

**T Cell Immunotherapy-
Optimizing Trial Design**

Session II

Potential Use of Stem Cells

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Caltech
September 10, 2013



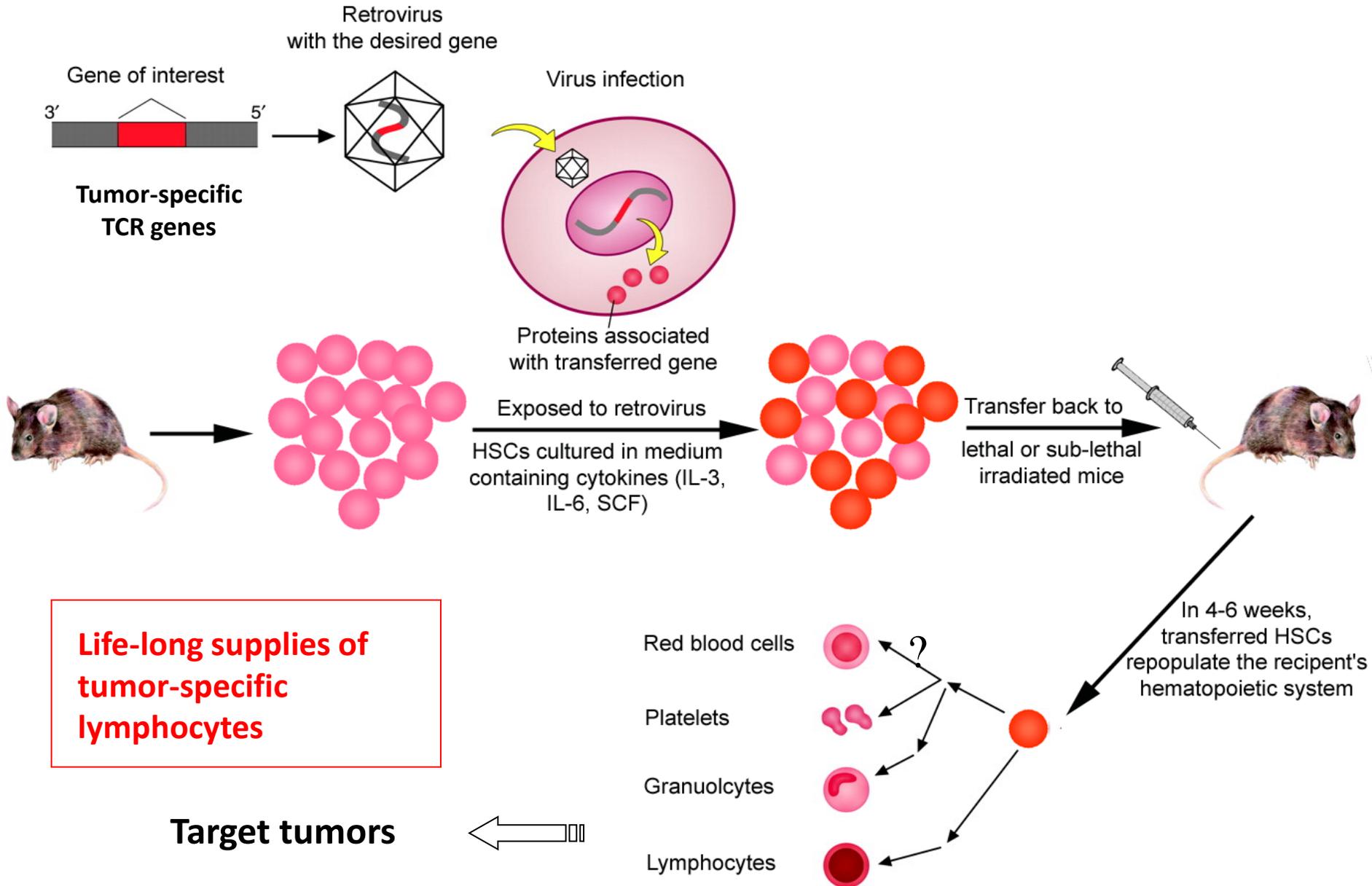
Outline

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

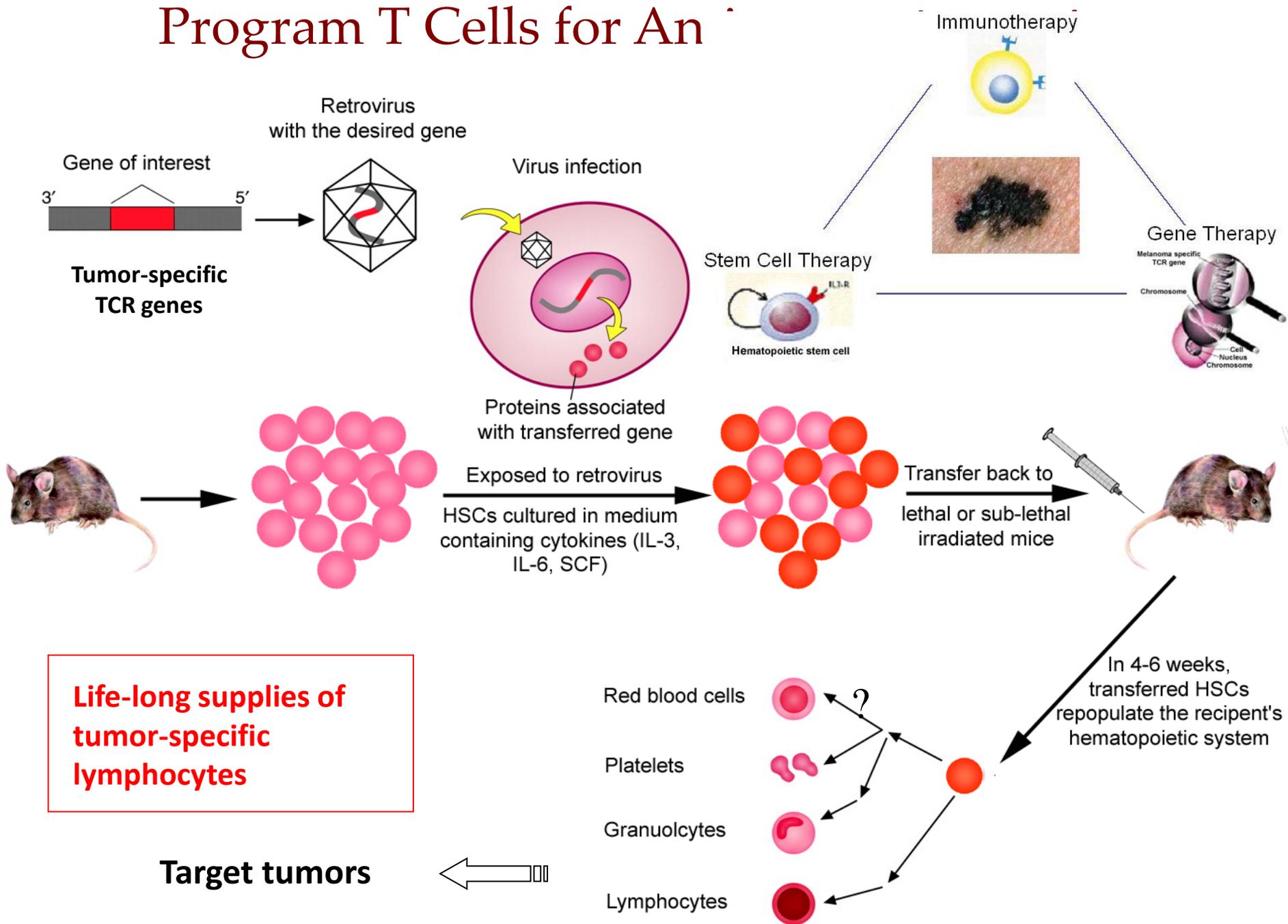
Perspective

- 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



Program T Cells for An



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



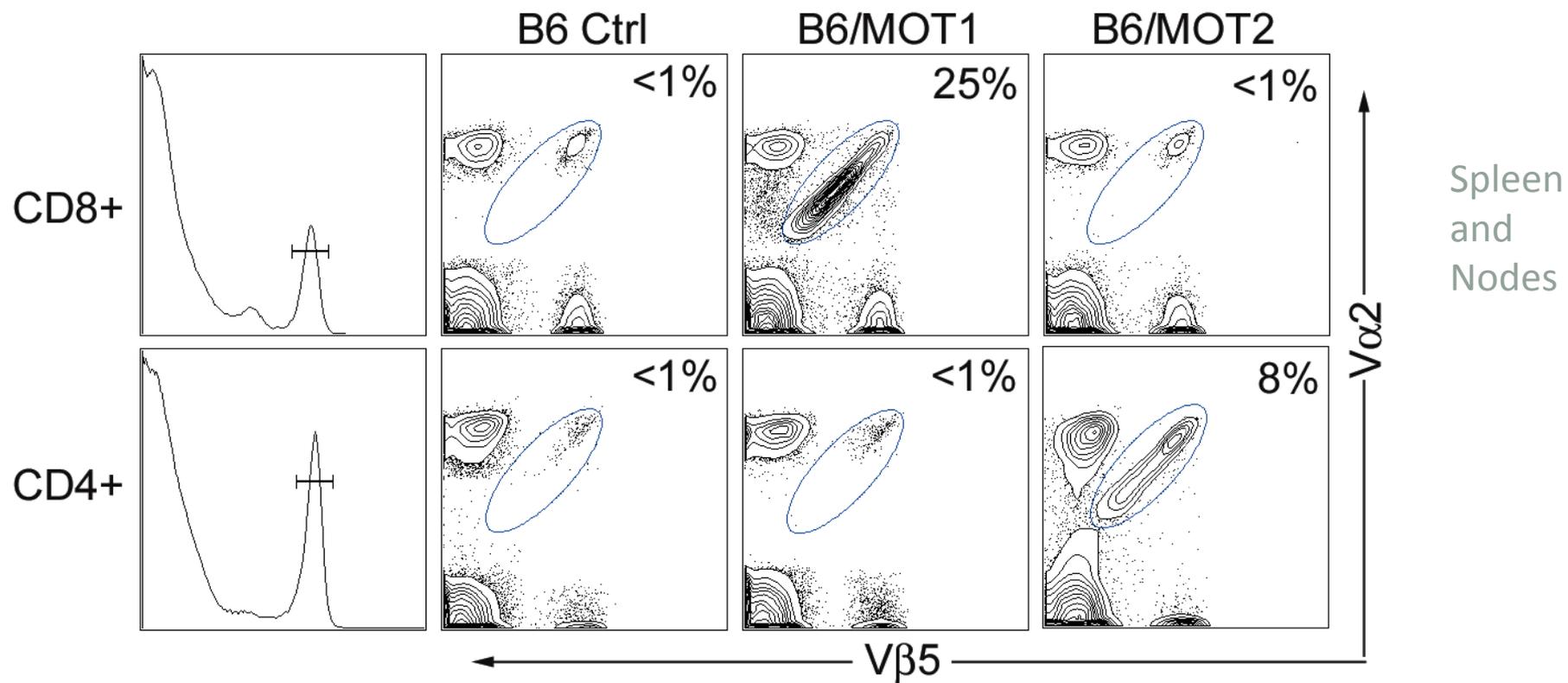
OT1 TCR: CD8 TCR that recognizes chicken OVA_{p257-264} (OVA_{p1}) restricted to class I MHC K^b

MOT2



OT2 TCR: CD4 TCR that recognizes chicken OVA_{p329-337} (OVA_{p2}) restricted to class II MHC A^b

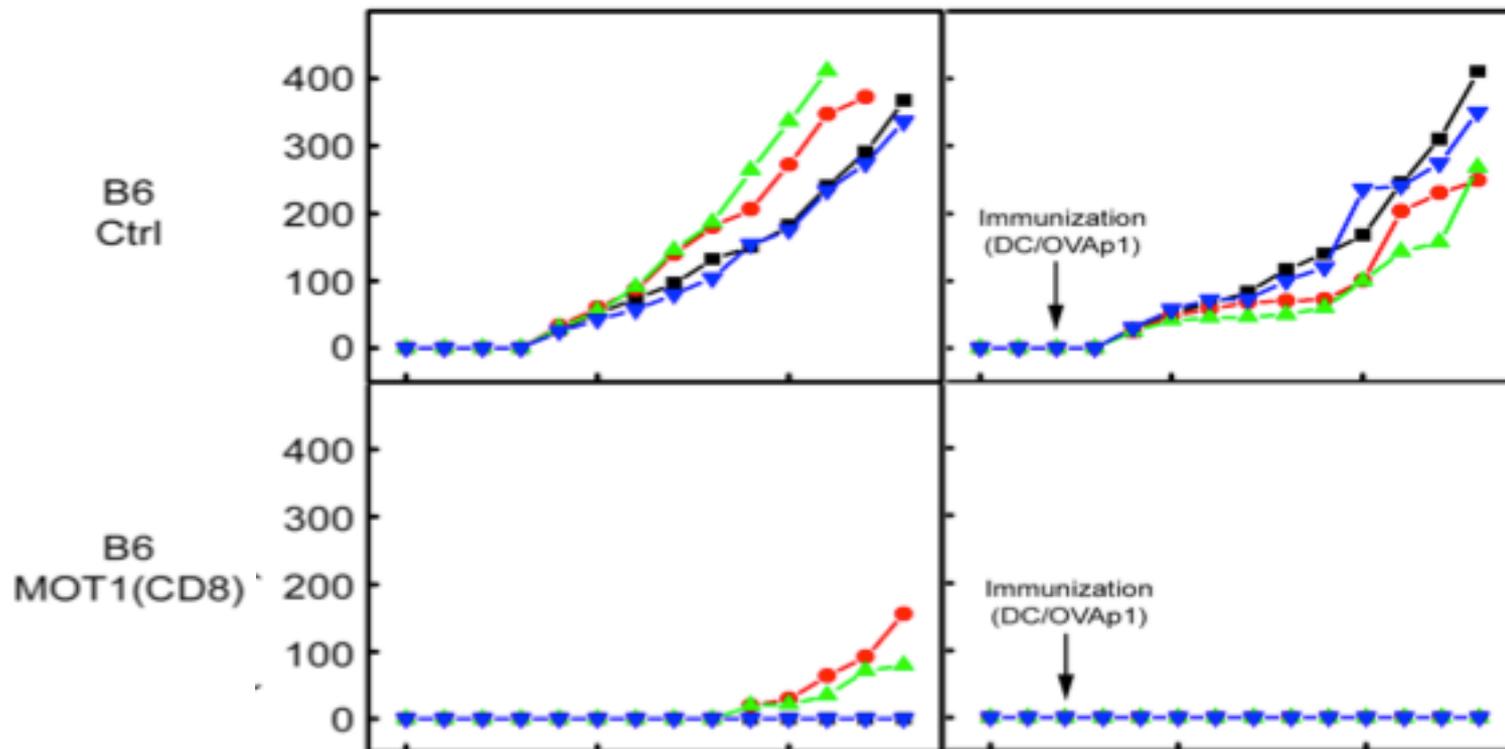
Imparting antitumor CD8 and CD4 T Cell specificities to the mouse T cell repertoire by Retroviral Transduction of HSCs



Protection of Mice Against an EL4/Ova Tumor with TCR Genes



E.G7



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...

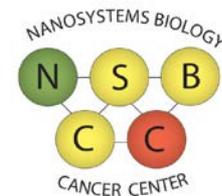
- Started by transferring genes to peripheral T cells– starting small
- Done in a consortium with UCLA, USC and others
- Began with anti-MART-1 TCR for melanoma but now using other TCRs and thinking about other tumors
- Moving now to the original plan, to target genes to HSCs using lentiviral vectors



February 2006

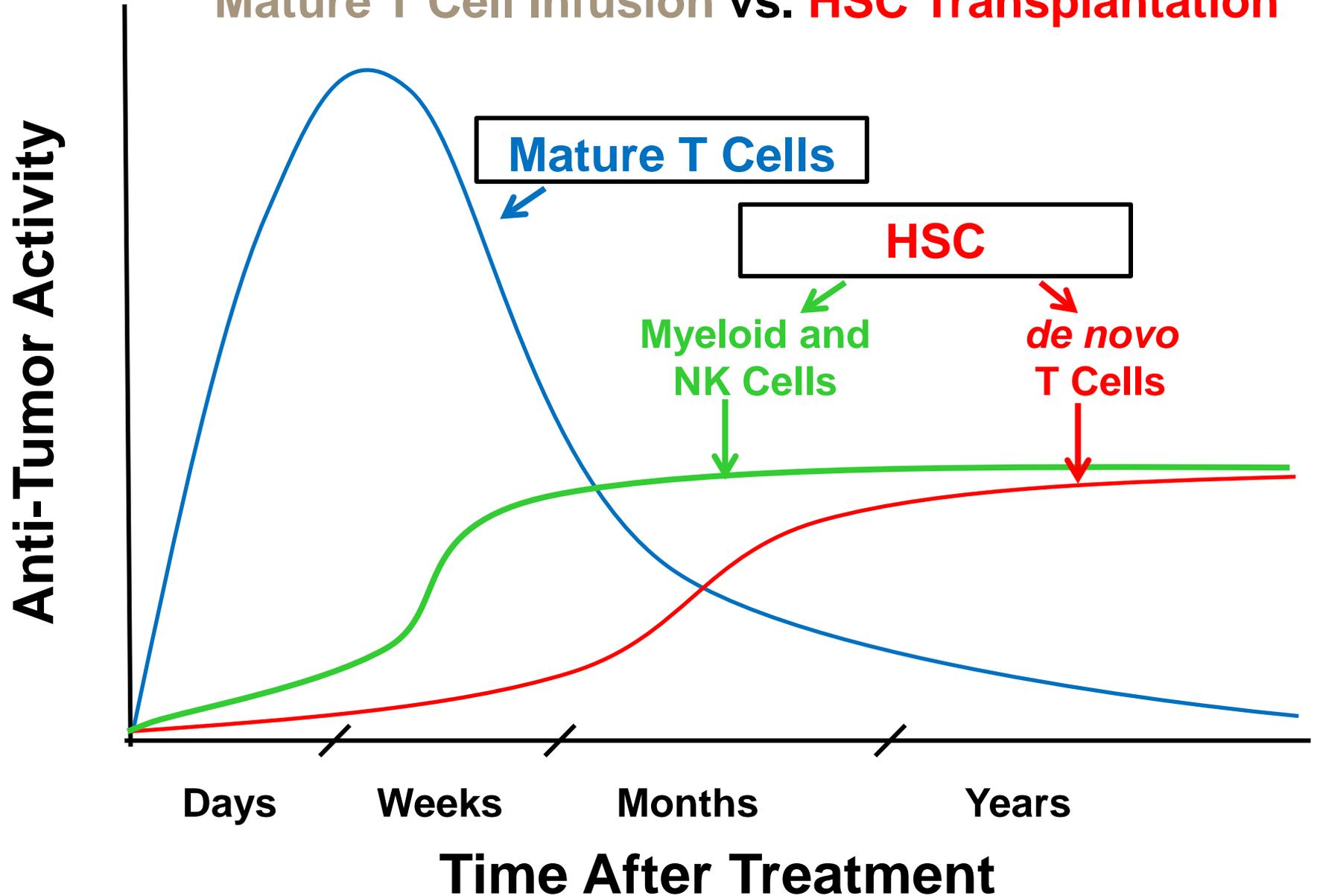


Engineered Immunity Program



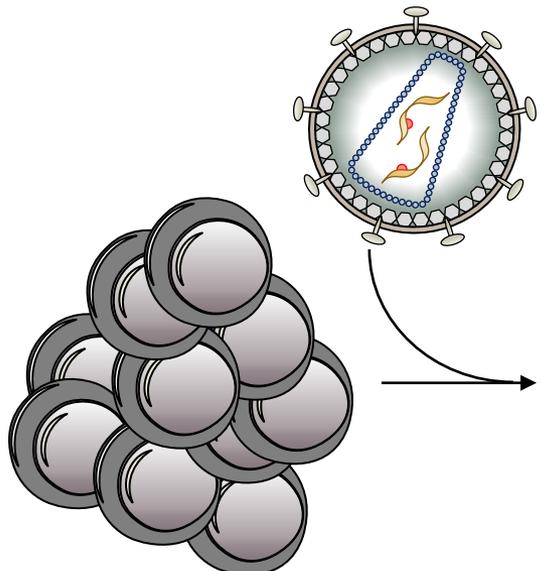
January 2011

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

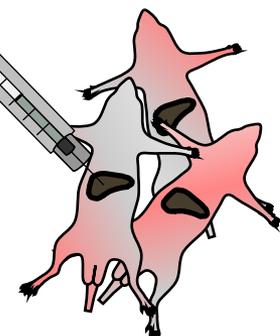
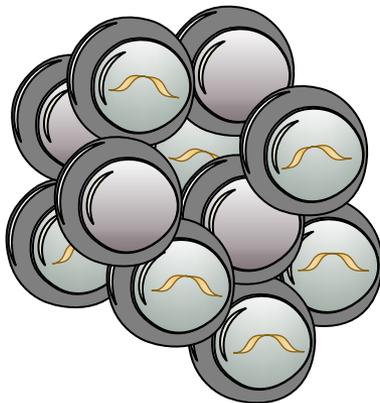


TCR or CAR Encoding Lentivirus

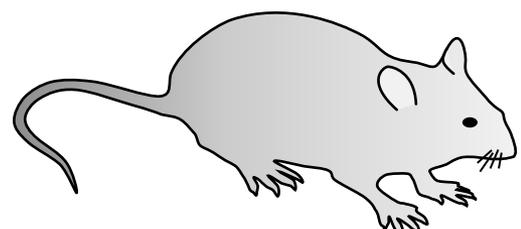
Preconditioning Irradiation



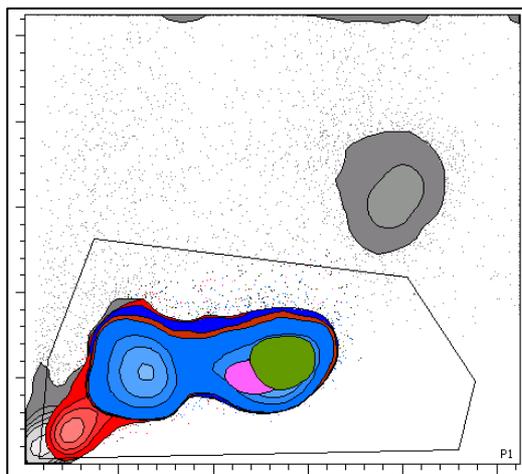
CD34+ UCB or PBSC



IH Transplant to Neonatal NSG

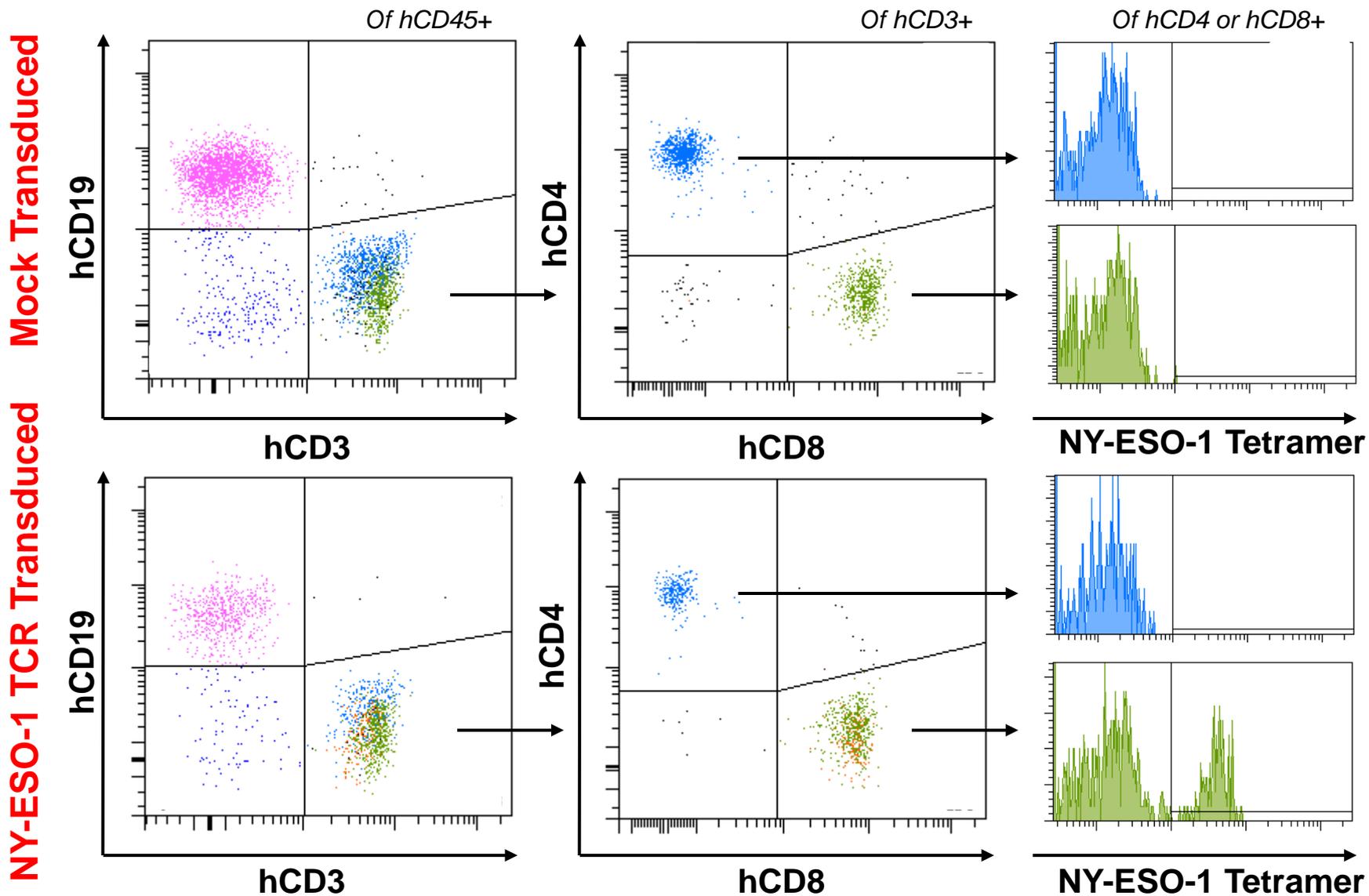


Peripheral Blood Screening
Beginning at 2 Months Post
Transplant



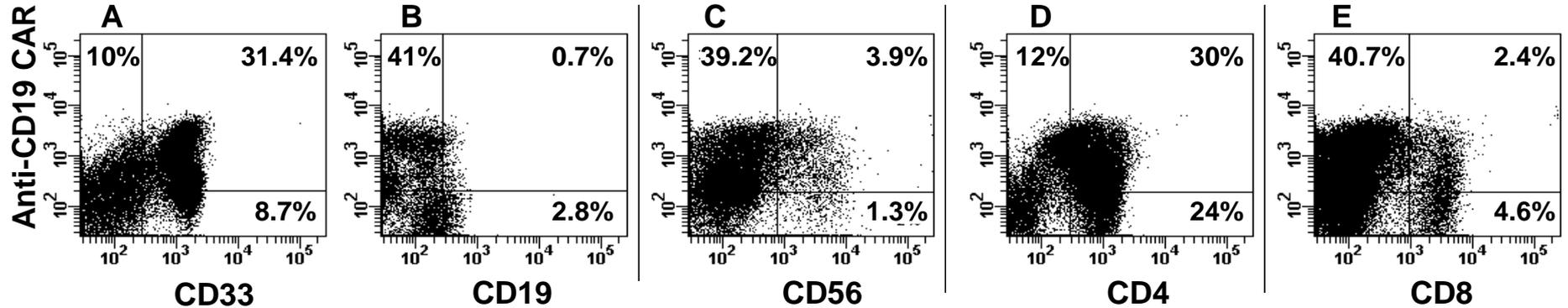
Immunophenotyping by
Flow Cytometry

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

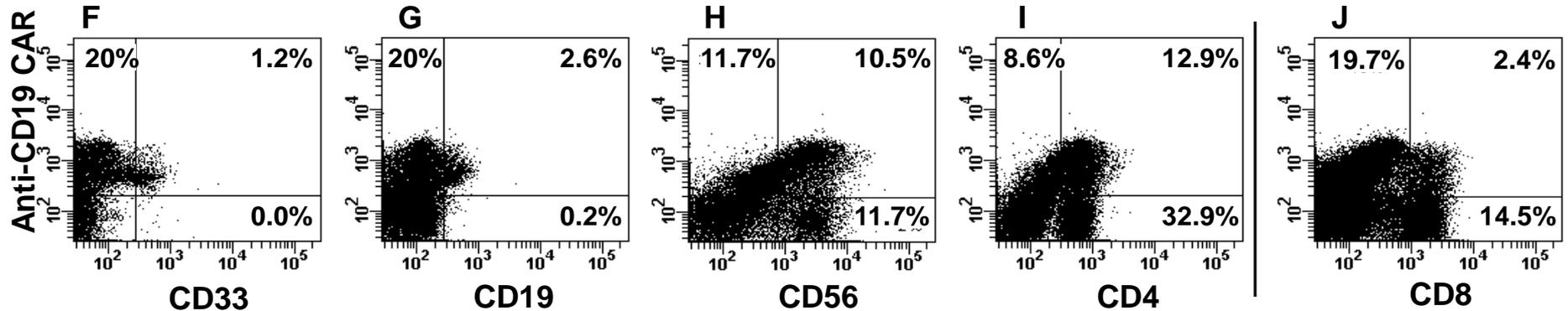


Expression of anti-CD19 CAR in Hemato-Lymphoid Cells after CD34+ Cell Transduction and Engraftment in NSG Mice

Bone Marrow



Spleen



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



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

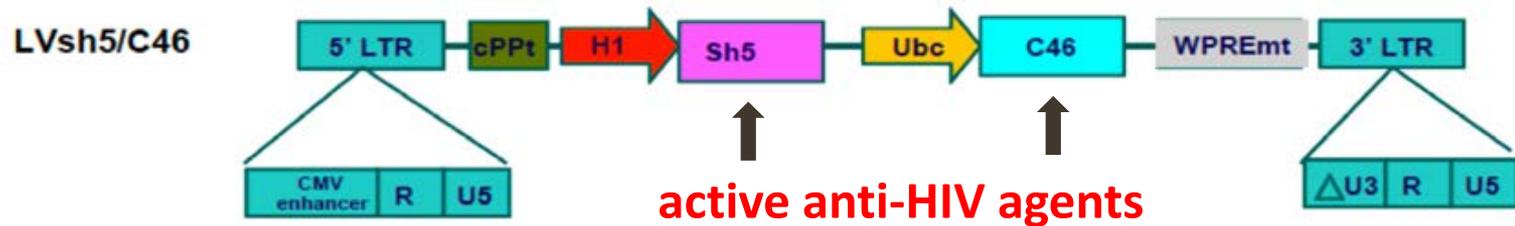
- ❑ Produce in the patients a population of functional CD4 cells to protect against opportunistic infections, gut dysfunction and loss of viral control
- ❑ Develop a large enough population of healthy CD4 cells to reduce viral load

Methodology

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

Investigational Product

Cal 1 Construct



- 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 myeloablation 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 rationale 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