

Current Status of Stem Cells and Regenerative Medicine Research in Argentina

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ABSTRACT

Since Takahashi and Yamanaka demonstrated for the first time that fully differentiated somatic cells can be reprogrammed to a pluripotent state with a small group of transcription factors a revolution erupted in the regenerative medicine field. New advances showing direct differentiation of mature cells increased the excitement of the field. This work describes the present situation of the field in Argentina and the efforts implemented by science authorities to strengthen and push the field forward

Historical context and current status of scientific research in Argentina

The area of stem cell research is revolutionizing historical concepts in biology and we are closer to the maturity of the field, implying the possibility of applying stem cells in regenerative medicine in the clinics. The emergence and the rapid maturity of the induced pluripotent stem cell (iPS) concept, that is, the possibility of reprogramming mature cells to obtain large amounts of embryonic-like cells that can then be differentiated to almost any kind of cell type, had transformed stem cell research and regenerative medicine

approaches in the entire world, including emerging countries such as Argentina.

Scientific research in Argentina was mainly characterized by the high academic level of its researchers combined with shortage of resources, poor infrastructure, and lean salaries. This cocktail led to the emigration of many Argentinean scientists and the chronic loss of “gray matter.” Of the three Argentineans awarded with the Nobel Prize in medicine/chemistry, the first two, Bernardo Houssay in 1949 and Luis Leloir in 1970, performed the studies that led to the award in Argentina. However, Cesar Milstein, who received the Nobel Prize in 1984, was forced to emigrate and was awarded for his studies in Cambridge, United Kingdom.

Nowadays, Argentina is enjoying a blossom in scientific research. Since 2003, the investment in research and development has increased in 2011 up to 0.65% of the internal gross product, most of the investment coming from the federal government. The personnel involved in R&D in 2014 are close to 70,000 people.



In research and development in Argentina, the regenerative medicine field has been a priority in the scientific policy of the MSTPI.

More than 1000 scientists have returned from abroad. This growth took speed by the creation of the Ministry of Science, Technology and Productive Innovation of Argentina (MSTPI) in 2007.

In late 2010 the MSTPI launched an ambitious plan to foster the incorporation of cutting-edge technology and disruptive science for the next 10 years named “Innovative Argentina 2020” [101]. The Health Committee that included stakeholders from the scientific, industrial, and education areas discussed and agreed on different areas that should be supported. As a result of these discussions, the committee selected “Regenerative Therapies and Stem Cell Research” as one of the most challenging areas.

Therefore, in a context of global growth in research and development in Argentina, the regenerative medicine field is being paid special attention as a priority in the scientific policy of the MSTPI since its creation.

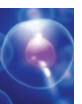
Many actions have been supported by the MSTPI to develop different aspects of

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A Brief Timeline of Stem Cell R&D in Argentina

- **2007:** Creation of the Ministry of Science, Technology and Productive Innovation of Argentina (MSTPI).
- **2008:** The MSTPI funded 18 basic research projects based on stem cells.
- **2008:** A consortium for stem cell research (CICEMA) was created.
- **2010:** The “Innovative Argentina 2020” plan was launched with a focus on regenerative therapies and stem cell research.
- **2012:** The MSTPI funded a platform, entitled PLACEMA, to provide human cell reprogramming services to academia, industry stakeholders, and clinicians.
- **2012:** The MSTPI funded 47 basic research projects based on stem cells.
- **2014:** The first Latin American Congress of Stem Cells and Cell Therapy in Foz de Iguazu, Brazil—a binational effort with Argentina.

regenerative medicine. These actions include the creation of the Advisory Committee on Cell Therapies and Regenerative Medicine, a binational cooperation program with Brazil, a consortium for stem cell research, and a human iPS platform. We will describe these initiatives in detail in the following sections.

The stem cells and regenerative medicine field in Argentina

The Advisory Committee on Cell Therapies and Regenerative Medicine

This committee was organized in 2006 by the present minister of Science, Technology and Productive Innovation,

Lino Baranao, when he was still the president of the National Agency for the Promotion of Science and Technology. Upon his appointment as minister, the committee was transferred to the area of the MSTPI. It is composed of 16 members, including biologists, medical doctors, bioethicists, lawyers, and regulators [102]. Its main aim is to advise the government and the general public in all areas of this field. This advisory committee has fulfilled its aim by organizing several workshops on the bioethical, legal, and scientific aspects of this field, producing 10 articles on topics such as cord blood banking, stem cell tourism, and regulatory issues, among others. It has signed a cooperation agreement with the University of Edinburgh, United Kingdom, “to explore the themes of the effective and optimal promotion, protection and regulation of biotechnology in a comparative study between the United Kingdom and Argentina.” It has a leading role in Argentina as an advocate against nonauthorized stem cell treatments. Its members, including the authors of this work, have actively warned against fraudulent offers of unapproved stem cell treatments in Argentina and overseas in newspapers, radio, and television. The targets of its communication are the general public and the government, including not only different ministries but also legislators, judges, and lawyers.

This committee has two subcommittees. One dedicated to discussing issues related to biobanking of human cells and tissues, including iPS, and a newly formed Association of Patients for Advanced Therapies (APTA) network that includes more than 30 patient advocates and associations. The aim of the APTA network is to provide genuine and responsible information about stem cell treatments and stem cell research to prevent patients from being deceived by false allegations of unrealistic cures and strengthen the voice of patients in the field of advanced therapies. As an effort to mend some flaws in the current legislation on cell therapy, this committee has written a bill of law to be presented for discussion to the National Congress.

Binational program on cell therapy with Brazil (PROBITEC)

As part of initial efforts to foster the stem cell area and enhance the awareness of the scientific community, the MSTPI co-organized with the International Society for Stem Cell Research (ISSCR) an international symposium on stem cell research in Buenos Aires in November 2009. Renowned scientists from the United States and Europe gathered with Latin American scientists mainly from Argentina, Brazil, and Chile and discussed for 2 days the state of the art in stem cell research [1]. This event was opened by the president of Argentina who stressed the commitment of her government to support science. This was also an opportunity to launch a binational call for translational research grants in the stem cell area.

As a result of that initiative, the Directorate for International Affairs of the MSTPI put in motion in 2010 the binational cooperation agreement with the Ministries of Education, Health and Science of Brazil. This program promotes common research activities, technological development, and building of qualified human resources in this field.

Both countries share strengths and also complement each other in several areas. Both have identified regenerative medicine as a strategic field for development. Argentina possesses a long tradition in excellent scientific research, a high academic level of its human resources, a growing incorporation of technology-based companies to the research and development fields, and a strong integration with the international community. Brazil has a higher involvement in cell therapy clinical trials, a clear regulation on embryonic stem cells, a strong investment in infrastructure, and critical mass in this area.

As a consequence of this program, since 2010, highly qualified human resources were generated through five international

courses mainly based on iPS technology and nine binational research projects were funded, including a clinical trial on stroke using bone marrow-derived stem cells.

Stem cell research in Argentina

The number of research projects in Argentina has risen geometrically. In 2008, the MSTPI funded 18 basic research projects based on stem cells. In the year 2012, 47 basic research projects were funded. Stem cells (including iPS) are being studied at the basic level or as tools in diabetes, neurodegeneration, cardiovascular diseases; in umbilical cord; and in Chagas disease, among others. Adult stem cells such as mesenchymal stem (stromal) cells are being studied in relation to hepatic cirrhosis, cancer, cardiovascular diseases, and others.

In 2008, a consortium for stem cell research (CICEMA) was created [103]. Its mission is to perform basic research on the therapeutic possibilities of stem cells in cardiology, neurology, and cancer, to develop high-quality human resources, to foster ties with the academy, the industry, and the clinic, and to interact with other consortia and teams in order to join efforts, identify changes, and respond to them. It is composed of 10 organizations, including research institutes and clinics (the Faculty of Exact and Natural Sciences, University of Buenos Aires, the Leloir Institute Foundation, the Foundation to Fight Neurological Diseases in Infancy and Childhood (FLENI), the Perez Compagnon Foundation, the Dr. René G. Favaloro University, the Pediatrics Hospital Prof. Dr. J. P. Garrahan, and the Faculty of Biomedical Sciences, Austral University), companies (Biosidus, Therafarma, and Veinifar), and the technology transfer arm of Leloir Institute Foundation (INIS Biotech). The expertise provided by each institution should facilitate the translation of the basic knowledge generated to the clinic or the productive sector with the help of the technological transfer unit. It has an external advisory board of renowned

scientists in the field (Armand Keating, Canada; Ernest Arenas, Sweden; Jose Krieger, Brazil; and José Cibelli, United States) and self-imposed external evaluation of the progress of projects. Since its creation, the consortium has published more than 25 peer-reviewed articles in international journals.

In 2012, the MSTPI has funded a technological platform to provide human cell reprogramming services to the academy, the industry, and the clinic (PLACEMA [104]). This technological platform led by one of the authors (F.J.P.) is a not-for-profit association between the Leloir Institute Foundation and FLENI, with a local pharmaceutical company (Veinifar) in charge of the quality control aspects of the platform. The general objectives of PLACEMA are to provide cell reprogramming and differentiation services according to the highest international standards, to contribute to the development of human resources in the field of reprogramming, and to intensify the international scientific cooperation in the field of cell therapy and reprogramming. The specific objectives of PLACEMA include three different types of services. The type 1 service is meant to develop cell lines to be used by research and development groups as in vitro disease models. The type 2 service is focused on developing a panel of iPS and hepatic, cardiac, and neuronal cell lines that represent the HLA repertoire of the Argentine population. The type 3 service seeks to produce clinical-grade iPS and derived cells to be used in regenerative therapies under strict clinical trial settings. Services 2 and 3 are developed under good manufacturing practice (GMP)-grade conditions. Recently, the Argentine initiative to produce an HLA-matched panel of iPS cells under GMP grade [2] has been accepted as part of an international effort to harmonize similar panels of iPS cells. Undoubtedly, the pace of development of the reprogramming field is vertiginous. PLACEMA has a prestigious advisory board to respond to the rapid changes in the field and keep the highest quality available of its services. This board is formed by Larry Couture,

Mahendra Rao, Gustavo Mostoslavsky, and Xiamin Zeng from the United States and Paulo Brofman from Brazil.

The stem cell arena has grown at a breathtaking pace, and new procedures for direct reprogramming through direct differentiation of adult mature cells are appearing in the literature that avoids a previous reprogramming step to iPS. In order to discuss and update the state of the art of the field, Latin American scientists gathered with renowned international scientists in October 2014 at the first Latin American Congress of Stem Cells and Cell Therapy, which took place in Foz de Iguazu, Brazil, as a coordinate binational effort with Argentina. This was a great opportunity to exchange ideas and knowledge to advance stem cell research in diverse areas such as basic research up to fields such as cardiology, neurology, bioengineering, and regulatory issues [105].

Author Disclosure Statement

No competing financial interests exist.

REFERENCES

Primary Literature

1. Podhajcer OL and S Miriuka. (2010). Stem cell research in South America coming of age. *Cell Stem Cell* 6:209–213.
2. Turner M, S Leslie, NG Martin, M Peschanski, M Rao, CJ Taylor, A Trounson, D Turner, S Yamanaka and I Wilmut. (2013). Toward the development of a global induced pluripotent stem cell library. *Cell Stem Cell* 13:382–384.

Websites

101. www.argentinainnovadora2020.mincyt.gov.ar
102. www.celulasmadre.mincyt.gov.ar/
103. www.cicema.org.ar/english/home_eng.html
104. www.placema.org.ar
105. www.congressoabtcel.com.br/index.html

