Final Report
National Heart, Lung, and Blood Institute
Level 1 Strategic Planning Working Group
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Blood Program – Theme # 4: Global Blood Safety and Availability

Introduction:

Blood transfusion is one of the oldest and most widely employed modern medical therapies. Transfusion may favorably or unfavorably alter the clinical outcomes of other therapies such as transplantation, surgery and medical treatment of malignancies. Nonetheless, there are many aspects of blood transfusion biology whose clinical utility and scientific basis are poorly understood.

The two most prominent unresolved issues in transfusion biology are the immunologic consequences of transfusion and the physiology of red cell transfusion. While the infectious risks have been managed to a large extent through donor screening, the immunologic effects of transfusion are poorly defined at both a basic and clinical level. If one views transfusion as a "mini-transplant" or a large bolus of cellular and soluble foreign antigen, it would be surprising if immune consequences did not occur. Such immunologic changes occur far more commonly than infectious complications of transfusion yet the nature, extent and clinical relevance are unknown. Red cell transfusion has been an empiric therapy for more than 80 years with consequences that remain poorly understood. More than 12 million units of red cells are transfused each year in the US with a fundamental lack of understanding of their physiologic consequences, their adverse cellular or tissue effect, or their appropriate clinical use. Clinicians cannot form any meaningful risk: benefit analysis for transfusion. These questions, while not new, have been difficult to study previously due to lack of needed technologies, animal models, or sufficient understanding to design relevant laboratory or clinical studies. New technologies such as genomics, proteomics, assays of gene regulation and expression, tissue imaging and nanotechnology sensors coupled with advances in the understanding of immunology, thrombosis and inflammation provide new opportunities to make major advances in transfusion biology and ultimately evidence based clinical practice. We have a unique opportunity to dramatically improve transfusion practice and positively impact patient health, reduce transfusion-transmitted infectious disease in less developed countries, increase blood collection and availability, and develop alternatives to standard allogeneic transfusions.

Recommendations:

1. Define the Immunobiology and Immune Consequences of Transfusion.
The effects of transfusion on host immune function the most common and clinically significant complications of current transfusion therapy. Immune effects include alloimmunization, tolerance, immunosuppression, and microchimerism with a likely broader impact on thrombosis, hemostasis and inflammation. The biology of the immune effects, the nature and extent of these effects, and the clinical impact are poorly understood. New tools and techniques allow broad monitoring of alterations in gene expression with transfusion, accurate measurements of biologic response modifiers, and development of relevant animal models to address these issues. These studies of transfusion consequences will also serve as models for similar investigations of other cell therapies and also lay the groundwork for immunologic acceptance of those therapies.

2. Define the biology and clinical indications for red cell transfusion.
Red cells are the most commonly transfused blood component in the US. However, little is known about the physiology of red cell transfusion and oxygen delivery at the cell or tissue level. The impact of component factors including storage age, leukocyte content, platelet and plasma content, and anticoagulant/preservative on the function of transfused red cells at physiologic or clinical levels are largely unexplored. The role of recipient factors, both genetic and acquired, on the physiologic benefit and adverse consequences of red cell transfusion need investigation. New imaging techniques, nano-oxygen sensors, mitochondrial assays and gene/protein tissue responses to transfusion provide opportunities to understand the physiology of red cell transfusion and obtain data needed to develop clinical trials which will establish evidence based clinical indications.

3. Promote initiatives to reduce infectious disease transmission (*International*).
Transfusion transmission of established pathogens (HIV, HCV, HBV, malaria) frequently occurs in less developed countries. This problem is largely preventable using available screening methodologies. Developing countries may represent important sites for monitoring the entry of new and emerging infectious agents into the blood supply, which have important implications for the safety of the US blood supply. The development of screening approaches that are applicable to these countries, as well as to establish donor-recipient repositories and sentinel sites to monitor for infectious agents, would have a high impact on these problems

4. Increase blood collection and availability (*International*).
The availability of transfusable blood is grossly inadequate to meet the needs of patients in many less developed countries, in part due to low donor recruitment and high infectious disease rates. Behavioral/outcomes research approaches to study mechanisms to identify and recruit low-risk donor and to accurately forecast blood supply and utilization could significantly improve this situation.

5. Develop alternatives to standard allogeneic donor blood (*International*).
Inadequate supplies of safe blood could be largely alleviated by research efforts to develop alternatives to standard donor blood. Alternatives could include whole blood that is subject to inexpensive and effective pathogen inactivation strategies, blood substitutes (hemoglobin- and nonhemoglobin-based), and pharmacological agents. Development of these strategies would also have important implications for the safety and availability of blood transfusions in the U.S.

6. Establish the scientific basis for a valid and effective national biovigilance program.
The US is the only major industrialized nation without a systematic method for identifying and analyzing complications resulting from transfusions, cellular therapies, tissues, and new biologics. It is critical to identify emerging safety issues and monitor the effectiveness of safety measures. Studies are needed to define the elements of a scientifically valid program.

Enhance training in transfusion medicine.
Fewer and fewer hematology trained internists and pediatricians enter the field of transfusion medicine. These specialties have provided many of the leaders in the field currently and in previous generations. There is need to enhance training opportunities in both clinical and research aspects. We believe that the K12 funding program is a critical component to training needed researchers in transfusion medicine.

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