



The EBMT: History, Present, and Future

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2.1 Introduction

“Only he/she who knows the past has a future” is a proverb attributed to Wilhelm von Humboldt (1767–1835), a great historian, scientist, and philosopher (Spier 2015). It appears as an ideal introduction to a chapter on the history of EBMT. The context by which HSCT evolved in the middle of last century fits with modern views on history. The novel “big history” concept attempts to integrate major events in the past, beginning with the “big bang” up to today’s industrial revolution number IV (Spier 2015). According to this model, nothing “just happens.” Progress occurs when the conditions fit, at the right time and at the right place. Such circumstances are called “Goldilocks conditions,” according to the novel by Robert Southey (https://en.wikipedia.org/wiki/Goldilocks_and_the_Three_Bears, accessed November 6, 2018). They hold true for the formation of galaxies, suns, and planets, for the appearance of life on earth, or for

the evolution of mankind. They apply specifically to the latter: as the one and only species, *Homo sapiens* managed to create “Goldilocks conditions” by him or herself. They allowed man to fit religion, art, or beliefs in such ways to master society. In our perspective, big history thinking helps to understand the development of HSCT and EBMT and to view it in a broader framework. It provides as well a caveat for the future.

2.2 The Past: Development of HSCT and EBMT

The use of bone marrow (BM) for healing purposes dates back long in history, and BM from hunted animals might have contributed as rich nourishment to the evolution of *Homo sapiens* (McCann 2016). Its recognition as primary hematopoietic organ in adult life with a hematopoietic stem cell as source of the circulating blood cells began in the middle of the nineteenth century (Schinck 1920). It did result in some early recommendations on the potential therapeutic use of bone marrow (JAMA 1997; Osgood et al. 1939), but with no broader application. All changed after the explosions of atomic bombs in Hiroshima and Nagasaki in World War II, when survivors of the immediate exposure died from BM failure (Van Bekkum and De Vries 1967). Research was directed to find ways to treat this lethal complication. It led to the discovery that bone marrow-derived stem cells

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from a healthy donor could replace hematopoiesis after total body irradiation (TBI); it provided at the same time, a tool, TBI, to eradicate aberrant hematopoiesis (Van Bekkum and De Vries 1967; Jacobson et al. 1949; Lorenz et al. 1951; Ford et al. 1956). The concept of HSCT was born, and “the conditions were right.” It is to no surprise that the first clinical BMT centers in Europe started in hospitals with close links to radiobiology research institutes in the UK, the Netherlands, France, and Germany. Funding of radiobiology fostered basic research and stimulated clinical application. In the first series of patients reported in the NEJM in 1957 by the late Nobel Prize winner ED Thomas, all six patients died but two of them with clear signs of donor chimerism (Thomas et al. 1957). And, BMT “saved” accidentally irradiated workers of a radiation facility in Vinca, a town in former Jugoslawia (Mathé et al. 1959). Hence, the clinical results confirmed the “proof of principle” obtained in mice: TBI could eradicate normal and malignant bone marrow cells, and the infusion of healthy donor bone marrow cells could restore the recipient’s depleted hematopoiesis with functioning donor cells. In reality, of more than 200 patients reported by M. Bortin for the IBMTR, all patients with leukemia had died, many of them free of their disease. Three patients survived, all with congenital immune deficiency and transplanted from HLA-identical sibling donors (Bortin 1970). Despite the dismal results, Goldilocks conditions prevailed. Armed forces were convinced of the need for a rescue tool in the event of a nuclear war, physicians viewed BMT as an instrument to treat hitherto incurable blood disorders, and patients envisioned a cure of their lethal disease.

In order to improve outcome, the “believers” joined forces. They met each other, openly reviewed their cases and charts one by one, exchanged views on hurdles and opportunities, spent time together on the slopes in the Alps, and became friendly rivals: EBMT was born. Goldilocks conditions still prevailed. Leukemia could be eradicated. BMT with haploidentical donor bone marrow for SAA after conditioning with ATG yielded spectacular results (Speck et al. 1977). Today, we know that ATG, rather than the cells, was responsible for the outcome.

The introduction of intensive induction regimens for AML enabled stable phases of complete first remission (CR1) (Crowther et al. 1970). The discovery of CSA, as the first of its kind of novel IS agents, opened new dimensions in BMT and other organ transplantation (Kay et al. 1980). It became acceptable to transplant patients in early phase of their disease, e.g., CR1 or first chronic phase (CP1) (Thomas et al. 1975). The boom of BMT began (Thomas 2007; Gratwohl et al. 2015a). The first patient in the EBMT database dates back to 1965. In 1973, at the first informal gathering in St. Moritz, the database comprised 13 patients; 4 transplanted in that year. In 1980, a total of 285 HSCT were performed, increasing to 4025 10 years later.

HSCT rapidly diversified in terms of donor type, by including autologous and allogeneic stem cells from related and unrelated donors, and of stem cell source, from bone marrow and peripheral blood to cord blood. Indications expanded from the early congenital immunodeficiency, leukemia, and aplastic anemia to a full variety of severe congenital disorders of the hematopoietic system, to other hematological malignancies such as myeloma and lymphoma, and to non-hematological malignancies, e.g., germ cell tumors. The HSCT technology improved to encompass a variety of in vivo and ex vivo GvHD prevention methods and conditioning regimens of varying intensities with or without TBI. HSCT became open to centers with no links to radiobiology institutes and was no longer bound to “sterile units” and to selected countries (Gratwohl et al. 2015a; Copelan, 2006).

The previously informal gatherings and the database no longer sufficed to share the urgently needed information exchange. EBMT became a formal structure, with elections for presidents and working party chairs. It was listed in PubMed for the first time in 1985 (EBMT 1985). The meetings were no longer confined to ski resorts and became open to all involved in patient care and scientific analyses (Table 2.1). Obviously, organization of the annual meeting is today a major undertaking and only possible with the support of corporate sponsors. Still, the initial spirit remains.

Table 2.1 List of EBMT meetings and presidents

Year	Location annual meeting	Participating groups	EBMT president
1974			Informal gathering
1975	St. Moritz, Switzerland	1st P	
1976	St. Moritz, Switzerland	2nd P	B. Speck ^a
1977	Courchevel, France	3rd P	B. Speck ^a
1978	Courchevel, France	4th P	B. Speck ^a
1979	St. Moritz, Switzerland	5th P	E. Gluckman
1980	Sils-Maria, Switzerland	6th P	E. Gluckman
1981	Courchevel, France	7th P	E. Kubanek
1982	Courmayeur, Italy	8th P	E. Gordon-Smith
1983	Oberstdorf, Germany	9th P	E. Gordon-Smith
1984	Granada, Spain	10th P	J. Barrett
1985	Bad Hofgastein, Austria	11th P, 1st N	J. Barrett
1986	Courmayeur, Italy	12th P, 2nd N	A. Marmont ^a
1987	Interlaken, Switzerland	13th P, 3rd N	A. Marmont ^a
1988	Chamonix, France	14th P, 4th N	G. Gharton
1989	Bad Hofgastein, Austria	15th P, 5th N	G. Gharton
1990	The Hague, Netherlands	16th P, 6th N	J. Goldman ^a
1991	Cortina d'Ampezzo, Italy	17th P, 7th N	J. Goldman ^a
1992	Stockholm, Sweden	18th P, 8th N	J. Goldman ^a
1993	Garmisch-Partenkirchen, Germany	19th P, 9th N	J. Goldman ^a
1994	Harrogate, UK	20th P, 10th N	A. Gratwohl
1995	Davos, Switzerland	21st P, 11th N	A. Gratwohl
1996	Vienna, Austria	22nd P, 12th N	A. Gratwohl
1997	Aix-les-bains, France	23rd P, 13th N	A. Gratwohl
1998	Courmayeur, Italy	24th P, 14th N	A. Bacigalupo
1999	Hamburg, Germany	25th P, 15th N	A. Bacigalupo
2000	Innsbruck, Germany	26th P, 16th N	A. Bacigalupo
2001	Maastricht, Netherlands	27th P, 17th N	A. Bacigalupo
2002	Montreux, Switzerland	28th P, 18th N, 1st DM	J. Apperley
2003	Istanbul, Turkey	29th P, 19th N, 2nd DM	J. Apperley
2004	Barcelona, Spain	30th P, 20th N, 3d DM	J. Apperley
2005	Prague, Czech Republic	31st P, 21st N, 4th DM	J. Apperley
2006	Hamburg, Germany	32nd P, 22nd N, 5th DM	D. Niederwieser
2007	Lyon, France	33rd P, 23d N, 6th DM, 1st P&F	D. Niederwieser
2008	Florence, Italy	34th P, 24th N, 7th DM, 2nd P&F	D. Niederwieser
2009	Goteborg, Sweden	35th P, 25th N, 8th DM, 3rd P&F	D. Niederwieser
2010	Vienna, Austria	36th P, 26th N, 9th DM, 4th P&F	A. Madrigal
2011	Paris, France	37th P, 27th N, 10th DM, 5th P&F	A. Madrigal
2012	Geneva, Switzerland	38th P, 28th N, 11th DM, 6th P&F, 1st QM, 1st Ped	A. Madrigal
2013	London, UK	39th P, 29th N, 12th DM, 7th P&F, 2nd QM, 2nd Ped	A. Madrigal
2014	Milan, Italy	40th P, 30th N, 13th DM, 8th P&F, 3d QM, 3d Ped	A. Madrigal
2015	Istanbul, Turkey	41st P, 31st N, 14th DM, 9th P&F, 4th QM, 4th Ped	M. Mohty
2016	Valencia, Spain	42nd P, 32nd N, 15th DM, 10th P&F, 5th QM, 5thPed, 1stPha	M. Mohty
2017	Marseille, France	43rd P, 33rd N, 16th DM, 11th P&F, 6th QM, 6thPed, 2nd Pha	M. Mohty
2018	Lisbon, Portugal	44th P, 34th N, 17th DM, 12th P&F, 7th QM, 7thPed, 3d Pha	M. Mohty
2019	Frankfurt, Germany	45th P, 35th N, 18th DM, 13th P&F, 8th QM, 8th Ped, 4th Pha	N. Kröger

Participating groups: *P* physicians, *N* nurses, *DM* data manager, *P&F* patient and family day, *QM* quality manager, *Ped* pediatricians, *Pha* pharmacists

^adeceased

2.3 The Present

Today, EBMT (www.ebmt.org) is a nonprofit organization with a clear mission statement: “To save the lives of patients with blood cancers and other life-threatening diseases by advancing the fields of blood and marrow transplantation and cell therapy worldwide through science, education and advocacy” (<https://portal.ebmt.org/Contents/About-EBMT/Mission-Vision/Pages/Mission%2D%2DVision.aspx>. Accessed 26 Feb 2018). It is formally a professional society with legal residence in the Netherlands and an administrative office in Barcelona, Spain. EBMT is chaired by the president, who is elected by the members for 2 years and for a maximum of two terms. He/she is supported by the board of association as the executive committee and the board of counselors as external advisors. The scientific council which represents the 11 working parties, the seven committees, and the groups guides the scientific work with the help of the seven offices (Table 2.2). The main task of the organizational body of EBMT is to collect, analyze, and disseminate scientific data; to conduct clinical trials; to improve quality through the close cooperation with JACIE and FACT; to plan the annual meeting, the educational events, and training courses, including the EBMT Handbook; and to provide assistance to patients, donors, physicians, and competent authorities.

Members of the EBMT are mainly centers active in transplantation of hematopoietic stem cells (HSC) or any other organization involved in the care of donors and recipients of HSC. Currently (January 1, 2018), EBMT holds 509 full center members and 55 associate center members, 122 individual, and 35 honorary members, from 65 different countries. EBMT is supported in its activities through the membership fees and the revenue of the annual meetings and by its corporate sponsors (<https://www2.ebmt.org/Contents/Members-Sponsors/Sponsors/Listofcorporatesponsors/Pages/List-of-corporate-sponsors.aspx>. Accessed 26 Feb 2018). EBMT is part of the global network of organizations involved in HSCT, the Worldwide Network for Blood and Marrow Transplantation (WBMT), and in close link with national and other

Table 2.2 EBMT working parties, committees, groups and offices

<i>Working parties</i>	
ADWP	Autoimmune Diseases Working Party
ALWP	Acute Leukemia Working Party
CMWP	Chronic Malignancies Working Party
CTIWP	Cellular Therapy & Immunobiology Working Party
IDWP	Infectious Diseases Working Party
IEWP	Inborn Errors Working Party
LWP	Lymphoma Working Party
PDWP	Paediatric Diseases Working Party
SAAWP	Severe Aplastic Anaemia Working Party
STWP	Solid Tumors Working Party
TCWP	Transplant Complications Working Party
<i>Committees</i>	
	Nuclear Accident Committee
	Donor Outcomes Committee
	Statistical Committee
	Registry Committee
	JACIE Committee
	Global Committee
	Legal & Regulatory Affairs Committee
<i>Groups</i>	
	EBMT nurses’ group with its own president
	Data managers’ group
	Statisticians’ group
<i>EBMT units</i>	
	EBMT Executive Office, Barcelona, Spain
	JACIE Accreditation Office, Barcelona, Spain
	EBMT Central Registry Office, London, UK
	EBMT Data Office, Leiden, The Netherlands
	EBMT Clinical Trials Office, Leiden, The Netherlands
	EBMT Data Office/CEREST-TC, Paris, France
	EBMT Activity Survey Office, Basel, Switzerland

Courtesy: EBMT office Barcelona, Marta Herrero Hoces

international professional organizations involved in HSCT, such as AFBMT, APBMT, CIBMTR, EMBMT, LABMT, or WMDA. The EBMT database now holds information on more than 500,000 transplants. Over 35,000 new patients were treated annually over the last 5 years and more than 40,000 HSCT performed (Fig. 2.1). An estimated number of more than 400,000 patients are currently alive after HSCT in Europe; they reflect the EBMT achievements and the challenges ahead.

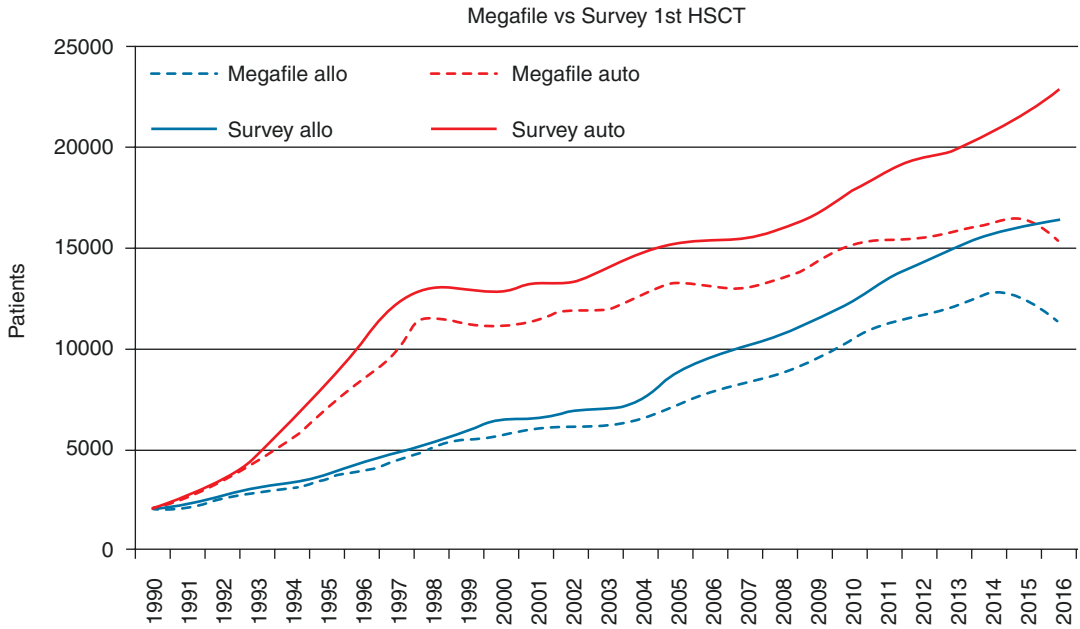


Fig. 2.1 Numbers of patients with a first HSCT by main donor type and year of transplant. The lines reflect the difference in patient numbers with and without information

in the database (megafile). Courtesy: Carmen Ruiz de Elvira, EBMT megafile office, London; Helen Baldomero, EBMT activity survey office, Basel

2.4 The Future

Again, according to the Big History concept, predicting the future is a difficult task: “There are no data about the future; from an empirical scientific point of view, it is impossible to say what lies ahead of us.” (Spier 2015). But we can project scenarios; we know the past, and we see the today. We live in the rapidly evolving world of the industrial revolution IV, dominated by globalization, digitization, and personalized medicine. Targeted therapies promise cures; gene-modified cells destroy hitherto untreatable cancers; immunomodulation with checkpoint inhibitors has become a reality (Hochhaus et al. 2017; Tran et al. 2017; Le et al. 2015). If HSCT is to remain a valuable treatment, mentalities and methods of the past no longer suffice. The idea of beliefs, hence physicians creating their own Goldilocks conditions, will lead to the end of HSCT. It has to be replaced by a stringent scientific approach. The sad story of HSCT for breast cancer, with more than 40,000 transplants but no clear answer, must not to be repeated (Gratwohl et al. 2010).

Hence, prediction number one: The idea of “a donor for everybody” will be abandoned. HSCT has to provide for the individual patient the best outcome regarding overall survival, quality of life and costs. The outcome after HSCT must be superior, in these three aspects, to any of the modern drugs or treatments, including “watch and wait” strategies or palliation. Assessment of risks needs to integrate risk factors relating to the patient, his or her disease, the donor, the stem cell source, the transplant technology, as well as micro- and macroeconomic risk factors (Gratwohl et al. 2015b; Gratwohl et al. 2017). For some patients, early transplant will be the optimal approach; for others, HSCT may need to be delayed. For others, HSCT will never be the preferred option. Obviously, the transplant physician is no longer in a position to adequately assess risk in comparison to the multiple alternative strategies, as it was possible in the old times of the simple EBMT risk score. Machine-learning algorithms will replace risk assessment; the competent physician will still be needed to discuss the results with his or her patients and their families and to conduct the transplant (Verghese et al. 2018).

Hence, prediction number two: The WHO guiding principles for cell, organ, and tissue transplants, “data collection and data analysis are integral parts of the therapy”, need to become a mandatory reality for all transplant teams (WHO 2010). The gap between transplant numbers and reports (Fig. 2.1) has to be closed. Reporting has to become real-time and life-long. The EBMT and transplant centers have to adapt. Data and quality management will become a “condition sine qua non” for all, with close interactions between local, national, and international organizations. Machine learning will end the individualistic center unique transplant techniques. It will no longer be possible to apply hundreds of different GvHD prevention methods and a multitude of conditioning regimens, just by the argument “I have good experience with my method.” Standardization will permit correct personalized medicine, as outlined above. Obviously, assessment of outcome can no longer be restricted to transplanted patients; it will need the correct comparison with non-transplant strategies on a routine basis.

Hence, prediction number three: HSCT centers and the EBMT will no longer be isolated in the treatment landscape. HSCT will need to be integrated into the treatment chain, from diagnosis to early treatment, transplant decisions, and secondary treatment, up to life-long follow-up. Not all of these steps have to occur at the transplant center, but they need to be coordinated by the expert team. Data have clearly shown that transplant experience, as measured in patient numbers and years, is associated with outcome (Gratwohl et al. 2015b). No center will have sufficient expertise for all diseases amenable to HSCT or for all transplant techniques, e.g., bone marrow harvest. HSCT centers will have to decide on their priorities, jointly with their referral and their after-care chain, within their city, their country, or with neighboring countries for coordination.

Hence, final prediction: EBMT can take the science-based lead for coordination and standardization, guide in reorganization of networks with non-transplant treatment chains, and priori-

tize comparative studies, independent of pressure groups. Then, history will tell, whether the proverb from a contemporary of von Humboldt, Georg Wilhelm Friedrich Hegel (1770–1831) “History teaches us that man learns nothing from history.” (Spier 2015), can be overcome. The potential is here.

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