

Celebrating the 50th Anniversary of the Center for International Blood and Marrow Transplant Research

By Sara L. Wilkins

In 1972, doctors from 35 centers in North America and Europe created a patient outcomes registry, housed at the Medical College of Wisconsin (MCW), containing data for the approximately 150 bone marrow transplants that had been performed worldwide beginning in 1968. With so few transplants, doctors needed to combine their data to determine which therapies worked best.

This collaboration was the humble beginnings of a research program now known as the Center for International Blood and Marrow Transplant Research (CIBMTR), which is jointly administered by MCW and the National Marrow Donor Program (NMDP)/Be The Match (*see below*) and has a current registry of more than 600,000 patients from approximately 500 centers worldwide.

It is so much more than a simple registry, however. Rather, the CIBMTR is a multifaceted research program that collaborates with the global scientific community to advance hematopoietic cell transplantation (HCT) and other cellular therapies to increase survival and enrich the quality of life for patients worldwide. Its programs include clinical outcomes research, health services research, immunobiology and genomic studies on its large repository of patient biospecimens, bioinformatics, statistical methodology and clinical trials.

Throughout 2022, MCW has been celebrating the CIBMTR's 50th anniversary and its global impact on a field that continues to see ever-increasing survival rates and improved quality of life. The CIBMTR is a major contributor to that advancement – with



(l-r) Dr. Mortimer Bortin, founder, with original statistician, Dr. Alfred Rimm, of the International Bone Marrow Transplant Registry (IBMTR), ca. 1972.

studies that provide important insights into biologic, clinical and socioeconomic determinants of outcome and lead to significant changes in practice. The CIBMTR has continued to maintain the core tenets of data sharing and collaborative research that led to its establishment in 1972 as the International Bone Marrow Transplant Registry (IBMTR).

Brief History of the CIBMTR

The deployment of the atomic bomb during World War II stimulated a wave of biomedical research aimed at both understanding the effects of radiation and developing treatments for radiation exposure, which ultimately led to the development of bone marrow transplantation – initially conceived of as way to treat radiation-related bone marrow failure.

In 1968, MCW faculty member Mortimer Bortin, MD '45, along with colleagues at the University of Wisconsin, performed one of the world's first successful allogeneic bone marrow transplantations. In 1972, collaborating with other pioneers in the field, Dr. Bortin and Alfred A. Rimm, PhD (also an MCW faculty member), created the IBMTR through a grant from the American College of Surgeons and the National Institutes of Health (NIH). In 1985, the IBMTR was awarded a program project grant (later converted to a resource grant) jointly funded by the National Cancer Institute, the National Institute of Allergy and Infectious Disease and the National Heart, Lung and Blood Institute, which



The National Marrow Donor Program/Be The Match – MCW's partner in the CIBMTR since 2004 – is the global leader in providing cellular therapies for patients with life-threatening blood and marrow cancers such as leukemia and lymphoma, as well as other diseases.

It manages one of the world's largest donor registries providing adult and cord blood stem cells for transplantation, educates healthcare professionals and patients, and provides supportive services to reduce patients' barriers to cell therapies.

has continuously funded the CIBMTR since that time.

Dr. Bortin served as IBMTR's chief scientific director from 1972–1991 and led some of the seminal early papers on clinical transplantation. He also had an active immunology laboratory focusing on immune effects of donor cells on normal and malignant recipient cells. In 1975, Dr. Bortin's lab was among the first to demonstrate the ability to separate the deleterious graft-versus-host from beneficial graft-versus-leukemia effects. He also continued to teach and recruit other physicians to MCW.



In 1985, Mary Horowitz, MD '80, GME '89, MS '91, joined the IBMTR; she succeeded Dr. Bortin as chief scientific director in 1991. Under her tenure, the CIBMTR continued to grow.

In 2004, the IBMTR and the NMDP affiliated to jointly operate the CIBMTR, bringing together complementary research resources and expertise. The NMDP and IBMTR had collaborated on multiple projects previously, including winning the NIH grant to jointly operate the Data and Coordinating Center of the newly established Blood and Marrow Transplant Clinical Trials Network (BMT CTN) in 2001. In 2007, the CIBMTR was awarded the contract for the Stem Cell Therapeutic Outcomes Database, part of the C.W. Bill Young Transplantation Program.

In 2011, Dr. Horowitz had the distinction of receiving the largest federal research grant in MCW's history – a \$45 million NIH grant to advance the interventional studies of the BMT CTN. In 2016, the CIBMTR established the NIH-funded Cellular Immunotherapy Data Resource (CIDR) to accelerate cancer research using novel cellular therapies such as chimeric antigen receptor (CAR)-T cells. Today, the CIBMTR captures data on more than 95 percent of all US HCT

recipients and about half of patients receiving CAR-T cells. The BMT CTN has enrolled more than 16,000 patients on more than 55 clinical trials.

Dr. Horowitz transitioned from her role as the CIBMTR's chief scientific director in 2021 and was succeeded by Bronwen Shaw, MD, PhD, an internationally recognized researcher with a focus on optimizing donor selection and patient-reported outcomes (*see sidebar on page 20*). Dr. Horowitz remains the principal investigator of the BMT CTN grant and currently serves as deputy director of MCW's Cancer Center. Dr. Horowitz was profiled as the "Change Agent" in the Winter 2017 issue of *MCW Magazine*.

Throughout its history, the IBMTR/CIBMTR has responded to international crises. In 1986, the IBMTR sponsored an international team of doctors who assisted radiation victims from the Chernobyl nuclear disaster. During the COVID-19 pandemic, the CIBMTR adapted data collection to better accumulate information about patients with COVID-19 and to define the effect that COVID-19 has during HCT. Also, its COVID-19 webpage included COVID-19 data submitted by other centers. In spring 2021, the CIBMTR rapidly published several analyses relevant to the pandemic and, in collaboration with the BMT CTN, recently completed a study of more than 500 patients which evaluated the antibody and T-cell responses to COVID-19 vaccines in HCT patients.

Overview of the CIBMTR

The CIBMTR represents an international network of centers that submit transplant-related data for patients. Collected data can be accessed for patient care decisions, developing research studies, education, transplant center administrative needs and CIBMTR research. These data are freely available to investigators with an interest in HCT and treatments for cancer and other life-threatening diseases. As a result, the CIBMTR has become a respected leader in HCT research by providing a unique resource of information and expertise to medical and scientific communities.

"Studies using the data from the CIBMTR's large research database drive practice change," Dr. Horowitz shares. With more than 1,650 publications, the CIBMTR's practice-changing studies



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help patients and physicians select donors and grafts, evaluate patient risk, identify long-term effects of cellular therapy, guide medical care for survivors and address access to care. For example, real-world evidence analyzed by the CIBMTR's team of highly trained and expert staff has paved the way for Medicare coverage for certain therapies as well as Food and Drug Administration approval of others.

"Promoting equitable access to cellular therapies is a top priority," explains Dr. Shaw. The CIBMTR recently completed the largest clinical trial of its kind, helping patients (particularly those who are ethnically diverse) without a well-matched donor. "Having strategies for safe, effective transplant expands access to a potentially curative therapy to all patients in need," adds Dr. Shaw.

The CIBMTR's strategic pillars include data (acquisition, analysis, sharing and visualization of diverse data); equity (elimination of barriers to ensure health equity); innovation (operational innovation and excellence); next generation (fostering the next generation of cellular therapy research professionals); and research (transformational, interventional and observational research).

The CIBMTR is supported primarily by grants and contracts from the US government. Additionally, the organization receives financial support from corporate partners and generous individuals who help fund the organization's efforts to share knowledge and hope.

Clinical Outcomes Research

Clinical outcomes research using the CIBMTR Research Database

Bronwen Shaw, MD, PhD

Dr. Shaw was named chief scientific director for the CIBMTR MCW in February 2021. She also serves as MCW professor of medicine (hematology and oncology).

Dr. Shaw received her MD (MBChB) from the University of Cape Town, South Africa. Her subsequent postgraduate hematology specialist training was completed in London, where she also received her PhD in clinical sciences and immunology.

Prior to joining MCW in 2014, Dr. Shaw was a consultant hematologist specializing in stem cell transplantation and survivorship issues in the United Kingdom. She simultaneously held the position of chief medical officer at the UK's national unrelated donor registry, where she had oversight of the donor research activities and the medical operations of the organization.



is a core activity of the organization. Fifteen Scientific Working Committees, comprising experts in multiple fields, oversee most of these studies. Each committee focuses on a specific disease, type of cellular therapy or complication of therapy. Volunteer members propose, design and implement studies.

The CIBMTR also administers the Stem Cell Therapeutic Outcomes Database – tracking and analyzing data for all allogeneic HCTs performed in the US and HCTs performed globally with products from the US.

Since 2019, the CIBMTR has worked with the Cure Sickle Cell Data Consortium to build a research data ecosystem designed to support investigator-initiated collaborative research. US HCT data received by the CIBMTR for sickle cell disease are now available for public use in the National Center for Biotechnology Information database of genotypes and phenotypes.

Health Services Research

Health services research is the multidisciplinary field of scientific investigation that studies how social factors, financial systems, organizational structures and processes, technology and behavior affect treatment outcomes, quality and cost. Investigators study value, quality and access to care, particularly for patients from disadvantaged and ethnically diverse patient populations. Patient-reported outcomes provide an essential perspective, particularly for late effects of treatment. The CIBMTR has developed an electronic system for collecting data directly from patients that supplements clinical data and provides important insights into the patient experience.

Immunobiology Research

The CIBMTR maintains a Research Repository at NMDP/Be The Match containing more than 195,000 related and unrelated HCT recipient/donor (or cord blood) samples with complete, validated clinical data. This is the result of the foresight of the NMDP founders who first established this resource in the late 1980s. Samples are used for CIBMTR studies but also by investigators for local projects. An additional 350,000 specimens collected from more than 5,000 patients on BMT CTN trials also are available. Studies using Research Repository specimens have allowed (among other things) identification of optimal donor selection strategies and molecular predictors of outcomes.

Bioinformatics Research

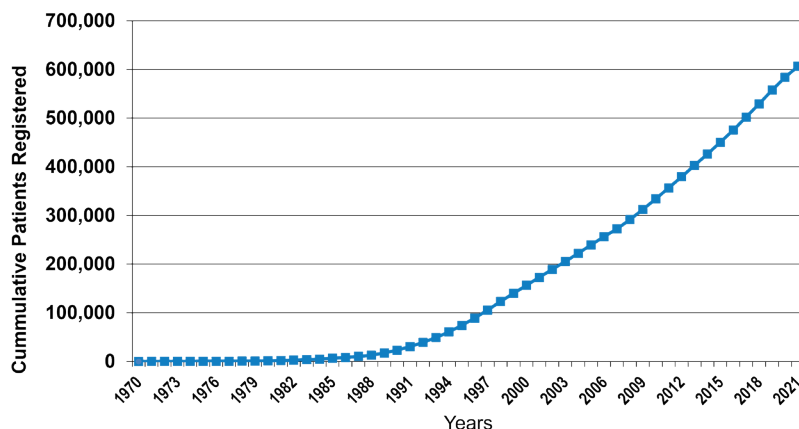
The Bioinformatics Research Program is at the intersection of science and technology. It pursues high-impact and innovative research and produces strategic applications to bridge the transition from research to operations and clinical care. CIBMTR bioinformatics research moves in the direction of computational biomedicine with activities in three main areas: genomics/omics and high-throughput bioanalytics; machine learning and clinical predictions; and cellular therapy matching and donor registry modeling.

Statistical Methodology Research

The CIBMTR/IBMTR has enjoyed a positive, collaborative



CIBMTR Number of Patients Registered, 1970-2021



association with MCW’s division of biostatistics since its inception. Dr. Alfred Rimm was its first statistical director. This association with a sophisticated biostatistics group is a distinctive asset and crucial to the success of CIBMTR research. Biostatisticians support investigators in developing scientific studies using CIBMTR data and ensure the statistical integrity of CIBMTR scientific activities.

CIBMTR biostatisticians also have pioneered novel methodologic approaches to analyzing cellular therapy data. HCT is a complex process with multiple competing risks and dramatic changes in the risks of specific events over time. The CIBMTR has developed and evaluated the statistical models used in cellular therapy research and helped guide the research community in their appropriate application and interpretation.

Clinical Trials Support

The CIBMTR manages a wide array of prospective studies in addition to those of the BMT CTN. These include multi-center Phase I-III trials, surveys and correlative studies. Clinical trial support capabilities include study planning; data collection; patient-reported outcomes; site management; study monitoring; immunobiology; statistical consultation; accrual assessment; trial interpretation; and long-term follow-up data. The CIBMTR’s observational Research Database is a valuable resource to support decisions regarding the design of prospective clinical trials.

Impact of the CIBMTR

The CIBMTR’s studies use sophisticated statistical techniques and the power of large numbers to address the most pressing issues in cellular therapy in a timely manner. CIBMTR research has determined outcomes of cellular therapy for rare diseases and new indications; defined trends in cellular therapy activity (such as increased use and success in older patients); identified factors affecting cellular therapy outcomes (such as age, stage and molecular markers of disease) and conditioning regimens; determined efficacy of various donor types (including sibling, unrelated and autologous) and graft sources (including cord blood, marrow and peripheral blood); compared HCT and non-HCT treatments; and assessed long-term quality of life and late complications after treatment.

This research reflects the dedication of thousands of hours of voluntary effort from physicians and scientists, their commitment to submit high-quality data to the CIBMTR, and their proposal and implementation of studies using those data. The unusually inclusive nature of the CIBMTR and its data access policies enables the CIBMTR to be available to a broad range of investigators in the field and, in a meaningful way, to physicians and patients dealing with difficult clinical decisions.

Accelerating Cellular Therapy Research

In 2016, the National Cancer Institute awarded the CIBMTR a grant to operate the CIDR as part of the Cancer Moonshot to accelerate cancer research under the Immuno-Oncology Translational Network. Through the CIDR, the CIBMTR gathers data on non-transplant cellular therapies for all cancers (including solid tumors), using a cellular therapy data infrastructure parallel to its HCT infrastructure.

New cellular therapies – such as CAR-T cells – bring extraordinary chances to help people with cancer. Through the CIDR, the CIBMTR collects data about the long-term safety and efficacy of these therapies, including conducting the FDA-required 15-year follow-up studies for all CAR-T cell products currently approved in the US. In turn, the CIBMTR will provide unprecedented access to these data to a diverse group of clinicians, researchers, manufacturers, payers, regulators and the public.

Cellular therapy has come a long way from its roots in the Cold War of the 1950s – from an experimental treatment for radiation sickness to a standard therapy for leukemia, lymphoma and sickle cell disease. Today, cellular therapy includes both blood and marrow transplantation and other adoptive cellular therapies.

As the CIBMTR celebrates its golden anniversary, it is poised to continue to expand the value that real-world data and clinical trials can bring to patients – saving lives by improving access to and outcomes of cellular therapies worldwide through research and translation. ■

