Final Report
National Heart, Lung, and Blood Institute
Level 1 Strategic Planning Working Group
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Blood Program – Theme # 3: Cellular Therapeutics

Introduction:

Stem cells hold tremendous potential for treating cardiovascular, pulmonary, and blood diseases, genetic disorders, and cancer. This includes allogeneic or autologous stem cells, whether gene-modified or not. Hematopoietic stem cell biology and manipulation serves as a model to conduct studies to: (1) direct differentiation of embryonic stem cells or other pluripotent cells (e.g., to generate blood cells) (2) enable isolation of adult stem cells (e.g., cardiac and lung) (3) optimize application of mesenchymal and other non-hematopoietic stem cells, and (4) permit targeted novel therapies. NHLBI is uniquely positioned to support emerging regenerative cell therapies through the expertise of its funded investigators, existing good manufacturing practices (GMP) cell production programs, and its leadership in education. NHLBI is well-positioned to establish a registry of cell-based therapies to study outcomes, particularly rare events and long-term effects because of ongoing NHLBI funded programs (e.g., SCCT, CIBMTR) and collaboration with other Institutes (e.g., NCI; NIAID) and agencies (e.g., HRSA).

Recommendations:

1. Define stem cells and their programs for self-renewal and differentiation. Fundamental properties of all stem cells are self-renewal and differentiation. Advances in adult stem cell biology provide the foundation for gaining an in-depth understanding of the molecular programs governing these processes, critical for therapeutic applications. The proposed approach would be to: (1) find signatures to identify and isolate stem and progenitor cells, and (2) define targets to: (a) expand stem cell numbers, (b) regenerate tissues, and (c) disrupt cancer stem cells. Such studies would make advances possible including isolation of human stem cells from different tissues and drug-based targeting that could be used to manipulate stem and progenitor cells for tissue regeneration. The aim of this recommendation is to create an important knowledge platform using a flexible, team-based, multi-disciplinary approach. Experts from around the country would participate based on ongoing performance metrics.

2. Define and overcome immunologic and genetic barriers to stem cell transplantation to permit successful allogeneic transplantation for all patients who could benefit. Allogeneic transplantation is the only curative therapy for many diseases. Advances in immunology, including understanding mechanisms of tolerance and directed anti-infectious and anti-malignancy responses, hold the promise for transplants with improved survival due to decreased graft-versus-host disease (GVHD), relapse, and infections. The plan would be to define and manipulate the mechanisms of tolerance in humans to: (1) achieve consistent engraftment, (2) eliminate GVHD, and (3) promote full immune reconstitution. Such advances would lead to safe and effective therapies of non-malignant and malignant disorders and would provide for safer organ grafting and improved clinical management of autoimmune diseases.

3. Validate regenerative cell therapies. Cellular therapeutics is hampered by conflicting laboratory data and unstandardized early phase clinical studies. To resolve these problems it is essential to establish (1) rigorous functional and phenotypic characterization of cell populations such as mesenchymal stromal cells and embryonic stem cells, and (2) accurate and appropriate preclinical models.

4. Exploit the unique immunologic setting following successful allogeneic hematopoietic stem cell transplantation for the administration of adoptive cellular therapy. The success of related or unrelated donor transplants for multiple indications established their therapeutic utility. This can be exploited, without the possibility of immune rejection, to: (1) improve solid organ transplant without immune suppression, (2) enhance tissue repair, and (3) improve control of cancer.

5. Advance genetic therapy of hereditary and acquired disorders by development of safe and effective gene-modification methods. The success of gene therapy in treating lymphoid immunodeficiency can be extended to other diseases, including hemoglobinopathies and thalassemias, and disorders of the heart and lung by: (1) developing safe, efficient, and specific vectors, (2) improving delivery of genes to cells in vitro and in vivo, (3) improving strategies for gene repair, and (4) achieving long-term persistence of genetically-modified cells.

6. Define stem cell niches and mechanisms governing stem cell localization and function under normal and disease conditions. The stem cell niche integrates signals of injury and homeostasis regulating stem cells of all types, and participates in dysplastic and malignant disease. Precise definition of cell localizing mechanisms can enable directed delivery of cell therapies. The goals are to (1) define cell localizing processes to direct delivery of cell therapies, (2) manipulate the niche to affect regeneration or malignancy, and (3) develop critical technologies in cell imaging, niche bioengineering, and high sensitivity biochemical techniques. Sensitive biochemical techniques are needed to define the molecular regulators of cell location and to understanding the dynamic interplay of heterologous factors that alter stem cell fate.

Obstacles and Actions to Overcome Them - Reagent generation and GMP production (cells, vectors, and biologics) of critical materials for translational and clinical studies are critically needed. To bridge this gap: (1) support a RAID-like mechanism for biologics, (2) increase availability of characterized reagents, (3) expand current GMP manufacturing capacity to include antibodies, vectors, and biologics such as cytokines, and (4) ease regulatory impediments, including the development of a standardized regulatory pathway for clinical trials.

NHLBI Operations - Changes Needed - Funding for early Phase clinical trials is difficult to obtain, especially in light of reduced GCRC funding. Funding opportunities could be facilitated by implementing: (1) a Quick-trial type mechanism, and (2) performance payments for clinical trials, including factors such as anticipated versus actual patient accrual.

Education - Cellular therapeutics is a rapidly evolving field in which both ongoing communication and a multidisciplinary approach are essential. This can be addressed by: (1) enhancing multidisciplinary training of postdoctoral fellows, e.g., by the use of multiple mentors who may be at different institutions, and (2) supporting educational symposia on fundamental stem cell biology at society meetings.

Unique Opportunities for NHLBI - NHLBI is in a unique position to establish a registry, in collaboration with other agencies, to track the long-term effects of cellular therapeutics. The Institute has resources and expertise from past activities in this area. In addition, NHLBI, in partnership with other Institutes/agencies, can help address the complex regulatory issues associated with cell and gene therapy clinical trials. This collaboration will ensure timely initiation of safe US clinical studies based on NHLBI-funded research. Further, it would increase US competitiveness and correct the current situation where recent gene therapy trials for hemoglobinopathies developed with NHLBI funds will begin in Europe, and where certain cancer treatments developed with US technologies are available in Asia, but not in the US.

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