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Toxinology in Brazil: A big challenge for a rich biodiversity

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ABSTRACT

Toxinology in Brazil developed specially during the 19th and 20th centuries. A very brief description of the main contributions made by pioneer toxinologists is presented here in an attempt to give an idea of the evolution of toxinology in our country, from its first steps until the XVI World Congress of the International Society on Toxinology, held in Recife, Brazil in March of 2009.

1. Prelude

It was on April 1500 that Pedro Alvares Cabral's expedition reached a new land. Among Cabral's men was Pero Vaz de Caminha, who despite not being the expedition's official diarist, wrote a long letter to the King of Portugal, Manoel I, with details of the voyage, the discovery, the first contact with the native Brazilian tribes and the numerous natural wonders. The letter is the first document about Brazil, and its final passage reveals the awe that Caminha felt in the face of the size and beauty of this new land:

"This land, Lord, it seems to me, from the southernmost point within my sight, to the northernmost point that can be seen from this port, is so vast that there must be 20 or 25 leagues of coast. Along the sea, in some parts there are great barriers, some red and others white, and the land above with plains covered in large trees. From one end to the other, it is all beaches….very level and most pleasant. From the sea, the remote and arid interior seems very large; as far as the eye can see there is tree-covered land – land which seems to us to be very extensive."

The name Brazil has a close relationship to nature. This is because 'pau-brasil' is the name of a tree with a reddish trunk abundant in the Atlantic rainforest, and at that time much in demand in Europe for its strong, red extract, used for dying, especially of clothes.

The astonishing diversity of fauna and flora and the yet immeasurable dimension of the land pointed out by Vaz de Caminha in his letter, accurately described this country, as we know today, as having the greatest biological diversity in the world (20% of the planet's species). Nowadays such biodiversity is recognized as an important source of natural substances derived from animals, plants and microorganisms of interest in toxinology, medicine and biotechnology.

In South America, the first documented use of a poison comes from natives with curare. Curare (from *woorari, woorali, urari,* Indian words for poison) is a generic term for

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various arrow poisons, generally obtained from different plants. These drugs have been used for centuries by native populations along the Amazon and Orinoco Rivers and in other parts of South America for food hunting. Soon, explorers and botanists became interested in curare and, in the sixteenth century, curare samples were sent to Europe to be studied. The pioneering investigation was performed by Von Humboldt, in 1805, followed by a number of other researchers. The curare from eastern Amazonia comes from various species of *Strychnos* (family *Loganiaceae*) plants (Fig. 1) that contain chiefly quaternary alkaloids with neuromuscular blocking action. Differently, the Asian, African, and Australian *Strychnos* species contain tertiary, strychnine-like alkaloids (Taylor, 1996). Claude Bernard used curare to characterize the unique aspects of nerve-to-muscle signaling (Taylor, 1996). The modern clinical use of curare seems to date from 1932, when purified fractions were used in patients with tetanus and spastic disorders. After that, many studies were performed using curare and its purified components (Taylor, 1996).

The use of curare by Indians makes a good example of the prelude of biotechnology using venoms. Indeed, in this sense, the Indians can be considered the precursors of toxinologists in South America.

Toxinology in Brazil developed specially during the 19th and 20th centuries. A very brief description of the main contributions made by pioneer toxinologists is presented here in an attempt to give an idea of the evolution of toxinology in our country, from its first steps until the XVI World Congress of the International Society on Toxinology, held in Recife, Brazil in March of 2009.

Fig. 1. *Strychnos toxifera*, one of the *Strychnos* species from which curare is extracted (Ilustration from the book "Plantas Medicinais de Köhler", de 1887) (from: http://pt.wikipedia.org/wiki/Curare).

2. The study of venoms and antivenoms

In Brazil, investigations on the composition of curare and on snake venoms properties had João Batista de Lacerda (1846–1915) from the National Museum (Rio de Janeiro) as a precursor (Bouquet, 1983; Vergara, 2005). In 1884, Lacerda managed to coagulate milk and dissolve fibrin and egg yolk with *Bothrops* venom and found that mammalian red blood cells were deformed and lysed in contact with *Lachesis* venom (Lacerda, 1884).

Remarkable progress on the field was undoubtedly due to Vital Brazil Mineiro da Campanha, born in the city of Campanha (Minas Gerais state) in 1865 (Fig. 2). As an inspector of the Department of Sanitation of São Paulo's state at a time when Public Health had deteriorated, following an abrupt increase in population due to immigration from Europe, Vital Brazil worked hard in the combat of morbid cholera and yellow fever (see Hawgood, 1992). In 1895, Vital Brazil had ample opportunity to examine cases of poisonous snakebites in Botucatu, then a small town in the state of São Paulo, which was on a railway line at the edge of the outback. He observed the different symptoms in *Bothrops jararaca* and in *Crotalus durissus terrificus* envenomation. In *Bothrops* accidents haemorrhagic edema and gangrene were common symptoms, whereas in *Crotalus* accidents neurotoxicity signs such as ptosis and asphyxia were predominant. Vital Brazil

Fig. 2. Vital Brazil Mineiro da Campanha (1865–1950) at the age of 20 years old (http://www.museuvitalbrazil.org.br/exposicoes_vb1.asp).

was testing native plant extracts for snakebite treatment when he read the work of Albert Calmette (1863–1933), a French physician, bacteriologist and immunologist, describing the ability of an anti-toxic serum to neutralize the effect of *Naja* venom. Vital Brazil realized, then, that serum-therapy was the right solution. Soon after, working as assistant of the Director of the Bacteriological Institute of São Paulo, Dr. Adolpho Lutz, Vital Brazil began to produce antivenom sera by injecting dogs and goats with small doses of crude *B. jararaca* or *C. d. terrificus* snake venoms. In 1898, he obtained clear evidence of antivenom specificity by showing that animals immunized with a given venom were capable of resisting the toxic effect of that venom. One year later, a severe epidemic of the Bubonic plague broke out in the port of Santos (São Paulo state) and soon spread to other cities of Brazil and other South American countries. Although affected by the disease himself, Vital Brazil isolated and identified the bacillus *Pasteurella pestis* (presently *Yersinia pestis*) as the agent of the plague. He also headed a project aimed to produce an anti-plague serum in a farm at Butantan, located 9 km from the center of São Paulo (Hawgood, 1992). In February 1901, the Institute Butantan was officially opened under the name of *Institute of Serum Therapy* with Vital Brazil as its Director. The antiserum to counter the plague epidemics in Campos was delivered in June 1901. At this time he reported the first case of snakebite by *B. jararaca* treated with anti-bothropic serum prepared at Butantan and announced the production of anti-ophidian serum, a polyvalent antiserum consisting of a mixture of anti-crotalic and anti-bothropic sera (Vital Brazil, 1987). With the support of the Brazilian government, Vital Brazil organized a scheme that made possible to ranchers, small farmers and railway companies the trading of captured snakes for Butantan's serum. This policy, which is still adopted nowadays by the Butantan Institute, ensured availability of venom for serum production. Another great merit of Vital Brazil was to undertake the publicizing of serotherapy amongst people in the rural areas, including teachers and authorities, by means of conferences, demonstrations and publications, despite the many superstitious or "magic" forms of treatments existing at that time. Later on, Vital Brazil and his assistants studied the physiological actions of spider and toad venoms, prepared an antiserum against *Phoneutria* spider venom and started the serum treatment for arachnidism (Hawgood, 1992).

Besides working on venomous animals, prophylaxis and treatment of snakes, scorpions and spiders accidents, this remarkable man left many disciples to continue his work (C. R. Diniz, personal archive). As pointed out by Simon Flexner, Director of the Rockefeller Institute for Medical Research, in a speech in 1927 "the entire world is indebted to Dr. Brazil for his fundamental researches on venoms and antivenoms, and the benefits accruing from the Institute he has developed are felt not only widely in Brazil but even in distant countries". Bernard Houssay (1966), in honoring the founder of anti-ophidian serotherapy in South America, described Vital Brazil as a modest, persistent man of endeavour with great faith in immunological methods and a large capacity for simplifying problems and finding practical, enduring and simple solutions. The importance of Vital Brazil's work is highlighted in face of the high number of accidents (26,786) due to poisonous snakes from June 1986 to December 1987 with 181 deaths, with a mortality rate of 0.7%, according to the Brazilian Ministry of Health (Hawgood, 1992). The Butantan Institute has continued and extended the work of Vital Brazil.

Among foreign scientists that worked at the Butantan Institute and that contributed to toxinology development in Brazil, we point out Karl H. Slotta (PhD in Chemistry) who left Germany under the oppression of the Nazi regime to take a post at the Brazilian Institute. While still working in German, he became known for the isolation and proposition of the structural formula of progesterone (1933, 1934). At the Butantan Institute, after working on coffee chemistry, he and his colleague Fraenkel-Conrat firstly isolated crotoxin, in a crystalline form, from *C. d. terrificus* snake venom (Slotta and Fraenkel-Conrat, 1938, cited by Hawgood, 2001). In addition, taking into account experimental evidence, they proposed that crotoxin toxicity was due to a phospholipolytic action on nerve lipids. These contributions were of major importance in the field.

Brazilian toxinology continued its development in the hands of a number of other distinguished scientists. In 1945, José Moura Gonçalves (1914–1995) isolated crotamin, a new toxic protein from *C. d. terrificus* snake venom, as a fellow from the Rockfeller Foundation in the University of Wisconsin. His work on crotamin, the most important in his scientific career, rendered him the Lafi Medical Sciences Award in 1965 (http://www.canalciencia.ibict.br/notaveis/txt.php?id=28).

In 1948, the description of bradykinin by Maurício Oscar da Rocha e Silva (1910–1983) (Fig. 3) and collaborators at that time in the *Instituto Biológico*, in São Paulo, revolutionized the studies on the regulation of arterial pressure (Rocha et al., 1949a,b). In the 50s, then at the Faculty of Medicine of University of São Paulo in Ribeirão Preto, a city 320 km from São Paulo, Rocha e Silva had the fundamental collaboration of Carlos Ribeiro Diniz, and Ulla Hamberg, as well as several scientists from other Brazilian institutions: Olga B. Henriques, Sebastião Baeta Henriques, Elisabeth Holzhaker, José Ribeiro do Valle, Eline Prado and José Leal Prado (http://www.fmrp.usp.br/rfa/Html/Historia.htm) (Beraldo, 1981). In the following years, Rocha e Silva and a second generation of disciples deepened the knowledge on the pharmacology and physiology of bradykinin (Hawgood, 1997). The most important papers on bradykinin from 1948 to 1974 were selected by Rocha e Silva himself and published as a book (Rocha, 1974).

An outstanding contribution derived from the bradykinin discovery was the isolation of the so-called BPF (bradykinin-potentiating factor), an active principle from *B. jararaca* venom by Sergio Henrique Ferreira (Ferreira, 1965). BPF was later shown to be a polypeptide inhibitor of the conversion of angiotensin I to angiotensin II (a potent vasopressor), also potentiating the vasodilator effects of bradykinin, thus reducing the arterial pressure in a dual manner (Ferreira et al., 1970a,b). Later on, BPF and other similar peptides, generally known as BPPs (bradykinin-potentiating peptides) served as scaffolds and molecular models for the development of "Captopryl"®, a synthetic

Fig. 3. Mauricio Rocha e Silva (1910–1983) (from: http://www.fmrp.usp.br/rfa/Html/Historia.htm).

Fig. 4. Carlos Ribeiro Diniz (1919–2002) (from: http://www.abc.org.br/resultado.php3?codigo=cdiniz).

anti-hypertensive drug largely employed in the control of hypertension and heart insufficiency, all over the world.

Another outstanding scientist was Haity Moussatché (1910–1998). Born in Turkey, he moved to Brazil when a child and started his scientific career as a physiologist in the Oswaldo Cruz Foundation (Rio de Janeiro). Author of numerous papers on pharmacology, physiology and biochemistry, his main contribution in toxinology was the investigation of the natural resistance of raccoons to snake venoms.

Lineu Freire-Maia (1935–1999) also made important contributions to Brazilian toxinology, with studies on the pathological effects of *Tityus serrulatus* venom and toxins that helped to shape the treatment of scorpion stings in Brazil. Working at the Federal University of Minas Gerais, he trained several scientist and physicians in toxinology, physiology and pharmacology. Freire-Maia also served on the editorial board of several journals including *Toxicon* (Prado and Gomez, 2000).

Carlos Ribeiro Diniz (1919–2002) (Fig. 4) represented an icon of the Brazilian Toxinology. He was born in Luminárias, a small village in the southern of Minas Gerais state, coincidently very close to Campanha, the birthplace of Vital Brazil. As an undergraduate Medicine student, he started working on research at the Laboratory of Physiology and Chemistry of the Federal University of Minas Gerais, under the supervision of Professor J. Baeta Vianna, an eminent researcher who left a series of disciples dedicated to life sciences in Brazil. After presenting his thesis on proteolytic enzymes from the thyroid gland, Diniz moved to Rocha e Silva's laboratory. There, besides relevant studies on the biochemistry and pharmacology of kininogen, he isolated and characterized neurotoxins from spiders and scorpion venoms, and elucidated the mechanism of the pre-synaptic actions of Tityustoxin from *T. serrulatus* scorpion venoms (Diniz, 1978).

Professor Diniz dedicated his life to research, education and scientific politics with great ability, always proposing new programs and projects to the funding government agencies. Indeed, he headed important structural modifications in biological and medical education, besides playing a crucial role as consultant of many financing agencies in Brazil, with great emphasis in the creation of FAPEMIG, the supporting agency for scientific research of the state of Minas Gerais. He also supported the creation in 1969 of the Ph.D. program in Biochemistry from Federal University of Minas Gerais, one among the first ones at this level in Brazil.

In 1985, he was invited to become the Director of the Research and Development Center of Fundação Ezequiel Dias (FUNED), an institution linked to the government of the state of Minas Gerais, where he dedicated the last years of his life. He took the job with the enthusiasm and energy that were the most amazing characteristics of his. During more than fifteen years, he persevered in the upgrading of many scientific aspects of the institution as a whole and formed a team of young toxinologists. It is worth noting that he also played a main role in the conception of Biobrás, a pioneer Brazilian biotechnological enterprise born in the

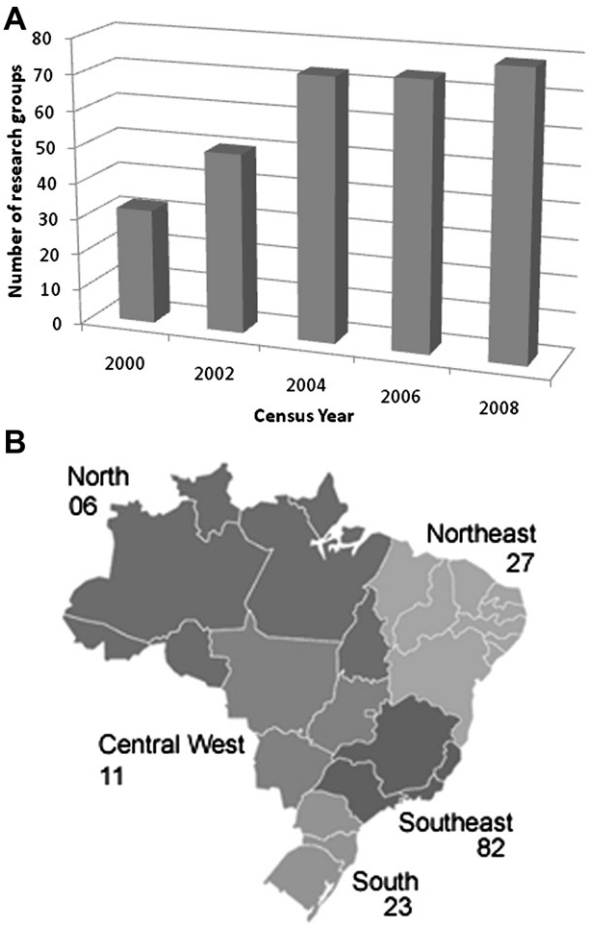

Fig. 5. Number (panel A) and geographical distribution (panel B) of research groups working on toxins/toxinology in Brazil. Data were taken from the "Lattes Research Group Directory" from the National Council for Scientific and Technological Development (CNPq) in December 2009. The word "toxin" was searched in the name, research line or key word of the group.

"heart" of Federal University of Minas Gerais dedicated to the successful production of insulin derivatives. Professor Diniz, together with José Moura Gonçalves and Haity Moussatché were among the founders of the International Society on Toxinology (Russell, 1987) and he was elected President of IST for the 1976–1979 period. He was one of the founders of the Brazilian Society of Toxinology. Professor Diniz was recipient of many awards and honour medals including the *Rio Branco* and *San Martin* medals from the Ministries of External Relationships from Brazil and Equator Republic, respectively, for his dedication to scientific interchange in Latin America.

3. Antivenom production in Brazil

In the last years of 1800 and early 1900s, Microbiology was the novelty in medical sciences (Chaves, 2007). The revolution in scientific practice caused by the microbiological paradigm, the threat of epidemics of bubonic plague and the difficulties to import the vaccine from the Pasteur Institute in France, led to the creation of a few

Table 1
Number of documents published in Toxicon (1963–2010).

	Period*	Toxicon		
		Articles-Reviews	Address	"Brazil" (%)
All years:	1963–2009	5035	784	15.6
	1963–1979	673	18	2.8
	1980–1989	850	49	5.8
	1990–1999	1301	204	15.7
	2000–2004	912	213	23.3
	2005–2010	1281	308	24.0

*Source: Thomson ISI Web of Science, date: March 14, 2010.

government's biomedical institutes in Brazil for serum production (Chaves, 2007).

In 1899, as cited above, the government of São Paulo's state created the Institute of Serum Therapy of São Paulo (linked then to the Bacteriological Institute) and Vital Brazil was nominated as Director. Two years later, this Institute became independent and it was renamed as Butantan Institute.

In 1900, the Brazilian government inaugurated the Federal Institute of Serum Therapy (popularly known as Manguinhos) in the state of Rio de Janeiro, capital of the Republic at that time. Oswaldo Cruz (1872–1917) became its Director in 1902 (Buss and Lima, 2001). This Institute, presently Oswaldo Cruz Foundation (FIOCRUZ), is internationally renowned for studies on infectious and tropical diseases.

A third institution was created as a branch of Manguinhos in Belo Horizonte (state of Minas Gerais) in 1907. Ezequiel Dias (1880–1927), a disciple of Oswaldo Cruz, was nominated Director. Presently, the so-called Fundação Ezequiel Dias (FUNED) is attached to the government of Minas Gerais state.

In 1919, Vital Brazil founded himself the Institute of Hygiene, Serum therapy and Veterinary in Niterói, a city of Rio de Janeiro state. Today, this institution is linked to the government of Rio de Janeiro state under the name Vital Brazil Institute.

Besides producing immunobiologicals, vaccines and drugs, all of these Institutes have been devoted to scientific research and technological development in Public Health, since their foundation. Presently, three of them (Butantan Institute, SP; Vital Brazil Institute, RJ and Ezequiel Dias Foundation, MG) account for the whole anti-venom production in Brazil, as members of the official group of laboratories linked to the Ministry of Health.

Table 2
Citations of articles and reviews in Toxicon.

Index	All countries	Address of authors			
		USA	Brazil	Japan	France
Articles + reviews	5035	1081	784	497	281
Total citations*	77,960	19,982	9982	9029	3998
Factor H	83	59	42	45	32
articles with 100 citations or more	53	14	6	5	1

Source: Thomson ISI Web of Science, date: March 14, 2010.
*Citations counted only for articles and reviews.

Table 3
Paper by Brazilian authors* with more than 100 citations.

Total citations	Authors (*address in Brazil)	Institutions in Brazil***	Subject	Toxicon's reference
179	R.K. Arni** R. Ward**	UNESP-SJRP	Phospholipase A2	Vol 34, **827-841**, 1996
152	M.I.Homsibrandeburgo** L.S. Queiroz** H.Santoneto** L. Rodrigues Simioni** J.R.Giglio**	USP-RP UNICAMP	Bothropstoxin (Lys 42 PLA2)	Vol 26, **615-627**, 1988
128	N. Lagos H. Onodera P.A. Zagatto** D. Andrinolo S.M.F.Q. Azevedo** Y. Oshima	UFRJ CETESB	Shellfish toxins	Vol 27, **1359-1373, 1999**
121	S.M.K. Rates**	UFRGS	Plant toxins as drugs	Vol 39, **603-613, 2001**
112	J.W. Fox S.M.T. Serrano**	Inst. Butantan	Snake venom metalloproteinases	Vol 45, **969-985**, 2005
111	C. R. Carlini** M. F. Grossi-de-Sá**	UFRGS Embrapa-Cenargen	Plant insecticidal proteins	Vol 40, **1515-1539, 2002**

*Source: Thomson ISI Web of Science, date: March 14, 2010.
**Authors with address in Brazil.
***UNESP-SJRP, Univ. Estadual de São Paulo at São José do Rio Preto; USP-RP, Univ. of São Paulo at Ribeirão Preto; UNICAMP, Univ. Estadual de Campinas; UFRJ, Univ. Federal do Rio de Janeiro; CETESB, Companhia Estadual de Saneamento Básico de São Paulo; UFRGS, Univ. Federal do Rio Grande do Sul; Embrapa, Empresa Brasileira de Pesquisa Agropecuária.

4. The Brazilian Society of Toxinology (SBTx)

The Brazilian Society of Toxinology (SBTx) was created on March 3rd, 1988, during the XII Annual Symposium of the Academy of Sciences of the state of São Paulo, and its subject at that time was "Proteins that are toxins". The foundation of SBTx was headed by Dra. Julia Prado Franceschi and supported by about one hundred scientists such as Carlos Ribeiro Diniz, Wilson Teixeira Beraldo, Lineu Freire-Maia, Eva Kelen, Olga Baeta Henriques, Sebastião Baeta Henriques, Haity Moussatche, William Beçak, Adolfo M. Rothschild, José Moura Gonçalves and Gastão Rosenfeld, among others.

The first President of the SBTx was Oswaldo Vital Brazil (1912–2008) from the University of Campinas in the state of São Paulo, son of Vital Brazil Mineiro da Campanha, who followed the steps of his father in the study of snake venoms pharmacology. A list of past and present officers of the Society can be found at the SBTx webpage (www.sbtx.org.br). Today, SBTx has two hundred and twenty members distributed among most Brazilian states and a few members from other Latin American countries. It congregates experts in animal, plant and microbial toxins focusing on biochemical, structural, biological, pharmacological and clinical aspects of toxinology.

Brazil hosted two congresses of the Pan-american section of IST: in 1992 (in Campinas, São Paulo state, organized by J. Prado-Franceschi) and in 2004 (in Angra dos Reis, Rio de Janeiro state, organized by Gilberto B. Domont and Jonas E. Perales), this last one co-sponsored by SBTx.

In 2009, the SBTx organized its 10th congress together with the XVI World Congress of the IST, which was held in Cabo de Santo Agostinho, near the city of Recife, state of Pernambuco. Toxinologists from all over the world attended the Brazilian meeting. About 550 participants from 45 countries from five continents presented results of 480 studies on toxins, under the theme "Biodiversity in Toxins: Tools for Biological Research and Drug Development".

Besides IST, many Brazilian funding agencies (CNPq, CAPES, FAP's from different states) as well as other governmental institutes (FIOCRUZ, Butantan Institute and FUNED) helped with financial support.

Table 4
Top five Brazilian authors and institutions with more publications in Toxicon.*

Brazilian author (institution)	Number of publications**
Sergio Marangoni (Unicamp)	48
Carlos R. Diniz (UFMG/FUNED)	36
José Roberto Giglio (USP-RP)	36
Carlos Chavez-Olortegui (FUNED/UFMG)	35
Marcos H. Toyama (UNESP)	31
Evanguedes Kalapothakis (UFMG)	31
Brazilian Institution	**Number of publications****
Inst. Butantan (IB)	244
Univ. São Paulo (USP)	203
Univ. Fed. Minas Gerais (UFMG)	124
Univ. Est. Campinas (UNICAMP)	123
Fund. Ezequiel Dias (FUNED)	57

*source: Thomson ISI Web of Science, date: March, 2010.
**includes co-authorships.

5. Research groups on Toxinology in Brazil

In Brazil, the National Council for Scientific and Technological Development (CNPq) maintains a database (Lattes Platform) with updated information on individual curricula (CV Lattes) and research groups (Research Groups Directory) in all areas of knowledge. It is a free access database service aimed to generate indicators of scientific and technological production, and for definition of R&D policies in our country. Since 1992, all researchers, graduate students pursuing a master or doctor degrees,

Table 5
Authors and institutions from other countries with at least 4 articles or reviews published in Toxicon in collaboration with Brazilian authors.

Country	Institutions – Authors	Number articles/reviews
Costa Rica	University of Costa Rica	36
	José M Gutierrez	29
	Bruno Lomonte	11
France	Institute Pasteur	12
	Cassian Bon**	12
	CNRS	12
	Claude Granier	12
United Kindgom	University of Liverpool	9
	Richard GD Theakston	8
	Aura Kamiguti***	13
	University of Oxford	7
	David Warrell	5
Cuba	University of Havana	8
	Carlos Alvarez	7
	Maria E. Lanio	7
	Diana Martinez	7
Germany	University of Frankfurt	4
	Dietrich Mebs	4
	Hannover Vet. Sch. Medicine	6
	Gerhard Habermehl	6
Mexico	Universidad Autonoma de Mexico	7
	Lourival Possani***	6
USA	University of Oklahoma	9
	Charlotte Ownby	10
	University of Virginia	6
	Jay W Fox	6

*Source: Thomson ISI Web of Science, date: March, 2010.
**deceased in 2008.
***born Brazilian.

undergraduate student enrolled in scientific initiation programs, and other clients of the Council shall have, compulsorily, a curriculum registered at the Minister of Science and Technology, forming the database of the Lattes Platform. The Brazilian Research Groups Directory (http://lattes.cnpq.br/english/conteudo/aplataforma.htm) is also based on the Lattes Platform.

Since the first biannual census performed by CNPq in 2002, the number of groups in the Lattes Research Groups Directory, using "toxin" as search entry, increased from 32 in 2000 to 79 in 2008 (Fig. 5a) (http://dgp.cnpq.br/buscagrupo/). In December 2009, the same Directory revealed 149 research groups registered therein (http://dgp.cnpq.br/buscaoperacional). Although heterogeneously distributed among the Brazilian states (Fig. 5b), they are present in almost every state with high numbers in the southeastern region. The great majority of these groups are led by second- or third generation disciples of the outstanding toxinologists mentioned in the previous sections.

6. Brazilian contribution to *Toxicon*

The heritage of our pioneer toxinologists and the commitment of Brazilian scientists to unravel our biodiversity are translated in the numbers of publications in *Toxicon* having author(s) with address in Brazil (Table 1).

In the last two five-year periods (2000–2004; 2005–2009 extended to March 2010), Brazilian scientists have contributed 23.5% of the publications appearing in *Toxicon*. After the United States only, Brazil is the second most frequent address of all papers and reviews (784) published in *Toxicon*, followed by Japan (495) and France (281). Papers and reviews having at least one Brazilian co-author received about 12.8% of the citations of *Toxicon* (Table 2), at a rate of approximately 1400 cites per year in 2008 and 2009.

Though other specific subjects have being explored by Brazilian toxinologists (Guimarães and Carlini, 2004), it is interestingly to note that the most cited paper of *Toxicon* (Kini and Evans, 1989, with 280 citations) and the most cited paper having a Brazilian address (Arni and Ward, 1996, with 179 citations) deal both with the same subject, phospholipases A_2. Table 3 shows details of the six papers in *Toxicon* having a Brazilian address with more than 100 citations in March 2010.

Table 4 shows the five Brazilian authors and the institutions with the greatest number of publications in *Toxicon*. It can be clearly seen that our pioneer toxinologists taught well their lessons.

In all areas of knowledge, Brazilian scientists are known to readily establish collaboration with colleagues abroad, a fact reflected in *Toxicon*'s publications as seen in Table 5, which shows the most frequent non-Brazilian authors and foreign address associated to Brazilian authors.

Finally, Brazilians have also served as members of *Toxicon*'s editorial council/board: José Moura Gonçalves (São Paulo, vol 1–11); WHA Schottler (Rio de Janeiro, vol 2–4); Gaston Rosenfeld (São Paulo, vol 7–14); Edson X. Albuquerque (based in USA, but born Brazilian, vol 12–14); Carlos R Diniz (São Paulo, vol 15–37), Lineu Freire-Maia (Belo Horizonte, vol 15–38), Gilberto Domont (Rio de Janeiro, vol 40–54); Antônio Carlos M Camargo (São Paulo, vol 41–50); Lourival Possani (based in Mexico, but born Brazilian, vol 28-today); Célia R Carlini (Porto Alegre, vol 50-today); Solange MT Serrano (São Paulo, vol 53-today); Russolina B Zingali (Rio de Janeiro, vol 54-today); Yara Cury (São Paulo, mini-reviews editor, vol 54-today).

7. Conclusion

Toxinology in Brazil has an enormous potential to be explored, with the responsibility to preserve the biodiversity, searching for new sources of drugs and models to develop biotechnological products, among others. A group of notable toxinologists, such as Vital Brazil, Rocha e Silva, Carlos Diniz, Sérgio Ferreira, amongst others have shown how a susceptible population can be protected against the action of venoms and toxins through serotherapy. Indeed, these pioneers, besides creating and training several disciples, have also opened frontiers in the immense universe of toxinology, quite often facing adverse work conditions and having a minimal financial support. As a result, both previous and present Brazilian works have shown the importance of venom components as tools to study biological systems and also how they can serve as models to drugs design and development of therapeutic products. The new generation of Brazilian toxinologists now faces much better institutional research conditions. Nowadays the budget applied to research in Brazil has augmented substantially, and the Institutions have

modernized their laboratories and equipped them with 21st century apparatus. In this context, the Brazilian Society of Toxinology, now in its 21st year, is dedicated to enroll new members, to congregate all toxinologists working in the country, and to stimulate cooperation among them as well as with toxinologists all around the world. Another essential role of SBTx is to foster studies on toxinology at a governmental level and to influence political decisions aiming to increment budget of Brazilian funding agencies financing research in topics related to toxinology. The identification and the proposition of essential and innovative research themes in toxinology, to be developed in cooperation joining interested groups, is a promising alternative, following the steps of IST initiatives worldwide.

Finally, biodiversity is a heritage of humanity, and in this context, scientific societies as IST and SBTx, amongst others, have a fundamental role leading the way to make a responsible and adequate use of this biodiversity.

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Conflict of interest

There are no conflicts of interest.

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