

AABB: Leading Biotherapies Past and Present

In 1947, a group of leaders in blood banking and transfusion medicine formed an association to share knowledge and best practices, set standards, standardize nomenclature and procedures, and ensure the continued advancement of the field. Originally known as the American Association of Blood Banks (AABB), the organization expanded alongside the field into the area now known as biotherapies. Today, AABB stands for Association for the Advancement of Blood & Biotherapies and remains true to its founders' original vision: to improve lives by making blood and blood products safe, available and effective worldwide. For more than 75 years, AABB has been at the forefront of blood therapy scientific research, clinical care, quality standards and industry collaboration.

Throughout that time, AABB's expertise in blood banking and transfusion medicine has allowed the Association to seamlessly move into the broader biotherapies space. In a sense, blood transfusion can be considered the first biotherapy, making AABB a natural leader in this area. Our name change to the Association for the Advancement of Blood & Biotherapies in 2021 reflects our commitment to further advancing biotherapies research and development.

Over the past three-quarters of a century, AABB has gained experience and expertise in an expanding list of cellular and gene therapies, beginning with bone marrow donation and transplant, followed by hematopoietic stem cell transplant (HSCT) and umbilical cord blood (UCB) transplant, and now more modern cellular therapies like chimeric antigen receptor (CAR) T cell therapy and gene therapies for cancer, rare diseases and chronic hematologic conditions like sickle cell disease. AABB's staff, members and community of experts is composed of leaders in the field of biotherapies.

AABB's background in blood banking and transfusion medicine laid the groundwork for our expertise in biotherapies. Many of the cellular therapies available today, and those under development now, rely on the knowledge, techniques and expertise involved in collecting, processing and distributing blood-based products. Expansion into the biotherapies space is a natural fit for AABB. AABB provides the highest quality resources and services in support of the transfusion medicine and biotherapies community throughout the world and is leveraging these in support of biotherapies. With research support, standards, accreditation, regulatory expertise, education, and industry support across this growing space, AABB is synonymous with biotherapies, and has been since the from the beginning.

CELLULAR THERAPIES

Cellular therapies to replace or repair damaged tissue and/or cells is an ever-expanding area of medicine and AABB has been part of this medical revolution since its early days. Potential applications of cellular therapies include treating cancers, autoimmune disease, urinary problems and infectious disease, rebuilding damaged cartilage in joints, repairing spinal cord injuries and helping patients with neurological disorders.

Bone Marrow and Hematopoietic Stem Cell Transplant

Bone marrow transplant was one of the first stem cell therapies to become a standard treatment for blood cell-forming disorders, including cancer. AABB's expertise in blood collection, processing and transfusion medicine made the Association a natural leader in bone marrow transplant and other therapies. The National Marrow Donor Program (NMDP)/Be the Match recognizes AABB Standards and Accreditation to support and improve HSCT and UCB transplant techniques, expanding the success and improves patient access to HSCT.

AABB has been instrumental in advancing the use of HSCT to cure hematologic disorders, such as sickle cell disease and beta-thalassemia. These conditions, primarily identified in childhood, subject patients to painful crises that may require emergency care, significantly limit their quality of life, and often leave them dependent on chronic transfusion to supply healthy red blood cells. HSCT now essentially cures patients by replacing their faulty red cell-producing bone marrow with correctly functioning allogeneic transplant material. In some cases, very young patients who undergo HSCT for sickle cell disease may not even know they were sick.

Umbilical Cord Blood and Tissues

UCB transplantation was first successfully performed in the late 1980s and, since then, has emerged as another source for treating patients with hematologic cancers, as well as other blood disorders, such as Fanconi anemia (the first use of UCB therapy), metabolic storage diseases and severe combined immunodeficiency diseases. UCB transplant has been expanded to other disorders and research continues to add to its possible uses, including treatment of HIV and pulmonary hypertension.

UCB transplant offers several advantages over bone marrow transplants. Because the immune system of newborns is not yet fully developed, cord blood can safely be used even if the donor cells have a less than perfect match with the patient. Cord blood is collected at birth and stored until necessary, making it readily available for patients. In addition, the likelihood of graft-versus-host disease is reduced with a UCB transplant; better long-term immune recovery with cord blood translates to improved long-term survival as well. Research is expanding the potential uses of UCB stem cell transplant to include neurologic disorders such as cerebral palsy, autoimmune disorders and wound care.

Researchers and companies are also looking into the potential use of other perinatal tissues as well, including amniotic membrane, amniotic fluid, umbilical cord tissue, Wharton's jelly and placental tissue. These tissues have typically been discarded as medical waste. However, stem cells, extracellular matrices and growth factors derived from these tissues hold tremendous possibility for regenerative medicine and tissue engineering.

AABB has long supported cord blood research through grants and awards and has provided guidance and other support to cord blood banks. In addition, many cord blood banks receive accreditation through AABB. AABB continues to play a key role in translating the techniques and processes used to collect and store whole blood and blood products to cell collection, processing and storage — opening up new revenue streams for existing blood collectors by helping them pair with partners who are developing stem cell-based treatments.

AABB's is helping to drive cell and tissue product development through cellular therapy quality standards for good tissue practice (GTP) support. In 2023, a joint working group including AABB and the International Society for Cell and Gene Therapy (ISCT) released a new GTP Interpretive Tool to educate those in the biotherapies community about the interpretation of GTP requirements and how best to prepare for FDA inspections of establishments that manufacture human cells, tissues, and cellular and tissue-based products (HCT/Ps).

The AABB/ISCT GTP Interpretative Tool provides section-by-section guidance specific to the needs of biotherapies programs to help them achieve regulatory compliance and prepare for unannounced FDA inspections. The tool consolidates references and provides links that aid in determining the correct regulatory pathways for Section 361-based products during early and late-stage development, excluding reproductive applications. The hope is that the tool will be a “living document” with periodic updates as new information from the FDA becomes available.

CAR T Cells, Natural Killer Cells and Beyond

Chimeric antigen receptor (CAR) T cells represent a type of immunotherapy called T cell transfer therapy — or adoptive T cell transfer — that makes patient’s own T cells better able to attack cancer. Tumor-infiltrating lymphocyte (TIL) therapy is another type of T cell transfer therapy that works by expanding outside of the body the number of TILs, which are already programmed to identify and destroy cancer cells in a patient. The greater number of TILs overwhelms the signals that cancer cells send the immune system to not attack cancer cells.

The approval of CAR T cells in the past decade opened up an entirely new branch of cancer treatment. This treatment involves isolating and harvesting T cells from a patient’s blood and engineering them to link a chimeric antigen receptor into the T cells, so that they deliver a “toxic” payload that targets specific antigens on cancer cells (such as CD19). These engineered T cells are expanded and reinfused into the patient. The first approved treatments of CARs target B-cell-derived cancers, such as acute lymphoblastic leukemia and diffuse large B-cell lymphoma.

Other immunologic cells, such as natural killer (NK) cells are also under investigation as cancer treatments. NKs are a type of immune cell that can attack any abnormal cells in the body, including cancer cells. One challenge is that these cells typically don’t live very long. Researchers are working to extend NK survival by adding certain immune proteins. NK therapies are also continually being modified similar to CAR T cells, to better target cancer cells. While there are still a number of barriers, it is possible that one day NK therapies could be used against solid tumors, which make up 90% of cancers.

These and other cell therapies are limited by the capacity to provide patient and donor source cells. With its legacy in cell collection and expertise in standardization/harmonization, AABB is helping blood programs and biotherapies developers to harness this experience and infrastructure to accelerate cell therapy research and production. AABB is focused on sharing our knowledge and capabilities to achieve AABB’s vision of advancing biotherapies — from donor to patient, from lab to bedside.

Gene Therapies

In 2022, U.S. Food and Drug Administration approved the first cell-based gene-edited therapy for the treatment of transfusion-dependent beta-thalassemia (TDT) in pediatric and adult patients. The therapy works by adding functional copies of a modified form of the beta-globin gene (β^{A-T87Q} -globin gene) into a patient’s own hematopoietic stem cells, allowing them to make normal to near normal levels of total hemoglobin without regular blood transfusions.

Later in 2022, the FDA announced the approval of the first gene therapy for adults with hemophilia B who are currently being treated with Factor IX prophylaxis and have a history of repeated, serious bleeding episodes. This one-time adeno-associated virus vector-based therapy works by carrying a gene for clotting Factor IX. The gene is expressed in the liver to produce Factor IX protein, which increases blood levels of Factor IX and helps to limit bleeding episodes.

The advent of gene therapies has changed lives for patients dependent on blood transfusion and intravenous infusion of concentrated Factor IX products. AABB has been part of this journey with its participation in the U.S. Department of Health and Human Services' Cellular, Tissue, and Gene Therapies Advisory Committee. The committee reviews and evaluates data related to the safety, effectiveness and appropriate use of human cells, human tissues, gene transfer therapies and xenotransplantation products that are intended for transplantation, implantation, infusion and transfer to prevent or treat of a broad spectrum of human diseases. AABB has been an active participant in committee discussions about adeno-associated virus (AAV) vector-based gene therapies and specific gene therapies for sickle cell disease, beta-thalassemia and hemophilia.

Product Development and Entrance into the Market

AABB's Cellular Starting Material (CSM) Qualification helps accelerate supplier qualification for biotherapies companies in start-up mode, at the commercial stage or in between relying on AABB-accredited facilities to support advanced therapies. AABB-accredited facilities achieving the CSM qualification have demonstrated that their quality system meets or exceeds AABB's evidence-based Standards for the collection, storage and/or processing of cellular starting materials. This program is designed to reduce your supplier qualification process, saving time and accelerating income during commercialization.

AABB offers a Transfusion and Cellular Therapies Supplier Guide, including our AABB Standards-Compliant Product Program, which benefits both vendors and customers by offering assurance that products for the blood and biotherapies communities are in compliance with AABB Standards. Products that achieve AABB's Standards-Compliant Product recognition have been thoroughly reviewed by AABB and have been confirmed as adhering to the AABB Standards that relate to equipment, process control and document control.

Educational Materials

AABB is continually updating and creating a wide range of professional development materials — all designed to help members and the biotherapies community extend their knowledge and further their careers. From e-learning courses to our Cellular Therapies Certificate Program to our news and publications, AABB offers the biotherapies community the professional development tools that fit their schedules and allows them to learn at their own pace.

AABB has hours of educational materials available in a wide range of topics related to biotherapies that those already in the field — and those just entering the field — to improve their knowledge of specific areas and increase their biotherapies skill set. Members have access to Meetings on demand, hot topic discussions, live e-Casts and, of course, educational content from our annual meetings.

Expert Consulting

Members also receive a \$10,000 consulting service retainer to access expert business innovation consultants. The portfolio of consulting services includes: quality management system design and implementation, regulatory assessments, process improvement, training and development built specifically to support the biotherapies industry.

AABB Consulting Services brings more than 50 years of experience as a leader in developing strategies and solutions for transfusion medicine and biotherapies specific to a variety of key projects in the field. Our team's innovative assessment methods are effective in identifying challenges and opportunities unique to each facility. AABB experts will then guide clients to achieve sustainable goals through consultations, interviews, and gap analyses. These services assist cell and tissue collection and/or management facilities, clinical laboratories and cellular and related biological therapy facilities to improve their quality management and process improvement systems. Quality management and process improvement are key to meeting regulatory requirements, expanding capacity and bringing products to market.

Standards

You could say that AABB has written the book on quality management systems in the biotherapies space. AABB Standards represent current best practices and state of the science and are based on the AABB quality system framework, which leads the blood and biotherapies field in quality standards worldwide. Our Standards incorporate both technical and quality systems standards to ensure that all facets are reviewed — from specification of equipment, materials management and organizational structure to documents, resource management and program assessment.

Each edition of AABB's Standards are developed by a multidisciplinary team of experts who volunteer their time as a member of a Standards Committee. Each edition is based on best clinical practice, scientific data, and principles associated with good manufacturing practices and quality assurance and applicable regulations. Each revision cycle — conducted every two years — includes a public comment period that seeks input from active professionals throughout the world.

The *Standards for Cellular Therapies* is in its 11th edition, and outlines requirements for the donor eligibility and collection, processing, storage and administration of cellular therapy products. This edition includes response to comments and significant changes to the 10th edition of CT Standards to modernize the content as the field advances.

Regulatory

Federal regulations can be challenging to track, interpret and implement under most circumstances. The rapidly evolving world of biotherapies makes this even more difficult. AABB has a long history of helping professionals in the field navigate new regulations, updates and related supporting materials (such as donor history questionnaires) for blood products. Our close interaction with our member experts and federal agencies affords AABB a unique position, from which to represent and support our membership, business partners and patients.

That expertise is also available to the biotherapies industry. Our experts monitor changing and expanding issues related to federal regulations and recommendations. AABB's regulatory staff also track federal agency practices and procedures. AABB has a long history of working closely with the U.S. Food and Drug Administration, the U.S. Centers for Disease Control and Prevention and other government agencies to promote safety, such as identifying and mitigating emerging threats to the safety of blood and biotherapies. For example, AABB experts offer interpretation of proposed and final regulatory guidances. AABB hosts regular FDA Liaison Committee meetings to address industry concerns and new science, and coordinates AABB Annual Meeting sessions where members can “Ask FDA/CLIA.” Regulatory updates and interpretations are included in AABB's Weekly Report as they happen.

AABB also collaborates with regional and international biotherapies organizations to define terms and harmonize best practices, data standards, quality measures, outside of federal regulations that encourages innovation and discovery.

Collaboration

AABB has a strong history of working with other like-minded organizations to move biotherapies forward, including harmonization of terms, data fields and quality requirements. AABB partnered with the International Society for Cell and Gene Therapy (ISCT) to form a Joint Working Group to tackle important biotherapy challenges and delivery bottlenecks.

One example of an AABB-ISCT collaboration is a project focused on pooled human platelet lysate. In 2015, the AABB-ISCT WG established a project team to address issues concerning the production and standardization of pooled human platelet lysate (pHPL) based on the increasing need for a non-animal derived source of cell culture growth supplement to support cellular therapy product development. The goal of the project was to identify gaps in the

information on pHPL and barriers to its translational use in production of clinical grade cell therapies. In 2017, the pHPL project team presented its progress at the AABB and ISCT annual meetings where they discussed:

- Standardization of pHPL production
- Measures for evaluation and pathogen reduction treatment of pHPL
- Differences between pHPL and fetal bovine serum (FBS)/fetal calf serum

This project team then prepared a manuscript that summarizes their findings offered as a joint submission to the *Transfusion* and *Cytotherapy* journals.

Considerations for the establishment of a *cellular therapy product stability* program is another joint AABB-ISCT project. The aim of a cellular therapy product stability program is to establish a product's shelf life (expiration) and to define storage instructions. Due to the expanding differences in product type and required regulatory pathways, the establishment of a stability program has become increasingly difficult. A goal of this project team is to create reference documents and/or other communication materials to help with the design of a stability program for hematopoietic progenitor cell (HPC) products including a standardized 'template' for use in performing stability testing of HCT/Ps. The project team members represent a wide selection of subject matter experts from academic institutions and industry.

To help interested parties better understand GTP-related regulations, the AABB-ISCT working group formed a team to develop a *GTP interpretative tool* which associates the GTP regulations with guidance references, considerations, and additional resources. The tool was developed by a joint team of industry leaders with expertise in cell- and tissue-based product development and manufacturing and published for public use.