# Engineered T cell therapies of cancer: critical parameters for clinical success

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LEUKAEMIA & LYMPHOMA RESEARCH

Beating Blood Cancers

# Overview

- **Engineered T cell therapies for cancer**
  - **Conceptual basis**
  - **TCR & CAR gene transfer**
  - **Clinical experience**
  - **Safety concerns**
  - **Critical parameters for clinical success**

# Conceptual basis for engineered T cell therapy of cancer

# Immunological tolerance impairs T cell immunity to cancer

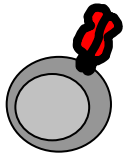
- **T cells are not strongly reactive with self-antigens (self-tolerance)**
  - Mechanisms of central and peripheral tolerance induction lead to deletion or suppression of T cells that react strongly with self-antigen
- **Most of the antigens presented by cancer cells that T cells can potentially recognize are self antigens**
- **Immunological tolerance prevents most T cells from recognizing cancer cells - therefore obstacle to using immune system to treat cancer**
  - Murine studies (Romieu *et al*. J Immunol 1997; Granziero *et al*. EJI 1999)
  - Clinical effect of most cancer vaccines disappointing (Rosenberg *et al*. Nat Med 2004)

→ Ability to vaccinate against cancer limited by immunological tolerance: can immunity to cancer be induced by other means?

# Transferring immunity to cancer

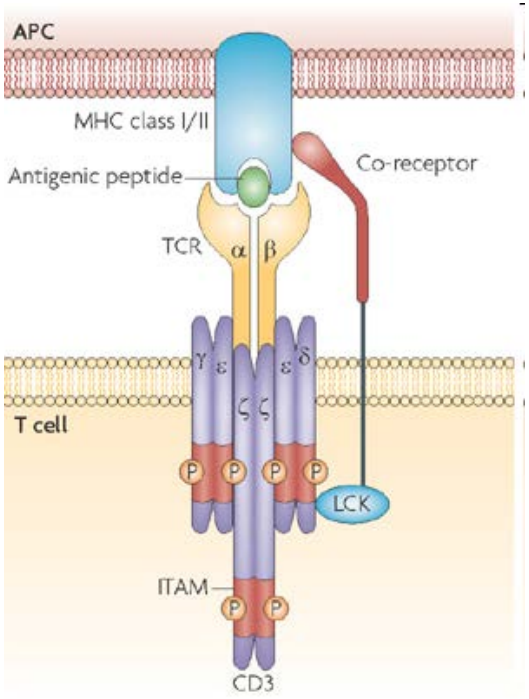
- **Passive transfer of antibodies can induce immunity to self-antigens expressed by tumors (e.g. Rituximab – B cell lymphoma/leukemiar)**

- **T cell immunity to tumours can be induced by adoptive T cell therapy:**

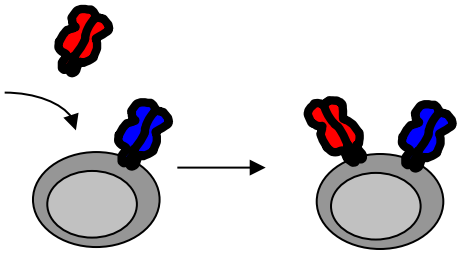
- **Transfer of T cells** 

  - **T cell replete allogeneic-HSCT & DLI for haematological malignancies**
  - **Mortality/morbidity due to GVHD limits use**

# Engineered T cell therapies: TCR gene transfer




**Antigen specificity of a T cells is determined by the TCR it expresses (Dembic *et al*. 1986 Nature)**



- **Transfer of genes encoding a TCR**
  - **Endow patient T cells with tumour-reactivity of a defined Ag-specificity**
  - **Destroy tumours without damaging normal tissues**

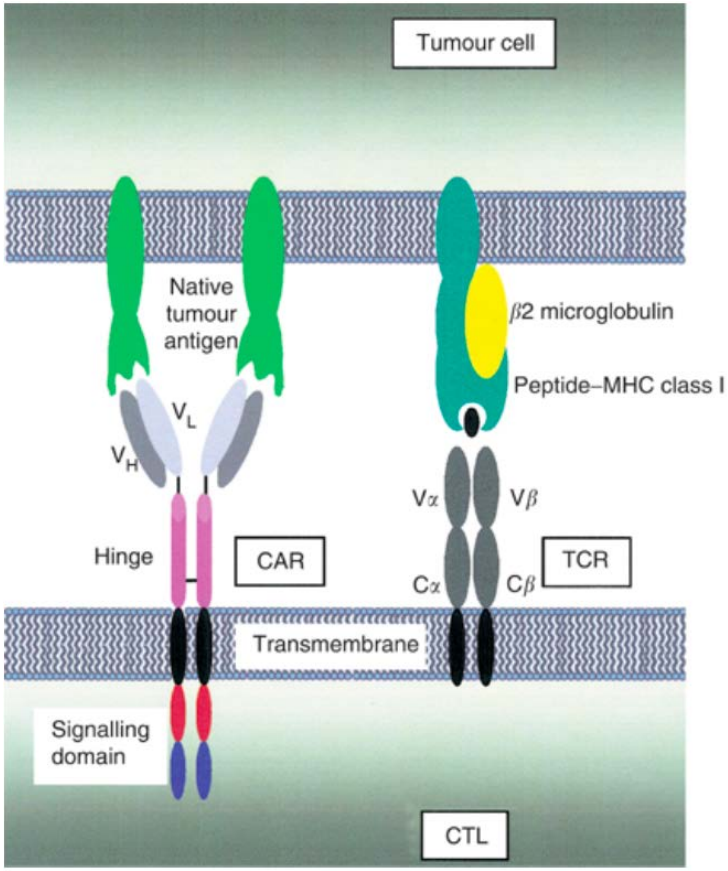
# Engineered T cell therapies: CAR gene transfer

- **T cell specificity can be redirected towards cell surface antigens by engineering T cells with a Chimeric Antigen Receptor (CAR)**

- **CAR:**

  - **Artificial T cell receptor that combines the antigen recognition domains of an antibody fused to T cell activating signalling domains**

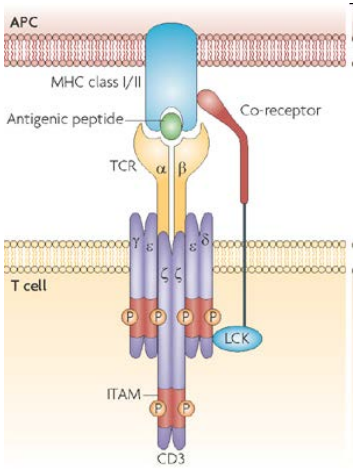
  - **Concept initially developed by Eshhar *et al*. (PNAS 1993 90:720)**



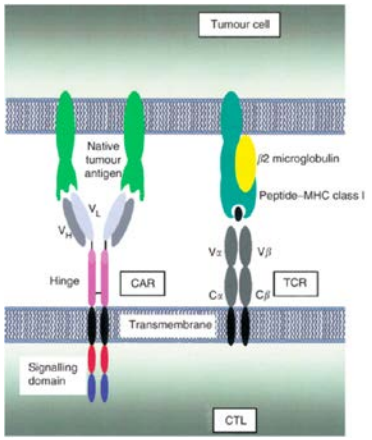

**Maher & Davies (2004) Br J Cancer 91:817-821**

# TCR or CAR gene transfer?

- **TCR**
  - **Recognition of antigen is MHC-restricted**
  - **Any cellular antigen can potentially be targeted**

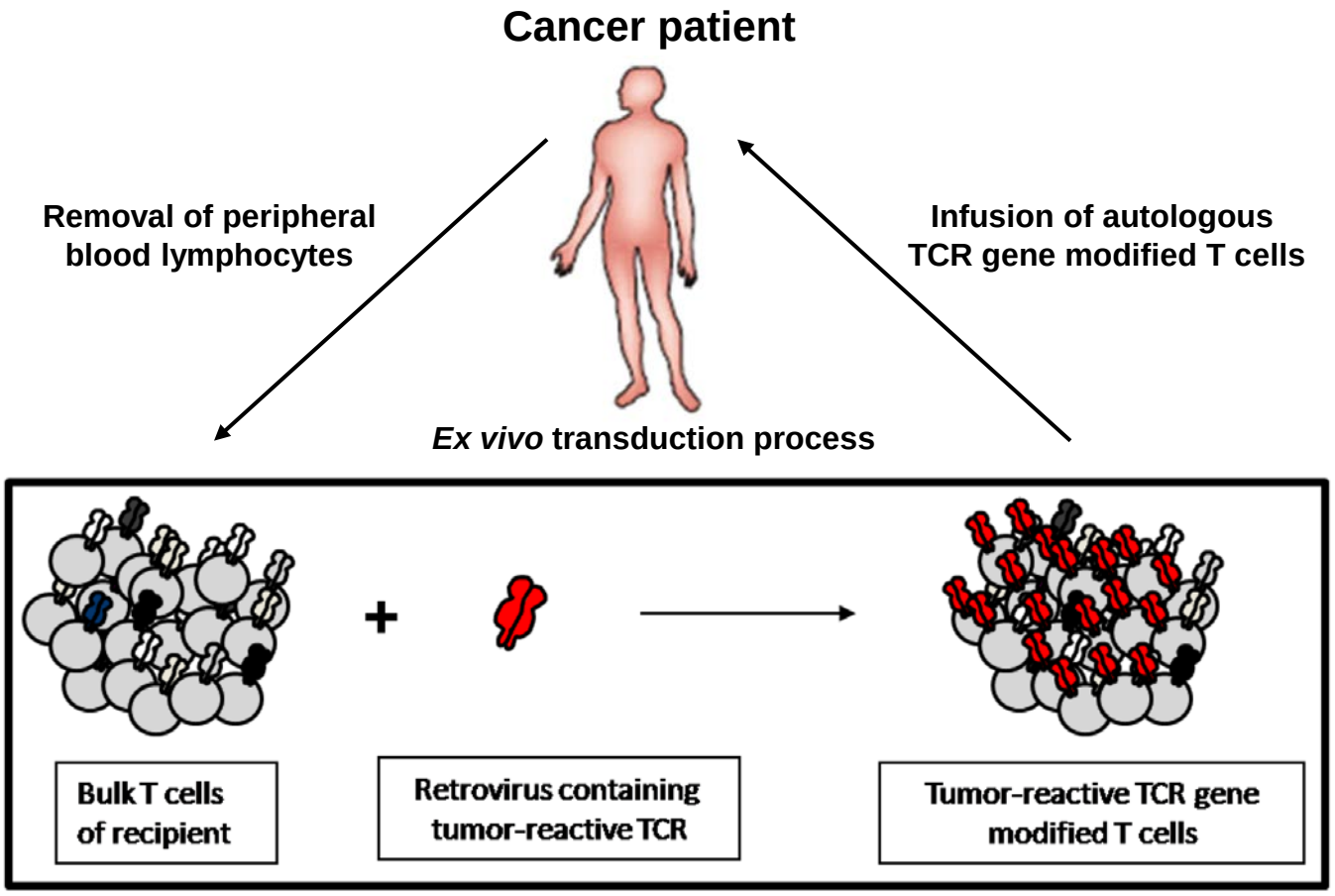



- **CAR**
  - **Recognition of antigen is not MHC restricted**
  - **Potential targets limited to cell-surface antigens**




**Whether CAR or TCR gene transfer is used for engineered T cell therapy of cancer Is dependent upon the nature of the tumour-antigen being targeted**

# Ag-receptor engineered T cell therapy



# Clinical testing of engineered T cell therapy

## Cancer Regression in Patients After Transfer of Genetically Engineered Lymphocytes

Richard A. Morgan, Mark E. Dudley, John R. Wunderlich, Marybeth S. Hughes, James C. Yang, Richard M. Sherry, Richard E. Royal, Suzanne L. Topalian, Udai S. Kammula, Nicholas P. Restifo, Zhili Zheng, Azam Nahvi, Christiaan R. de Vries, Linda J. Rogers-Freezer, Sharon A. Mavroukakis, Steven A. Rosenberg*

SCIENCE VOL 314 6 OCTOBER 2006

RESEARCH ARTICLE

LEUKEMIA

## T Cells with Chimeric Antigen Receptors Have Potent Antitumor Effects and Can Establish Memory in Patients with Advanced Leukemia

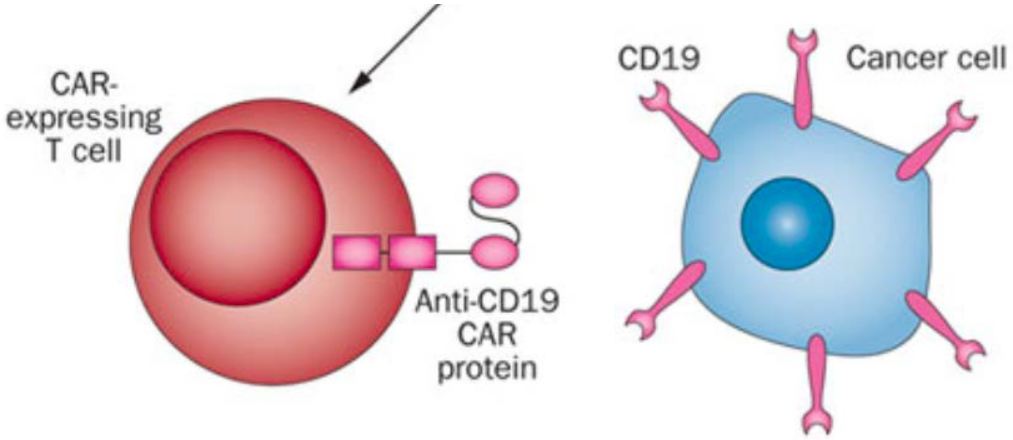
Michael Kalos,[1,2*] Bruce L. Levine,[1,2*] David L. Porter,[1,3] Sharyn Katz,[4] Stephan A. Grupp,[5,6] Adam Bagg,[1,2] Carl H. June[1,2†]

www.ScienceTranslationalMedicine.org 10 August 2011 Vol 3 Issue 95 95ra73


**Engineered T cell therapies:**

**potentially curative treatments for advanced forms of cancer**

# CAR T cell therapy of advanced B cell leukaemia targeting CD19




•CD19 – expressed on normal B cells and malignant B cells

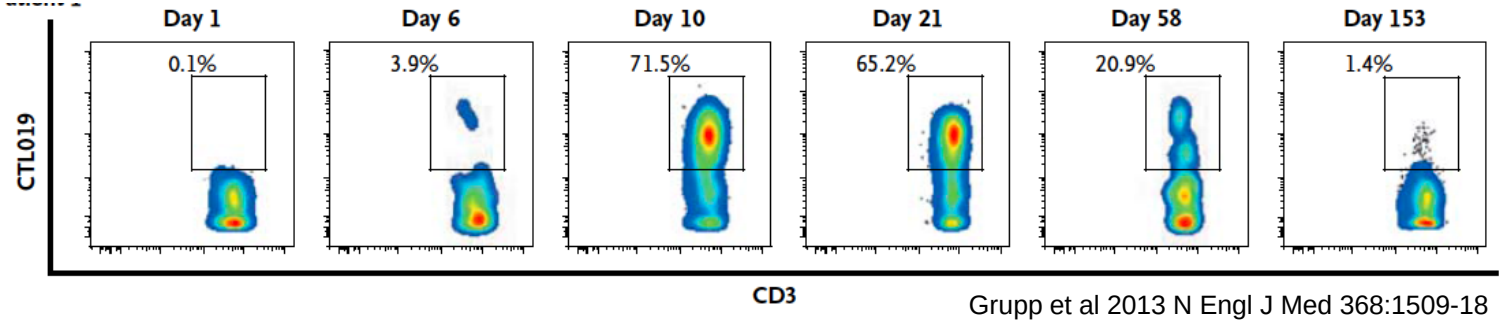
•Identified as potential target for CAR T cell therapy

•Early phase clinical trials with 2G & 3G CD19 CARs reported very encouraging results:

- Kalos et al. 2011 Science Translational Medicine 3:95ra73
- Kochenderfer et al Blood 2012 119:2709-20
- Grupp et al 2013 N Engl J Med 368:16
- Brentjens et al 2013 Science Translational Medicine 5;177ra39
- Kochenderfer et al 2013 Blood 122:4129-39
- Cruz et al. 2013 Blood 122:2965-73

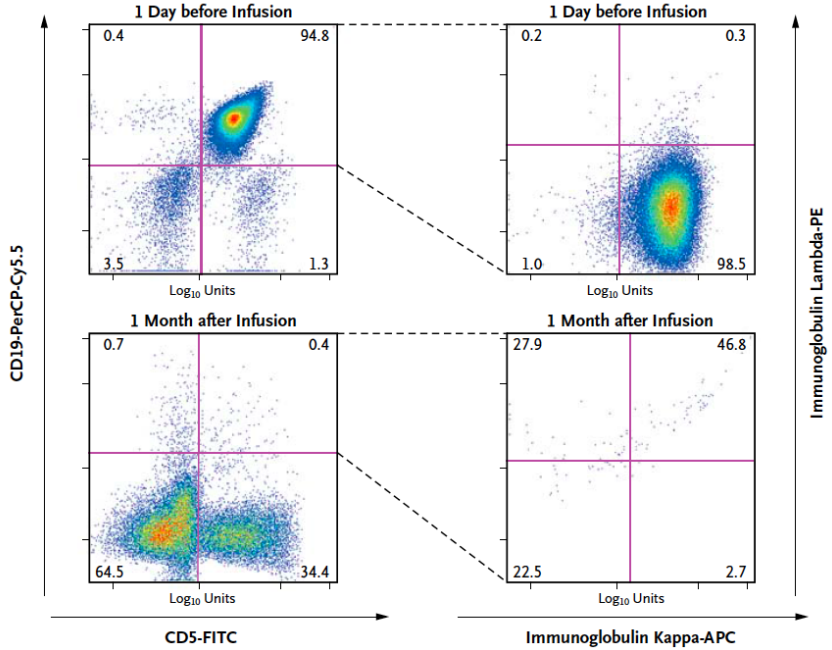
# CAR T cell therapy of advanced B cell leukaemia targeting CD19

**Persistence of CD19 CAR T cells in peripheral blood after infusion**



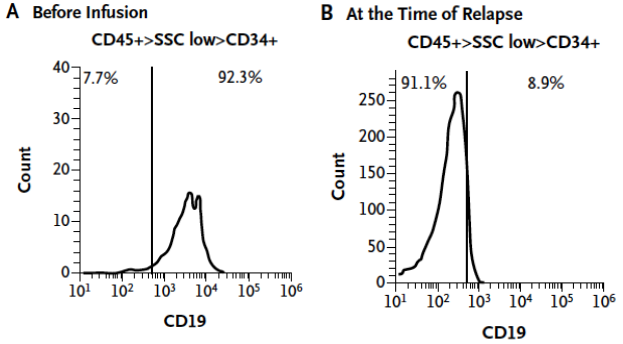

Grupp et al 2013 N Engl J Med 368:1509-18

**Absence of normal and malignant B cells In bone marrow 31d after CD19 CAR T cell infusion**




Porter et al 2011 N Engl J Med 365:725-33

**CD19 expression on malignant B cells at time of treatment and at the time of relapse after CD19 CAR T cell therapy**




Grupp et al 2013 N Engl J Med 368:1509-18

**22 pediatrics with ALL: 19 (86%) had complete response – 5 later relapsed**

**32 adults with CLL: 15 (47%) responded to therapy – 7 (22%) had complete response**

Grupp et al Abstract 67 ASH 2013; Porter et al Abstract 4162 ASH 2013; Porter et al Abstract 873 ASH 2013; Kalos et al Abstract 163 ASH 2013

# Safety concerns associated with engineered T cell therapies

# Genotoxic risk associated with engineered T cell therapies

- Current engineered T cell therapy protocols:
  - Genetic modification of mature T cells with gamma retroviral vectors or lentiviral vectors
  - Risk of cellular transformation due to insertional mutagenesis

## Resistance of mature T cells to oncogene transformation

Sebastian Newrzela,[1] Kerstin Cornils,[2] Zhixiong Li,[3] Christopher Baum,[3] Martijn H. Brugman,[3]
Marianne Hartmann,[1] Johann Meyer,[3] Sylvia Hartmann,[4] Martin-Leo Hansmann,[4] Boris Fehse,[2] and Dorothee von Laer[1]

[1]Georg-Speyer-Haus, Institute for Biomedical Research, Frankfurt; [2]University Hospital of the Johann Wolfgang Goethe-University, Experimental Pediatric Oncology and Hematology, Frankfurt am Main; [3]Hannover Medical School, Department of Experimental Hematology, Hannover; and [4]University of Frankfurt, Department of Pathology, Frankfurt, Germany

Newrzela *et al*. Blood 2008

→ Genotoxic risk of retroviral or lentiviral gene transfer substantially lower for mature T cells compared to hematopoietic progenitor cells

# Safety risks associated with engineered T cell therapy

- Most targets of engineered T cells are tumor-associated self-antigens
- Toxicity may occur if target antigen is also expressed by some normal tissues
- If vital normal tissues express target antigen toxicity can be severe or even fatal



original article

**T Cells Targeting Carcinoembryonic Antigen Can Mediate Regression of Metastatic Colorectal Cancer but Induce Severe Transient Colitis**

Maria R Parkhurst[1], James C Yang[1], Russell C Langan[1], Mark E Dudley[1], Debbie-Ann N Nathan[1], Steven A Feldman[1], Jeremy L Davis[1], Richard A Morgan[1], Maria J Merino[2], Richard M Sherry[1], Marybeth S Hughes[1], Udai S Kammula[1], Giao Q Phan[1], Ramona M Lim[1], Stephen A Wank[3], Nicholas P Restifo[3], Paul F Robbins[3], Carolyn M Laurencot[1] and Steven A Rosenberg[1]

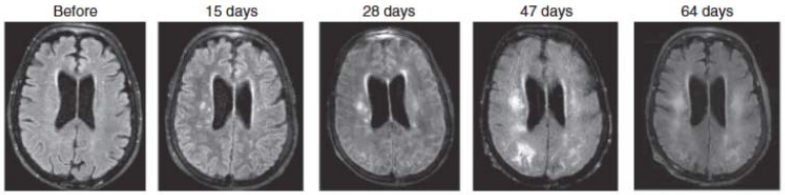
*Molecular Therapy*


CLINICAL STUDY

**Cancer Regression and Neurological Toxicity Following Anti-MAGE-A3 TCR Gene Therapy**

*Richard A. Morgan,* Nachimuthu Chinnasamy,* Daniel Abate-Daga,* Alena Gros,* Paul F. Robbins,* Zhili Zheng,* Mark E. Dudley,* Steven A. Feldman,* James C. Yang,* Richard M. Sherry,* Giao Q. Phan,* Marybeth S. Hughes,* Udai S. Kammula,* Akemi D. Miller,* Crystal J. Hessman,* Ashley A. Stewart,* Nicholas P. Restifo,* Martha M. Quezado,† Meghna Alimchandani,† Avi Z. Rosenberg,† Avindra Nath,‡ Tongguang Wang,‡ Bibiana Bielekova,‡ Simone C. Wuest,‡ Nirmala Akula,§ Francis J. McMahon,§ Susanne Wilde,‖ Barbara Mosetter,‖ Dolores J. Schendel,‖¶ Carolyn M. Laurencot,* and Steven A. Rosenberg**

*J Immunother* • Volume 00, Number 00, ■■ 2013




**Expression profile of target antigen in normal tissues:**
**the critical parameter determining the safety of engineered T cell therapy**

# How can engineered T cell therapy realize its potential and become a clinically relevant treatment option for many cancer patients?

- **Three main areas in which further progress is required**

  1) **Isolate and validate large collection of TCRs that can kill cancer cells without causing serious damage to normal tissues**

  2) **Further enhance efficacy of engineered T cells to obtain durable clinical responses in more cancer patients**

  3) **Improve & simplify T cell engineering process to enable it to become more mainstream technology and more readily available to patients**

## Our current research aims to contribute towards progress of (1) & (2)

1) **Isolation and validate large collections of TCRs that can kill cancer cells without causing serious damage to normal tissues**

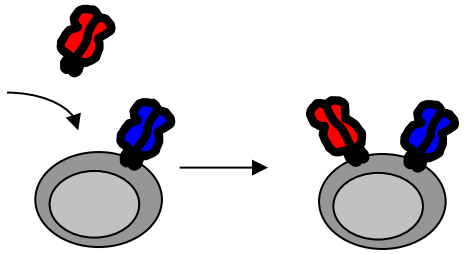
2) **Further enhance efficacy of engineered T cells to obtain durable clinical responses in more cancer patients**

3) Improve & simplify T cell engineering process to enable it to become more mainstream technology and more readily available to patients

# Enhancing the therapeutic efficacy of engineered T cell therapies

## Can additional genetic modification of TCR transduced T cells be used to promote durable clinical responses with engineered T cell therapy ?

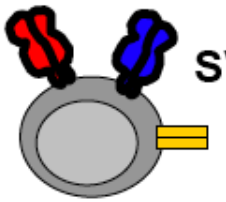
- TCR gene transfer endows patient T cells with desired antigen-specificity



- Additional genetic modification to tailor the activity of these cells & endow them with optimal functional properties

**Assessed the value of this approach in a mouse prostate cancer model**

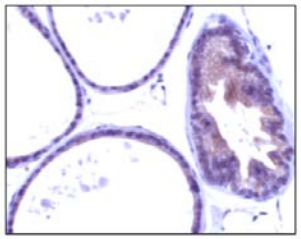
# Additional genetic engineering of T cells to tailor their activity profoundly enhances the therapeutic efficacy of engineered T cell therapy



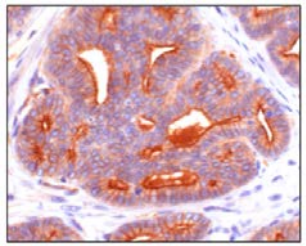
SV40 TCR & dnTGFβRII co-Td T cells

TGF-β1

Normal prostate

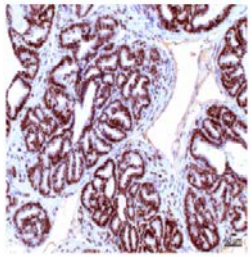


Prostate carcinoma

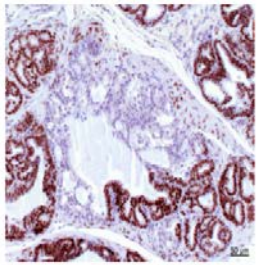


Tumour marker

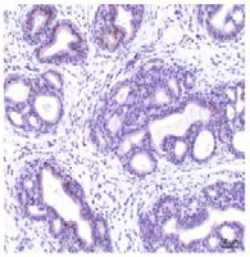
Non-Td

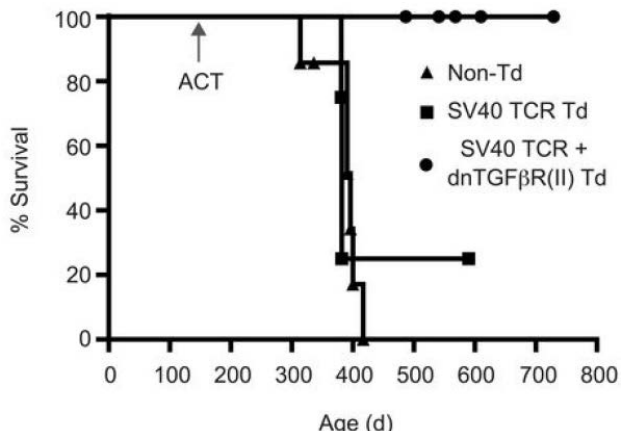


TCR Td



TCR & dnTGF-βRII co-Td






Bendle *et al*. J Immunol 2013

# Summary

- **Engineered T cell therapy of cancer holds great promise as a treatment**
- **Clinical experience demonstrated:**
  - **Potentially curative treatment for advanced forms of cancer**
  - **Expression profile of target antigen largely defines safety**
- **Further progress required for engineered T cell therapy to become a clinically relevant treatment option for many cancer patients**

# Acknowledgements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