

Connecting to society

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PUBLISHED IN OCTOBER 2012

Accustomed to both genetic and hematological studies and the twists and turns of political science, Marco Antonio Zago assumed the position of Dean of Research at the University of São Paulo (USP) in 2010 and soon faced a challenge. How do you inspire the most successful researchers to become more interested in the university that is responsible for their training?

Zago identified in many USP scientists a certain disconnect from the institution. To Zago, it is important to establish ways to strengthen everyone's connection to the university and thus to society itself. «You have to provide some coherence to the research within the university,» he believes.

The measures that the dean adopted apparently followed his desired course. The creation of multidisciplinary Research Support Centers (NAPs), for example, modeled after the Research, Innovation and Dissemination Centers (RIDCs) – a program created by FAPESP in 2000 – have attracted 118 groups of researchers since 2010. The USP Innovation Agency is closer to researchers and assists them with patent-related issues. New professors who join the university are encouraged to seek outside resources and join research teams. “Undoubtedly, we were able to improve the university in many respects,” says Zago. This assessment has been confirmed by the favorable position achieved in all of the rankings that evaluate universities – strong rankings despite the enormous size of USP, which is unusual in the best institutions that invest in scientific research.

Marco Antonio Zago graduated from the University of São Paulo (USP) School of Medicine of Ribeirão Preto. He spent part of his career as a researcher and also worked as a physician. He was the clinical director of the Hospital das Clíni-

cas and the scientific director of the Fundação Hemocentro, both of Ribeirão Preto. In 2007, he chaired the National Council on Scientific and Technological Development (CNPq) and created the National Institutes of Science and Technology (INCTs), which was an attempt to change the scientific production model in Brazil.

As a researcher, he contributed to the study of sickle cell anemia and thalassemia, fighting to establish methods to diagnose and treat these diseases. He went on to study population genetics and was able to identify the regions of Africa that had been home to the slaves brought to Brazil. He also performed outstanding work on the genomic sequencing of the bacterium *Xylella fastidiosa* and on the cancer genome. As the leader of the Cell-Based Therapy RIDC2, he has focused its efforts in recent years on studying stem cells. Below are the main excerpts from the interview.

What is the role of the Dean of Research at a university the size of USP?

I believe my role is to provide a certain direction and unity to the research performed by the university. And when I say a certain direction, it is not to perform or promote targeted research, in the traditional sense of the word, by defining lines of research; this is not possible at a university like USP. In terms of size and range of areas covered, we are one of the largest universities in the world. It is hard to find an area or sub-area of knowledge in which USP does not have qualified specialists. And, therefore, the research activity is very heterogeneous and takes various forms.

What exactly is that “certain direction”?

Perhaps to lend coherence and synergy to the university's research. When I arrived here, I realized that the sense of unity at USP was low. The

AGE 65

SPECIALTY

Hematology and genetics

EDUCATION

University of São Paulo (undergraduate and PhD)
Oxford University (post doctorate)

INSTITUTION

University of São Paulo



most successful groups were those that were less tied to the university, that were independent and that claimed that their resources came from outside, and not from USP.

There was a certain amount of detachment...

Yes, a detachment from the university, which leads to a degree of separation.

Where does USP stand among the world's largest universities?

UNAM [the National Autonomous University of Mexico] has 270,000 students, and the University of Buenos Aires around that number; they are institutions that have no *numerus clausus* and therefore any student who wishes to enroll may do so. On the other hand, when we look at the best universities in the world – those that everyone cites as examples of universities that we want to emulate – the most important universities of the United States, England, Japan and South Korea have an average of 17,000 students. And many of them have more than 60% of their students in graduate school.

And USP?

We have 91,000 students, 30% of whom are in graduate school. One of the common characteristics of universities with a strong commitment to research, in addition to teaching, is a mission to produce scientific research and transfer knowledge. USP fits that description. We must emphasize a commitment to teaching. This commitment is important because many are of the opinion that I am monomaniacal at times in thinking that the university should only do research. I do not think so. I understand that the basic role of the university is education, to train qualified people at a higher level.

Does USP fit that description and rank high among research universities?

USP ranks high in all types of rankings. There is unanimous agreement that USP is Latin America's premier university. There are other good universities in Brazil, but they are few in number. The club of research universities in Brazil is very small.

How do you take this diverse university and make the research activity developed by so many groups with different goals coherent?

First, you need to draw these groups' attention once again to the center, which is the university. And, through the university, these groups resume their relationship with society. We do not perform superficial research because we are seeking new knowledge, which may or may not have an immediate application. Research is not just a laboratory activity but also a creative activity in every respect, including the development of culture, which is the responsibility of the university.

Including art?

Arts and humanities represent a very important contribution for USP. If we look at some rankings that sub-

divide the university's performance, USP ranks high in the humanities. We must promote a more intense dialogue among these academic cultures.. When I speak of providing unity or coherence, it is to get the attention of researchers, especially the most successful ones, and to get them to return to the university and through the university, to society. One of the ways that we found to do this was to provide our own resources to support research; this has never been done at such an intense level at any Brazilian university. This level of commitment to research started here, although the amount of resources is not very large compared to what USP already applies to research. We invest approximately R\$2 billion per year in research, although this is not apparent to people.

Does this account include resources from FAPESP and CNPq?

No. The R\$2 billion refers to the budgeted resources that USP distributes to its activities. A considerable portion goes to pay technicians, laboratory infrastructure, improvements, water, electricity, and the share for full-time research activity. The university pays for everything. In American universities, these funds come from the researcher's grants, which pay for scholarships, technicians, the telephone bill and laboratory improvements, everything. This budgeted money is used for various purposes. We provide the basic infrastructure and some resources that go unnoticed on the pay slip. In addition to this, there is money from FAPESP that is distributed on the basis of proposals submitted for external review based on the merits of the project. This introduces a quality-control component to the distribution of money.

How is the research support program you created going?

In two successive internal requests for proposals, we placed R\$73 million in the first administrative year, which was 2010/2011, and then an additional R\$73 million in 2011/2012. To make these investments, we invited the researchers to submit research proposals, whose merit would be analyzed; the proposals were to envision the formation of a group of limited duration that was required to have a multidisciplinary aspect. The proposals also had to focus on a problem that was important to society, for immediate application or theoretical analysis. With that, from the two requests for proposals, we selected 43 in the first year and 75 in the second, for a total of 118 cores, or research centers. We called them NAPs, Research Support Centers.

Is there any overlap between the NAPs, the RIDCs and the INCTs?

You are always talking to the same individuals. Of course, the idea of people coming together around a subject arose there. I have been coordinating an RIDC since 2000. When I was chairman of the CNPq, we also had the idea of trying to do something that involved forming groups. I used the RIDC model and, considering what could be done with it on a national scale, we designed the INCTs,

which were and still are the largest science and technology programs that the CNPq has coordinated to date.

Do the NAPs then have the clear objective of bringing together more groups of researchers at the university? Yes. Another complementary measure comes from the USP Innovation Agency, which is today linked to the Office of the Dean of Research. This agency has been completely transformed and plays an important role in solving the problems of the various research lecturers, for example, writing patents, treating this from a legal standpoint, and negotiating with companies that want to license patents, in addition to other tasks. Researchers today recognize that the landscape has changed to such a degree that USP is the Brazilian university that files the highest number of patents with the Brazilian Industrial Property Institute (INPI).

This piece of information is interesting because when it comes to university patents, Unicamp stands out.

That is a tradition because Unicamp was actually organized long before USP. Unicamp is extremely competitive in this regard. From 2000 to 2006, USP filed, on average, 29 new patents per year, which increased to 81 new patents per year between 2007 and 2011. Between 2009 and 2011, the three-year accumulated data are USP 231, UFMG 178 and Unicamp 170. In addition, the Innovation Agency acquired other functions, such as acting decisively in the education area. If the university's main contribution is education, we must also train people to have an innovative way of thinking. It is not the number of patents filed by researchers that will change the landscape of Brazil. What will change the landscape is training the young people who are about to graduate from the university to make things happen. This year, we created an entrepreneurship course, and there are 200 undergraduate students taking it.

In 2009, you said that the INCTs could change the scientific production model in Brazil. Have you come close?

I think that the INCT's wide scope and some of the goals have been abandoned. Today, the national science and technology plan is to send students abroad. When we created the INCTs, we had a program that involved many components, not only providing sources of funding but also planning and performing the follow-up. We convinced the FAPs [foundations that support research] to participate. The first to join was FAPESP, and then others followed. We had a great initial program with a single objective in which CNPq, Capes, the major FAPs, Petrobras, and BNDES were involved. If the program had continued along that initial path, we would have had an increasing role for the Ministry of Science, Technology and Innovation, not just as a source of funding. We would have been able to attract significantly more money than the ministry is able to distribute and we would have encouraged everyone to talk to each other and settle their differences, with the influence of the Southeast acting as a counterweight in relation to the Northeast and the North, and so on.

What other projects could encourage the USP researchers to congregate more around the university?

All of the newly hired professors receive resources to meet their basic needs as an instructor as long as they provide evidence of having submitted a request for research assistance to FAPESP. The success of this program since 2010 has resulted in a seven-fold increase in terms of what we are investing and how much research support has been brought in.

Let's talk about rankings. Is USP going up in all of the rankings because the university has, in fact, improved, or because you are doing a better job of promoting this improvement?

I think the rankings are a result of both. The university has improved in some respects and in others, it has been better promoted. There are extremely objective rankings that do not depend on analyzing opinions, such as the Webometrics Ranking of World Universities. This ranking works with Internet traffic measurements and the quantity of documents available. We improved enormously in this ranking – USP ranks 15th. This improvement occurred partly because the university is better organized and partly because as the university becomes more well-known, Internet traffic increases.

And the other rankings?

Other rankings are based on performance. In an important ranking such as Shanghai, which places a high value on research, when we look at the scores, we see that USP has performed exceptionally well. Nevertheless, Shanghai uses additional important criteria when deciding which universities to place first and in these, we do not perform as well. They take into account the number of Nobel prize winners who teach at the university, the number of alumni who have been awarded the Nobel Prize and the Fields Medal, etc. These factors are important in the decision concerning Cambridge, Harvard, or MIT, but they can cause a huge imbalance when an institution has only one winner. For example, if a university that is previously ranked unfavorably hires a Nobel Prize winner, it will soar. Does that mean that the university has shown enormous improvement? No.

And the rankings that measure opinion?

Some rankings are undoubtedly more influenced by factors such as opinion. To evaluate research, good or bad, we look at data, the number of papers published, the number of citations and the impact of the journals. An evaluation is a combination of information that gives us

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an idea of how the research is going, at least for the experimental areas. Other evaluation tools have recently begun to emerge for the purpose of improving this process. There is Google Scholar, which is now having a greater impact on the social sciences. Sometimes, they resort to expert opinion.

It's just another criterion...

Subjective, but it is a criterion. The most valued ranking, whose results should come out in a few weeks, is the Times Higher Education (THE) ranking. The so-called prestige ranking makes up 30% of the overall ranking. That is, the THE ask a large number of people around the world what their evaluation is of the different universities. And this weighs in the final ranking. This aspect, the fact that USP has had more exposure, or better exposure, is perhaps what was most influential. What does someone in Paris or Hong Kong think of USP or other universities? This opinion may be influenced by knowing people from here, by visiting, or by having people from here visiting their university.

Do these opinions impact the Times Higher Education (THE) ranking?

They have a very positive impact. In the prestige ranking that THE published earlier this year, USP was ranked among the world's top 70. And it will certainly influence the ranking that is about to come out because 70% is an objective evaluation, which is indicators, and 30% is opinion.

What has been done at USP about the need to internationalize Brazilian research?

The road to more productive internationalization is to establish partnerships with a select group of universities. We chose some of them here at the Office of the Dean of Research and try to enter into agreements, set up joint seminars and then propose bilateral research projects. We are currently finalizing an agreement with the University of Toronto, Canada, one of the 15 or 20 best in the world, which includes joint conferences and public notices for collaborative research. The same is happening with other major universities.

Let's jump ahead here. We would like to know how your own research is going since you became dean?

It would be unrealistic to think that since I left to become chairman of the CNPq in 2007 and then went on to become Dean, I have kept up the same level of activity in the laboratory. The intense and personal involvement of daily checking the method, of personally seeing a result, redoing, setting up bench experiments, this I don't do anymore. On the other hand, there is a group of researchers who has been working with me for a long time, and I have discussions with them almost every week.

From your point of view, what is your greatest contribution to knowledge at USP?

I would divide my contribution into three fundamental

periods. In the initial phase, I went to Oxford University for a post-doctorate and returned able to perform basic biochemistry research involving hemoglobins. At Oxford, I worked with David Weatherall, one of the pioneers in the field of hemoglobinopathies. Working as a physician in Southeast Asia, he saw a large number of children with thalassemia, a very special form of the disease, and along with biochemist John Clegg, he investigated the basic mechanism of the disease. There was evidence that this disease was caused by an imbalance in the synthesis of the two chains of hemoglobin: alpha and beta. These chains are very similar, synthesized under the control of different genes. In normal individuals, there is a balance: two alphas and two betas form a chain of hemoglobin. These two scientists developed a method to measure the synthesis of these chains. With this measurement, they proved that there is an imbalance in thalassemia. When I returned to Brazil, I knew that these diseases were common here, and I began to study them. I found a large number of patients and was able to establish methods to diagnose and treat these diseases.

Was there any way to treat them back then?

There was not. It was very disorganized; there were no segment protocols, no treatment protocols... I became involved not only with research but also in organizing activities as well as treatment. I persuaded the Ministry of Health to establish a program to treat patients with sickle cell anemia. The program still exists today and has evolved to include neonatal diagnosis.

So it was a contribution both in terms of basic research and direct intervention in the application.

Exactly. There was another component of these diseases, such as in the case of thalassemia, which is a complex disease in terms of its treatment because it requires that the patient receive regular blood transfusions. There must be a place to take in and follow these patients on a monthly basis. One of the complications is the accumulation of iron in the body. At that time, there was only one drug that could eliminate this element, which had to be given by injection – an injection that took a long time. An infusion pump is normally used to do this, but there was no such thing in Brazil, nor was there any way to import it. A colleague, Sebastião Ismael, and I designed one of these pumps, which were fabricated back in the time of Ibexc (the Brazilian Institute of Education, Science and Culture) with Isaías Raw.

Is thalassemia less prevalent than sickle cell anemia?

It is roughly half as prevalent. The severe form of sickle cell anemia is due to the homozygous hemoglobin S gene. The prevalence of the heterozygote is approximately 2% of the population here in the state of São Paulo – it varies from place to place in Brazil because it was brought with the slave trade. The frequency is greater where you have a population with a higher incidence of African genes. Thalassemia is another type of change of the same beta gene so that when an individual is homozygous, s/he

has a very serious illness. This mutation came from the Mediterranean region, primarily Italy, Portugal, and Spain and, to some extent, from Lebanon.

Did these studies lead to another field of research, population genetics?

That is what happened. The world changed, and everyone began to study DNA. And in Ribeirão Preto in the 1980s, my group began to examine DNA related to some diseases, and then to population genetics. Our first study focused on the sickle cell anemia gene (beta S). In regions near the gene, there are elements, which we call polymorphisms, that define haplotypes. In the sickle cell anemia gene, depending on the location in Africa, the beta S gene is always the same, but the haplotype with which it is associated is different. When we look at blacks in the Brazilian population who have sickle cell anemia, we look at the gene and what is around it. This examination enables us to determine which part of Africa their ancestors came from and to reconstruct the history of the slave trade in Brazil. Once we performed this reconstruction, we were in for a surprise. The pattern of Africans who were brought to Brazil is very different from those who were taken to the United States. We were the first to demonstrate this difference.

And did this work demonstrate which region of Africa they came from?

Yes, it did. Approximately 60% came from regions with the Bantu haplotype, that is, Mozambique, the Central African Republic, Angola and South Africa; 30% to 35% came from the Benin region; and 1% to 2% came from the region of Gambia and Senegal. In the United States, the prevalence is approximately 60% from Benin, 15% from Senegal, and 15% from Gambia. After we performed this study, I found a book called *The Atlantic Slave Traffic* by Philip Curtin, who on the basis of working with primary source documents from the ports of departure and arrival, showed numbers that were identical to ours.

And did your third phase involve genomic contributions?

Yes, at that time I was out of medicine, and I had a group that addressed issues of molecular genetics and population genetics, when it began sequencing the bacterium *Xylella fastidiosa*, in 1998, which was an important milestone for Brazilian science.

Did your laboratory own any of this technology?

Yes, but the genome program focused attention on the work, and this has helped us significantly. After *Xylella*, we spliced into the cancer genome with Ricardo Brentani of the Cancer Hospital and Andrew Simpson of the Ludwig Institute. At the same time, the opportunity arose in 2000 to organize ourselves around an RIDC, and we decided to invest in cell therapy and stem cells. We were very successful, and we made progress on things that were not known at the time. Mesenchymal cells, for example, were regarded as exclusively deriving from bone

marrow. We were the ones who showed that these cells are found in the umbilical vein, in the saphenous artery, and then we described how they are found in virtually all fetal and adult tissues because the cells are present on the outside of the small vessels known as pericytes. We made an important contribution to this type of knowledge.

Is your work cited more often?

The most cited is the sequencing of the *Xylella*, for which there are more than 100 authors. The second is the world's first analysis conducted on the gene expression pattern of mesenchymal cells in 2003. And, the third is the work showing that mesenchymal cells, obtained from very different sources, have a pattern and property that are very similar to fibroblasts and pericytes.

You lived through a phase of genomic euphoria and live in the current phase, where it's clear that there is still a long way to go. How do you see this issue today?

That is the way it always is in science. I wrote a book with Covas Dimas called *Stem Cells, the New Frontier of Medicine*, about cell therapy. I say in the preface that exaggerated enthusiasm, largely inflated by the press, occurs repeatedly. I warned that there was, at that time in 2006, an expectation that was absolutely unrealistic regarding stem cells, as if they were going to save humanity over the course of just a few days. The technique of producing strains of embryonic stem cells is very difficult. It was the same thing with genomics. It is hard to see a work of molecular cell biology today that does not involve gene sequencing. And to think that gene sequencing will solve the entire question of knowledge with regard to biology would be very naive.

USP has performed exceptionally well in the Shanghai ranking of scores

But there has been progress.

History shows that no scientific question can be answered with one technique or a single discovery. We take one step forward and we increase our knowledge. However, today, we already have a drug sold in pharmacies that was developed because they took a neoplastic gene, sequenced it and discovered that it was a hybrid gene that altered the synthesis of a particular protein. The pharmaceutical industry has produced an inhibitor that is used orally that impedes the gene function – and the individual recovers from the disease. So yes, genomics has produced results and will continue to do so. The yellowing disease caused by *Xylella* has not yet been cured, but that is minor compared to the benefits we have already achieved. ■