

UNESCO Chair of Developmental Biology: how an initiative that fostered careers in Developmental Biology impacted Brazilian Science

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ABSTRACT The UNESCO Chair in Developmental Biology started in 1998, at the Institute of Biomedical Sciences of the Federal University of Rio de Janeiro, in Brazil. This Chair was a Brazilian-French initiative led by Professor Vivaldo Moura Neto and Professor Nicole Le Douarin, one of the most inspiring Developmental Biologists of the 20th and 21st centuries. The UNESCO Chair wanted to stimulate interest in Developmental Biology among Brazilian students and scientists by organizing annual international courses on Evolution and Developmental Biology at an advanced level. At the Federal University of Rio de Janeiro, the UNESCO Chair established an international laboratory for the permanent training of researchers and the development of research programs in Developmental Biology and related areas. Moreover, the program aimed at establishing an international network connecting Brazilian Universities and research centers in Latin America and Europe. The advanced hands-on courses, symposiums, and workshops promoted by this Chair inspired the careers of many young scientists. They generated new lines of research in Developmental Biology using a variety of animal models. This review does not intend to bring up all the historical events that marked the beginning of Developmental Biology in Brazil. Instead, it will be dedicated to highlighting one specific initiative that inspired a new generation of Developmental Biologists who established important research lines and contributed to the advance of this scientific field in Brazil.

KEY WORDS: *UNESCO, Brazil, Nicole Le Douarin, Evo Devo, training, teaching*

Introduction

Different initiatives have influenced the consolidation of Developmental Biology research groups in Brazil. Some initiatives came from researchers who individually sought to obtain postdoctoral training in internationally well-known Developmental Biology laboratories. Others sought to import to Brazil classical animal models of Developmental Biology or to adapt their research investigation lines to Brazilian species, such as birds, fish, bees, and beetles, among others. However, in the late '90s an initiative led by Professor Vivaldo Moura Neto, a respected Brazilian Developmental Neurobiologist, changed the scientific destiny of young and senior scientists and many students, including myself. Professor Moura Neto has strong connections with French science and culture since his *Doctorat en Sciences, Doctorat D'état - Université Pierre et Marie Curie* (1984) under Professor François Gros's supervision.

In 1997, on one of his trips to Paris, he attended a College de France conference of Professor Nicole Le Douarin, the perpetual secretary of the *Académie Française des Sciences* and one of the most respected Developmental Biologists worldwide. After the conference, Professor Moura Neto had the privilege to address the scientific advances in Developmental Biology and exposed his wish to promote this field in Brazil.

Historically, Brazilian scientists had advanced well in fields such as anatomy, embryology, biophysics, neuroscience, genetics, biochemistry, and cell biology, but developmental biology was still incipient. The idea of creating the UNESCO Chair in Developmental Biology in Brazil was born thanks to the meetings and discussions of Professor Vivaldo Moura Neto with Professor Le Douarin. To-

Abbreviations used in this paper: UNESCO, United Nations Educational, Scientific and Cultural Organization.

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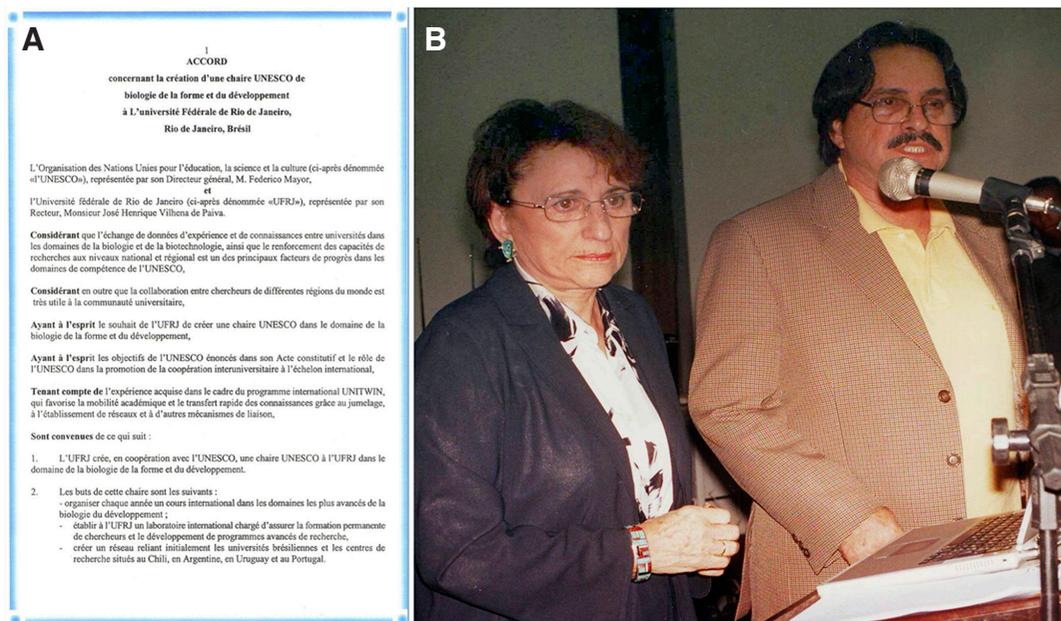


Fig. 1. Initial steps in the creation of the UNESCO Chair in Developmental Biology in Brazil. **(A)** The first page of the UNESCO agreement that established the Chair. **(B)** Introduction of Professor Nicole Le Douarin at the Federal University of Rio de Janeiro by Professor Vivaldo Moura Neto on the occasion of her opening lecture at the UNESCO Chair course.

gether these professors proposed the following aims to the Chair:

1. To organize annual international courses, at an advanced level, in the areas of Evolution and Developmental Biology.
2. To establish an international laboratory for the permanent training of researchers.
3. To develop of research programs in Developmental Biology and related areas at the Federal University of Rio de Janeiro.
4. To establish an international network of Developmental Biology, connecting Brazilian Universities with other research centers worldwide.
5. The UNESCO agreement of the Chair was signed, and Professor Nicole Le Douarin, the head of the Chair, together with Professor Vivaldo Moura Neto, started the planning of activities (Fig. 1).

The first course in Developmental Biology of the UNESCO chair: the introduction of different embryology animal models

Between 1996 and 1997, I was about to finish my doctoral thesis. For this reason, I began to contact and to visit laboratories in the United States in search of a postdoctoral position, possibly in Neurobiology. I was interested in deepening my knowledge of the role of glial cells in the nervous system. Coincidentally, in 1998, the first advanced course in Developmental Biology was held at the Federal University of Rio de Janeiro (UFRJ), and I attended it. Professors Nicole Le Douarin and Vivaldo Moura Neto organized the course with the support of the Graduate Programs at the Center for Health Sciences, by the directors of the Institute of Biomedical Sciences and the Institute of Biophysics Carlos Chagas Filho. The course offered practices in the main models used in Developmental Biology. A large number of international researchers from different institutions participated in this first edition of the UNESCO Chair in Developmental Biology. It was a hands-on course with lectures and practical activities. This course had a very innovative approach in the Brazilian scenario, as it sought to reach the level of advanced international courses, such as the ones offered by the European

Molecular Biology Laboratory in Germany and Cold Spring Harbor Laboratory in the United States. The level of commitment of the researchers involved, who were responsible for both the lectures and practices in the different model organisms of Developmental Biology, was very attractive to seniors, young scientists, and students. It goes without saying that this event changed my view on Biology and shaped the next steps of my scientific career.

One of the highlights of the course was the team that presented us with the embryogenesis of the chick. The chicken embryo model was well known in Brazil because it was used in undergraduate classes for the study of Embryology, as well as courses in the health area. The approach was mostly theoretical and focused on the anatomical changes of the developing embryo. During the course, a new approach to this model was presented by Professors Nicole Le Douarin, Françoise Dieterlan, Marie-Aimée Teillet, and Anne Eichmann of the Institut d'Embryologie Cellulaire et Moléculaire, CNRS, and College de France, Paris, France. We learned the theory and how to do chimeras of chicken and quail embryos. Professor Le Douarin and her team manipulated the embryos by transplanting portions of the cephalic and trunk neural crest from quail embryos to different body segments of chicken embryos at a similar stage. These experiments enabled us to identify quail neural crest cells integrated into the tissues of the chick embryo thanks to the characteristics of quail cell nuclei observed in the generated chimeras. Professor Anne Eichmann demonstrated the process of vasculogenesis in the chicken embryo, where we could identify the entire capillary network and the blood pumping exerted by the heart in the living embryo. During these chicken embryo instructions, we learned how to observe the embryo inside the egg shell, opening and closing the shell. Besides, we learned to contrast the embryo from the yolk by the use of ink.

Another novelty in the course was the teaching presented by Professor Marnie E. Halpern of the Department of Embryology, Carnegie Institution of Washington, Baltimore, USA, a specialist in neurodevelopment. She introduced the zebrafish model. She showed genes that organize the boundaries between the brain vesicles of *in situ* hybridized embryos. It was fascinating to learn

how the embryos were obtained and how they develop. Due to its transparency, we were able to detect several embryological details. It was the first time that the zebrafish, as a model organism, was presented in Brazil, with a focus on Developmental Biology.

The classes of Professor Anne-Marie Duprat and Professor Marc Moreau of the Center de Biologie du Développement, CNRS, Université Paul Sabatier, Toulouse, France were particularly attractive to me. Professors Duprat and Moreau were experts in analyzing the role of ion channels in the neural induction process of the amphibian *Xenopus laevis*. They presented the Hans Spemann concepts about embryonic induction and introduced the experimental embryology studies done with the *Xenopus* embryo. In their sessions, we learned how to fertilize the *X. laevis* eggs and how to stage embryos from the 4-cell stage to the tadpole stage. Then we performed the classical animal cap experiment by dissecting the embryo at the blastula stage and culturing the explants under different conditions. In this so-called animal cap experiment, the growth factors induce pluripotent cells to develop into different germ layer derivatives. Although there was incipient research using *Xenopus* at UFRJ, the instruction of Professors Duprat and Moreau introduced fundamental concepts of Developmental Biology. They provided the technical domain of *Xenopus* embryo manipulation.

At the time, the rodents, in particular mice, were one of the most explored biological models at UFRJ. Brazilian laboratories mastered the primary cell culture of neural cells, fibroblasts, bone marrow cells, macrophage cells, among others, derived from mouse. However, it was not common to use transgenic mice or to analyze the early stages of the development of the mouse embryo. Professor Charles Babinet, a geneticist from the *Unité de Biologie du Développement, Institut Pasteur*, Paris, France, introduced the methodology for obtaining transgenic mice and carried out mating for the collection of embryos from stage 7.5 to stage 11.5 post-fertilization.

The fruit fly *Drosophila melanogaster* is another biological model established at UFRJ and in other laboratories in São Paulo.

Professors Jean-Antoine Le Pesant, from *Université Paris VI* and Professor Jean R. David, from the *Laboratoire de populations, Génétique et Évolution, CNRS, Gif-sur-Yvette*, France, an evolutionary naturalist who investigates global natural populations of the genus *Drosophila* introduced us to the *Drosophila melanogaster* fruit fly model. While Professor Le Pesant addressed the genetics and molecular biology of *Drosophila*, Professor Jean David addressed concepts based on the studies of Charles Darwin, Jean-Baptiste Lamarck, Gregor Mendel, and other Evolutionists. It was also in his classes that we were introduced to Evo-Devo, the convergence of two fascinating fields: Evolution and Developmental Biology. It was the first time Evo-Devo was ever discussed in UFRJ. Professor Jean David carried out field trips around the UFRJ campus by placing fly traps, assessed the fly's morphological characteristics and taxonomic evaluation.

While the Developmental Biology practical classes were very attractive and intense, the lectures were just as stimulating for us. One of the key speakers in this edition of the UNESCO chair was Professor David Sabatini from the Department of Cell Biology, New York University School of Medicine, USA. Professor Sabatini is one of the most important cell biologists in Latin America that gave a historical lecture about important aspects of biological membranes and cell organelles in different contexts.

The course of the UNESCO Chair in Developmental Biology had a pioneer and innovative approach. However, it is important to highlight the various difficulties encountered to guarantee practical classes with so many animal models and with such profound methods. The practical demonstrations required the involvement of many laboratories to provide microscopes, bench, equipment, and reagents. In this regard, it was stimulating to witness Professor Nicole Le Douarin's participation. Professor Le Douarin supervised and demonstrated the practices, actively participated in the lectures, and talked with each student to make sure that there was understanding about the subjects and if they were getting along with the laboratory practices. In addition, we, the students, were motivated

by having a researcher of her academic prowess living daily with us, as if she had known us for a long time. It was impressive the great attention that she gave us (Fig. 2). A significant challenge was the importation of biological materials to Brazil. This task was performed by Professor Moura Neto, who coordinated with international scientists before they arrived in Brazil. In this way, transgenic mice, zebrafish, *Xenopus*, chicken, and quail eggs were ready for practical activities of the course. Transgenic mice and *Xenopus* were imported, but the customs clearance was quite elaborate due to Brazilian customs regulations. Custom clearance required the presence of Professor Moura Neto at the airport every time a box of



Fig. 2. Chicken embryo manipulation during a practical experiment. Participants of the course surround professor Nicole Le Douarin. She is observing a chick embryo at the stereoscope. Professor Jose Brito, who did his postdoctoral training under Professor Nicole's supervision, is observing on her left side.

animals arrived in Rio de Janeiro. Professor Marnie Halpern brought a styrofoam box containing fishes, and Professor Moura Neto was at the airport upon her arrival to tell the customs officers about the importance of this material. The box was transported immediately to the laboratory. Quail and chicken eggs were obtained from a farm that already offered embryonic eggs to UFRJ. Fortunately, the animal models arrived in large quantities and were accommodated until their use in the experimental practices.

This course was one of the most significant endeavors within the scope of the Institute of Biomedical Sciences at UFRJ and paved the way for the UNESCO Chair in Developmental Biology for the next 18 years. There were many young researchers who, like me, started their careers in Developmental Biology at the UNESCO Chair and made Developmental Biology their life project. The association with foreign partners promoted the consolidation of the bilateral exchanges between researchers – seniors and juniors – to ensure the sustainable development of new lines of research in developmental biology, morphology, and reproduction.

The impact of the UNESCO Chair on the career of young Brazilian researchers

The UNESCO Chair in Developmental Biology existed for 18 years (1998-2016). During this period, the UNESCO Chair offered courses and workshops across the country, in different Brazilian Universities (Fig. 3). The board of the UNESCO Chair decided about the theme of the workshops in many editions of the course. There were workshops in emerging topics such as in Neuroscience (2001) “What the developing cerebral cortex tells about adult cortex and vice versa”; “Cell and Developmental Biology” (2003 and 2004) “Cell therapy: Basic and clinical aspects” and “Stem cells and therapy”; “Medicine” (2008 and 2011) “Cellular and Molecular basis of 20th-century diseases” and “Cell Therapy, Biomaterials, and Bioengineering” among others. These workshops required the largest conference rooms of the Universities as they usually congregated more than 300 participants on average. Renowned speakers such as Nicole Le Douarin (College de France, Paris, France), Lewis Wolpert (Department of Anatomy and Developmental Biology at University College, London, UK), Irving Weissman (Institute for Stem Cell Biology and Regenerative Medicine, Stanford Medicine, CA, USA) Philippe Vernier (Paris Saclay Institute of Neuroscience, CNRS, Gif-Sur-Yvette, France), Peter Currie (Australian Regenerative Medicine Institute, Monash University, Australia), Lilliana Solnika Krezel (Department of Developmental Biology Washington University School of Medicine, USA), Shigeru Kuratani (Laboratory for Evolutionary Morphology, RIKEN Center for Developmental Biology, Japan), among others participated in the UNESCO Chair symposia in different editions of the workshop. These activities promoted an extraordinary environment of interaction among young professors and distinguished international scientists.

The Chair's activities disseminated Developmental Biology always with Professor Vivaldo Moura Neto and Professor Nicole Le Douarin as leading figures. In this way, the Brazilian funding agencies supported the Chair's actions, such as courses, work-



Fig. 3. Distribution of the UNESCO Chair activities and Developmental Biology research laboratories in Brazil. Red circles appear in states where UNESCO chair organized courses, workshops, and symposiums from 1998 to 2016. Blue circles indicate Brazilian states or cities where Evolution and Developmental Biology laboratories are located. A list of Brazilian researchers that attended, supported, or promoted the activities of the UNESCO Chair in Developmental Biology during its 18 years of activities appears in the supplemental Table S1.

shops, and two Schools of High Studies. The Chair also attracted the Calouste Gulbenkian Foundation from Portugal, represented by Professor Antonio Coutinho, who organized activities inside of the Chair programs and opened up opportunities for Brazilian scientists.

Eventually, the UNESCO chair activities were offered as satellite into Brazilian meetings such as the one of the Brazilian Society of Cell Biology in 2003 or supported the participation of internationally renowned scientist Developmental Biology meeting such as in the 6th international meeting of the Latin American Society for Developmental Biology, held in Montevideo, Uruguay in 2012

One of the great fruits of the activities of the Chair in Brazil was the visit of renowned foreign researchers during the courses, symposiums and workshops, and their interactions with young graduate students and established researchers. This interaction created an environment of opportunities for doctoral and postdoctoral internships in American and European institutions. These activities and interactions exposed the great potential of Brazilian science in the formation of a well-prepared group of young scientists.

My personal experience in 1998 depicts how participation in the UNESCO Chair guided several young scientists in the search for training in Developmental Biology. During the course, I had the opportunity to talk with professors Vivaldo Moura Neto and Nicole Le Douarin about how much the course had encouraged me to do a postdoctoral appointment in Developmental Biology. Profes-

sor Nicole then asked me what attracted me most in the course. Without a doubt, I answered that the *Xenopus* model impressed me. I expressed to her my desire to explore earlier aspects of the development of the Nervous System in *X. laevis*. Professor Le Douarin and Professor Moura Neto suggested me to contact Professor Eddy De Robertis at the University of California, Los Angeles. I followed their advice, and in 1999, I started my post-doctoral training in Eddy's laboratory, which is among the most prestigious laboratories in the world in the field of embryonic axis formation and patterning. The research from his laboratory led to the discovery of the molecular mechanisms in the establishment of the dorsoventral axis and the BMP-Chordin signaling pathway using *Xenopus* as a model organism. In the De Robertis laboratory, I gained profound knowledge of embryology and molecular signaling. The outcome was the publishing of important articles in this field (Abreu *et al.*, 2002; Garcia Abreu *et al.*, 2002), and my return to Brazil in 2002. I was committed to continue doing scientific work, to promote Developmental biology, and to establish *Xenopus* as a biological model in Brazil. Thus, I started my research group at the Institute of Biomedical Sciences, UFRJ. Six years later, I worked as a visiting scientist in Professor Xi He laboratory at the Boston Children's Hospital, Harvard Medical School, MA, USA. During 18 months, I could deepen my knowledge of Wnt/ β -catenin signaling and uncover the functional role of the Spemann Organizer gene *Tiki1* in the *Xenopus* embryonic head formation (Zhang *et al.*, 2012). This collaboration, which lasts up to date, was crucial to the establishment of my research group in Brazil and provided international training for several Brazilian students.

Other researchers who participated in the UNESCO chair activities followed similar paths. They searched for training abroad in excellent laboratories and eventually introduced new technologies and models in Developmental Biology at different Brazilian Universities. In this context, I highlight professors Andrea Trentin, Giordano Calloni and Juliana Coelho-Aguiar who studied the differentiation of the neural crest progenitors from chick embryos under the supervision of the Professors Elisabeth Dupin and Nicole Le Douarin (Calloni *et al.*, 2007; Calloni *et al.*, 2009; Coelho-Aguiar *et al.*, 2013; Trentin *et al.*, 2004). Back in Brazil, they established these study models at their laboratories in Santa Catarina and Rio de Janeiro, where they got tenure positions. I also highlight the careers of professors Jose Marques Brito, Ricardo Garcez and Diego Aguiar who studied the influence of the cephalic neural crest on Cranio-cephalic development of the chick embryo under the supervision of Professors Marie A. Teillet, Nicole Le Douarin and Sophie Creuzet (Aguiar *et al.*, 2014; Brito *et al.*, 2006; Brito *et al.*, 2008; Garcez *et al.*, 2014). These six researchers trained by Professor Nicole Le Douarin and members of her team in France established research on the neural crest in Brazil. They contributed to the advances in this field, together with other Latin American scientists (Pescador *et al.*, 2018). Professor Katia Carneiro de Paula, who worked for her doctorate on the *Drosophila* dorsoventral axis, sought postdoctoral training under the supervision of Professor Michael Levin, Department of Biology Center for Regenerative and Developmental Biology Tufts University. She investigated the histone deacetylase activity and left-right asymmetry of *Xenopus* embryos (Carneiro *et al.*, 2011). Currently, these Brazilian scientists hold positions in Brazilian Universities and head their laboratories with consolidated research lines. These are just a few examples of Brazilian professors that were influenced and motivated for

Developmental Biology by the UNESCO Chair. They sought for training in laboratories of great worldwide prominence and established research groups in Developmental Biology in Brazil. It is important to note that many researchers obtained a position at a Brazilian University after returning to Brazil. They participated as invited professors and speakers in the activities of the UNESCO Chair. Some of these professors hosted the UNESCO courses and workshops in their affiliated institutions providing conditions for the execution of the activities. One example is the young scientist Rodrigo Fonseca who participated in an activity of the UNESCO Chair in 2002, where he became interested in Evo-Devo. He sought a postdoctoral fellow in the evolution and development of arthropods in the laboratory of Professor Siegfried Roth, Institute of Developmental Biology of the University of Cologne in Germany. After a very successful postdoctoral study, he returned to Brazil, where he established his research laboratory in a branch of the Federal University of Rio de Janeiro at the northern region of Rio de Janeiro, researching functional genomics, biochemistry, and biology of arthropod development. Rodrigo hosted some editions of the hands-on course in Developmental Biology opening opportunities for young students and local professors.

Concluding remarks

The consolidation of research in the field of Developmental Biology in Brazil took place through several initiatives. Some of them were individuals, and others came from groups that collaborated with international researchers to implement cutting-edge research in Brazilian laboratories. The actions and impacts of the UNESCO Chair in Developmental Biology on Brazilian and international science were discussed in this article. A Franco-Brazilian initiative led by professors Nicole Le Douarin and Vivaldo Moura Neto, which involved a significant number of international collaborators and young and senior researchers, started in the late 90s. Since the first advanced course in 1998 with the introduction of the main biological models in Developmental Biology in practical classes carried out by renowned international scientists, the Chair sowed a fertile environment. In this environment, many young and senior researchers opted to pursue training abroad in excellent laboratories. Upon returning, they implemented research laboratories and activities in Brazil. These Brazilian scientists collaborated with other researchers and established fundamental themes of research for the understanding of the mechanisms that guide embryonic development and its evolutionary conservation. The impacts of these research groups have synergized with several other actions carried out by researchers who were not necessarily influenced by the UNESCO Chair. As a result, the Brazilian academy recognized the importance of Developmental Biology. As a result, many professorships in Developmental Biology were opened in the best Brazilian universities, and in all regions of the country. Research professors with training in Developmental Biology, Evolution, and Systems Biology, capable of establishing research at the frontiers of knowledge, were recruited to fulfill these positions.

In the curricula of Brazilian universities, Morphology is the chapter that concentrates on Cell Biology, Histology, Embryology, and Anatomy. In the 2000s, due to the emergence and consolidation of research groups, Developmental Biology appeared as a subchapter within the Morphology curriculum of several Brazilian universities. Consistent with this growth, many projects focusing on

questions of Developmental Biology were presented as a response to public calls issued by Federal and State funding agencies. One of the great difficulties that Brazilian researchers working in Developmental Biology is the competition for research grants with researchers from other areas, where investigations led to more abundant results in a short time. To be significantly competitive in the international environment, projects in the field of developmental biology require *in vivo* experiments in complex biological models, and multidisciplinary and mechanistic approaches. Besides, due to the Brazilian higher education system, scientific research is generally carried out by master or doctoral students over 24 or 48 months, respectively. In contrast, in other countries, postdoctoral appointees conduct the investigations of the projects. Completion of a research project in Developmental Biology takes around 4-5 years. However, financial support for individual projects lasts only 2 to 3 years. This temporal asymmetry between the execution of the project and the publication often hampers the results and the writing of solid articles. To circumvent this difficulty, Brazilian Developmental Biologists have established international cooperation that generally translates into important advances in their lines of research. This diagnosis of the area may seem pessimistic, but it reaffirms the initial and long-lasting goals of the UNESCO Chair that left an important legacy for Brazilian science.

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that Chair, which contributed to the growth of Developmental Biology in Brazil and provided opportunities for several generations of researchers. This article expresses the author's opinion and interpretation of the facts cited therein. Other opinions should also be considered, and the author apologizes for any omissions and forgetfulness related to the events and people covered in the article.

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