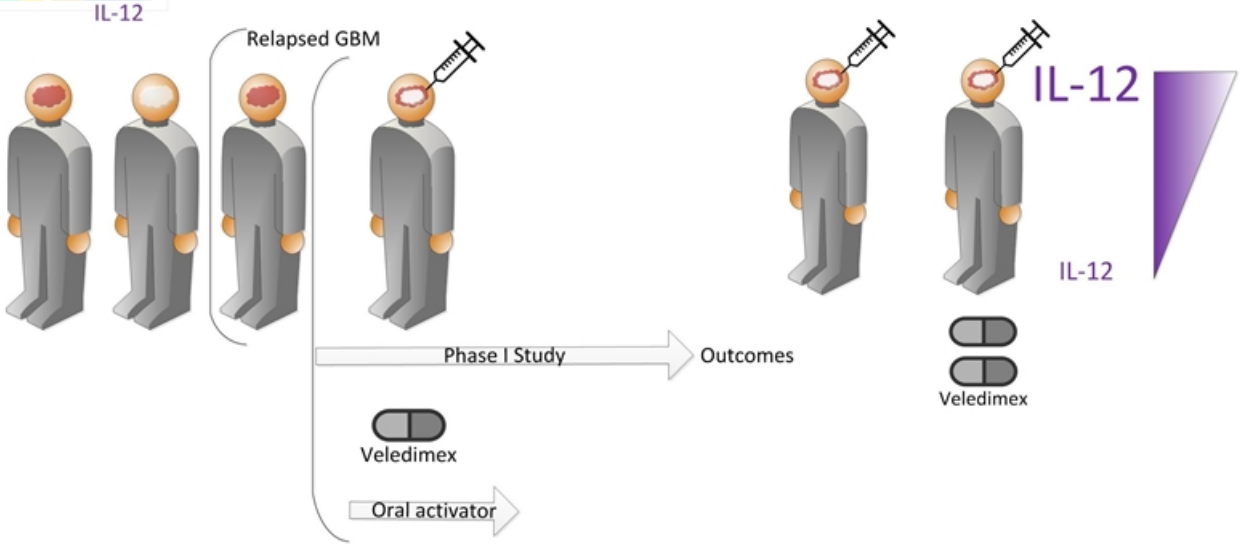
Oral ligand to conditionally express CARs using RTS®



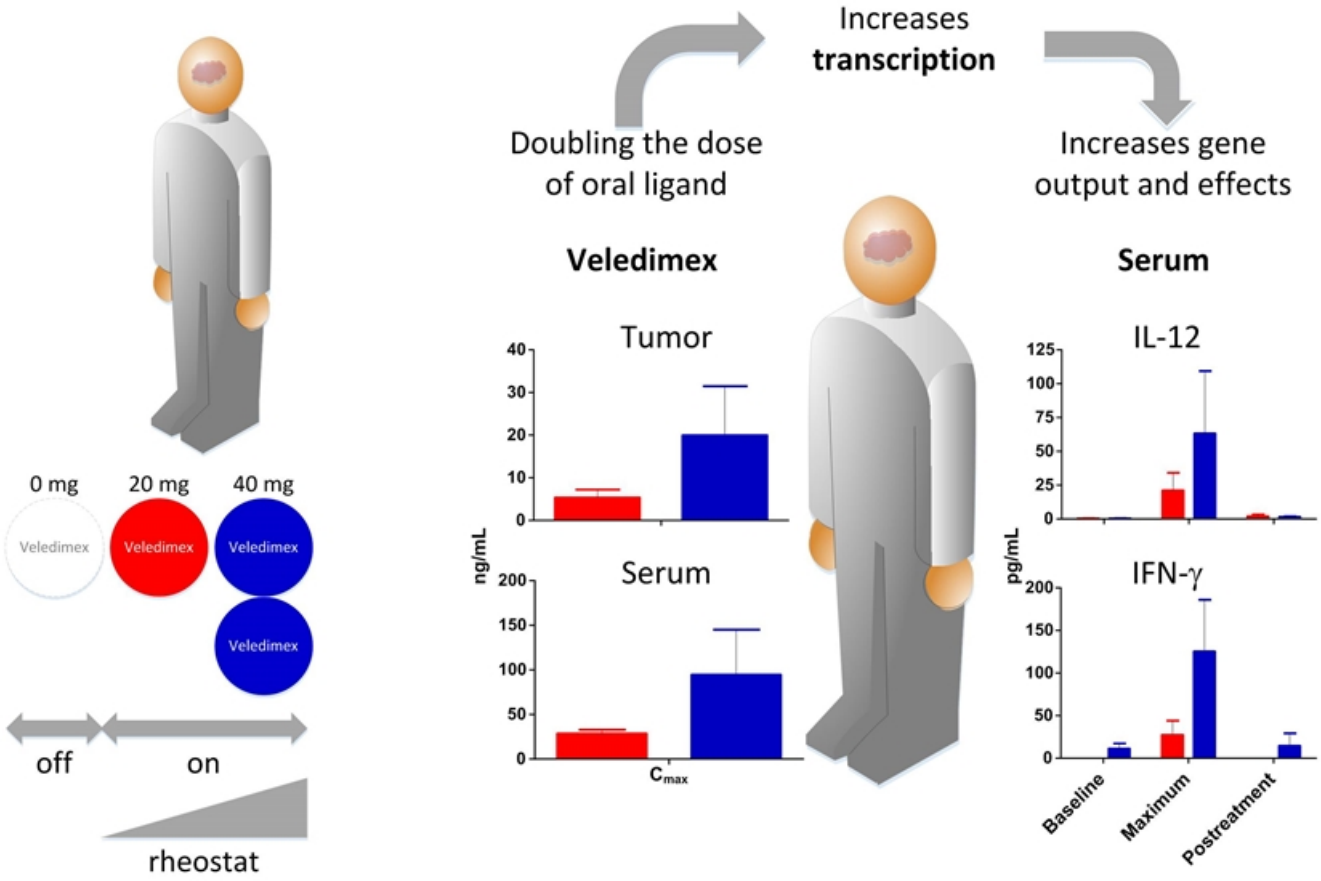
Human experience with conditional expression using RheoSwitch® System (RTS®)



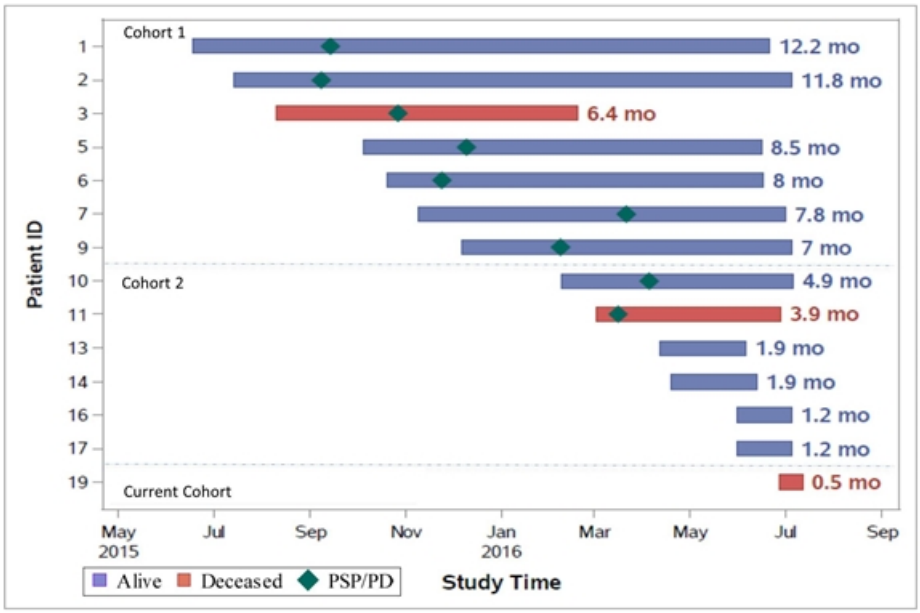




RTS® switch responds to the dose of veledimex in GBM patients



Early data suggests benefit with a favorable trend in overall survival for patients with recurrent GBM



- Median OS has not been reached; 11 patients out of 14 alive
  - In Cohort 1 (N=7), the median follow up is 8.0 months with 6 patients out of 7 alive.
  - 1 patient in Cohort 1 (20 mg) died due to disease progression after 6.4 months
  - 1 patient in Cohort 2 (40 mg) died at 3.9 months – unrelated to study drug.
  - 1 patient in the current cohort (30 mg) died due to intracranial hemorrhage 15 days after starting study drug
- Reported as of July 13, 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.

Conditional expression of CAR under RTS®

RTS® Conditions

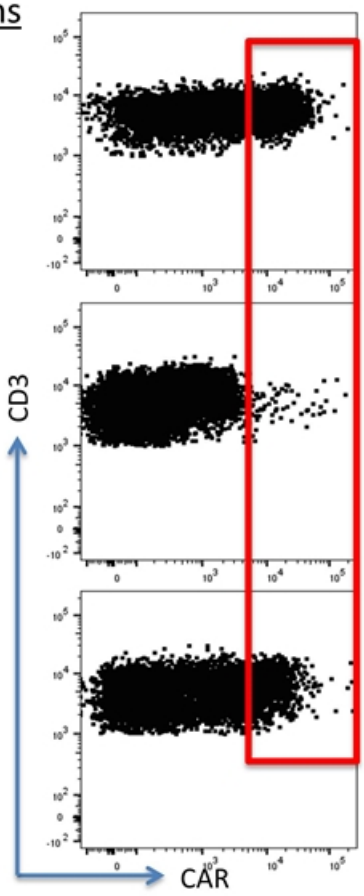
ON

Veledimex

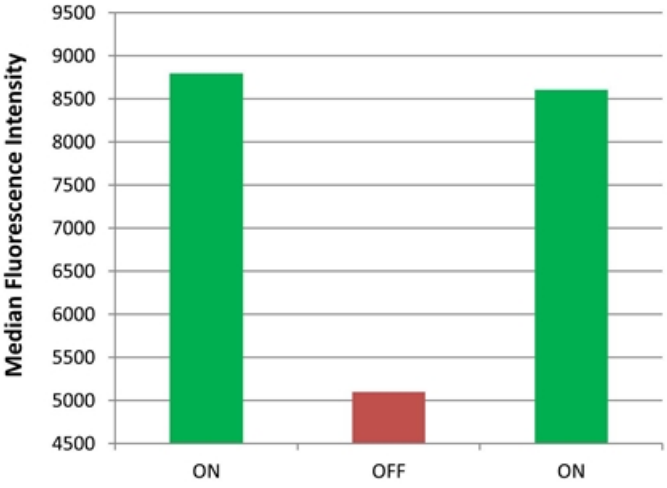
OFF

ON

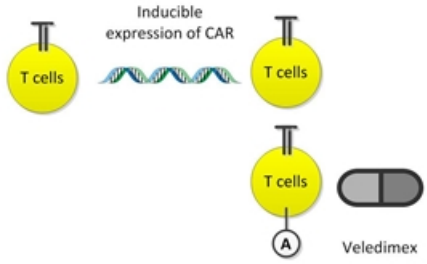
Veledimex



Veledimex added to culture for ON; withdrawal is OFF



* based upon CAR gated population



Safety: Exemplary Suicide Genes

Gene	Kill mechanism	Mechanism	Immunogenicity
iCasp9	AP1903 (dimerizer)	Apoptosis	No
tEGFR	Cetuximab	ADCC? ADCP? CDC?	No (very rare)
CD20R RQR8	Rituximab Rituximab, anti-CD34	ADCC? ADCP? CDC? αCD34 Magnetic beads in vitro	No
HSV-tk	Ganciclovir prodrug	Block DNA synthesis	Yes
CYP4B1 Pro427Ser	4-ipomeanol, Perilla ketone prodrugs	Alkylator, DNA interstrand crosslinks	Unknown (Roellecke 2016 Gene Ther)

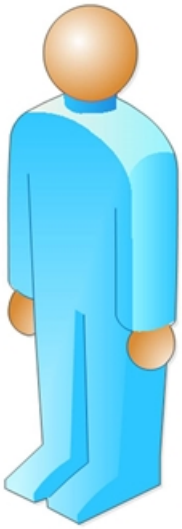
Karjoo Z et al 2016 Adv Drug Disc Rev 99: 113-128. GDEPT gene directed enzyme prodrug therapy

Table 2
This table summarizes the most important features of six main enzyme/prodrug systems that are used in GDEPT.

Immunogenicity	Enzyme	Prodrug	Toxic metabolite	Mechanism of action	Bystander effect	Distant bystander effect
Yes	Herpes simplex virus thymidine kinase	Ganciclovir (GCV)	Ganciclovir Triphosphate (GCV-TP)	Blocks DNA synthesis. S and G2 phase arrest. Mitochondrial damage. Active in dividing cells.	High, when GJIC exists Low, when GJIC doesn't exist	Yes
Yes	Cytosine deaminase	5-Fluorocytosine (5-FC)	5-Fluorouracil (5-FU)	Blocks DNA and RNA synthesis. Active mostly in dividing cells, but at high concentrations can inhibit growth of both dividing and non-dividing cells.	High, independent of GJIC	Yes
Yes	Nitroreductase	CB1954 and analogs	2-Hydroxylamine and 4-hydroxylamine derivatives	DNA interstrand cross linker. Active in both dividing and non-dividing cells	Very High, independent of GJIC	Yes
Yes	Carboxypepti-dase G2	CMDA; ZD-2767P	N,N-2(-chloroethyl)(2-mesyloxyethyl)aminobenzoic acid (CMBA); Bis-iodophenol mustard	DNA interstrand cross linker. Active in both dividing and non-dividing cells.	High, independent of GJIC	Yes
No	Purine nucleoside phosphorylase	6-Methylpurine deoxyriboside	6-Methylpurine	Inhibits DNA, RNA and protein synthesis. Active in both dividing and non-dividing cells.	High, independent of GJIC	Yes
No	Cytochrome P450	Cyclophosphamide; ifosfamide	Phosphoramide mustard; acrolein	DNA interstrand crosslinking agent. Active mostly in dividing cells.	Medium, independent of GJIC	Unknown

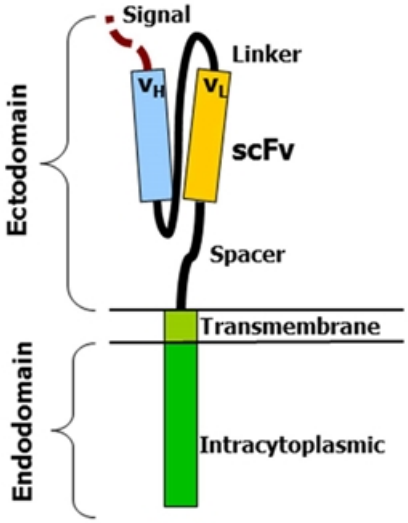
As of 1/2015, 157 suicide gene therapies of 2076 clinical trials (7.7%). 45 in phase III.

Improving therapeutic potential of CAR^{+} T cells

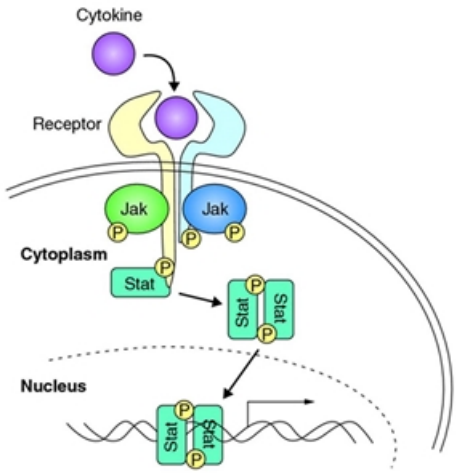


Recipient

Effector cells

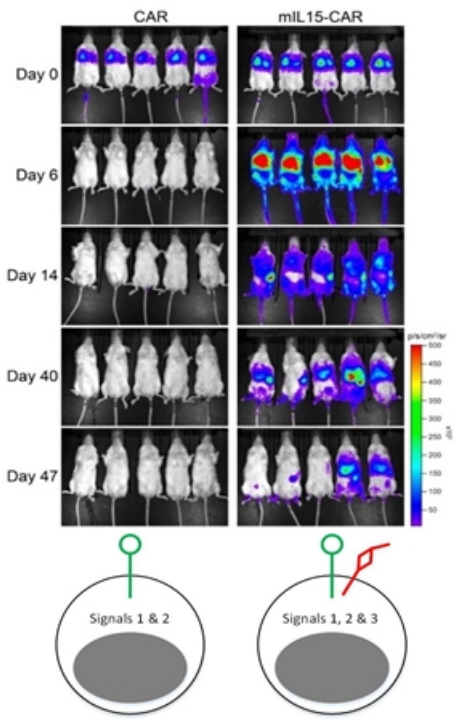


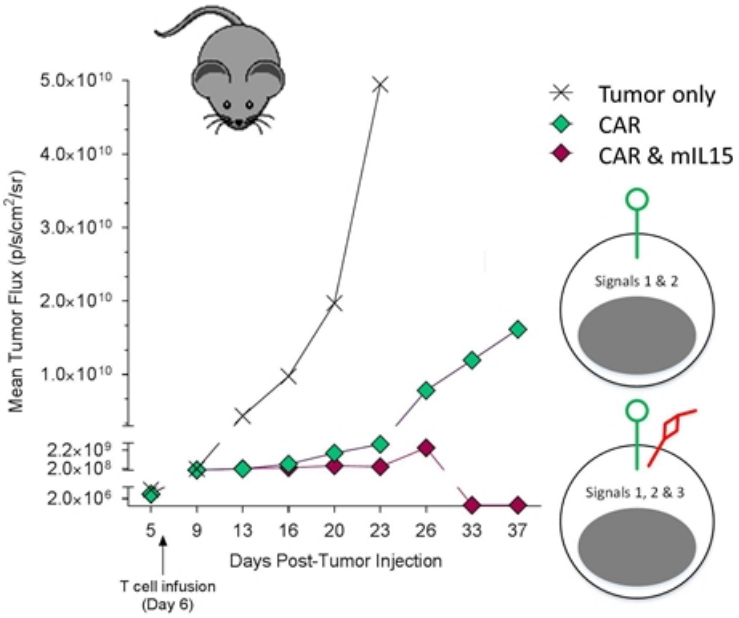
Chimeric antigen receptor



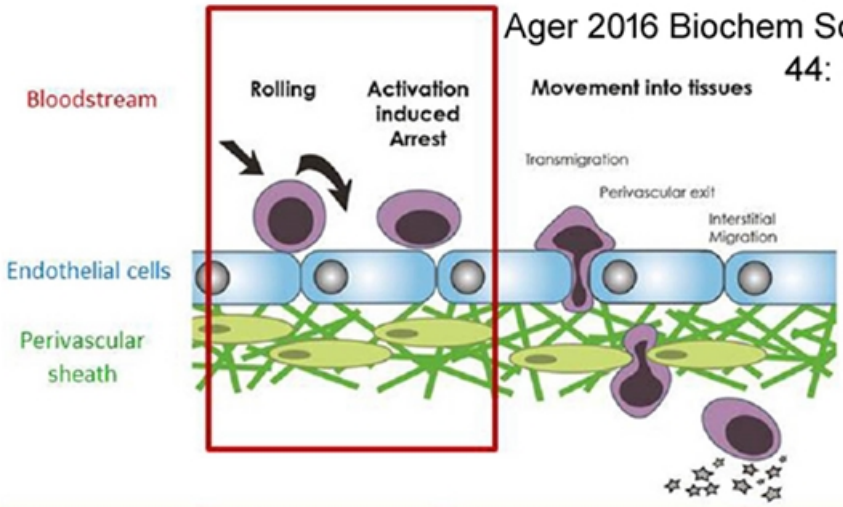
Cytokine

Improving CAR^{+} T cells by co-signaling through IL-15 receptor





Improving therapeutic potential of CAR$^+$ and TCR$^+$ T cells by co-signaling through homing receptors



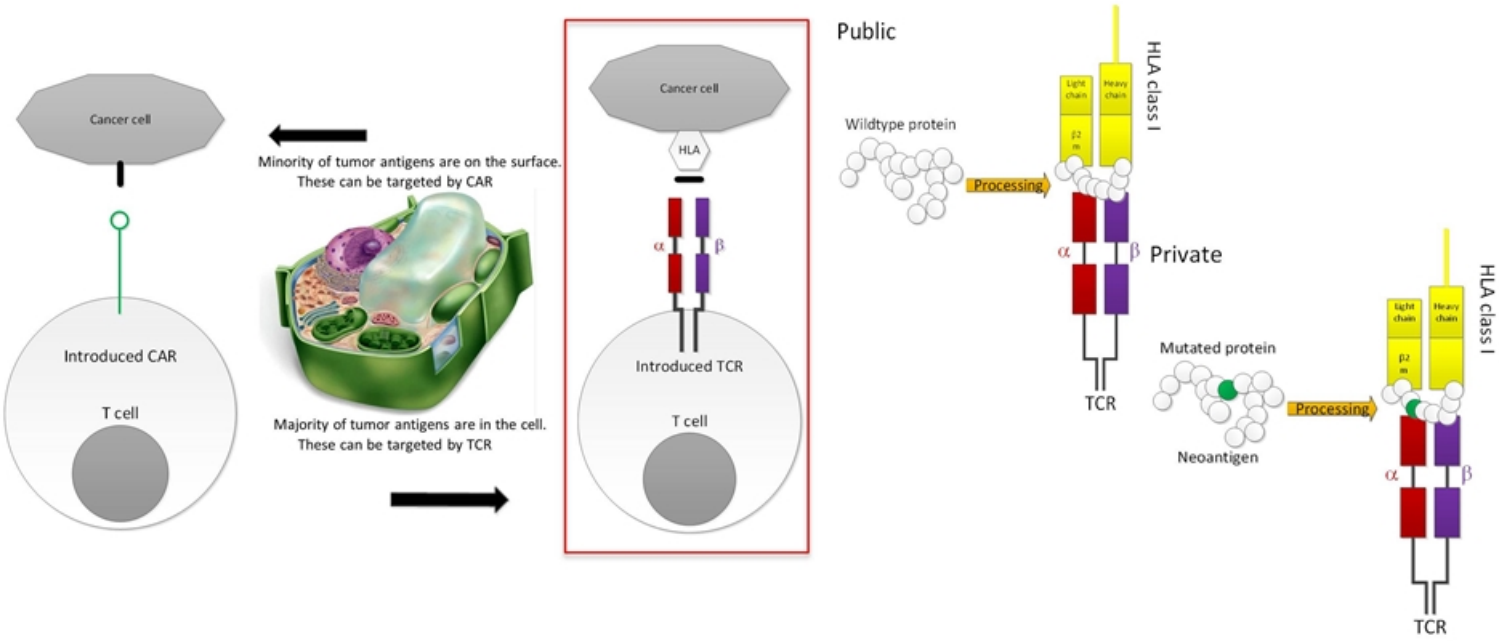
Ager 2016 Biochem Soc Trans 44: 377-385

Organ	Rolling	Activation	Arrest
Lymph node	L-selectin/PNAd, α4β7/MAdCAM-1	CCR7/CCL21	LFA-I/ICAM-1
Inflamed skin, lungs, kidney, brain, peritoneum	E- selectin/sLe^x P-selectin/PSGL-1 CD44/Hyaluronan	CXCR3/CXCL9 BLT-1/LTB$_4$ TCR/peptide-MHC	LFA-1/ICAM-1 VLA-4/VCAM-1
Cancer	L-selectin/PNAd [25]	CCR7/CCL21 [25] CXCR3/CXCL9 [24] BLT-1/LTB$_4$ [23]	LFA-1/ICAM-1 [22]

Tissue specific homing involves sequential molecular interactions, concurrent with activation

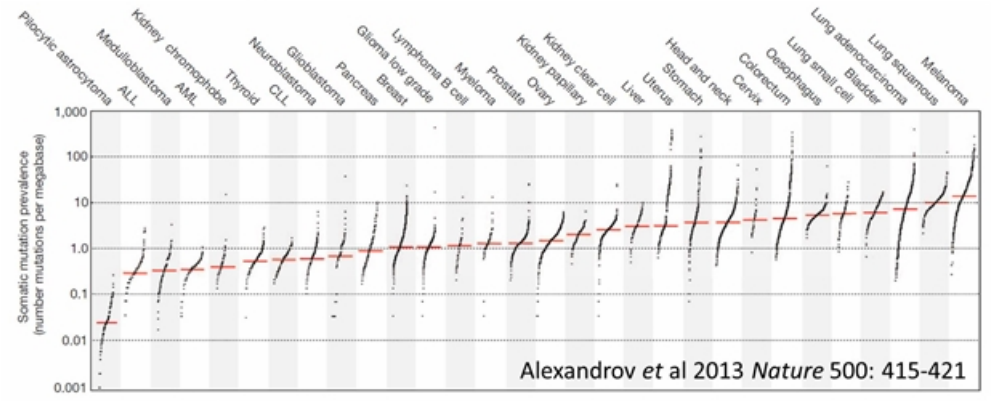
1. Rolling
2. Activation
3. Arrest
4. Transmigration
5. Perivascular exit
6. Interstitial migration (often chemotaxis).

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

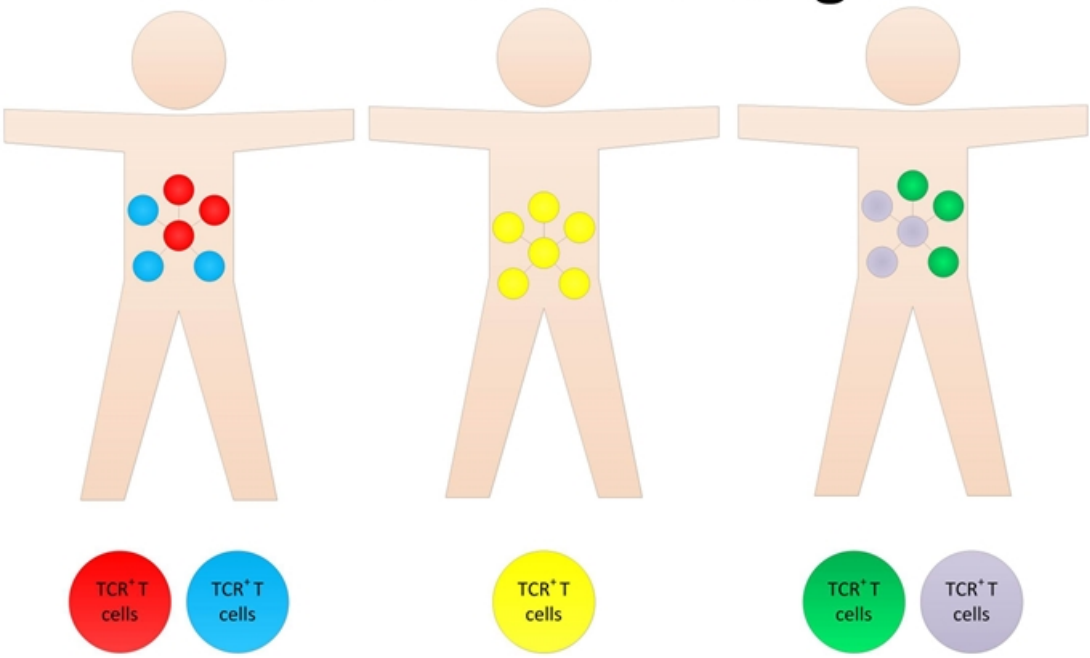


TCR targets (using genetically modified T cells)

- Shared antigens
  - Cancer-testis antigens (NY-ESO-1)
  - Oncogenic drivers (Her-2, K-Ras^{G12D})
  - Onco-enzyme products (PhosImmune, Tn)
- Patient specific neoantigens
  - Mutanome



Inter- & intra-tumor heterogeneity of tumor-associated antigens

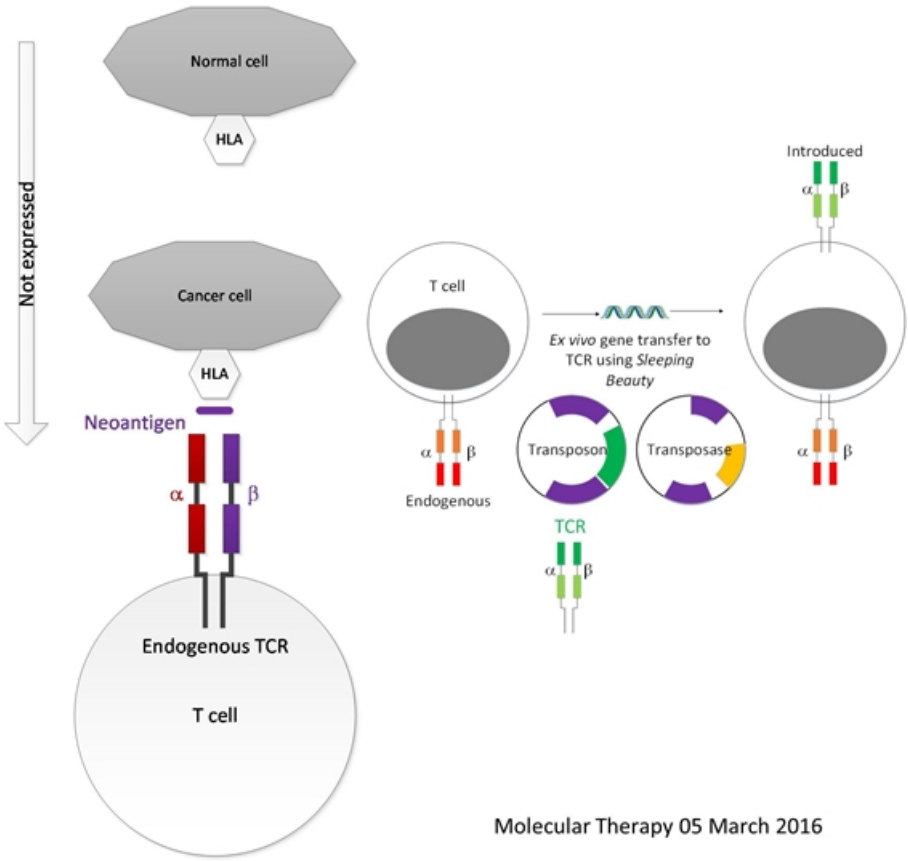


Infuse T cells with one or more specificity

Personalized for the patient

“N=1” trial paradigm

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



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]

[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*

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^{4218R} or ERBB2^{R478I} or the *HLA-DQ8*0601*-restricted neoantigen ERBB2IP^{E805G} 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.

Received 9 November 2015; accepted 21 February 2016; advance online publication 5 April 2016. doi:10.1038/mt.2016.51

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^{E805G} 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.[3,9,10] 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.

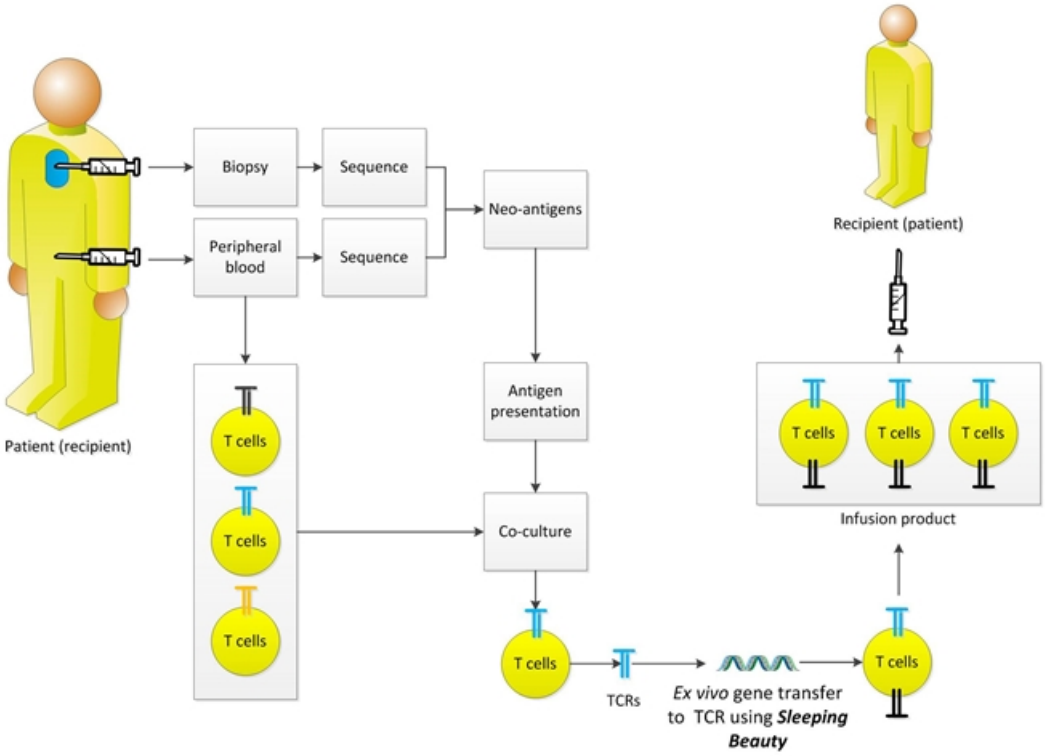
However, the direct use of TIL with desired antigen specificity is not always feasible. Our current method relies on screening multiple independently grown TIL microcultures for reactivity against the patient mutanome, which can be problematic if the tumor/mutation-specific TIL are infrequent or in late/terminal 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.[16,18] 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.

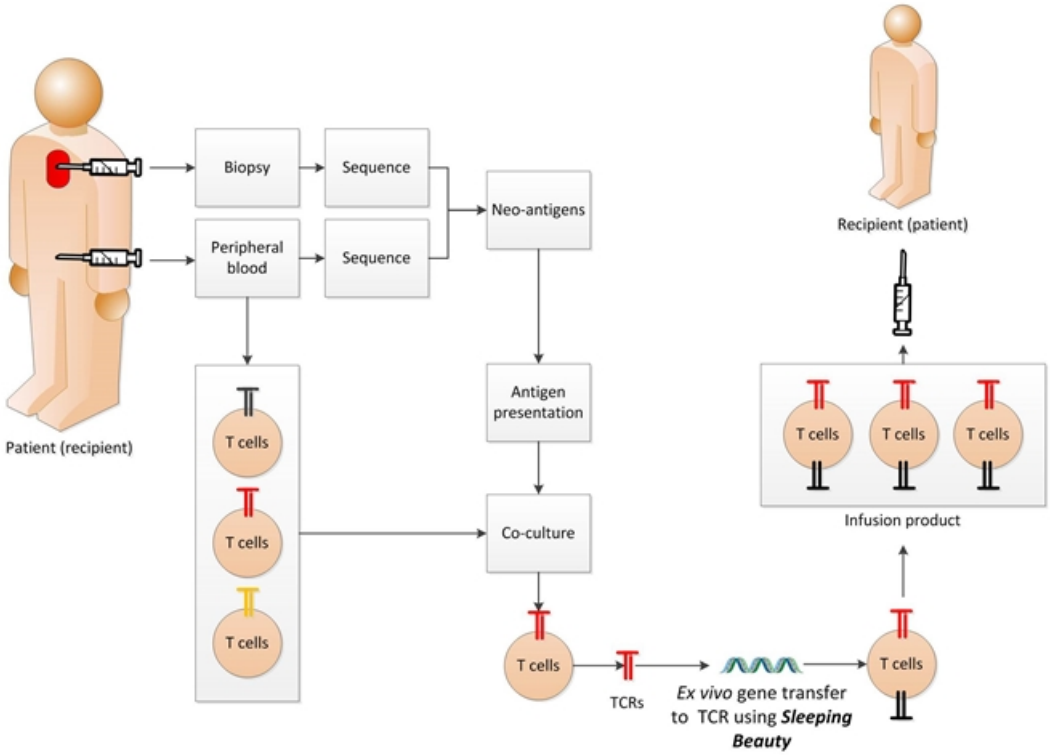
Sleeping Beauty plasmids have been approved for use in clinical trials evaluating the ability of T cells modified with chimeric

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

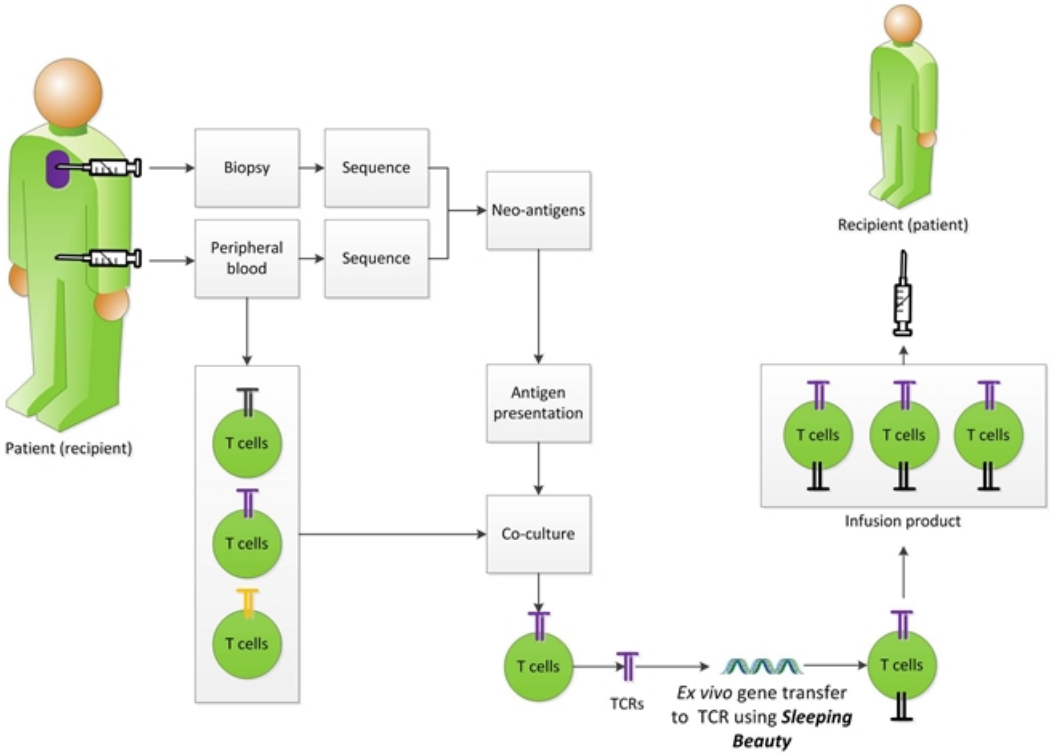
Targeting neo-antigens



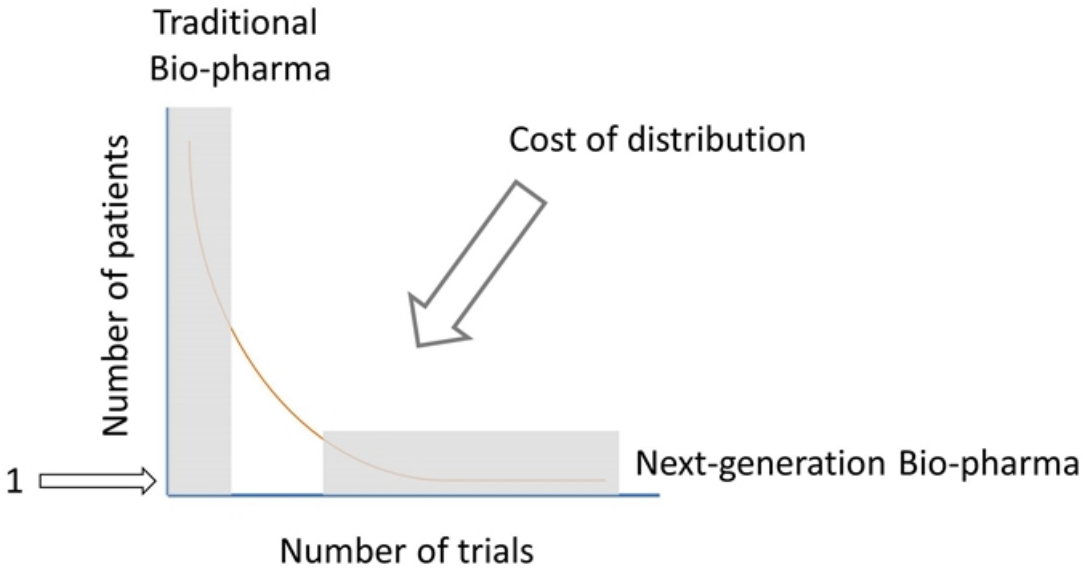
Targeting neo-antigens



Targeting neo-antigens



Power-law curve
The new industrialization of TCR+ T cells



Thank you