Final Report
National Heart, Lung, and Blood Institute
Level 1 Strategic Planning Working Group
June 5-6, 2006

Cardiovascular Program – Theme # 8: From Discovery to Clinical Application

Introduction:

The application of basic science to clinical medicine provides the opportunity to identify the fundamental causes of human disease and provide improved approaches to disease prevention, diagnosis and treatment that can have important impact on the health of the nation. This working group discussed the opportunities and challenges of facilitating and implementing high impact translational research.

Recommendations:

1. Identify and validate targets and pathways that cause heart, lung and blood diseases and which can be manipulated for health benefit. Identification of highly validated targets will increase the likelihood of development and success of new therapeutics. NHLBI is uniquely suited to achieving these critical goals. New tools with enormous promise to this end have been developed and should be decisively exploited.

- Large-scale genome wide case-control linkage disequilibrium studies using well-matched disease cases and unaffected controls have great potential to identify genes and variants that contribute to or protect from disease susceptibility; rigorous replication of results will be necessary to provide convincing evidence that susceptibility factors have been identified. In addition, the study of rare extreme phenotypic outliers at both ends of quantitative distributions has the potential to identify new genes and pathways that can be exploited to improve health in the general population. NHLBI should be open to investigation of such outliers from unique populations from around the world and can catalyze investigation by establishing web sites for reporting patients with extreme or unusual phenotypes.
- Identified genes and pathways will be starting points for characterizing the physiologic mechanisms that link genotypes to disease endpoints.
    - Studies of humans stratified for risk genotypes have great potential to define disease pathophysiology and systems biology downstream of functional variants.
    - Development of new cell based and animal models based on susceptibility genotypes and development of chemical probes acting at identified targets will provide in vivo systems and tools useful for preclinical testing of new therapies.

2. Develop and validate suitable biomarkers of disease and non-invasive imaging techniques in humans and new animal models (e.g., in fish, fly, mouse, rat, dogs, pigs and non-human primates) that faithfully replicate human counterparts. These will provide important means to study pathways related to human diseases. These efforts include opportunities for comprehensive forward genetic screens in vertebrate and mammalian models. Particularly for atherosclerotic coronary disease, there is a pressing need for advances in non-invasive imaging that can accurately assess risk for myocardial infarction before and after therapeutic intervention- these have great potential to reduce the

need for clinical trials that rely upon clinical endpoints for the development of new therapeutic agents.

3. Devise effective new training programs to fill the vacuum in the workforce within the translational and physiological sciences and keep young investigators in the system:

- Human biologists (physician scientists) must be chaperoned to become effective leaders or members of translational research teams; support beyond KO8/K23 is crucial since many outstanding young investigators fail to obtain RO1 support before the end of KO8/K23 funding.
  - Suggested mechanisms: New grant mechanisms (Translational Investigator Awards) to provide salary support for translational and integrative scientists beyond KO8/K23 with review by an NHLBI special emphasis panel and/or institutionally awarded grants which would permit promise of support for the most promising investigators. Supplements to ongoing grants and programs. K-24 mid-career awards could be linked to CTSA. Start-up positions (Pioneer Awards) could be supported by NHLBI.
- A small minority of NIH-supported PhD trainees are currently exposed to areas of anticipated need and opportunity: computational sciences, basic physiology and patho-physiological sciences. NHLBI should encourage and support increased exposure of all PhD trainees in biomedical sciences to these areas.
- Develop consensus for the emergence and naming of a new discipline to capture the concept of translational science and its projection into the clinical domain. This will help attract trainees, focus institutional investment and amplify the impact novel interdisciplinary initiatives

4. Re-invent biomedical research teams. Real progress to understand the pathophysiology of human disease can be catalyzed by effective collaboration of experts in diverse areas (eg, clinical medicine, computational biology, and basic/integrative sciences). Fostering true interdisciplinary programs with expertise in these areas can advance several areas:

- Advanced methods of clinical and animal phenotyping for pathways explorations.
- Development of biomarkers to identify vulnerable populations. These can clarify pathophysiology by enabling study of more homogeneous populations and importantly can enable much more efficient clinical trials.

5. Support the development of new therapeutics. While the committee was skeptical of NIH efforts to develop small molecule therapeutics, there was consensus that NIH has a key role to play in development of new therapeutic modalities and devices. These include gene therapy, use of RNA interference, novel protein therapeutics, and drug delivery devices. NIH support through proof of concept studies with subsequent hand-off to industry seems the most useful model. In addition, it is apparent that there are orphan diseases that will not be pursued in industry and which will only be effectively addressed by either collaboration with industry (preferred approach) or independent small molecule development efforts.

6. Foster partnerships to improve interaction among extramural NHLBI-supported investigators, intramural NHLBI investigators and industry.

- Leverage unique resources of NIH/NHLBI intramural programs to support and facilitate translational studies in collaboration with extramural community (e.g., high end imaging of unique patient populations).

- NHLBI should develop ways to provide better access to biological materials (e.g. DNA, serum, biopsies) and data (e.g. phenotypes and genotypes) from NHLBI-funded studies to maximize the chance of new insights being made by investigators with new technological/analytic approaches.
- Samples from large clinical trials in industry or academia provide opportunities for academic advances of mutual interest. For example, extremes of the distribution of response to drugs in large trials can be pursued to define predictors of beneficial or adverse response and may identify targets for new development.
- NHLBI can better leverage its participation in clinical trials to increase transparency of design and analysis and ensure access to collected samples.

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Business Operations
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Recommendations:

The working group participants identified business operations and business practices where NHLBI could remove barriers and facilitate conduct of scientific priorities. The working group considered as highly important the following four recommendations:

1. Create incentives and mechanisms for cross-Institute and inter-agency funding of large projects

a. Develop mechanisms for detailed studies to follow up extreme responses to drugs found in academic or big pharmaceutical drug trials.
b. Partner with patient advocacy organizations (e.g., of rare diseases), and societies such as AHA, ACC, and ADA.

2. Funding and award mechanisms for translational research

a. Increase funding opportunities for junior faculty after the K-award stage.
b. Create new grant mechanism for translational and integrative scientists reviewed by NHLBI SEP.
c. Provide supplements to ongoing grants for translational research.
d. Link K24 mid-career award to CTSA.
e. Create awards to institutions for young clinical investigators in transition to be trained for translational research.
f. Promote pre-doctoral training programs that teach computational sciences, physiological and pathophysiological sciences.

3. Streamline and consolidate the regulatory review process for human research while protecting safety of subjects.

a. Ultimate goal: one federal, one local review body.
b. Consolidate resources to maintain quality, science-based review/decision processes.
c. Standardize contract language for multi-site trails and provide reciprocity for IRB approval and HIPAA compliance between institutions.
d. NHLBI consider going to protocol specific DSMBs.
e. NHLBI fund research to determine patient attitudes regarding their participation and protection related human research (e.g. privacy concerns versus personal risk factors). These studies should collect data according to gender and ethnicity.

4. Issues related to CSR and study sections.

a. Recruit more review expertise in integrative physiology and translational research
    - Create new study sections in integrative physiology and translational research (with expertise in physiology, computational sciences, genomics, proteomics, etc.), as a short term solution.
    - Include expertise in integrative physiology and translational research in all study sections, as a long term solution.

b. Develop incentives for senior investigators to serve on study sections, e.g., for each year served, increase one year of funding for current grant(s).
c. For easier review, cut the number of pages of all grant applications.

09/29/06