Cellular Therapies for Use in Public Health Emergencies

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Fostering Research through Collaborations with Other Offices, Agencies, and NIH Institutes

- DHHS, Office of the Assistant Secretary for Health, Office of HIV/AIDS and Infectious Disease Policy
- FDA
- DoD
- HHS Office of the Secretary for Preparedness and Response (ASPR), Biomedical Advanced Research Development Authority (BARDA)
- NIH Institutes – NIAID, NICHD, NIA, NIDCR, NCI
Cell Therapy: An Intersecting Interest
Hematopoetic System

- **0.1-1 Gy**: Slight decrease blood count
- **1-3.5 Gy**: Mild to severe bone marrow damage, 1 hour- 48 hours
- **3.5-7.5 Gy**: Pancytopenia, 1 hour- 48 hours
- **7.5-10 Gy**: Bone marrow damage, <1 hour- 48 hours
- **>10 Gy**: Severe bone marrow damage, minutes- 48 hours

Gastro-intestinal (GI)

- **3.5-7.5 Gy**: Mild to moderate GI damage, 1 hour- 48 hours
- **7.5-10 Gy**: Moderate to severe GI damage, <1 hour- 48 hours
- **>10 Gy**: Severe GI damage, minutes- 48 hours

**Cutaneous Radiation Injury**

- **>2 Gy**

**Cardiovascular**

- **>10 Gy**: Minutes- 48 hours

**Neurological**

- **>10 Gy Neurological damage 1-10 days**
Hematopoietic Stem Cell Transplantation and Chernobyl: Granulocytes

Time to Granulocyte Recovery: Treatment vs Control in Grade 2 or 3 ARS

- 500 x 10^3/ul
- 1000 x 10^3/ul
- 2000 x 10^3/ul
Hematopoietic Stem Cell Transplantation and Chernobyl: Platelets

Time to Platelet Recovery: Treatment vs Control in Grade 2 or 3 ARS

- 30 x 10^3/ul
- 50 x 10^3/ul

% Recovery vs Time (days)
Establishing a Strategic Research Agenda

- Need to continuously monitor and identify scientific priorities
- Know what research and resources are currently supported
- Identify and rectify gaps in research support and funding mechanisms, and provide funding opportunities
- Monitor progress using established metrics
NHLBI-supported Programs: Bench to Bedside

- Basic
- Preclinical
- FDA
- Phase I
- Phase II
- Phase III
- Phase IV

Contracts: T-Cell & COBLT

P01's

SCCT

Resources: PACT, GTRP, TRND, SMARTT, R24 grants

U10s: BMT CTN

U24: CIBMTR

R21's / R01's
Timeline Post-Detonation

0 - 72 hrs
- Administer fluids
- Secure airway
- Manage pain
- Provide early nutrition
- Prevent wound infection

72 hrs - Beyond
- Conclusive burn wound care
- Functional recovery
- Provide fluids & nutrition

GOALS

Burn Wound Treatments
1. Anti-microbial barrier burn bandages

Key Complementary Products
A. Oral rehydration therapy sachets
B. Point-of-care airway management
C. Analgesics (oral/intramuscular)
D. Nutritional supplies (oral)

Phase I Products
Field Care

Phase II Products
Definitive Care

Burn Wound Treatments
2. Autologous-based treatment products
3. Natural biological products
4. Manufactured biological products
5. Anti-microbial burn dressings

Key Complementary Products
E. Burn care surgical equipment
F. Rehydration fluids (oral/intravenous)
G. Nutritional supplies (oral/nasogastric)
H. Pharmaceuticals (analgesics, sedatives, systemic antibiotics)
Priorities for Cellular Therapies

- Support basic research needed for future cellular therapies – large portion of TMCTB’s grant portfolio.

- Support preclinical studies, including scale-up and validation of new cellular products for clinical trials (i.e., ex vivo-expanded umbilical cord blood, NK cells and T regulatory cells) using
  - New funding opportunities and review criteria appropriate for preclinical research, i.e. do not require hypothesis-driven research
  - Resource Programs such as the Production Assistance for Cellular Therapies (PACT) program
Priorities for Cellular Therapies

- Support early-phase clinical studies
  - Constitute specialized review panels with the appropriate expertise for these studies, including regulatory, statistical, and cell-manufacturing
  - Foster novel early-phase clinical trials
    - when possible, try to use an existing infrastructure for cell therapy trials (such as the BMT CTN) to hasten the transition into definitive trials

- Complete high priority phase II and III clinical trials in hematopoietic stem cell transplantation
  - 2007 State of the Science Symposium in Blood and Marrow Transplantation identified some of the high-priority trials.
PACT’s Role in Supporting Pre-Clinical Work and Phase I Clinical Trials

**Pre-clinical**

- Discovery; Proof of concept; cell Product potential; therapeutic mechanism and pathway; cell and disease interaction

**Phase I**

- IND Filing
- Dose escalation; safety and toxicity studies; small trial size

**Phase II**

**Phase III**

**Manufacturing**
- Scale up
- Validation
- Release Criteria
- CMC

**Animal Studies**
- GLP/GMP product
- Efficacy
- Toxicity

*Manufacturing*

- Scale up
- Validation
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*Animal Studies*

- GLP/GMP product
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**IND Filing**

**Dose escalation; safety and toxicity studies; small trial size**

**Efficacy and safety studies; full product characterization; potency; scale up; full GMP**
# Cell Product Manufacturing Capabilities

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<tr>
<th>PROGENITOR CELLS</th>
<th>CELL DEPLETION/CELL ENRICHMENT (BM/PB/UCB)</th>
<th>DENDRITIC CELLS</th>
<th>LYMPHOCYTES</th>
</tr>
</thead>
</table>
| - Corneal progenitor cells<br>- HPC<br>- Hepatic progenitor cells<br>- hESC<br>- IPS<br>- Neural progenitor cells<br>- Mesenchymal stem cells | - CD3 depletion<br>- CD34 selection<br>- CD133 selection<br>- CD34+/CD3-<br>- CD56 selection<br>- Counterflow elutriation | - Adenovirally transduced<br>- Apoptotic tumor cell pulsed<br>- Peptide pulsed<br>- Transfected<br>- Tumor lysate pulsed<br>- Tumor-dendritic cell hybrids | - Peripheral blood-derived lymphocytes<br>  
  - Lymphocyte activated killer cells<br>  
  - Activated NK cells<br>  
  - Invariant NKT cells<br>  
  - CD8+/CD4+ T cells<br>  
  - CD4+/CD25+ T regulatory cells<br>  
  - CTLs (TGFβ, chimeric antigen receptors) |

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<tr>
<th>LYMPHOCYTES</th>
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<th>ANTIGEN PRESENTING CELLS</th>
<th>DONOR LEUKOCYTES</th>
</tr>
</thead>
</table>
| - Umbilical cord blood-derived lymphocytes<br>  
  - CD4+/CD25+ T regulatory cells | - EBV-transformed B cell lines (LCLs)<br>  
  - LCLs +/- genetic modification-intermediate product | - Dendritic cells<br>  
  - Leukemic cell lines<br>  
  - Monocytes | - Donor leukocyte infusion<br>  
  - Alloreactive T cell depleted (immunotoxin)<br>  
  - Thymidine kinase (suicide gene)-transduced T cells |

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<tr>
<th>GENETICALLY MODIFIED CELLS</th>
<th>TUMOR VACCINES (translational development)</th>
<th>MASTER/WORKING CELL BANKS</th>
<th>OTHER</th>
</tr>
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</table>
| - Activated T cells<br>- Fibroblasts<br>- Cytotoxic T-lymphocytes (CTLs)<br>- Hematopoietic stem cells (HSC)<br>- Lymphoblastoid cell lines (LCLs)<br>- Mesenchymal stem cells (plasmid or viral vector)<br>- Neural stem cells<br>- Tumor cells<br>- Tumor vaccines | - CLL-directed vaccine (autologous)<br>  
  - Large multivalent immunogen vaccine (autologous)<br>  
  - Breast adenocarcinoma<br>  
  - Melanoma<br>  
  - Renal cell carcinoma<br>  
  - Neuroblastoma-directed vaccine | - Artificial antigen presenting cells (K562)<br>  
  - Fibroblasts<br>  
  - Human embryonic stem cells<br>  
  - Mesenchymal stem cells<br>  
  - NK cell lines | - Aseptic filling<br>  
  - B95-8 EBV<br>  
  - Cell culture and expansion<br>  
  - Immune monitoring<br>  
  - Cell manufacturing for large animal models<br>  
  - Potency assay development<br>  
  - Cryopreservation technologies<br>  
  - Monoclonal antibodies<br>  
  - Plasmids<br>  
  - Suspension and adherent cell banks |
40 ongoing projects

- **23 - Clinical**
  - Delivering clinical product (cardiac; GVHD; post transplant viral infections; hematological malignancies; X-linked severe combined immunodeficiency [SCID-X1])

- **17 - Translational** (pre-clinical animal studies for cardiac & lung indications; Wiskott Aldrich Syndrome; stem cells for corneal transplantation)
Specialized Centers for Cell-Based Therapy Phase II Clinical Trials

- **CHALLAH – Allo CTL’s to treat specific viral Infections after transplant**
- **LYPTAIST - Auto CTL’s to Treat Adenovirus Infection after Transplant**
- **CADUCEUS - Intracoronary Cardiosphere-Derived Stem Cells in With Ischemic Pts.**
- **POSEIDON - Transendocardial Injection of Auto- vs. Allo-MSC in Chronic Ischemic Pts.**
- **CASPALLO - Allodepleted T Cells with Inducible Caspase 9 Suicide Gene after Transplant**
- **PROMETHEUS - IM Injection of Auto-MSCs for Ischemia in CABG pts.**
- **UCBT PTH - PTH after Sequential Unrelated Cord Blood Transplant**
- **PGE2 - Reduced Intensity two Cord Transplant Using PGE2 Treated Units**

Institutions:
- Baylor
- Mass Gen
- Cedar Sinai / Miami / Hopkins
- National Heart Lung and Blood Institute
Blood and Marrow Transplant Clinical Trials Network Years 1-10

- Expansion of donor availability and alternative graft sources
  (Auto vs Allo for myeloma; BM vs PBSC unrelated donor transplants; 3 trials addressing cord blood transplantation; Haploidentical donor transplants)

- Reduction in regimen-related toxicity (BM vs PBSC unrelated donor transplants, 3 trials studying reduced intensity conditioning, Etanercept for Idiopathic Pneumonia Syndrome)

- Graft versus host disease (GvHD) (Prevention of GVHD, treatment of acute GvHD, T-cell depleted allografts)

- Improved control of malignancy (decreased recurrence) (Post-transplant maintenance for myeloma, Auto vs Allo for myeloma, Radioimmunotherapy for conditioning)

- Infections and immune reconstitution (Antifungal prophylaxis, BM vs PBSC, ancillary studies)

- Late Complications and Quality of Life
SBIR/STTR: 3-Phase Program

PHASE I
- Feasibility Study
- $150K and 6-month (SBIR) or 12-month (STTR) Award

PHASE II
- Full Research/R&D
- $1 Million for 2-year Award (SBIR/STTR)

PHASE III
- Commercialization Stage
- Use of non-SBIR/STTR Funds
Questions?

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