Tamer of Crises

The immunologist talks about his experience as head of InCor and Butantan and suggests that the development of a Brazilian vaccine against dengue is showing encouraging results

Ricardo Zorzetto | PHOTO Léo Ramos Chaves

PUBLISHED IN FEBRUARY 2016

Skills in managing groups and identifying the core of a problem have put immunologist Jorge Kalil at the head of two large Brazilian institutions: the Heart Institute (InCor) at the University of São Paulo (USP), the country's leading center for research, education, and cardiology care, and the Butantan Institute, Brazil's largest sera and vaccines producer.

Appointed president of the InCor board and later of the Zerbini Foundation, the organization that manages InCor, Kalil led the team responsible for solving the foundation's financial problems. At Butantan, he coordinated the updating of sera production protocols, the modernization of the factories, and the development of new vaccines, including the vaccine against dengue fever.

Kalil isn't shy about expressing his opinions and is critical of the bureaucratic obstacles imposed on research. His work as a researcher has helped to reduce rejection rates in transplant recipients and to identify the causes of rheumatic heart disease and to create a vaccine against it.

Born in the city of Porto Alegre, he has been married for 38 years to Liana, with whom he has two children—Emmanuelle, who has a degree in business administration, and Fernando, an engineer who is works in the financial market. He dreams of establishing a center at Butantan for the development of compounds with potential medical use. His interview for *Pesquisa FAPESP* in November 2015 follows.

AGE 62

SPECIALTY
Immunology

EDUCATION
Federal University of Rio Grande do Sul (undergraduate)
Paris VII University (specialization, Master's, and doctorate)

INSTITUTION
School of Medicine of the University of São Paulo, Heart Institute, Butantan Institute

SCIENTIFIC PRODUCTION
522 articles published in scientific journals, with 5,600 citations; advisor for 14 Master's theses and 19 doctoral dissertations

Kalil, at the headquarters of Butantan, where he supervised the modernization of the serum factories and production of new vaccines

You are regarded as an excellent manager and administrator. Do you have a talent for resolving complicated disputes?

I think so. Despite my career as a scientist, ever since I was a young man my friends have always said that I was bound to be an executive or a businessman. After I got my degree in medicine and started my residency in clinical medicine, I went to France as an intern in 1978. Two years later, when I had barely finished my Master's, Marc Fellous, my advisor and head of the laboratory, went to Israel on a sabbatical and left me in charge of the group. When he returned, I took a job at the Pasteur Institute and stayed on as chief lab chief at Hospital Saint Louis. I was already in charge of the laboratory when I earned my doctorate. Fellous had helped me take on the laboratory and, in fact, when Professor Jean Dausset, my PhD advisor, won the Nobel Prize in Physiology or Medicine in 1980, he invited me to stay there permanently. I was 27 at the time, soon to be 28. I thought about the opportunity and talked it over with my wife, who didn't want to stay in France any longer. And I talked to Fellous, who said "Go back to Brazil. You can make a difference there." I took that as my mission and came back.

To São Paulo?

No. In 1983, I went back to Rio Grande do Sul, where I stayed for a little over a year, before Professors Fulvio Pillegi and Adib Jatene invited me to work at InCor. I was 30 years old and came here to set up and run a research laboratory that had initially been installed at the USP School of Medicine and was later moved to InCor. There, I had to manage people, administer the institution, conduct research, and raise money. At the age of 32, I created the Brazilian Association of Organ Transplantation (ABTO) and was its first president. In 1991, when I went to the United States for a sabbatical at Stanford, I was also asked to head their laboratory.

As soon as you arrived?

I went as a visiting assistant professor, and they assigned me as chief of the laboratory that was run by Rose Payne, a very charismatic woman who had competed with Dausett for the Nobel Prize. She was leaving, so I took over the Tissue Typing Laboratory for a year. I had

never formally studied business but I had always been curious about it. I talked to some friends who were businessmen, did some reading, and learned the basic methods and concepts. After my first month at Stanford, I was terrified because I had lost money, according to a financial report that was sent to me. It was a research lab that also provided services in transplant immunology, and we had performed lots of medical tests. So I thought we had made a fair amount of money. But the rent on the lab was extremely high because, although it was affiliated to the university, it was located Palo Alto's most expensive area. So I was taught a lesson in management. Despite that, I think I did well. They wanted me to continue running the laboratory and practicing science and they offered me a permanent position as professor at Stanford. But again, the idea of helping develop Brazil, made me come back.

Do you regret having returned?
I don't think I made the wrong choices. At Stanford, perhaps, I might have made more important scientific and technological contributions. But I think that, by being here, I've done more to help this country. By that I mean that I have always been involved with science and administration and have always had a strong desire to teach and form groups. Those who work with me don't want to leave.

How do you keep these people with you?
I respect the people who work with me. When I came back from the United States, I thought for a while that I needed to earn more money, and so I worked at the Sirio-Libanês Hospital. In 1995, I organized the hospital's clinical analysis laboratory. I spent 10 years there. The laboratory, which was losing money, became profitable. And since my salary depended on the operational results, greed reared its ugly head. I decided that I didn't want to do that anymore and went back to USP. That was when the big InCor crisis broke out .

The Zerbini Foundation crisis?
First it was at InCor, and they asked me to take over as president of the institute. When I realized the problem wasn't in InCor, that it was in a sector of the Zerbini Foundation, I also assumed the foundation's presidency. I succeeded in straightening things out at InCor, and after two years, I stepped down as president, although I still chaired the board of the foundation. We are still paying off some of the debts. But the foundation dealt with the problem and recovered its credibility by resuming its main function, which is to support the work done at InCor. Now, it is a healthy and legitimate foundation. And once again, it's respected.

> “At InCor, we are paying off the debts, and the credibility of the Zerbini Foundation has been restored

Did the problems arise during the construction of the new InCor building?
There was an issue with the construction of the new building, but there was also the InCor unit in Brasília and poor allocation of resources. The foundation was heavily in debt. The operation was being paid for by taking out loans, which compromised the institution's assets. At the time, it owed more than $150 million. But we worked it out. Once things had stabilized, Giovanni Cerri took over as Secretary of Health of the State of São Paulo and asked me invited me over to Butantan, which was having problems. Funds had been embezzled, and there had been a fire in the building that housed the collections. In addition, morale was poor among the people who worked at the institute. There was a schism between the institute and the foundation, even though the foundation was made to assist the institute. After working with José da Silva Guedes, the foundation's president, for a year and a half, we discussed the subject and realized that we needed to consolidate the leadership of both entities as a matter of corporate governance. I hired consultants from the Getúlio Vargas Foundation, who helped me set up a governance system, which I later implemented when Guedes decided it was best that I assume both directorships.

The Foundation's and the Institute's?
Exactly. I ramained in those posts until October 2015, when David Uip, state secretary of health, decided it was time for me to step down again. Now I'm chairman of the board of the foundation, and André Franco Montoro Filho, who works closely with me, is its CEO. It is important that there be no rift between the activities of the foundation and those of the institute. That was what happened at InCor, and again at the foundation when the management and administrative problems arose.

What had changed before the crises?
In the case of the Zerbini Foundation, the first problem was the establishment of InCor-Brasília. InCor is an institution that belongs in the state of São Paulo. It has a role to play here as an affiliate of the USP School of Medicine. In addition, the Zerbini Foundation had established an independent hospital in Brasília. And, just to give you an example, the foundation was thinking about going into the trash collection business in the Northeast. It began getting involved in businesses that had no connectio to its primary activity, which was to support InCor.

How did you solve this?
We cleaned things up, dropped projects which the foundation had no competence to develop, and brought it back to its proper function.

What was the situation like at Butantan?
When I first arrived, the vaccine and sera factories were at a standstill. They were state of the art when they were

built, but they were now outdated and no longer met the current demands of ANVIS's standards - the Brazilian Health Surveillance Agency. The registrations were expiring, and the facility was undergoing serious inspections. One of the problems was the water quality, which didn't meet ANVISA's production facilities standards for. There was also a problem with the clean zones for those units, which needed air conditioning equipment with different kinds of filters, and with the ftransportation of materials because clean materials must not come into contact with unclean ones. But the biggest problem, perhaps, was the flu vaccine. In 1999, Butantan had signed a technology transfer agreement with the French pharmaceutical firm Sanofi, and I was a part of that because I'd worked with Jatene at the Ministry of Health. The technology had been transferred, but the vaccine unit was not in operation. We produced the first batches in 2011, but ANVISA did not allow them to be handed over to the ministry.

PERSONAL ARCHIVES

At the ABTO foundation in 1986, Kalil, center, accompanied by surgeons Euryclides Zerbini, third from the left, and Adib Jatene, last on the right

Because of the water quality?
No. By that time, we had solved those problems. We had a license from ANVISA to prepare the formulation of the flu vaccine, divide it into doses, and put it into ampoules. In 2011, I was able to get ANVISA to approve the production of the virus in eggs in Brazil. Once I had the virus production going, the next step was to formulate and package it. We produced the virus, we formulated it, and packaged it, but ANVISA said that the resulting product could not be sold to the ministry because we did not have a license for the entire product line. It was considered to be a new product and had to be registered in a different way. It's just bureaucracy. I had some tremendous fights. ANVISA demanded changes in the area where we formulated and packaged the vaccine, and in 2012, we had already done that. In 2013, we delivered seven million doses. From 2013 to 2014, we had to carry out the second phase of the changes. Once again, ANVISA said we had not finished in time and the Health Ministry made me buy 10 million doses off Sanofi. We had produced the 20 million that I said we would, but they only bought 10 million. Then, I prepared myself and we delivered 34 million doses in 2015.

Is that enough for this country?
Brazil uses 54 million doses and immunizes one-quarter of the population. When the campaign began, we immu nized only the elderly, the children, and the health professionals. That's why the factory was designed in the early 2000s to produce 20 million doses. The rest is supplied by companies in other countries. We help with the importing.

What about the problem with the sera?
When I first arrived, sera were being produced albeit with some difficulty. The immunization protocols are over 100 years old, and the level of antibodies produced against diphtheria and tetanus by the horses was not high enough. There wasn't a problem with the final product because we had quality control. We reviewed our processes and improved the animal immunizations. That was when ANVISA said that all three Brazilian producers of sera were not in a position to continue production and that we needed to renovate our facilities. In 2014 and 2015, we renovated our factory. We doubled the production capacity and are now going through a validation process.

When does production start? Will you make the 12 sera that used to be produced by Butantan?
The idea is to begin production by early 2016. We are the sole producers of some of the sera. During the renovations, we arranged for shared production with the Vital Brazil Institute, in Rio de Janeiro, and the Ezequiel Dias, FUNED, in Minas Gerais. We got the plasma from Butantan's horses and took it to FUNED to prepare the sera.

How much was spent on those renovations and upgrades?
In 2014 and 2015, we invested R$300 million from the Butantan Foundation in factory renovations. We still need to renovate the facilities where the vaccines against tetanus, diphtheria, and pertussis—the DTP—are produced and the factory where the vaccine against hepatitis B is made. But we don't have the funds. Butantan is a public institution, and its profit margins are small. The vaccines that we deliver to the Ministry for R$9, are sold by private companies to immunization clinics for R$100 or R$120. We sell them at cost value. That's our mission.

How is the dengue vaccine going?
The dengue fever vaccine project was slow-going, but we have sped it up a lot. It started in 2008 during one of the PIPE programs - Innovative Research in Small Businesses Programs - run by FAPESP in partnership with the National Council for Scientific and Technological Development (CNPq). We completed phase 2 of the clinical tests with excellent results. The production of neutralizing antibodies for all four serotypes of dengue occurred in approximately 90% of trial participants. We are ready to begin phase 3.

PERSONAL ARCHIVES

In excellent company: Kalil, his wife Liana, and Nobel laureate Jean Dausset, friend and mentor

Who will get the vaccine in that phase?
In phase 2, there were 300 people. In phase 3, there will be 17,000; 12,000 will get the vaccine, and 5,000 will get the placebo. Testing will happen in 14 health centers around Brazil, which were selected according to the incidence of dengue and the different virus serotypes. The vaccine is ready. It was approved by the FM-USP Ethics and Research council, by the National Commission for Ethics in Research (CONEP), and also by the National Biosecurity Commission (CTNBio) because we are working with a recombinant virus. The last series of questions from ANVISA has been answered. We are waiting for our license so we can begin the study. [In December 2015, ANVISA approved phase 3, and Butantan, having implemented the new manufacturing requirements set by the agency, began producing the test batches. Immunization should begin in February 2016, although some of the funding for the clinical trials has yet to be allocated.]

That vaccine was developed together with the National Institutes of Health (NIH), in the United States, right?
The NIH performed the deletions that resulted in the attenuated virus. They selected the virus and produced a frozen liquid formulation, which cannot be used in countries such as Brazil and India. At Butantan, we worked on the industrial development. We developed ways to cultivate the cells in which the virus is inoculated and to obtain significant yields. We also found methods for purifying, lyophilizing (freeze-drying),increasing stabilization of the product after reconstitution. We did that and compared the results to those of the NIH vaccine. We have a new vaccine that resulted in a new patent. Our product is different.

Have you already compared it with the NIH vaccine? What do the tests show?
We compared it to the NIH vaccine and found that our results have the same degree of immunity. In second phase of the study, we tested the vaccine both in individuals who had been in contact with dengue virus and those who had not. Working in my laboratory with Esper Kallas at USP, we analyzed antibody production and the cellular response. That second part isn't usually studied. Everyone evaluates the level of antibodies, which are produced by B lymphocytes. But in order to make antibodies, B lymphocytes need to interact with another type of cell, helper T lymphocytes. We conducted an unprecedented study, with exceptional results; this explains why our vaccine works so well, while the others, made from the skeleton of the yellow fever virus and part of the dengue virus, do not offer such good protection. When I arrived, this project was dormant, but today, it's Butantan's main project. Both Brazilian and international pharmaceutical firms are interested in it.

What amount of dengue vaccine can be produced at Butantan?
We are still discussing this because the permanent factory isn't ready yet. We have a plan that, if optimized, will permit the production of enough viruses for 100 million doses a year. But we don't have the capacity to lyophilize and formulate that amount. We will need more investment, or else we'll need to hire that service. First, we are going to build the factory, the plans of which are ready. It will take a little more than a year to build it.

Will that depend on phase 3 results?
Sanofi built a factory to make dengue vaccines when it finished phase 2. Competitive international companies have a notion of risk, something we don't have in Brazil. Here, we don't build a factory until we receive an order from the government. Ideally, we should build the factory before finishing phase 3. If we wait for completion of the clinical trials, the arrival of the vaccine on the market will be delayed by two years. But we don't have the resources to do that.

How much will it take to build that factory?
To conduct phase 3 and build the factory, we need $100 million. Sanofi spent €300 million on phase 3 alone and €1.5 billion on the entire project. I don't think we have spent even $10 million, and that was obtained with the help of the BNDES – the Brazilian Development Bank – that, along with the FINEP – the Brazilian Innovation Agency – is one of the institutions that Brazil needs to preserve.

What is the status of Butantan today?
There are two financial problems. In 2014, the federal government and the judiciary said that a resolution had been enacted, which prohibits the government from signing contracts with foundations. Government procurement contracts need to be executed with a public institution, which in our case is the State Department of Health. This meant that we ceased to receive funds. When the government of São Paulo sends out an invoice and receives payment, it has to contribute 13% of what it recieves to reducing the federal debt, plus 1.5% for the payment of court-issued warrants and 1% for contribution to the Pasep (Civil Service Asset Formation Program). The Bu-

tantan Foundation does not make enough profit to pay that. In 2014, those withholdings amounted to 15.5%. It also takes time for the funds to reach us. We have R$300 million floating around there, out of a total of R$1.2 billion, which we are going to earn in 2015 from the sale of sera and vaccines. The second problem is that in 2014, we had to sign contracts with companies outside Brazil for the purchase of vaccines that are delivered to the Ministry of Health, and that burdened us. I didn't want to sign those contracts because the dollar had begun to fluctuate. But there was no alternative. Butantan buys in dollars or euros, and the government doesn't want to give us the funds to cover the cost difference we experienced due to devaluation of the *real*. Because of these issues, Butantan is having trouble paying its suppliers.

Where do the foundation's funds come from?
From a profit margin on sales of vaccines to the government. I would like to see some income from royalties.

Is there any interest in transferring technology to companies?
If Butantan gains anything from it, yes. There are 3 billion people living in areas where dengue fever is a threat. Butantan can't produce enough for everyone, but it does have distribution channels. If we could get the vaccine distributed worldwide, with Butantan's due royalty earnings, we would teach Brazil a lesson. This country could come to understand that planting soybeans isn't the only way to generate wealth; we can also create technologies and earn royalties from them. We don't know how to be competitive. Bureaucracy and rules tie us down. I have tremendous difficulty managing things as a government administrator. The Public Prosecutor's and the state Court of Accounts are always calling us up to find out what we are doing. At Butantan, we have the Innovation Center, the NIT, which holds a large number of patents. There are people interested in working those patents, but the bureaucracy is strangling us.

Why is it hard to innovate in that field?
Because it's bureaucratic. Either Brazilian pharmaceutical companies are not innovating or they are doing it in the United States and Europe. The universities, when they make a discovery, think they are going to earn a lot of money from the patent, and so they don't facilitate its use. The State Prosecutors don't want the responsibility for a patent to rest on a single company, although that exclusivity results from the patent application itself. It exists so that a company that develops a compound might obtain a financial return. We could have more investment in innovation. The problem is both regulatory and managerial. Innovation law is complicated. All these rules can become an obstacle. The result is that there is no innovation in the pharmaceutical and health fields in Brazil.

> “Our dengue vaccine generates high levels of antibodies against the four serotypes of the virus

Do you experience any retaliation because you talk about those problems?
I make enemies, certainly. But the majority, sometimes silent, agree with me. Of course, it is complicated and it bothers me. Anyone can go to the Public Prosecutor's Office and tell them that I'm doing something wrong, and then I'll have some explaining to do. They lack burden of proof; I am the one who must defend myself. But every time the people from the Court of Accounts come here and realize what we are doing, they help us.

What is your most important scientific contribution?
The international scientific community has given awards to the papers in which, in collaboration with Luiza Guilherme, I described the mechanisms of induction and progression of human autoimmune disease, especially the mechanism by which an infectious agent causes the organism to break down its own tolerance and starts to attack its own body. Among these are the papers in which we discovered how *Streptococcus* breaches immunological tolerance and elicits the disease known as rheumatic heart disease. It's an important model of an autoimmune disease that is unleashed by an infectious agent. Other diseases such as type 1 diabetes and multiple sclerosis seem to work the same way. Working with Edecio Cunha Neto, I saw observed similarities with Chagas disease.

Some time ago, you said that you were at a point in your career when you wanted to practice translational science with more speed.
I'm already doing that. We signed a contract for R$20 million with GSK (GlaxoSmithKline), financed by FAPESP, to set up one of GSK's centers for new drug development at Butantan. We have several compounds at the developmental stage; the active ingredients for these were obtained from venoms. I would also like to establish the Butantan Institute of Biotechnological Innovation, the IIBB. The idea would be to take compounds that have the potential to become new drugs or vaccines and develop them in partnership with companies. It would be like an incubator.

Various compounds have come out of the Butantan laboratories, but they are unable to overcome the innovation barrier and give birth to new drugs.
We working with 40 active patents. It's what I have to do. I have my fair share of scientific publications and citations. I want to develop something that can actually help people. When the Zika virus emerged, I got the people from the Institute together and designed a program to study the disease. I like administration, because it enables me to put my scientific ideas into practice. To be part of the group of industrialized countries, Brazil has to show that it is able to solve its own problems. ■