Personalized Medicine

Engineered T Cell Therapies: Regulatory perspectives from academia

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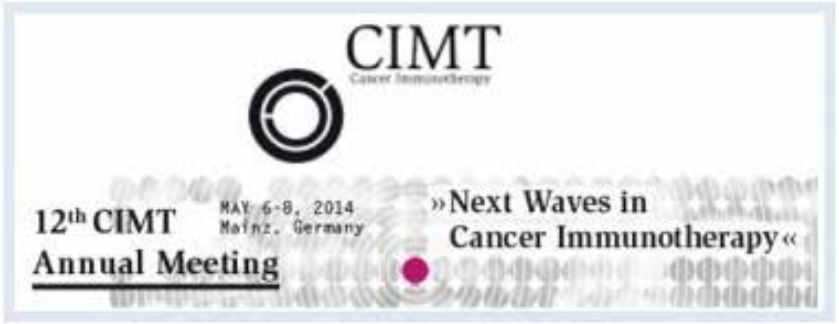
May 8, 2014



Disclosure Information
Engineered T Cell Therapy
Carl June

- PI – David Porter, MD (CLL trial)
  PI – Stephan Grupp, MD, PhD (ALL trial)

  Sponsor - Carl June:
- Speaker and members of his laboratory have financial interest due to IP and licensure to Novartis.
- Funding support for trials: ACGT, LLS, NCI, Lustgarten and Novartis
- COI managed in accordance with University of Pennsylvania policy and oversight.

Regulatory Challenges with Engineered T Cells Outline

- Preclinical studies
- Clinical trial design isssues
- Toxicity management issues
- Integrating vectors
- Cell manufacturing issues

CAR T Cell Trials at UPENN
Lessons Learned

- Have treated >70 adult and pediatric B cell malignancy patients to date: potent responses observed in all age groups
- CLL: ~50% overall response rate in patients with bulky relapsed and refractory disease. Patients who achieve CR have not relapsed. Longest duration of response is > 3 years.
- ALL: >85% complete remission rate in pediatric (n=25) and adult (n=5) patients.
- CART19 cells traffic to CSF in pediatric ALL and persist for at least 3 years
- On target cytokine release syndrome and macrophage activation syndrome in responding patients
- Infusions of mRNA electroporated, mesothelin-redirected CARTmeso T cells are safe to date

Preclinical studies

- Studies in humanized mice or syngeneic mice with engineered T cells:
  - Advantages and limitations
  - Preclinical mouse studies did not identify cytokine release syndrome or macrophage activation syndrome
  - Preclinical syngeneic mouse models may be optimal to study combination therapies due to microenvironment?
- Biotox studies for novel signaling domains or new specificities
- Preclinical studies have generally failed to identify toxicity with new CARs and TCRs:
  - Carbonic anhydrase IX CAR
  - MAGE A3 TCR

Preclinical Evaluation – Gene Therapy and Immunotherapy Agents

- the approach by which safety data are obtained will differ:

Gene Modified Cell Products

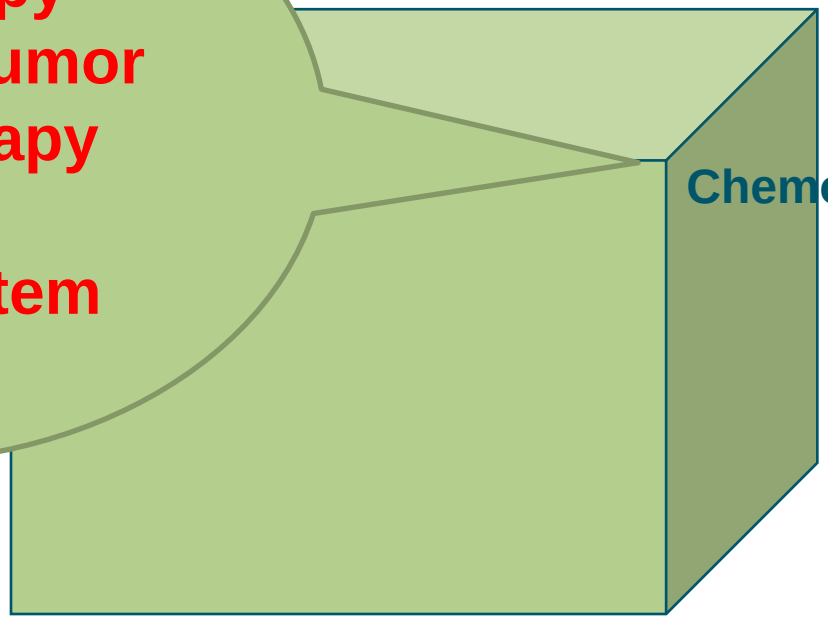
- Ø Biodistribution of vector/virus
- Ø Kinetics of gene expression
- Ø Immunogenicity to allogeneic cells
- Ø Uncontrolled cell proliferation following *ex vivo* modifications

Ying Huang, Ph.D.

FDA/CBER/OCTGT/DCEPT/PTB

Combinatorial Cancer Immunotherapies: Many possibilities

- **Chemotherapy targets the tumor**
- **Immunotherapy targets the immune system**



Targeted Small Molecule Drugs

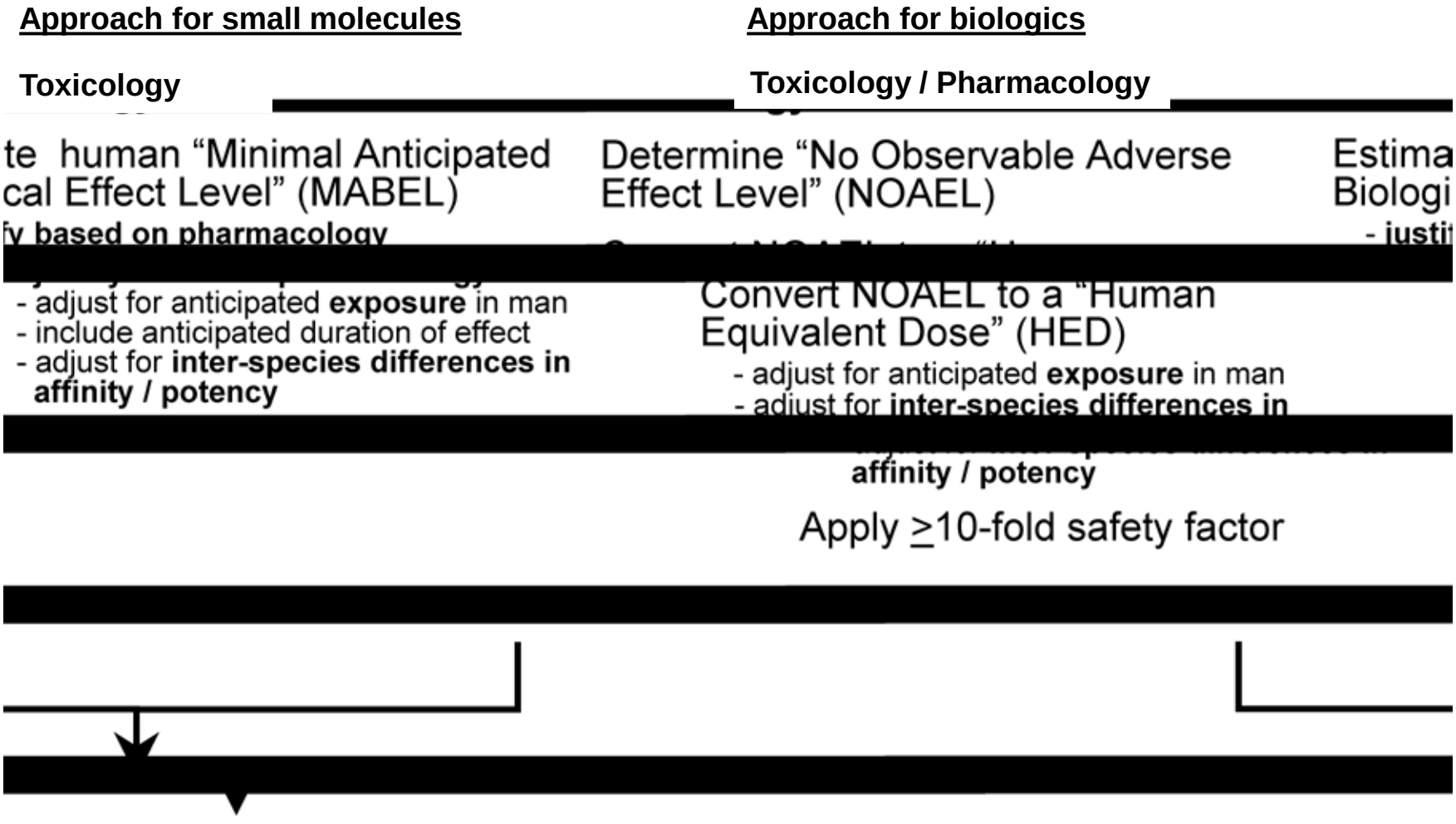
Chemotherapy

Radiation

Antibodies

Cell Based Therapies

Clinical Trial Design Issues
First in Human Trials with Biologics



Specific Considerations for First in Human Trials with Gene Modified T Cell Products

- Metabolism does not follow standard pharmacokinetics and/or pharmacodynamics
- Distinct product mechanism of action requires different trial design
  - Defining optimal biologic dose (OBD) rather than maximum tolerated dose (MTD)
  - Consideration of unique monitoring

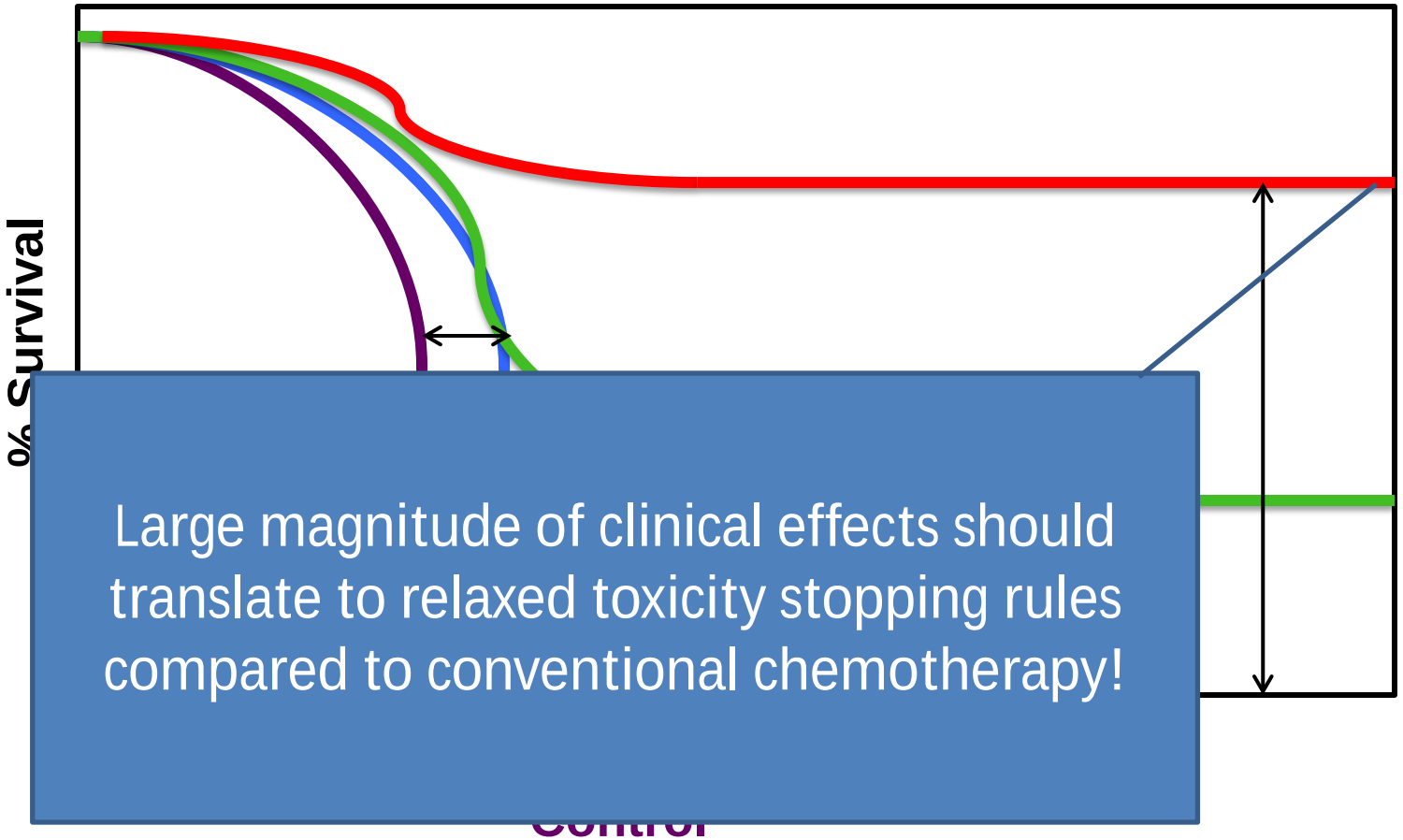
Gene modified T cells are self-replicating drugs!

Clinical Trial Design Issues

- Dosing with a “self-replicating” drug
- Phase I trials: defining dose
  - Optimal biologic dose?
  - Maximum tolerated dose?
- Relation of dose to age: youth vs old cells
  - would telomeres be a surrogate to determine dose?
- Dose measurement: flat dosing vs BSA vs cell/kg?
  - Total cell dose vs gene modified cell dose
- Relationship of dose to disease burden: inverse?

Clinical Trial Design Issues

Improving Survival with Combination Therapy



Clinical Trial Design Issues

- **Inclusion criteria**
  - **Classic performance status = ECOG 0,1**
  - **Because ACT/CARs/TCRs can induce remission in only a few weeks (i.e. not months like vaccines), then consider liberalizing performance status to ECOG 2, or 3?**
  - **Pre-existing organ damage: level of tolerable dysfunction is probably different than for chemotherapy. But, patients need to be able to withstand metabolic "stress test" for T cell therapies.**
- **Acceptable toxicities**
  - **If major benefit possible, then patients are willing to accept more toxicity than with conventional chemotherappy that has limited curative potential**

Toxicity Management Issues

July 2010 – August 2013*

- **About 40 SAEs reported that were possibly related to the genetically modified T cells**
- **Across TCR and CAR protocols the most commonly reported events involve fevers and hypotension that usually occur either in the immediate 24 - 48 hours after infusion or about a week after infusion.**
  - **In at least one case of fevers, hypotension, increased liver enzymes and thrombocytopenia, with elevations in cytokines occurred more than a month after infusion of cells.**

*** NIH RAC meeting, Bethesda, August 2013. Jacqueline Corrigan-Curay, J.D., M.D.**

Toxicity Management Issues

July 2010 – August 2013*

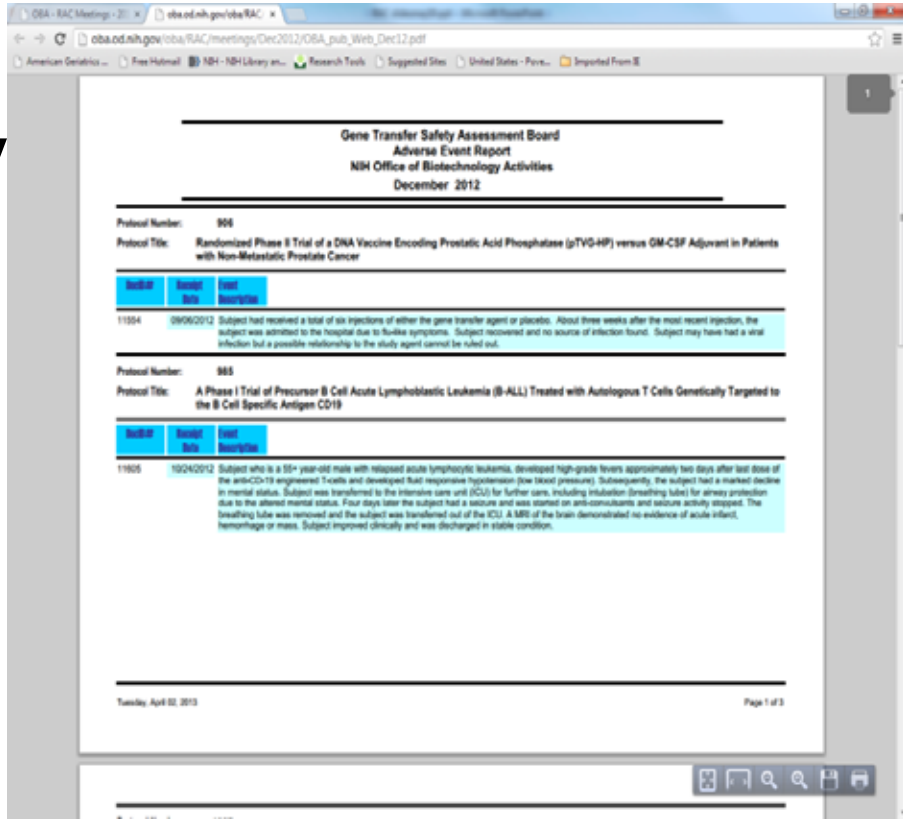
- **In some cases, these symptoms resolve quickly with supportive care, but in about three-fourths of cases admission to intensive care required**
- **In some cases, those with severe cytokine release syndrome are also reported to have significant tumor regression**
- **Cytokine data reported on some events, with elevations in IFN gamma, IL-6 and TNF most often reported**
- **Cytokine data sometimes used to distinguish infection from cytokine release syndrome due to cells – not currently practical. Need better biomarkers**

*** NIH RAC meeting, Bethesda, August 2013. Jacqueline Corrigan-Curay, J.D., M.D.**

Availability of Summary SAE Data

http://oba.od.nih.gov/rdna_rac/rac_meetings.html

Short summaries of significant adverse events that are possibly related to the gene transfer and are reviewed by the RAC Gene Transfer Safety Assessment Board are available on OBA's Website with the RAC Meeting quarterly meeting materials.



Gene Transfer Safety Assessment Board
Adverse Event Report
NIH Office of Biotechnology Activities
December 2012

Protocol Number: 906
Protocol Title: Randomized Phase II Trial of a DNA Vaccine Encoding Prostatic Acid Phosphatase (pTVG-HP) versus GM-CSF Adjuvant in Patients with Non-Metastatic Prostate Cancer

SeqID#	Receipt Date	Event Description
11504	09/06/2012	Subject had received a total of six injections of either the gene transfer agent or placebo. About three weeks after the most recent injection, the subject was admitted to the hospital due to flu-like symptoms. Subject recovered and no source of infection found. Subject may have had a viral infection but a possible relationship to the study agent cannot be ruled out.

Protocol Number: 905
Protocol Title: A Phase I Trial of Precursor B Cell Acute Lymphoblastic Leukemia (B-ALL) Treated with Autologous T Cells Genetically Targeted to the B Cell Specific Antigen CD19

SeqID#	Receipt Date	Event Description
11505	10/24/2012	Subject who is a 55+ year-old male with relapsed acute lymphocytic leukemia, developed high-grade fevers approximately two days after last dose of the anti-CD-19 engineered T-cells and developed fluid responsive hypotension (low blood pressure). Subsequently, the subject had a marked decline in mental status. Subject was transferred to the intensive care unit (ICU) for further care, including intubation (breathing tube) for airway protection due to the altered mental status. Four days later the subject had a seizure and was started on anti-convulsants and seizure activity stopped. The breathing tube was removed and the subject was transferred out of the ICU. A MRI of the brain demonstrated no evidence of acute infarct, hemorrhage or mass. Subject improved clinically and was discharged in stable condition.

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*** NIH RAC meeting, Bethesda, August 2013. Jacqueline Corrigan-Curay, J.D., M.D.**

Toxicity management issues

- On target toxicities reported with TCRs and CARs:
  - B cell aplasia
  - Tumor lysis syndrome
  - Cytokine release syndrome
  - Macrophage activation syndrome
- Relation of dose to age: pediatric vs elderly patients?
- Is there an increased risk in patients with autoimmune disease?
- Dose measurement: flat dosing vs BSA vs cell/kg?
  - Total cell dose vs gene-modified cell dose
- Relationship of dose to disease burden?

First Pediatric ALL Patient: April 16, 2012

The New York Times

Sunday, December 9, 2012 Last Update: 7:53 PM ET

In Girl's Last Hope, Altered Immune Cells Beat Leukemia

By DENISE GRADY 5:48 PM ET

Emma Whitehead, with her mother, right, has been in full remission for months after scientists used a disabled form of H.I.V. to reprogram her immune system to kill cancer cells.

• Slide Show

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Jeff Swensen for The New York Times

The Child

By LYDIA MIL

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Censoring

Success

By K'NAAN

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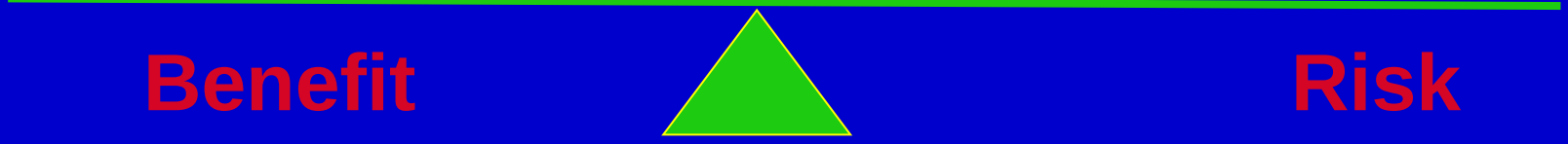
US FDA Regulation: 21 CFR §50.52: Subpart D

- **Why did we have to treat adults with leukemia before children?**

Pedi CARs

Reassessing Risk:Benefit Ratio for Breathrough Therapies



1. If Emily Whitehead (1st pediatric patient) had died, the trial would have been closed!

2. For therapies that have curative potential, an increased tolerance for reversible toxicity is required

3. In US, recommend reconsideration of Subpart D

Issues with Integrating Vectors in T Cells

- Infusions of CD4z CAR T cells results in long term (>decade) persistence at stable levels of ~0.5% of T cells.
- 37 of 39 patients have CD4z CAR T cell persistence in PBMC up to 11 years post infusion.
- No integration near oncogenes or tumor suppressor genes
- No SAE in >568 years of patient followup

=> Gene modified T cells are “safe” as a platform (“safer” than chemotherapy!)

Scholler et al. *Science Translational Medicine 4:132Ra153, 2012*

Issues with Integrating Vectors in T Cells - II

- Insertional oncogenesis appears safer in T cells than in HSC. Potential mechanism is cell extrinsic "crowd control" in T cells but not in other cell types:
  - ü Hataye et al. Naive and memory CD4+ T cell survival controlled by clonal abundance. Science. 2006;312:114-116.
  - ü Newrzela et al. T-cell receptor diversity prevents T-cell lymphoma development. Leukemia. 2012;26:2499-2507.
- Recommend relaxation of vector manufacturing testing given the safety record: no rationale for continued testing of individual cell lots for RCL or RCR

Personalized "N=1" Cellular Therapies

Companies ponder how truly 'personal' medicines can get

Take it personally: Tailored drugs cost more.

Optimists are quick to cite Provenge as the crest of a wave of new therapies. "It has huge implications," says Ronald Levy, a co-founder of Idec Pharmaceuticals (which merged to form Biogen Idec in 2003). "There may be 50 other therapies who hope to follow in the Provenge example."

It has been a long, hard road since the start of efforts to make medicines from patients' own cells, says Brenner, and personalized therapies are still very much a work in progress. "It's twenty years on," Brenner says, "and we still only have Provenge."

Monya Baker

Cell Manufacturing Issues
Cell Cullture: “N of 1”

- Robotic and automated cell culture be required to move beyond botique. An engineering issue...

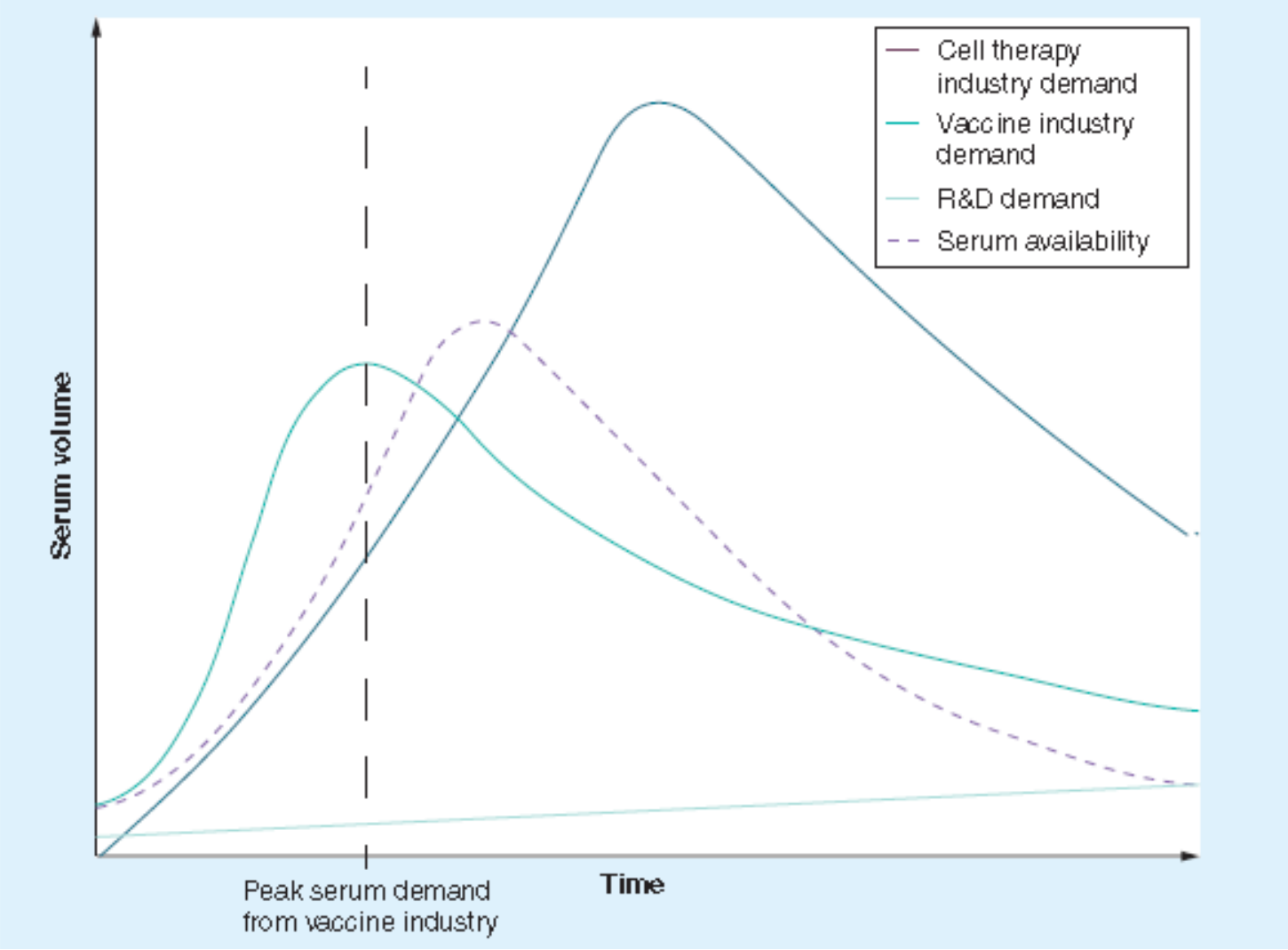
- Education of patients and physicians regarding specific issues with immune based therapy...

- Serum free is essential

Levine, B.L., and C.H. June. 2013. Perspective: assembly line immunotherapy. Nature 498:S17.

Peak Serum: Like Peak Oil?

Global supply of serum:



- **Brindley et al. 2012. Regenerative medicine 7:7-13.**

Issues and Challenges: Engineered T Cells

- Multiicenter trials w personalized cell and gene based therapies
  - cooperative groups: no history of successful cell based trials
  - Manufacturing and liability issues with cell and gene based therapies: can government provide indemnification?
- Changing paradigms for toxicity management
  - physician and patient education
- Trial design: OBD vs MTD
  - Secondary endpoint assays are more challenging
  - "Bucket" trials: need CLIA assays for target identification?
- Regulatory environment more complicated: RAC, FDA, etc.
- Therapy for cancer prevention: need policy changes to incentivize

Summary: Regulatory Challenges Cell Based Therapies

1. **There are 1000's of potentially novel therapies that need to be tested, given the current "toolbox" of targeted agents.**
2. **Urgent need for relaxation of GMP manufacturing for pilot trials. GMP rules need not apply for late stage patients on phase I cancer trials: Patients are willing to accept increased risks:**
   - **At the current pace of development, decades will be required to optimize combination immunotherapies**
   - **Financial costs of combinatoral trials will be prohibitive unless GMP requirements are relaxed**
3. **Identify optimal inclusion/exclusion criteria for immune-based therapies rather than for cytotoxic chemotherapy**
   - **Relax inclusion criteria on performance status?**
   - **Should history of autoimmunity disqualify?**
   - **Reconsider subpart D**
4. **Manufacturing issues**
   - **Financial waste of resources for full GMP phase I pilot trials**
   - **Assays for RCL and RCR on each celluarl product are not necessary (Bear et al. Molecular Therapy. 2012;20:246-249)**