Final Report
National Heart, Lung, and Blood Institute
Level 1 Strategic Planning Working Group
May 11, 2006

Blood Program – Theme # 5: Acquired and Inherited Blood Diseases

Introduction:

The mission of the NIH in the next 10 years will be to make medicine more predictive, personal and preventive. To accomplish this several important questions must be addressed. First we need to determine how genes interact with one another thereby modifying severity and phenotype of complex and simple (single gene) disorders. Second we must go beyond genomics to understand how genes are turned off and on and how biologic systems (complex networks of genes) interact. Third we need to create a clinical trials system which is creative, agile and resourceful that will take discoveries from basic research to the bedside and into the community.

The DBDR research portfolio focused on acquired and inherited non-malignant hematologic disorders has developed the model systems to study these questions. The hematopoietic stem cell is an excellent model to study how genes are turned off and on during development and differentiation. The hemoglobinopathies offer wonderful examples of single gene disorders which are very heterogeneous in severity, presenting excellent opportunities for studying genetic modifiers. Hemoglobinopathies and other disorders (affecting hematopoietic cell lineages) allow one to study how the hematopoietic system interacts with vascular, inflammatory, and immune biologic systems and how the environment (infection, iron overload, and iron deficiency) can modify these systems. Finally curative therapies such as stem cell transplantation, gene therapy, and hemoglobin switching offer significant pathways to develop effective and curative therapies for blood disorders and other human diseases.

Recommendations:
The panel for acquired and inherited blood diseases recommends the following six areas of priority listed in order.

1. Training of new investigators in non-malignant hematology. A new award, the Research Career Development Merit Award, should be created to identify and train promising young investigators. Outstanding individuals finishing fellowships or K awards should be given these special Merit awards.. This award should be coupled with loan repayment. This new system should be based on interim evaluations by external panels of both the trainees and the mentors with clear benchmarks. Awards should be focused on trainee/mentor relationship and performance and not on overall institutional performance.

2. An expanded, coordinated and stable clinical trial system for blood diseases. This system will insure the smooth transition from basic science discoveries to Phase I, II, III and IV (outcomes and health services research) trials. Centers of Excellence which focus on successful transformation of basic research to Phase I and II trials need to be developed. A separate group of special centers, constituting clinical trials networks, should be responsible for Phase II to III and IV studies. Uniform and specific productivity metrics in each group need to be assessed and maintained. All Phase III

trials should incorporate outcomes and health services research parameters to insure that efficacy is translated to effective new therapies. Open access to infrastructure of these centers should be available to all NHLBI investigators. These centers may be disease specific or emphasize more general blood disease research.

3. Exploration of the source of human variation (genetic modifiers) in single gene disorders using sickle cell disease or thalassemia as models. A phenotype database coupled with a DNA resource bank needs to be developed which will allow accurate identification of genetic modifiers for better characterized phenotypes (stroke, frequent vaso-occlusive crisis, kidney and lung diseases, opioid addiction, etc). Such acquisition and analysis projects should also insure identification of predictors of clinical severity, which will be vitally important to make clinical trials more risk based.

4. Studying the interfaces between different biologic systems by examining the interactions of hematopoiesis, vascular biology, immunology, inflammatory states and iron metabolism. Using sickle cell disease or thalassemia as models, one can begin to understand how products of hematopoiesis interact with the endothelium, the inflammatory cascade and the immune system. Understanding the influence of environmental factors (infections, iron overload/deficiencies, etc.) on single gene disorders offers a powerful approach to studying the influence of acquired factors on these complex biologic systems.

5. Understanding how genes interact with each other and are activated or silenced. This problem can be approached by examining the molecular control of hematopoiesis (stem cell development, commitment, and differentiation). Fundamental basic research insights into gene interaction and epigenetic changes in gene expression are vital to our understanding and eventual manipulation of stem cells.

6. Expansion of basic research in gene therapy, stem cell biology and transplantation, and small molecules. This avenue of research offers the best chance of translating basic discoveries to curative therapies. Some progress has been made in all these areas, but continued support of basic investigation is needed to realize our ultimate therapeutic goals.

Current obstacles to achieving these goals are as follows:

1. Lack of existing cohesive clinical trials systems that can rapidly carry basic research to the bedside and the community.
2. Decreasing incentives for expanding the currently meager workforce of experts trained in non-malignant hematology.
3. Caps on individual grants that do not allow important questions to be answered by single or groups of investigators.
4. Restrictions preventing individual investigators from accessing archives of other centers' clinical trial database after completion of study.
5. Cumbersome nature of relationships between multiple NIH institutes with regard to sharing resources with academic centers and private industry.
6. Lack of centralized research cores for health science research, advanced imaging, laboratory assays, registries of research subjects, animal models, and templates for acquiring phenotype/genotype data.

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