Review

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Regenerative Medicine

Stem cell research in Latin America: update, challenges and opportunities in a priority research area

Stem cell research is attracting wide attention as a promising and fast-growing field in Latin America, as it is worldwide. Many countries in the region have defined Regenerative Medicine as a research priority and a focus of investment. This field generates not only opportunities but also regulatory, technical and operative challenges. In this review, scientists from Uruguay, Mexico, Chile, Brazil and Argentina provide their view on stem cell research in each of their countries. Despite country-specific characteristics, all countries share several issues such as regulatory challenges. Key initiatives of each country to promote stem cell research are also discussed. As a conclusion, it is clear that regional integration should be more emphasized and international collaboration, promoted.

Keywords: Latin America • regenerative medicine • stem cells

Verónica Palma*,‡,[1], Fernando J Pitossi**,‡,[2], Stevens K Rehen***,‡,[3], Cristina Touriño****,‡,[4] & Iván Velasco*****,‡,[5]

[1]FONDAP Center for Genome Regulation, Faculty of Science, University of Chile, Santiago, Chile

[2]Institute Leloir Foundation-IIBBA-CONICET, Buenos Aires, Argentina

[3]D'Or Institute for Research & Education (IDOR) & Institute of Biomedical Sciences, Federal University of Rio de Janeiro, Brazil

[4]Hospital de Clínicas Dr Manuel Quintela, Facultad de Medicina, Universidad de la República, Montevideo, Uruguay

[5]Instituto de Fisiología Celular - Neurociencias, Universidad Nacional Autónoma de México, México

*Author for correspondence: vpalma@uchile.cl

**Author for correspondence: fpitossi@leloir.org.ar

***Author for correspondence: srehen@lance-ufrj.org

****Author for correspondence: ctourino@hc.edu.uy

*****Author for correspondence: ivelasco@ifc.unam.mx

‡Authors contributed equally

Background

Latin America is a fast-growing region conscious of the relevance of stem cell research for the development of Regenerative Medicine, which we think will play a major role in healthcare. In October 2014, the authors of this review met at the I Latin American, VIII Brazilian and I Argentine Congress of Stem Cells and Cell Therapy that took place in Foz de Iguazú, Brazil. We decided to write about stem cell research in these countries since we detected common setbacks and areas of opportunity (Table 1). We hope that the presented view is useful to join efforts in Latin America countries and tackle problems such as regulatory issues and also set up regional collaborations in complementary areas. In addition, international collaboration to foster human capability building and technological transfer in key research areas is critical for the field to develop.

Stem cell research in Uruguay

General vision

Uruguay is the second smallest nation in size in South America with 3.3 million people. According to the World Bank, Uruguay spends about 0.4% of its gross domestic product (GDP) on research and development (R&D; Table 2) [2,3]. According to calculations of the Organization for Economic Cooperation and Development, this rate should double in the next 5 years to 1.5% by 2030.

As is typical throughout the region, the public sector is responsible for most of the country's R&D spending. This is the case of the Ministerial Bureau for Innovation, in which four ministries interact together with the Office of Budget and Planning in order to define general policies; the Sectorial Commission for Scientific Research (CSIC) at the public 'Republic University' (UR); the Directorate of Innovation, Science and Technology for Development of the Ministry of Education and the National Agency for Research and Innovation (ANII) [4].

CSIC is an organization that promotes research at the university through several programs for the allocation of competitive grants. In 1985, when democracy was restored, Uruguay had to start the process of rebuilding its ability to undertake research in the fields of science and medicine. Crucial

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Table 1. Current initiatives and areas of opportunity in some Latin American countries.

Country	Key initiatives	Strengths	Weaknesses	Opportunities
Uruguay	Creation of a national GMP Facility for Advanced Therapies Products in the Clinical Hospital Dr Manuel Quintela	Existence of a regulatory framework for management and manipulation of cells, tissues and organs Prioritization for the development of Regenerative Medicine and Cell Therapy by the Republic University and the Ministry of Health Ongoing research groups studying basic and clinical aspects of stem cells	Low medical research investment Scarce population for clinical trials	Participation in multicenter clinical trials in collaboration with the countries of the region Human resources training
Mexico	Public banking of newborn cord blood	Well-established programs on transplantation of stem/progenitor hematopoietic cells A small but solid community of scientists working on stem cells, including those that established the Mexican Society for Stem Cell Research	Low investment in science and technology (around 0.4% of GDP for the last years) Unclear regulation for treatments involving stem/progenitor cells, which results in risky medical practices for both local and foreign patients	Approve legislation that combines proper use and oversight of treatments involving stem/progenitor cells Establish stem cell programs that include basic scientists and clinicians within Latin America
Chile	Highly qualified human resources Promotion of translational research through new government initiatives targeting the development of new stem cell technologies	Long-term provided funding for basic and translational research Strong developmental science	Lack of specific regulation regarding biomedical scientific research or clinical trials with human stem cells Low private investment, research is basically performed at the Academia Poor influence of scientist in the respective environments in terms of the direction of research, public information and equitable access to treatments with stem cells in the country	Creation of a Ministry of Science and Technology Establishment of a national public GMP Facility for Advanced Stem Cell Therapies Repatriation of young high-qualified investigators, scientist working overseas not only in academia but also in government-supported research institutes
Brazil	The Biosafety Act, which allows scientists to work with human embryonic stem cells Creation of the National Network for Cell Therapy Creation of Cell Technology Centers Grants tailored to Stem Cell Research	Acquired knowledge on clinical trials using adult stem cells Acquired internal capacity to culture GMP adult stem cells Acquired internal capacity to derive and culture both embryonic and human induced pluripotent stem cells	Red tape on import of scientific goods Low critical mass Modest record of scientific publications Rare interactions with industry	Creation of the Brazilian Bank of Induced Pluripotent Stem Cells

Table 1. Current initiatives and areas of opportunity in some Latin American countries (cont.).

Country	Key initiatives	Strengths	Weaknesses	Opportunities
Argentina	Promotion of basic and translational research, stem cell consortium (CICEMA); human iPS Platform (PLACEMA), Binational program with Brazil (PROBITEC), advisory committee	Sustained increase in R&D investment during the last 10 years Regenerative Medicine as a priority area in a National Strategic Plan Highly qualified human resources, including >1200 returnees Existence of a guideline for management and manipulation of cells, tissues and organs Extensive experience in bone marrow transplantation and registry. Public cord blood bank accredited by AABB	Low critical mass in key areas Low private investment Absence of regulation in embryonic stem cells and improved regulation needed Stem cell research mostly centered in Buenos Aires and surrounding areas	Regional and international collaboration in basic, translational and clinical research Induced pluripotent stem cell Haplobank in the frame of international collaboration

to this effort was the creation of several programs for research promotion like the Program for the Development of Basic Sciences (PEDECIBA), the Program for Technological Development and the Program for Biomedical Research (PROINBIO). PEDECIBA was key to the reorganization of research in biology and other basic sciences. While biological research exponentially grew between 1985 and 1998, the generation of medical research during this period was poor. In an effort to address this problem, the PROINBIO was set up in the School of Medicine from the UR (SM-UR) to foster medical research by introducing master and doctorate degrees in biomedicine [5]. Although other schools of the UR perform health-related research, the SM-UR is the main producer of health research in the country [6]. In 2006, ANII was created as a public nonstate body to promote scientific and technological development and innovation. In 2007, the National System of Researchers was established to encourage research dedication through a system of economic incentives [7,8]. The National Institute for Donation and Transplantation (INDT) is the only governmental organization responsible for the regulation, policy and management of donation and transplantation of cells, tissues and organs operating within the UR and the Ministry of Health (MH) [9,10]. In Uruguay, there is extensive experience in hematopoietic stem cell transplantation, which is funded by the National Resources Fund allowing data centralization and research in this field [11,12].

Stem cell regulation in Uruguay

The MH is responsible for approving programs and authorizing centers to work with human stem cells with either clinical or nonclinical purposes. Each program and center with their human resources is technically and ethically evaluated before being enabled to develop human stem cell research. An unsolved problem in Uruguay is the existence of clinics offering unproven stem cells treatments. These clinics have established before approved laws and continue to be operative. In the last years, the National Ethics Committee for Human Research and the Ethics Committee of the Medical College from Uruguay were created and began to work in the regulatory field.

In the last years and due to private clinics offering stem cells banking and therapies, the Uruguayan authorities were concerned about the security and safety of these procedures. Thus, a strategic plan was developed by promoting regulation about standards, quality control and safety for cells and human tissue transplantation [13], as well as for research involving human beings [14].

Stem cell initiatives in Uruguay

The population of Uruguay is old with high incidence of degenerative and cardiovascular diseases similarly to developed countries. This population profile reflects a need to develop, or adopt once approved, similar therapies as the ones underdevelopment in developed countries. In 2009, the project 'Creation and Development of Cell Therapy and Regenerative Medicine (CTRM) Area at the Clinical Hospital' was approved for funding by CSIC-UR. The project objectives are to: consolidate a multidisciplinary academic group, develop a CTRM Program, create a Cell Therapy Unit, develop research projects and provide human resources training in this field. In 2013, this initiative was declared of national interest by the MH and in 2014, a strategic alliance was established with the INDT for the construction of a GMP Facility for Advanced Therapies including the Tissue Engineering Laboratory and the Cell Therapy Unit, transforming the proposal in a national project with academic, scientific and healthcare relevance. In addition, the MH decided the creation of the National Public Umbilical Cord Blood Bank, which was inaugurated in 2014 in the Clinical Hospital Dr Manuel Quintela from the UR under the direction of INDT [13].

Other research institutions related with stem cell research and tissue engineering in Uruguay are the Biological Research Institute 'Clemente Estable,' the Pasteur Institute of Montevideo, the Uruguayan Center of Molecular Imaging and the Pando Technological Pole (School of Chemistry Faculty and Industry). Besides, there is a research group in the UR working on stem cell therapies in Veterinary Medicine.

Some examples of stem cell research initiatives include, but are not restricted to, studies on mesenchymal stromal cells (MSCs) properties from different sources, growth on scaffolds, effects on Parkinson's disease and ischemic myocardial disease animal models, adult neurogenesis, clinical studies on bone marrow derived stem cells transplantation in patients with venous chronic ulcers and open fractures of lower limbs. No research with embryonic stem cells is being performed.

Strengths, weaknesses & opportunities in Uruguay

Despite the increase in national investment in science in the last years, funding remains insufficient to meet research needs and scientists' salaries are still low. This is particularly evident in health research and therefore affects research on stem cells and regenerative medicine. Average amounts available per project are small in comparison with the international context and the number of research teams that usually have access to international research funds is limited. There is also little, if any, research conducted by multinational private companies in Uruguay and the lack of research investment by the national private institutions probably contributes. In this context, the UR has played a key role in keeping health research alive, while funding agencies depending on the national state have had a limited participation. This seems to correspond to a perception of health research as 'nonstrategic,' which in turn correlates with the absence of the MH from the newly created Ministerial Bureau for Innovation [6]. By contrast, the UR and the MH have prioritized the development of CTRM for its importance in human resources formation and to generate a critical mass of professionals in this field.

Besides, due to the scarce population is very difficult to make relevant clinical trials in this field in Uruguay, making crucial to perform multicentric and cooperative trials with other countries of the region. However, this characteristic allows centralizing and better regulating the activities in this field. The creation of a national GMP facility at the University Hospital with mixed support will be very important for the development of this new discipline in Uruguay.

More randomized, controlled, multicentric clinical trials are needed and demographics of Uruguay make essential the collaboration with the region. Stem cell research is needed to have critical mass of researchers to avoid stem cell tourism and for intellectual sovereignty. These will provide appropriate facilities and trained staff for stem cells research and also improve collaboration with developed countries to translate validated therapies to South American countries.

Stem cell research in Mexico

General vision

Mexico's current population is over 122 million (Table 2). Mexico is part of the North America Free Trade Agreement together with Canada and the USA, belongs to the Organization for Economic Cooperation and Development, is the 15th economy in the World and has an upper middle income [15]. The percentage of the GDP devoted to science and technology has been between 0.32 and 0.42% for the 2003–2012 years, according to the National Council of Science and Technology (Table 2) [16]. Most research in the country is performed at public universities and research centers. The National Investigator System was created on 1984 and has been an important institutional program, based on peer evaluation, to support the career of researchers. Currently, there are over 23,000 investigators, resulting in 18.8 investigators per 100,000 inhabitants. Although there are not many

Table 2. Economic support and stem cell research indicators for the presented countries.

Country	National GDP (US$ billions)	Population (millions of people)	Population of scientists	Overall science funding (% of GDP)	Stem cell publications (% of total country publications)	Funding of stem cell research (% of GDP)
Uruguay	55.7	3.4	538	0.43	1	Estimated <0.01%
Mexico	1261	122.3	23,000	0.42	0.2	Estimated <0.01%
Chile	277.2	17.6	6160	0.44	0.51	Estimated <0.01%
Brazil	2246	200.4	130,000	1.21	0.6	0.0021
Argentina	609.9	40.1	35,000[†]	0.65[‡]	0.35[§]	Estimated <0.01%

Data from 2010 to 2013.
[†]Full-time scientists.
[‡]US$132.75 per inhabitant invested in research and development.
[§]Bone marrow transplantation studies not included.
GDP: Gross domestic product.

groups in Mexico working with stem/progenitor cells, last year the Mexican Society for Stem Cell Research was formed [17]. This group published in 2011 the book 'Stem Cells and Regenerative Medicine,' written in Spanish, which can be useful from bachelor to graduate students. In addition, its members have organized scientific meetings with recognized professors in Mexico City in 2011 and 2013.

Stem cell initiatives in Mexico

The National Council of Science and Technology has several grant programs. A special subprogram in health-related projects aims to support transplantation and preservation of organs, tissues and stem cells. Unfortunately, only a handful of grants are given every year in this and other programs. As in many other countries, private banking of cord blood cells is offered to parents-to be. The loose information provided about the current usefulness of having these frozen cells has invigorated the conception that cell therapy might be useful in any needed way in the future. Costs for collecting and keeping the cells frozen can be significant (US$1200–1800 for collection/processing + US$130–175 per year for storage), creating a use restricted to those that can afford the price. However, public banks have been set up in large hospitals. The informed donation of cord blood to public banks does not involve payment, and the family is aware that they might or might not benefit from this public initiative.

Mexican early works on the biology of hematopoietic stem cells from cord blood [18,19], growth factor dependence of developing midbrain neural stem cells [20,21] and the effects of retinoic acid on embryonic stem cells [22] were made in the 1990s. Later on, papers describing mesenchymal cells from bone marrow from myelodysplastic patients [23], the isolation of stem cells from the enteric nervous system [24] and collaborative studies addressing factors that influence adult neural stem cell differentiation or survival [25,26] were reported. More recently, cancer-initiating cells from cervical lines were characterized [27]. Some published studies use mouse embryonic stem cells for neuronal differentiation [28–30] and there is no paper with a Mexican corresponding author that uses human pluripotent cells. Thus, these examples show that hematopoietic, neural, embryonic, mesenchymal and cancer stem cells are the main interest of basic researchers in the country.

In the clinical setting, transplantation of hematopoietic cells is performed on regular basis to treat blood-related disorders after 1995 in both public and private institutions [31]. The most common procedure is donation of bone marrow or mobilized peripheral blood from a compatible donor. Recently, a public cord blood bank has provided hematopoietic cells for transplantation [32]. Public cord blood banks aimed for unrelated grafting might be of particular interest to developing countries [33], because the probability of finding a match is higher than with other donor cells [32]. Such public endeavors contrast and rise ethical concerns on the existence of private banks, because it is more altruistic to donate than to preserve the newborn own cells [34]. In order to decrease costs associated to mobilized peripheral blood allotransplantation, a nonmyeloablative immunosuppressive scheme was designed to avoid the hospitalization required after myeloablation [35], with 81% of fully outpatient treatment, significantly reducing the overall price of the procedure, which is desirable everywhere, but more important where resources are limited.

Stem cell regulation & strengths, weaknesses & opportunities in Mexico

The General Health Law [36] for the use of human organs, tissues, cells and corpses set the general frame, which unfortunately is related only to hematopoietic stem/progenitor cells, for both the procurement and

clinical applications. Then, there are specific guidelines in NOM-253-SSA1-2012 for the use of human blood and its components for therapeutic purposes. This regulatory frame can accommodate human cells that are obtained from neonatal o adult persons, leaving out the derivation of human embryonic stem cells. The rules for clinical application of human pluripotent cells are nonexisting. Cofepris (acronym for Federal Commission for the Protection against Sanitary Risks) grants Sanitary Certifications for medical facilities and holds the National Registry of Clinical Trials in Public and Private Institutions. In addition to review cell-based applications, Cofepris has a large catalogue of health-related issues to oversee: quality of water, foods, drugs, medical equipment, cosmetic products; it also informs about potential risks in the environment or the workplace, and promotes prevention and good practices. This ample range of activities makes hard to keep up when surveillance of medical practice is required. Cofepris can halt unproven clinical procedures, but this requires a complaint filed for the specific medical facility.

Recent changes introduced on 24 January 2013 to the General Health Law have opened a practice that was forbidden: to charge a recovery fee for procedures that involves therapies with cells, when they were altruistic and without cost to patients before. There is no justification for charging the patients receiving a not-proven therapy. The scientific basis and oversight approval are important to build confidence on hospitals interested more in the patients than in their profit. It is the privilege, and also the duty of both patients and physicians to adhere to international standards and to report the results. The International Society for Stem Cell Research published guidelines a few years ago [37]. It is of the uttermost importance to cluster and coordinate hospitals to perform clinical trials involving stem/progenitor cells, since individual cases can be anecdotal, but double-blind procedures can significantly contribute to agree on effectiveness, times for intervention, preparation/manipulation of cells and end points to be measured.

An area of opportunity to increase the investment is science and technology to 1% of the GDP and also to create at-large stem cell initiatives funded by the government. In particular, the creation of human pluripotent stem cell banks and GMP facilities to prepare cells aimed for transplantation. This can be especially important in Latin America, where only a few human pluripotent lines have been derived, and the array of histocompatibility antigens (haplotypes) might preclude the use of cell lines produced in developed countries. Training and enough funding shall promote a critical mass of people interested in stem cell projects that will benefit Mexico in the future.

Cancer is prevalent in Mexico as it is worldwide. However, the incidence of infant acute leukemias is particularly high [38]. Another important health problem in the Mexican population is obesity, often linked to metabolic syndrome. Removal of fat can be a source of mesenchymal cells that can be used for research purposes and, if applicable, also build a bank of donor cells for therapy. These challenging conditions offer a large number of patients that will encourage stem cell scientist to find novel treatments.

The public health system in Mexico is composed by federal and local institutions, but is saturated. This situation has favored private practice, because even when people are publicly insured, they do not want to wait. In addition, some private hospitals offer treatments and equipment that are hard to find in public hospitals. The average income per person in Mexico is significantly less to that in the USA, which has promoted that persons from this country cross the border to receive private consultation from dentists and medical doctors, since the costs in Mexico are more affordable than in their home country. Stem cell treatments are also offered in Mexico to foreigners, most of the times patients that seek for a self-paid experimental treatment for intractable conditions, which can be ethically unfair, considering their serious illness [39].

Clearly, regulatory laws are lacking for human fertilization, the derivation of human pluripotent stem cells, either form developing embryos [40] of from reprogramming somatic cells with the Yamanaka factors [41] and the clinical application of human pluripotent cells. Such laws are urgent and should consider the professional opinion of legislators, bioethicists and scientists. At-large institutions, such as the Mexican Academy of Sciences, the National Academy of Medicine and Conacyt, ought to participate. The Human Fertilisation and Embryology Act of the UK is well-balanced and a good starting point for the discussion. Although Mexico is permissive with regards to the use of adult stem cells, there are bioethical and political factors that will influence, and probably delay, this new legislation [42].

Stem cell research in Chile

General vision

Chile, like many Latin American countries, has not been oblivious from political turmoil until the late 1980s. Since the early 1990s, with the advent of the democracy, Chile has developed interesting initiatives encouraging the development of Science and Technology. More recently, in 2005 the National Innovation Council for Competitiveness was created, which aims to achieve an economic growth that allows the country to shorten, in minimum time, the economical gap that separates our country to developed countries.

Paradoxically, despite the diversity of instruments to promote the scientific-technological development the existing institution is extremely fragile and dispersed. Administration of science and research is scattered across government ministries. Among these are, by the volume of managed resources, Innova Chile CORFO and Chile's National Commission for Scientific and Technological Research (CONICYT). The first, which operates under the Ministry of Economy, has its focus on innovation and technology transfer. Chile's main funding body, CONICYT, follows two broad strategic objectives: promoting the training of human capital and strengthening Chile's scientific and technological base. Although the establishment of a Ministry of Science and Technology has long been under debate and the majority of the involved players agree that this is a necessary action to centralize a state policy, it was only this year that the actual government announced its creation.

The amount of Chilean Science and Technology has doubled in the last 10 years maintaining and even improving their quality when compared with many developed countries, being among the best in Latin America. In 2012, Chile was 46th in the Global Ranking of Journals and Country Scientific Indicators, well below the USA but fourth in Latin America, after Brazil, Mexico and Argentina. However, since the year 2000 Chile has increased its scientific output, with an annual growth of 11% between 2006 and 2011, with 75% of publications in English [43].

Chile leads the region in the number of patents granted, according to Nature suggesting greater investment from the country's private sector [44]. Yet, barriers to the growth of its research community remain. The total number of scientists, less than 6200 in the country, is still very small; scientists comprise less than 0.1% of the Chilean workforce. These numbers are explained by the fact that Chile only invests approximately 0.45% of GDP in Science, Technology and Innovation, which internationally is very low. One of the central elements, as pointed in a recent study conducted by the Chilean Academy Science, is the dramatic lack of specialized human capital.

In relation to the training of researchers, efforts are being made. Since 2008, there have been 5809 graduate scholarships abroad, with expectations of increasing this indicator in the near future [45]. Nevertheless, a big handicap is the repatriation; talented Latin American scientific investigators are not encouraged to return to their home regions after training considering that fewer than 200 awards were granted to incorporate scientists into the academic and industrial sectors.

Stem cell regulation in Chile

In Chile, there is no specific regulation regarding biomedical scientific research or clinical trials with human stem cells. Research is not specifically prohibited, but therapeutic and reproductive cloning and the funding of such activities are as of 1993. Furthermore, currently in Chile, there is no specific regulation regarding donation, testing, processing, preservation, storage, distribution, application or treatment using human stem cells. In 2006, Chile's government enacted a law that 'has as its purpose the protection of human life from the moment of conception, its physical and psychic integrity, as well as its diversity and genetic identity with regard to biomedical research and its clinical applications'.

Regulatory frameworks for cellular therapies are only now being established, driven greatly by the Academia; scientists, clinical researches and doctors are presently working in the establishment of The Chilean Society for Stem Cell Research and Regenerative Medicine. The legislation associated with the development and approval of market entry of products based on cells or tissues or use as medical devices, is another important issue. A law that is built by legislators, bioethicists and scientists is mandatory in the short term.

Several private (family) banks are operating in Santiago; special concern in the area of ethical and scientific implications of storing cord blood and advertising and the information given to parents about their potential benefits is required. Furthermore, the emergence of the stem cell clinics for cosmetic purposes has raised concerns among scientists and doctors who raise serious scientific and ethical issues underlying this situation about the prestige of stem cell research and patient safety.

Stem cell initiatives & strengths, weaknesses & opportunities in Chile

Research in Chile is mainly performed at the academia (two-thirds of the academic publications come from just five universities). Chilean groups are well grounded in classic developmental biology. They produce innovative and high-quality research and are striving hard to incorporate new technologies. There is currently a critical mass of young scientists working in this field. Several groups nowadays are working on stem cells, regeneration and tissue repair in different animal models. Unquestionably, to move stem cell from promising research into practice will require contributions from fundamental research, from developmental biology to the 'omics' technologies and advances in immunology.

In recent years, the potential of stem cell research for tissue engineering-based therapies and regenerative medicine clinical applications has also become popu-

lar in Chile, focusing in particular on the use of adult stem cells (ASCs) considering the aforementioned law. Chile is an Asia-Pacific Economic Cooperation (APEC) and the first South American OCDE member and as such has committed 'to establish a harmonized understanding of cell and tissue-based therapies and to establish training programs which impact on innovation performance, including R&D policies' [46].

Since the pioneer work by Minguell and colleagues on ASCs in the late 1990s, mainly bone marrow and umbilical cord MSCs, ASCs have aroused considerable interest for potential therapeutic and drug discovery applications in Chile [47]. As a result, there are a number of new government initiatives to target the development of new stem cell technologies and support registration of medical devices. Public funding (Innova Chile – CORFO and/or Fondef program – Conicyt) has supported initiatives such as Cells for Cells (C4C) S.A. or Inbiocriotec SA, biotech-based consortiums, launched as spin-off from Universities. The Center for Regenerative Medicine (Universidad del Desarrollo) and the 'Center for Regenerative Therapy – Clínica Las Condes,' the first laboratory of MSCs nationwide located in a private Clinic, are also subsided by Innova-CORFO funding.

So far, stem cell treatment has mainly involved proven ASCs, especially those related to bone marrow transplantation for malignant blood diseases. In 2007, a public cord blood bank (Banco de Vida; agreement signed between the Department of Obstetrics and Gynecology, Pontifical Catholic University of Chile and the Foundation Genómika; with CORFO cofunding) was established and the first allogeneic transplants were done [48]. There are also some experimental studies for the treatment of dystrophic epidermolysis bullosa, diabetes mellitus Type 1, lupus erythematosus, osteoarticular pediatric diseases and amyotrophic lateral sclerosis with small groups of patients [49,50]. Currently, according to Clinicaltrials.gov, there are two registered clinical trials for the use of MSC in patients in Chile. Most established groups offering stem cell therapy for now claim working under GMP international standards of quality to ensure the quality and safety of their products. It is of the uttermost importance to cluster and coordinate hospitals to perform clinical trials involving stem/progenitor cells.

As stated by M Khoury, a former junior group leader at the Singapore-MIT Alliance for Research and Technology (SMART) in Singapore, now scientific director of C4C: "The hype for these innovative strategies did not reach Chile only with hope but also with lot of confusions. Currently, there is an important misinformation of the general public opinion regarding this topic. The doubtful claims and promises that have been diffused in the local media will surely impede the effort and the work of many of the academic laboratories in the country. However, a leap of faith resides in an emerging brain-gain trend of Chilean scientist working overseas, in long-term provided funding and a regulatory frame that is currently being drafted."

To the best of our knowledge, no group in Chile is working with embrionic stem cells.

Stem cell research in Brazil

General vision

Over the past 15 years, stem cell biology has expanded significantly in Brazil. Among the factors that contributed to the interest for the field are historical reasons. Brazil has tradition in cell biology. One example dates back to 1952, when Rita Levi-Montalcini, invited by Carlos Chagas Filho, came to the Institute of Biophysics, at the Federal University of Rio de Janeiro, to culture cells from the sensory dorsal root ganglia. This approach allowed the identification of the NGF that later awarded her the Nobel Prize [51].

Since then, the scientific community grew in Brazil to beyond 130,000 scientists, which, however, is still not enough for a country with over 200 million people. Around 250 researchers are affiliated to the Brazilian Association for cell therapy.

Stem cell initiatives in Brazil

In the 2000s, Brazilian scientists and physicians launched clinical trials testing autologous bone marrow stem cells to revert diabetes, stroke and heart conditions. Brazil had achieved international recognition in the field [52] with at least 17 clinical trials in progress applying ASCs especially in cardiology, orthopedics, diabetes and neurology. While these endeavors sound like a good plan, the country lagged behind in the basic science [53,54].

As an attempt to revert this scenario, the Ministry of Health, Ministry of Education, Ministry of Science and Technology and the State Funding Agencies have sponsored more than 50 laboratories in 20 institutions spread across nine Brazilian states to study basic and translational aspects of stem cells. Since 2001, a total of US$50 million has been allocated specifically to support the stem cell field in Brazil.

Recent initiatives, led by Reinaldo Guimarães and Antonio Carlos Campos de Carvalho, former directors of the Department of Science and Technology at the Ministry of Health, with the support of the Funding Authority for Studies and Projects (FINEP) and the Brazilian Development Bank (BNDES), have also created eight cell technology centers (CTCs) dedicated to stem cells. These CTCs have the mission of producing

adult and pluripotent stem cells to be used in research and future clinical trials [52].

Stem cell regulation & strengths, weaknesses & opportunities in Brazil

The number of stem cell articles published by Brazilian researchers has increased more than 16-times; however, this expansion still holds Brazil in a reserved 19th position in comparison to other countries [52]. Furthermore, despite the Biosafety Act, until 2014, only 10 original articles about human embryonic stem cells and 12 original articles about iPS cells have been published by authors affiliated with Brazilian institutions [55]. During 2015, at least eight new original manuscripts have been published about human pluripotent stem cells, both embryonic and iPS, in the country.

The Biosafety Act permits scientists in Brazil to work with stem cells obtained from left over nonviable embryos that have been frozen for at least 3 years. Brazil passed the legislation in 2005, however; a petition backed by Catholic Church challenged the law, claiming that embryonic stem cell research fails to comply Brazilian's Constitution and the moral principle that a human being has the right to live. In 2008, Supreme Court refused the appeal, giving authorization to embryonic stem cell research in the country.

A new initiative to boost basic studies was the creation of the Brazilian Bank of iPS cells, sponsored by the Ministry of Health, Ministry of Education and the Ministry of Science and Technology. The consortium of 14 Brazilian laboratories will have 2 years to collect and reprogram cells from patients with 17 different diseases including Diabetes, Parkinson, Alzheimer, Amyothrophic Lateral Sclerosis, Autism, Down Syndrome, QT long syndromes, cystic fibrosis, etc. This biobank will produce stocks of iPS cells to the scientific community.

Bottlenecks for the progress of the stem cell field in Brazil comprise the modest record of scientific publications, rare interactions with industry and limited capabilities to perform stem cell basic research, which could be bypassed by fostering scientific collaborations and also by bringing international scientists to work in the country. But to be successful in attracting foreign scientists, the main barriers that are well known for Brazilian scientists would have to be overcome: namely, the lack of speed and high costs associated with the import of research materials [56,57], together with the lack of guarantee of constant funding, especially following the recent presidential election.

Stem cell research in Argentina

General vision

Argentina has a long tradition in high-quality scientific research, based on the free access to public education, including university, and the excellent training of its human resources. Three Nobel Prizes in medicine and chemistry (Bernardo Houssay, Luis F Leloir and Cesar Milstein) account for this aspect, even though Milstein developed his work abroad.

However, the scientific productive matrix was traditionally affected by political turmoil. The budget dedicated to scientific research was one of the first to be trimmed upon an economical and/or political crisis. This situation led to the emigration of well-trained Argentine scientists, generating massive brain drainage. The country suffered a last economic crisis in 2001. Since 2003, a sustained, proactive policy in favor of scientific research and development has invigorated scientific research in our country, as in no other historical period. This political decision to support scientific research was embodied and exalted by the creation of the Ministry of Science, Technology and Productive Innovation (MSTPI) of Argentina in 2007 [58]. Since its creation, scientific infrastructure was increased with more than 150,000 m^2 and the brain drainage was reverted by the return of more than 1200 scientists from abroad [58]. A study published by Nature in 2014, indicates that Argentina was the second most prolific country in terms of publications in the region, after Brazil and the impact factor of its publications grew over the international and regional average [44]. Argentina also possesses the highest number of researcher per capita (3 every 1000 workers), only below the USA [44].

Importantly, a national strategic plan was generated as a result of several rounds of consultations among 300 scientists, clinicians, entrepreneurs, regulators, public officers and other key stakeholders [59]. This plan defines priorities on research and development in the health, energy, agroindustry, environment and sustainable development, social development and industry sectors till the year 2020.

In the health sector, one main strategic area is Regenerative Medicine and Tissue Bioengineering [59]. Thus, Regenerative Medicine is a main priority of the Argentine government in terms of research and development. This definition initiated a number of stem cell-related initiatives by the MSTPI to develop this field. In parallel, since access to health is a constitutional right in Argentina, it is of fundamental importance to be able to provide stem cell treatments in the country that are approved worldwide.

Stem cell regulation in Argentina

In 2007, the Ministry of Health has passed an internal regulation (610-2007) defining the National Regulatory Authority on organ, tissue and cell transplantation (INCUCAI) as the regulatory authority on cell therapy. Also, INCUCAI has generated Guidelines

for Good Laboratory and Manufacturing Practice for Cellular Preparations in 2012. In addition, Argentina has contributed to the Spanish version of the web page from the ISSCR on unproven stem cell treatments. Still, offerings of unproven stem treatments can be detected. As a consequence, law to regulate all aspects of cell therapy is under preparation. As a weakness, areas such as embryonic stem cell research are not clearly regulated.

Stem cell initiatives in Argentina

Due to the increased support to research in general and stem cell-research in particular, the field has experienced a blossom. The 18 stem cell research projects funded in 2008 increased to 47 projects in 2012.

In 2008, as a result of a Request For Applications from MSTPI, a stem cell consortium called CICEMA was generated [60]. CICEMA is composed by 11 organizations including clinics, basic and translational research groups, a technology transfer unit, as well as private foundations and companies. All projects require the interaction of different groups and each composing institution provides matching funds to the initiative. In addition, this array of institutions promotes the translation of the consortium's research in cardiology, neurology and cancer to a clinical setting.

In order to speed up the impact of reprogramming technology on stem cell research, PLACEMA, a human iPS cell platform was financed by the MSTPI in 2012 [61]. PLACEMA's objective is to provide the scientific community, the clinics and the pharmaceutical industry with state-of-the-art reprogramming and cell differentiation services. The ultimate goal is to produce GMP-grade cells for which GMP facilities are under construction. The MSTPI is supportive of an international initiative to generate a global GMP-compliant iPS cell bank of nondiseased donors homozygous for highly represented human leukocyte antigen (HLA) subtypes. This so-called Haplobank should enable future iPS cell-derived therapies compatible with a high percentage of the HLA repertoire of the local population and, in a similar fashion as the bone marrow donors worldwide, should contribute internationally with requests of iPS cells with defined HLA [62].

Lino Barañao, the Minister of STPI of Argentina has created an Advisory Committee on Cell Therapies and Regenerative Medicine in 2006, when he was head of the National Agency for the Promotion of Science and Technology. This Advisory Committee is composed of 16 members including scientists, lawyers, regulators, bioethicists and medical doctors and functions nowadays under the MSTPI [63]. Its mission is to advise the government and the general public in all areas of the stem cell field and has become a main advocate against stem cell tourism. Internationally, a Binational Program on Cell Therapy with Brazil (PROBITEC) is running since 2008 [63]. This program fosters the development of human resources by international courses and research development by joint research projects. Eight basic-translational research projects are in progress as well as a binational clinical trial on the use of bone marrow mononuclear cells in stroke patients. In addition, the PROBITEC coorganized the I Latin American, VIII Brazilian and I Argentine Congress on Stem Cell Research and Cell Therapy that took place at Foz de Iguazú, Brazil in 2014, gathering main scientists and stakeholders in the field from Chile, Mexico, Uruguay, Brazil, Argentina, USA and Europe [64]. Furthermore, a very successful MSTPI-ISSCR congress took place in Buenos Aires in 2009. Besides renowned scientists from the region and the world, it is noteworthy that the event was inaugurated by the President of Argentina, Cristina Fernandez de Kirchner, as a sign of the public support to this research area [65].

Strengths, weaknesses & opportunities in Argentina

As mentioned before, governmental support is a main strength and driving force in stem cell research. Increased and improved infrastructure, augmented critical mass in qualified human resources, promotion of international cooperation and enhanced research budget are pillars for stem cell development in Argentina. Currently, the investment in science and technology accounts for 0.65% of the country GDP, an increment of 0.16% since 2008. However, despite proactive governmental policies to involve the private sector in R&D, only 25% of this investment comes from the private sector.

In terms of established stem cell treatments such as bone marrow transplantation for blood-derived diseases, Argentina possesses the required infrastructure and know-how to facilitate its access to patients in the vast majority of the country. In addition, a public cord blood bank, located at the Garrahan Hospital, is world-wide recognized by its excellence and it is certified internationally by the AABB [1]. In parallel, an Argentine Bone Marrow registry with over 45,000 donors registered operates under the INCUCAI and in coordination with the bone marrow donors worldwide [66]. In conclusion, Argentina has the necessary human and material resources to provide, at the highest international standards, established treatments using bone marrow for blood-related diseases.

As weaknesses, the country still misses human resources on strategic areas such as tissue bioengineer-

Executive summary

Stem cell research in Uruguay

- In Uruguay medical research is scarce, as it is the national funding devoted to it. In the last years, some strategies like the Program for Biomedical Research (PROINBIO) and the creation of the National Agency for Research and Innovation are helping to foster research in this area.
- Due to some offers of unproven treatments, a strategic plan was developed by the Ministry of Health to promote regulations about standards, quality control and safety for cells and human tissue transplantation concurrently with the creation of the National Ethics Committee for Human Research and the Ethics Committee of the Medical College.
- The main stem cell initiatives include the creation of the National Public Umbilical Cord Blood Bank, the construction of a GMP Facility for Advanced Therapies with a Tissue Engineering Laboratory and a Cell Therapy Unit and the development of a Cell Therapy and Regenerative Medicine Training Program as national projects.

Stem cell research in Mexico

- Although Mexico has a high economical ranking, its investment in science, technology and innovation is scarce and should increase to at least 1% of GDP in the short term.
- Mexican scientists have published stem cell papers from the mid-1990s and the Mexican Society for Stem Cell Research was created in 2014.
- Both private and public umbilical cord blood banks are available and treatments for patients with hematological disorders have been made for more than two decades.
- Legislation on pluripotent stem cell derivation and oversee on the clinical application of unproven treatments are urgently needed.

Stem cell research in Chile

- Chile does not currently have a specific regulation or set of guidelines related to biomedical scientific research or clinical trials with human stem cells. On-going plans foresee the establishment of The Chilean Society for Stem Cell Research and Regenerative Medicine aiming to advocate government and relevant regulatory authorities on policy-making and legislation on stem cell biology and to promote the disciplines of stem cell research and therapies.
- Main initiatives include the recent creation of the Ministry of Science, Technology and Productive Innovation and significant investment in the last decade in both publicly funded organizations and companies that are becoming involved particularly in adult stem cell research and in the development of new stem cell technologies and support registration of medical devices.

Stem cell research in Brazil

- Key initiatives of Brazil include the Biosafety Act, which allows scientists to work with human embryonic stem cells, a national network of cell therapy and the creation of several cell technology centers to cultivate cells under GMP conditions.
- As weaknesses, Brazil has issues on importation of scientific goods, low critical mass, a modest record of scientific publications and rare interactions with industry.
- Brazil has developed capacity to run clinical trials using stem cells.
- Creation of a disease-oriented bank of induced pluripotent stem cells (iPS) is seen as an opportunity.

Stem cell research in Argentina

- This country has experienced a formidable growth in its economy and scientific investment in the last 12 years. This political decision to support scientific research was embodied and exalted by the creation of the Ministry of Science, Technology and Productive Innovation in 2007.
- A national strategic plan on research and innovation was created that includes Regenerative Medicine as a strategic area.
- The Ministry of Health has passed an internal regulation on cell therapy in 2007. Guidelines for Good Laboratory and Manufacturing Practice for Cellular Preparations are in place since 2012. Still, offerings of unproven stem treatments can be detected and no legislation on embryonic stem cells is available.
- Stem cells initiatives include a stem cell consortium, a human iPS platform, an advisory committee, a binational cooperation program on cell therapy with Brazil, an iPS HLA-selected Haplobank and an increase of 261% of stem cell research projects between 2008 and 2012.
- In general terms, Latin American countries have developed a renewed interest in research and development in the last years, in hand with economic growth.
- In parallel to this, stem cell research has been defined as a priority research area in many Latin American countries.
- These countries also share concerns toward unproven stem cell treatments and regulatory loopholes or absence of regulation.

ing, 3D bioprinting and translational research in general. Most of stem cell research is located in Buenos Aires and its surrounding areas. In addition, only five clinical trials are in progress, highlighting the strength in basic/translation research and a deficit in moving forward to the clinical stage [63].

As an emerging field, stem cell research creates a variety of opportunities for development and cooperation internally and at the international level.

Conclusions & future perspective

Latin American investigators working with stem cells have several problems to deal with such as few initiatives that frequently have limited funding and insufficient colleagues working at the bench and in the clinic. Defects in medical and/or regulatory oversight are an issue that are not distinctive of this region, since proper behavior of physicians offering novel treatments involving stem cells is mandatory worldwide [67–69]. On the other hand, the combination of a fast-growing field in a fast-growing region creates a unique opportunity for scientific and regional development, which must be based on open interactions among countries in the region and worldwide, public and private support and clear regulations. Besides keeping and increasing the excellence of the quality of scientific publications, initiatives, such as the iPS Haplobank, that relies on the regional characteristics of the HLA profile of the population of each country should be points of convergence to integrate to the global stem cell community.

In the region, biologists, clinicians, regulators and bioethicists should come together to establish proper and stringent regulations and standards for stem cells therapies, being important to articulate these criteria for the Latin America region.

Our shared vision is that our countries should keep an effort in promoting innovative research of excellence, establish or improve regulations to the highest international level, increase regional and international cooperation and identify country- or region-specific opportunities to collaborate worldwide without diminishing identity or sovereignty. The vastness and early development of the field provides a unique opportunity to find topics or areas of collaboration where the strengths of each country could be value in a win-to-win collaborative frame.

Financial & competing interests disclosure

FJ Pitossi is the scientific coordinator of PLACEMA and CICEMA. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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