Personalized Medicine

Challenges in the codevelopment of cell and biologic cancer therapies: Perspectives from academia

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June 13, 2011

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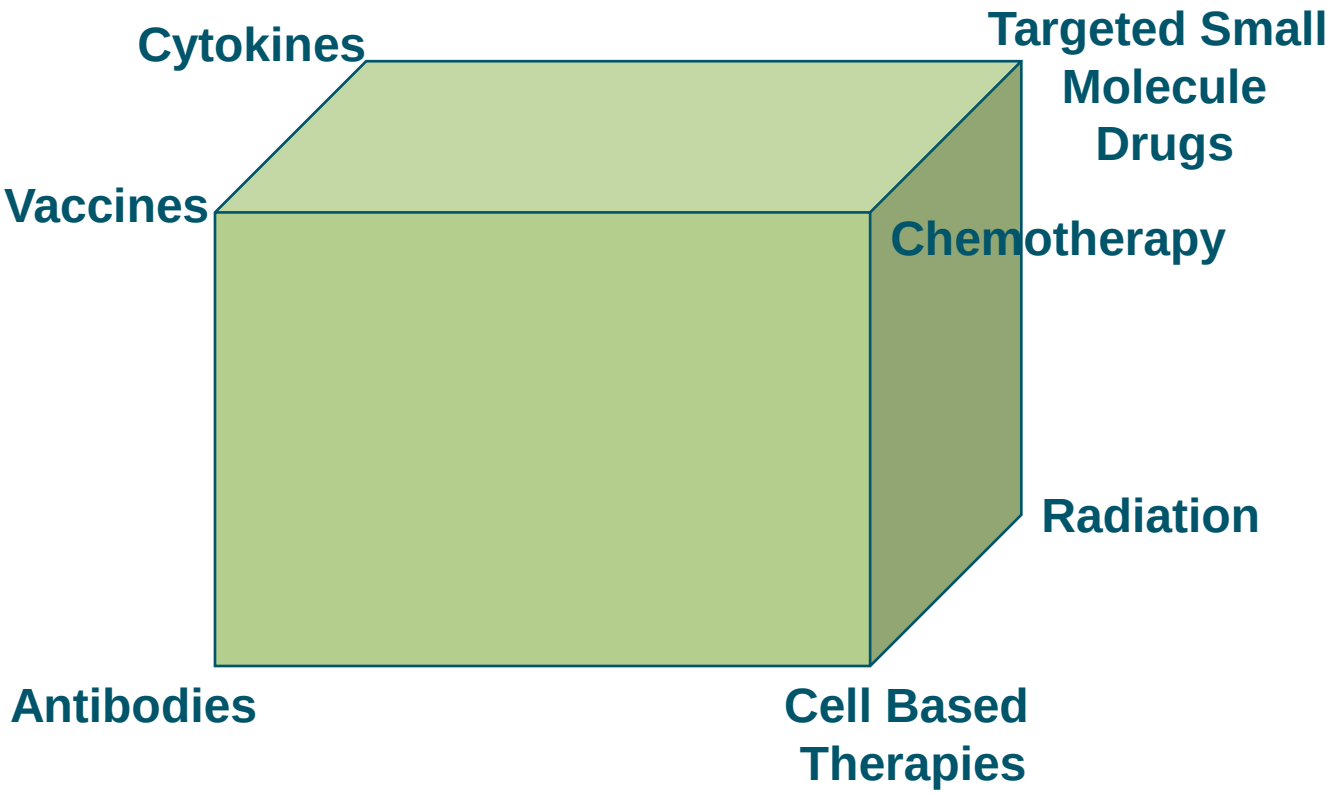
Combinatorial Cancer Immunotherapies



Combinatorial Cancer Immunotherapies Prioritized Agents: Examples

Antigen targets prioritized by the IRMP WG (2009)

Prioritized Antigen Target	Antigen Target Category		
	Vaccine	T-Cell Therapy	Antibody & T Body
HER2	x	x	x
HPV E6/7	x	x	
MAGE A3	x	x	
MUC1	x	x	
NY-ESO-1	x	x	
PSA	x	x	
WT1	x	x	

Initial ranked list of high-priority agents* (2007)

Category	Agents
T cell growth factors	**IL-7** **IL-15**
Dendritic cell activators	**Anti-CD40** CD40L
Dendritic cell growth factors	**Flt3L**
Vaccine adjuvants	**IL-12** **CpG** **MPL** Poly I:C Resiquimod, 852A
T cell stimulators	**4-1-BB** Anti-GITR Anti-OX40
T cell attracting chemokines	**CCL21**
Inhibitors of T cell checkpoint blockade**	**Anti-PD1 & PD1 Ligand** Anti-B7-H4 Anti-LAG-3 LIGHT
Inhibitors	IDO immunosuppression (**1-methyl tryptophan**) Signaling (**Anti-TGF-β**) Inhibition (**Anti-IL 10** & anti-IL 10R)

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

Challenges with Cell Based Therapies

Other than Dendreon/Provenge, there is no established business model for cell based personalized cancer immunotherapy.

- Development occurring largely in academic centers
- Little biotech support

Trials are expensive because drug manufacturing as well as clinical trial costs must be covered

- IND costs
- Manufacturing costs: Treatment INDs have not met the need
- NCI grants do not cover costs of trials

Multicenter trials are required to validate and move cell based therapies from the 'boutique stage'

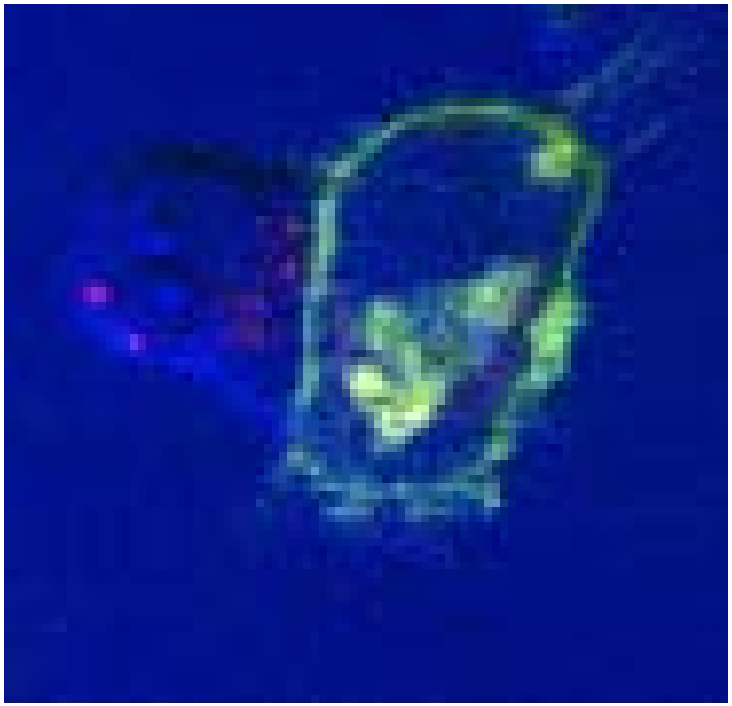
- Academic centers are not "good" at scale up issues
- Indemnification is an issue with multicenter trials

Failure to engage pharma until phase II randomized data available

CTLs (Killer) T Cells: Primary Weapons for Cancer Gene Therapy

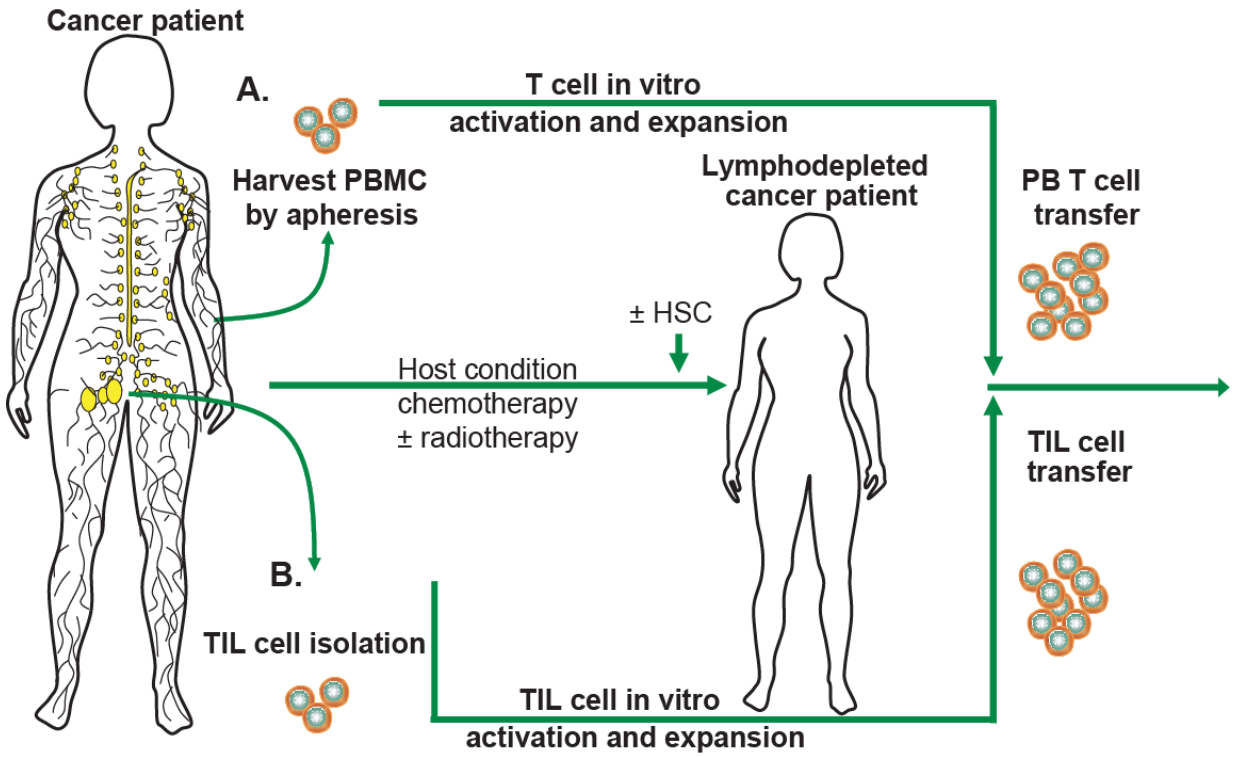
- **CTLs kill cells via peptide:MHC on target cells**
- **Most tumor cells express peptide: MHC**
- **CTLs can be "serial" killers: One T cell can kill many tumor cells**
- **T cells evolved to kill cells with new RNA or DNA, i.e. viruses (and tumors)**
- **Non-cross resistant killers: Because T cells have many killing mechanisms, they can be more effective than any single drug**
- **T cells can be self replicating, unlike drugs**

Example of CTL killing a tumor cell: rapid induction of apoptosis



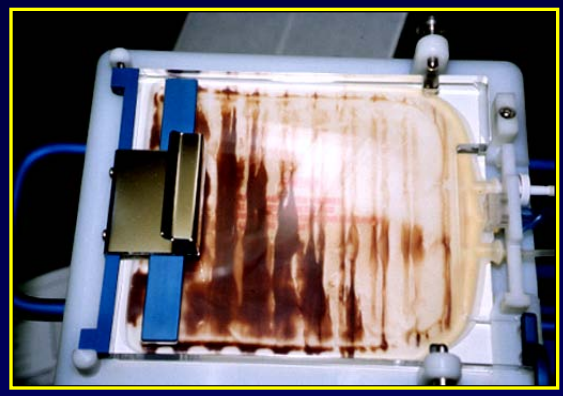
Stinchcombe J, et al. The immunological synapse of CTL contains a secretory domain and membrane bridges. Immunity 2001;15:751-61.

Adoptive T Cell Transfer Therapy

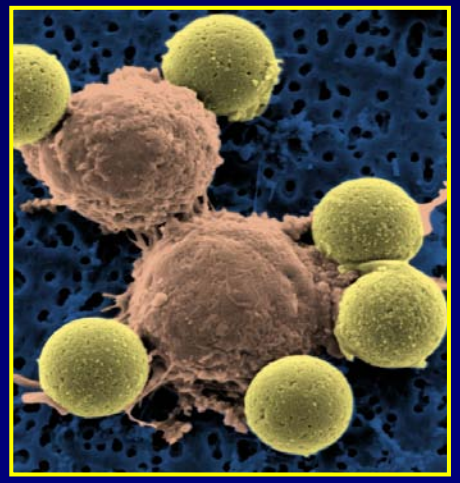


- **Adoptive transfer therapy is working in early stage trials:**
  - **melanoma: infusions of tumor infiltrating effector T cells**
  - **leukemia: infusions of gene modified memory and effector T cells**
- **Issues facing the field**
  - **What is the best starting cell population?**
  - **Dosing / scheduling**

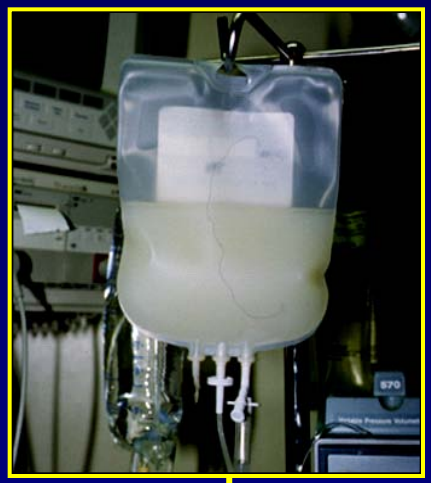
Clinical Scale T Cell Culture Process



Day 0



+/- CAR Lentiviral Vector

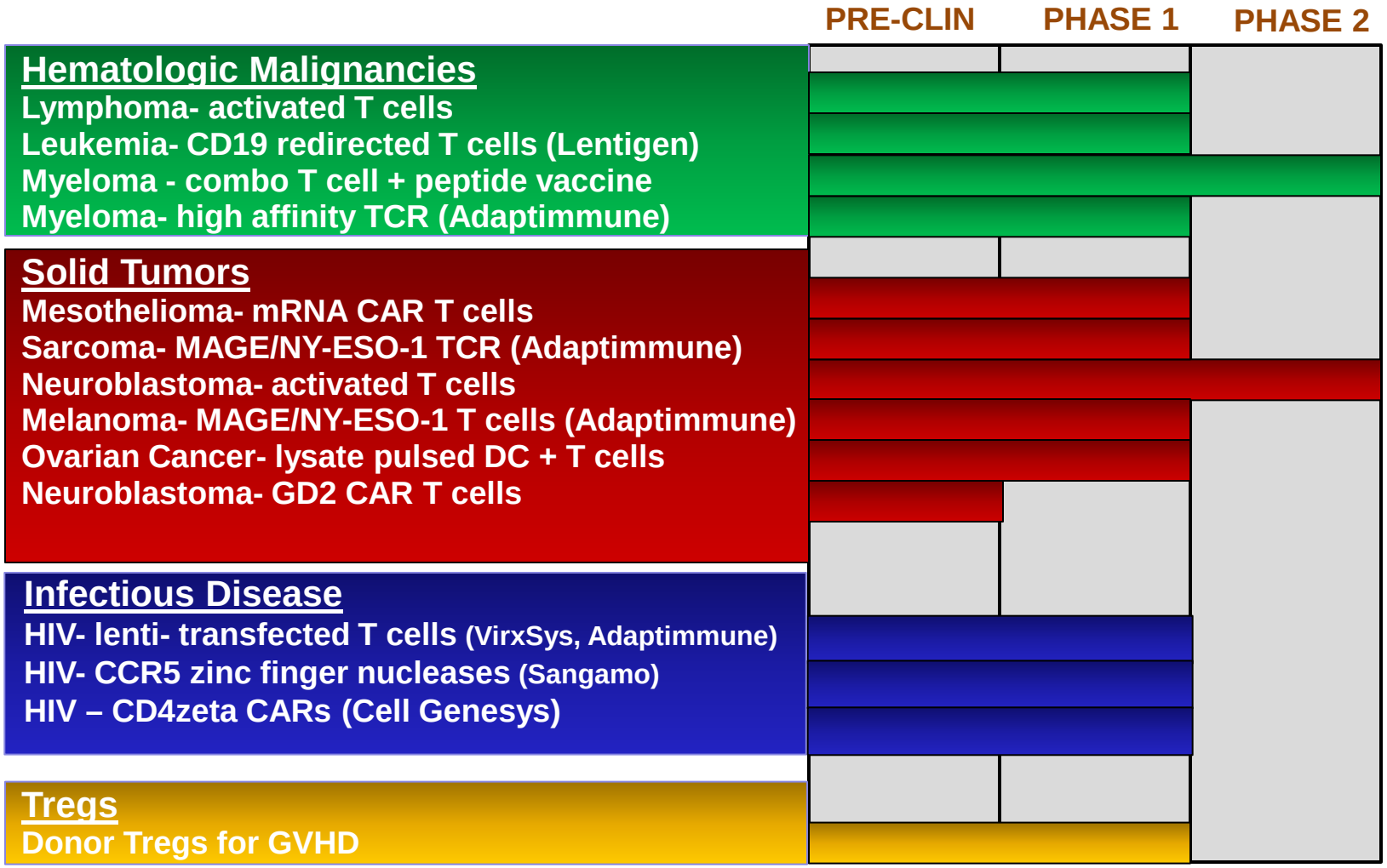


Day 12

Cost of goods: <6 weeks bevacizumab or ipilimumab

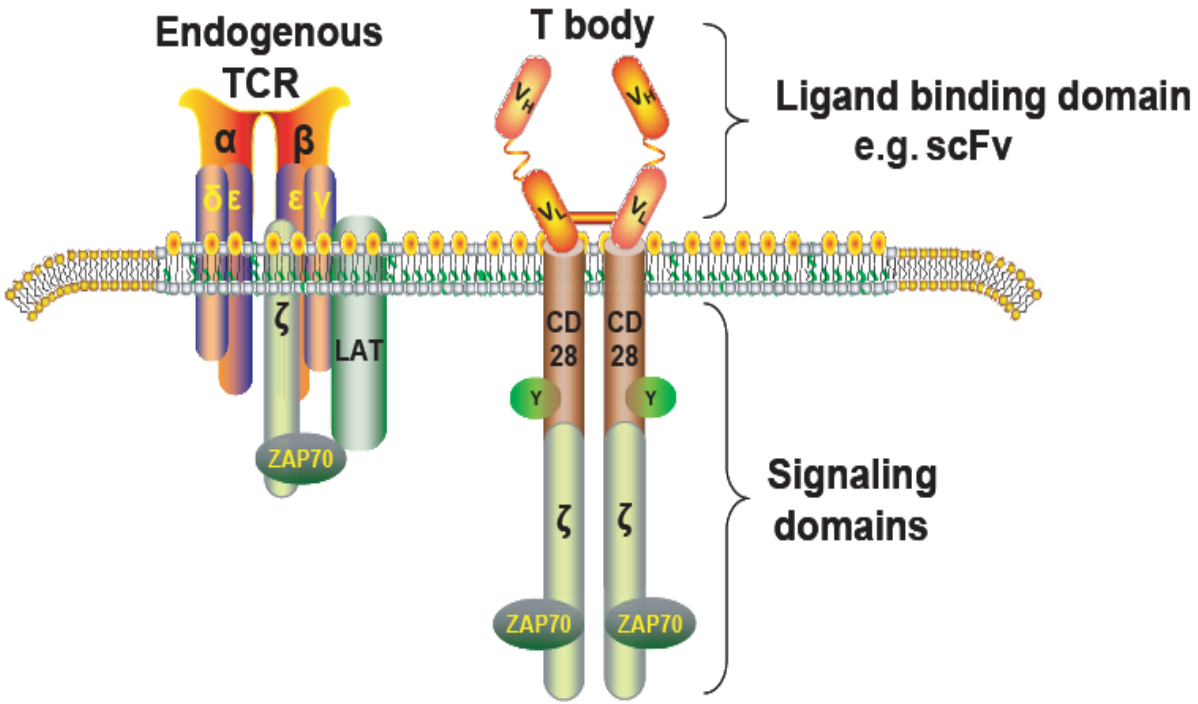
Levine et al. *J Hematotherapy* 1998: 7:437

T Cell Trials at Penn: Clinical Trials by Disease



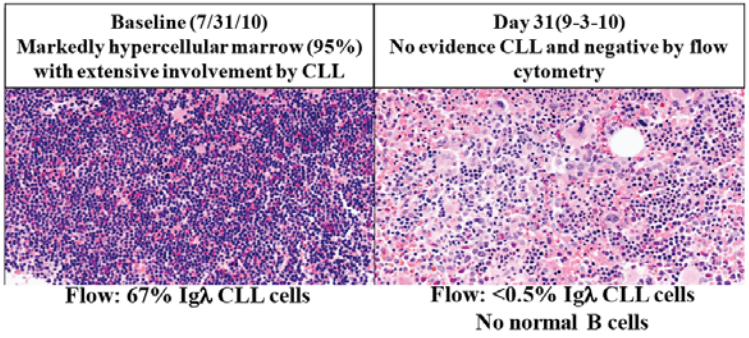
CD19 CARs for Incurable B Cell Malignancies

- Chimeric antigen receptors (CARs) or “T bodies”
- MHC independent retargeting of T cells to targets on the tumor surface
- Intracellular signaling domains to mimic TCR and costimulatory signals

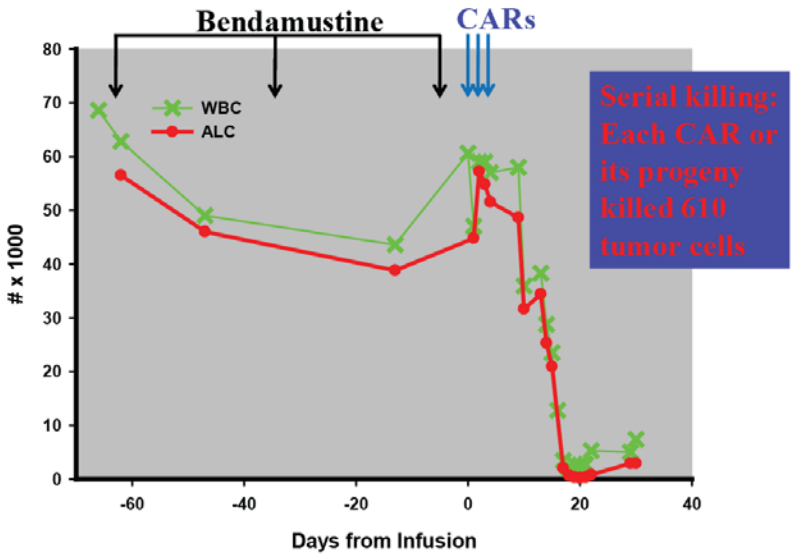


CD19 CAR Protocol: Status

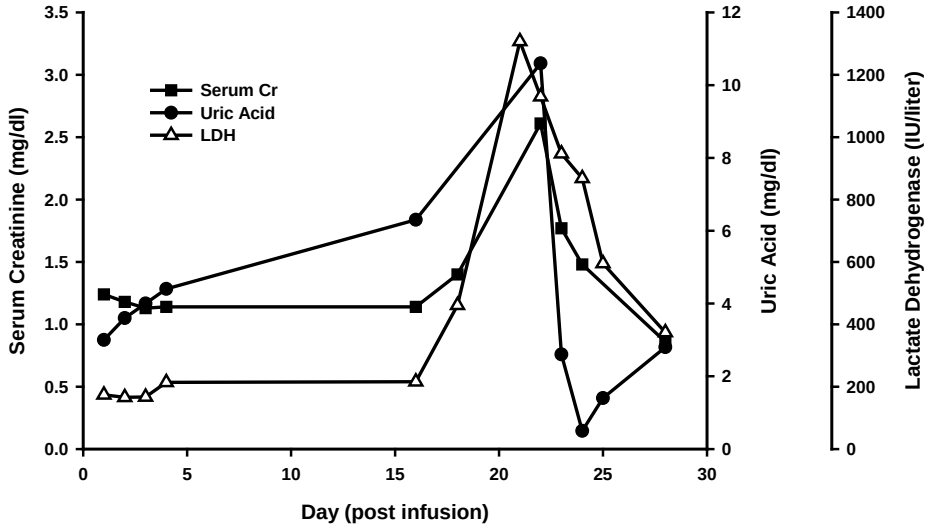
Bone Marrow: Patient 1



Patient #2. Clearance of p53 deleted CLL Cells



Patient #3: Delayed Tumor Lysis Syndrome



CART-19 Trial: Interim Analysis

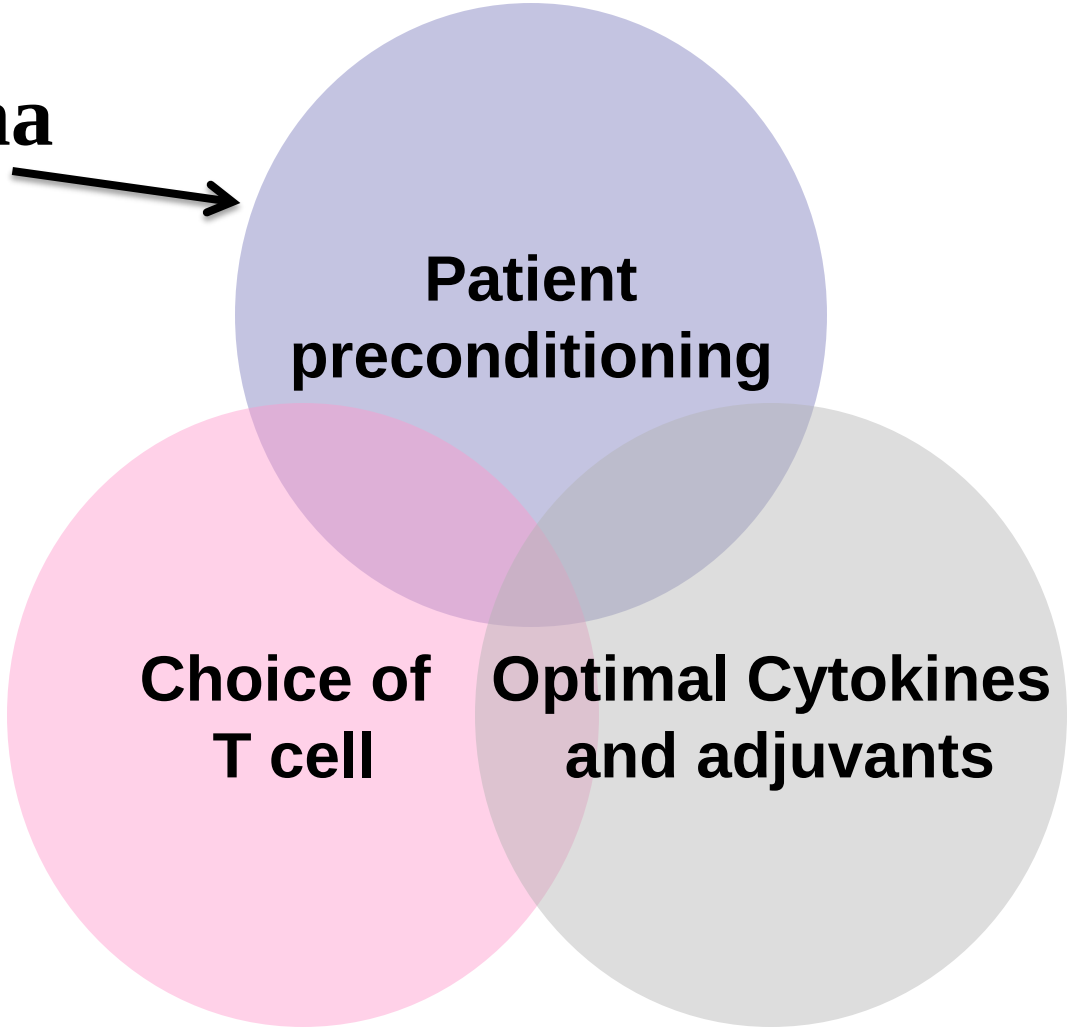
- 3 CLL patients enrolled and infused to date, with successful expansion and transduction of T cells. Manufacturing of final product is more difficult in CLL patients than in previous myeloma trials.
- CARs with 4-1BB:z signaling domains have massive expansion in vivo in 2 of 3 patients with advanced CLL.
- Persistence in blood and migration to bone marrow for at least 90 days in substantial numbers. CAR T cells have expanded in vivo compared to the infused amount.
- Promising anti-tumor effects observed in chemotherapy refractory patients : pt 1 CR; pt 2 PR; pt 3, CR w delayed onset tumor lysis syndrome.

Multi-Center Trials Testing Adoptive Transfer of Costimulated T Cells

Disease (PI)	T cell product	# patients	Reference
	Completed		
HIV (Deeks)	CD4zeta	40	PMID:12027564
HIV (Deeks)	CD4zeta	24	PMID:10910888
HIV (Aronson)	CD4zeta	15	NCT01013415
Myeloma (Rapoport)	Vaccine + T	52	NCT00046852
Myeloma (Rapoport)	Vaccine + T	53	NCT00499577
Neuroblastoma (Grupp)	T cells	44	PMID:20700700
	Ongoing		
Myeloma (Rapoport)	Vaccine + T	8	NCT01245673
CLL (Keating/Schuster)	T cells	35	NCT01013441
Total		**271**	

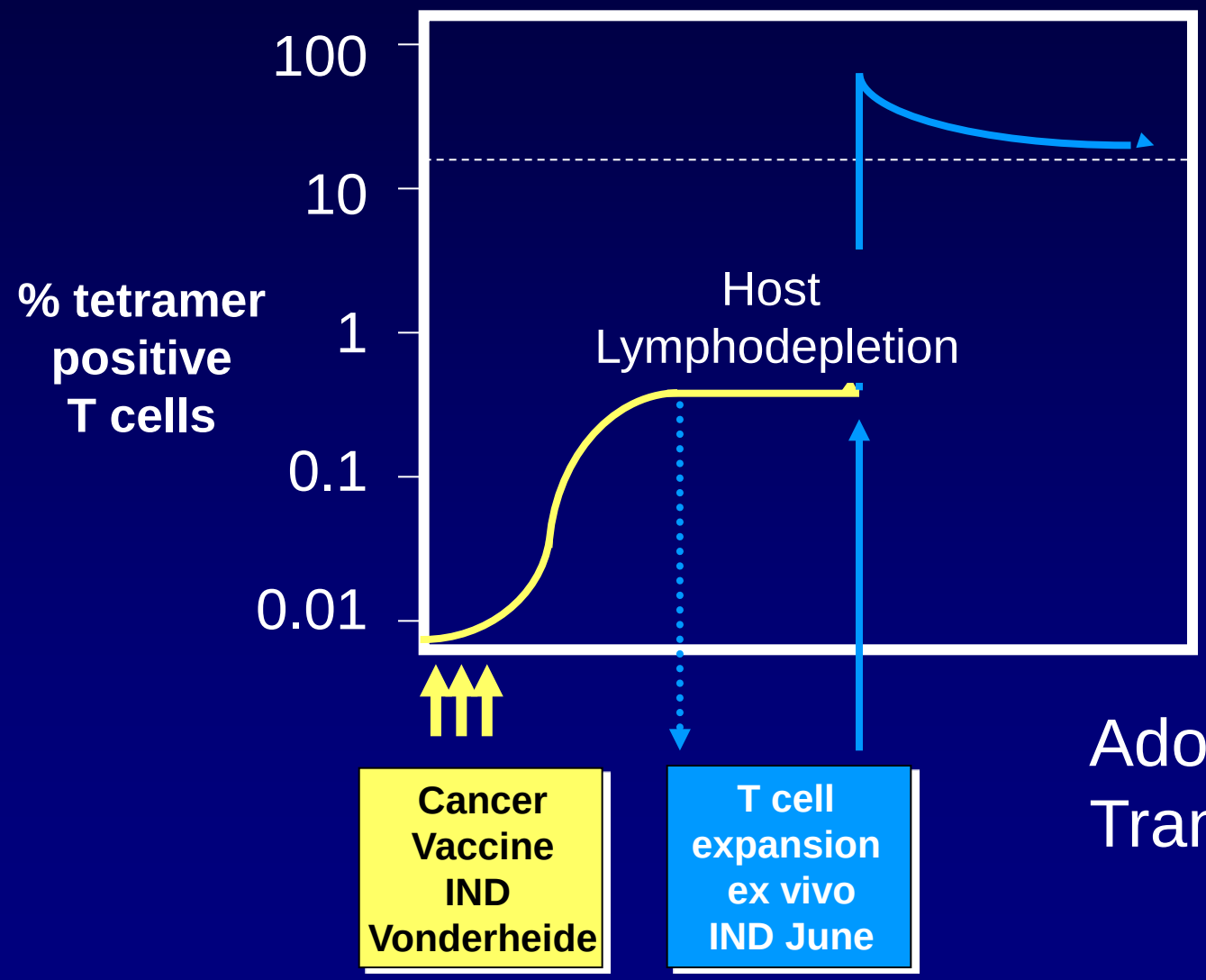
Optimizing Effector T Cell Therapy (and vaccine and antibody therapies)

Myeloma trials →



"Prime Boost" Cancer Vaccine Approach

Combination of Active + Passive Immunotherapy?



Current trial:

N=52

Myeloma
HLA-A2+
(Arm A)

IND, Vonderheide

PCV/Flu + hTERT, Survivin, CMV

T Cell Collection

Mobilization
Stem Cell Collection
High-dose Melphalan
Stem Cell Transplant

T Cell In Vitro Activation and
Expansion to Infuse 10^{10} Cells

IND, June

T Cell Infusion Day 2

hTERT, Survivin, CMV
+ Prevnar

Immune Assessment Studies

Equal number of HLA-$A2^{neg}$ patients but no peptide vaccine (Arm B)

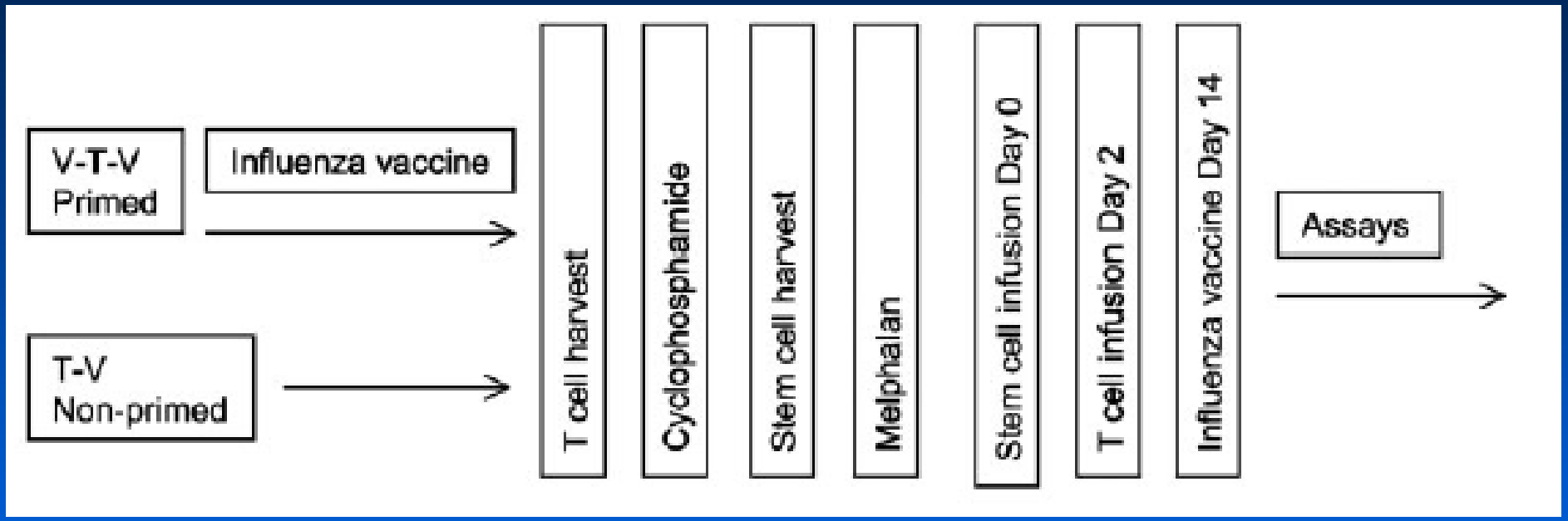
Myeloma: Adoptive transfer of vaccine primed T cells augments immunity in lymphodepleted hosts: Summary of first trial

- Accelerated recovery of CD4 and CD8 counts to near-normal levels by day +42 post-transplant
- Protective (anti-pneumococcal) antibody levels established by day 30
- Improved proliferation of CD4 T cells to CRM-197 vaccine carrier antigen ($P<0.01$) and to Staphylococcal enterotoxin B ($P=0.004$)

  => Adoptive transfer of vaccine primed T cells facilitates reconstitution of CD4 T central memory cells

Rapoport et al. *Nat. Med.* 2005; 11: 1230

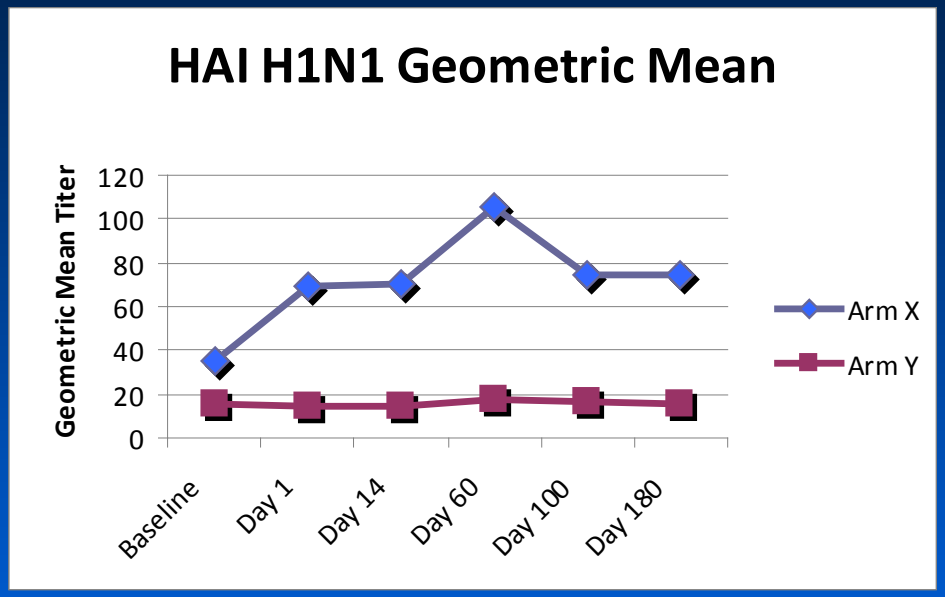
Myeloma Trials #2 and #3: Randomized Design

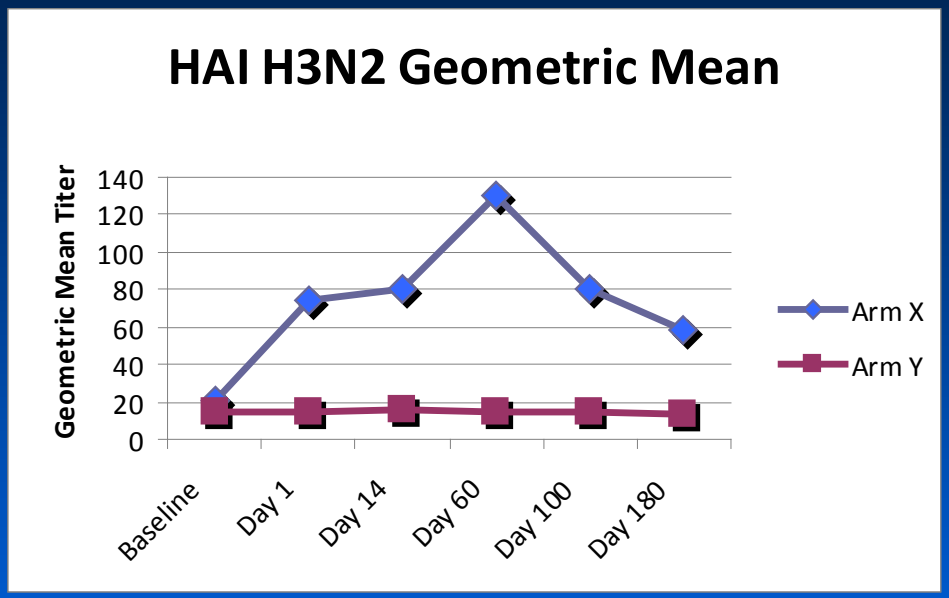


V-T-V: Vaccine-Transfer-Vaccine group
T-V: Transfer-Vaccine group

Rapoport et al. Blood. 2011;117: 788-97.
Stadtmauer et al. Blood. 2011;117: 63-71.

Hemagglutination Inhibition (HAI) Assay Results: Randomized data





- **HAI titer is the parameter with strongest correlation to protection from wild type infection**

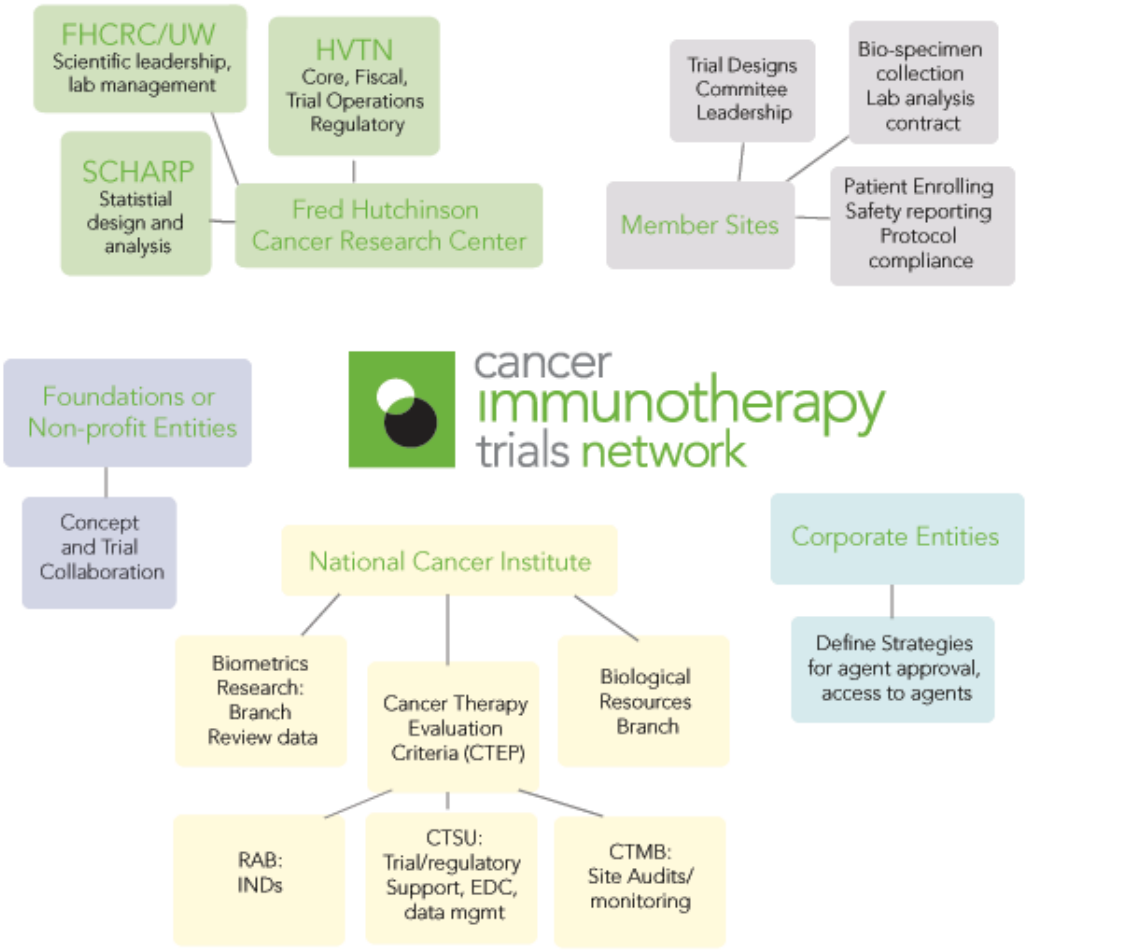
- **HAI titers higher at all three time points in Vaccine Primed T Cell Group H3N2 (p=0.007) and H1N1 (p=0.009). Vaccine + naïve T cell group remained near baseline throughout all time points.**

Stadtmauer, Blood (2011)

Myeloma Summary: Vaccine Primed T Cell Transfers

- After high dose chemotherapy, myeloma patients fail to respond to FDA approved vaccines
- Randomized protocols demonstrate restoration of vaccine responses to influenza and pneumococcus, and improved “self” responses to hTERT and survivin
- Schedule dependent engraftment syndrome identified
- The magnitude of early T cell and Ig recovery is associated with improved EFS.
- Feasibility of randomized multicenter trials testing T cell transfer therapy

Cancer Immunotherapy Trials Network



FHCRC:	Fred Hutchinson Cancer Research Center
UW:	University of Washington
HVTN:	HIV Vaccine Trial Network
SCHARP:	The Statistical Center for HIV/AIDS Research & Prevention
CTSU:	Cancer Trial Support Unit
CTMB:	Clinical Trial Monitoring Branch
RAB:	Regulatory Affiars Branch

http://citninfo.org/collab/index.html

CITN Member Sites

Institution	Principal Investigator(s)
Baylor Research Institute & Mt. Sinai School of Medicine	Karolina Palucka, MD, PhD
Case Western Reserve University	Pierre Triozzi, MD
Dana Farber Cancer Center	Steven Hodi, MD
Dartmouth-Hitchcock Norris Cotton Cancer Center	Marc Ernstoff, MD
Duke University Medical Center	Kim Lyerly, MD, FACS
Emory University	Edmund Waller, MD, PhD
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University of Wisconsin	Paul M. Sondel, MD, PhD
Yale University	Mario Sznol, MD

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Categories of Combination Trials: Institutional Perspectives

Academic: Single Center PI⇔PI

[Academic#1]:[Academic#2]

[Academic]:[Govt]

[Academic]:[Biopharma]

Major challenges:

- Who holds IND?
- Institutional risk for indemnification.
  - Different criteria at private, state and government institutions.

Manufacturing and Testing Considerations
Multicenter Cell Production

- Manufacturing
  - Stimulation, Media, Culture vessels, Formulation
- Testing
  - Release criteria, QC Assays, Potency
- Cost
  - COGS, Labor
- Centralized vs Site Specific Cell Production
  - Criteria for standardization/comparability
    - Manufacturing, release and characterization Assays
  - Logistic considerations, shipping/timing

Regulatory Considerations
Multicenter Cell Production

- **Single IND Sponsor for Trial**
  - **Academic Sponsor: Institutional vs. Investigator-Initiated** (Which institution to hold?)
  - **Sponsor Monitoring / GCP compliance** (What are sponsor obligations to ensure compliance at the other site (especially for manufacturing tech transfer)?
  - **Electronic data management** (Web-based compatibility and access for both sites- How to decide which institutional DMS best to use)
  - **IND Cross-reference** (Relevant only if more than one investigational product being evaluated)

Legal Considerations
Multicenter Cell Production

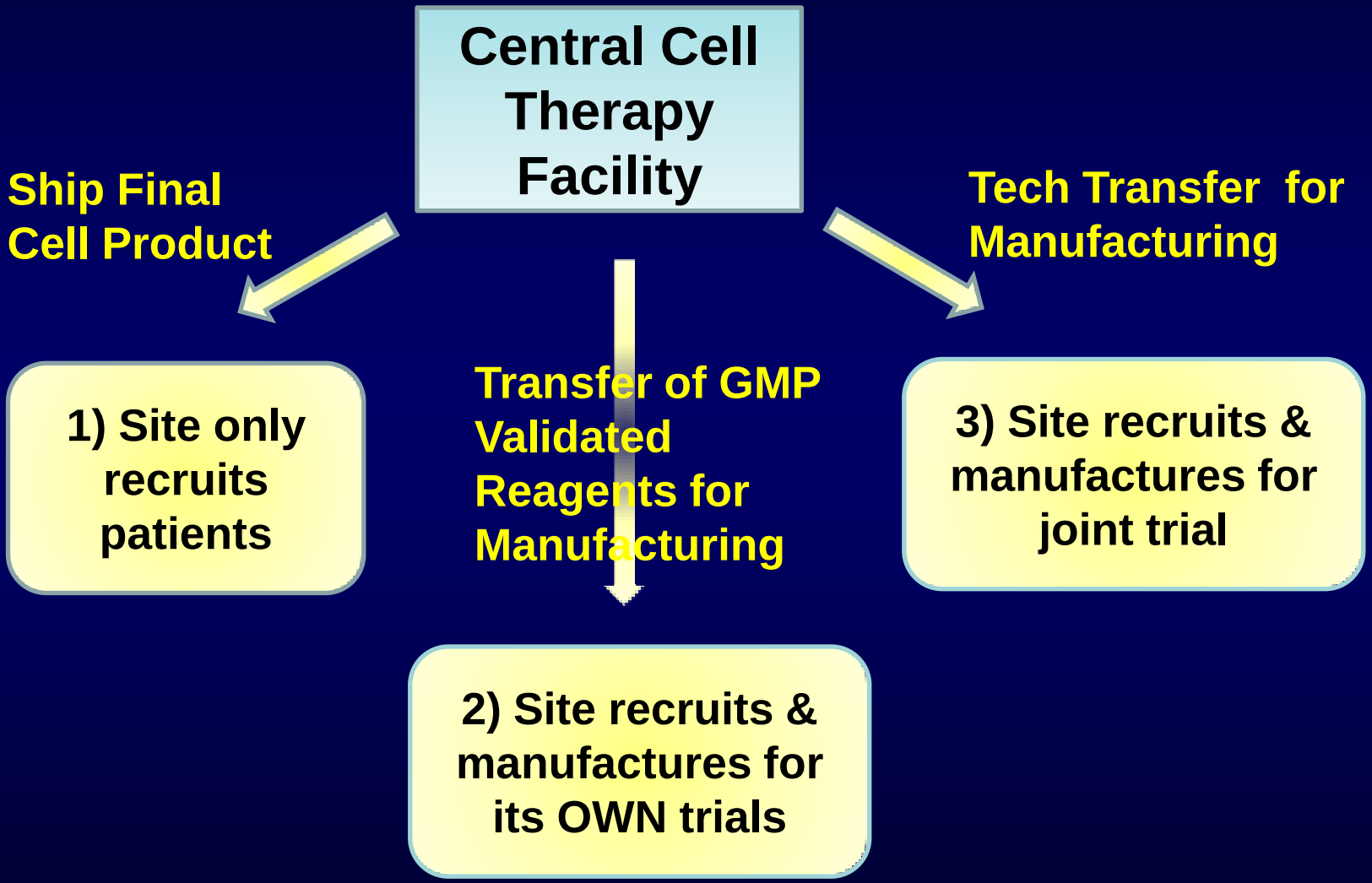
- **Institutional Agreements are needed**

  - Need to get the lawyers involved- takes months! Start early

  - Key provisions to be agreed on:

  - **Intellectual Property /Data Ownership and Use (Separate vs. Joint IP/Inventions)**
  - **Publication Rights (Terms under which to publish after 1st joint manuscript)**
  - **Confidentiality and Disclosure (Terms for tech transfer SOPs and for trial data)**
  - **Indemnification (Institutions have strong stance on this)**

Multi-Center Manufacturing Models



Multi-Center Manufacturing Models

1) **Central Manufacturer with shipping to recruiting sites**

   - Cryo vs. Fresh formulation depending on distance between manufacturer and site

   - Ex: WRAMC, CHOP, Boston Children's, Moffit Cancer Center, U. Maryland, Washington U.

2) **Manufacturer of GMP, clinical grade reagents**

   - Release-tested GMP reagents with CofA provided to sites for their own trial manufacturing

   - Ex: NCI, U. Minnesota

3) **Manufacturer transfers SOPs and know how**

   - Recruiting site also has cell therapy facility. Tech transfer to manufacturer for its own patients in joint trial. Scenario when distance precludes #1

   - Ex: MDACC, MSKCC

Lessons Learned from Combination Trials Cell Based Therapies

Pre-clinical models in mice often do not replicate the tumor microenvironment
- What data is required to justify a combination trial?

What is the proper clinical trial design?
- For living cells, phase I dose escalation is often inadequate
- How to determine optimum biologic dose?

Access to reagents is often difficult or not possible
- Will CITN improve this barrier?

Trials are expensive because drug manufacturing as well as clinical trial costs must be covered
- IND costs
- Manufacturing Costs: Treatment INDs have not met the need
- NCI grants do not cover costs of trials

Collaborators and Acknowledgements

U. Penn
Gwen Binder
Carmine Carpenito
Naoki Kunii
Jihyun Lee
Michael Milone
Chrystal Paulos
John Scholler
Michael Kalos
Yangbing Zhao

PENN - CVPF
Andrea Brennan
Anne Chew
Julio Cotte
Dawn Maier
Zoe Zheng
Bruce Levine

Hospital U. Penn
David Porter
Elizabeth Hexner

Clinical Consulting Board
Glenn Dranoff
Drew Pardoll
Robert Seder
Marcel van den Brink

Funding of CLL trial:
NCI IRM STRAP Award

NANOMEDICINE CENTER FOR MECHANOBIOLOGY
DIRECTING THE IMMUNE RESPONSE

Penn Medicine

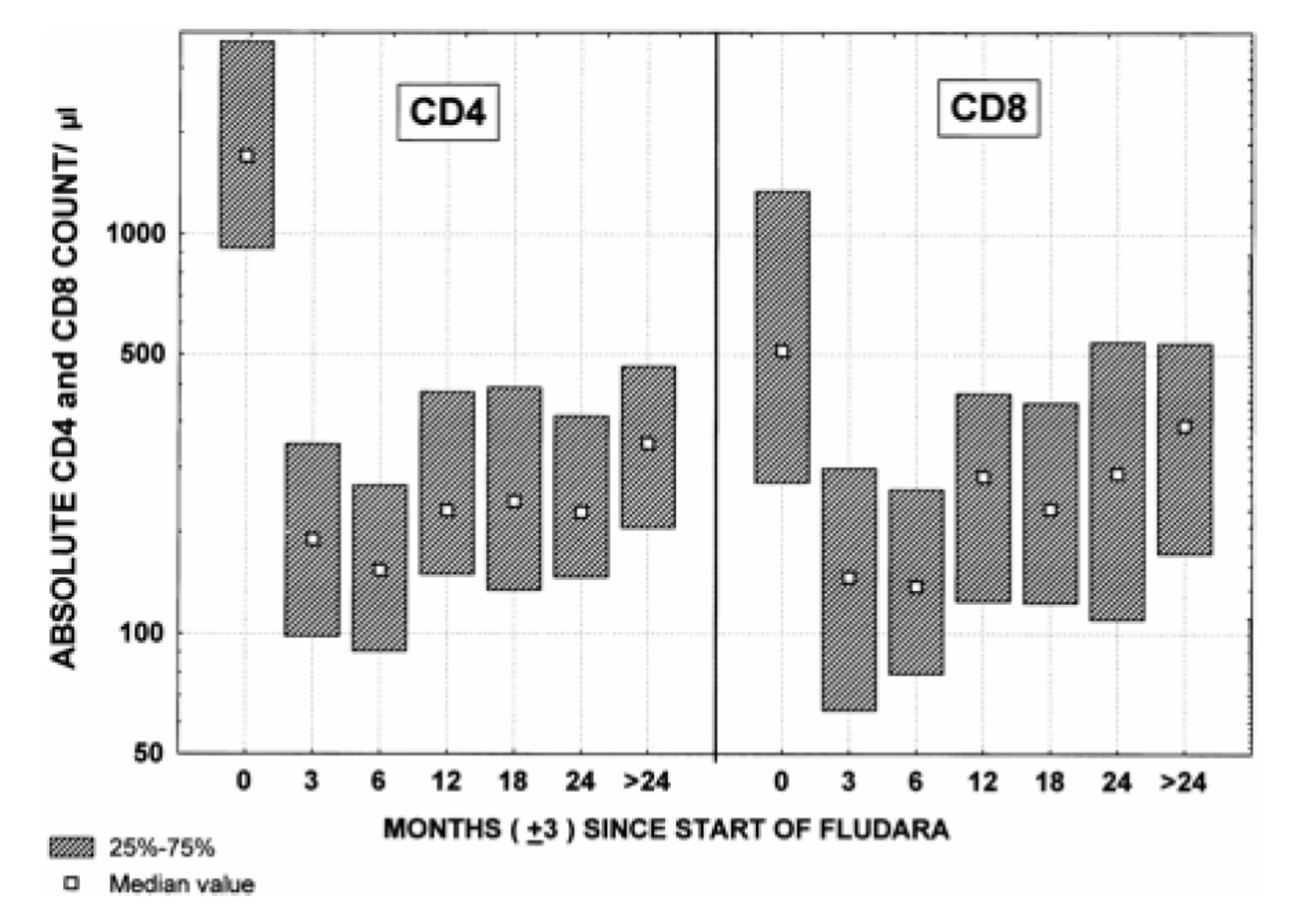
The NIH Common Fund
WE ACCELERATE DISCOVERY.

NIH 1PN1-EY016586

The Leukemia & Lymphoma Society®
Fighting Blood Cancers

ACGT
ALLIANCE FOR CANCER GENE THERAPY
National grants for cancer research

Effect of Fludarabine on T Cells



Keating MJ, et al. Long-term follow-up of patients with chronic lymphocytic leukemia (CLL) receiving fludarabine regimens as initial therapy. Blood 92:1165-71, 1998