The scientific muscle of Brazil's health biotechnology

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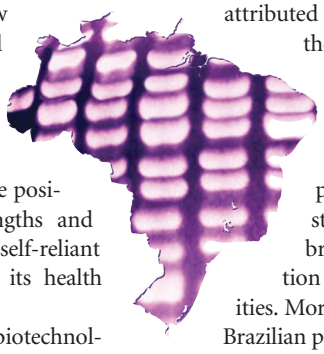
BRAZIL has a relatively long history of science and technology, and the current leftist government of President Luiz Inácio Lula da Silva continues to prioritize scientific and technological development in the country. Successes in the agricultural, energy and engineering (e.g., aeronautics) sectors reflect its scientific strength. Brazil's terrestrial biodiversity, with numerous diverse biomes including the Cerrado, Amazon rainforest, Pantanal wetlands, Caatinga region, and Araucaria and Atlantic forests, is also unrivaled in the South American continent and probably elsewhere. This combination of natural and scientific resources gives the country great potential to promote health biotechnology. In 2004, a DNA bank was established at the Jardim Botânico (Botanical Garden) in Rio de Janeiro to preserve the genetic material of endangered plant life. With an expected 1,000 specimens to be collected per year, researchers at the two laboratories at the Jardim Botânico are currently involved in both plant conservation and development of plant-based medicines and treatments[1].

The success of Brazil's health biotechnology sector

According to the World Health Organization (WHO, Geneva), diabetes affected about 33 million people in South America in 2000, and by 2030 the number is expected to rise to 66.8 million. Brazil ranks eighth in the world for the rate of diabetes in the population[2]. The demands for public health, such as diabetes management, and reliance on imports create major financial costs for Brazil. Statistics from the United Nations Conference on Trade and Development (Geneva) show Brazil's imports of medicinal and pharmaceutical products increasing from nearly $170 million in 1981 to just under $2 billion in 2002 (ref. 3). However, Brazil is in a favorable position to use its existing strengths and achievements to become more self-reliant in these fields by developing its health biotechnology sector.



One case of Brazilian health biotechnology success cited by several of the 33 Brazilian experts interviewed for this study is its recombinant human insulin product. Regarded as a collaborative success in terms of tackling a health burden and increasing technoscientific capacity, the Federal University of Minas Gerais (Belo Horizonte, Brazil) and the Brazilian biopharmaceutical firm Biobrás (São Paulo, Brazil) developed and patented a process for recombinant human insulin in the 1990s. Biobrás became one of only four companies in the world producing recombinant human insulin at the time. Although Biobrás has since been acquired by Novo Nordisk (Bagsværd, Denmark), there continue to be numerous examples of Brazil's growing capacity to meet its own health needs (see **Table 1**).

The nation has a strong diagnostics sector[4] and established competencies in the manufacture of conventional vaccines (e.g., yellow fever), a recombinant vaccine for hepatitis B and other recombinant proteins. The growth of health biotechnology has largely been attributed to the research efforts of the public sector. Nowhere is this more evident than in Brazil's sequencing of the plant pathogen *Xylella fastidiosa*. Acting as a launch pad, this public initiative instilled national confidence and brought international recognition for Brazil's genomics capabilities. More importantly, it is catalyzing Brazilian postgenomic research into diseases, such as Chagas disease and cancer, with vaccines and stem cells (see **Box 1**).

Comparing Brazil's health biotechnology publications in international peer-reviewed journals and health biotechnology patents granted in the United States Patent and Trademark Office (USPTO, Washington, DC, USA) between 1991 and 2002 provides another indicator of Brazil's innovation level in terms of scientific output and commercial potential in the field (**Fig. 1**). Data derived from Science-Metrix (Montréal, PQ, Canada) shows that Brazil's publications have been steadily increasing in health biotechnology[5]. Its patent activity based on inventors' addresses in USPTO-granted patents in health biotechnology is not as strong, and patent activity does not occur in this period until 1996 (based on an analysis of USPTO's database, July 2004; http://www.uspto.gov/). Thus, in contrast to

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its publication record, Brazil's patenting has been uneven and limited.

Main features of the Brazilian sector

From as early as the 1970s, Brazilian national governments have focused efforts on promoting health biotechnology in the region. This has resulted in close collaborations between research institutes and universities and an expanding, but as yet rather small and fragmented, private sector. Because the Brazilian public has difficulty clarifying differences between health biotechnology with agricultural biotechnology, further efforts are required to inform the population about the risks and benefits of biotechnology and the science underlying it.

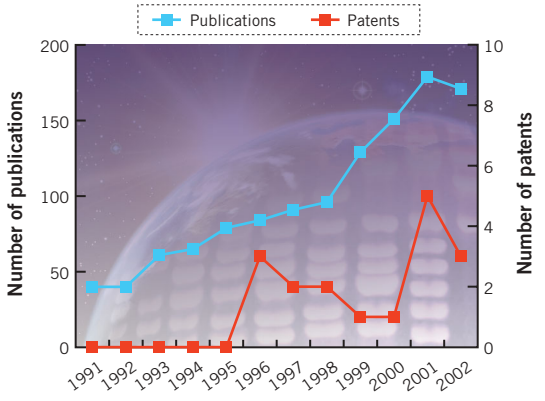

Figure 1 Brazilian publications and USPTO patents in health biotechnology (1991–2002). Source: Publication data are from ref. 5. Patent data are from the USPTO.

Government. Biotechnology development was an early priority for Brazilian governments. In the 1970s, Brazil's National Research Council (CNPq) launched two programs that pioneered biotechnology work in the country, the Integrated Programme on Genetics (PID) and the Integrated Programme on Tropical Diseases (PIDE). In 1981, the government set up the National Biotechnology Programme (PRONAB) to integrate institutions and budgets in agricultural, energy and health biotechnology. Three years later, it set up a national program aimed at supporting science and technology development (Programa de Apoio ao Desenvolvimento Científico e Tecnológico; PADCT) that included capacity building in biotechnology as an important element. The main goals of the program were to train scientists, develop scientific infrastructure and promote linkages among universities, institutions and industry. The third phase of this program started in 1997, and approximately 17% of its budget was allocated to biotechnology[6].

Despite the frequent turnover of governments in Brazil, biotechnology development has received uninterrupted support. At the federal level, the Ministry of Science and Technology has played a leading role in biotechnology development, and at the state level, leadership has come from the States Research Support Foundations (FAPs). The FAP in São Paulo, FAPESP, has been especially active and instrumental in organizing and financing biotechnology projects concentrated in the southeast part of the country.

Brazil is revising its regulatory and legal system in response to biotechnology developments. For instance, the government passed a patenting law in 1997 to be compatible with the World Trade Organization's (Geneva) Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), to which Brazil is a signatory[7]. Although drug regulation laws have existed in Brazil since the late 1970s, the National Sanitary Surveillance Agency (ANVISA, Brasilia) was established later, in 1999, to regulate all drugs and medical equipment in the country[8]. The first biosafety law was ratified in 1995 to regulate the introduction of genetically modified organisms. However, it covered more than environmental biosafety and broadly encompassed areas related to health biotechnology research such as the banning of genetic manipulation of germline cells and the production, storage, or manipulation of embryos. These put tight restrictions on health biotechnology research in the country[9]. In October 2004, the senate amended and approved a new biosafety law that would allow research on stem cells taken from surplus embryos, left over from *in vitro* fertilization procedures and already frozen for three years. Before it becomes law, it will need to be approved by the Chamber of Deputies[10]. Brazil's Ministry of Environment is now revising legislation on access to biological resources to ease restrictions on Brazilian scientists carrying out biodiversity research. The restrictions will be focused more on the commercialization of findings[11].

Research institutes and universities. Brazilian research institutions and universities are both productive in the health biotechnology field. The number of health biotechnology papers published in the international peer-

Table 1 Examples of Brazilian health biotechnology products

Sector	Type	Application	Producer[a]
Vaccines	Recombinant hepatitis B surface antigen	Hepatitis B	Instituto Butantan
	Attenuated virus	Yellow fever	Bio-Manguinhos (FIOCRUZ)
	Autologous whole cell	Prostate cancer	FK Biotecnologia
Therapeutics	Recombinant human insulin	Diabetes	Biobrás/Novo Nordisk
	Recombinant erythropoietin-α	Anemia	Instituto Butantan
	Monoclonal antibodies	Immunotherapy	FK Biotecnologia
Diagnostics	Recombinant antigens	Chagas disease	Bio-Manguinhos (FIOCRUZ)
	Peroxidase/anti-peroxidase and alkaline phosphatase/anti-alkaline phosphatase immunoassays	Antibody detection	FK Biotecnologia
Services	Molecular Novel natural molecules	Various R&D	Simbios Produtos Biotecnológicos (São Paulo, Brazil) Extracta Moleculas Naturais
	Biomedical software	Genomics R&D	Scylla Bioinformatics (São Paulo, Brazil).
	DNA services	Genetic testing	Gene–Núcleo de Genética Médica (Belo Horizonte, Brazil)

[a]Name of an associated research institute is in parentheses.

Illustration by R. Henretta

Box 1 *Xylella fastidiosa*: a model for success

In 2000, Brazil established itself as a leader in gene sequencing when the Brazilian consortium the Organization for Nucleotide Sequencing and Analysis (ONSA) surprised the international scientific community by making Brazil the first country to decode the genome of a plant pathogen, *Xylella fastidiosa*, a bacterium that attacks citrus fruits[20].

This impressive example of national collaboration has encouraged health-related genomics projects, including the jointly funded FAPESP and the Ludwig Institute cancer genome project and the Brazilian National Genome Project (NGP). Using the research model for the *Xylella* project, the NGP consists of 100 scientists from 25 laboratories in Brazil. Its first achievement has been to complete the genome sequence of *Chromobacterium violaceum*, which is of potential interest in developing therapies against certain cancers, tuberculosis and Chagas disease.

reviewed literature by Brazilian scientists has increased substantially since the early 1990s (ref. 5). The number of publications in health biotechnology jumped from 96 in 1998 to 179 in 2001. According to the respondents in this study, a few public research institutes, mainly the Oswaldo Cruz Foundation (FIOCRUZ, Rio de Janeiro, Brazil) and the Institute Butantan (São Paulo, Brazil), play a leading role in the nation's health biotechnology sector.

FIOCRUZ is a federal institute founded in 1900 with the goals of controlling bubonic plague, yellow fever and smallpox[12]. This institution, affiliated to Brazil's Ministry of Health (Brasilia), has become a strong producer of new knowledge in the health biotechnology field in Brazil, and its scientists published more than 16% of the Brazilian papers in the international peer-reviewed literature from 1991 to 2002. In addition, it provides training on a variety of topics related to the biomedical field. The institute also runs a manufacturing plant, Bio-Manguinhos (Rio de Janeiro, Brazil), that has vaccine and diagnostics production facilities (it is the largest Brazilian manufacturer of vaccines).

The Butantan Institute was established in 1989 and has had a strong public health connection. Like FIOCRUZ, it plays diverse roles in the health biotechnology sector, including research, training, technological development as well as manufacturing and commercialization of health biotechnology products. In addition to these two public research institutes, respondents in this study identified the Ludwig Institute for Cancer Research, a private institution in São Paulo, Brazil, as an active contributor to the health biotechnology sector.

There are about 100 universities in Brazil, and they publish 80% of all Brazilian health biotechnology papers in international peer-reviewed journals[5]. The largest contributor is the University of São Paulo, publishing almost 26% of this type of paper. Both the Federal University of Rio de Janeiro and the Federal University of Minas Gerais are also publishing extensively in this field, with around 11% of these papers each. The universities are heavily involved in domestic collaboration, which has increased extensively since 1991 (ref. 5). For instance, the Ludwig Institute collaborates extensively with the Federal University of Minas Gerais, and both the University of Rio de Janeiro and the Federal University of Minas Gerais collaborate extensively with FIOCRUZ. The *X. fastidiosa* sequencing project is an example of the close collaboration among researchers in the universities and the public research institutes. They set up a 'virtual institute', in which scientists remained in their original institutions but collaborated closely. The project involved 34 biology laboratories and one bioinformatics center located across the country[13].

Industry. In the past decade, the Brazilian private biotechnology sector has quickly expanded, with most companies concentrated in the south and southeast parts of the country. In 1993, there were 76 biotechnology firms in Brazil; by 2001, their number had increased to 354 (ref. 4). Approximately 70% are local private firms, 25% are multinational and 5% are state-owned firms[14]. Of their combined products, 26% are for the health care market and the rest are for agricultural, environmental and industrial fields.

Brazil has a large pharmaceutical market (the 11th largest in the world), attracting multinational pharmaceutical companies, such as GlaxoSmithKline (London, UK), Roche (Basel, Switzerland) and Sanofi-Aventis (Strasbourg, France). Those firms are not heavily involved in health biotechnology innovation in the country, however. Similar to multinational firms found in other developing countries, large Brazilian companies have low innovation and patenting rates[15].

Efforts by the government to attract private sector investment in biotechnology commercialization are limited by a decree prohibiting university professors from being employed by industry. This discourages them from becoming involved in the formation of spinoff companies. A new bill to encourage private sector participation, the so-called Innovation Law, was approved in 2004 by the Chamber of Deputies and is now under discussion at the Senate[16]. If approved, professors will be able to work for limited periods in the private sector. Respondents in this study said that researchers from both public research institutions and universities and even the government have mixed opinions about this law. However, university spinoffs are not unheard of in the country, and Brazil's first biotechnology company, Biobrás, was created as a spinoff from the Federal University of Minas Gerais.

There are also a few biotechnology incubators in Brazil, with the Biominas Foundation (Belo Horizonte, Brazil) generally recognized by the respondents as the most successful example. Most of them have extensive support from public institutions, such as state governments and the public research system, but they generally also have some private sector support (see **Box 2**). Even though venture capital investment is increasing in the country, it continues to be limited, especially for health biotechnology. Overall, the respondents in this study were generally skeptical about the role of incubators in Brazil's health biotechnology development. One respondent said, for example, that the incubators "have not moved forward, they have not been able to grow up, and I think that this reflects the lack of an industrial policy."

The general public. Given the large socioeconomic and educational differences within the population, as well as minimal biotechnology information programs for the public, most of the respondents concluded that the majority of the population were not knowledgeable about this science. Moreover, the respondents noted that public discussion of biotechnology was frequently associated with transgenic foods, which is a controversial issue in Brazil. Some of the respondents felt that there was not full awareness and understanding in the general population of what constitutes genetically modified organisms.

Those interviewed from civil society organizations stressed the need to distinguish between agricultural and health biotechnology because of the key differences in regulations and in relative risks and benefits. However, this has proven to be problematic. For example, some respondents felt that the absence of a clear government stance on biotechnology was contributing to the general lack of public knowledge. Many regarded the media's coverage of biotechnology as unbalanced and

Box 2 FK Biotecnologia: a fine balance

FK Biotecnologia was established in 1999, incubated by CIENTEC in southern Brazil. Its mission is to perform R&D, production and commercialization of immunodiagnostic products and anticancer vaccines. The company received venture capital funding for its operations and has been able to grow at a steady pace. Its possession of a proprietary patent in the cancer vaccine field has made it easier for the firm to attract the attention of investors and the government.

The firm balances its operations in two major domains so as to raise funding and increase its innovation capacity. On the one hand, it focuses on immunodiagnostics that are based on readily available knowledge with low IP protection. This work requires a relatively low capital infrastructure, and it is possible to develop immunodiagnostic products that can reach the market in a reasonably short time. FK Biotecnologia's product line in immunodiagnostics has more than 70 items at present. On the other hand, FK Biotecnologia focuses on cancer vaccines that are based on carrying out science-intensive research. This work requires a relatively capital-intensive research infrastructure and needs a longer development and commercialization time. FK Biotecnologia carries out the latter work in extensive collaboration with local universities and hospitals. The fine balance of these two domains is the key to the company's success[21].

excessively focused on negative aspects. This problem is compounded by the widely divergent views of the organizations that provide information to the public. These organization range from nongovernment organizations such as Greenpeace to industry organizations such as Brazil's Biotechnology Information Council (Conselho de Informacoes de Biotecnologia, CIB, Sao Paulo, Brazil) and stakeholder groups, such as the National Biosafety Association (ANBio, Rio de Janeiro, Brazil).

Given this context, public receptivity to health biotechnology is difficult to gauge. Nevertheless, the common sentiment among those interviewed was that, despite the overall general confusion between agricultural and health biotechnology, the population is more accepting of health biotechnologies, given the readily apparent benefits associated with them.

Main challenges for development

The volatility of the Brazilian economy has presented problems to many enterprises not only in health biotechnology but also in other sectors. The region has encountered difficulties in creating an infrastructure to share knowledge and resources among ventures, and the knowledge flow between academia and the private sector has been slow. At the level of government, legislative measures to promote health biotechnology have been confined to the Ministry of Science and Technology and ties to industrial development have been lacking. In addition, the Brazilian system for patent protection is inefficient and inadequately resourced, reducing incentive for entrepreneurs to form biotech companies, the value of which is mostly based on intellectual property (IP).

Macroeconomic conditions detrimental to industrial development. Even though Brazil's economy is now showing impressive growth[17], it has gone through periods of instability with frequent changes in government, especially in the late 1980s and early 1990s. With unstable economic conditions, such as a high inflation rate, there were limited incentives to invest in long-term and risky fields such as health biotechnology development.

The result has been a lack of continuity in funding, resulting from changing governmental priorities and budgetary delays. This instability has also discouraged venture capital investments.

Private sector firms lack linkages. Most of the respondents in this study said that Brazilian health biotechnology has not been as successful as it should have been, especially in transferring scientific knowledge into products. The Minister of Science and Technology, Eduardo Campos, echoed this sentiment when he said recently, "Brazilians get lost between basic research and its transformation into technology, between academic life and the manufacturing system."[18]

A major contributor to this problem is the lack of linkages among biotechnology firms. As one respondent noted, "There is no coordination among enterprises. They are more worried about their own problems than about trying to generate some kind of synergy that could develop business everywhere." Cooperation between firms and the actors most active in health biotechnology research, such as the universities and research institutes, has also been limited. These actors generally lack mutual understanding, do not trust each other and operate in very different cultural environments. Consequently, the considerable research capacity within the public research system in health biotechnology is not exploited to its full potential by the industrial sector.

Lack of governmental policies. The government of Brazil has placed an emphasis on stimulating scientific research in the health biotechnology field and in encouraging linkages between the public research system and enterprises. To promote industrial development in the health biotechnology sector, governmental policies must be more decisive, especially those targeted at promoting private sector development. According to some respondents in this study, health biotechnology development has to have a wider governmental mandate and involve more ministries than the Ministry of Science and Technology. In other words, it has to be identified as a national priority that contributes toward Brazilian development.

There are signs of movement. In April 2004, four federal cabinet ministers sent a joint letter to President Da Silva asking him to develop an industrial policy focusing on innovation aimed at industrial goods, pharmaceuticals, software and semiconductors—and listing biotechnology, biomass and nanotechnology for medium-term consideration.

Inefficient patenting system. Until the mid-1990s, Brazil did not allow patenting of pharmaceutical or biopharmaceutical products. This restriction discouraged industrial development in health biotechnology and promoted the copying of innovations from other countries. The introduction of a patent law in 1997 has changed this climate and is encouraging greater commercialization of innovation in this field. The system is not yet operating efficiently, however. Patenting is a very slow process. According to interview evidence, the examining body—the National Institute of Intellectual Property (INPI)—can take 7 years to process a patent application. There is a need to simplify the process and to increase the staff in the patenting office.

According to some respondents in this study, this situation is beginning to improve, and INPI now has more patent examiners than in the past. Respondents in this study also pointed out that universities need more knowledge and resources to encourage and manage patenting of their inventions. Patenting is therefore still a challenge for health biotechnology development in Brazil and remains a hindrance to encourage local innovation.

Conclusions

Despite the challenges facing the Brazilian health biotechnology sector, the interviewees in this study were optimistic that the sector

will be able to operate more successfully in the future. They felt that the country has all the conditions needed for success, especially a strong, well-trained scientific community. Respondents also recognized that the government is trying to encourage participation by the private sector and to encourage linkages among universities, public research institutions and private companies. Four major lessons in encouraging an environment for venture creation are evident from our analysis of the Brazilian health biotechnology sector.

Focus on developing a strong scientific capacity. Brazil has built up a critical mass of very well-trained people in health biotechnology research. The government emphasized training in the sector from the early 1980s, and universities have been able to advance both their training and research mandates. Some respondents in this study stated that Brazil generally had an excess of human resources in science and technology. The market is unable to absorb all the new PhDs graduating from the universities, and as a result many well-educated Brazilians emigrate. Nevertheless, this high level of education in the health biotechnology field has been a resource for research in the field and the development of the industrial sector so far.

These public investments in human resources and a public research infrastructure have resulted in a strong scientific capacity. Brazilian scientists are increasing their publications in health biotechnology at an impressive rate. The specialization index is an indicator that expresses the intensity of research in a specific field that a country publishes in, relative to the intensity of publications in the field by the world. A specialization index of 1 means a country (i.e., Brazil) publishes proportionally as much in a specific field as the world does. Their specialization index in health biotechnology has risen from 0.57 in 1990 to 0.95 in 2002 (ref. 5), suggesting an increase in research intensity in health biotechnology compared with other research fields. Brazilian scientists are also increasingly publishing in higher impact journals[5] than previously. From a scientific standpoint, Brazil has several research groups in health biotechnology that work at the international level, including those that have made significant contributions to the worldwide genome sequencing efforts.

Promote linkages and exploit existing strengths in disparate fields. Even though the private sector lacks linkages, public sector scientists often work together within and between institutions. Respondents in this study said that they collaborate extensively, and their cooperation is rising. In this way, knowledge flows and the use of resources such as research equipment are optimized. This makes it possible to establish virtual institutes, which are networks that allow researchers located throughout the country to work on the same project. An example of that is the National Genome Project discussed in **Box 1**.

By drawing upon traditional strengths in other fields of research, such as agbiotech, these collaborations are galvanizing health biotechnology. The success of the *X. fastidiosa* sequencing project directly stimulated the development of the cancer sequencing effort. Many of the respondents in this study said Brazilian health biotechnology efforts should apply the model used in Brazilian agbiotech. The successes of the *Xylella* project are also opening the eyes of venture capitalists in Brazil to investment opportunities in biotechnology, including the health sector.

Exploit local biodiversity for health. Brazil's richness in biodiversity includes numerous plants with medicinal properties that offer the possibility of health products of both national and global interest[19]. This field is still in its infancy, but the potential of the Brazilian biodiversity seems to be vast.

The government has set up regulations to control the use of this resource, which can strengthen the potential for the country to capitalize on its biodiversity. Some small firms have also been established in this area, such as Extracta Moleculas Naturais (Rio de Janeiro, Brazil). Management of these resources must ensure that the benefits accrue to the population in Brazil.

Gain access to key actors. Brazilian health biotechnology has benefited from several pioneers who have overcome considerable challenges and rallied support for the sector. According to the respondents in this study, Marcos Luiz dos Mares Guia played a pivotal role in the human insulin project, acting as a mediator between the university and the private sector. For pulling together resources and managing collaborations in the sequencing of *X. fastidiosa*, some respondents also identified the scientific director of FAPESP, Jose Fernando Perez, as an instrumental player. What these individuals have been able to accomplish is monumental for the Brazilian biotechnology sector.

Sustaining their successes, however, will require systemic development. On the basis of the strength of the health biotechnology sector and enthusiasm of its main actors, there is reason to believe that Brazil will be able to build up a closely linked health biotechnology innovation system that truly encourages knowledge flows and innovation.

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