Final Report
National Heart, Lung, and Blood Institute
Level 1 Strategic Planning Working Group
June 29, 2006

Blood Program – Theme # 1: Critical Role of Inflammation in Ischemic Disorders

Introduction:

Ischemic disorders remain the leading cause of mortality and morbidity involving heart disease, stroke and thromboembolism. In addition, there is mounting evidence that the major national health concerns of today, such as diabetes and obesity, exert some of their serious adverse effects through biological processes that are related to cardiovascular diseases involving thrombosis. The NHLBI is the principal Institute responsible for maintaining and promoting public health in this critical area. Current antithrombotic drugs often suffer from the risk of potential bleeding. The pathways leading to thrombosis in ischemic areas may diverge from physiologic hemostasis and offer novel approaches to control without increased risk of bleeding. Organ-, vascular bed -, and disease-specific features of the inflammation/coagulation nexus can be exploited to diagnose at-risk sites in the presymptomatic phase and target treatment with improved risk:benefit over current systemic anticoagulation.

Inflammation contributes to chronic atherosclerotic vascular damage, acute thrombosis, and the acute / subacute changes associated with ischemia/reperfusion injury. Both humoral and cellular factors are involved. Examples of cellular involvement include the ability of activated platelets to initiate the inflammatory response, activated inflammatory cells to synthesize tissue factor and thrombin, and circulating platelet-leukocyte aggregates to serve both as a biomarker and contributor to acute vascular injury. The endothelium participates by regulating proinflammatory, prothrombotic, and anticoagulant proteins. Moreover, in the microvasculature, leukocytes can contribute to vascular occlusion as observed in animal models of sickle cell disease and after ischemia/reperfusion injury. The inflammatory mediators influence not only cell number, but also phenotype including the cellular responsiveness to mediators. The inflammatory process likely alters metabolic control that itself augments the inflammatory process. As the disease processes progress, either acutely or chronically, reperfusion injury may further perturb normal cellular functions, particularly in the microcirculation. In addition to the coronary and cerebral circulation, other organs like the eye, lower extremities, kidney and lung are also targets of inflammatory mediator damage. Loss of normal regulatory functions of these sites may exacerbate thrombotic disease progression.

To better diagnose and treat the development of ischemic disorders, the working group believes that it is vital to develop an improved appreciation and a comprehensive understanding of the following areas: (1) the initiation and regulation of inflammation, (2) the vascular bed-specific effects of inflammation, (3) the interface between inflammation and other blood cellular elements and fluid phase systems, (4) the contributions of inflammation to both acute and chronic events. There is an urgent need for improved animal models and new analytic approaches that bridge basic and clinical investigations. The group identified stroke, myocardial infarction, obesity / metabolic syndrome, deep vein thrombosis, acute and chronic lung disease, peripheral arterial disease and sickle cell disease as being of special importance based on their prevalence, the clinical need for improved therapy, and/or the value of the illness as a model system. Recognizing the need to validate therapeutic

targets as proof of concept, develop biomarkers and surrogate end points and make the link between therapeutic intervention and modification of disease processes, it is essential to establish a Clinical and Basic Science Net Work on Inflammation and Atherothrombotic Diseases that will collaborate with the industry and FDA.

Recommendations:

1. Study the initiation and regulation of inflammation in ischemic disorders: The inflammatory and thrombotic processes are intimately linked by fundamental mechanisms and one impacts on the other. Defining the conserved points of interface between the metabolic, inflammatory and thrombotic systems that evolved to cope with nutritional, traumatic, infectious and environmental stress may allow identification of targets for prevention / treatment of atherothrombotic disorders. The areas of emphasis are: (i) the basis of inflammation in the vasculature and its regulation, (ii) the role of inflammation in the atherothrombotic complications of diabetes, obesity, and smoking, (iii) the contribution of platelets to inflammation and its vascular complications, and (iv) the endogenous protection mechanism against inflammation-induced injuries.

2. Define the vascular bed – specific effects of inflammation in atherothrombosis: The vascular beds in the body are heterogeneous and have distinct structure and function. It is critical to understand how inflammation regulates atherosclerosis, thrombosis, and bleeding in different vascular beds in order to define the organ-specific diseases in the heart, brain and lower extremities.

Study the interface of inflammation with other blood elements and fluid phase: Vascular integrity is compromised in an inflammatory environment and the blood coagulation and fibrinolytic components are exposed to receptors and interactions in the extravascular tissues that remain unknown as for example in sepsis and stroke.

3. Establish the relative contributions of acute vs chronic inflammation: The mechanism, impact and clinical manifestations of inflammation in ischemic disorders are time and context dependent. Although there is no mechanistic explanation, it is known that age, obesity and sex are critical risk factors for venous thrombosis. There is a need to study the role of inflammation in the context of age, gender and timing in temporal relationship to the disease process. Another area that needs better understanding is the propagation of injury, repair and tissue remodeling in ischemia – reperfusion focusing on the interplay between the coagulation and fibrinolysis.

4. Develop better animal models of inflammation in atherothrombosis and enabling technologies: The current mouse models (ApoE, LDLR) do not adequately reflect the complex process of atherothrombosis in humans. An important need is to develop better animal models that more accurately reflect the disease in humans and provide enabling technologies for cell- and tissue-based analyses, and bioinformatics.

5. Establish a network on basic and clinical research on anti-inflammatory therapy of ischemic disease: Inflammation plays a critical role in the initiation, progression, and complications of atherothrombosis. Despite this importance and the availability of promising agents, we have no therapies that specifically target inflammation. A priority need is to establish a basic science and clinical network to analyse relevant animal models, conduct pilot clinical research on existing anti-inflammatory agents and develop new therapeutic targets. Both basic and clinical investigators will participate in mechanistic studies,

developing imaging modalities, creating sample banks, and validating surrogate end points and biomarkers. The network will design and execute pilot studies on safety and efficacy of novel agents while simultaneously testing basic mechanisms; developing imaging modalities, creating banks of plasma, cells and genetic materials, and validating surrogate end points and biomarkers that can facilitate future studies. The network will provide an ideal environment for multidisciplinary training of basic scientists and physician-scientists.

09/29/06