Genomic Psychiatry

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INNOVATORS & IDEAS: RESEARCH LEADER

Mayana Zatz: Two critical questions take center stage – Which variants mitigate the impact of lethal mutations in severe conditions with mild phenotype? What factors contribute to the health and longevity of centenarians?

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Mayana Zatz has been a Professor of Genetics at the Institute of Biosciences, University of São Paulo (USP), Brazil, since 1982. She became an assistant professor after a postdoc at the University of São Paulo and a second postdoc at the University of California, Los Angeles. Her current research is focused on neuromuscular disorders, aging, genomics, and, more recently, xenotransplantation and the use of the Zika virus as an oncolytic therapy against brain tumors. Functional studies are done in genetically engineered mouse and cell models. She is particularly interested in investigating protective mechanisms in rare patients with Duchenne dystrophy and a milder clinical course, as well as in centenarians' health determinants. Mayana Zatz is also involved in ethical aspects of genomic studies and government political decisions related to science. Professor Zatz is pleased to offer our readers insights into her personal and professional experiences.

Part 1: Mayana Zatz – Life and Career

Could you give us a glimpse into your personal history, emphasizing the pivotal moments that first kindled your passion for science?

I have been fascinated with science for as long as I can remember, and I loved reading the biographies of famous scientists such as Madame Curie or Pasteur. In high school, I fell in love with genetics. It was in the pre-molecular era, but I was intrigued by how genetic traits were transmitted across generations. I decided to pursue these studies in my adult life.

Figure 1. Mayana Zatz, PhD, University of São Paulo, Brazil.

We would like to know more about your career trajectory leading up to your most relevant leadership role. What defining moments channeled you toward that leadership responsibility?

When I started to study genetics, I did not imagine I would be a leader. My ambition was to pursue a career as a geneticist at the University of São Paulo, which was and still is the best Brazilian University. After returning from my postdoc at the University of California, Los Angeles, I submitted a small grant to FAPESP (São Paulo Research Foundation, in Portuguese: Fundação de Amparo à Pesquisa do Estado de São Paulo), our leading research funding agency, to continue my research on muscular dystrophies. DNA technology was unavailable; therefore, my studies used serum enzymes to investigate different forms of muscular dystrophy. I started forming a group of young students, primarily undergraduates, interested in this subject. One day, I was invited to a meeting at FAPESP, and I learned that only scientific leaders had been invited. That was when I realized that I was considered a leader and that I had a greater responsibility.

Please share with us what initially piqued your interest in your favorite research or professional focus area.

My initial interest was muscular dystrophies. A turning point in my career was when a young woman who had three nephews affected by Duchenne dystrophy came to me for advice. She was getting married and worried about the possibility of having affected sons. At that time, nobody was working with muscular dystrophies in Brazil, and it attracted my interest. I wanted to understand the clinical variability among different forms of muscular dystrophies and the underlying genetic mechanisms. I also aimed to estimate the genetic risks for healthy female relatives to have affected sons. With my colleagues, Maria Rita Passos Bueno and Mariz Vainzof, we identified several novel genes responsible for neuromuscular disorders. Later, we discovered that patients with the same pathogenic mutation could have a highly variable course, showing that other factors could modulate the phenotype. Since then, my research has focused on studying protective genetic variants in sporadic patients with Duchenne muscular dystrophy who are not as weak as one would expect from examining their genotype. We are also generating mice models carrying candidate modifier variants. Understanding the underlying "protective" mechanisms could open new avenues for treatment. More recently, my research focus has been on healthy centenarians. We are doing functional studies with IPS-derived cell lines from these centenarians. One intriguing question is whether they have genetic variants similar to top athletes.

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What impact do you hope to achieve in your field by focusing on specific research topics?
I hope to find novel therapies for muscular dystrophies if we can understand the protective mechanisms against the effects of pathogenic mutations. In the case of centenarians, we are also trying to understand the role of protective aging variants and whether their product could help promote healthy aging for people who were not born with these protective variants. I decided to focus on centenarians because it is known that genetics plays a significant role in older people's resilience, particularly after the age of 90.

Please tell us more about your current scholarly focal points within your chosen field of science.
I am coordinating several projects on the subjects I just described: Duchenne muscular dystrophy, centenarians, genomics, and ethics. I am also involved in two other projects: xenotransplantation (aiming to use genetically modified pigs as organ donors), and using the Zika virus as an oncolytic vector against brain tumors.

What habits and values did you develop during your academic studies or subsequent postdoctoral experiences that you uphold within your research environment?
In my research environment in Brazil, one must be prepared to deal with much bureaucracy; therefore, you need to manage frustration and be resilient. However, in São Paulo, where I live, we have an excellent research funding agency, FAPESP. Therefore, we are in a much better situation than scientists from other Brazilian states. I believe that contact with patients is precious for enhancing research motivation. Knowing the story behind the sample you are working with and the hope patients put into your research gives you a tremendous sense of responsibility. You know that you have to try your best.

At Genomic Press, we prioritize fostering research endeavors based solely on their inherent merit, uninfluenced by geography or the researchers' personal or demographic traits. Are there particular cultural facets within the scientific community that warrant transformative scrutiny, or is there a cause within science that deeply stirs your passions?
In Brazil, the main challenge is to increase funding for science. Another significant challenge is to have a dramatic cost reduction in newly developed treatments for rare diseases, such as spinal muscular atrophy, hemophilia, or sickle cell disease, in order to make them available to all patients.

What do you most enjoy in your capacity as an academic and research leader?
Being a scientist is fascinating. When you understand a question, you open many others, and it is like playing an endless puzzle. You never get bored because what drives our motivation are the questions. What moves us as scientists is our tremendous curiosity. I love to discuss ideas with my students or try to solve problems while jogging in the morning. Also, I love it when young students approach me and say that they decided to be scientists because of my influence.

Outside professional confines, how do you prefer to allocate your leisure moments, or conversely, in what manner would you envision spending these moments given a choice?
I like to read primarily biographies of interesting people; I love traveling and good movies. I love to be with my family and friends.

Part 2: Mayana Zatz – Selected questions from the Proust Questionnaire[1]

What is your idea of perfect happiness?
I do not believe in perfect happiness. We have moments when we are delighted and others when we may be sad.

What is your greatest fear?
To lose my independence or cognitive capacity with aging.

Figure 2. Mayana Zatz and Laura, a 104-year-old swimming champion.

Which living person do you most admire?
I hold great admiration for several pioneers in genetics, notably Shinya Yamanaka, Emmanuelle Charpentier, and Jennifer Doudna.

What is your greatest extravagance?
Spending on traveling.

What are you most proud of?
My children and grandchildren and also some of my former students who became great scientists.

What is your greatest regret?
Not having more children.

What is the quality you most admire in people?
Honesty and courage.

What do you consider the most overrated virtue?
Modesty.

What is your favorite occupation (or activity)?
Scientific research.

[1]In the late nineteenth century, various questionnaires were a popular diversion designed to discover new things about old friends. What is now known as the 35-question Proust Questionnaire became famous after Marcel Proust's answers to these questions were found and published posthumously. Proust answered the questions twice, at ages 14 and 20. Multiple other historical and contemporary figures have answered the Proust Questionnaire, such as Oscar Wilde, Karl Marx, Arthur Conan Doyle, Stéphane Mallarmé, Paul Cézanne, Martin Boucher, Hugh Jackman, David Bowie, and Zendaya. The Proust Questionnaire is often used to interview celebrities: the idea is that by answering these questions, an individual will reveal his or her true nature. We have condensed the Proust Questionnaire by reducing the number of questions and slightly rewording some. These curated questions provide insights into the individual's inner world, ranging from notions of happiness and fear to aspirations and inspirations.

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Where would you most like to live?
I love the place where I live now.

What is your most treasured possession?
My house.

When and where were you happiest? And why were you so happy then?
When my daughter was born. I wanted to have a girl as I already had a son. And right before she was born, I finished writing my PhD thesis and moved to the house where I now live. I remember that coming from the hospital with her into my new house was the happiest moment in my life.

What is your most marked characteristic?
I am incredibly driven.

Among your talents, which one(s) gives you a competitive edge?
Creativity, not giving up quickly, and not being afraid to test new ideas.

What do you consider your greatest achievement?
My scientific career.

If you could change one thing about yourself, what would it be?
My age.

What do you most value in your friends?
Sincerity.

Who are your favorite writers?
George Orwell (1984) and Walter Isaacson (biographies).

Who are your heroes of fiction?
Forrest Gump.

Who are your heroes in real life?
My greatest hero was Nobel laureate Rita Levi-Montalcini, who died at age 103 while still active.

What aphorism or motto best encapsulates your life philosophy?
Never believe that you have achieved the best. There is always room for improvement.

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