Immunology south of the equator in the Americas

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Despite a troubled economic and political past, a tradition of fundamental research in immunology and infectious diseases has been fostered in Argentina, Brazil and Chile, as well as in other South American countries.

Science in South America has always exemplified the paradox of countries with vast, sparkling potential but suffering, often at the same time, the greatest extremes of political and economical turbulence[1]. Nevertheless, a strong tradition of science thrives in the atmosphere of many South American institutions of higher education and research. Motivated by new public and private incentives in the past decade that have stimulated science and technology, as well as the possibility of creating stronger ties with international institutions and industry, young, talented immunologists are establishing independent careers in the region, thus avoiding the trend toward 'brain drain' to other countries and boosting the region's profile on the science and technology map. In this commentary we summarize the origin, present status and future challenges facing immunology research in Argentina, Brazil and Chile.

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Challenging sociopolitical turbulence

Argentina, despite many years of political unrest, has been the source of many recognized leaders in the international scientific community. Among these are Bernardo Houssay, who received the Nobel Prize in physiology in 1947 and was the founder in 1949 of the Argentinean National Research Council of Scientific and Technical Investigations; Luis Federico Leloir, who received the Nobel Prize in biochemistry in 1970; and César Milstein, who was a Nobel laureate in physiology and medicine in 1984.

César Milstein, a pioneer of modern immunology, was born, educated and trained in Argentina[2]. He was on the staff of the National Institute of Microbiology 'Carlos Malbrán' in Buenos Aires until 1963, when, disagreeing with institutional politics, he left the country to join the staff of the Medical Research Council in Cambridge (UK)[2]. The Nobel Prize he shared with George Köhler, resulting from their discovery of monoclonal antibodies at the Medical Research Council, not only illustrates the serious errors made by past governments in permitting substantial 'brain drain' but also serves as an example for future governments of how an investment in basic science and a focus on experimental work not initially conceived as applied research can ultimately have enormous economic effect on both biomedicine and industry.

Despite isolated efforts during the 1950s and 1960s, immunology was officially 'born' in Argentina in 1972 when a group of pioneers, led by Christiane Dosne Pasqualini, Osias Stutman, Jorge Manni, Juan Andrada, Alois Bachmann and Marta Braun, created the Argentinean Society of Immunology[3]. Twelve years later, the Latin American Association of Immunology was founded and its first meeting was held in Buenos Aires. However, many years before, in 1949, another society, The Argentinean Association of Allergy and Immunology, was created to serve as a forum for specialists in allergy and clinical immunology. Not unexpectedly, the first efforts of the immunology community in Argentina were devoted to the study of microbial infections such as hemorrhagic fever, leprosy, tuberculosis and Chagas' disease, although there was also a strong pioneer school of autoimmunity introduced by Salvador Zingale, Roberto Mancini and Carlos Yantorno and a branch for tumor immunity initiated by Christiane Dosne Pasqualini at the National Academy of Medicine[3]. Notably, a milestone in Argentinean immunology was the creation in 1973 of the first formal course of immunology at the School of Pharmacy and Biochemistry of the University of Buenos Aires by Ricardo Margni, who served as the inspiration for many scientists and spread immunology through the whole continent. Another landmark was established by Carlos Yantorno, who in 1971 created the Division of Immunology at the National University of Córdoba and was the 'guiding star' for the large immunology community in Córdoba, whereas Sol Rabassa and Mauricio Londner were pioneers of immunology in Rosario[3].

Political and economical instability in Argentina, which resulted in marginal support for scientific research during the 1970s

and 1980s, critically affected all the scientific institutions and considerably delayed the progress of biomedical sciences including immunology. Notably, the Argentinean National Research Council of Scientific and Technical Investigations successfully survived these adverse circumstances, still serving as the main traditional scientific institution, providing salaries, fellowships and grants to most of the Argentinean scientific community. In addition, in the late 1990s, another agency, The National Agency for Promotion of Science and Technology, was created to provide funding on a permanent basis for high-quality research. Despite this progress, after the economic crash of 2001–2002, Argentinean scientists again faced a nearly insurmountable funding reduction in grants and salaries, which fueled fears of another 'brain drain' that could turn back the clock of scientific development[4]. Yet fortunately, major talent was retained and more favorable 'winds' have arrived with the governmental decision to create the first-ever Ministry of Science and Technology in Argentina[5].

In Brazil, the birth of immunology coincided with the boom of vaccine development and the foundation of the Pasteur Institute in Paris at the end of the nineteenth century. The nascent republican government, aiming to cope with various epidemics, including (among others) bubonic plague, cholera and yellow fever, decided to create research institutes, two in the state of São Paulo (now called the Butantan Institute and Bacteriological Institute) and one in the city of Rio de Janeiro (now The Oswaldo Cruz Foundation, Fiocruz), with the main goal of producing vaccines and antisera. Soon thereafter, Fiocruz expanded its activities to include research in tropical medicine with the discovery of Chagas' disease as a chief accomplishment[6]. Why Carlos Chagas did not receive the Nobel Prize in 1921 despite two official nominations remains an unresolved mystery[7].

Despite the existence of immunology research in Brazil since the beginning of the twentieth century, the Brazilian Society of Immunology was created in 1972; its first meeting was held in December 1973 at the Brazilian Academy of Sciences[8]. The entire Brazilian immunology community is beholden to the founders of the Brazilian Society of Immunology and its first board of directors: Otto Guilherme Bier, Humberto de Araújo Rangel, Antonio de Oliveira Lima, Ivan da Motta Albuquerque, Wilmar Dias da Silva, Nelson Vaz, Benedito Oliveira and Maria Siqueira Pinheiro. Since then, and despite the difficulties experienced during the military dictatorship, Brazilian immunology continued to grow, finally culminating in July 2007 with the World Congress of Immunology in Rio de Janeiro—the result of considerable effort by the entire Latin American immunology community.

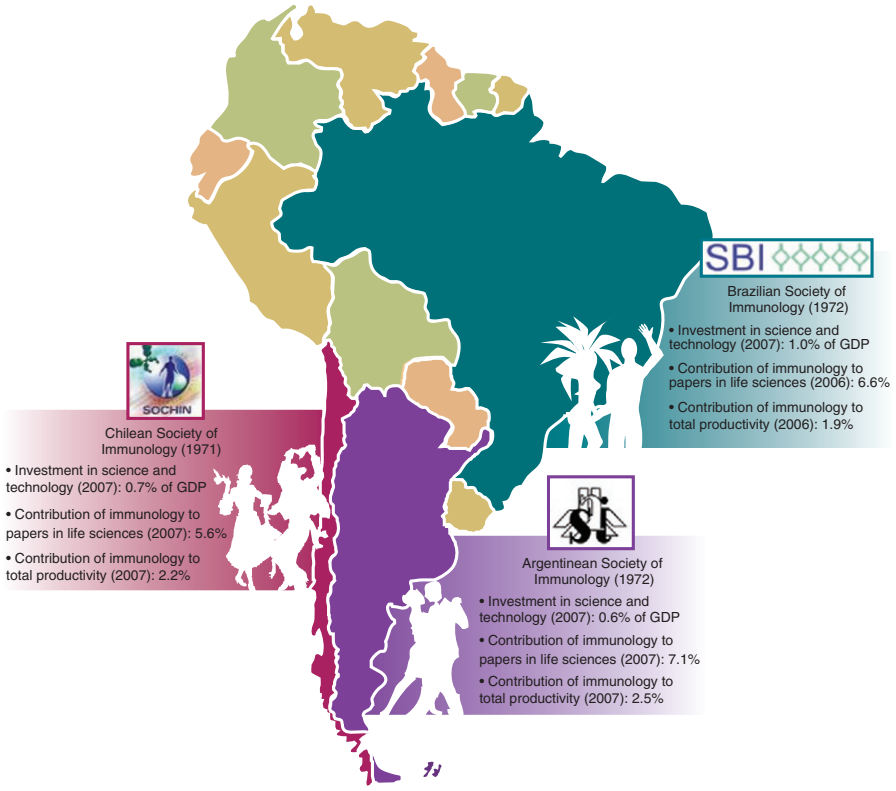

Figure 1 Immunology in the land of tango, carnival and *cueca*. The development of immunology in Argentina, Brazil and Chile has faced the contradiction of countries constantly struggling with unstable political and financial conditions, which have facilitated a 'brain drain'. Motivated by more investment in science and technology, as well as the possibility of creating stronger ties with industry, young immunologists are now establishing independent careers in the region, thus creating the 'critical mass' needed to boost the region's profile on the science and technology map and connect fundamental immunology to local and global public health demands. Data on publications refer to the most recent available information from each country.

Chilean immunology was formally organized in 1971, when the Chilean Immunology Society was founded as a result of interactions between basic and clinical immunologists. Among the first scientists who participated in these early steps were Gustavo Hoecker, Olga Pizarro, Ricardo Sorensen, Mario Andreis, Carlos Moreno, Pablo Rubinstein, Arturo Ferreira and Fernando Morgado. Gustavo Hoecker obtained the Chilean National Science Prize for his pioneering work on the H-2 complex (the mouse major histocompatibility complex) and his considerable efforts to develop science in Chile. In addition, other scientific societies have also contributed to the development of Chilean immunology, such as the Chilean Society of Rheumatology (founded in 1950), the Chilean Society of Infectology (founded in 1983) and the Chilean Society of Allergy and Immunology (founded in 1946). The first research programs of Chilean immunology were devoted to infectious disease, which remains the most serious public health problem in the region. Combined efforts by immunologists and microbiologists contributed to the implementation of highly effective vaccination programs that substantially decreased infant mortality and the spread of infection[9]. Some of the chief scientists (among others) involved in this transforming process were Conrado Ristori, José Manuel Borgoño, Abraham Horwitz and Jorge Jiménez. Despite the success in diminishing the prevalence of vaccine-preventable diseases, during the 1970s the country incorporated only a small number of new research programs on immunology because of the adverse socio-political situation; the few vaccines that were produced in Chile during those years were discontinued. During the 1980s and early 1990s, young investigators opted to train in laboratories abroad (mostly in the USA and Europe) because of the limited budgets and the small number of laboratories in Chile. However, this scenario began to change during the late 1990s, when some of the basic and clinical immunologists who had

trained abroad returned to the country and began their independent research careers.

Thus, these three South American countries share a notably similar history of immunology that tightly mirrors the social, political and economical scenarios of the region.

Generation of new technology

Motivated by sustained economic growth in the region, the governments of Argentina, Brazil and Chile are increasing their investments in basic and applied research[1,5,10]. In the past 5 years, funding for biomedical research in Argentina, including immunology, has increased considerably. This funding has been provided mainly by The National Agency for Promotion of Science and Technology, the Argentinean National Research Council of Scientific and Technical Investigations and some private foundations. Notably, immunology proposals have accounted for 23% of all biomedical projects and 3% of the total projects funded by The National Agency for Promotion of Science and Technology over the past 3 years. The consequence of sustained funding is reflected by an increase in the number and quality of publications. In 2007, immunology contributed to 7.1% of papers published by Argentine authors in the life sciences and contributed to 2.5% of all scientific production by the country. The greater competitiveness of Argentinean immunologists is reflected not only by the rising number of papers in the most rigorous journals but also by the establishment of longstanding international collaborative programs. Most of this scientific production is generated at institutes of the Argentinean National Research Council of Scientific and Technical Investigations and universities in Buenos Aires, Córdoba, Rosario, La Plata, but it is also generated in other places such as Tucumán, San Luis and Mendoza. Notably, immunology is one of the most popular disciplines among young scientists in Argentina. This fortunate event is mainly due to the large number of courses, masters and doctoral programs focused on basic and advanced immunology and the enormous human potential devoted to teaching and mentoring. At present, autoimmunity, infectious disease, inflammation and tumor immunity are the most important fields covered by Argentinean immunologists, although there is a strong focus on other topics, including neuroimmunomodulation, allergy, reproductive immunology, immunogenetics and vaccination, at the crossroad of innate and adaptive immunity[11]. Present approaches involve the integration of immunology with genomics, proteomics and systems biology and the implementation of interdisciplinary programs. However, the most critical priority on the agenda of Argentinean immunologists still involves the establishment of strong connections between academia and biotechnology companies in the arena of public health, and in fact there are already important efforts in this direction that include the development of new biological products such as vaccines, monoclonal antibodies, cell-based therapies and immunomodulatory drugs.

As in other South American countries, infectious disease remains one of the most important research areas covered by Brazilian immunologists[8]. Nevertheless, basic immunology, transplantation, inflammation, allergy, autoimmunity and neuroimmunomodulation are also fields of intense interest[6], with nearly 150 independent research groups actively contributing to Brazilian immunology. In 2006, immunology accounted for 6.6% of articles published by Brazilian authors in the life sciences and 1.9% of all scientific production. Yet over 80% of these articles were generated in four states of the Brazilian Federation: São Paulo, Rio de Janeiro, Minas Gerais and Bahia[6,8]. Of note, 251 of 26,090 projects in the life sciences approved in 2007 by the National Council of Technological and Scientific Development of Brazil corresponded to immunology. Also, many foundations for supporting research in the many states of the Federation were developed and provide substantial contributions to funding research in the country, including the State Research Foundation of São Paulo, the State Research Foundation of Rio de Janeiro and the State Research Foundation of Minas Gerais.

A long-term policy of post-graduate programs has been critical to fostering Brazilian scientific production. In 1995, there were 1,387 and 630 Master of Science and PhD programs, respectively; in 2006, these numbers doubled[10]. This was paralleled by an increase in scientific publications that also resulted in a considerable relative augmentation of the Brazilian contribution to scientific production in Latin America[10]. This general profile can be extrapolated to the contribution of Brazil to global science, as shown by the results of the period from 1981 to 1995 (ref. 6), and is also reflected by the increasing numbers of Brazilian patents registered in Brazil and the USA[10]. In addition to contributing to scientific production, Brazilian immunology is also present in the biotechnology sector. As has been reported, most Brazilian biotechnology companies (whether in the public or private sector) deal with immunology-related products[12]. This includes the development and production of vaccines and antigen-antibody–based diagnostic kits, as well as monoclonal antibodies. For example, between 2003 and 2006, Butantan Institute plus Fiocruz produced nearly 100% of all common vaccines in the country, mainly with technology developed 'in-house'[12].

In Chile, a synergistic process has taken place combining the expertise of local immunologists and those returning home from postdoctoral training, which has led to the establishment of teams covering several areas of modern fundamental immunology, such as innate and adaptive immune responses, pathogen and tumor immunity, reproductive immunology, vaccine development, inflammatory and autoimmune diseases and transplantation[11,13]. Furthermore, other groups have focused their efforts on the generation of veterinary vaccines against pathogens that can damage the productivity of Chilean industries such as salmon and cattle production[14]. Most immunology laboratories have been successful in obtaining governmental funding, mainly from FONDECYT and FONDEF, two programs of the Chilean National Research Council. In addition, the Chilean National Research Council has considerably increased its support of graduate students and postdoctoral trainees by means of specific fellowships. As a result, immunology laboratories in Chile have become attractive places for students seeking high-quality training in both basic and applied research. As a result of the increased funding, in 2007, immunology contributed to 5.6% of the papers published by Chilean authors in the life sciences and to 2.2% of the entire scientific production. In addition, an increasing number of immunologists are actively working in close collaboration with biotechnology companies to generate innovative products for the prevention or treatment of prevalent diseases, such as cancer, inflammatory-autoimmune disorders and infectious disease[15,16]. These projects have expanded, thanks to programs implemented by the Chilean government to encourage applied research in priority areas. These programs have stimulated innovative research on immunology as collaborations between investigators at universities and private companies. The first excellence funding grant on immunology was the Millennium Nucleus on Immunology and Immunotherapy supported by the Iniciativa Científica Milenio. This is a multidisciplinary program involving nine head researchers based at two of the largest Chilean universities (Pontificia Catholic University of Chile and University of Chile) and includes over 100 young investigators (undergraduate, graduate and postdoctoral fellows), three large hospitals and six biotechnology companies. Some of these companies, including Biosonda and Oncobiomed are 'spin-offs' created by immunologists participating in this program grant. The nucleus aims to improve the quality of basic immunology research, to

train young investigators and to do 'translational' biomedical research on immunotherapy for cancer, inflammatory-autoimmune disorders and infectious disease[15,16]. This association of researchers has already begun with the first clinical trials in Chile of immune-based therapies for cancer, autoimmune disorders and infectious disease[15–17]. Other immunologists have established other successful models of association, such as private foundations that contribute to basic and applied immunology research[14]. In addition, efforts are being made to establish networks in the clinical investigation and epidemiology of immune-mediated diseases, as shown by the successful creation of the Latin American Group for Primary Immunodeficiency Diseases, in which Chile, Brazil and Argentina are actively involved[18]. Finally, in addition to Argentina, Brazil and Chile, other South American countries, including Uruguay, Colombia, Venezuela and Perú, are also improving their policies for science and technology, with obvious beneficial effects for their immunology communities. These synergistic associations will be further encouraged by the upcoming Latin American Association of Immunology meeting to be held in Chile in November 2009.

Capitalizing on investment in science

Admittedly, conditions remained complicated for many years in South America and progress sometimes seemed uncertain, with governments continually introducing new schemes to support science and then failing to find the financial resources to follow through. There is still considerable distance between developed and South American countries in terms of investment in science and technology. In 2007, Brazil invested 1% of its gross domestic product; Chile, 0.7%; and Argentina, 0.6%. These financial limitations, which result in low salaries and limited grants, are sometimes aggravated by other difficulties, including bureaucratic problems associated with the importing of equipment and reagents. In particular, in Argentina, the salaries of young doctoral or postdoctoral fellows are still insufficient to meet the cost of living, which suggests an impending need to provide more support for the early stages of scientific careers to avoid 'brain drain'.

Yet the international influence of South American immunologists is steadily expanding, and there is every indication that it will continue to do so, as shown by the greater proportion of scientific papers in high-impact journals, the rising number of patents filed and the great enthusiasm of the new generation of young scientists in immunology programs and courses. This situation is now accompanied by increased awareness by the progressive governments of the importance of scientific research and development for improving the countries' economy.

The future of Brazil, Chile and Argentina promises the integration of immunology with emerging areas, including nanotechnology and stem cell research and the implementation of interdisciplinary approaches combining *in vivo* studies, 'new-generation' microscopy, genomics, proteomics and systems biology. In terms of infectious diseases, further progress in microbial immunity is expected; this will obviously include human immunodeficiency virus but will also include dengue virus and other emerging pathogens that affect the region. These studies should encompass immunopathology and immunoprophylaxis, with various strategies of vaccination undergoing evaluation. In Latin America, more than 210 million people live below the poverty line and bear the burden of neglected diseases such as schistosomiasis, Chagas' disease and leishmaniasis[19]. Investments are critical for 'scaling up' effective strategies to control neglected diseases as well as to develop new pharmacological approaches. We also expect a gradual increase in research into the immunology of noninfectious chronic degenerative diseases, including cancer, one of the main causes of death in South America[20]. In this context, we also foresee a further increase in studies on transplantation immunology and autoimmune disorders, including stem cell biology and cell or gene therapy. The establishment of stronger ties with the industry promises an exciting future in which high-quality basic research can be 'translated' into new vaccines and therapies for diseases prevalent not only in the region but also around the world.

Obviously such predictions entail the maintenance and further development of massive governmental commitment and investment in health sciences, including fundamental immunology, a policy that we hope will be mirrored by the private sector. This will certainly contribute to minimizing the 'brain drain' of young South American immunologists to North American or European research centers.

As immunology in Latin American grows in scope and confidence, the region will greatly increase its ability to compete internationally by combining forces to retain talent and create the 'critical mass' needed to produce science of even higher quality in the region.

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