COMMENTARY

National Blood Foundation 2021 Research and Development summit: Discovery, innovation, and challenges in advancing blood and biotherapies

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Over the last 75 years, the Association for the Advancement of Blood and Biotherapies (AABB) has been advancing blood and biotherapies through professional development, the establishment of standards, and the accreditation of facilities. In 1983, AABB expanded its vision and contribution to advance research, through its National Blood Foundation (NBF). Its early-career grant program has funded more than 200 investigators, many of whom have blazed the trail to become subject matter experts in the field of transfusion medicine, cellular therapies, and regenerative medicine science. Industry contributors represented by the Council on Research and Development (CORD) and other partners are key for financial contribution, engagement, and direction.

Despite AABB’s advocacy, innovations have been incremental, primarily due to risk tolerance, resources...
| Advancement | Year | Significance |
|-------------|------|--------------|
| **Polymerase Chain Reaction (PCR) methodology for nucleic acid capture and amplification** | 1983 | - Laboratory methodology to capture and amplify nucleic acid led to early detection of TTIDs before immune response detected by serology  
- 1993 Nobel Prize in Chemistry Drs Karry B Mullis and Michael Smith for contributions to the development of methods within DNA-based chemistry |
| **Hepatitis C Virus (HCV) as the etiological agent of non-A, non-B hepatitis** | 1989 | - Non-A, non-B virus was first discovered by scientists from Chiron collaborating with CDC  
- 2020 Nobel Prize for Physiology or Medicine awarded to Drs. Harvey J. Alter, Charles M. Rice, and Michael Houghton |
| **Human Immunodeficiency Virus (HIV) as the etiological agent of acquired immunodeficiency syndrome (AIDS)** | 1984 | - Dr. Robert Gallo (National Cancer Institute, NIH), Dr. Luc Montagnier (Pasteur Institute in Paris), and Jay Levy (University of California, San Francisco) attributed to the discovery of HTLV-III as the etiological retrovirus of AIDS  
- 2008 Nobel Prize in Physiology or Medicine – HIV discovery to Drs Montagnier and Francoise Barre-Sinoussi |
| **Hepatitis B Virus (HBV) Vaccine** | 1969 | - Drs Blumberg and Millman developed the first heat-treated vaccine 4 years after Blumberg's discovery of the Australia Antigen as the etiology of HBV. FDA approved a plasma-derived HBV vaccine for human use in 1981. Blood establishments began testing for HBV in 1971 and were mandatory in the USA (1972)  
- 1976 Nobel Prize for Physiology or Medicine - Dr. Blumberg |
| **Advances in infectious disease donor screening for HIV, HBV, HCV** | 1972 | - HBV: Anti-HBsAg mandatory screening in USA (1972)  
- HIV: Anti-HIV ELISA (1985)  
- Surrogate testing for Anti-HBc and ALT (1986–87) voluntary in the USA  
- HCV: Anti-HCV EIA (1990)  
- NAT: Donor screening initiated for HIV, HBV, and HCV in Germany (1997) |
| **Genetic/biochemical interrogation and elicitation of blood groups** | 1990's | - Multiplex polymerase chain reaction and DNA microarray hybridization  
- International Society of Blood Transfusion (ISBT) Working Party for Red Cell Immunogenetics and Blood Group Terminology recognizes currently 43 blood group systems genetically determined by 48 genes; 345 red cell antigens (June 2021) |
| **Recombinant growth factors** | 1983 | - Erythropoietin (EPO) – stimulates erythropoiesis; isolated in 1977; gene decoded 1985; FDA approved 1993  
- Granulocyte colony-stimulating factor (G-CSF) first recognized and purified in Australia (1983); bind to hematopoietic cell surface receptors to stimulate proliferation and differentiation  
- Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) - hematopoietic growth factor; FDA approved 2020 |
| **Peripheral blood – Stem Cells (CD34) collection** | 1990's | - Peripheral blood progenitor cells mobilization and collection by apheresis  
- Marrow reconstitution |
| **Gene manipulation** | 1987 | - First chimeric antigen receptor and coding implanted in T cells (CAR-T)  
- Advances in gene therapy for the potential cure of Sickle Cell Disease, thalassemia, and Severe Combined Immune Deficiency (SCID) |
| **Immunosuppression** | 1980's 1990's 2019 | - Successful use of cyclosporine in kidney transplantation (first used 1978–79)  
- Tacrolimus as an immunosuppressive agent in transplantation (1995)  
- Rituximab in common variable immunodeficiency |
These understood limitations to high-risk–high-reward transformations may require a risk-tolerant ecosystem of academic, clinical, corporate, and government partners. To explore current innovations, ecosystems, and challenges, the NBF of the AABB hosted an inaugural research and development (R&D) virtual summit over 3 days for an hour a day, October 17–19, 2021. The Summit focused on:

- Advances in transfusion medicine over the last 40 years that improved practice and patient outcome;
- Highlighted innovation in blood and biotherapies;
- Newly sponsored programs to invest in next-generation blood products and innovations in trauma; and
- Exploration of the greatest challenges facing the blood and biotherapies fields and innovations to address these challenges.

There have been significant discoveries and innovations over the last 40 years that have impacted the state of the science in immunohematology, transfusion medicine, and biotherapies (see Table 1). Prevention of transfusion-transmitted infectious diseases (TTID) through donor screening has driven safety advancements in blood, organ, tissue, and cellular therapies.\(^1\)–\(^3\) Development and public health advocacy of hepatitis B virus (HBV) vaccine, as well as the identification of human immunodeficiency virus (HIV), and hepatitis C virus (HCV) have significantly impacted blood safety. First tackled through non-renumerated whole blood donations and high-risk donor interview questions, testing significantly reduced TTIDs. Generational advancements in serological detection and development of polymerase chain reaction (PCR) amplification methodology closed the gap between infection and detection.\(^4\) Nobel Laurates have been honored for the HBV vaccine, PCR development, HIV as the etiologic agent of acquired immunodeficiency syndrome (AIDS), and the discovery of HCV as the etiologic agent of non-A, non-B hepatitis.\(^5\)–\(^8\)

Advancements in the use of Rh immune globulin (Rh Ig) and pre-storage universal leukoreduction (ULR) are worth noting. At first, Rh Ig was used as a postpartum therapy in eligible women at risk of Rh alloimmunization from an Rh-positive fetus or newborn.\(^9\) Protocol modification to include antepartum administration has been significant to reduce Rh alloimmunization and the risk of hemolytic disease of the fetus and newborn (HDFN).\(^10,11\) Likewise, the use of pre-storage leukoreduction, though slow to achieve universal acceptance, has significant benefit to reduced adverse events of transfusion at an incremental cost.\(^12,13\)

Advances in the 21st century have been primarily attributed to scientific knowledge at the molecular level of cells.\(^14\)–\(^18\) This has contributed to early advancements of recombinant growth factors, gene manipulation for cellular therapies, and molecular interrogation of blood systems.\(^19,20\) Process improvements in apheresis have also contributed to the ability to collect human peripheral blood progenitor cells and other starting materials for biotherapies.\(^21\) Incrementally these discoveries continue to advance the safety and availability of blood and biotherapies.

| Advancement                              | Year | Significance                                                                 |
|------------------------------------------|------|-----------------------------------------------------------------------------|
| Universal Pre-Storage Leukoreduction     | 1996 | • Pre-storage leukoreduction reduces the risk of HLA alloimmunization, CMV transmission, febrile non-hemolytic transfusion reactions, post-operative infections, and cardiac surgery mortality |
|                                          |      | • FDA guidance was first issued in 1996                                    |
| Antenatal RhIg                           | 1978 | • Rh immune globulin (RhIg) for management of Rh-negative women with Rh-positive fetus to reduce risk of alloimmunization and hemolytic disease of the fetus and newborn |
|                                          |      | • Antenatal prophylaxis with RhIg to reduce risk of Rh immunization during pregnancy |

**Table 1** (Continued)

**Commentary**

Advances in transfusion medicine over the last 40 years have improved practice and patient outcome; highlighted innovation in blood and biotherapies; newly sponsored programs to invest in next-generation blood products and innovations in trauma; and exploration of the greatest challenges facing the blood and biotherapies fields and innovations to address these challenges.

Table 1 shows the advancements and year of significance:

- **Universal Pre-Storage Leukoreduction**: 1996
  - Pre-storage leukoreduction reduces the risk of HLA alloimmunization, CMV transmission, febrile non-hemolytic transfusion reactions, post-operative infections, and cardiac surgery mortality
  - FDA guidance was first issued in 1996

- **Antenatal RhIg**: 1978
  - Rh immune globulin (RhIg) for management of Rh-negative women with Rh-positive fetus to reduce risk of alloimmunization and hemolytic disease of the fetus and newborn
  - Antenatal prophylaxis with RhIg to reduce risk of Rh immunization during pregnancy

**Abbreviations**: CDC, Centers for Disease Control and Prevention; ELISA, enzyme-linked immunosorbent assay; FDA, Food and Drug Administration.

**1 | Innovative Diagnostic and Therapeutic Products**

**1.1 | Erythrocyte membrane modification with peptide and glycan epitopes**

Cell surface modification with designer epitopes has potential as diagnostic, therapeutic, and R&D tools. Such modification to the erythrocyte has been done by Kode technology using Functional head, Spacer, and Lipid (FSL) constructs.\(^{22-25}\) The lipid is necessary for integration into the cell membrane while the different spacers facilitate a variety of conformational and functional properties. The functional head of peptide epitopes...
is typically less than 20 amino acids and specifically selected to represent the most antigenic regions of a protein; which improves both sensitivity and specificity. Intriguingly, kodycyte with peptide epitopes react better with IgG than with IgM antibodies. Over 200 functional Kode constructs have been created using carbohydrates, peptides/proteins, and labels (such as biotin, fluorophores, metals, DNA, and radiolabels).

In immunohematology, kodycytes have been used to quality control weak expression of A and B antigens using FSL-A and FSL-B and are suitable for quantification ABO antibodies in undiluted plasma. Glycan and peptides kodycyte panels have also been developed for the identification of various blood groups (i.e., Lewis, FORS, and Miltenberger) and as indicators for diagnostic detection of organisms (Treponema pallidum, leptospira, babesia protozoa, cytomegalovirus, Trypanosoma cruzi, and SARS-CoV-2).  

1.2 | Human platelet lysates for cell therapy and regenerative medicine

Human platelet lysates (HPL) from outdated platelet concentrates are an animal-origin-free substitute for fetal bovine serum (FBS) in manufacturing a variety of cell-based products for regenerative medicine. Large-scale pooling of HPL and use in good manufacturing practice (GMP) laboratories for human primary cell propagation of mesenchymal stem cells and other cells, highlights the requirement for standardization in cell expansion to support safety, efficiency, efficacy, and potency. Since pooled HPLs are not routinely subjected to robust viral removal steps like plasma-derived medicinal products (PDMP), there is a risk that expanded cells propagated in HPL may be contaminated with pathogens that could be transmitted to the recipient of cellular therapy. As pooled HPL is increasingly used as a substitute for FBS, it is evident that similar safety nets such as those used for PDMP need to be established. This includes a GMP environment with donor epidemiology, donor screening, pathogen reduction of the platelet concentrates, when implemented, manufacturing pool testing, viral inactivation, or removal during the HPL process, and traceability.

A solvent/detergent (S/D) treatment process for HPL, capable of inactivating lipid-enveloped viruses, was reported over a decade ago. Expansion of adipose tissue-derived mesenchymal stromal cells (AT-MSC) using S/D-treated HPL has been reported as good as or better than FBS based on the International Society of Cell and Gene Therapy (CGT) criteria. Nanofiltration, similar to that used in plasma fractionation has also been reported to provide over 5 log reduction of non-enveloped viruses as well as the removal of extracellular vesicles.

Table 2 highlights the numerous trophic factors associated with viral-inactivated human platelet lysate (HPL). To pursue the regenerative concept of HPL, a tailor-made purified human platelet pellet lysate (HPPL) has been developed for neurologic treatment and is in pre-clinical testing as an intranasal or intracerebroventricular drug. This requires a target HPPL product profile with low protein, fibrinogen-depleted, free of coagulation and thrombogenic factors, no proteolytic activities, and virally-reduced. This HPPL provides strong neuroprotection of Lund human mesencephalic (LUHMES) cells against various neurotoxins, as well as in a mouse model of Parkinson’s disease. The use of pathogen-reduced platelet concentrates to produce HPPL has been investigated as well with similar results. These were non-toxic, non-inflammatory, and promote wound healing of neuronal cells and neuronal differentiation. In traumatic brain injury (TBI) mouse models using topical and intranasal delivery, the HPPL improved motor and cognitive functions while decreasing neuroinflammation and oxidative stress in the injured cortex. This implies protection against the loss of cortical synaptic proteins. Using HPPL treatment it was noted that 60% of the genes upregulated by TBI were significantly downregulated. Taken together, these data
suggest potential applications of platelet lysates in the treatment of various neurological diseases.

1.3 Linking research and discovery into routine blood operations

Linking research and discovery into the routine blood operation requires a flexible environment to bridge the gap between a creative research environment and the controlled, regulated manufacturing environment. Canadian Blood Services (CBS) representing the national blood service to a majority of Canadian Provinces and Vitalant, the largest independent non-profit blood supplier in the United States have developed an incubator or “sandbox” to translate projects to a process-controlled manufacturing procedure.

The incubator or “sandbox” concept is key to bridging from the less regulated environment of the research laboratory to the far more stringently regulated environment of formal preclinical development, controlled manufacturing, and clinical trials (see Figure 1). Independent investigators doing basic and applied research and development are subject to less extensive regulations and in general have more flexibility in designing, executing, and documenting studies. As discoveries and development progress, however, there is a need to transition to the more controlled, regulated environment of preclinical development, manufacturing, and clinical trials. The extent and types of control needed are defined by Good Laboratory Practices (GLPs), which cover formal preclinical animal studies, Good Manufacturing Practices (GMPs) which define manufacturing process control and product characterization, and Good Clinical Practices (GCP), which specify requirements for clinical trials.

To facilitate innovation, CBS established a network of Centers for Applied Development (netCAD) linking research and discovery with routine operations and creating a mutual support process among university-based laboratories. Initially, a developmental laboratory was designed as a miniature blood center to explore various processes for buffy coat platelet production supporting the design, development, and validation of the new product and processes without compromising operations. This has been extremely beneficial for CBS operations and research as well as commercial companies to develop a next-generation product for Transfusion Medicine. The “sandbox” concept has enabled CBS to create and validate new standard operating procedures (SOP) as well as a means of monitoring the quality of components to ensure these processes hold to accepted standards.

Directing and encouraging deferred donors to the developmental laboratory added a significant contribution for the donor and provided a wealth of information from these deferred donors to inform policy, especially those deferred for men having sex with other men (MSM). Figure 2 focuses on the significant contribution of the developmental laboratory within Canada. It is interesting to note that the developmental lab has a bioregistry of 1200 deferred donors and has provided blood products both internally to CBS and blood researchers in Canada.

Vitalant has long valued blood research through its research institute founded by Dr. Herb Perkins in 1959. The evolution of the research laboratory today is the Vitalant Research Institute (VRI) and the newly established Vitalant Innovation Center (VIC). While the VRI “is dedicated to advancing blood safety worldwide through scientific research, education and the promotion of evidence-based policies,” the VIC is focused on translational science (see Figure 3).

The VIC, acting as a “sandbox,” bridges innovation from research discovery or customer requirements, process improvements, or changes implemented by regulatory mandates into a safe environment for evaluation and migration into a regulatory controlled process. This enables Vitalant to develop and validate products and procedures while monitoring quality and training before launching the product in the operational environment. Similar to netCAD, the VIC can provide cell sourcing to support preclinical and basic research, perform preclinical and clinical testing of investigational devices for regulatory submissions, manufacture for clinical trials, and provide a biorepository for biological sample storage.
Since the launch of the Sputnik 1 satellite in 1957, the Defense Advanced Research Projects Agency (DARPA) of the U.S. Department of Defense (DoD) has been investing in breakthrough technologies for U.S. national security. The high-risk-high reward objectives are aimed for transformational versus incremental advances as it works within an innovation ecosystem that includes the collaboration of academic, corporate, and government partners for pushing boundaries in its research programs.

Seeing the need for specific biologic programs, in 2014 DARPA stood up the Biological Technologies Office (BTO), although programming with biological elements continues in other offices. The blood and biotherapy communities have a great opportunity to tap into DARPA’s BTO to sharpen the research focus. Brainstorming with and proposing research opportunities to BTO has the potential to bring new solutions to problems within blood and biotherapies, embracing big risks with great reward.

Careful evaluation of risks and focusing on risks worth taking are integral to DARPA’s approach. George H. Heilmeier, former DARPA Director (1975–1977), established a set of questions known as the “Heilmeier Catechism” to evaluate proposed research programs (see Table 3). This evaluation starts with a description of why the new approach will be successful based on the
TABLE 3 “Heilmeier catechism” for research programs evaluation

| Question                                                                 | Answer                                                                 |
|--------------------------------------------------------------------------|------------------------------------------------------------------------|
| What are you trying to do? Articulate your objectives using absolutely no jargon | All objectives should be clear and free of jargon.                      |
| How is it done today, and what are the limits of current practice?       | Identify current limitations and how they can be improved.             |
| What is new in your approach and why do you think it will be successful? | Highlight novel aspects and their potential for success.               |
| Who cares? If you are successful, what difference will it make?          | Describe the impact and relevance of success.                          |
| What are the risks?                                                      | Identify potential risks and mitigation strategies.                    |
| How much will it cost?                                                   | Estimate costs and potential cost-reduction strategies.                |
| How long will it take?                                                   | Set realistic timelines and milestones.                                 |
| What are the mid-term and final “exams” to check for success?            | Define success criteria and verification methods.                      |

current limit of practice and those of the new approach. The “who cares” factor must also be asked and answered to understand the impact and relevancy of the success of the new approach. Through this process, the risk is identified as well mitigations to help establish cost, timelines, and milestones with quantitative metrics of success.

1.5 Funding opportunities

DARPA funding opportunities are made through Broad Agency Announcements (BAAs) for specific programs and for a range of technical areas of interest to each office and can be found with timelines on the DARPA website (https://www.darpa.mil/work-with-us/opportunities). In addition, many DARPA programs include independent verification and validation by US Government partners, which enables testing in additional relevant settings and technology transitions. As well, funded research may be identified to support offshoots or “seedlings” to explore gaps such as the evaluation of technological potential. Small Business Innovation Research (SBIR) or Small Business Technology Transfer (STTR) opportunities may be identified by any US Government department or agency.

A new program of interest to blood and biotherapies is the Fieldable Solutions for Hemorrhage with bio-artificial Resuscitation Products (FSHARP), which will challenge researchers to develop blood and biotherapy products for resuscitation in settings where whole blood may not be available in quantities needed, such as austere field settings, prolonged field care, and mass casualty scenarios. Many consider whole blood to be the optimal resuscitation fluid for reversing volume deficit and restoring oxygen-carrying capacity in hemorrhage. FSHARP envisions a field-deployable, shelf-stable, bio-synthetic whole blood alternative as a hemorrhage countermeasure to sustain warfighters and civilian casualties when whole blood is not an option (see Figure 4). FSHARP products would be suitable for hemorrhage in complex physiological contexts such as TBI or trauma-induced coagulopathy.

The concept of FSHARP is to develop a resuscitation fluid that recapitulates the key functions of whole blood in trauma resuscitation, including components that deliver oxygen, slow bleeding, and restore adequate blood pressure. These components must be developed for mutual compatibility and therapeutic functionalities.

The FSHARP program has two technical areas. The first is the development of the blood substitute, and the second is the development of scale-up manufacturing and stabilization strategies. Shelf-stable without cold storage and capable of rapid reconstitution for administration are product requirements. The FSHARP program is not a foundational program looking for “proof of concept” but is designed to identify a scalable, stable product at an acceptable cost.

1.6 DARPA-funded biostasis research for potential human whole blood storage

DARPA-funded biostasis research at the University of Wyoming is tasked with developing methods to stabilize and extend the shelf-life of resuscitation products for acute hemorrhage. Specifically, the goal is to develop new methods of the dry preservation of human blood without refrigeration. The approach is to identify molecules and mechanisms employed by extremophile and extremotolerant organisms to survive in a dry state.

Extremophilic and extremotolerant organisms in nature have evolved mechanisms to stabilize sensitive biological material into a state of suspended animation. Using extremophiles to understand what molecules and mechanisms have evolved to stabilize sensitive biological material in a dry state hopefully will permit researchers to co-opt and engineer novel stabilization strategies to eliminate the need for a cold storage supply chain.

To this end, Thomas Boothby and his research team from the University of Wyoming applied lessons learned from the study of tardigrades. A model organism, commonly known as water bears, tardigrades are renowned for their ability to survive extreme conditions, evolving at least 250 million years ago with over 1400 described species, found on every continent and nearly every condition. They are extreme survivors and robust, tolerating extreme conditions from -272 to 151°C, ionizing radiation, little or no oxygen, pressure extremes, and desiccation. To survive this final stress, desiccation, the tardigrade enters into an ametabolic state when dry, shutting down all metabolic functions and surviving for years or decades. However, when placed back in water tardigrades quickly...
rehydrate, resume metabolism and life processes, and reactive preserved proteins, nucleic acids, and cells.

By understanding gene regulation (transcriptomics) and metabolomics during extreme desiccation in tardigrades has helped to identify functional mediators that these animals make to allow them to survive the drying process—which is key to understanding how scientists might stabilize whole blood. Common to many organisms' desiccation tolerances are disaccharide sugars and special proteins. One class of protein is an intrinsically disordered protein (IDP), which lacks rigid three-dimensional structures and exist in an ensemble of interconverting structural states which can be adaptive under various environmental conditions. The ability of IDPs to protect other proteins, especially enzymes, may be essential to the tardigrade's survival under extreme environmental conditions. The Boothby lab at the University of Wyoming has explored how the engineering of IDPs can be used to tune their function(s) and how these approaches can be used to enhance IDPs' applicability to stabilizing blood and biotherapies. One protein family important to tardigrades is the cytoplasmic abundant heat soluble (CAHS) protein family. The Wyoming team found that manipulation of CAHS proteins can affect their ability to preserve sensitive biomolecules during desiccation. Tardigrade CAHS proteins undergo a phase transition to form hydrogels, which are concentration and temperature-dependent. As water is lost, a gel-like network with other proteins is thought to occur to protect the enzyme proteins. The enzyme, lactate dehydrogenase (LDH), which is known to destabilize during desiccation and becomes inactive, has been used as a model to investigate protein protection during drying. Studies showed that gelation of CAHS D correlates with protection against desiccation-induced protein folding. When studies were expanded to citrate synthase, known to become inactivated due to aggregation during desiccation, freezing and high temperatures, CAHS D gelation did not correlate with protection against protein aggregation. However, engineered variants of CAHS D that cannot undergo gelation did protect against aggregation. This indicates that different sequence features can be modified to prevent different types of dysfunctions during desiccation and extreme conditions.

Lessons learned through understanding protectants as a cellular component are now being transferred to explore protection with different cell types both anucleate (platelets, red cells) and nucleate (white cells). It is hoped that with this knowledge on stabilization, a cocktail of different engineered or natural proteins and small molecules could be designed to protect whole blood.

FIGURE 4 The concept of fieldable solutions for hemorrhage with bio-artificial resuscitation products (FSHARP) envisions a field deployable, shelf-stable, bio-synthetic whole blood alternative as a hemorrhage countermeasure to sustain warfighters and civilian casualties when whole blood is not an option [Color figure can be viewed at wileyonlinelibrary.com]
2.1 | Challenge in the commercial pipeline of cellular therapy products

Mononuclear cells collected by apheresis are the starting material for manufacturing many types of CGT products, particularly cellular immunotherapies such as chimeric antigen receptor T cells (CAR-T), natural killer cells (NK), and T cell receptor-engineered T cells (TCR-T).

During clinical development, apheresis collections for CGT manufacturing are performed by apheresis programs at the academic medical centers serving as clinical trial sites. Mononuclear cell collection for manufacturing CGT products at full commercial scale requires far greater capacity, however.

Currently, there are over 90 marketed CGT products worldwide with cellular immunotherapy products, particularly CAR-T cell therapy, the major driver. Over 700 clinical trials of CAR-T cell therapy are listed on www.clinicaltrials.gov, about 70 percent of which involve apheresis collection of autologous cells. In the United States alone, there are six marketed CAR-T cell therapy products, all of which require autologous apheresis. It is estimated that by 2030, 350,000 patients will be eligible for treatment with 30–60 CGT products.

Apheresis programs at academic medical centers cannot be expected to meet demand at this scale. The forecasted need within the next decade demonstrates the need for greater apheresis collection capacity to support large-scale commercialization of CGT products. Process development may eventually enable use of whole blood as starting material for manufacturing some cellular immunotherapies but this is unlikely to be a near-term solution, nor is it likely to altogether eliminate the need for apheresis collection in CGT production.

Moving from clinical trials to full-scale commercialization will require standardization of procedures, instruments, quality parameters, and training of staff, at a scale of operations beyond the mission or capacity of academic apheresis collection programs. Cellular apheresis collection centers, separate from the in-house programs at academic medical centers, are needed. A potential solution may be to leverage existing infrastructure such as dialysis centers or plasma collection centers, though this would require substantial adaptation of the current operations.

2.2 | Challenges inadequate blood supplies for all populations

Achieving an adequate blood supply to meet clinical needs is problematic, particularly for transfusion-dependent patients including those with Sickle Cell Disease (SCD). Despite RH (D, C, E) antigen matching for transfusion-dependent patients with SCD, diversity in patients and donors contributes to RH alloimmunization. Adequate supplies of red cells from African-American (AA) donors are needed for prophylactic Rh and Kell matching.

Since the RH allele frequency is similar between SCD patients and AA donors, determination of genotypes could provide improved red cell matching if new tools were available. The feasibility of genotype matching was assessed by Chou et al. using a simulated electronic RH and Kell genotype matching protocol of approximately 28,000 units for 200 patients with SCD transfused over 4 years. Based on the observed RH genotype frequencies of the AA donor pool, this approach would require approximately twice the number of AA donors screened per day for serologic antigen matching (D, C, E, and K).

While feasible, the barriers to the implementation of genotype matching are recruiting a robust AA donor pool and the cost of RH genotyping. Currently, the use of low-cost next-generation sequence (NGS) based assays is limited based on RHD and RHCE homology and hybrid alleles. In addition to the challenge of alternative low-cost genotyping methods to detect RH variants, information technology (IT) systems are needed to support data management of patient and donor genotypes, selective genotype recruitment of valuable donor populations, and inventory.

2.3 | Challenges in donor recruitment and retention for precision transfusion medicine

Linked to the challenge of achieving an adequate blood supply to meet the needs of patients with wide-ranging clinical needs are the implications of obtaining, managing, and using confidential data along the blood/biotherapy supply chain which will allow for precision transfusion medicine. This requires the identification and recruitment of the most appropriate donors whose blood products will achieve the best transfusion or biotherapy outcome for each patient. Challenges include understanding how to optimize therapy outcomes coupled with complex considerations of blood service IT infrastructure and data security of personal health information and genetic testing of donors and recipients.

Globally many blood suppliers along with academic research institutions and genomic array providers are actively working to identify biological characteristics to improve transfusion outcomes. Large discovery arrays probing 800,000–1,000,000 single nucleotides polymorphisms (SNP) variants...
are used to identify the genetic traits of donors and donations as well as common diseases. Blood services are actively moving from discovery arrays to use of production arrays to type donors and patients for DNA variants of known importance to match blood products for transfused patients, especially those who are chronically transfused. Although both discovery and production arrays are being used today, IT infrastructure is currently not available for routine use of data generated from these arrays to manage blood product inventories in ways that improve transfusion or biotherapeutic outcomes.

Management of these data, on the one hand, to recruit donors with precise characteristics for specific patients, or on the other hand, to potentially discourage donors from certain kinds of donations, is a major challenge to overcome. Adoption of precision transfusion medicine approaches and data collection may simultaneously lead to a desire to pull some donors toward specific types of donations and push some donors toward other types of donations. How such messaging will be achieved needs thoughtful attention. Balancing the practical requirements and utility of the data with perceptions and ethical implications needs to be well thought through.

At present, the blood and biotherapy supply chain is not ready for full-scale implementation of these genetic trait characterization technologies. A full research agenda is needed to optimize donor communication, ethics, omics, and the IT infrastructure to support precision medicine for blood and biotherapies.

2.4 | Challenges achieving ULR

Although extensive beneficial data have been established, ULR of blood products has not been universally accepted.52 These benefits include reduction in febrile transfusion reactions,53 platelet transfusion refractoriness/HLA alloimmunization,54 cytomegalovirus (CMV) transmission,55 post-operative bacterial infections,56–59 red cell alloimmunization,60 TRALI,61 TACO,61 line-related sepsis,62 post-transfusion purpura,63 and graft versus host (GVH).63 Post-operative mortality in cardiac surgery has been reported to be reduced approximately in half with leukoreduction.64 In addition, post-operative infections have a mortality of 8%–15%; this is the leading cause of multiorgan failure syndromes and death in hospitalized patients.65

Although ULR has been shown to reduce the overall cost to the hospital system,66,67 the cost of leukoreduced products is an expense borne by the transfusion service as it is not directly covered by the inpatient diagnostic-related grouping system. In addition to cost savings from avoidance of adverse outcomes, ULR mitigates the need for dual blood inventories.

2.5 | Challenges in the workforce and medical training

The future of biotherapies at academic health centers faces a conundrum in maintaining non-faculty cellular therapy staffing. Such staffing is needed to manufacture cellular products following principles of GMP. Workforce attrition has been primarily due to lack of career progression and competitive wages as well as merit-based incentives.

In a case study from the University of Pennsylvania spanning 2012–2019, 60% of all staff who resigned left for industry and/or higher salary offers with better advancement opportunities. Similar to blood establishments, positions in an academic GMP facility require knowledge of regulatory, compliance, and accreditation standards. Since a GMP facility in an academic setting is considered research, positions do not typically recognize unique cell manufacturing qualifications and responsibilities for creating drugs for treating human diseases. As a consequence, the loss of GMP-trained cell manufacturing staff (non-faculty) to industry has a financial impact on the academic institution in loss of productivity, staff reassignments, and retraining. The cost exceeded millions of dollars/year to the university in this case study.

In this case, university leadership determined that a career progression system was needed to put control and ownership in the hands of the employee similar to how university faculty are evaluated and subject to promotion and increased compensation. To compete with industry, the University needed to create new positions for cell therapy technologists with new titles to differentiate the position from conventional bench research technicians. Merit-based incentives were also needed to compensate for work beyond the normal schedule of “exempt” employees. These job descriptions included positions typical of a GMP facility but directed to cellular therapy technologists with levels of progression, management, and quality control.

3 | SUMMARY

Reflecting on the current challenges helps define and envision the opportunities for the future of blood and biotherapies. These opportunities may be transformational, such as in the FSHARP program, foundational for discovery, or translational for process/product improvement. No matter
how defined, deficit resources of manpower, donors, and funding inhibit translational pathways, especially commercialization.

Today and tomorrow, there is a critical need for Transfusion Medicine specialists, Biotherapy specialists, researchers, clinical laboratory scientists, GMP technologists, nurses, quality managers, operational managers, and business leaders, to name a few. Projections up to 2030 indicate a demand greater than normal of 11% to meet clinical laboratory needs.68 This will require a revamp of education and training, especially in medical and clinical laboratory science programs to ensure talent is not lost to other specialties. The role of the mentor is probably more critical as the field expands.

Diverse donors are critical to precision medicine. If not cognizant of their value, these donors may require recognition and incentivization to ensure the growing need for specialized donors as a source of raw material or starting material. As unique, diverse donors are identified and valued, data sharing also becomes essential to patient care.

The advancement of blood and biotherapies will continue to need foundational discoveries as well as translation implementation pathways for process/product improvement leading to better patient outcomes. These opportunities will require innovative thinking to mitigate risk for the potential reward. AABB’s NBF has a significant role in charting the course as a change agent.

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CONFLICTS OF INTEREST

SMH has disclosed Kode Biotech Ltd – Founder, CEO, Director, stockholder. TB has disclosed Invenis Biotherapies – Founder. DD has disclosed Macopharma – Chair, Scientific Advisory Board, STRM Bio – Member, Board of Directors, Canadian Blood Services – Chief Scientist, American Red Cross – Chair, Medical Advisory Committee. SRB has disclosed Discovery Life Sciences – Apparent professional COI. Advanced Cell & Gene, Therapy is a consulting firm, and one of our clients is Discovery Life Sciences, an, apheresis services provider. My advice to DLS is the same as what I say in this manuscript. Hemacare, Key Biologics – Advanced Cell & Gene Therapy has consulted for other apheresis providers in the past, but not at present. BC has disclosed ThermoFisher – Collaborating institution on research related to the content of R&D, Summit presentation (array manufactured by ThermoFisher) Vitalant – Employer. SLS has disclosed TCIP, Inc. – Shareholder, Hemanext, Inc. – Scientific Advisory Board, Tioma, Inc. – Consultant, WIRhE – Executive Director, JAH, SM, TCB, STC, NB and DLS have disclosed no conflicts of interest.

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