T Cell Immunotherapy- Optimizing Trial Design

Session II
Potential Use of Stem Cells

David Baltimore
Caltech
September 10, 2013
Outline

• A little perspective
• Short history in mice
• Plans in humans
• On-going trial with an anti-HIV therapy
Perspective

• T cells derive from hematopoietic stem cells (HSCs) following thymic processing and selection.
• Genes inserted into HSCs can be expressed in all or in a limited range of progeny of HSCs.
• Vectored TCRs are found on the surface of only T cells because of the requirement for CD3 co-expression.
• Vectored TCRs should allelically exclude rearrangement of endogenous TCR genes yielding monoclonal cells.
Program T Cells for Anti-tumor Immunity

Target tumors

Life-long supplies of tumor-specific lymphocytes
Program T Cells for Anti-tumor Immunity

Target tumors

Life-long supplies of tumor-specific lymphocytes

Gene of interest with the desired gene

Retrovirus

Gene

Virus infection

Proteins associated with transferred gene

Exposed to retrovirus

HSCs cultured in medium containing cytokines (IL-3, IL-6, SCF)

Transfer back to lethal or sub-lethal irradiated mice

In 4-6 weeks, transferred HSCs repopulate the recipient's hematopoietic system

ImmunoTherapy

Gene Therapy

Stem Cell Therapy

Proteins

Hematopoietic stem cell

TCR genes

Tumor-specific

3' 5'
Developed the TCR Transfer Methodology in Mice (Lili Yang)

• Tumor antigen: chicken ovalbumin (Ova)
• Genes to be transferred into stem cells: T cell receptor chains reactive with a dominant Ova epitope for CD8 cells (or for CD4 cells)
• Test tumor: EL4 carrying the Ova gene (compared to EL4 lacking Ova)
• Showed complete resistance to tumors and clearing of existing tumors but required a peptide-pulsed dendritic cell boost
Retroviral Vector (MSCV-based) for TCR Gene Transfer to HSC

**MOT1**

5’ LTR  OT1\(\alpha\) cDNA  IRES  OT1\(\beta\) cDNA  WRE  3’ LTR

OT1 TCR: CD8 TCR that recognizes chicken OVA\(p_{257-264}\) (OVA\(p1\)) restricted to class I MHC K\(b\)

**MOT2**

5’ LTR  OT2\(\alpha\) cDNA  IRES  OT2\(\beta\) cDNA  WRE  3’ LTR

OT2 TCR: CD4 TCR that recognizes chicken OVA\(p_{329-337}\) (OVA\(p2\)) restricted to class II MHC A\(b\)
Imparting antitumor CD8 and CD4 T Cell specificities to the mouse T cell repertoire by Retroviral Transduction of HSCs

B6 Ctrl  B6/MOT1  B6/MOT2

Spleen and Nodes
Protection of Mice Against an EL4/Ova Tumor with TCR Genes
Can we Beef up the Response Further?

• Because we are putting genes into vectors, we could add genes that would improve the response

• IL-15 is known to increase T cell memory responses and incorporation the IL-15 gene into vectors does greatly improve anti-tumor responses
To Humans...

- Started by transferring genes to peripheral T cells—starting small
- Done in a consortium with UCLA, USC and others
- Began with anti-MART-1 TCR for melanoma but now using other TCRs and thinking about other tumors
- Moving now to the original plan, to target genes to HSCs using lentiviral vectors
Engineered Immunity Program

February 2006

Engineered Immunity Program

January 2011
Time-Course of Anti-Tumor Effector Cell Activity: Mature T Cell Infusion vs. HSC Transplantation

CD34+ UCB or PBSC

TCR or CAR Encoding Lentivirus

Preconditioning Irradiation

IH Transplant to Neonatal NSG

Peripheral Blood Screening Beginning at 2 Months Post Transplant

Immunophenotyping by Flow Cytometry

Expression of NY-ESO TCR in T Cells after CD34+ Cell Transduction and Engraftment in NSG Mice

Expression of anti-CD19 CAR in Hemato-Lymphoid Cells after CD34+ Cell Transduction and Engraftment in NSG Mice

Phase I Study of Autologous CD34+ PBSC Transduced using a Lentiviral Vector with a CD19-Specific, CD28-Costimulatory Chimeric Receptor and a Truncated EGFR (CAR-PBSC) for Patients with High-Risk Intermediate Grade B-Lineage Non-Hodgkin Lymphoma.

University of California, Los Angeles – Donald Kohn, Satiro deOliveira
City of Hope Medical Center – Steve Forman, Christine Brown

Dose Escalate – CAR-modified CD34+ PBSC with fixed dose unmodified PBSC

Primary safety end-points:
  RCL
  Clinical toxicity
  IO/clonal expansion

Secondary efficacy end-points for:
  engraftment of CAR gene-modified HSC
  expression of CAR in leukocyte lineages
  antigen-specific responses of CAR-expressing cells
Eradicate HIV/AIDS

CALiMMUNE

engineering immunity
Aim of Cal-1

To provide a therapy that produces a population of hematopoietic cells that are resistant to infection and subsequent pathogenicity of HIV, protecting patients from the ravages of HIV/AIDS

- Produce in the patients a population of functional CD4 cells to protect against opportunistic infections, gut dysfunction and loss of viral control
- Develop a large enough population of healthy CD4 cells to reduce viral load
Methodology

Ex vivo transduction of CD4+ T cells and CD34+ hematopoietic stem/progenitor cells that are infused into the individual
Investigational Product

- A self-inactivating lentiviral vector (based on HIV) with internal promoters driving sh5 and C46
- Consistent expression, no toxicity (phenotype, viability) and effective inhibition of HIV
- Transduce CD4+ T lymphocytes and autologous CD34+ HSPC
Progress in Cal-1 Trial

• Three patients leukophoresed, cells transfected ex-vivo and cells reinfused—pts are HIV-infected but off chemotherapy by choice
• Trial will test busulfan partial myeloablative to assist engraftment; first patients got no busulfan
• No adverse events
• After 4 patients, will start dose escalation of busulfan
• Only very preliminary data
Summary

• The rational for directing TCR or CAR immunotherapy to HSC is well-developed
• Clinical trials are being initiated
• Clinical trials of other potentially therapeutic agents will help to pave the way for this mode of therapy