Access to new technologies in multipatented vaccines: challenges for Brazil

Cristina Possas, Adelaide Maria de Souza Antunes, Flavia Maria Lins Mendes, Suzanne de Oliveira Rodrigues Schumacher, Reinaldo Menezes Martins & Akira Homma

Partnerships, technology transfer and targeted policies are needed to accelerate Brazil's participation in global vaccine research and development.

The global vaccine landscape has undergone drastic changes in the past three decades. New, innovative vaccines have emerged in the market, which has resulted in an increasing number of patents with different patent holders. The advent of vaccines as complex, multipatented products[1] raises a broad range of issues, including in the areas of innovation policy and the conditions of access to crucial technologies by developing countries' scientists and manufacturers. These issues have emerged in international and national legal frameworks, in both litigation and nonlitigation contexts. Several vaccine patent cases have emerged globally: *Microbix Biosystems v. Novartis Vaccines and Diagnostics*[2], related to Microbix's Virusmax technology for increasing virus yields in egg-based vaccine manufacture for influenza vaccine; *Boehringer Ingelheim Vetmedica v. Schering-Plough*[3], involving a process for growing and isolating virus; *Medeva Pharma v. American Home Products*[4], related to a method of detecting pertussis antigen; and *Embrex v. Service Engineering*[5], concerning a method of injecting vaccine into egg.

On the basis of our survey of vaccine patent deposits in Brazil, we examine the increasing complexity and role of patents as an incentive to vaccine innovation. We also consider patents' potentially detrimental impacts on access to new vaccine technologies in emerging countries, and particularly in Brazil, as a consequence of higher production costs related to royalty payment and other market barriers. Finally, we discuss possible implications and consequences of the global patent regime in the development of new innovative vaccines in emerging countries.

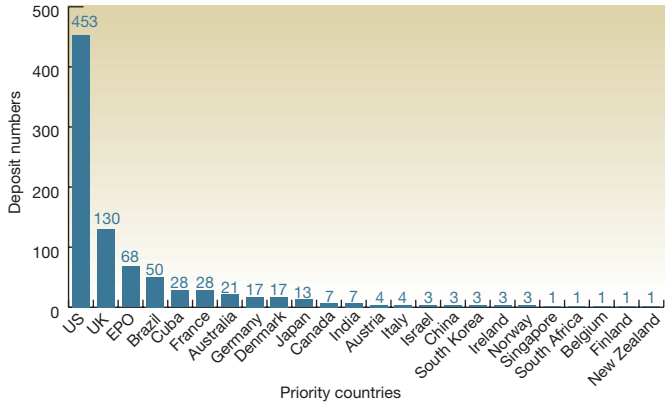

Figure 1 Countries of priority of patent deposits for vaccines against infectious and parasitic diseases, Brazil, 2000–2011. Source: Federal University of Rio de Janeiro School of Chemistry Information System on the Chemical Industry (SIQUIM); Derwent Innovations Index.

These issues are discussed in the context of the international legal framework. In the pharmaceutical sector, the detrimental consequences of the global patent regime introduced by the World Trade Organization (WTO) Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), the development and production of low-cost generic drugs and the access to these drugs by the poorest populations in developing countries have become evident. These detrimental consequences have been mainly related to the impact of patents increasing the prices of new pharmaceutical products and to the constraints to the access to innovative technologies in technology transfer agreements, particularly affecting local manufacturers in developing countries. However, for other health products, such as vaccines, intellectual property (IP) and market issues affecting prices are still unclear, and the relative lack of literature on this, despite important contributions from several researchers, contrasts starkly with the high impact of vaccines and the contribution of national immunization programs to global public health.

Vaccine innovation

New approaches to vaccine development have resulted in diverse innovation-intensive and multipatented products, including DNA vaccines, recombinant vaccines based on antigens expressed in vectors (viral, bacterial, yeast) and vaccines obtained through reverse vaccinology, in which the selection of potential candidates is

Cristina Possas, Reinaldo Menezes Martins and Akira Homma are at Bio-Manguinhos, Oswaldo Cruz Foundation (FIOCRUZ), Rio de Janeiro, Brazil; Adelaide Maria de Souza Antunes, Flavia Maria Lins Mendes and Suzanne de Oliveira Rodrigues Schumacher are in the School of Chemistry, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil; Cristina Possas is also at Evandro Chagas National Institute of Infectology, FIOCRUZ, Rio de Janeiro, Brazil; and Adelaide Maria de Souza Antunes is also at the National Institute of Industrial Property, Rio de Janeiro, Brazil.
e-mail: cristina.possas@bio.fiocruz.br

Table 1 Ten largest patent holders in Brazil for vaccines against infectious and parasitic diseases, 2000–2011

Company or organization	Country	Total number of deposits	Deposits without partnership	Deposits with partnership	Most significant partnership (number of deposits together)
GlaxoSmithKline (including deposits from SmithKline Beecham and Corixa)	UK	79	50	29	SmithKline Beecham (19)
Novartis (including one deposit from Chiron)	Switzerland	61	11	50	Chiron (47)
Pfizer (including deposits from Wyeth)	US	38	19	19	American Cyanamid (4)
Center for Genetic Engineering and Biotechnology (CIGB)	Cuba	21	20	1	Pedro Kourí National Institute of Tropical Medicine (1)
Sanofi Pasteur (including deposits from Aventis Pasteur)	France	28	8	20	Aventis Pasteur (10)
3M Innovative Properties	US	18	4	14	Coley Pharmaceutical Group (11)
Pasteur Institute	France	17	5	12	French National Center for Scientific Research (CNRS) (9)
Bristol-Myers Squibb	US	16	11	5	ZymoGenetics (3)
Oswaldo Cruz Foundation	Brazil	15	11	4	No partnerships
US Department of Health and Human Services	US	13	4	9	US Department of the Navy

Source: University of Rio de Janeiro School of Chemistry Information System on the Chemical Industry (SIQUIM); Derwent Innovations Index; and the European Patent Office (EPO).

made at the genetic level, rather than at the protein level, in a quick and efficient process and in only a few years[6,7]. It is estimated that by 2030, owing to factors related to vaccine innovation, availability and prices—including patents—the required global expenditure for vaccines in routine program use could increase to $20 billion a year[7]. In this regulatory and market scenario, one of the biggest challenges to policymakers and manufacturers in developing countries is the incorporation of these expensive and technologically complex vaccines into their national immunization programs[8,9]. Innovative and effective products such as conjugate vaccines against *Neisseria meningitidis* A, C, W-135 and Y, *Haemophilus influenzae* type b, *Streptococcus pneumoniae*; new combination vaccines including *Haemophilus influenzae* type b, pertussis, tetanus, hepatitis B and diphtheria (DPT-HB-Hib); and human papillomavirus vaccines in virus-like particles (HPV) are requiring more effective governance strategies in developing countries to accelerate the availability of these products through public-private partnerships and technology transfer agreements[10]. In this context, vaccine patents emerge as a crucial issue for vaccine development[11].

This new global situation and the important contribution of previous studies in developing countries[12,13] has indicated the need for a comprehensive survey of vaccine patents in Brazil. The methodology for the search is described in **Supplementary Methods**.

Patent survey

The search for patents from 2000 to 2013 related to vaccines for selected infectious and parasitic diseases with deposits in Brazil resulted in 871 documents corresponding to 2000–2011 (the numbers for 2012 and 2013 were negligible). The United States leads with 453 patent deposits (**Fig. 1**), followed by the United Kingdom and the European Patent Office (EPO), where European countries usually make the first deposit to guarantee protection in contracting states. If we consider all deposits in European countries and the EPO, 279 deposits were made by Europe. In Brazil, 50 deposits were identified, with half deposited only in that country. Breaking down these results, for patent deposits on vaccines for infectious diseases, the United States leads once again, with 334 deposits, followed by the United Kingdom and the EPO and Brazil (**Supplementary Fig. 1**). And for deposits on vaccines for parasitic diseases, the United States leads, with 47 deposits, followed by Brazil (**Supplementary Fig. 2**).

Table 1 indicates the ten largest patent holders for vaccines against infectious and parasitic diseases and number of deposits in Brazil. GlaxoSmithKline is the largest, with 79 deposits, followed by Novartis with 61, Pfizer with 38 and Sanofi Pasteur with 28.

The incorporation of new adjuvants to boost immune responses is becoming crucial to the development of innovative vaccines, as new antigens with purer and smaller molecules may not elicit the immune responses necessary for long-term vaccine protection. The malaria vaccine candidate RTS provides a good example of the crucial part new adjuvants can play. This vaccine, based on the *Plasmodium falciparum* sporozoite antigen circumsporozoite protein, was successful in providing protection against clinical malaria only when combined with a powerful adjuvant (AS02 or AS01)[6,7]. Other examples include the tests using hybrid flagellins in malaria vaccines. Hybrid bacterial flagellins associated with malaria antigens can boost the immune response in tests with new malaria vaccines.

Adjuvants have emerged as an alternative route for vaccine development and are an instrumental technology for new vaccines, with enormous potential in the global market[6,7]. The development of powerful and safe adjuvants is therefore a key component of vaccine research (**Table 2** lists several important licensed vaccine adjuvants). **Figure 2** shows the country of priority for 246 patent deposits for vaccine adjuvants: US companies and organizations lead, with 99 deposits, followed by the United Kingdom, with 49. Brazil submitted 12 deposits, all from residents and most of them in partnership with universities and research institutes. **Table 3** indicates the largest vaccine adjuvant enterprises and the total number of

Table 2 Licensed vaccine adjuvants[23]

Adjuvant	Company	Class	Indication (vaccine)
Alum	Various	Mineral salts	Various
MF59	Novartis	Oil-in-water emulsion	Influenza (Fluad) and pandemic flu
AS03	GlaxoSmithKline	Oil-in-water emulsion + α-tocopherol	Pandemic flu (Pandemrix)
AS04	GlaxoSmithKline	Monophosphoryl lipid A + alum	Hepatitis B (Fendrix), HPV (Cervarix)
Liposomes	Crucell	Oil-in-water emulsion	Hepatitis A, influenza (EU)

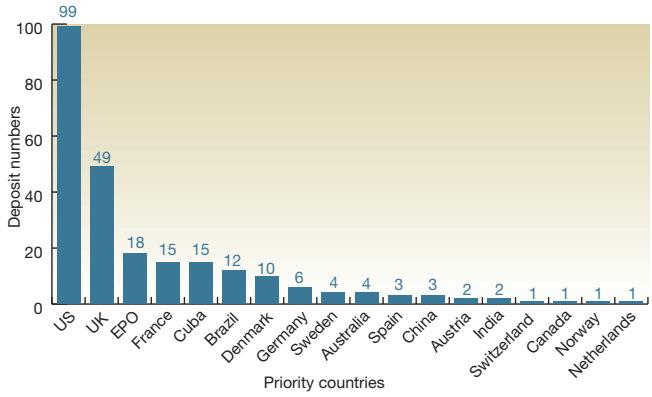

Figure 2 Number of patent deposits on vaccine adjuvants per country of priority. Source: Federal University of Rio de Janeiro School of Chemistry Information System on the Chemical Industry (SIQUIM); Derwent Innovations Index.

applications filed, led by Glaxo Group and Novartis.

Figure 3 shows the number of patent deposits for selected infectious and parasitic diseases in Brazil: HIV, influenza, malaria, tuberculosis and dengue. HIV vaccine patent applications account for 29% of the total. Most of these deposits, particularly for HIV and tuberculosis, were submitted through scientific and technological partnerships (**Supplementary Table 1**).

The Brazilian patent regime

The TRIPS Agreement, which ushered in a new global patent landscape, also led to the emergence of legal constraints on the local development of and access to low-cost drugs and other medicinal products in developing countries. These constraints have affected national laws in different ways according to local political and socioeconomic contexts. Many emerging countries have since then incorporated even stricter rules into their free-trade agreements.

In Brazil, the consequences of the global patent regime introduced by TRIPS have been worse than in other emerging economies, such as China and India, as a result of the National Congress's decision to create the Brazilian National Industrial Property Law in 1996. Designed to be stricter than TRIPS, the new law did not allow Brazil to benefit from the TRIPS provision allowing countries a waiver period of ten years to build national capacity before adhering to the international agreement. Despite some benefits, the new law had a clear detrimental impact on the local pharma industry as well as research institutes. India and China, by contrast, benefited from the waiver period by building their local pharma capacity, thus becoming important exporters of generic drugs and active principals in Brazil.

This situation increased Brazil's dependence on foreign enterprises for pharmaceuticals and immunobiologicals. In one example, after unproductive and difficult negotiations in which the Brazilian Ministry of Health issued warnings of compulsory licensing of some antiretroviral drugs for HIV and AIDS owing to high prices (in some cases more than four times the international market price for several drugs), the Brazilian government finally issued a compulsory license of Merck's drug Sustiva (efavirenz) in May 2007.

Previous studies[14,15] have indicated the need for urgent reform of the Brazilian IP regime and more speed in a system viewed as inadequate and bureaucratic[16–18]. Despite some progress made in the past decade, the patent process for drugs, vaccines and other health products is slow and has been dissociated from the country's innovation policy and R&D strategy, causing significant detrimental impact on the local capacity for innovation, which in turn has increased uncertainty on whether and when novel technologies will be protected.

Legal reform

The National Congress recently stressed the consequences of the National Industrial Property Law: a sharp decline in the participation of Brazilian residents in patent deposits, from 32.4% in 1996, when the law was enacted, to 17% in 1997. In 2004, Brazil registered only 106 patents with the US Patent and Trademark Office (USPTO), whereas China had 403. In 2007 Brazil registered 90 patents, ranking twenty-ninth worldwide, behind China (1,121 patents), India (545) and Malaysia (158). In 2009 China registered 1,655 patents with the

Table 3 Largest vaccine adjuvant applicants and number of patent applications filed, Brazil, 2000–2011

Company or organization	Number of applications	Partnerships (number of deposits)
Glaxo Group	37	SmithKline Beecham (16)
Novartis	17	Chiron (10)
3M Innovative Properties	12	Coley Pharmaceutical Group (8)
Wyeth	10	American Cyanamid (4)
Center for Genetic Engineering and Biotechnology (CIGB)	8	N/A
Minas Gerais Research Foundation (FAPEMIG)	6	N/A
Sanofi Pasteur	6	N/A
Pierre Fabre Pharmaceuticals	5	N/A
São Paulo Research Foundation (FAPESP)	5	N/A
Intervet International	4	Akzo Nobel (4)
Akzo Nobel	4	Intervet International (4)
American Cyanamid	4	Wyeth (4)
Bavarian Nordic	4	N/A
Becton Dickinson and Co.	4	N/A
Federal University of Minas Gerais (UFMG)	4	N/A
Cytos Biotechnology	3	N/A
French National Center for Scientific Research (CNRS)	3	N/A
Total	168	

N/A: not available.

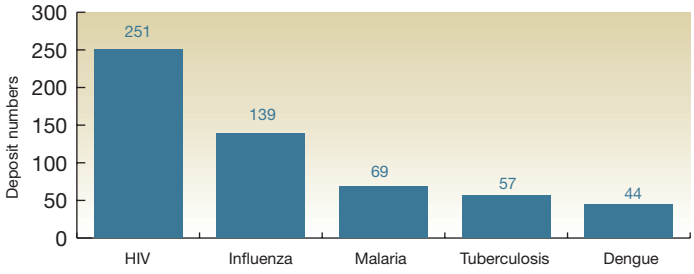

Figure 3 Number of vaccine patent deposits for major infectious and parasitic diseases, Brazil, 2000–2011. Source: Federal University of Rio de Janeiro School of Chemistry Information System on the Chemical Industry (SIQUIM); Derwent Innovations Index.

USPTO; Brazil registered 103, ranking one-hundred-third globally. As a result, a proposal to reform the National Industrial Property Law is currently under debate by the National Congress.

On the basis of the argument that innovation and development will not occur without strong IP protection, the National Confederation of Industry (CNI) has provided several recommendations for a new national IP agenda: (i) to increase the autonomy and operational capacity of the National Institute for Industrial Property; (ii) to reduce the average time for patent evaluation; (iii) to assure the legal and economic security in IP; (iv) to improve the National Industrial Property Law and the Authorship Rights Law; (v) to improve the regulatory framework and stimulate R&D in biodiversity; (vi) to combat crimes against IP; and (vii) to increase the international integration of Brazil in the IP area[17]. Several organizations representing industrial sectors, such as the Brazilian Fine Chemicals, Biotechnology and Specialty Industries Association (ABIFINA), have joined in the intensifying debate[18] along with leading economists[19–21]. These organizations understand (in agreement with our perception) that, on the contrary, innovation does not depend mainly on strong IP protection but on the accumulation of knowledge and on state participation in scientific research.

Another important component of this legal framework is the Brazilian Innovation Law (2004), conceived to stimulate the participation of science and technology institutes in innovation. The law establishes that each institute create a 'nucleus for technological innovation' to manage its innovation policy, stimulate patent deposits and transfer knowledge generated by the institute into a productive setting.

Capacity for innovation

Brazil boasts high-quality scientific and technological institutes and an incipient biotechnology industry, with significant potential for vaccine innovation and development. It is the world's seventh-largest pharmaceutical market, second only to China among emerging markets, with a public budget for vaccine purchase of around $800 million in 2011. The country has increased its scientific production tenfold during the past two decades, ranking thirteenth in international comparisons, and accounts for 18.4% of global scientific output in tropical medicine. However, this scientific capacity has not yet been adequately translated into innovative projects, and the low number of local patents indicates that the interest in discovery and patenting is still limited.

As a result, initiatives and policies have been conceived to stimulate public and private partnerships: the Brazilian Innovation Law, which allows for flexibility and interaction among researchers in universities and research centers with the commercial sector, and—in the context of the government's new economic-industrial healthcare complex—new partnerships for product development (PDPs), linking public and private laboratories with an enterprise (usually a foreign company) that provides production technology. The country has now formalized 104 PDPs, but only seven are for the development and production of vaccines.

As a consequence of national scientific and technological policies, the number of groups researching vaccines has increased. There are now 48 Brazilian groups involved in vaccine R&D for infectious and parasitic diseases, in areas such as immunology, virology, scale-up and clinical research. Most of them are still in the pre-development stage[10]. In evaluating the national capacity related to research and the main infectious and parasitic diseases for this article, we considered all the components of the technological vaccine complex: industry, public laboratories and universities. In this complex, our mapping of vaccine R&D competence in Brazil identified research leaders registered in the National Council for Scientific and Technological Development in diverse areas such as vaccine research, vaccine development, quality control and clinical trials.

Challenges and conclusions

The results of this case study indicate heavy participation by foreign companies, mainly from the United States and Europe, in patents for vaccines for infectious and parasitic diseases in Brazil. In contrast, in spite of a significant and increasing role for some Brazilian universities, research institutes and companies, the number of patents for vaccines in the country is still low, indicating the need for a national strategy supporting innovation and technological development. The deposits by foreign companies for the diseases selected in this study are concentrated in a few diseases: HIV and AIDS, influenza, malaria, tuberculosis and dengue. Most of these deposits were submitted through scientific and technological partnerships.

The growing global number of patent deposits based on minor incremental processes that do not configure real vaccine innovations is a justifiable concern for many scientists and policymakers (who are, as a result, critical of the global patent regime), but it would be naïve to ignore the crucial role of patents in vaccine development and in increasing competitiveness in the global market. However, in the post-TRIPS landscape, patents on vaccines—and particularly on crucial technologies for vaccine development, such as adjuvants—increasingly constitute market barriers for Brazil and other developing countries. Few vaccine products and adjuvants have been licensed through technology transfer agreements in these countries, and from this perspective many patents now constrain vaccine development and access, operating as a market reserve.

Nevertheless, vaccine patents are just one of the many barriers faced by Brazil and other developing countries. Most of these barriers are related to insufficient regulatory structures and procedures and to limited investment in local capacity, human resources, technology and logistics. A good example of these constraints is the average time for patent registrations by the Brazilian National Institute for Industrial Property (INPI): 10.8 years, in contrast to the United States (2.6 years); Europe (3 years), China (1.9 years) and South Korea (1.8 years). This slow pace affects the annual number of patents granted: according to the USPTO, in 2013, Brazil granted only 254 patents, in contrast to the United States, at 133,593, and far behind China (5,928), India (2,424) and Russia (417) (ref. 22). Therefore, the main challenge for Brazil and other developing countries is to accelerate and streamline the procedures of their national patent offices (the INPI in the case of Brazil). In this scenario, more effective knowledge governance systems and management strategies should be conceived

to minimize the detrimental effects of patents constraining access to new and innovative technologies.

Better IP management is necessary but not sufficient. Funding R&D, improving regulatory mechanisms and strengthening the infrastructure and logistics are key issues for developing countries. Brazil should try, as part of a long-term patent strategic plan, to put in place a powerful patent policy, supported by skilled researchers and patent managers to explore the full strategic potential of patent documents to build an innovation-based economy in which technological prospect plays a crucial role. A good example is China's national patent development strategy for 2011–2020, which aims for 2 million annual patent filings by 2015, half of them based on innovative invention patents. As part of this, China intends to roughly double its number of patent examiners to 9,000 by 2015.

Brazil should also work to boost the number of patents that its residents and companies file in other countries, as the data presented here indicate that 50% of Brazil's patents are deposited only in that country. To increase the number of patents submitted by residents in Brazil, the National Research Council (CNPq) should establish a new policy and new criteria for evaluating the scientific productivity of the researchers. This policy should provide incentives to researchers who submit and are granted patents; a patent submitted should be worth ten times more than a published paper, and a patent granted should be worth 100 times more than a published paper. These would be fair criteria, because the researchers cannot publish the data before the patent is granted. Other incentives and rewards should also be developed to increase the social value of patents. In addition, any other government process that includes evaluation of the curriculum vitae for scholarships, public contests or awards should be reviewed by the CNPq and other federal and state research funding agencies in Brazil. And incentives such as prizes for innovation, cash bonuses, tax breaks for companies that are prolific patent producers and other individual incentives should also be put in place.

To promote and accelerate innovation and autochthonous technological development, it will also be necessary to overcome economic barriers to existing patents resulting from public funding. To that end, a legal provision that gives the government the right to use patented products originating from government-funded projects without payment should be created and incorporated into IP law.

To stimulate vaccine innovation it is also urgent that Brazil overcomes other gaps in the flow from research to product—a new culture of innovation and investment in qualified human resources, institutional environments favorable to discovery and innovation, and adequate technological platforms are all necessary. It will be also necessary to overcome gaps at the preclinical stage, such as inadequate infrastructure and lack of certified laboratory animals.

It is important to stress that, despite their relevance as a main innovation indicator, patents are not sufficient if the country is not able to put in place a scientific structure and technological capacity that can provide new health products and vaccines to the population.

Note: Any Supplementary Information and Source Data files are available in the online version of the paper (doi:10.1038/nbt.3244).

ACKNOWLEDGMENTS

The authors thank Bio-Manguinhos/FIOCRUZ for research support and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) for access to the Derwent Innovations Index (available at http://www.periodicos.capes.gov.br).

AUTHOR CONTRIBUTIONS

C.P., A.M.d.S.A., A.H. and R.M.M. conceived and designed the research; C.P., A.M.d.S.A., F.M.L.M. and S.d.O.R.S. organized and analyzed the data; C.P., A.M.d.S.A., A.H. and R.M.M. wrote the paper.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

1. Geradin, D. & Layne-Farrar, A. TILEC discussion paper 2011–010. Santa Clara University Computer & High Tech Law Journal Symposium (21 January 2011).
2. *Microbix Biosystems v. Novartis Vaccines and Diagnostics*, 6:14-cv-00003, No. 76 (E.D. Tex. Feb. 18, 2015).
3. *Boehringer Ingelheim Vetmedica v. Schering-Plough*, No. 02–1026 (Fed. Cir. Feb. 21, 2003).
4. *Medeva Pharma v. Am. Home Products*, 201 F.R.D. 103,104 (D. Del. 2001).
5. *Embrex v. Service Engineering*, 216 F.3d 1343 (2000).
6. Greenwood, B., Salisbury, D. & Hill, A.V. *Phil. Trans. R. Soc. Lond. B* **366**, 2733–2742 (2011).
7. Sette, A. & Rappuoli, R. *Immunity* **33**, 530–541 (2010).
8. Homma, A. *Biologicals* **37**, 173–176 (2009).
9. Milstien, J.B., Gaule, G. & Kaddar, M. *Vaccine* **25**, 7610–7619 (2007).
10. Homma, A. *et al. Vaccine* **31S**, B54–B60 (2013).
11. Mahoney, R., Pablos-Mendez, A. & Ramachandran, S. *Vaccine* **22**, 786–792 (2004).
12. Santos, P.R., Chamas, C.I. & Morel, C.M. *Intel. Prop. Rights* **2**,119 (2014).
13. Padmanabhan, S. *et al. Nat. Biotechnol.* **28**, 671–678 (2010).
14. Rezaie, R. *et al. Nat. Biotechnol.* **26**, 627–644 (2008).
15. Brazilian National Congress. Review of the patent law—innovation to support national competitiveness (2013). http://infojustice.org/wp-content/uploads/2013/09/Brazilian_Patent_Reform.pdf
16. Basso, M. *Int. J. Intel. Prop. Mgmt.* **1**, 54–74 (2006).
17. Brazilian National Confederation of Industry. Intellectual property: changes in industry and the new agenda (CNI, Brasilia, 2014). http://arquivos.portaldaindustria.com.br/app/conteudo_18/2013/12/09/5640/39_Intellectualproperty_miolo.pdf
18. Oliveira, M.H. *Facto ABIFINA* **43**, 18–21 (2015).
19. Dosi, G. & Mazzucato, M. *Knowledge Accumulation and Industry Evolution* (Cambridge University Press, 2006).
20. Block, F. & Keller, M. *State of Innovation: US Government Technology Policies, 1969–2008* (Paradigm, 2011).
21. Mazzucato, M. The Entrepreneurial State: Debunking Public vs. Private Sector Myths (Anthem, 2013).
22. US Patent and Trademark Office. *All Technologies Report - A Patent Technology Monitoring Team Report, Electronic Information Products Division* (USPTO, March 2015). http://www.uspto.gov/web/offices/ac/ido/oeip/taf/all_tech.pdf
23. Mbow, M.L. *et al. Curr. Opin. Immunol.* **22**, 411–416 (2010).