FDA Perspective on the Regulation of TCR/CAR T-cell Products

Raj K. Puri, M.D., Ph.D.

Director, Division of Cellular and Gene Therapies, FDA, CBER

CIMT2014 Talk *(by Phone)*
Date: May 8, 2014
Time: 12:30 PM to 14:30 PM German Time
(6:30 to 8:30 AM EST USA Time)
Location: Mainz, Germany

FDA Organization

- CBER (Center for Biologics Evaluation and Research): vaccines, blood and blood products, human tissue/tissue products for transplantation, cells, gene therapy

  -Office of Cellular, Tissue, and Gene Therapies
  -Office of Vaccines Research and Review
  -Office of Blood Research and Review
  } Product Offices

- CDER (Center for Drug Evaluation and Research): drugs, some biological products
- CDRH (Center for Devices and Radiological Health): devices for treatment, implants, diagnostic devices
- CVM
- CFSAN
- NCTR
- CTP
- ORA
- OC

FDA Regulation of Oncology Products

- Office of Hematology and Oncology Drug Products (OHOP), CDER
  - Drugs (small molecules)
  - Biologics, including Monoclonal Antibodies, Therapeutic Proteins, Cytokines
- Office of Cellular, Tissue and Gene Therapy, (OCTGT) CBER
  - Cell therapies
  - Gene Therapies - Oncolytic viruses
  - Therapeutic vaccines and immunotherapies
- Center for Device Radiological Health (CDRH):
  - Devices
    - Companion Diagnostics
    - Delivery devices

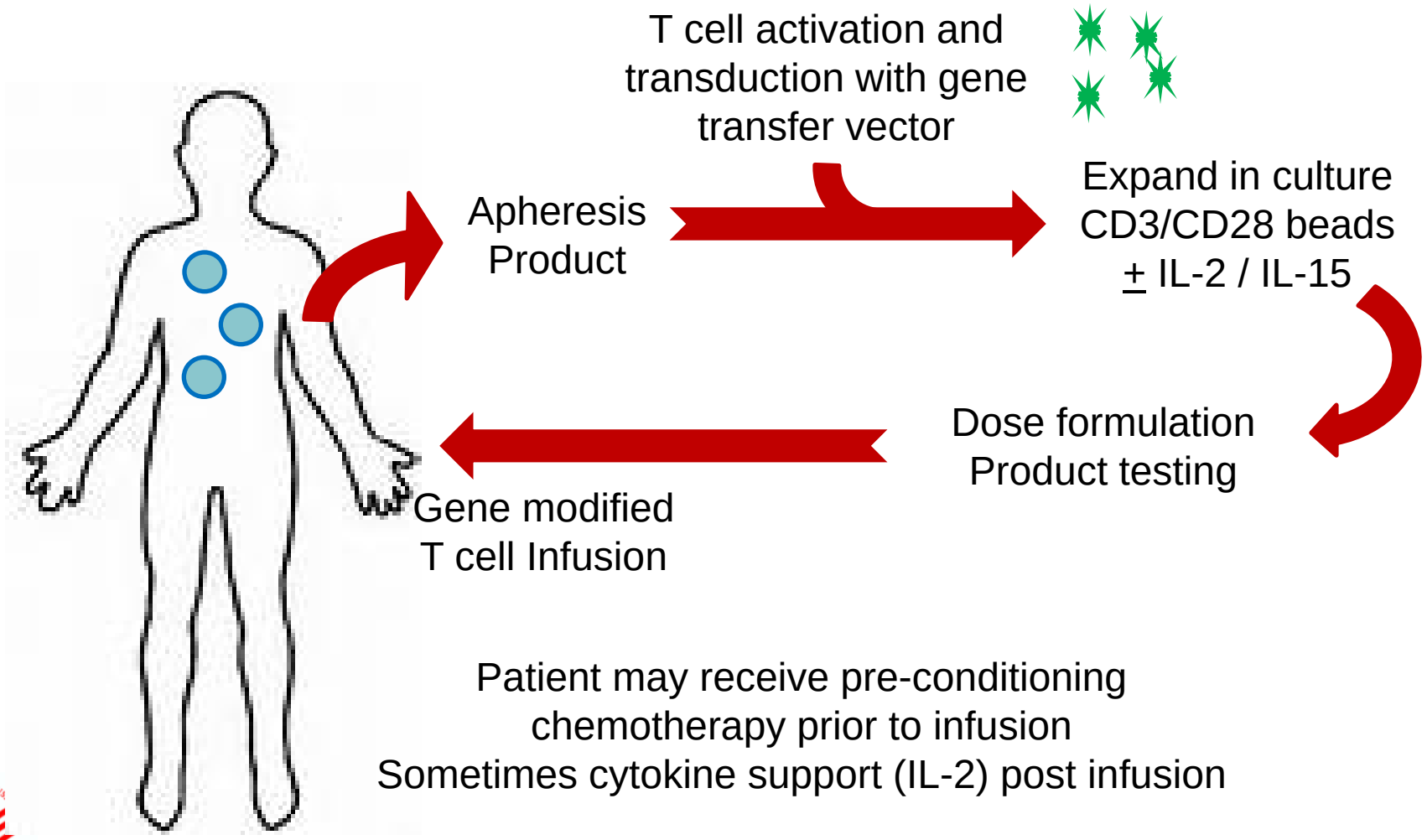
Oncology Product Approvals by OCTGT

- Provenge (sipuleucel-T) – Dendreon
  - ARPC
- BCG Live (Intravesical) - TheraCys, Sanofi Pasteur Limited
- HEMACORD (HPC, Cord Blood) – NY Blood Center
- HPC, Cord Blood – Clinimmune labs, University of Colorado Cord Blood Bank
- DUCORD (HPC, Cord Blood) – Duke University
- HPC, Cord Blood - LifeSouth Community Blood Centers, Inc.
- Allocord, HPC Cord Blood - SSM Cardinal Glennon Children's Medical Center
- *Indication:* HPC, Cord Blood is an allogeneic cord blood hematopoietic progenitor cell therapy indicated for use in unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment.

Gene modified T cells?

- Harness T cell immunity (cytotoxic functions, cytokine secretion, etc.) to attack tumor cells
- Conventional *ex vivo* expanded T cells targeting tumor antigens show some efficacy, but poor persistence (low affinity?)
- Use gene transfer to improve functional properties of transduced T cells
  - Control of T cell specificity (recognition of defined tumor antigens)
  - Remove need for HLA specificity
  - Enhanced engraftment and proliferation
  - More potent effector function
- The above properties are encoded by the transgene

T cell immunotherapy: Basic overview



Patient may receive pre-conditioning chemotherapy prior to infusion
Sometimes cytokine support (IL-2) post infusion

Gene modified T cell products

Engineered TCR

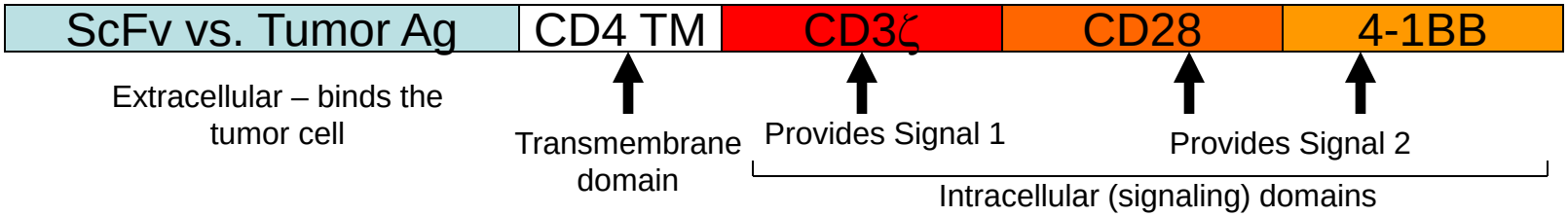
- Express α/β TCR
- TCR often "affinity enhanced" (mutated for >IFN-γ secretion)
- Recognize tumor antigen-derived peptide/MHC complex
- Tumor antigen can be intracellular or cell surface
- Require co-stimulation (host antigen presenting cells)

Chimeric Antigen Receptor

- Express ScFv from mAb fused to CD3ζ (+CD28 and/or 4-1BB)
- Recognize tumor antigen via ScFv (MHC-independent)
- Tumor Antigen must be cell surface
- Do not require additional co-stimulation (provided by construct)

Gene delivery usually via retroviral/lentiviral vector (sleeping beauty transposon, mRNA electroporation also used – rarer) into autologous cells, generally expanded in culture with Ab vs. CD3/CD28 + IL-2 (sometimes + IL-15)

Typical CAR construct

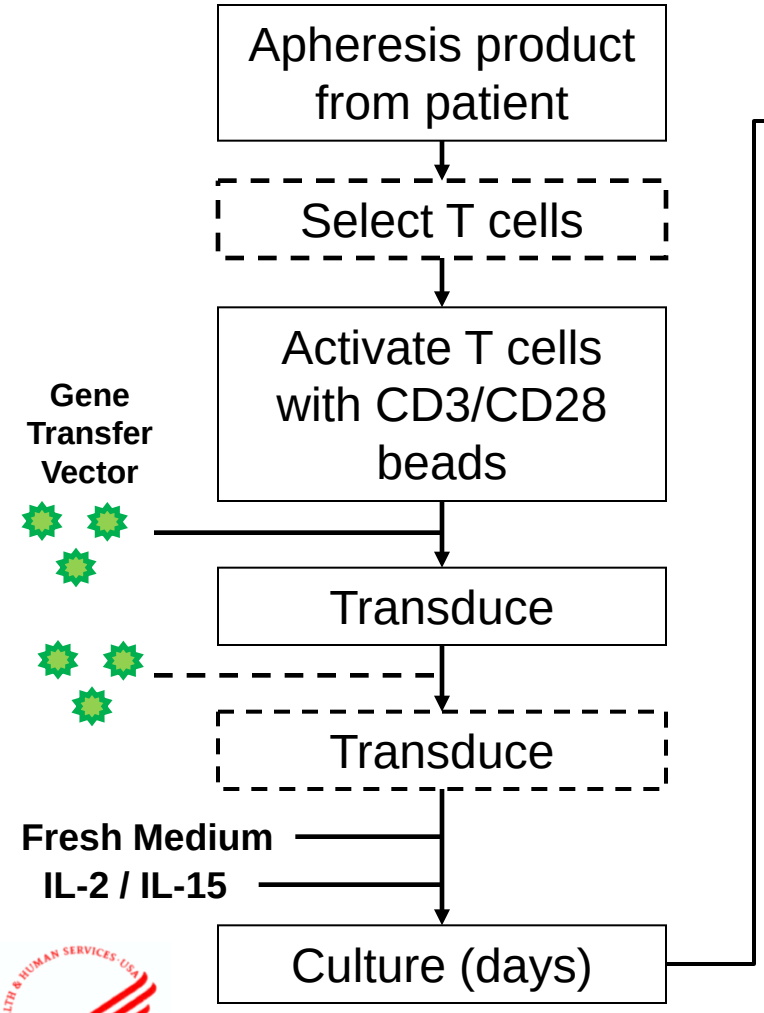


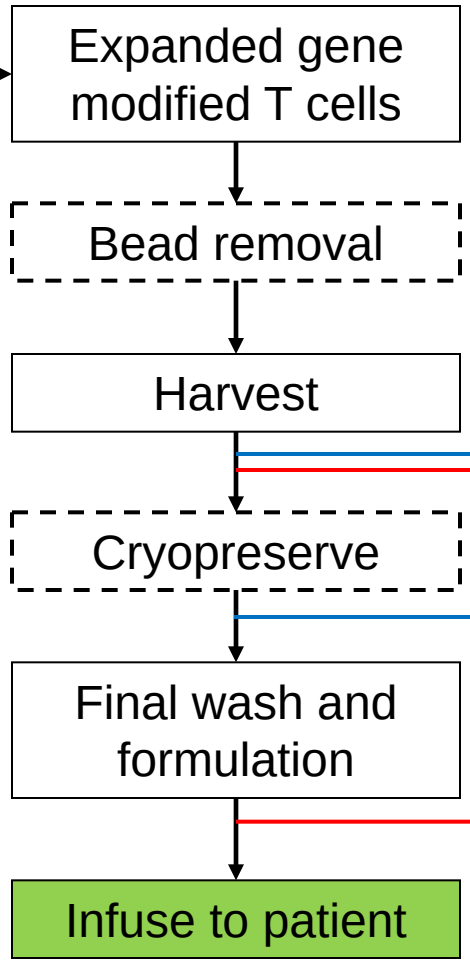
- Antigen recognition via ScFv from a monoclonal antibody targeting Tumor Antigen (eg. CD19, Her2/neu, or CEA)
- After ScFv binding to Tumor Antigen, the initial signal ("Signal 1") for transduced T cell activation is via CD3ζ intracellular domain
- Co-stimulation ("Signal 2") via CD28 and/or 4-1BB intracellular domains
- Signal 1 + Signal 2 triggers CAR T cell cytolytic function, cytokine secretion and proliferation

Potential problems with CAR approach

- Requirement for Signal 1 + Signal 2 evolved to prevent autoimmunity – eliminating this checkpoint could "take the brakes off" a T cell response
- Differences in affinity for ligands:
  - endogenous TCR μM range
  - mAbs nM range (CD19 ScFv 2.3 nM)
- T cells transfected with CAR still have their endogenous TCR (we have no way of telling what these would be specific for – Viruses? Autoantigens?)

Product manufacture and testing





Additional (in-process) tests during manufacture

- Viability
- Cell count
- Phenotype
- Sterility

Product release tests

- Flow cytometry (phenotype/ScFv)
- Residual bead count
- Potency (cytokine production?)
- Vector copy number (PCR)
- Mycoplasma
- Replication-competent vector (PCR + culture)
- Viability / cell count
- Sterility (bacterial and fungal)
- Endotoxin

Some test results may not be known at time of infusion

Manufacturing challenges

- **Product consistency**
  - Lot to lot variation in transduction efficiency (i.e. how much vector gets into the T cells: % transduced cells and copy number per cell)
    - Standardization of Retro/Lentivirus vector stocks to give a constant multiplicity of infection (MOI)
    - Patient to patient variation in autologous T cell substrates (may depend on many factors including age, prior therapies)
  - Is there an “optimal” T cell population?
    - CD4+ vs. CD8+? Effector vs. Naïve vs. Memory?
    - Select at start of culture or end of culture
- **Product tracking and labeling**
  - Autologous products; critical to ensure patient receives the correct product

Product testing challenges

- **Testing for potency**
  - What assays are most appropriate?
    - Cytokine production or lytic activity when incubated with target cells?
    - Phenotypic characteristics by flow cytometry?
    - Does potency correlate with transduction efficiency (% transduced cells/vector copy number per cell)?
      - Not necessarily (cells expand in patient post-infusion)
  - Potency testing required for late phase clinical trials and pre-licensure
- **Testing for replication-competent vector (RCR/RCL)**
  - Culture based methods are “gold standard”: expensive, time consuming, technically challenging
  - PCR-based methods (detecting viral envelope gene) faster and cheaper, but problems with false positive results
  - Long term follow up (15 years) for RCR/RCL required
- **Personalized products; time window for release testing may be limited**

Pre- and post-infusion issues

- **Patient pre-conditioning to make "immunological space"**
  - Thought to be needed for optimal cell engraftment
  - Typically non-myeloblative chemotherapy regimen

    (e.g. course of cyclophosphamide + fludarabine prior to infusion)
  - Note many investigators give product fresh (before product testing is complete)
- **Post infusion cytokine support**
  - Often IL-2 to promote T cell proliferation (can mask acute SAEs)
  - Also give G-CSF to support neutrophil recovery

Clinical challenges

- **Dosing Issues**
  - Cells expand post infusion: does infused dose reflect actual *in vivo* situation?
    - Total T cells dose
    - Transduced cell dose
    - Dose based on body weight
    - Dose based on body surface area
    - Interpreting safety data
    - Cross study comparisons
  - Monitoring: Infused cells may expand locally (e.g., in bone marrow): does measuring cells (or cytokines) in blood represent what's happening in tissues?

Clinical challenges

- **Toxicity**
  - On target toxicity
    - Expected
    - Risk mitigations strategies
    - Safety thresholds
  - Off target toxicity
    - Unexpected
    - Greater risks to subjects
    - Complex go-no go decisions
  - Cytokine Release Syndromes
    - Infusional reactions

Clinical challenges

- **Toxicity**
  - Cytokine Release Syndrome / Macrophage Activation Syndrome ("on target" toxicity: cytokine storm as T cells expand and exert anti-tumor activity)

    (What cytokines are important? Unclear (in part because different Sponsors monitor different cytokines)
  - Can toxicity be dissociated from anti-tumor activity?

    CD19 CAR T cells: Responses associated with some degree of toxicity
  - If not, how best to manage toxicity?
    - Tocilizumab (blocks IL-6 receptor) – seems to have helped in some cases
    - Steroids? Potential interference with T cell activity/expansion
    - Suicide genes? Do these deplete cells fast enough?
    - Monitoring and timing of interventions?

Serious Adverse Events from autoreactive TCRs

- **TCRs may recognize self antigens and cause SAEs**
  - Autoreactivity has always been a theoretical possibility, what has changed recently?
    - Actual SAEs
    - Better understanding of risk factors
    - New strategies to screen for autoreactivity before using TCRs in clinical trials
  - Any TCR might be autoreactive, but risk is higher for certain engineered TCRs:
    - Non-human TCRs
    - Affinity-enhanced TCRs
    - Why is the risk higher for these? These TCRs have not been "self-educated" in thymus

- **NCI** (Morgan *et al*. J Immunother. 2013 36(2); 680-8)
  - Mouse TCR targeted against MAGE-A3 / HLA-A*02
  - CNS toxicity due to unexpected expression of MAGE-A12 in CNS
    - MAGE-A3/12 epitopes are similar

- **UPenn** (Cameron *et al*. Sci Transl Med. 2013 5(197); 197ra103)
  - Human affinity-enhanced TCR targeted against MAGE-A3 / HLA-A*01
    - (Also reacts against similar epitopes in MAGE-A6 and MAGE-B18)
  - Rapid cardiac toxicity due to unexpected "off target" TCR cross-reactivity with Titin (a muscle protein)
    - Steroid treatment didn't help

Future gene modified T cell products

- **Allogeneic CAR T cells?**
  - "off the shelf" platform therapy (not bespoke/patient specific)
  - Potential for Graft versus Host Disease (GvHD)
    - Genome engineering to remove/suppress endogenous TCR?
  - Potential for rejection
    - Circumvented by immunosuppression?
- **Limitation of "on target, off tumor" toxicity**
  - Co-express inhibitory CAR (based on PD-1 or CTLA-4) that binds antigen expressed on non-tumor cells but **not** on tumor cells (Federov *et al*. 2013; Sci Trans Med 215ra172)
- **Improved suicide genes/deletion methods**
  - Inducible caspases, antibody deletion targets
  - Might allow "tuning" of response
- **Non-viral transduction methods**
  - mRNA electroporation?
- **Move from fresh to cryopreserved cells**
  - More time for release/characterization testing
  - Delay pre-conditioning until a product passing release tests is available
  - Allow re-dosing?

Pathway to licensure: Challenges

- **Access to key reagents/ IP issues**
  - Need GMP grade materials/reagents
  - Certain reagents often only available from a single supplier
- **Move from academic to industrial manufacturing settings**
  - Manufacturing capacity (patient-specific products: manufacturing currently labor intensive)
  - Central manufacturing facilities?
  - Comparability studies needed if manufacturing methods/sites changed between early and late stage studies
  - Product characterization is critical
- **Funding of late-stage trials?**
  - Trial support networks?
  - Cost recovery?
- **Key next step will be moving to Phase III Trials**

Summary

- CAR T cells are novel products that have unique characteristics that may impact product and clinical aspects of regulating these products.

- There are challenges with almost every aspect of the product development including CMC, patient monitoring, and trial design from eligibility to long term follow up.

- CAR T cell science is a moving target and maintaining regulatory flexibility as knowledge improves is key to effective drug development.

Acknowledgement:
OCTGT T Cell Working Group

- Andrew Byrnes, PhD
- **Bindu George, MD**
- Robert Le, MD, PhD
- Ke Liu, MD, PhD
- Jinhua Lu, PhD
- Brian Niland, PhD
- Maura Oleary, MD
- **Graeme Price, PhD**
- Daniel Takefman, PhD
- Ramjay Vatsan, PhD
- Allen Wensky, PhD
- Cheng-Hong Wei, PhD

Useful FDA Information

- References for the Regulatory Process for the Office of Cellular, Tissue, and Gene Therapies (OCTGT)
  http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/ucm094338.htm

- OCTGT Learn Webinar Series:
  http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm

- FDA Clinical Investigator Training course (Nov 12-14 2013):
  http://continuingeducation.dcri.duke.edu/fda-clinical-investigators-training-course-registration

Public Access to CBER

- CBER website:
http://www.fda.gov/BiologicsBloodVaccines/default.htm
Phone: 1-800-835-4709 or 301-827-1800

- Consumer Affairs Branch (CAB)
Email: ocod@fda.hhs.gov
Phone: 301-827-3821

- Manufacturers Assistance and Technical Training Branch (MATTB)
Email: industry.biologics@fda.gov
Phone: 301-827-4081

- Follow us on Twitter
https://www.twitter.com/fdacber

Contact Information

Raj K. Puri, M.D., Ph.D.,
Director,
Division of Cellular and Gene Therapies
Office of Cellular Tissue and Gene Therapies
CBER/FDA
Raj.puri@fda.hhs.gov

Regulatory Questions:
Contact the Regulatory Management Staff in OCTGT at
CBEROCTGTRMS@fda.hhs.gov
or Lori.Tull@fda.hhs.gov
or by calling (301) 827-6536