Interview

Mayana Zatz

One eye on reason, the other on the heart

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Mayana Zatz is a highly respected scientist, with the discovery of some important genes written into her curriculum. She has won awards both here in Brazil and abroad, and openly declares with all of her might that she loves what she is doing. Further: she considers herself to be extremely lucky to be working on that which she adores. She is also a woman capable of passionately taking up causes in which she believes and fighting, warrior like, for her points of view, as it could be seen in the days that anticipated the voting of the Biosafety Bill in the Chamber of Deputies in Brasília: all of a sudden her beautiful face seemed omnipresent on the television. On the TV Globo national news, on the Sunday night TV program *Fantástico*, on anchorman Bóris Casoy's talk show, apparently over the entire Brazilian media, there she was, being interviewed; giving her opinion, serene and strong-minded; defending research with embryonic stem cells, one of the new law's most polemic points and explaining how in the future this could save thousands even perhaps millions of human lives.

She is full professor at the Biology Institute of the University of São Paulo and the coordinator of the Human Genome Research Center. Mayana, at the same time that she began her life as a researcher in the 80s, and we have to add, a senior—as at that time she had already been researcher during her undergraduate program, during her master's, doctorate and post-doctorate degrees—, had also implanted into her work a social characteristic, that of assisting the physically handicapped and their families, which resulted in the creation of the Brazilian Muscular Dystrophy Association (ABDIM in the Portuguese acronym).

Very discrete about her private life, it was with economy of words that the Brazilian Mayana Zatz, 57years of age, born Mayana Eden in Israel, of Romanian parents, made reference to her family in this interview: she is recently separated and the mother of two boys. She spoke a little about her routine, which is organized around hours and hours of work, but she includes the habit of daily jogging, which may in part explain her graceful silhouette and elegant figure.

In the pages that follow, it is possible to make more direct contact with a little of the practice and thinking of this fascinating personality from within the realms of the Brazilian scientific scenario that is indeed Mayana (*a fuller version of the interview can be found on the website: www.revistapesquisa.fapesp.br*).

■ *How did you discover your vocation for scientific research?*

– It started in my childhood. I thought this notion about scientists, books and plants to be the greatest thing. But I also had a leaning towards medicine. And consequently I remained between medicine and research, but for sure I had to be a scientist. So, then when I went to high school I fell in love with genetics and decided: This is what I want to do.

■ *Where were you living at that time?*

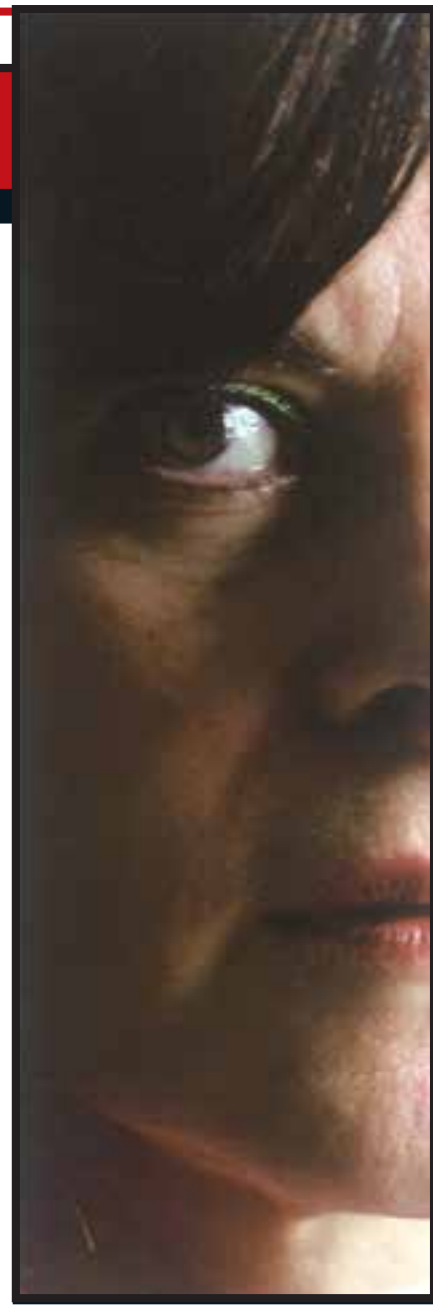
– I was here. I came to Brazil when I was seven. I was born in Israel, left, went to France and afterwards came to Brazil. By then I could already read and write.

■ *You came directly to São Paulo?*
– It has always been São Paulo.

■ *You were the taking a science course* [one of the kinds of high school courses of that time; the other was classics, for those who would dedicate themselves to humanities], *studying biology through which you then discovered genetics?*
– Clearly we didn't have molecular biology then, there was nothing of what exists today. It was that idea of blue eye and brown eye, those genetic crossings... but I became interested and when I went to university I directed my energies to this.

■ *Where did you complete your high school?*
– At the São Paulo State High School, at that time a super high school. I took my university entrance exam in biology since, as I wanted to major in genetics, I went where it existed. And another influence was professor Oswaldo Frota-Pessoa, whose books on biology I already had and thought they were the greatest. When I entered the school, the first thing I did was to attempt to get to know professor Frota. And I became one of his students. It was scientific initiation right from the word go—he had already been working on human genetics. Professor Frota got us working with patients right away. Back then I was seventeen or eighteen.

■ *What like was this attention to patients?*
– Professor Frota was a medical doctor. He gave genetic counseling to families who had patients with various illnesses, he made risk calculations and we participated in this. He though that we must learn everything, all of the techniques that there were. I have a lot of respect and admiration for professor Frota, to whom I owe a lot. His scientific questioning was very impressive, when you though you had understood a problem he would ask you a question that would revolutionize everything, he would turn everything upside down in order to make you think. Afterwards there would be the didactic part. And then thirdly was the fact that he was the example of how to deal with patients, always with kindness and the human touch.



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■ *This was around 1967... 1968, about then?*
– About then. At that time my mother didn't know how to explain to her friends what her daughter did in genetics, simply because nobody knew what this was. I ended up specializing in human genetics and medicine because this would give me the possibility of doing research and dealing with patients as well. I graduated, wrote my master's and doctorate theses at USP, again under the supervision of professor Frota, and afterwards did my post-doctorate work at Ucla (the University of California, in Los Angeles). When I returned at the beginning of the decade of the 80s, I started a research group in USP's Biology Department. And I also founded the Brazilian Muscular Dystrophy Association.

■ *How did you manage to link together a career as a researcher with work of a social assistance nature?*
– B efore I had went off to the United States, we had begun to study enzymes and we had found that some of them, for example the enzyme creatine-kinase, which comes from the muscles, was increased in the blood at a rate of 60% to 70% in people at risk of having their children affected by Duchenne muscular dystrophy. We had studied those affected, the mothers, sisters and afterwards we explained all of this to the families, still then under the guidance of professor Frota. Shortly after I returned, some students sought me out and asked to start researching, and one of the things that had intrigued me was to know what had happened to those families.

■ *Were these cases spread all over the city of Sao Paulo?*
– Well spread out, the majority of them in shantytowns. We went everywhere. The level of violence was nothing when compared with today and the people opened their doors to us. We had a very welcome surprise because the families understood the high risk and most of them had not had children. But I was shocked to see the conditions of the children who had been born before genetic counseling and had no wheelchair, no access to physiotherapy or access to schooling, because nobody wanted to take them on. This was even more shocking in the face of the gigantic support that I had seen in the United Sates for families with identical problems. Then I said to myself "I need to do something", and so I

founded the Brazilian Muscular Dystrophy Association.

■ *How did you manage to mobilize people here? Who gave you support?*
– At the beginning professor Frota was the Association's scientific director and Maria Rita Passos-Bueno, if I'm not mistaken, was one of our directors. We went about mobilizing people, I used the money from my grant to have the statutes drafted and to pay for a lawyer... The headquarters was here in my office. Afterwards we began to set up a bazaar, to sell raffle tickets until I met Pedro Moreira Salles, the president of the Unibanco bank, and asked him for more substantial support in order to help these children.

■ *Did he already have a dystrophy problem?*
– Yes, he did. Then we rented a house near the entrance to USP to act as the Association's headquarters. Pedro has sustained the costs for all of this time. We only managed an important financial source just over a year ago in a partnership with the State of São Paulo Public Health Department, which is helping not only to sustain the ABDIM, but also to pay for the genetic testing involved in neuromuscular illnesses.

■ *Is this occurrence very high?*
– All of these illnesses have an occurrence of one child affected in every one thousand born. Within genetic illnesses, which affect 3% of children, perhaps this (neuromuscular) is the most common. And what becomes more important is that the vast majority of cases are highly serious and progressive.

■ *That is to say they place those who are inflicted in grave risk of early death?*
– That's so. Some adult forms exist, but in many cases it is infants or youths who die. And what I always say is that it's not a child or an adolescent who's affected, but an entire family.

■ *How did you come into contact with those suffering from muscular dystrophy?*
– The first patient who caught my attention was a young girl who came for genetic counseling because she had three nephews affected by Duchenne dystrophy. I was still a student. She was going to get married and was very worried about the possibility of having children who would be affected. Nobody worked on anything in relation to this situation at that time. Then together with professor Frota, I discovered an article that had been published about an enzyme that could help to define if she was a carrier or not. I ended up studying this in research work that involved one thousand people, that I began during my master's degree and continued during my doctorate degree.

■ *And how did your work evolve up until the identification of the first genes involved with waist dystrophy?*
– We had been working with enzymes until, at the start of the decade of the 80s, molecular biology began to be developed abroad. We got left behind because we were doing nothing in this field. Then Rita, who had just completed her doctorate, said she was willing to go abroad to learn this technology. I got in touch with Kay Davies's group in Oxford, UK, as she was the best at that time, and Rita went there. And then another of my friends, Mariz Vainzof, who had been working with proteins, and with muscles, said she wanted to go to Canada to learn how they had been studying muscular proteins. When the two of them returned, we set up this sector of molecular biology to study neuromuscular illnesses. We managed to publish a lot of work; we found new genes and in fact we managed to take an enormous qualitative leap forward.

■ *I remember one of your reports about paternity secrets in this work on genetic counseling that for its part often generated immense fears in people that, if they knew the truth, would have nothing to fear. How did you and your group get over this trauma in order to deal with the most complicated cases?*
– We don't always overcome this. Each case is a case in itself, but frequently it's discovered that when a DNA exam is made there exists a paternity situation that is unexpected.

■ *You then said that that was the situation in more or less 10% of the cases. True?*
– Yes, 10%. So, what are we going to do? If the result is not going to interfere in our genetic counseling, we have nothing to do with this situation. If it is going to interfere, then we have to talk to someone. One case in particular that you may remember was that of a girl whose father had hemophilia, and she had become pregnant. She could be a carrier of this illness that, although it doesn't show up in women, would give her a 50% chance of having a hemophilic son. Indeed, she came to us already with the pre-natal diagnosis. When the exams were completed, it was seen that her father was not actually her biological father. She herself was not risk at all, not in that particular pregnancy or in any other. But she had a lot of love for that father and to have told her the truth could well have meant the destruction of all of the family. So we had a difficult choice to make. In the end, our idea was to talk with the mother who knew everything. The mother had a talk with her daughter and that was the best solution.

■ *Have you come across many cases like that?*
– Yes. And, when people begin to discuss ethical questions in this field, like a heap of theories, I find it interesting to tell some very hairy practical cases. I remember another case... that of a couple who had a child with a neuromuscular illness. The father felt guilty because he had believed that he had transmitted the mutation to his son. Through a DNA exam, it was discovered that he was not the biological father. Whereupon came that anguish: to tell or not to tell, that is the question? I told this story at a bioethical congress that had only lawyers in attendance and they told me: "Look, you could well be sued in both situations, if you tell or you don't tell".

■ *In the end, did the supposed father get to know?*
– He didn't come back here.

■ *I would like you talk a little about the national and internationals awards that you have conquered. What were they?*
– I won the Women in Science Award from Unesco-L'Oréal in 2001. I believe that that award opened up many doors. I had no notion that it would have such an impact. And afterwards, in 2003, I was awarded the prize in Basic Medical Sciences from the Third World Academy. It's very fulfilling to win an award. In the case of the Women in Science from L'Oréal a pile of money goes with the prize, so we had a lovely and emotional party in Paris at the Unesco headquarters.

■ *And national prizes?*
– I've won the Claudia Award, the Ro-

tary Club Award and some others.

■ *Before going on to stem cells, I'd like you to speak a little about your Cepid (Research, Innovation and Diffusion Center) funded by FAPESP.*

– I'm convinced that the Cepid was an extremely important initiative. It created the possibility of not only associating various researchers, but of bringing together three trends: that of scientific and innovative research, the transfer of technology and thirdly the spreading of knowledge. We've learned a lot over these first five years and I believe that now we have the opportunity of making a very important advance. In terms of research, the Center has allowed us to purchase equipment that would not have been possible with an isolated group and has given us the opportunity to inter-react. In the area of technology transfer, we've improved in attending to patients and the tendency is for continued improvement.

■ *Today, annually how many patients are treated at the Center?*

– Around one thousand.

■ *How many researchers work in the center?*

– There are ten full time researchers, but there are people who come and go, if we count each one with their trainee students, then there must be around one hundred people.

■ *Over your many years of work, has your research team added up many people they have been in direct contact with?*

– Only in neuromuscular illnesses we're at number 21,000, between patients and members of their family. There've been 21,000 people who have been tested and this is the highest sample in the world, unquestionably, that have been studied at the same Center. Today we're following up the second generation of these patients.

■ *In terms of the treatment of these illnesses, have you seen some effective changes?*

– The major hope now lies exactly with stem cells, for this reason I battled so hard for them. A lot was spoken about a decade ago concerning genetic therapy, but I see it much more distant than cellular therapy, which is an improvement to transplants. In genetic therapy one has to manipulate the gene, you have to be sure that you'll arrive at the right gene, whilst in cellular therapy there's a substitution of the tissue.

It's heart breaking to have to say to a father or mother that their son has an illness and nothing can be done. It was for this reason that I got myself mobilized

■ *And advances in diagnostic methods?*

– The following has happened: as we have money for technical support—it's still only a little and we need much more —we can get people who are highly qualified and skilled to carry out the technical part of the technological transfer, instead of students, as had been happening. The Cepid Center had given us this possibility.

■ *What exactly are these tests?*

– Tests, for example, on the diagnosis of waist dystrophy, in which we find out which are the most frequent mutations. The test for cystic fibrosis, which is not neuromuscular, but is the most common genetic illness in Caucasians, and in which you can have more than one thousand mutations, at the Center we have developed a test that manages to detect 80% of these mutations.

■ *And today, where are these tests available?*

– Here at USP. The only thing is that we have another battle on our hands: the Public Health System doesn't pay for the cost of these exams. We have a convention with the State Public Health Department only for neuromuscular illnesses. For the others and for patients outside of São Paulo, we have nothing.

■ *Is the cost of these tests very high?*

– It depends. They can cost between R$ 300 and R$ 500, but if we think that because of them one no longer needs to carry out a muscular biopsy; very often there is no need for the hospitalization of a child; one can begin precocious treatment; prevent the birth of others affected, etc. etc., the cost is derisive. Mainly because a genetic test is done once during a lifetime and doesn't need to be repeated.

■ *Are these tests available through private laboratories?*

– Some are. But in truth, throughout the world there are reference centers of determined specific tests. So we choose some illness for testing, because each one of them gives a lot of work, and consequently it's not worth while everyone doing everything. There is a group in the south of Brazil that works with metabolic problems. It's the same idea throughout the world. We send DNA, in blood or saliva, for testing and we can receive the result throughout Brazil in order to make a diagnosis. But we have no way of covering this cost. Because therein there is no research, it's a service that will need to be covered.

■ *Why did you decide to take up the fight for the approval of research with stem cells extracted from human embryos?*

– Besides my obvious interest in the scientific question, what mobilized me was my direct contact with patients. This is the other side of the team on which I'm playing. It's heart breaking to have to say to a father or mother that their son has an illness and that there's nothing that can be done. They become desperate and want to take their child to any place on earth. I even encourage those who have the financial means to do that. I believe that it's important that they see and hear everything that there is in order to be certain that the best is being done right here. I have attended to patients who had spoken all the time:

"I'm praying for your research to go well". And I said to them: "There's no point in praying because I don't have access to stem cell embryos". It was this situation that truly gave me the force to start the mobilization.

■ *When did you realize that, "We're going to have to fight up front for this situation"?*
– When I saw that the bill might not be approved. The first bill, moved by the parliamentarian Aldo Rebelo (Communist Party of Brazil), allowed research with embryonic stem cells. That was in the middle of 2004. The project was forgotten about. It had contemplated putting everything together, embryonic stem cells and genetically modified organisms. But in the end everything was to be allowed and everyone had been happy. Then, all of a sudden, in the middle of the night, everything was changed and the proposal was modified. I was really disillusioned. Then we began to get ourselves mobilized. We divided up the project and a group re-wrote the part about the stem cells. Another group dealt with transgenics, and we went back to Brasília to talk to senators in search of support. At that moment I met Drauzio Varella and I asked for his support: "You need to help us in this cause! Give us some help through TV Globo". He agreed and we carried out a public hearing, which was the watershed.

■ *How was the experience of dawn raids into the National Congress?*
– It was a very enriching experience. In the first place I got to understand how the Congress works, something about which I had had the slightest notion. Secondly, I believe that we managed to de-mystify lots of pre-conceptions during out public audiences. The Church had been speaking about abortion (when they referred to research with embryos).

■ *You defended the idea that in the same way that complete brain damage means death, in legal terms, life also begins when the nervous system is formed?*
– Yes. But even in relation to abortion, there's a fundamental difference, and I even said this to a priest. If you don't interfere in an unwanted pregnancy, life goes on. It is interrupted with an abortion. However, in research with embryos from reproduction clinics the situation is exactly the opposite: they don't exist without the intervention of man. They were created through the intervention of man because the couple could not manage to reproduce naturally. And, if they were not to be introduced into the uterus, they wouldn't have a future. Even if they were to be introduced quickly into the uterus, the chances of transforming into a life are 10%. Embryos frozen for three or four years would have a chance of perhaps 2% to 3% of becoming a life. To say that this, research with embryos, is killing lives is an enormous, enormous exaggeration. We suffered major opposition from the Catholic Church. The Evangelists are divided over the question.

■ *In this fight did you feel that you were supported by the scientific community?*
– I felt I was. I believe that the Brazilian Academy of Sciences supported us along with FAPESP as well. However, I believe that the scientific community could have mobilized itself more effectively.

■ *How did you react, in the face of criticism from some quarters, about the presence of handicapped people in wheelchairs inside the Chamber of Deputies in order to press for the approval of the new law?*
– Those people in wheelchairs asked us if they could be heard — and I believe they have that right. They're the people who suffer most, I always say this. We, the organizers, didn't ask anybody to go (to Brasília) against their will. On the contrary, they demanded: "For the love of God, let us speak to these Parliamentarians, let them see us". And there was a difference in this mobilization: the presence of youngsters and children in wheelchairs. Research can help these young people and not only the patients with Parkinson and Alzheimer ailments. A person with Parkinson's disease, like the recent Pope, can live to eighty years of age. Good, bad or indifferent, he is there and has lived his life. Now a child with neuromuscular problems... well that's very sad. I believe that this brought out a sense of reality.

■ *When will it be possible to start research with embryonic stem cells?*
– I'm hoping that we can begin this year. We're going to press for that to happen. We don't want to wait very long. I believe that this type of research needs to be regulated — and very well controlled. I'm concerned because there are a lot of smart conmen out there offering treatments that don't exist with embryonic stem cells. Now we need to pour cold water on the hot plate. Many people have telephoned here offering themselves as guinea pigs for experimental treatment. We don't accept these kinds of offers. So the smart boys appear saying that they're carrying out treatment with imported embryonic stem cells. Now they're going to say they're doing this with national cells.

■ *Do you expect to have to work for a long time with animals before switching to research with embryonic stem cells in humans?*
– I hope not. We've already been working with stem cells from the umbilical cord on a canine model of dystrophy. And we're about to start work on immune-deficient mice. Animal research did not need the new Biosafety Law for authorization. It's a lot easier to work with a mouse although it's a model that is very distant from a human being. The dog is closer to man, but we can't manage to carry out fertilization in vitro in the dog. As well, it's very difficult to capture stem cells from it.

■ *Why?*
– Because, when the dog becomes pregnant, it's only after fourteen or fifteen days that the embryo lodges itself in the uterus. So much so that you don't really know if the dog is pregnant until the start of its second month. In collaboration with professor Maria Angelica Miglino (from USP's Veterinary Medicine and Zootechnology School), we're attempting to cross a dog and to carry out a uterus washing in order to attempt to obtain embryos. But it's difficult to make a lineage of stem cells from these embryos. Until today nobody has succeeded. The problem is that the dog's embryos, when they lodge in the uterus, they're already at a more advanced stage than those of human embryos, which are only a dozen or so cells.

■ *The stem cell is a complex question. Don't you think that people are confusing the study of human stem cells, which is about to begin in this country, with clinical experiments that have already been done using adult stem cells?*
– This is a very important question. In terms of therapies, the only certainty that there is today is the use of adult stem cells, from bone marrow and from the

umbilical cord, for treatment of illnesses such as hematologic diseases, anemia and leukemia. We know for sure that the stem cells of the umbilical cord are better than those of the marrow. But there's a need for umbilical cord public banks. There's no point in stocking your own son's umbilical cord. Outside of this, all that is being done at the moment is therapeutic trials. There's no treatment with adult stem cells. People are confusing therapeutic trials with a treatment. When it appears on the television that injecting adult stem cells into a woman who has had a stroke, this is a therapeutic attempt to improve her condition. Nobody knows how her recovery would have progressed if she hadn't received the stem cells. The same rationale holds true for heart case studies. Everything is experimental. The Ministry of Health's program that has been launched is very important because it's really going to show what is the potential for cellular therapy to improve heart problems.

■ *So, you don't recommend guarding ones son's umbilical cord then?*
– No. Where's the logic in guarding the umbilical cord of your son? Is it that in thirty or forty years from now he might make use of it, for example if he were to have a heart problem and then the stem cells from his umbilical cord could be used in a possible treatment? But who's going to guarantee that in three or four decades these cells will be viable for use? Who's guaranteeing that the person who sells you the service for guarding the cord will be here to complete the service, even to begin a discussion? As well as this, the cells of the very person himself do not serve for (treating) genetic illnesses, not even leukemia. Do you understand? People are paying for something that has a minute chance of serving for anything. For me, it's smoke and mirrors.

■ *Do you believe that embryonic stem cells, by theoretically being capable of transforming themselves into all types of tissue, could generate more therapies than those of adult stem cells?*
– People who are against studies with embryos say that the results with adult stem cells are much better. But the embryos have yet to be tested. How can you say something like this without having done the research? We, for example, have been working with umbilical cord stem cells for more than two years, attempting to transform them into muscle. Up until now we have seen that the potential is extremely low. I don't know if we got to the correct stem cell, but the results are frustrating. We know that embryonic stem cells have the capacity to form any specialized tissue. But there's no point in putting them into the organism and waiting to see if they play their role. We need to understand how they transform themselves into the various tissues that we need. Nobody would be foolish enough to inject embryonic stem cells indifferently into a person. This could well bring about tumors.

Neuromuscular illnesses will perhaps be the first to benefit from studies with embryonic stem cells

■ *Do you believe that in five years some treatment based on the use of embryonic stem cells could come forward?*
– I do. There are many people working on this throughout the world. The technology for injecting stem cells into the body would be similar to that already in existence, for example, with leukemia treatment and transplants. The part concerning the immune-suppressive situation has also advanced a lot. I think we'll get there, yes. However, genetic therapy is a situation that is much more complex.

■ *What illnesses could well be the first to benefit from treatment based on studies with embryonic stem cells?*
– The neuromuscular illnesses, which I am studying, may well be the simplest and the first to benefit from these studies. In spite of having lots of muscles in the organism, it's a lot easier to substitute them than to make a new organ. In these illnesses a natural degeneration of the muscle occurs. For this reason, we're attempting to substitute it with a normal muscle. For me, this is something that may be possible to do in the not too distant future. Now, before starting any treatment, one needs to be certain that you're going to inject embryonic stem cells into the body that know the right road and have the commitment to becoming muscle. We could inject these cells into immune-deficient mice and see how they react, discover where these cells go and where they lodge in the body.

■ *Once you stated that you had never felt any discrimination in your professional life by being a woman. Is that true?*
– Not only did I not feel discriminated against, but I believe that it was a great advantage being a woman. At the time when I had to look after my children, something highly expensive, to pay for their schooling, I had a husband who paid the house bills. In spite of the fact that today we're separated, we're still good friends. And I owe a lot to him. There was a time when I didn't have a grant, or had a very small grant, which wouldn't even have paid the school fees. Before becoming a professor at USP, in 1982, I spent thirteen years as a grant holder, a little from the CNPq (the National Council for Scientific and Technological Development), afterwards came FAPESP, which supported me right from the start.

■ *Have you stopped to think that perhaps you're the best known woman scientist in Brazil?*
– I never thought about it. But it's very funny. Once Leopoldo de Meis (from the Biomedical Sciences Institute of the Federal University of Rio de Janeiro) said to me that he had written a book, interviewing children and showing the pictures that they had drawn of scientists. The children painted the scientists full of crazy things, smoke coming from everywhere. At least we have to de-mystify that image, showing that scientists can be women. You don't need to be that crazy thing. •