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Pioneering 30 years of hematopoietic stem cell transplants in Puebla, Mexico.

Pioneros 30 años de trasplantes de células madre hematopoyéticas en Puebla, México

Javier Garces Eisele,[1,2] Juan Carlos Olivares Gazca[2,3,4]

"If I have seen further, it is by standing on the shoulders of giants"
Isaac Newton, 1676

The history of hematopoietic stem cell transplantation is marked by remarkable milestones. In the mid-20th century, Dr. E. Donnall Thomas achieved a landmark breakthrough by successfully performing the first bone marrow transplant between identical twins in 1956 (Thomas et al., 1957). This pioneering work laid the foundation for the exploration of hematopoietic stem cells and their role in treating diseases of the blood and immune system. Dr. Thomas' achievements earned him the Nobel Prize in Physiology or Medicine in 1990 – a testament to his groundbreaking contributions. Dr. George Mathé explored the transplantation of bone marrow cells from healthy donors to treat patients accidentally irradiated at high dose, expanding the possibilities of this life-saving technique (Mathé et al., 1959).

At the time they performed the first transplants surprisingly little was known about hematopoietic stem cells, immune responses to transplants or the complex human leucocyte antigen system. The work of Jean Dausset, whose discovery of the human leukocyte antigen (HLA) system revolutionized our understanding of tissue compatibility for transplantation (Dausset J, 1958). This breakthrough, for which Dausset was awarded the Nobel Prize in Physiology or Medicine in 1980,

[1] Laboratorios Clínicos de Puebla, Puebla, México.
[2] Universidad Popular Autónoma del Estado de Puebla, Puebla, México.
[3] Centro de Hematología y Medicina Interna de Puebla, Puebla, México.
[4] Universidad de las Américas Puebla, Puebla, México.

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Correspondence
Javier Garces Eisele
javier.garces@gmx.de

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opened the door to safer and more successful organ and stem cell transplantation. In April 1960, Dr. Álvaro Gómez-Leal, presented during the first meeting of the Agrupación Mexicana para el Estudio de la Hematología, A.C., data on a transplant of allogeneic stem cells in a patient with acute leukemia done in Monterrey, Mexico: the patient received high-dose chemotherapy followed by stem cells from the bone marrow of his brother, improving and obtaining remission for months but relapsing and subsequently died. This was the first report of a hematopoietic stem cell transplantation (HSCT) conducted in Mexico, only 4 years after the pioneer work by E. Donnall Thomas in Cooperstown, New York, USA (Ruiz-Argüelles et al., 2021). Twenty years later, in 1980, Ricardo Sosa and his coworkers at the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán conducted and published another HSCT (Sosa-Sánchez et al., 1980). As with many countries embarking on this procedure, there were challenges related to transplant-related morbidity and mortality. It was only until 1988 when the same group could report on their first successful bone marrow transplant (León-Rodríguez et al., 1992). In the late 1980s and early 1990s, the field of HSCT was still evolving globally. Changes in the sources and handling of hematopoietic stem cells were introduced. Stem cells were susceptible to cryo-preservation (Stiff et al., 1987). Umbilical cord blood was recognized as an alternative source of hematopoietic stem cells (Gluckman et al., 1989). Hematopoietic stem cells could be harvested easier from peripheral blood after mobilization with G-CSF (Sheridan et al., 1992). Since then, hematopoietic stem cells, with their unique ability to differentiate into various blood cell types, have proven to be a revolutionary tool in the treatment of numerous hematological disorders. The successful application of HSCT for diseases such as leukemia, lymphoma, myeloma, and inherited blood disorders underscored its broad applicability in clinical practice (Snowden et al., 2022).

The efficacy of HSCT extends to conditions beyond these well-established diseases. Research explored its use in autoimmune disorders with excellent results. HSCT offers a way to reset the immune system, providing a novel approach to treating conditions such as multiple sclerosis, systemic sclerosis, and rheumatoid arthritis (Swart et al., 2017; Alexander et al., 2021).

Furthermore, this approach is being investigated for its potential in non-hematological diseases. Promising preclinical studies suggest that hematopoietic stem cells could be harnessed to target genetic disorders, metabolic diseases, and neurodegenerative conditions. By utilizing the stem cells' remarkable ability to differentiate into various cell types, researchers are envisioning a future where hematopoietic stem cell transplantation could address a broader spectrum of medical challenges (Chen et al., 2021).

However, back in the early 1990s, while high-income countries were making strides in research and application, access to this life-saving treatment in middle-income regions like Mexico was limited mainly due to economic constraints and a lack of specialized facilities (Gale et al., 2016). These centers were concentrated in Mexico City. The development of infrastructure and expertise for HSCT was a gradual process. The cost of HSCT was high. Given the limited economic resources available to many in Mexico, not everyone could afford the procedure. Recognizing early this disparity since he initiated the program in 1993 (Ruiz-Argüelles et al., 1993), the group of Ruiz-Argüelles has made it his mission to increase accessibility of this pioneering therapy by focusing on the cost-effectiveness of transplant procedures without compromising on quality and outcomes. **Figure 1**

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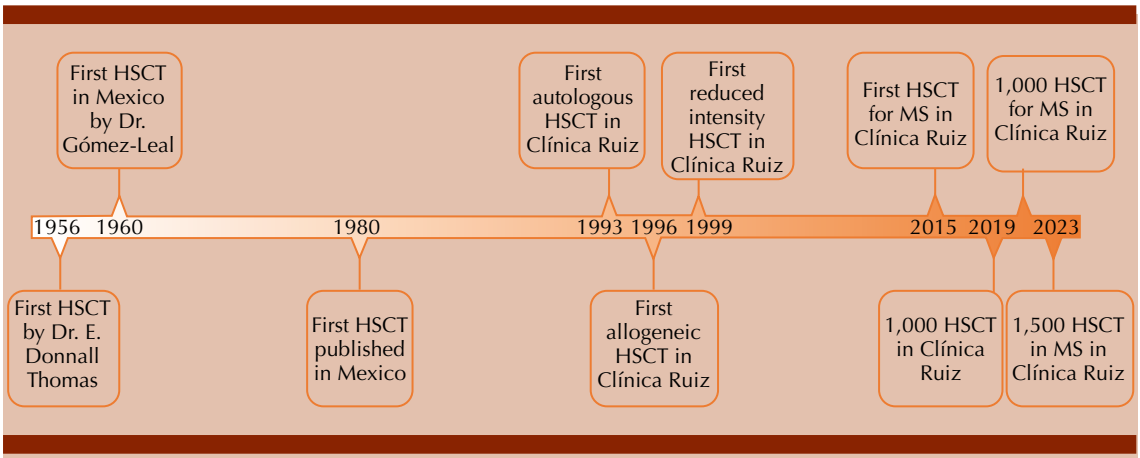

Figure 1. Timeline that depicts the history of HSCT in Mexico and Clínica Ruiz.

This goal was approached by the following measures:

1. **Outpatient transplantation:** Challenging conventional norms, one of the most significant changes introduced by Ruiz-Argüelles and coworkers was the concept of outpatient HSCT. Instead of keeping patients hospitalized for extended periods (which is standard in many high-income countries), he developed protocols where patients could receive transplants on an outpatient basis. This reduced significantly the costs associated with prolonged hospital stays while maintaining patient safety and outcomes are even better reducing the incidence of graft versus host disease (GVHD) and infections rate decreases. (Ruiz-Argüelles et al., 1998; Gómez-Almaguer et al., 2000; Ruiz-Argüelles et al., 2002).

2. **Modified conditioning regimens:** Increasing safety while maintaining efficacy of HSCT was the goal of modifying the conditioning regimens; nowadays they have been classified according to the duration of cytopenia and the requirement for stem cell support to three categories: (1) myeloablative conditioning, (2) reduced-intensity conditioning, and (3) non-myeloablative conditioning. As myeloablative regimens cause irreversible cytopenia, failure in engraftment is lethal. On the other hand, non-myeloablative regimens and reduced-intensity conditioning regimens may recover as cytopenia may not be irreversible (Bacigalupo et al., 2009). The first one relies on tumor destruction partly by chemotherapy as well as by the GVHD effect, while the second relies exclusively on GVHD. Ruiz-Argüelles, Gómez-Almaguer and coworkers refined the conditioning regimens used and achieved a delicate balance between safety (reduced degree and duration of cytopenia and thus the risk of complications) and efficacy, optimizing engraftment rates while minimizing adverse effects and, importantly, the risk of a graft failure (Gómez-Almaguer et al., 2000). These reduced conditioning regimens eliminated the need of laminar flow rooms and HEPA filters and thus were the cornerstone for the ability to perform the transplants on an outpatient basis (Ruiz-Argüelles et al., 2022).

3. **Utilization of biosimilar drugs:** When available and of good quality, the use of biosimilar drugs can reduce further the costs of transplantation. The groups of Ruiz-Argüelles and Gómez-Almaguer have been advocates for the appropriate use of national biosimilars in the HSCT process, ensuring of course, that cost savings do not compromise the efficacy of the treatment (León-González et al., 2017; Ruiz-Argüelles et al., 2022; Gómez-Almaguer et al., 2022; Gallardo-Pérez et al., 2023).

4. **Streamlined procedures**: By refining and streamlining the transplantation procedures, Ruiz-Argüelles et al. ensured that resources were used optimally, avoiding wastages and unnecessary expenses. One of these avoidable expenses is the cryopreservation of mobilized hematopoietic stem cells in autologous HSCTs (Ruiz-Argüelles et al., 1995; Gómez-Almaguer et al., 1997; Ruiz-Argüelles et al., 1998). Engraftment rate was even higher and thus reduced further the associated risks, in more than 70% of cases the procedure could be completed totally on an outpatient basis (Ruiz-Argüelles et al., 2008).

5. **Haploidentical transplants**: Recognizing the challenges in finding suitable unrelated donors and costs in obtaining a suitable graft, the groups of Gómez-Almaguer and Ruiz-Argüelles explored the potential of haploidentical transplants, where the donor is a half-match to the recipient. The advantages were evident: a donor is almost always (in 95% of the cases or higher) available immediately, it can be better selected based on natural killer cell alloreactivity, and the donor is available for repeated infusions, among others. By adapting chemotherapy to mitigate graft rejection and GVHD, he expanded transplant options for patients without fully matched donors (Ruiz-Argüelles et al., 2015; González-Llano et al., 2016). Again, the procedure could be safely conducted on an outpatient basis (Murrieta-Álvarez et al., 2021; Murrieta-Álvarez et al., 2021b). Very recently, the groups of Ruiz-Argüelles and Gómez-Almaguer have shown that the doses of post-transplant cyclophosphamide employed in the conduction of haploidentical transplantation, can be safely reduced to 50% of the original proposed doses (Olivares-Gazca et al., 2023)

6. **World class quality HSCT in Mexico**: The international community of bone marrow experts have analyzed the outcomes obtained by Ruiz-Argüelles and his team using his modified protocol to conduct HSCT. Nowadays, other programs in the world are replicating the method. On the other hand, this recognition by his pairs gave him the opportunity to share his experience in multiple meetings in different countries and very recently, the Ruiz-Argüelles program has been certified with the first step of two of the FACT-JACIE accreditation, being the third program in Latin-America to achieve this quality certification and the first one as a fully outpatient program.

There is an ever-increasing number of alternatives to HSCT for treating onco-hematological diseases, whose spiraling costs (Green et al., 2016; Weisdorf et al., 2017), however, are prohibitive to most patients in middle-income countries. Even conventional HSCT are out of reach to many patients in Mexico. The non-myeloablative allo-HSCT procedure cuts the cost (Ruiz-Argüelles, 2010) and has stimulated the instantiation of similar programs and influenced the development of simplified HSCT programs in other middle-income countries (Schroeder

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et al., 2011; Ramzi et al., 2012; Bittencourt et al., 2019; Aljurf et al., 2020; Bekadja et al., 2021; Ahmed Al-Anazi et al., 2023). Built on his ample experience, Ruiz-Argüelles and coworkers have elaborated guidance on how to start and stepwise develop an affordable HSCT program in resource-limited settings (Ruiz-Argüelles GJ, 2020; Ruiz-Argüelles et al., 2021; Ruiz-Argüelles et al., 2022).

Drawing from his experience in HSCT, the groups of Ruiz-Argüelles and Gómez-Almaguer began exploring further the potential of an autologous HSCT (aHSCT) for patients with autoimmune conditions such as multiple sclerosis (MS). His vision was to offer an alternative treatment option for patients who were not adequately responding to conventional therapies or experiencing significant disease progression (Ruiz-Argüelles et al., 2017; Ruiz-Argüelles & Gómez-Almaguer, 2017).

MS is a chronic autoimmune disease that affects the central nervous system, causing inflammation, demyelination, and neuronal damage. This leads to a wide range of neurological symptoms, including asthenia, balance disorder, fatigue, and cognitive impairment. MS is a complex and unpredictable disease, and while there are disease-modifying therapies available, not all patients respond adequately to these treatments (Dobson & Giovannoni, 2019; Piehl F, 2021; Kuhlmann et al., 2023).

Treatment by aHSCT aims at "resetting" the immune system by controlling autoreactive clones and instilling immunological tolerance upon the reestablishment of the immune system. The results showed encouraging evidence of disease stabilization and even improvement. Patients who underwent aHSCT reported a reduction in relapse rates, disability progression, and inflammatory disease activity, leading to an improved overall quality of life (Ruiz-Argüelles et al., 2018; Ruiz-Argüelles et al., 2019; Murrieta-Álvarez et al., 2021c; Olivares-Gazca et al., 2022; Olivares-Gazca et al., 2022b; Sánchez-Bonilla et al., 2023).

Four years ago, the 1000th HSCT was performed by the group of Ruiz-Argüelles (Gómez-Cruz et al., 2019; Maziarz RT, 2020) and 2 years ago it has been the 1000th aHSCT in patients with MS and other autoimmune disorders, highlighting the success of this program (Murrieta-Álvarez et al., 2021). In this year, the program led by Ruiz-Argüelles accomplished the first 1,500 patients engrafted with MS as depicted in **Table 1**. The work by both Gómez-Almaguer and Ruiz-Argüelles has been acknowledged by the Center for International Blood and Marrow Transplantation Research (CIBMTR), who presented them with the Distinguished Service Award in 2017, as a reflection of a lifetime commitment with improving the accessibility of patients to high-cost therapies in an underdeveloped country always thinking "outside the box". Now, México as a country and Monterrey and Puebla as cities are on the map as the most important centers for HSCT in the country and a reference to the world.

Table 1. Number of HSCT performed in centers that report to the CIBMTR since initiating their programs

Mexican Centers Reporting to the CIBMTR			
Institution	**Year of first report**	**Total number of alloHCTs**	**Total number of autoHCTs**
Centro de Hematología y Medicina Interna, Clínica Ruiz de Puebla	1993	194	1067
Hospital Ángeles Lomas	1999	15	3
Hospital Civil de Guadalajara	2005	1	1
Hospital de Especialidades, Centro Médico	1989	258	154
Hospital San José Tecnológico de Monterrey	2003	14	11
Hospital Universitario Dr. José Eleuterio González, Universidad Autónoma de Nuevo León	2003	504	210
Instituto Nacional de Cancerología	1993	0	56
Instituto Nacional de Pediatría	2005	102	8
Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán	2014	31	49

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