Final Report
National Heart, Lung, and Blood Institute
Level 1 Strategic Planning Working Group
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## Blood Program – Theme # 2: Diagnosis and Treatment of Thrombotic Disorders

### Introduction:

More than 1 million cases of thrombotic disease occur each year in the USA, and approximately half of the population in the USA and Europe will eventually die from thrombotic occlusion. Thrombosis is a major complication of surgery and is closely intertwined with many important human diseases including atherosclerosis, obesity, infection, diabetes, sickle cell disease, cancer and autoimmune disorders. Normal physiologic processes, such as aging and pregnancy, are also associated with increased thrombosis risk. Despite advances in diagnosis and treatment, thrombosis remains one of the greatest challenges facing the US biomedical community.

NHLBI-funded research over the past 25 years has improved treatment of coronary artery and cerebral vascular thrombosis, and significantly reduced morbidity and mortality from myocardial infarction and stroke. These advances generally depend on technically demanding and expensive acute interventions, while only limited progress has been made toward correcting or preventing the underlying pathophysiology. Although a number of risk factors associated with thrombosis have been identified, this information has not yet yielded improved treatment or prophylaxis. Moreover, the treatment of venous thrombosis relies mainly on pharmacologic agents that have changed little during the past 50 years.

Research has identified the key genes, proteins and physiologic control systems required to prevent thrombosis. Many inherited clotting and bleeding disorders have been dissected at the molecular level and gene targeting approaches have provided animal models for human disease and powerful tools for examining gene interactions. However, fundamental questions remain to be addressed that provide unique opportunities to develop improved diagnostic and therapeutic strategies. In addition, recent progress in human genome research offers the potential for new insight into the genetic predisposition to bleeding and thrombosis.

### Recommendations:

**1. Study the initiation and regulation of thrombosis in primary vascular diseases and the mechanisms linking thrombosis to inflammation and tissue remodeling in other complex disorders.** The blood and cellular components of coagulation are intimately intertwined with inflammation, innate immunity, and angiogenesis. These links play critical roles in the pathogenesis of diverse diseases including cancer, bacterial and viral infection, sickle cell anemia, myocardial infarction and stroke. These mechanisms also contribute to thrombosis as an important complication of other common medical conditions, including aging, obesity, pregnancy and many surgical and pharmacologic therapies. Thrombosis research is thus inherently multidisciplinary, crossing many boundaries between institutes at the NIH, and interconnecting basic research and medical practice.

**2. Identify new biomarkers for thrombosis predisposition and response to therapy.** Expanding genomic and proteomic resources provide unprecedented opportunities to characterize inherited and environmental predispositions to thrombosis. These new data should be exploited to develop individually tailored therapies that optimize response and

minimize adverse events. To ensure that these goals are accomplished efficiently, appropriate infrastructures should be established for the design of clinical studies and trials that incorporate new basic information, and for collection and analysis of clinical samples to be shared among clinical and basic investigators.

**3. Exploit new therapeutic targets and interventional approaches identified through basic research on thrombosis and bleeding.** Future progress in translational and clinical thrombosis research will be critically dependent on continuing discoveries in the basic hemostasis and thrombosis laboratory, including studies of the structure and function of key protein components, biochemical mechanisms, and the control of platelet and endothelial cell function. Advances in stem cell biology, gene therapy, proteomics, RNA interference, chemical biology and other emerging technologies also provide exceptional opportunities to develop new therapeutic approaches for thrombotic disorders.

**4. Define the critical factors determining vascular bed heterogeneity and their contributions to hemostasis and thrombosis.** Blood vessels in different locations display extraordinary heterogeneity in caliber, cellular composition, and patterns of blood flow. The genetic and environmental factors contributing to venous, arterial or microvascular thrombosis and to localization of disease in the myocardial, carotid, or peripheral vasculature are clearly distinct, as are the responses to treatment. A clear picture of vascular heterogeneity is critical to understanding and treating many important human diseases.

**5. Develop improved animal models for arterial and venous thrombosis and exploit novel model systems in lower organisms.** Transgenic and gene targeting technologies have generated faithful mouse models for many important single gene human disorders, and a few models have also been developed in larger animals. However, it has proven more difficult to study complex human diseases such as thrombosis and atherosclerosis in mice. More sophisticated animal models and technologies for studying them are needed to provide insights into normal physiology and disease pathogenesis. Such models would also facilitate the development of new therapies. In addition, powerful model systems in lower organisms may provide unique opportunities to discover new pathways and mechanisms that also function in higher animals and humans.

**6. Develop improved imaging technologies and better laboratory assays for the diagnosis and management of thrombotic and bleeding disorders.** Despite remarkable progress in the understanding of disease pathogenesis and the development of therapeutic approaches that have improved mortality and morbidity, the clinical tools available for direct visualization of thrombi and the laboratory assessment of thrombotic and hemorrhagic risk have lagged significantly. Improved methods for imaging an evolving thrombus, as well as sensitive laboratory tests to detect and monitor clot formation and dissolution, are needed and would markedly improve the diagnosis and management of patients with thrombosis.

To achieve the scientific goals outlined above, it will be critical to balance expenditures for the generation of new resources with the need to protect the funding for investigator-initiated research that has been at the heart of NHLBI's success over the past 25 years. It is also vitally important to expand support for the training of basic and clinical scientists specializing in thrombosis and hemostasis, to ensure that the pipeline of new investigators is maintained. The creation of integrated training programs and centers for thrombosis biology and medicine may be a particularly useful approach to facilitate these goals.

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