

Cellular Therapies for Use in Public Health Emergencies

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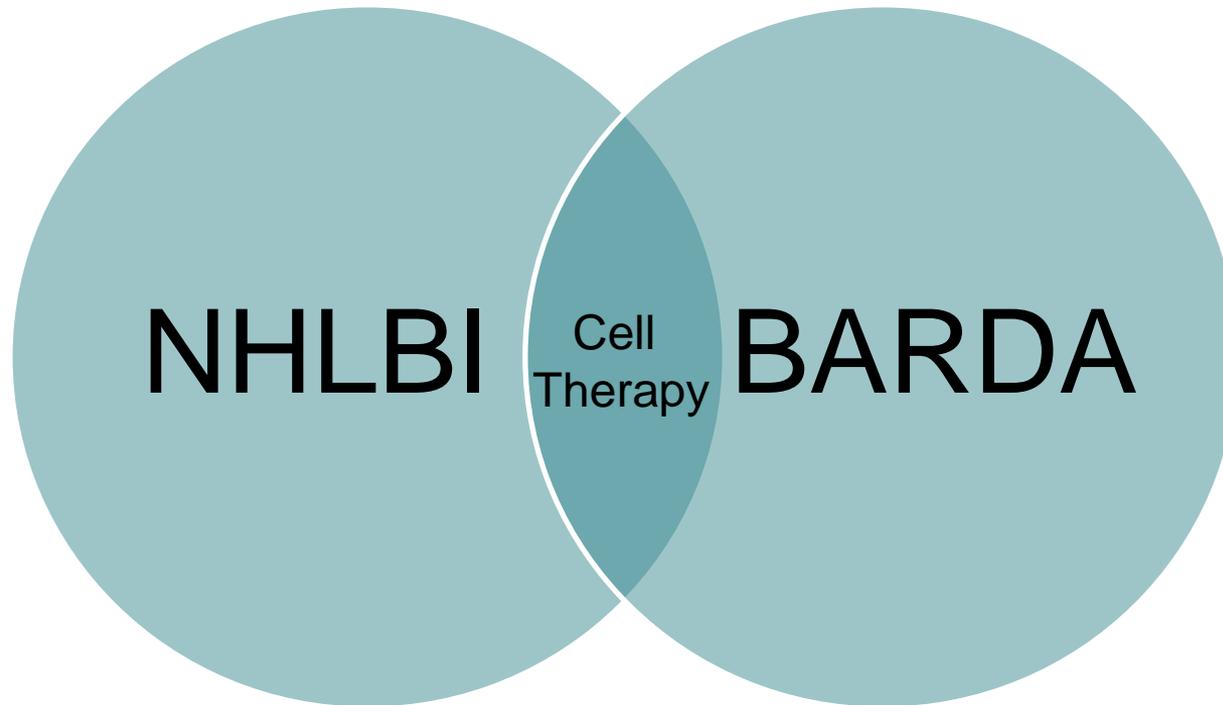
**Transfusion Medicine and Cellular
Therapeutics Branch**

**Division of Blood Diseases and Resources
National Heart, Lung, and Blood Institute, NIH**

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



Acute Radiation Syndrome (ARS)

Hematopoietic 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
- ✓ >10Gy: Severe bone marrow damage, minutes- 48 hours

Neurological

> 10 Gy Neurological damage 1-10 days

GI System

Cardiovascular
>10Gy
Minutes- 48
hours

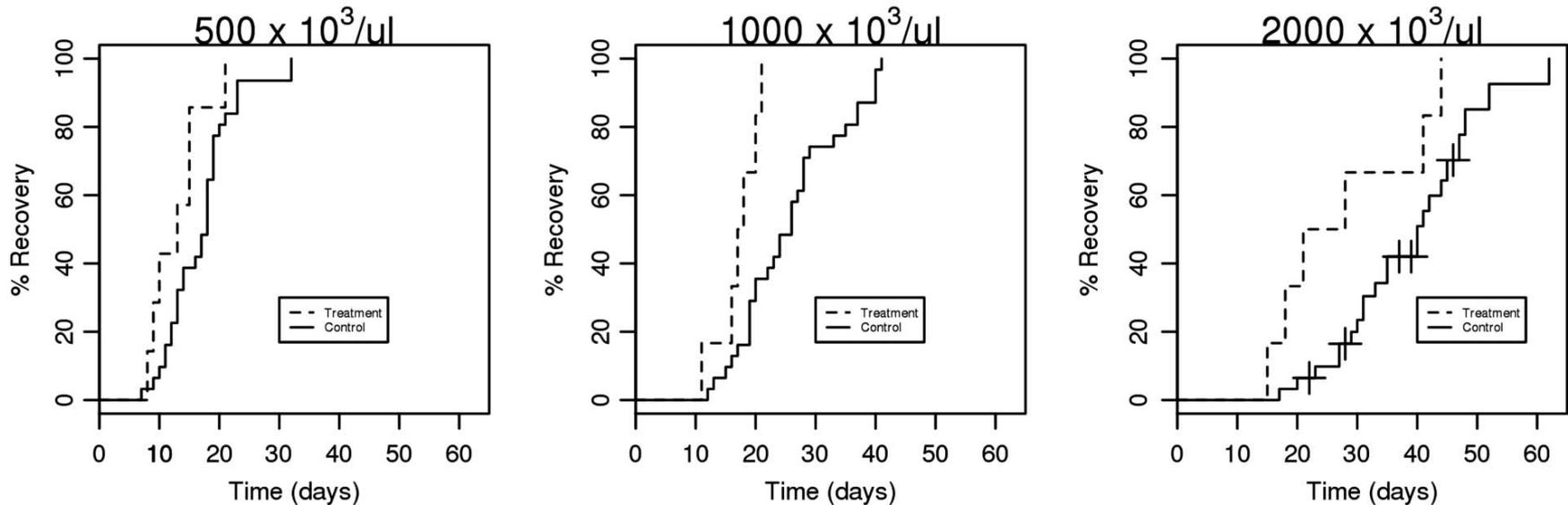
- ✓ 3.5-7.5 Gy: Mild to moderate GI damage, 1 hour- 48 hours
- ✓ 7.5-10 Gy: Moderate to severe GI damage, <1 hour- 48 hours
- ✓ >10Gy: Severe GI damage, minutes- 48 hours

Cutaneous Radiation Injury ≥ 2 Gy

Gastro-intestinal (GI)

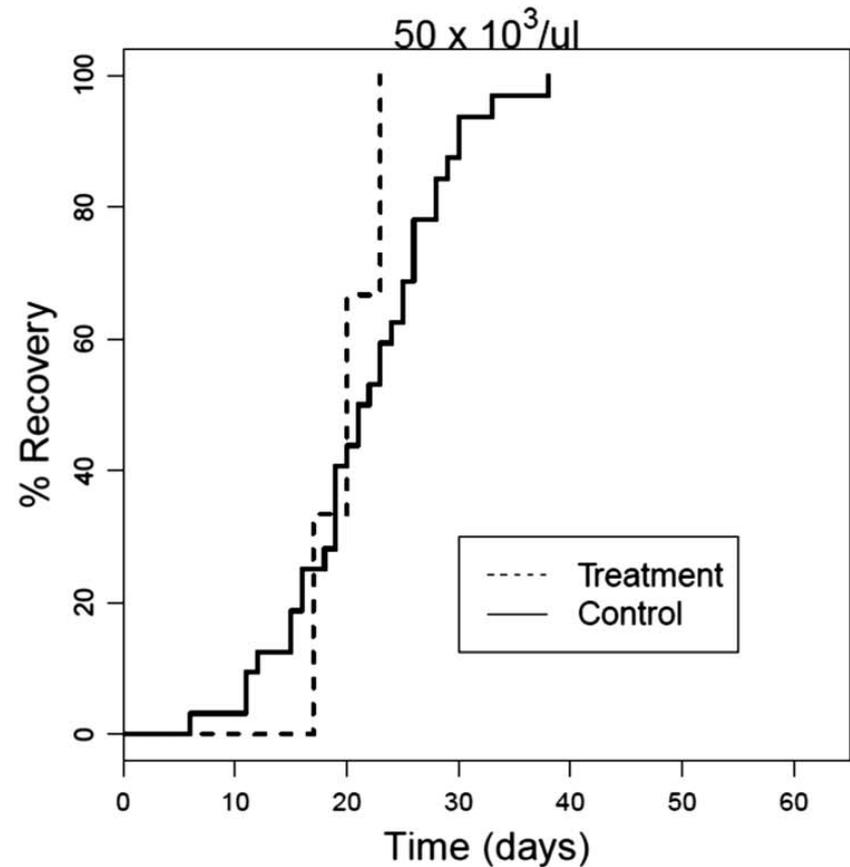
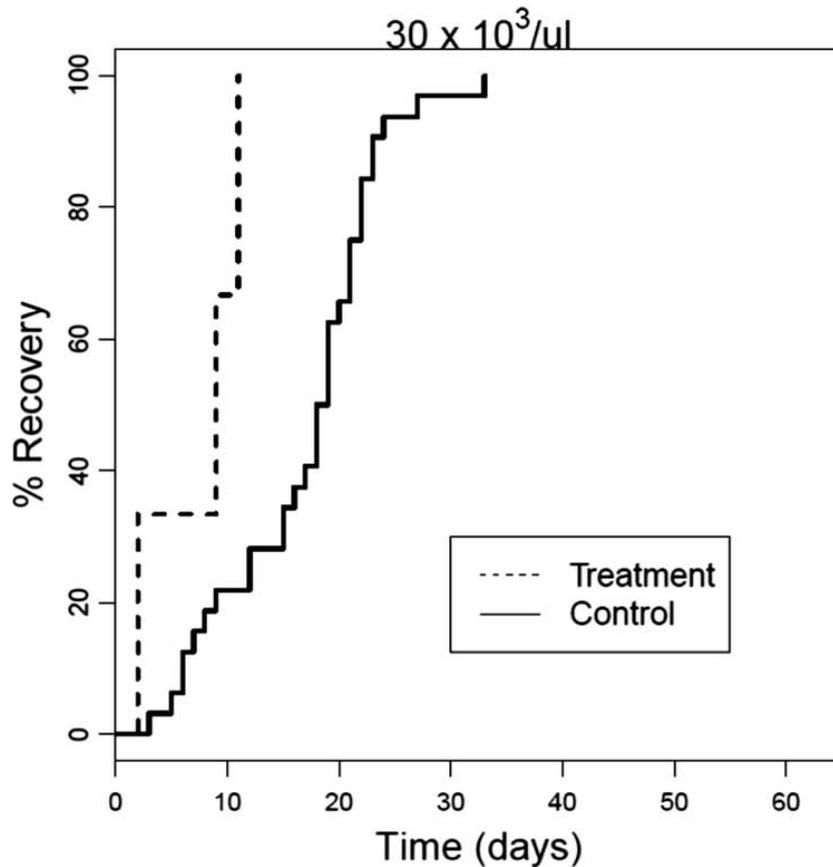
Hematopoietic Stem Cell Transplantation and Chernobyl: Granulocytes

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



Hematopoietic Stem Cell Transplantation and Chernobyl: Platelets

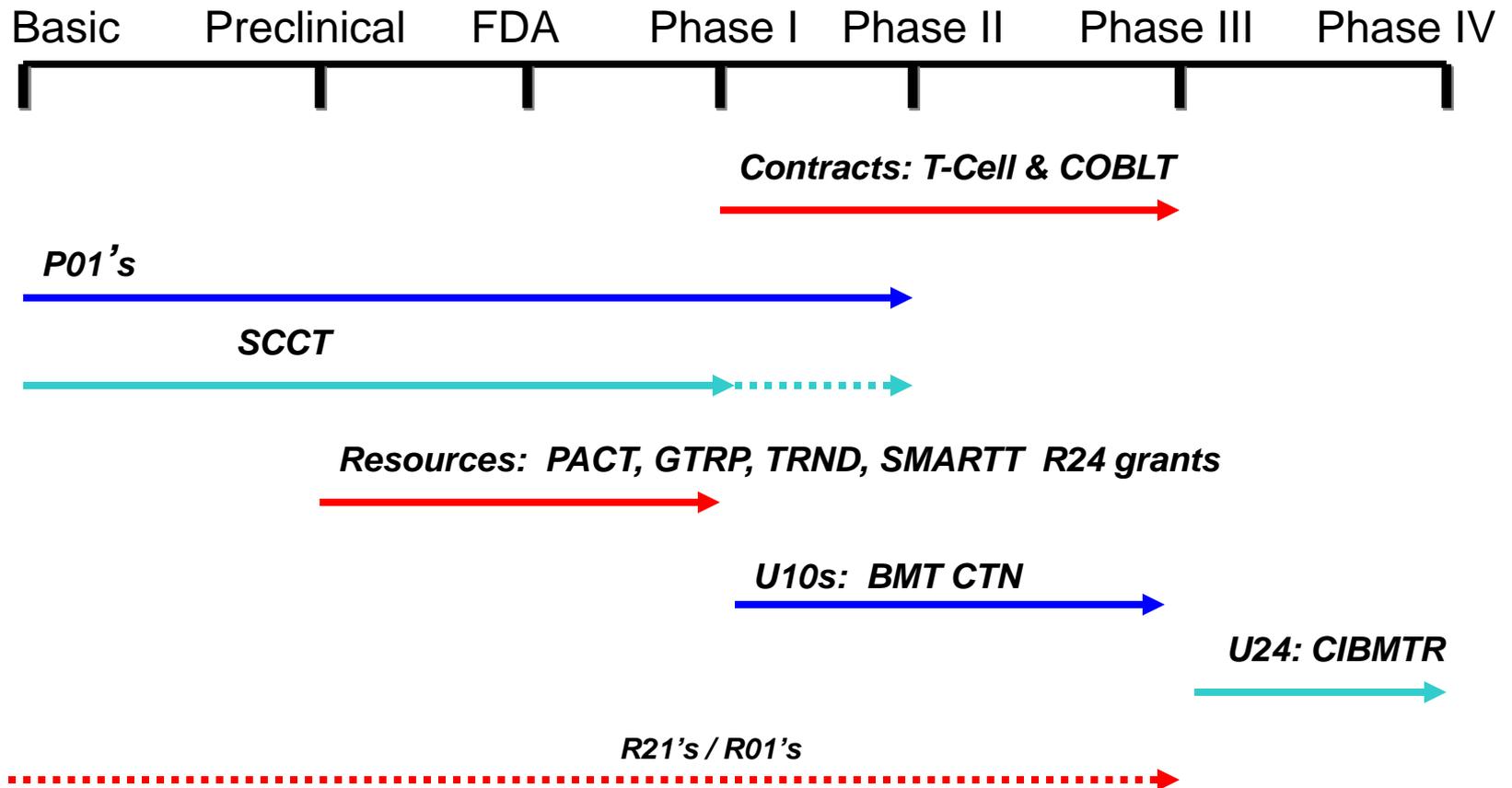
Time to Platelet Recovery: Treatment vs Control in Grade 2 or 3 ARS



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





Timeline Post-Detonation

0 - 72 hrs

GOALS

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

72 hrs - Beyond

GOALS

- Conclusive burn wound care
- Functional recovery
- Provide fluids & nutrition

Phase I Products

Field Care

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 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.

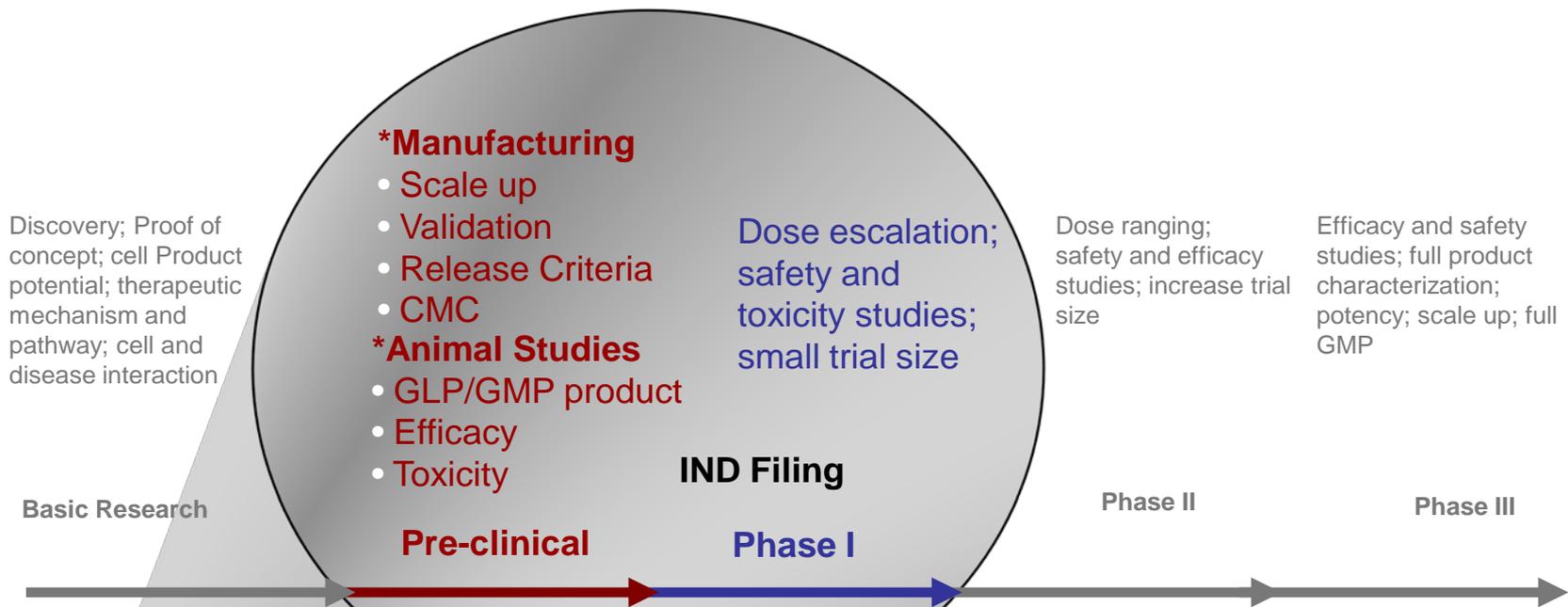
- ❑ Support preclinical studies, including scale-up and validation of new cellular products for clinical trials (i.e., ex vivo-expanded umbilical cord blood, NK cells and T regulatory cells) using
 - New funding opportunities and review criteria appropriate for preclinical research, i.e. do not require 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



Cell Product Manufacturing Capabilities

<i>PROGENITOR CELLS</i>	<i>CELL DEPLETION/CELL ENRICHMENT (BMPB/UCB)</i>	<i>DENDRITIC CELLS</i>	<i>LYMPHOCYTES</i>
<ul style="list-style-type: none"> • Corneal progenitor cells • HPC • Hepatic progenitor cells • hESC • iPS • Neural progenitor cells • Mesenchymal stem cells 	<ul style="list-style-type: none"> • CD3 depletion • CD34 selection • CD133 selection • CD34⁺/CD3⁻ • CD56 selection • Counterflow elutriation 	<ul style="list-style-type: none"> • Adenovirally transduced • Apoptotic tumor cell pulsed • Peptide pulsed • Transfected • Tumor lysate pulsed • Tumor-dendritic cell hybrids 	<ul style="list-style-type: none"> • Peripheral blood-derived lymphocytes <ul style="list-style-type: none"> ◦ Lymphocyte activated killer cells ◦ Activated NK cells ◦ Invariant NK T cells ◦ CD8⁺/CD4⁺ T cells ◦ CD4⁺/CD25⁺ T regulatory cells ◦ CTLs (TGFβ, chimeric antigen receptors)
<i>LYMPHOCYTES</i>	<i>LYMPHOCYTES</i>	<i>ANTIGEN PRESENTING CELLS</i>	<i>DONOR LEUKOCYTES</i>
<ul style="list-style-type: none"> • Umbilical cord blood-derived lymphocytes <ul style="list-style-type: none"> ◦ CD4⁺/CD25⁺ T regulatory cells 	<ul style="list-style-type: none"> • EBV-transformed B cell lines (LCLs) • LCLs +/- genetic modification-intermediate product 	<ul style="list-style-type: none"> • Dendritic cells • Leukemic cell lines • Monocytes 	<ul style="list-style-type: none"> • Donor leukocyte infusion • Alloreactive T cell depleted (immunotoxin) • Thymidine kinase (suicide gene)-transduced T cells
<i>GENETICALLY MODIFIED CELLS</i>	<i>TUMOR VACCINES (translational development)</i>	<i>MASTER/WORKING CELL BANKS</i>	<i>OTHER</i>
<ul style="list-style-type: none"> • Activated T cells • Fibroblasts • Cytotoxic T-lymphocytes (CTLs) • Hematopoietic stem cells (HSC) • Lymphoblastoid cell lines (LCLs) • Mesenchymal stem cells (plasmid or viral vector) • Neural stem cells • Tumor cells • Tumor vaccines 	<ul style="list-style-type: none"> • CLL-directed vaccine (autologous) • Large multivalent immunogen vaccine (autologous) <ul style="list-style-type: none"> ◦ Breast adenocarcinoma ◦ Melanoma ◦ Renal cell carcinoma • Neuroblastoma-directed vaccine 	<ul style="list-style-type: none"> • Artificial antigen presenting cells (K562) • Fibroblasts • Human embryonic stem cells • Mesenchymal stem cells • NK cell lines 	<ul style="list-style-type: none"> • Aseptic filling • B95-8 EBV • Cell culture and expansion • Immune monitoring • Cell manufacturing for large animal models • Potency assay development • Cryopreservation technologies • Monoclonal antibodies • Plasmids • Suspension and adherent cell banks

PACT Program Status



- 40 ongoing projects
 - 23 - Clinical
 - 12 - 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

Baylor

LYPTAIST - Auto CTL's to Treat Adenovirus Infection after Transplant

CASPALLO - Alodepleted T Cells with Inducible Caspase 9 Suicide Gene after Transplant

Mass Gen

CHALLAH - Allo CTL's to treat specific viral Infections after transplant

UCBT PTH - PTH after Sequential Unrelated Cord Blood Transplant

SCCT

Specialized Centers for Cell-Based Therapy
NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

PGE2 - Reduced Intensity two Cord Transplant Using PGE2 Treated Units

CADUCEUS - Intracoronary Cardiosphere-Derived Stem Cells in With Ischemic Pts.

POSEIDON - Transendocardial Injection of Auto- vs. Allo-MSc in Chronic Ischemic Pts.

PROMETHEUS - IM Injection of Auto-MSCs for Ischemia in CABG pts.

Cedar Sinai / Miami / Hopkins

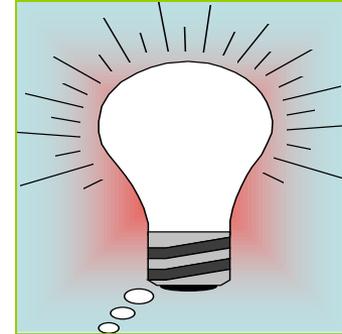
Blood and Marrow Transplant Clinical Trials Network Years 1-10

- ❑ 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

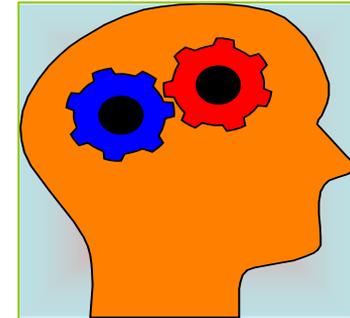
PHASE I

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



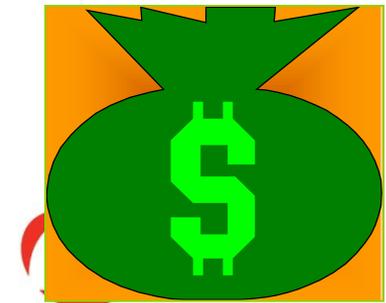
PHASE II

- 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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