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Mark Yazer

Genetically Engineered Pigs as a Source for Clinical Red Blood Cell Transfusion 365

David K.C. Cooper, Hidetaka Hara, and Mark Yazer

The transfusion of animal blood or red blood cells (RBCs) into humans goes back to 1667, and the practice persisted until the early 1900s. In recent years, in part because of the shortage of acceptable and safe human blood worldwide, there has been renewed interest in the possibility of using genetically-engineered pigs as sources of RBCs for clinical transfusion. Pigs are becoming available in which the cells, tissues, and organs are to some extent protected from the human immune response. This extends significant protection from antibody-mediated complement lysis. Transfusion of these RBCs into nonhuman primates, however, indicates that they are rapidly lost from the circulation, almost certainly through the phagocytic activity of macrophages. Further genetic manipulation may resolve this problem. In view of the potential advantages of pig RBCs with regard to the absence of infectious microorganisms and the rapid progress being made in genetically modifying pigs, pig RBCs may eventually become a feasible source of blood for clinical transfusion.

Setbacks in Blood Substitutes Research and Development: A Biochemical Perspective 381

Abdu I. Alayash

Recent setbacks in using Hb-based technology to develop oxygen carriers or blood substitutes may spur new and fundamentally different approaches for the development of a new generation of hemoglobin-based oxygen carriers (HBOCs). This article briefly details some underlying mechanisms that may have been responsible for the adverse-event profile associated with HBOCs, with a focus on the contribution of the author's laboratory toward identifying some of these biochemical pathways and some ways and means to control them. It is hoped that this will aid in the development of a safe and effective second generation of HBOCs.

From Stem Cell to Red Blood Cells In Vitro: "The 12 Labors of Hercules" 391

Luc Douay

This article describes the research in progress that will permit the large-scale production of human red blood cells from hematopoietic stem cells. It also discusses the current state of this research, suggests the obstacles to be overcome to pass from the laboratory model to clinical practice, and analyzes the possible indications in the medium and long term. The potential interest of pluripotent stem cells as an unlimited source of red blood

cells is considered. If it succeeds, this new approach could mark a considerable advance in the field of transfusion.

The Three "R"s of Blood Transfusion in 2020; Routine, Reliable and Robust

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Stewart Abbot

To predict the timing and nature of future changes in the practice of blood transfusion, several factors must be considered. The historical rate of change of a scientific field can often provide a rough guide to the rate of future progress. To improve the accuracy of these predictions, historical rates must be adjusted to take into account the decelerating effects of technological or methodological barriers to progress, together with the potentially accelerating effects of transformative technology breakthroughs and unmet needs in the field that act as drivers for change. The cumulative impact of unpredictable and, often, limited availability of traditional blood donors, increasingly elderly populations, the potential for storage-associated adverse events, and increasingly prevalent transfusion-transmittable diseases is likely to provide significant drive to develop transformational alternatives to current transfusion practices. Considering the current stage of development of stem cell-based therapeutics and the rates of change in clinically compatible bioreactors and cell sorting systems, it is reasonable to believe that stem cell-based *ex vivo* manufacture of blood components will become routine, robust, and reliable within the next decade.

Future of Molecular Testing for Red Blood Cell Antigens

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Joann M. Moulds

When one looks at the field of molecular pathology or transplantation, it is evident that molecular biology has made a positive impact on medicine. However, the progress in transfusion medicine has been slower and more cautious than in other areas of the clinical laboratory. To understand where the field may go in the next 10 years requires that the reader understand what technology is available now. Therefore, this article discusses the current state of the art for red-cell genotyping and newer, ever-evolving molecular technologies. Because it is impossible to present all of the molecular techniques and their variations in this article, the author selects a group of methodologies to review and speculates where the field of molecular immunohematology may be in 2020.

Noninvasive Fetal Blood Grouping: Present and Future

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Geoff Daniels, Kirstin Finning, and Pete Martin

Identification of the molecular basis of the D polymorphism of the Rh blood group system in the 1990s made it possible to predict D phenotype from DNA. The most valuable application of this has been the determination of fetal D type in pregnant D-negative women with anti-D. Knowledge of fetal D type reveals whether the fetus is at risk of hemolytic disease of the fetus and newborn so that the pregnancy can be managed appropriately. Noninvasive fetal D typing for D-negative pregnant women with anti-D, performed on the small quantity of fetal DNA present in the blood of pregnant women, is now routine practice in several European countries. Noninvasive fetal blood

grouping for C, c, E, and K also may be provided as a routine service for alloimmunized pregnant women. In many countries, all D-negative pregnant women are offered anti-D prophylaxis antenatally, yet in a predominantly Caucasian population, about 38% will be carrying a D-negative fetus and will receive the treatment unnecessarily. Large-scale trials to ascertain the accuracy of high-throughput, automated methods suggest that fetal D screening of all D-negative pregnant women is feasible, and it is likely that fetal D screening in D-negative pregnant women will be policy in some European countries within the next few years.

Current and Future Cellular Transfusion Products

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Monique P. Gelderman and Jaroslav G. Vostal

Novel red blood cell and platelet transfusion products may be synthetic or may result from modifications to approved collection, processing, and storage procedures for existing cellular products. They must be reviewed and evaluated by the Food and Drug Administration before being legally marketed in the United States to ensure they are safe, pure, and potent. This article reviews the literature and discusses the current and future state of cellular transfusion products.

The Future of Blood Management

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Jonathan H. Waters

An evolving understanding of the consequences of allogeneic blood transfusion and escalating costs of providing allogeneic blood have resulted in an interest in blood management. Understanding the consequences of allogeneic transfusion includes a recognition of the immunosuppressive effects of allogeneic transfusion, a growing awareness of transfusion-related acute lung injury, and a rediscovery of transfusion-associated circulatory overload. More recently, interest has focused on the effect of stored blood on patient outcome. Although this discussion is not all-inclusive, it is intended to show that many techniques can be applied to decrease the exposure to allogeneic blood.

Recent Developments and Future Directions of Alloimmunization to Transfused Blood Products

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James C. Zimring

Monitoring and managing alloimmunization are among the primary functions of the clinical transfusion medicine laboratory. However, despite hundreds of different blood group antigens that vary from person to person, only a minority of transfusion recipients become alloimmunized. Currently, there are no tests that predict which patients will become alloimmunized. Moreover, there are no therapeutic interventions to prevent alloimmunization (outside of RhD immune globulin) besides phenotypic matching. Understanding the biologic factors that regulate alloimmunization may allow the generation of clinical tests with predictive capabilities and provide a rational basis for developing therapeutic interventions. This article

summarizes recent advances in understanding alloimmunization, with a focus of identifying future directions in laboratory testing and management of transfusion. In addition to analyzing humoral alloimmunization, potential extensions of transfusion medicine to sequelae of cellular immunization are explored.

The Platelet Storage Lesion

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Dana V. Devine and Katherine Serrano

The gradual loss of quality in stored platelets as measured collectively with various metabolic, functional, and morphologic *in vitro* assays is known as the platelet storage lesion. With the advent of pathogen reduction technologies and improved testing that can greatly reduce the risk for bacterial contamination, the platelet storage lesion is emerging as the main challenge to increasing the shelf life of platelet concentrates. This article discusses the contribution of platelet production methods to the storage lesion, long-established and newly developed methods used to determine platelet quality, and the significance for clinical transfusion outcome. Highlighted are the novel technologies applied to platelet storage including platelet additive solutions and pathogen inactivation.

Governance in the European Union: The European Blood Directive as an Evolving Practice

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Hannes Hansen-Magnusson

This article reconstructs governance practices related to blood policy that have developed within in the European Union (EU) over the last 15 years. It describes core aspects of the policy and argues that, despite an integrated cooperative approach between policy-makers and practitioners, this policy remains an open and evolving process. The European Blood Directive (2002/98/EC) and its subsequent directives managed, for the first time, to create an overarching framework for transfusion procedures. This framework consists of a number of standard definitions as well as detailed standard operating procedures, yet leaves room for interpretation and different practices between EU member states. A recently published report on the progress of transposition of the Directives into national legislation reveals different standards, suggesting a lack of uniformity of safety and quality requirements. Further, gaps in the directives amount to practical medical problems, while increased mobility among EU citizens may add further problems to achieving the objective of a self-sufficient supply of blood and blood products. This might undermine public confidence in the quality of blood products and the health protection of donors, which, in turn, must be countered by a cooperative effort of policy-makers and blood establishments.

Emerging Pathogens in Transfusion Medicine

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Roger Y. Dodd

Although the risk of infection with hepatitis and human immunodeficiency viruses from blood transfusions has been reduced to negligible levels,

emerging infections continue to offer threats. Such threats occur with any infection that has an asymptomatic, blood-borne phase. In the past, it was thought that any emerging transfusion-transmitted disease would have epidemiologic properties similar to those of AIDS or viral hepatitis. Over the past 20 years, however, greatest concern has arisen from variant Creutzfeldt-Jakob disease, West Nile virus, and Babesia. These and other emerging infections are discussed in the context of blood safety.