Final Report
National Heart, Lung, and Blood Institute
Level 1 Strategic Planning Working Group
July 6-7, 2006

Cardiovascular Program – Theme # 6: Regenerative and Reparative Medicine

Introduction:

Endogenous repair mechanisms are inadequate to reconstitute cardiac myocyte loss from acute infarction or on-going apoptosis in heart failure. Regenerative and reparative strategies for treating cardiovascular disease include cell-based therapies, which have demonstrated exemplary promise in animal models and encouraging but limited benefits in controlled phase II human studies. Fully exploiting the therapeutic potential of stem and progenitor cells will require significant advances in the underlying science, including knowledge of cellular mechanisms of benefit, and the pathways driving their differentiation and function. Gene therapy directed towards cardiac and vascular cells, tissue engineering, and xenotransplantation are complementary approaches, presently at earlier stages in the translational pipeline. Beyond addressing scientific priorities that pertain to each of these areas individually, recommendations of the Working Group (WG) on Regenerative and Reparative Medicine specifically emphasize steps to maximize the opportunity for successful translation from proof-of-concept studies in animals to workable therapies in humans. In these rapidly-emerging, potentially revolutionary areas of investigation, it is crucial to evaluate promising preclinical results in patients without undue delay. The National Heart, Lung, and Blood Institute (NHLBI) is uniquely positioned to address these distinct challenges and imperatives of the cardiovascular system through the following recommendations:

Recommendations:

1. Accelerate discovery in the preclinical biology and therapeutic testing of circulating and tissue-resident stem/progenitor cells, including studies of cell characterization, propagation, mobilization, homing, differentiation and function; mechanisms and predictors of benefit and risk; imaging sciences; and Phase I/II trials of novel cardiovascular progenitor cells, mobilization strategies and cell delivery systems.

- Characterize diverse stem/progenitor cell types, across disciplines, with prospective and retrospective (banking of cells) analysis of phenotype and function, at the level of the human genome project scale
- Maintain and/or build research infrastructure to support translation of promising regenerative cell therapy into clinical studies [e.g., large animal cores, clinical research organizations (CROs), cell repositories]
- Develop improved imaging reagents and technology to track differentiation and cell fate at high resolution, both in vivo an in vitro

2. Improve opportunities for translational research in cardiovascular gene therapy.

- Develop cardiotropic and vasculotropic vectors (e.g., viral coat manipulations and/or tissue-specific promoters)
- Support National Gene Therapy/Vector Cores for access to high-titer research and clinical grade vectors
- Use cardiovascular delivery methodologies
- Develop non-viral, gene-based alternatives

- Encourage human-based immunological studies on the consequences of virus-mediated gene delivery

3. Exploit emerging high throughput technologies, such as systems biology, chemical genomics and automation to identify the signaling pathways that direct stem and progenitor cell proliferation, differentiation, maturation, survival, function, and trafficking.

- Explore activation of these pathways in disease progression and validate their use for human cardiovascular regeneration
- Continue support of multi-investigator, multi-disciplinary research
- Encourage development of transgenic animals with gene reporter or pathway biosensors
- Facilitate the development of high throughput assays and technologies

4. Integrate advances in the fundamentals of regenerative biology, nanotechnology, biotechnology and bioengineering to develop clinically feasible applications of tissue engineering in a true bench-to bedside sequence.

- Identify suitable cell sources, biomaterials, and cell-instructive strategies for specific application targets
- Foster the development of assays, bioreactors, automation methods, and functional testing including imaging, 3D tissue phenotyping, and animal models to accelerate strategies toward practical uses
- Promote translational approaches into true clinical applications, including tissue repair, replacement, and in vitro models of human disease for testing therapies and toxicities

5. Establish the required resources to enable clinical xenotransplantation in human cardiac and vascular disease.

- Target the production of genetically-altered, inbred swine with optimized characteristics as organ donors for humans
- Extend currently successful tolerance-induction regimens to xenogeneic organs
- Explore the feasibility of cardiac repair with xenogeneic and allogeneic cells

6. Facilitate clinical translation of NIH-supported pre-clinical discoveries in cardiovascular reparative and regenerative medicine, filling the gap between traditional R01 funding and Phase II human trials.

- Implement Centers of Excellence (P50) and Research Service Support Core Laboratories (P30, U24) to promote therapeutic innovations, establish the groundwork for preclinical development and human studies, directly support phase I studies, and disseminate essential enabling technologies
- Centers should be multi-disciplinary and built upon the best possible scientific team, drawing liberally across institutions and from non-US expertise, where justified
- Increase use of strategic supplements to fund the gap between discoveries and proofs of concept in relevant pre-clinical models, and the data needed by FDA and IRB's for successful IND applications
- Improve coordination between NIH and FDA to facilitate investigators' translation efforts (e.g., create an NIH-based regulatory division)
- Promote partnerships and collaborations between academic investigators and industry/biotech that are needed for clinical translation of novel therapeutic products

09/29/06

Business Operations
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Recommendations:

The WG discussed and prioritized the seven EPC recommendations:

1. **Create streamlined procedures for renewing grant**
2. **Funding and award recommendation**
3. **Create incentives and mechanisms for cross-Institute and Interagency**
4. **Issues related to CSR and study sections**
5. **Review the NHLBI pre-approval process for investigator-initiated grants**
6. **Create a mechanism to provide infrastructure support for large observational**
7. **Dissemination and communication of advances and discoveries**

Additionally, several new business practice areas were identified:

a. Attract new people, new ideas to regenerative medicine field by promoting multidisciplinary grant mechanisms.

- Linked R01s
- Multiple PI Option mechanism (NOT-OD-06-069)
- Establish NHLBI Biotechnology Research Partnerships based on the existing model for the Bioengineering Research Partnerships
- Close the gap between R01s and SBIR/STTRs, analogous to the one on directed differentiation of stem cells, for topics relevant to industry like cell imaging, delivery devices, and hands-off cell processing

b. Transition research from proof-of-concept in animals to phase I clinical studies.

- Utilize the R24, R21/R33, etc., for high-potential technology development
- Encourage industry and investor representation on new "applied science" study sections
- Use contracts, analogous to GMP facilities, to promote the availability of analytical services that are not widely available to investigators (e.g., proteomics, two-photon microscopy for electrical connectivity)

c. Explore ethical mechanisms of recovering a "return on investment" on successful licenses based on technology that NHLBI has funded.

- Percentage royalty on downstream licenses based on NIH-funded technology
- Equity stake
- Income to be incremental and to fund translational projects

d. Reconsider the role of the NHLBI intramural program in the context of the above recommendations.

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