

A propósito del trasplante de células hematopoyéticas número 1000 efectuado en la Clínica Ruiz en Puebla, México

À-propos of the 1000th stem cell transplant conducted at the Clínica Ruiz in Puebla, Mexico.

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Resumen

El primer trasplante de células hematopoyéticas (TCH) en la Clínica Ruiz en Puebla, México, se realizó el 5 de mayo de 1993, fecha importante en Puebla debido a la conmemoración de la batalla librada en 1862, en la cual el ejército mexicano derrotó al francés en los fuertes de Loreto y Guadalupe. Desde entonces y hasta enero de 2019, se han realizado 962 trasplantes (735 de células autólogas y 227 de células alogénicas) y se calcula que para mayo de 2019, 26 años después del primer trasplante, se realizará el trasplante número 1000. Usando modificaciones a las formas tradicionales de llevar a cabo los TCH, hemos podido realizar el procedimiento con células hematopoyéticas alogénicas, autólogas, haploidénticas, de donadores compatibles no emparentados y de células placentarias. El programa se ha convertido en el programa de trasplantes de práctica privada más grande de México y el tercero entre todos los programas de TCH en nuestro país. Trabajando en conjunto con el programa de TCH en el Hospital Universitario de Nuevo León, hemos publicado alrededor de 160 artículos en revistas nacionales e internacionales revisadas por pares. Algunas de estas publicaciones han sido premiadas por instituciones nacionales e internacionales, como la Agrupación Mexicana para el Estudio de la Hematología, la Academia Nacional de Medicina, la Fundación Mexicana para la Salud, el Instituto CARSO, el Latin American Bone Marrow Transplant Group, el Center for International Blood and Marrow Transplant Research (CIBMTR) y el Programa Universitario de Investigación en Salud-UNAM. Asimismo, en febrero de 2017, los doctores Guillermo J Ruiz-Argüelles y David Gómez-Almaguer recibieron el Premio del CIBMTR al Servicio Distinguido 2017 por sus contribuciones a la actividad de los TCH en todo el mundo. La **Figura 1** muestra la actividad de TCH en la Clínica Ruiz iniciando el 5 de mayo de 1993 con el trasplante autólogo hasta el mes de enero de 2019. En los últimos 4 años, la actividad del TCH se incrementó sustancialmente, principalmente como resultado de la inclusión de personas con esclerosis múltiple. Nos hemos convertido en la instalación más grande del mundo que realiza trasplante autólogo en pacientes con esclerosis múltiple y otras afecciones autoinmunitarias. La **Figura 2** indica el diagnóstico de los pacientes que han recibido un trasplante autólogo en la Clínica Ruiz, mientras que la **Figura 3** muestra el diagnóstico de los pacientes con trasplante alogénico realizado en nuestras instalaciones.

PALABRAS CLAVE: Trasplante de células hematopoyéticas; trasplantes; publicaciones.

Abstract

The first hematopoietic stem cell transplant (HSCT) at the Clínica Ruiz in Puebla, Mexico, was done on May 5, 1993. The date is particularly important for Puebla, since that date, in 1862, the Mexican army defeated the French army precisely in Puebla, Mexico, in the forts of Loreto and Guadalupe. Since then and until January 2019, 962

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transplants have been performed (735 autologous and 227 allogeneic), and it is calculated that by May 5, 2019, 26 years after the first transplant, the 1000th transplant will have been done. Employing modifications to the traditional ways to conduct HSCT, we have been able to graft allogeneic, autologous, haploidentical, matched unrelated and placental cells. The program has become the largest private practice transplant program in Mexico, and the third among all programs in our country. Working together with the transplant program at the University Hospital of Nuevo Leon, our program has published around 160 papers in national and international peer-reviewed journals. Some of these publications have been awarded by national and international institutions such as: *Agrupación Mexicana para el Estudio de la Hematología*, *Academia Nacional de Medicina*, *Fundación Mexicana para la Salud*, *Instituto CARSO*, Latin American Bone Marrow Transplantation Group, *Programa Universitario de Investigación en Salud-UNAM*. On the other hand, in February 2017, doctors Guillermo J Ruiz-Argüelles and David Gomez-Almaguer were granted the *2017 Distinguished Service Award* for their contributions to the HSCT activity worldwide. The **Figure 1** depicts the HSCT activity of the Clínica Ruiz starting the autograft done in May 5, 1993 and ending in January, 2019. In the last 4 years, the auto-HSCT activity has increased substantially, mainly as the result of the inclusion of persons with multiple sclerosis (MS). We have become the largest facility in the world autografting patients with MS and other autoimmune conditions. The **Figure 2** indicates the diagnosis of the patients who have received an autograft at the Clínica Ruiz, whereas the **Figure 3** depicts the diagnosis of the patients who have been allografted at our facility.

KEYWORDS: Hematopoietic stem cell transplant; Transplants; Publications.

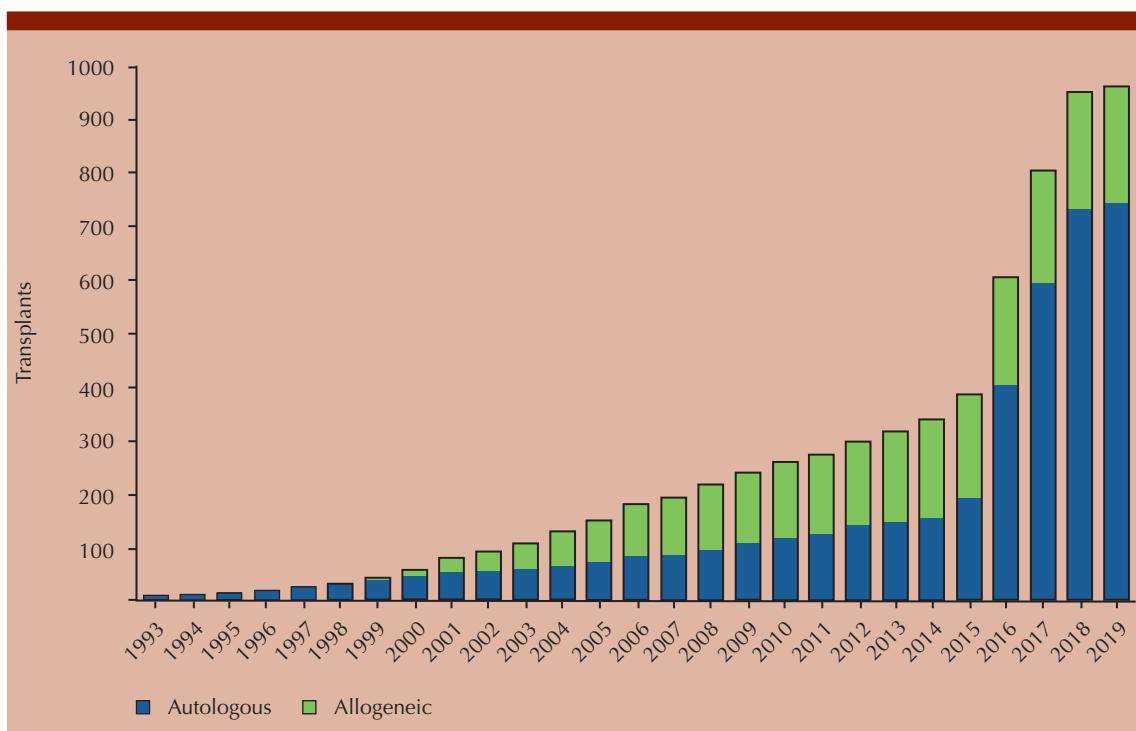


Figure 1. Hematopoietic stem cell transplants done at the Clínica Ruiz between May 1993 and January 2019.

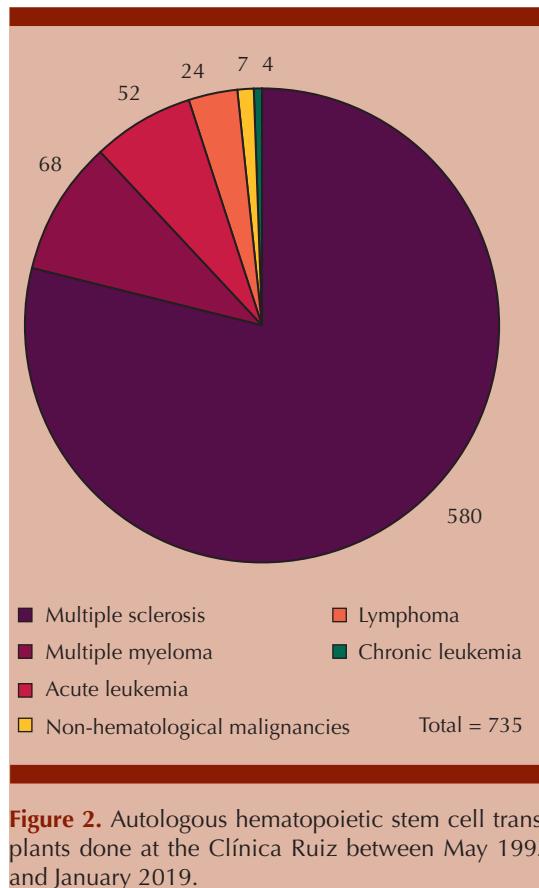


Figure 2. Autologous hematopoietic stem cell transplants done at the Clínica Ruiz between May 1993 and January 2019.

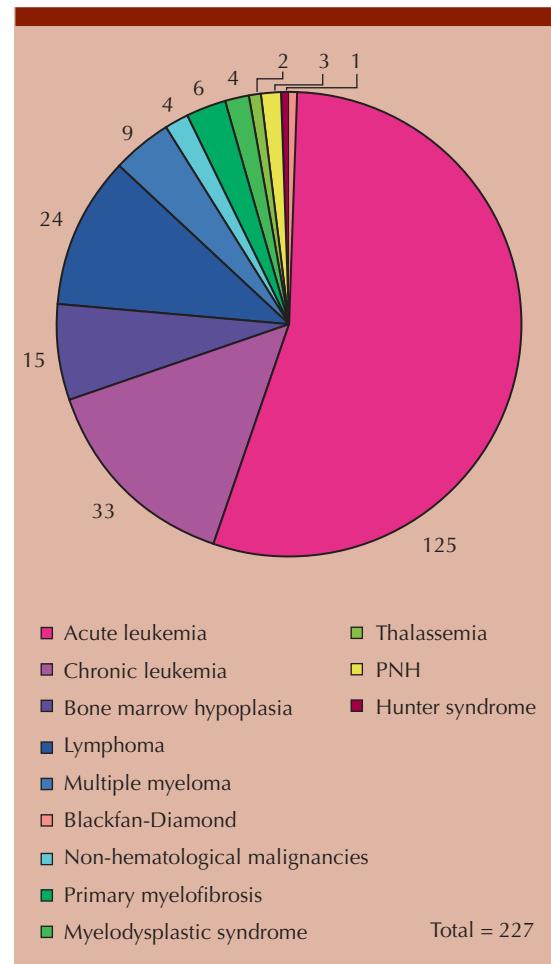


Figure 3. Allogeneic hematopoietic stem cell transplants done at the Clínica Ruiz between May 1993 and January 2019.

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Establishing stem cell transplantation programs globally

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The team at Centro de Hematología y Medicina Interna de Puebla are to be congratulated for the team they have constructed to deliver stem cell transplantation to the people of Mexico. They have provided a remarkable example of how a dedicated private organization can deliver high quality low cost care and be academically productive. This team has produced a number of important contributions that ultimately allow stem cell transplantation both allogeneic and autologous to be conducted throughout the developing world.

There have been remarkable developments in the treatment of multiple sclerosis particularly the introduction of ocrelizumab a recombinant human anti CD 20 monoclonal antibody designed to deplete B cells and significantly reduce the risk of disability in patients with progressive multiple sclerosis. In lymphoma the development of PD-1 inhibition has resulted in deeper response and more durable responses when combined with traditional chemotherapy. In myeloma the introduction of novel agents particularly lenalidomide and bortezomib have deepened response and have been responsible for improved survival. However the prohibitive cost of these drugs puts them out of reach for the majority of patients suffering with these disorders globally. The team led by Professor Ruiz-Argüelles has focused on stem cell transplantation which can be done at a fraction of the cost compared with the acquisition of new drugs. Much of their research in the private setting has been to reduce the cost of

transplantation and in so doing make it widely available throughout the world.

They have pioneered techniques in both autologous and allogeneic transplant to allow widespread utilization across the globe. There among the 1st groups to perform both allogeneic and autologous transplantation slowly as an outpatient. The elimination of hospitalization for the majority of patients reduces the cost substantially and makes it available to the masses. Some of the major technologic breakthroughs that further reduce the need for a massive infrastructure have included the use of stem cells that do not require cryopreservation but are merely refrigerated for up to 48 hr and can then result in prompt and stable engraftment. They have focused on non myeloablative conditioning regimens to reduce hospitalization risks associated with pancytopenia. They have described transplantation free transplantation as well as transplantation accomplished with only a single apheresis of a donor. The use of oral fludarabine as conditioning for allogenic grafting instead of parenteral fludarabine has made the cost of condition within the reach of almost anyone.

These contributions that allow implementation of a program in almost any country cannot be underestimated. The team has also published important data on outcomes and prognosis particularly the role of body mass index in predicting outcomes following transplantation. I very much look forward to the ongoing publications of this group as they move forward to 2000 transplants.

Stem cell transplantation in the Clínica Ruiz

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By May 2019, the Ruiz Clinic in Puebla, Mexico, will have performed 1,000 stem cell transplants since their first transplant in May 1993. More than 75% of the transplants were autologous with the remainder being allogeneic. This transplant program is the largest private practice program in Mexico and the third among all groups in the country. The Ruiz Group has published more than 150 national and international peer reviewed journal articles. They have been recognized by multiple national and international institutions. The number of patients transplanted has increased markedly in the past four years. Multiple sclerosis was the single most frequent disease that has undergone an autologous transplant accounting for almost 80%. An allogeneic transplant was performed on 227 patients.

I believe that an autologous stem cell transplant is a major therapeutic modality for patients with multiple myeloma. The problem, of course, is to determine whether the patient is eligible for the procedure. One must remember that the median age of patients with multiple myeloma is about 70 years. Thus, nearly one-half of patients are ineligible because of their age. We generally think of 70 years as the upper limit for stem cell transplantation, but we have transplanted many patients with multiple myeloma who are in their 70s. It depends upon the condition of the patient. If risk factors are modest, we feel that stem cell transplantation is an early and important procedure for multiple myeloma. Ordinarily we would give 4-6 weeks of chemotherapy followed by stem cell collection and transplantation.

Stem cells should be collected before the patient is exposed to alkylating agents. Peripheral blood is preferred compared to collection from the bone marrow. G-CSF with or without cyclophosphamide is the most common regimen used for stem cell mobilization. Plerixafor in combination with G-CSF is helpful for those patients who have failed stem cell collection with only G-CSF or G-CSF plus cyclophosphamide. A total of 3×10^6 CD34+ cells/kg are collected if one transplant is planned or 6×10^6 CD34+ cells/kg if two transplants are a possibility. Purging of the collected stem cells before transplantation is not of benefit. The stem cells are frozen and still retain their activity even after storage for many years. We recommend high-dose chemotherapy

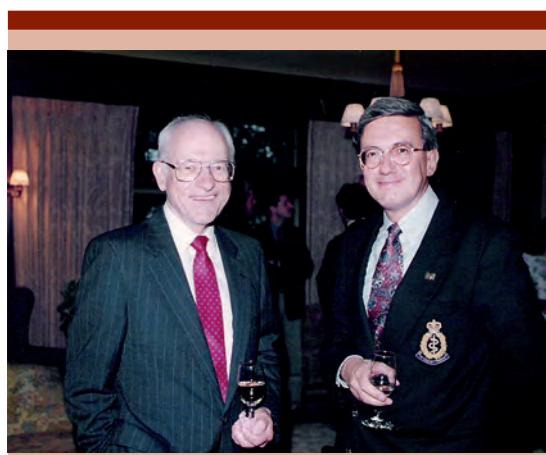


Figura 1. Profs. Robert A Kyle and Guillermo J. Ruiz-Argüelles at the Mayo Foundation House in Rochester MN, USA, in 1983.

(melphalan 200 mg/m²) as soon as the patient has recovered from the collection process. If the patient wishes to delay transplant until the first relapse he may do so because either early or delayed autologous transplantation for multiple myeloma produces comparable results.

Our criteria for stem cell transplantation are patients < 70 years of age, but we have transplanted patients well into their 70s providing that their "biologic" age is approximately 70 years.

We begin the procedure in most individuals as an outpatient. They are seen daily and if fever or other evidence of infection occurs the patient is treated with antibiotics and then either hospitalized or monitored very closely. Usually the duration of hospitalization is only a few days.

The accomplishment of the Ruiz Clinic in reaching 1000 stem cell transplants is impressive. It is interesting to note that multiple sclerosis patients are treated by transplantation.

The evolving landscape of (bone marrow) transplantation: a personal perspective in celebration of a landmark event

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There are many achievements that need to be celebrated. In Australia, it is usual to celebrate a birth, various 'comings of age' (such as a 21st birthday), a new and exciting job, weddings and anniversaries to name a few. My own personal milestones include many of the above, as well as two separate careers. My current career, in the specialized field of thrombosis and hemostasis, has passed its 25th year anniversary, and seen me reach a kind of peak in my career, for example with various positions on scientific journals and societies, including my 11th year

as Editor in Chief (EIC) of the journal *Seminars in Thrombosis and Hemostasis (STH)*. However, this is my 'second' career. Prior to switching to thrombosis/hemostasis, I spent some 10 years in the field of leukemia research. My main activity then was to produce and evaluate monoclonal antibodies for potential use in leukemia diagnosis and treatment. Indeed, although not generally known by colleagues in my current field, I was involved in various bone marrow transplant (BMT) related activities in the late 1980's.¹⁻³ In those days, monoclonal antibodies were the

new kids on the block and being widely investigated for potential utility in a wide assortment of applications. These were also the days when autologous and allogeneic BMT protocols were being developed or extended for an increasing number of indications, although clearly blood malignancies were where most of the focus was then placed.

I do not profess to be a current expert in this field, and indeed essentially started another path in my own life's journal some 25 years ago. Nevertheless, one's life journey takes you to many places to meet many people. I attend many scientific meetings, and as EIC of STH I read much in the scientific field, especially as related to thrombosis/hemostasis. Dr. Guillermo Ruiz Argüelles is one of the people that I crossed paths with along our separate journeys through life. Our first encounter was when he sent in some correspondence to STH around one of his other passions, Sticky Platelet Syndrome (SPS), which notably resides in the field of thrombosis/hemostasis. Guillermo wrote in response to a paper that STH had published on SPS⁶ and authored by another with a passion in the topic, Peter Kubisz, from a place called Martin in Slovakia. Well, this led to an eventual collaboration between Mexicans and Slovaks, supported by me as an Australian/Italian, culminating in another (jointly authored) paper on SPS in STH,⁶ as well as a couple of meeting invitations for both Guillermo and myself from Peter Kubisz and colleagues in Europe. Accordingly, I was fortunate to meet both Peter and Guillermo in Sarajevo in 2015, when we all attended the 18th International Meeting of Danubian League Against Thrombosis and Haemorrhagic Disorders (DLTH) International Meeting, Sarajevo, Bosnia and Herzegovina. On one of the meeting-free days, Guillermo and his wife Guadalupe agreed to accompany my wife (Beryl) and I on a side trip to the city of Mostar. That is an interesting story. When we enquired at the hotel reception in Sarajevo of a local tour

operator that could take us on a day trip to Mostar, a local employee, who also doubled as the local hotel barista and alternate keeper of the hotel's two-lane 10-pin bowling room offered to done his tour hat for the day. He did not really know where he was going, or where to take us, or indeed what to show us, but we nonetheless had a wonderful day on this road trip.



Figure 1. Prof. and Mrs. Emmanuel Favaloro; Mrs. and Prof. Guillermo J Ruiz-Argüelles in 2015, at Mostar, Bosnia-Herzegovina.

Our last reunion was in the city of Martin, attending the XXVth Slovak-Czech Conference on Haemostasis and Thrombosis, in 2018, where Guillermo was again accompanied by his wife Guadalupe, but also by a son, Manuel Ruiz-Delgado and his wife Edurne Ocejo-Fernandez. In the intervening period, Guillermo and I have shared many family photos and email correspondences. In the last photo he sent, he was a grandfather yet one more time.

Guillermo and I both share a common interest in both thrombosis/hemostasis and transplantation,

although we have pursued different paths in these fields. My main professional preoccupation is with thrombosis/hemostasis, but Guillermo's main professional preoccupation is with transplantation. Like me, Guillermo has also celebrated many milestones. He loves to share photos of his expanding family, is extremely proud of his children, and loves to celebrate his many times grandfather-hood (something that I am yet to attain). Within his career, a special milestone is approaching –that of the 1000th stem cell transplant (SCT) conducted at the Clínica Ruiz in Puebla, Mexico. As background to this milestone, their clinical research group has published over 150 papers in the field. Transplantation has evolved greatly from the time I was involved. Not only are outcomes much improved historically, but transplantation has moved from BMT to SCT with even better outcomes. Moreover, the clinical triggers for SCT are also shifting. Once the trigger was essentially a blood malignancy. Within the SCT practice undertaken in Mexico, blood malignancies comprise a smaller slice of the treatment pie, with most SCTs these days being performed as autologous hematopoietic SCTs for multiple sclerosis. This particular milestone is of course not just Guillermo's alone. Indeed, there are many clinical collaborators. And of course, there are the patients themselves. Most of these patients will have longer better lives because of this work. How many extra children have been born, and how many more grandparents been created, because of this work?

1000 SCTs. This is indeed a legacy. Congratulations to Dr. Guillermo Ruiz Argüelles and his team. Yet other legacies are created, such as the children –both Guillermo's and also those of the patients. I hope that these children and their children also excel in their chosen career. Several of Guillermo's children have followed his footsteps into medicine, and also into the 'family business' of SCT. So, 1000 SCTs... this is perhaps just the beginning!

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Stem cell transplantation in developing countries

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Unless my memory fails me, I believe I first met Guillermo Ruiz-Argüelles in 1987, when I attended for the first time the Annual Meeting of the American Society of Hematology held in Washington DC. Since then, we have forged a great friendship and mutually shared the development of our professional careers. I greatly admire the special innovative spirit that Guillermo has imprinted on his research activity that, to a large extent, he has carried out in collaboration with our common friend David Gómez-Almaguer. Although today we have been invited to celebrate the 1000th hematopoietic stem cell transplant (HSCT) performed at the Ruiz Clinic in Puebla, Mexico, I would like to emphasize that Guillermo's vast research activity has covered all areas of hematology, with HSCT being one of the most prominent among the many I should quote. In relation to the transplant activity led by Dr. Ruiz-Argüelles, I would like to highlight the innovative aspect of his contributions in the field of HSCT. Within the limitations of a developing country, such as Mexico, Dr. Ruiz-Argüelles has

always sought imaginative formulas that would allow for the administration of the most modern and sophisticated treatments at the lowest possible cost, but with an efficiency level comparable to that achieved in the economically more privileged countries. The innovations introduced in the strategy of HSCT ("Mexican approach") have allowed not only Mexican, but also patients from many other countries, to benefit from these effective and cost-beneficial strategies. It is not necessary to describe these contributions in detail, may it suffice to mention the recognition received by doctors Guillermo Ruiz-Argüelles and David Gómez-Almaguer who were awarded the 2017 Distinguished Service Award by the Center for International Blood and Marrow Transplantation Research (CIBMTR) for their contributions to the HSCT activity worldwide. I had the privilege of personally attending this thrilling award ceremony. I wish Guillermo to continue such outstanding activity for the benefit of many patients with hematologic diseases living in Mexico and Latin America.

Another Puebla milestone?

Robert Peter Gale

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History has a way of repeating itself. After the Reform War (1858-60) President Benito Juarez declared Mexico would stop interest payments on debt to members of the Triple Alliance (Bri-

tain, France and Spain). The French and Spanish invaded Veracruz but the Spanish withdrew and the French, directed by Napoleon III and led by General Charles de Lorencez, headed for Mexico

City. On May 5, 1862 the French expeditionary force approached Puebla from the North en route to Mexico City. There 8,000 well-equipped French troops faced off against 4,000 Mexican fighters led by Commander General Ignacio Zaragoza. The result was a stunning loss for the French, mostly because of an unorthodox plan by Zaragoza to dig a trench in the valley between Forts Loreto and Guadalupe (Figure 1). The message: ingenuity led to the Mexican victory (Figure 2). Oddly, Cinco de Mayo is widely-celebrated in Estados Unidos de America but only in Puebla state in Mexico.

A second point of interest is mole poblano, Mexico's unique contribution of the world's culinary heritage and, I think, the best of all of Mexico's moles. Although the origin of mole poblano is obscure and contested (I discount claims it was invented in Oaxaca) I prefer the legend it was created by nuns at the Convent of Santa Clara early in the colonial period. Upon hearing that the archbishop was to visit, the convent nuns panicked having no food suitable for such a distinguished guest. They prayed (naturally) and put together a dish of chili peppers, chocolate, almonds and an old turkey (a mole is a mix in Renaissance Spanish). The Archbishop loved it; the rest is culinary and cultural history.

Lastly, I point out the many interesting sites in Puebla including the old town and zócalo, the cathedral, the new Museo Internacional del Barroco by Toyo Ito and the Museo Amparo amongst others.

You may be wondering how any of this relates to celebrating of the 1000th haematopoietic cell transplant at the Clínica Ruiz. 1st, there is the ingenuity of the poblanos: Commander General Ignacio Zaragoza and the nuns of Convent of Santa Clara. Similarly, Prof. Ruiz-Argüelles and his colleagues developed innovations such as outpatient transplants and using refrigerated,

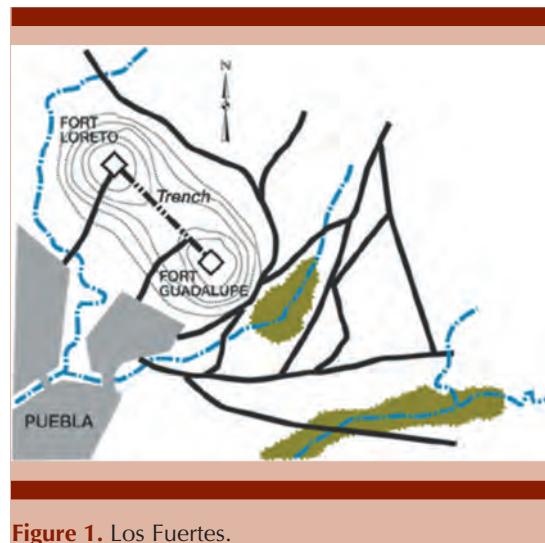


Figure 1. Los Fuertes.



Figure 2. Battle of Puebla.

non-frozen haematopoietic cell grafts which have helped expand transplants to developing

countries with technical and fiscal limitations. On to mole poblano, a mestizaje creation. This is also like Prof. Ruiz-Argüelles who claims Aztec, Amerindian and European ancestry. Next, there is the question of whether Clínica Ruiz should be added to Wikitravel as a must-see tourist sight in Puebla. Lastly, there is the issue of history repeating itself. Somehow, the mis-adventures of Napoleon III in Mexico remind me of President Trump and his Wall the cost of which he claimed Mexico would pay for. Dream on. We all recall what happened to Emperor Maximilian (**Figure 3**). Let's hope things turn out better for Estados Unidos de America under the current Administration. So, congratulations to Prof. Ruiz-Argüelles and his colleagues on their 1000th transplant!



Figure 3. Execution of Emperor Maximilian by Manet.

One thousand stem cell transplants (SCT) in Clínica Ruiz, Puebla, Mexico

David Gómez-Almaguer

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In the early nineties during a friendly dinner at Guillermo J. Ruiz-Argüelles and his wife Guadalupe's comfortable house in Puebla, Mexico, I remember a discussion that we had regarding the biological, technical complexity and also high cost of stem cell transplantation. At that time the stem cell transplantation (SCT) procedure was performed in special bone marrow transplantation units, the results were not always good and the task for doctors, nurses, family and more important the patient, was formidable. At that time death in this field was "around the corner" and also depression and burnout were not rare in SCT health professionals dedicated to the care of those patients. Back in

Puebla, I remember that we were enjoying dinner and some tequila when we finally agreed that no matter what, we should be involved in this complicated but unavoidable procedure. In Mexico in those days, only a few SCT had been performed with results far from those obtained in developed and rich nations.

Guillermo and I trained together in hematology in the same Mexican Institution in Mexico City: Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán. We have been close friends since the early eighties and shared the idea of developing a more sophisticated hematology practice in our country, always trying to

find ways to avoid great expenses in medical procedures, since Mexico was and still belongs to a low or middle economical ranking. We used to say "bring the best medicine possible at the lowest cost possible" in order to help not only the privately insured patient but also those persons living in poverty. Therefore, we soon began to perform outpatient autologous SCT. In the nineties this was purely the so called "disruptive innovation".



Figure 1. Mrs. and Prof David Gomez-Almaguer; Mrs. and Prof. Guillermo J Ruiz-Argüelles at Talin, Estonia in 2013.

We dedicated more time to develop our personal style of SCT procedures and in October 1998 at the Universidad Autónoma de Nuevo León the first reduced-intensity conditioning stem cell transplant was successfully performed, af-

terwards Guillermo in Puebla proposed that that kind of transplants could be done 100% as outpatients, and together developed this important program. The results were good, the costs low and therefore we were able to help more patients in our twin programs in Puebla and Monterrey.

Guillermo, his colleagues and our group in Monterrey have published many papers (more than 150) together sharing scientific ideas, many articles were created in order to promote new practical ways to make SCT more affordable (1-3). Curiously we both also share the honor of being recognized during the ASBMT/CIBMTR Tandem Meetings in Orlando, February 2017 with the "Distinguished Service Award" for our significant contribution and work in this field. Furthermore, the efforts at Clínica Ruiz by Guillermo and now together with his son Guillermo Ruiz-Delgado, have developed one of the most important and successful autologous SCT programs for multiple sclerosis patients.

Many hematologists from Mexico and also Latin-American have now been trained in this way to perform SCT, therefore the work at Clínica Ruiz and Guillermo's leadership have now a more positive impact in many patients living in less fortunate countries around the globe. There is much more to celebrate, but for now we congratulate Clínica Ruiz for their first 1000 SCT. Keep up the good work!...

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Our professional admiration to the work developed by the Clínica Ruiz

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The relationship between the Clínica Ruiz de Puebla (Mexico) and the Hematology Department at the University Hospital in Salamanca (Spain) started in the lates 80's, and settled on two outstanding figures of hematology for both countries: Dr. Guillermo Ruiz-Reyes in Mexico and Dr. Antonio López-Borrasca in Spain. They worked together with the common goal of establishing a solid collaboration between the hematologists of both sides of the Atlantic, and in order to achieve this goal they created the "Asociación Iberoamericana de Hematología", with the first congress held in Salamanca in 1992. But probably, the most ambitious dream for them was to publish, under the umbrella of the events of the Vth century of the arrival of the Spaniards into América, the *Enciclopedia Iberoamericana de Hematología*, fully written in Spanish. They did a huge effort by putting together over 300 hematologists leading the most important teams in Latin America and Spain, including some of them working in Europe or the USA but with Latin roots. The final result was a comprehensive text-book divided in four volumes.

Since then, we started a close collaboration with Guillermo and his brother Alejandro, who created the first flow cytometry laboratory in Mexico and one of the first in Latin America. They visited us in Salamanca and attended several Spanish meetings, at the same time we were invited several times to Mexico (including obviously Puebla), to scientific meetings and we have to

say that in all of them the team of Dr. Guillermo Ruiz-Argüelles had an important role, with his leadership capacity and hospitality. Over the time we had had the pleasant opportunity to see how much they have contributed to the development and visibility of Mexican Hematology and in favor of patients.

Now in the 21st century, when cell therapy and immunotherapy are magic words in medicine, it is important to remember that hematologists already pioneered this field, 46 years ago, when the first hematopoietic stem cell transplant was performed.

Today, it is a great pleasure for us to speak about the development of Clínica Ruiz, in one of the most complex procedures in Medicine, the hematopoietic stem cell transplant (HSCT). Guillermo J. Ruiz-Argüelles team started to do transplants in Mexico in 1993 and now they are celebrating the transplant number 1000. Congratulations!

When we think about the clinic activities of Ruiz-Argüelles team having in mind how difficult it has to be in Latin-American countries, as compare with USA or European countries, we realize how amazing their activity in hematopoietic stem cell transplant has been. They started with autologous stem cell transplant, but what is most relevant was the adaptation of their transplant program to scientific evolution.

It should be highlighted how the Clínica Ruiz adapted to patients necessities...many times with imagination but always with efficacy and safety. They performed autologous stem cell transplants without cryopreservation, they introduced reduced intensity conditioning (RIC) to offer transplant to more patients; they started as well ambulatory allogeneic transplants in order to offer the transplant to patients with few resources. They had the hypothesis that living at home is associated with less infections. Today, the importance of a diverse microbiota is being tested in prospective studies and, if you had spoken to Guillermo his assumption was that to keep the patients at home, with a diverse flora, was safer. How intelligent! More recently, in order to offer Mexican patients an allogeneic transplant, a haploidentical transplant program is running on.

Among the indications of these 1000 patients, they have included not only malignant but also non-malignant diseases; the Unit put their attention in multiple sclerosis, and probably they have one of the highest single center experience in the world.

The Puebla transplant Program has demonstrated its capacity to collaborate with National (Nuevo Leon Hospital) and international Societies (CIB-

MTR) projects. Nuevo León and Puebla have been recently granted and awarded by CIB-MTR because of their HSCT activities.

In summary, congratulations to the Ruiz-Argüelles team and family! We are very proud to be considered among their many, many, friends... because it is always an honor to be close to people that is never totally satisfied with the work they have accomplished, because they consider that there is still room to improve in benefit of their patients. Thanks...!!



Figure 1. Profs. Celso Campos-Guerra, Antonio Pa-
reira, Santiago Pavlovsky, Antonio Lopez-Borrasca,
Carmen Luisa Arocha-Piñango, Guillermo J Ruiz-
Argüelles and Jesús F San Miguel at Salamanca, Spain
in 1992.

A few additional observations

Carlos R Bachier

Secretary, FACT-JACIE. Sarah Cannon Center for Blood Cancer, Nashville, TN, USA.

Hematopoietic stem cell transplant (HSCT) activity in Latin America dates back to the early 1980's.¹ Since then the number of transplant programs has increased with a reported 11, 519 transplants in 94 programs and 12 countries in Central and South America. The Latin American Bone Marrow Transplant Group (LABMT), organized in 2011, represents programs in Latin America and promotes quality, reporting and education among transplant centers.

Clínica Ruiz HSCT program, under the direction of Dr. Guillermo J. Ruiz-Argüelles, standout among centers in Latin America through participation in clinical research, volumes, outcomes and quality programs. The program and its leaders are active members in the LABMT and the Worldwide Network for Blood and Marrow Transplantation (WBMT). Physicians, nursing

staff and other quality personnel are also active in organizations involved in quality including FACT and JACIE. Clínica Ruiz is included in programs seeking certification through the recently developed FACT-JACIE stepwise approach to accreditation. This accreditation requires program to comply with international standards and onsite evaluation by international inspectors.

Clínica Ruiz, as it reaches the milestone of 1000 transplant, will continue to lead Latin America as an example of high quality and exemplary care to patients in need of stem cell transplant therapies.

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Millennial patient in Puebla

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On the occasion of the millennial patient undergoing hematopoietic cell transplantation at the Clínica Ruiz in Puebla, Mexico, it is imperative that we review, and recognize, the achievements

of this institution. In the article in this issue of the *Revista de Hematología de México*, the author remarks on the commemoration of 5 May as the inaugural date of the transplant unit, a date redo-

lent with history in Mexico for its defeat of French forces. Still, given my heritage, my sympathies lie with Emperor Maximilian who was dealt a cruel fate, one that transplant patients in Mexico need not suffer, thanks to the skill and expertise of the medical and nursing staff at Clínica Ruiz!

The Clínica Ruiz, with the transplant program at Hospital Universitario de Nuevo León, has made a significant impact on the way we, in the field of Hematology and Transplantation Biology, think about management of acute and chronic leukemias. Clinical observation, and scientific inquiry by the program in Puebla has led to significant findings particularly as they pertain to delivery of care in an environment where there are challenges to drug procurement, radiographic imagine, and delivery of care. Some of these studies have had a direct impact on how we, in the transplant community, procure hematopoietic progenitors for cryopreservation and transplantation. Others have critically analyzed the impact of transplantation in the management of diseases such as multiple myeloma. The work at Clínica Ruiz has had a significant impact on how we deliver allogeneic grafts after a reduced-intensity or nonmyeloablative preparative regimen, and has

also provided the world community insights into haplo-identical transplantation.

For this investigator, one of the most valued contributions of the Clínica Ruiz has come from considering the escalating costs of transplantation, and the challenges that will come from administrative and regulatory processes in our field. I often reference the work of Drs. Ruiz-Argüelles and Gomez-Almaguer discussing allogeneic transplantation for CML in the era of tyrosine kinase inhibition, and the societal, and personal costs of our interventions. These same authors have recently asked the same questions about hematopoietic transplantation for non-malignant conditions such as multiple sclerosis and severe aplastic anemia.

The Clínica Ruiz has established itself as a leader in Latin America for delivery of high quality care in the setting of autologous and allogeneic transplantation. Its publications set a standard of high quality clinical inquiry throughout the world, and have made a valued contribution to literature in our field. I send my heartfelt congratulations to its medical and nursing staff and best wishes for continued success in the field.

Opinion piece

Linda J Burns

National Marrow Donor Program/Be the Match.

Since the first non-twin, allogeneic hematopoietic cell transplant (HCT) in 1968,¹ HCT has emerged throughout the world as a potentially curative therapeutic option for patients with over 70 hematologic and non-hematologic malignant and non-malignant diseases. Autologous and

allogeneic HCT is now performed in more than 1500 transplant centers in 75 countries.²

Since 1993, the transplant program at Clínica Ruiz in Puebla, Mexico has contributed significantly to the global advancement of the field

through clinical research and contributing patient outcomes to international observational databases such as the one maintained by the Center for International Blood and Marrow Transplant Research (CIBMTR). In fact, their contributions have been so significant that Dr. Guillermo J. Ruiz-Argüelles and Dr. David Gomez-Almaguer were recognized with the CIBMTR Distinguished Service Award in 2017.

The Clínica Ruiz physician-investigators have demonstrated the feasibility of autologous and allogeneic HCT with all donor (including umbilical cord and haploidentical donors) and graft sources in a developing country, often via novel approaches to circumvent obstacles to success. For example, cryopreservation of filgrastim-mobilized peripheral blood stem cells for use in autologous HCT is quite expensive. Dr. Ruiz-Argüelles, Dr. Gómez Almaguer, and colleagues demonstrated in a multi-center study of 259 consecutive subjects undergoing autologous HCT for myeloma and lymphoma that mobilized

stem cells can be stored at 4°C for 2-6 days with comparable post-transplant count recovery to those using cryopreserved stem cells. This method, as they noted, is "simple, inexpensive, and widely applicable".

Clínica Ruiz has also expanded the use of autologous HCT for autoimmune diseases such as multiple sclerosis and scleroderma. While much more about the long-term impact of HCT on autoimmune diseases is needed, the team at Clínica Ruiz is contributing to the world's knowledge about the outcomes of these patients who undergo HCT.

It is only through collaboration among transplant physicians around the world that knowledge is gained in a timely manner to benefit the patients we serve. Clínica Ruiz is certainly doing their part, and I offer my sincere congratulations to the entire team on reaching the milestone of the 1000th HCT performed.

Leading the way in access to care. Celebrating the 1000th transplant at the Clinic Ruiz, Mexico

George M Abraham

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As mentioned in other places in this publication, Clínica Ruiz in Puebla, Mexico performed its first hematopoietic stem cell transplant (HSCT) on May 5, 1993. It is expected that by May 5, 2019, 26 years after the first transplant, Clínica Ruiz will have completed its 1000th transplant procedure. While this is a singular milestone for any

organization, this is all the more noteworthy as the setting is an independent physician practice, collaborating with an academic medical center, but not deriving its financial support from it.

More importantly, the accomplishment is singular in its opening up access for patients

who might otherwise not have had access to such technology, making it affordable and accessible, in a resource-poor setting. Through their prolific publication about their work, they have shared their experience and methodology with the world at large, allowing duplication of such work in other resource-poor settings.

From a public health standpoint, the Clínica Ruiz experience provides valuable insight for others:

1. Access to care is a challenge in many parts of the world. Access includes affordability of care and resources in terms of technological advancements. Poorer countries are unable to devote the financial and other technological infrastructure necessary to develop newer advances in medicine, as the more affluent counterparts in the Western hemisphere are able to do. Thus, they are left to either importing such technology, often at staggering cost, or access on an experimental basis through 'grants' or 'charity'. This leads to the problem of selective centers developing technological advances which are not generalizable to a larger population. Additionally, such care becomes 'unaffordable' and out of the reach of the common person, leading to care being accessible only to those who can afford it.
2. There is a wider education that is developed, of the public at large, through news of such available technologies locally. The lay public understands that diseases once considered incurable may now be curable or manageable on a long term basis. This also leads to a general awareness about chronic disease, in the general public. Through such awareness, there is a new opportunity to enhance awareness of transmissibility, risk factors for acquisition, health lifestyle, inheritance patterns and acceptability of disability, when such exists.

3. Lastly, the development of such technology through the entrepreneurship of entities such as Clínica Ruiz can serve as a model for development of other such partnerships, or hybridization of newer technologies in other spheres, possibly even in the larger realm of biotechnology, not exclusively to medicine alone. The greatest strength is the ability to develop technology at a fraction of the cost, the ability to tailor it to local needs and its availability in the local vernacular that makes it understandable to the patient, leading to better compliance.

From an infectious disease perspective, hematopoietic stem cell transplantation (HSCT) has revolutionized the treatment of hematological malignancies and several other chronic diseases as outlined in Dr. Ruiz' bibliography of their clinical experience. It also brings with it, its share of challenges. Describing all the infectious complications of HSCT may be outside the scope of this narrative, suffice it to say, the biggest challenge is in making the immune system 're-learn' all its prior immune memory, which has been wiped out in the process of engraftment. Two big challenges exist in such patients:

1. The use of immunosuppressive therapy, post-HSCT, leads to vulnerability to a host of different bacterial, viral and fungal infections, at various time points, mostly in the first year after HSCT. Treatment of such infections can, sometimes, necessitate the use of broad-spectrum antibacterial, antiviral or antifungal medications that come at a price and with its own share of complications. Other challenges may include availability of such medications on a consistent basis, especially if they have to be imported.
2. Recipients of HSCT need their immunizations redone, much like, a child getting their immunizations for the first time,

with the exception of some live vaccines. Challenges of an effective cold chain or affordability, can be challenges to completion of a revaccination program.

In summary, despite the potential barriers, the accomplishments of Clínica Ruiz in making

HSCT available to the people of Mexico, and their singular efforts over the last quarter century, is laudatory and commendable. It is our hope that this accomplishment serves as the foundation for continued growth in this arena, as also the advancement of numerous other frontiers in the healthcare field, in Mexico.

Trasplante de médula ósea en México: ¡Sí se puede!

Rafael Fonseca

Mayo Clinic in Arizona, Getz Family Professor of Cancer. Chair, Department of Medicine, Distinguished Mayo Investigator.

En esta edición el Dr. Guillermo Ruiz Argüelles presenta la casuística de su centro, reportando el trasplante de médula ósea (TMO) como tratamiento para enfermedades malignas e inflamatorias, como es el caso de la esclerosis múltiple. Es notable que el trabajo de la esclerosis múltiple representa la mayor experiencia en todo el mundo para el manejo de esta terapia contra esta enfermedad devastadora. Las pautas de servicio y calidad siempre han sido reconocidas para la Clínica Ruiz y el número de casos que se trasplantan sigue aumentando. ¿A qué se refiere este autor cuando dice "sí se puede"? Varios rubros lo demuestran.

Práctica e independencia

El aspecto emprendedor de iniciar un programa de trasplante de médula ósea tan grande y exitoso, fuera del marco de un hospital universitario o de un sistema de salud grande, es en sí mismo de gran valor. En Estados Unidos la mayor

parte de los programas de trasplante de médula ósea están afiliados a centros académicos y son menos comunes los que pertenecen a sistemas privados. En este último caso, estos sistemas generalmente son de tamaño más grande de lo que es la Clínica Ruiz. De tal forma que tener un programa en un hospital independiente, de gran calidad y que no directamente depende de un sistema de salud es admirable. Y es aún más admirable cuando este espíritu empresarial ocurre en México por las limitantes económicas extras y en el marco de un volumen de pacientes muy significativo. Sin embargo, los nexos con investigadores en Monterrey, y también a nivel nacional y mundial, han creado sinergias para la generación y transmisión de información médica nueva, originada por la investigación.

Acceso

Uno de los aspectos más innovadores del trabajo de la Clínica Ruiz ha sido el análisis detallado

de costos y necesidades para poder optimizar al grado máximo el acceso al trasplante de médula ósea como tratamiento, de tal forma que su impacto es mayor. Aspectos técnicos de uso común han sido retados y en algunos casos desechados. Por ejemplo, uno de los impedimentos más grandes para la diseminación del trasplante de médula ósea es la criopreservación de las células progenitoras. Esto aumenta de forma considerable el costo del procedimiento. El Dr. Ruiz-Argüelles y su equipo han sido líderes en el manejo de células tallo sin congelación, con un ahorro muy importante. Esto, aunado al manejo cuidadoso de otros gastos de apoyo al paciente, han hecho del trasplante de médula ósea algo accesible a un segmento mucho más grande de la población, que indudablemente sin esta innovación no tendría acceso a estas terapias.

Investigación

El trabajo realizado en la Clínica Ruiz no sólo tiene un carácter asistencial, sino que también ha contribuido a la investigación internacional. La experiencia se ha publicado en revistas nacionales e internacionales. Cabe la pena recalcar que en sí mismo el aspecto de investigación es de gran magnitud y refleja el deseo del grupo médico de compartir su experiencia. El total de publicaciones corresponde al volumen que normalmente se observa para un investigador exitoso, cuyo único deber es publicar. En este caso la publicación va aunada a una clínica muy activa. Las modificaciones que se han realizado

para el manejo de los medicamentos, procesos y productos celulares generan grandes ahorros y, en consecuencia, la diseminación de esta información es de gran importancia para optimizar los recursos, quizás con mayor importancia en países de economías emergentes.



Figura 1. Dr. Rafael Fonseca, Dr. Guillermo J Ruiz-Argüelles, Dr. Eduardo Cervera y Dr. Rubén Mesa.

CONCLUSIÓN

Como se menciona previamente, el sistema es exitoso y su futuro es brillante. Cuando uno tiene el deseo de crear procedimientos que se adapten a distintas economías y que proveen la misma calidad la palabra éxito sale a colación. En pocas palabras, ¡sí se puede!

Important milestone for the stem cell transplant program in Puebla, Mexico: on the edge of 1000 transplants

Dietger W Niederwieser

Past-president. Worldwide Network for Blood and Marrow Transplantation.

In May 2019, an important transplant center in Puebla Mexico will celebrate an impressive milestone. The program was initiated on May 5, 1993 under the direction of Guillermo Ruiz-Argüelles and has been developing steadily ever since, beginning with autologous HSCT, then progressing to include allogeneic transplantation from related and unrelated donors in 1999 and subsequently to haploidentical and cord blood transplants thereafter. From the very beginning up until March 2019 the program in Puebla performed a total of 962 HSCT and will reach the 1000 HSCT landmark in May 2019. This is a great achievement, particularly considering the challenges posed by the region and the difficulties that must be overcome. In a recent publication of the LABMT, Mexico was shown to have a team density of just 0,9 Teams /10 million inhabitants and in 2012 a total TR of only 19 HSCT /10 million inhabitants, 8 of which were autologous and 11 allogeneic (Jaimovic). The median TR rate in Latin America at this time was 64, ranging from 14 in Paraguay to 300 in Uruguay. In light of this situation, the activities at Puebla, that now span more than 26 years and have grown to more than 140 HSCT/year are particularly impressive. Among the 962 HSCT performed to date, the majority (n=735, 76%) were autologous. The program has become one of the largest in Mexico and contributes substantially to patient care on a national level. From the very start, the program has had a sound scientific foundation

leading to numerous national and international publications in peer reviewed journals covering key issues including transplantation techniques, indications for HSCT and the role of HSCT in severe aplastic anemia to mention just a few. The program in Puebla was also pivotal in founding the Latin-America Blood and Marrow Transplantation Group, a society that meets an urgent need on this continent by collecting survey data on a regular basis, initiating a system of accreditation and establishing a program of education in Latin America.

A closer examination of the HSCT program reveals unique regional characteristics in terms of indications but also some similarities with activities worldwide. Interestingly, the major indication in autologous HSCT is multiple sclerosis, which has accounted for 580 patients (78.9% of autologous HSCT). Only 9% of the patients received autologous HSCT for myeloma, 7% for acute leukemia and 3% for lymphoma. This is a remarkable difference to the worldwide pattern, where 89% of autologous HSCT were performed for plasma cell disorders, non-Hodgkin and Hodgkin diseases. The percentage of autologous HSCT carried out worldwide for autoimmune disorders is low but increasing. This unique and valuable experience employing non-cryopreserved peripheral blood stem cells in 286 patients is one of the largest and most informative worldwide to date.

The indications for allogeneic HSCT resemble the published worldwide experience with the majority being for acute leukemias (n=125) or chronic leukemias (n=33), followed by lymphomas, bone marrow failure, multiple myelomas and non-hematological diseases. In comparison, transplant indications worldwide involve acute

leukemias (55.4%), MPS (14.7%), chronic leukemias (4.1%) and bone marrow failure (6.5%).

We would like to congratulate the program in Puebla for these unique achievements and pay tribute to the contribution made by this centre to patient care in Mexico and worldwide.

Stem cell transplantation in developing countries

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The practice of medicine, among other areas, in developing countries does not keep pace with the progress in developed ones. The greater the complexity and cost of new procedures the greater becomes this distancing, in spite of the widespread dissemination of these achievements and their potentialities, especially those with great impact in the prevention, control and even cure of certain diseases. These advances become quickly known by the communities involved in each area of science, and these professionals are eager to apply these new resources for their own patients.

In developing countries, the factors that prevent or delay the availability of these cutting-edge resources are several, not to mention countless. These include lack of the required infrastructure, insufficient training in the various categories of participating professionals, scarce resources to cover the costs of the new therapeutic modality. This scenario may lead to distinct reactions ranging from an early and pessimistic decision

of not introducing a new resource to the incessant efforts to endow one's institution with ideal conditions to utilize the forefront therapeutic strategy. The implementation of any new procedure usually requires that parallel actions be taken, which can potentially contribute to its success, and this obviously triggers its cost.

Dr. Guillermo Ruiz-Argüelles, always paying attention to the advances in medicine, particularly in the field of Hematology, felt the need and the great disposition to make the hematopoietic stem cell transplantation feasible at the Clínica Ruiz in Puebla, Mexico. This clinic is a traditional Reference Center in Hematology in this country. This fact occurred on 05/05/1993 when the first autologous transplant was performed, and from year 2000 on the allogeneic HSCT were also made available in this service. This year Clínica Ruiz will perform the thousandth transplant. It is noteworthy that 75% (735) of these transplants were autologous, and in this modality the massive experience of this service was concentrated

in the application of this procedure in patients with multiple sclerosis. These numbers were achieved due to the drastic reduction in the costs of this procedure by re-dimensioning actions recognized as responsible for the higher cost, and also those related to the greater toxicity and its subsequent complications. This initiative aimed at increasing the availability of this treatment modality in countries with insufficient resources to carry it in larger scale. The achievements at Clínica Ruiz are particularly valuable because of the large casuistic of autologous transplants in patients whose bone marrow is intact, and most of them without previous exposure to chemotherapeutic treatment. The performance of BMT mainly at the outpatient clinic, the non-myeloablative conditioning regimen, the non-freezing of HTCs and the use of generic drugs resulted in fewer complications as well as similar hematopoietic recovery. These facts contributed to a major reduction in costs, and in turn, significantly expanded the range of the population with financial resources to undergo this procedure. Although the efficacy of this set of actions is clearly demonstrated, the long-term results in the different kinds of disease should be individualized and confronted before consecrating it as a model for reducing complications and greatly lower their cost.

In developed countries, the existing infrastructure in the medical field greatly facilitates the implementation of new and more complex diagnostic and therapeutic interventions. This same environment is rarely found in developing

countries, a fact that discourages and slows the implementation of these actions. The example demonstrated by Clínica Ruiz that sought incessantly to make BMT more accessible by searching for alternatives that until now show similar results compared to those existing in the medical literature where they use traditional methods. Since 1993 Clínica Ruiz's profile is of innovation and cooperation with other Mexican institutions. They have registered through numerous publications the results obtained using the various innovations introduced. The robust and unique accumulated experience in the field of multiple sclerosis will certainly contribute to more accurately assess the effect of high-dose chemotherapy on the best timing of application and the potential of this type of therapy to alter its natural history.

This experience led by the Ruiz Clinic Group, together with other Mexican institutions, demonstrate that developing countries when faced with challenges inherent to the implementation of more complex medical procedures may suggest and develop strategies that make them feasible and safe within the socioeconomic reality of their country.

Congratulations to Dr. Ruiz and his team for their contribution to the hematopoietic stem cell transplantation, as this initiative will increase the number of patients that will benefit from this new therapeutic procedure not only in Mexico but also in other developing countries.

What is behind a number?

Javier Bolaños-Meade

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A landmark that cannot go unnoticed in Mexican medicine is the fact that the Clínica Ruiz in Puebla plans to perform their one-thousandth haematopoietic stem cell transplant in the near future. This is no small accomplishment given the economic and scientific realities of Mexico. Reviewing the history of the Clínica Ruiz is reviewing the history of modern medical care in our country. The institution opened its doors in January of 1950, initially concentrating its efforts in the area of clinical laboratory medicine. Over the next 70 years, the institution evolved into a full-fledged medical institution capable of supporting both, allogeneic and autologous stem cell transplant care. Since their first transplant (curiously or purposely performed on May 5th, 1993) the research of the clinic has left a mark in Mexican transplant medicine:

1. The development of the "Mexican Method" for conditioning before a reduced intensity stem cell transplant.¹
2. Development of affordable schemas for stem cell transplantation, this is of great relevance for Latin American (as well as other) countries where health care expenses are limited and, in many cases, are paid in full by patients.²
3. Introduction of haploidentical transplantation to Mexico offering near-universal donor availability to all patients.³
4. The development of one of the largest transplant programmes in the world for

the treatment of patients with multiple sclerosis.⁴

5. The awarding of the CIBMTR Distinguished Service Award for contributions to the development of bone marrow transplantation in Mexico and Latin America. This was awarded during the BMT Tandem Meeting in Orlando, Florida in 2017.
6. And from my perspective, the most important achievement of all was the demonstration that multi-centre studies are possible in Mexico given the association of the medical centres in Puebla and Monterrey, allowing patients to stay closer to home during their treatments.

This list of achievements is in no way comprehensive, but it should give the reader pause to realize the impact that the group has had in the practice of medicine in our country. I hope that the group continues to perform cutting edge quality medical research, and to provide superb medical care so that the next thousand patients will benefit from their expertise.

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Another point of view

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Some 25 years ago Guillermo (Memo) Ruiz-Arquelles and I recognized that we had a common interest in the importance of nutrition in children with leukemia. Memo and his colleagues in Puebla had reported their first observations in 1989.¹ Our recognition prompted a face-to-face meeting over dinner during the annual meeting of the American Society of Hematology in 1993 in St. Louis. As usual Memo was accompanied by his great friend and long-time colleague David Gomez-Almaguer. On that occasion David fell asleep! What follows is a chronology of events in which I was privileged to form a close bond with multiple generations of family Ruiz and a rewarding friendship with Memo.

At the meeting of the International Society of Hematology (ISH) in Cancun in 1994 I met Memo's elegant wife Guadalupe (Lupita) and his parents, Rosa and Guillermo (Memo Grande). Guillermo Ruiz-Reyes, still the family patriarch, was then the President of the ISH.

Three years later Memo segundo and I organized the first international workshop on nutrition in children with cancer. It was held in Puebla at the Camino Real hotel, a converted 400-year-old convent (¡qué poblano!). The event was supported by the Union for International Cancer Control and the proceedings were published as a supplement to the International Journal of Cancer.²

In the following year, after a successful meeting in Monterrey hosted by David, I was introduced to caballitos by Memo Grande and his contemporary Ruy Perez Tamayo who is still working as a pathologist in Mexico City. Some years later Ruy gave me a beautifully illustrated book dedicated to the work of the late Spanish-Mexican artist Remedios Varo whom he had come to know. At some point in this saga I had received a special numbered bottle of tequila añejo from Memo Grande and we agreed that it would remain unopened until we savoured it together in Canada.

The opportunity came in 2000 when the ISH meeting was held in Toronto. Memo, Memo Grande, Rosa and Lupita came to visit my wife and me in Hamilton, and duly opened the bottle with the requisite accompaniment of sangrita (Rosa's recipe) and lemon juice served in a collection of caballitos which had been brought for the purpose by Memo.

That year was also a banner year for Clinica Ruiz as it celebrated its 50th anniversary and recognition of its laboratories by the International Organization for Standardization one year earlier; a first in Mexico and a tribute to the expertise of Memo's brother Alejandro. In 2001 it was a particular pleasure for me to join Memo, Lupita and his parents in my original home city when, on my nomination, Memo was inducted as an Honorary Fellow of the Royal College of Physicians and Surgeons of Glasgow, founded in 1599 (Figure 1).



Figure 1. Memo and family in Glasgow.

Back to Puebla in 2004 to celebrate Memo Grande's 80th birthday. Two years later we hosted the second international workshop in Puebla, again at the Camino Real hotel (Figure 2), this time supported by the Public Health Agency of Canada with the proceedings published as a



Figure 2. Group at Camino Real hotel, Puebla.

supplement to the journal *Pediatric Blood and Cancer*.³ And so to 2007 when Memo's accomplishments were recognized nationally with the Miguel Otero Arce award presented to him by President Felipe Calderón (Figure 3).

The pace picks up after a short hiatus. Memo served as the President of the ISH from 2010-2012 and presided over the meeting in Cancun in 2012, as Memo Grande had done 18 years



Figure 3. Memo with President Calderón.

earlier. In the following year he became a Master of the American College of Physicians. One year later my wife and I attended the wedding (**Figure 4**) of Memo and Lupita's middle son Manolo, Manuel Ruiz-Delgado, with whom I continue to share opinions on fine single malt Scottish whisky. In the following year Manolo's older brother Guillermo celebrated the arrival of Guillermo cuarto.



Figure 4. Manolo's wedding.

On a more mundane level, also in 2016, we (Memo, David and me) finally collaborated on a review of nutrition and leukemia in children.⁴ The relationship between Puebla and Hamilton was cemented professionally when we hosted three of the trainees at Clinica Ruiz for electives in laboratory medicine. Multiple visits to Niagara Falls and the neighboring wine country were an essential component of the experience (**Figure 5**).

September 2018 saw my daughter and I in Puebla (**Figure 6**). The highlight was a visit with Memo Grande in his home. He made us most welcome and engaged in fluent English, although he had not spoken his second language in 8 years. A remarkable, accomplished and generous man,



Figure 5. Mexican ladies at Thirty Bench.



Figure 6. CJ at lunch in Puebla.

he has an extraordinary legacy in his family and in the facility which he had the vision to create almost 60 years ago. Now we recognize one of its singular achievements, the 1000th hematopoietic stem cell transplant at Clinica Ruiz. Family Ruiz is well positioned to build on its successes with Manolo and Rodrigo Ruiz-Delgado having the business acumen and the oldest son Memo

tercero following in the hematological footsteps of his great grandfather, grandfather and father, my valued friend Memo (Figure 7).

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Figure 7. Four generations of Guillermo Ruiz.