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

Carl June, M.D.
Professor of Pathology and Lab Medicine
Abramson Cancer Center
University of Pennsylvania

June 13, 2011
Combinatorial Cancer Immunotherapies

- Vaccines
- Antibodies
- Cytokines
- Targeted Small Molecule Drugs
- Chemotherapy
- Radiation
- Cell Based Therapies
## Combinatorial Cancer Immunotherapies

### Prioritized Agents: Examples

**Antigen targets prioritized by the IRMP WG (2009)**

<table>
<thead>
<tr>
<th>Prioritized Antigen Target</th>
<th>Antigen Target Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2</td>
<td>Vaccine, T-Cell Therapy, Antibody &amp; T Body</td>
</tr>
<tr>
<td>HPV E6/7</td>
<td>Vaccine, Antibody &amp; T Body</td>
</tr>
<tr>
<td>MAGE A3</td>
<td>Vaccine, Antibody &amp; T Body</td>
</tr>
<tr>
<td>MUC1</td>
<td>Vaccine, Antibody &amp; T Body</td>
</tr>
<tr>
<td>NY-ESO-1</td>
<td>Vaccine, Antibody &amp; T Body</td>
</tr>
<tr>
<td>PSA</td>
<td>Vaccine, Antibody &amp; T Body</td>
</tr>
<tr>
<td>WT1</td>
<td>Vaccine, Antibody &amp; T Body</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Category</th>
<th>Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>T cell growth factors</td>
<td>IL-7, IL-15</td>
</tr>
<tr>
<td>Dendritic cell activators</td>
<td>Anti-CD40, CD40L</td>
</tr>
<tr>
<td>Dendritic cell growth factors</td>
<td>FLT3L</td>
</tr>
<tr>
<td>Vaccine adjuvants</td>
<td>IL-12, CpG, MPL, Poly I:C, Resiquimod, 852A</td>
</tr>
<tr>
<td>T cell stimulators</td>
<td>4-1-BB, Anti-GITR, Anti-OX40</td>
</tr>
<tr>
<td>T cell attracting chemokines</td>
<td>CCL21</td>
</tr>
<tr>
<td>Inhibitors of T cell checkpoint blockade**</td>
<td>Anti-PD1 &amp; PD1 Ligand, Anti-B7-H4, Anti-LAG-3, LIGHT</td>
</tr>
<tr>
<td>Inhibitors IDO immunosuppression (1-methyl tryptophan) Signaling (Anti-TGF-β) Inhibition (Anti-IL 10 &amp; anti-IL 10R)</td>
<td></td>
</tr>
</tbody>
</table>
Personalized “N=1” Cellular Therapies

Companies ponder how truly ‘personal’ medicines can get

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
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

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

Cost of goods: <6 weeks bevacizumab or ipilimumab


Day 12
# T Cell Trials at Penn: Clinical Trials by Disease

<table>
<thead>
<tr>
<th>Disease Type</th>
<th>PRE-CLIN</th>
<th>PHASE 1</th>
<th>PHASE 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematologic Malignancies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphoma- activated T cells</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukemia- CD19 redirected T cells (Lentigen)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myeloma - combo T cell + peptide vaccine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myeloma- high affinity TCR (Adaptimmune)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Solid Tumors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mesothelioma- mRNA CAR T cells</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sarcoma- MAGE/NY-ESO-1 TCR (Adaptimmune)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuroblastoma- activated T cells</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melanoma- MAGE/NY-ESO-1 T cells (Adaptimmune)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovarian Cancer- lysate pulsed DC + T cells</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuroblastoma- GD2 CAR T cells</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Infectious Disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV- lenti- transfected T cells (VirxSys, Adaptimmune)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV- CCR5 zinc finger nucleases (Sangamo)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV – CD4zeta CARs (Cell Genesys)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Tregs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donor Tregs for GVHD</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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

Baseline (7/31/10)
Markedly hypercellular marrow (95%) with extensive involvement by CLL
Flow: 67% IgA CLL cells

Day 31 (9-3-10)
No evidence CLL and negative by flow cytometry
Flow: <0.5% IgA CLL cells
No normal B cells

Patient #2. Clearance of p53 deleted CLL Cells

Bendamustine
CARs
Serial Killing:
Each CAR or its progeny killed 80 tumor 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

<table>
<thead>
<tr>
<th>Disease (PI)</th>
<th>T cell product</th>
<th># patients</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Completed</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV (Deeks)</td>
<td>CD4zeta</td>
<td>40</td>
<td>PMID:12027564</td>
</tr>
<tr>
<td>HIV (Deeks)</td>
<td>CD4zeta</td>
<td>24</td>
<td>PMID:10910888</td>
</tr>
<tr>
<td>HIV (Aronson)</td>
<td>CD4zeta</td>
<td>15</td>
<td>NCT01013415</td>
</tr>
<tr>
<td><strong>Myeloma (Rapoport)</strong></td>
<td>Vaccine + T</td>
<td>52</td>
<td>NCT00046852</td>
</tr>
<tr>
<td><strong>Myeloma (Rapoport)</strong></td>
<td>Vaccine + T</td>
<td>53</td>
<td>NCT00499577</td>
</tr>
<tr>
<td><strong>Neuroblastoma (Grupp)</strong></td>
<td>T cells</td>
<td>44</td>
<td>PMID:20700700</td>
</tr>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myeloma (Rapoport)</td>
<td>Vaccine + T</td>
<td>8</td>
<td>NCT01245673</td>
</tr>
<tr>
<td><strong>CLL (Keating/Schuster)</strong></td>
<td>T cells</td>
<td>35</td>
<td>NCT01013441</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>271</td>
<td></td>
</tr>
</tbody>
</table>
Optimizing Effector T Cell Therapy (and vaccine and antibody therapies)

Patient preconditioning

Choice of T cell

Optimal Cytokines and adjuvants

Myeloma trials
“Prime Boost” Cancer Vaccine Approach
Combination of Active + Passive Immunotherapy?

Hypothesis
“Threshold for regression”

% tetramer positive T cells

Host Lymphodepletion

Cancer Vaccine IND Vonderheide

T cell expansion ex vivo IND June

Adoptive T Cell Transfer
Current trial: N=52

Myeloma HLA-A2+ (Arm A)

Mobilization
Stem Cell Collection
High-dose Melphalan
Stem Cell Transplant

PCV/Flu + hTERT, Survivin, CMV

T Cell Collection
Mobilization
Stem Cell Collection
High-dose Melphalan
Stem Cell Transplant

T Cell Infusion Day 2

hTERT, Survivin, CMV + Prevnar

Immune Assessment Studies

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

Equal number of HLA-A2$^{\text{neg}}$ patients but no peptide vaccine (Arm B)
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
Myeloma Trials #2 and #3: Randomized Design

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


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.
## CITN Member Sites

<table>
<thead>
<tr>
<th>Institution</th>
<th>Principal Investigator(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baylor Research Institute &amp; Mt. Sinai School of Medicine</td>
<td>Karolina Palucka, MD, PhD</td>
</tr>
<tr>
<td>Case Western Reserve University</td>
<td>Pierre Trizio, MD</td>
</tr>
<tr>
<td>Dana Farber Cancer Center</td>
<td>Steven Hodi, MD</td>
</tr>
<tr>
<td>Dartmouth-Hitchcock Norris Cotton Cancer Center</td>
<td>Marc Ernstoff, MD</td>
</tr>
<tr>
<td>Duke University Medical Center</td>
<td>Kim Lyerly, MD, FACS</td>
</tr>
<tr>
<td>Emory University</td>
<td>Edmund Waller, MD, PhD</td>
</tr>
<tr>
<td>Fred Hutchinson Cancer Research Center</td>
<td>John A. Thompson, MD</td>
</tr>
<tr>
<td>MD Anderson Cancer Center</td>
<td>Laurence J.N. Cooper, MD, PhD</td>
</tr>
<tr>
<td>H. Lee Moffitt Cancer Center</td>
<td>Scott J. Antonia, MD, PhD</td>
</tr>
<tr>
<td>Memorial Sloan-Kettering Cancer Center</td>
<td>Jedd D. Wolchok, MD, PhD</td>
</tr>
<tr>
<td>New York University Cancer Institute</td>
<td>Nina Bhardwaj, MD, PhD</td>
</tr>
<tr>
<td>Ohio State University</td>
<td>William E. Carson, MD</td>
</tr>
<tr>
<td>Providence Cancer Center</td>
<td>Walter J. Urba, MD, PhD</td>
</tr>
<tr>
<td>Roswell Park Cancer Center</td>
<td>Kunle Obinu, MD, PhD</td>
</tr>
<tr>
<td>Rush University Cancer Center</td>
<td>Howard Kaufman, MD</td>
</tr>
<tr>
<td>Stanford University</td>
<td>Ronald Levy, MD</td>
</tr>
<tr>
<td>University of California, San Diego</td>
<td>Thomas J Kipps, MD, PhD</td>
</tr>
<tr>
<td>University of California, San Francisco</td>
<td>Lawrence Fong, MD</td>
</tr>
<tr>
<td>University of Chicago</td>
<td>Thomas Gajewski, MD, PhD</td>
</tr>
<tr>
<td>University of Miami</td>
<td>Joseph D. Rosenblatt, MD</td>
</tr>
<tr>
<td>University of Minnesota</td>
<td>Jeffrey S. Miller, MD</td>
</tr>
<tr>
<td>University of Pennsylvania</td>
<td>Carl June, MD</td>
</tr>
<tr>
<td>University of Pittsburgh</td>
<td>Robert Louis Ferris, MD, PhD</td>
</tr>
<tr>
<td>University of Toronto Ontario Cancer Institute</td>
<td>Hassane M. Zarour, MD</td>
</tr>
<tr>
<td>University of Toronto Ontario Cancer Institute</td>
<td>Pamela Ghaffi, PhD</td>
</tr>
<tr>
<td>University of Virginia</td>
<td>Craig Slingluff, MD</td>
</tr>
<tr>
<td>University of Wisconsin</td>
<td>Paul M. Sondel, MD, PhD</td>
</tr>
<tr>
<td>Yale University</td>
<td>Mario Szol, MD</td>
</tr>
</tbody>
</table>

Categories of Combination Trials: Institutional Perspectives

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

Central Cell Therapy Facility

1) Site only recruits patients

2) Site recruits & manufactures for its OWN trials

3) Site recruits & manufactures for joint trial

Ship Final Cell Product

Tech Transfer for Manufacturing

Transfer of GMP Validated Reagents for Manufacturing
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
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
Effect of Fludarabine on T Cells