For more than three decades the National Heart, Lung, and Blood Institute (NHLBI) has supported research and sponsored programs in basic cell biology and stem cell research. Many NHLBI-funded investigators contributed to the characterization of the hematopoietic stem cell, which has served as a prototype for other stem cell systems. This research has led to successful clinical applications of bone marrow stem cell harvests, umbilical cord blood units, and peripheral blood cell apheresis products for the treatment of genetic and malignant blood diseases, and the evaluation of new hematopoietic cell-based therapies by an NHLBI/NCI-sponsored transplant network.1

This experience provided the framework for the institute’s current programs and resources for exploring potential application of novel cell-based therapies to a wide array of heart, lung, and blood diseases. This includes more recent clinical testing to determine whether bone marrow cells are useful in the treatment of cardiovascular diseases2 and a program beginning in the fall of 2007 for collaborative studies on lung stem cell biology and cell-based therapy.3 This article outlines the programs in stem cell research and cell-based therapies that have led to these new opportunities as well as current research opportunities, available resources, and training programs. Future directions for regenerative medicine at NHLBI will include these strategies and integrate “advances in regenerative biology to develop clinically feasible applications” (Goal 2.1a).4

National Institutes of Health Organizational Approaches

NHLBI Cell-based Therapy Group
To promote a coordinated approach to stem cell research leading to cell-based therapies, NHLBI established its own cell-based therapy group in August 2001. The NHLBI group, composed of program officers from the Heart, Lung, and Blood Divisions, convened a 2-day meeting of 24 experts in May 2002 to define state-of-the-science, identify opportunities and roadblocks, and assist in formulating a strategic NHLBI plan for new cell-based therapies. The working group’s top recommendation advocated continued, strong basic research programs in stem cell biology and cell-based therapy. The group recommended new programs related to the stem cell niche, regeneration mechanisms, immunogenic responses to cells, in vivo cell-tracking techniques, lung stem cell research, and the cardiomyogenic potential of stem cells. The complete working group report is available on the NHLBI web site.5

National Institutes of Health Stem Cell Task Force
Our institute is a member of the National Institutes of Health (NIH) Stem Cell Task Force, formed to seek the advice of scientific leaders, identify limiting steps and resources, and develop initiatives to advance stem cell research. The 15-member task force formed in 2002 developed and implemented new stem cell programs including the NIH Short-Term Courses in Human Embryonic Stem Cell Culture Techniques, Human Embryonic Stem Cell Research Resource Infrastructure Enhancement Awards, the National Embryonic Stem Cell Bank, and the NIH Centers of Excellence in Translational Human Stem Cell Research.6,7

Programs to Advance the Science

Basic Research Programs
In 2001, NHLBI began a basic research initiative to support R01 grants on stem cell plasticity (Table 1, HL-01-007). In 2002 the Institute provided support for R21 grants on innovative concepts and approaches (Table 1, HL-02-017) that included grants for the development of new stem cell technologies and tissue engineering to repair organ function. As part of the Institute’s strategic plan, the NHLBI Cell-based Therapy Group formulated two basic stem cell research programs in 2002, one on “Basic Research on Mesenchymal Cell Biology” (Table 1, HL-02-018) and a second on “Research on Stem Cell Biology and Cell-based Therapies for Heart, Lung, Blood and Sleep Disorders” (Table 1, HL-02-019) to accelerate translational research efforts. Although not directed specifically to stem cell research, the Institute has also sponsored enabling technology initiatives on imaging, proteomics, and nanotechnology.

Translational Research Programs
The NIH is supporting two Centers of Excellence in Translational Human Stem Cell Research that combine basic and translational efforts, one at the University of California at Davis administered by the NHLBI and a second at Northwestern University, administered by the National Institute of Neurological Disorders and Stroke (Table 2). The Center of
Excellence at the University of California at Davis includes a pilot and feasibility program, which provides an annual opportunity for investigators nationwide to conduct research projects within the center. Investigators outside the center can take advantage of the large animal models including nonhuman primates to test their translational ideas; interested investigators are encouraged to contact the center at Davis for application information.8

In addition, NHLBI supports R01 research project grant programs in clinically-relevant stem cell diseases; the myelodysplastic syndrome and the myeloproliferative disorders (Table 2). The myelodysplastic syndrome research program seeks to understand the etiology of the disease with the goal of developing new treatments, and the myeloproliferative disorders research program supports the search for new cellular and genetic markers associated with origin and disease progression, again with the goal of developing new treatments.

Clinical Cellular Therapy Programs

The Blood and Marrow Transplant Clinical Trials Network (BMT CTN) started by NHLBI and NCI in 2001 includes 16 member (core) transplant centers and more than 50 affiliated non-core centers conducting advance phase research trials (Table 2). Network studies are evaluating cellular sources, transplant-related toxicities, disease recurrence, infectious complications, immune reconstitution, and late effects after transplantation including quality-of-life issues. Examples of specific protocols include the cellular source study (BMT CTN #0201) comparing bone marrow stem cells grafts to G-CSF mobilized peripheral blood stem cells. An example of a study of transplant-related toxicities is a clinical trial (BMT CTN #0302) comparing four new agents (etanercept, pentostatin, mycophenolate mofetil, and denileukin diftitox) along with corticosteroids for the initial treatment of acute graft versus host disease.

In 2004 NHLBI announced a program for specialized centers for Cell-Based Therapy for Heart, Lung, and Blood Diseases and a Data Coordinating Center (Table 2, HL-04-017). This program uses a cooperative U54 mechanism to support three specialized centers and one data-coordinating center for preclinical and clinical research using new cell-based therapies. The specialized centers are located at the Baylor College of Medicine in Houston, Tex, the Massachusetts General Hospital in Cambridge, Mass, and the Johns Hopkins University in Baltimore, Md. The EMMES Corporation in Rockville, Md, serves as the data-coordinating center. Each specialized center includes two clinical projects and one or two basic or preclinical projects. To foster work in the developing area of cell-based therapy, the clinical projects can include preclinical studies in the first and second year, with the aim of starting a clinical trial no later than the beginning of the third year.

At Baylor the first trial is a phase I study where adenovirus specific cytotoxic T-lymphocytes are being administered to allogeneic stem cell transplant recipients to determine whether the procedure is safe and for a preliminary indication as to whether the infused cells might protect against adenoviral infection that can be life-threatening in these immunocompromised patients. At the Massachusetts General Hospital the first trial is a phase II study to evaluate if parathyroid hormone administered to patients transplanted with two unrelated cord blood units may shorten the time to neutrophil engraftment. The first trial at Johns Hopkins, currently under development and scheduled to open later in 2007, will examine the use of autologous mesenchymal stem cells in cardiac patients.

In recognition of the need to facilitate the clinical implementation of cell-based therapies for cardiovascular disease, NHLBI started the Cardiovascular Cell Therapy Research Network (CCTRN) in January 2007 (Table 2). Five centers were awarded: 1) Cleveland Clinic; 2) University of Florida; 3) University of Minnesota; 4) Texas Heart Institute; and 5) Vanderbilt University. The University of Texas serves as the data coordinating center. The objective of the CCTRN is to accelerate research in the use of cell-based therapies for the management of cardiovascular diseases, improving outcomes through the development and application of cell-based therapies and evaluation of these novel therapies. The network provides the necessary infrastructure to develop, coordinate, and conduct multiple collaborative clinical protocols to facil-
itate application of emerging scientific discoveries into clinical investigations. Results of the studies conducted in this network are expected to be widely disseminated to improve the care of affected individuals.

**Resources for Cell-Based Therapies**

Both NHLBI and NIH currently provide resources for cell-based therapies and stem cell research (Table 3). GMP-grade cells are provided through the NHLBI Production Assistance for Cell-based Therapies (PACT) and the Center for Human Cellular Therapy. An NIH program provides human embryonic cell lines through the National Stem Cell Bank.

A think-tank held on April 26, 2002 after a NHLBI workshop on “Immune Reconstitution and Cell-Based Therapy following Hematopoietic Stem Cell Transplantation” recommended that NHLBI support cell processing facilities.10 The think-tank recommended support for cell processing facilities, infrastructure to produce clinical-grade reagents (eg, cytokines and monoclonal antibodies), training on regulations, quality control and assurance, and basic and clinical research for cell-based therapies.

NHLBI implemented this recommendation in the fall of 2003 when contracts were awarded to three cell processing centers: (1) the Baylor College of Medicine’s Center for Cell and Gene Therapy; (2) the University of Minnesota’s Molecular and Cellular Therapeutics Facility; and (3) the University of Pittsburgh’s Immunologic Monitoring and Cellular Products Laboratory. The EMMES Corporation (Rockville, Md) serves as the administrative center for the facilities. The program, which adopted the name Production Assistance for Cell-based Therapies or PACT, is designed to develop novel somatic cell-based therapies to aid investigators by providing support in areas ranging from basic science through animal...
studies to proof-of-principle and eventually human trials. The PACT facilities are charged with implementing the rapid and safe transition of basic research ideas to clinical practice as well as supplying clinical-grade products produced in a manner that is compliant with all regulatory requirements. The PACT administrative center serves as the monitor and coordinator for organizational and regulatory aspects of the program.

PACT is currently manufacturing cell products of differing types for diverse clinical studies. Examples of cell products include: (1) CMV pp65 specific cytotoxic T lymphocytes to be used for the prevention and treatment of CMV infections after allogeneic stem cell transplantation; (2) autologous mature dendritic cells loaded with HIV-1 infected apoptotic cells that will be used to improve host immune control of residual viral infection during highly active antiretroviral therapy; and (3) allogeneic natural killer cells to be used for cardiac repair during placement of a left ventricular assist device.

As translational research becomes a major focus in cell-based therapies, cellular processing facilities can assume the responsibility of bridging the gap between basic and clinical research. The purpose of PACT is to focus on translational work to address the lack of assistance in transporting cell-based therapies from the bench to the bedside. Another objective of the PACT program is to develop programs and mechanisms to facilitate the training and development of investigators in areas of cell therapy manufacturing and clinical studies with a focus on clinical-grade reagent production and FDA regulatory procedures.

Two other resource programs are worth noting as listed in Table 3. For investigators in the Boston area, NHLBI supports a resource program at the Center for Human Cell Therapy that can provide clinical-grade cells and assistance related to developing new cell therapies. Investigators in the Boston area should check the center’s web site (http://www.chct.org/) for information on resources available and on project selection.

Finally, for investigators interested in human embryonic stem cell lines, a National Embryonic Stem Cell Bank has been established and ten NIH registered human embryonic stem cell lines are currently available. Each cell line is provided for $500 per vial. Laboratories that have not yet grown human embryonic stem cell lines are strongly encouraged to have a laboratory member attend one of the seven human embryonic stem cell training courses offering hands-on training courses (see below).

### Training Programs

#### Career Training for Stem Cell Research

Career training for stem cell research includes both short-term courses on specific topics and long-term career opportunities (Table 4). Investigators interested in incorporating approved human embryonic stem cell (hESC) lines into their research may apply for a “Short-Term Course in Human Embryonic Stem Cell Culture Techniques” and obtain 5 to 10 days of hands-on laboratory training. The list of course sites is available at the NIH web site under Stem Cell Information & Training Programs (http://stemcells.nih.gov/research/training/). Investigators inter-
ested in human multi-potent adult progenitor cells (MAPC) research may apply for the Human MAPC Culture Training Program at the University of Minnesota’s Stem Cell Institute. This 6-week training course covers techniques required for MAPC derivation from human bone marrow cells, maintenance of MAPC and MAPC differentiation.

In addition to these short-term cell training courses, investigators wishing to redirect their research toward stem cells may apply to the NIH K18 Career Enhancement Award for Stem Cell Research (Table 4, PA-07-359) program. This program can provide either junior or senior investigators with 6 to 24 months of salary support and up to $50,000 in direct costs per year.

**PACT Training Program**
The PACT facilities also provide training in the field of cell-based therapy production. General training topics include the core requirements for good manufacturing and good tissue practice (GMP/GTP), compliance of a cell-processing facility, overall good laboratory practice (GLP) and cell/tissue processing methods that are common among various cell and tissue-based products. Specific topics may focus on particular products with regard to GMP/GTP compliance; translational development, scale-up and manufacture; quality assurance; and regulatory issues. Six audio-conferences and web-based seminars have been offered to all interested investigators and future seminars will be listed on the PACT web site.11

**TABLE 6. Current NHLBI and NIH Mechanisms Supporting Stem Cell Research (applications can be submitted)**

<table>
<thead>
<tr>
<th>Program</th>
<th>Purpose</th>
<th>Status</th>
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<tr>
<td>Novel Approaches to Enhance Animal Stem Cell Research (R01) (R21)</td>
<td>To enhance animal stem cells as model biological systems. Innovative approaches to isolate, characterize and identify totipotent and multipotent stem cells from nonhuman biomedical research animal models, as well as to generate reagents and techniques to characterize and separate those stem cells from other cell types is encouraged. Studies involving human subjects are not allowed.</td>
<td>Announced January 18, 2007 Expires January 3, 2010</td>
</tr>
<tr>
<td>Directed Stem Cell Differentiation for Cell-Based Therapies for Heart, Lung, and Blood, and Aging Diseases (R21) (SBIR) (STTR)</td>
<td>To define the factors and mechanisms controlling the differentiation of embryonic or adult stem or progenitor cells, either in vitro or in vivo. It is designed to stimulate new scientific advances in stem cell differentiation including technology research that may not be hypothesis driven. The long range goal of this program is the development of methods to direct the differentiation or development of stem cells along specific cell lineages to yield replacement cells for clinical use, whether the replacement cells are formed in vitro for delivery or formed in vivo in the tissue or organ environment.</td>
<td>Announced May 11, 2006 Expires July 2, 2008 Announced January 20, 2006 Expires August 2, 2008 Announced January 20, 2006 Expires August 2, 2008</td>
</tr>
<tr>
<td>Exploratory/Developmental (R21) Bioengineering Research Grants (EBRG)</td>
<td>To support innovative, high risk/high impact bioengineering R21 research grants in new areas including stem cell research that are lacking preliminary testing or development.</td>
<td>Expires September 2, 2009</td>
</tr>
<tr>
<td>PA-06-418</td>
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<tr>
<td>Bioengineering Research Partnerships (BRPs)</td>
<td>To encourage basic, applied, and translational bioengineering research including stem cell research that could make a significant contribution to improving human health. Supports integration of physical, engineering, and computational science principles.</td>
<td>Expires May 8, 2010</td>
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<tr>
<td>PAR-07-352</td>
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</table>

As program availability may change, please consult web site or program officer for current information.

**Other Resources**

**NHLBI Proteomic Centers**
In 2002, the NHLBI funded 10 interactive multidisciplinary proteomic centers to enhance and develop innovative proteomic technologies and apply them to relevant biologic questions that will advance our knowledge of heart, lung, blood, and sleep health and disease. More information can be found at http://www.nhlbi.nih.gov/resources/proteomics/.

**NHLBI Biologic Specimen Repository**
The NHLBI Biologic Specimen Repository is administered by the Division of Blood Diseases and Resources. The Repository includes ~4 million biospecimens from multiple NHLBI studies. Investigators can request biospecimens of interest by completing an application form. Further information on the Repository and sample request forms are available at http://www.nhlbi.nih.gov/resources/medres/reposit/.

**Research Funding Opportunities**
NHLBI participates in research project grant and program announcements to foster basic stem cell research. General research mechanisms are listed in Table 5 and specific program announcements that are currently accepting applications are listed in Table 6. For example, the program announcement “Novel Approaches to Enhance Animal Stem Cell Research” (Table 6) encourages submission of both R01 and R21 applications to develop animal stem cells as biologic models.
Summary
NHLBI is committed to supporting basic, applied and clinical research in the area of cell-based therapy. Clinical practice and research in all areas are becoming a team effort, and NHLBI is increasingly interested in supporting team building through outreach, training programs and resource building as well as research. The current progress in the field of cell-based therapy is a prime example of teamwork and cooperation, and NHLBI looks forward to supporting this growing field of research.

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J.W.T. is the Stem Cell and Cell-based Therapy Coordinator for the Division of Blood Diseases and Resources, National Heart, Lung, and Blood Institute, National Institutes of Health.

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None.

References

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