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PEOPLE & IDEAS

Gustavo Silva: Translating the ubiquitin code

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Silva investigates how ribosomal protein complexes are regulated by K63 ubiquitination.

A "bouncing rubber egg" made by soaking an egg in vinegar to dissolve the shell and denature the egg white was Gustavo Silva's first introduction to science. Although this was an experiment in a chemistry set given to his brother, Silva was more excited by the present and ultimately became a researcher while his brother took up professional boxing. Silva remembers, "after playing with the rubber egg, we realized—in the worst way possible—that the egg was still raw on the inside. We used to keep the egg inside one of our clothes' drawers and we got in big trouble when that egg broke!" Although further egg experimentation might have been forbidden by her, Silva's mother was a key influence on his career path while growing up in Sao Paolo, Brazil. She provided the emotional support, instilled the value of education, and helped develop the confidence necessary to lead Silva to pursue his dreams of a career in science.

Silva recently started his own group at Duke University, North Carolina, and we contacted him to find out more about his plans to investigate how protein dynamics control stress responses.

When did your interest in science begin?

Interestingly, biology was not my favorite subject. Biology classes relied heavily on memorization and I was always more motivated by challenges, competitions, and problem-solving subjects. For that reason, I was initially drawn to math and chemistry. Although I thought the mysteries of life were fascinating, I had no idea how to solve them. In high school I was exposed to some laboratory activities but for most of the questions I had, my teacher told me I would have to go to college to find the answers, and so I did.

My discovery of the scientific method as a way to build knowledge and of science as a possible career happened in my first year at the University of Sao Paulo while attending a Genetics course. It was amazing to learn about the history of modern genetics and the contribution of outstanding geneticists. The course involved a project performing classic *Drosophila* genetic crossing to analyze allele segregation. Doing genetics in "real life" was mind-blowing! I ended up applying for an undergraduate research position with my genetics professor, Dr. Luis Netto, and investigated the regulation of the proteasome and protein degradation in response to oxidative stress. I still remember the excitement of seeing the bands of my first PCR, which is a feeling that will always remind me of the beauty of science. We published a paper on the chemical mechanism regulating a redox posttranslation modification (PTM) of the proteasome (1) and that was when I realized that science was something I could see myself doing for the rest of my life.

What drew you to study proteostasis?

There is a lot of emphasis on the role of gene expression in cellular physiology, with the role of protein synthesis and degradation underestimated on many occasions. As a student, I focused on the proteasome and its central role in degrading damaged protein during oxidative stress (2, 3). I was super excited about the major biological questions of which proteins were being ubiquitinated and degraded in vivo, the molecular pathways impacted, their cellular importance during stress response, how this whole system was regulated, and much more.

In graduate school I used mass spectrometry to identify PTM in the proteasome (2). I was fascinated by the power of this methodology and how I could use proteomics to evaluate ubiquitin's roles in the oxidative stress response at the systems level. I searched for postdoctoral positions where I could learn more about proteomics. I landed in the laboratory of Christine Vogel, then a young assistant professor (now tenured) starting her group at New York University. Christine was always very supportive of my research ideas and desire to study the ubiquitin proteasome system as a key regulator of protein abundance. I showed that a unique type of ubiquitin chain linked by its own lysine 63 (K63) accumulated in response to stress, in a proteasome-independent fashion (4). We identified ribosome proteins as K63 ubiquitin's main target, which enhances their stability and cellular resistance to stress (4). I became very interested in understanding the molecular mechanism by which ubiquitin controls the opposing processes of protein synthesis and degradation, the cradle and the grave. Understanding these pathways is key to understanding the progression and development of many stress-related diseases such as Parkinson's and Alzheimer's.

Gustavo Silva. Photo courtesy of Andrew Gorman.

What are you currently working on and what is on the horizon?

My laboratory is focused on solving what I call the Rubicode—the ribosome ubiquitin

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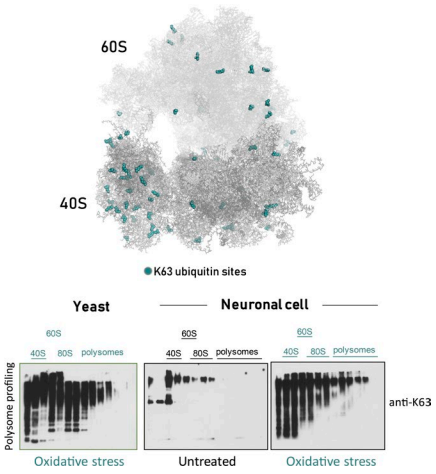


The 3D structure of the ribosome with sites for K63 polyubiquitin marked in teal and K63 ubiquitin immunoblot of polysome fractions from yeast and neuronal cells exposed to oxidative stress. Image courtesy of Gustavo Silva.

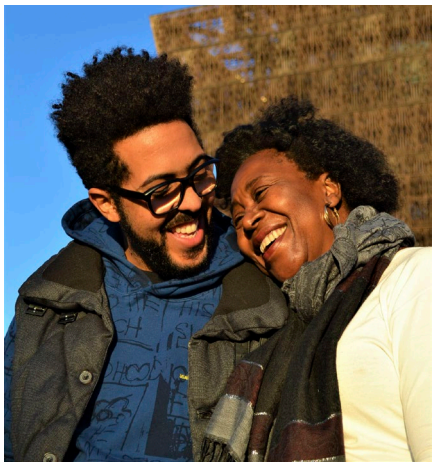
code. The ribosome is a hub of distinct ubiquitin linkages, whose dynamics depend on multiple ubiquitin enzymes and serve a multitude of biological functions. To solve this ubiquitin ribosome code, my research combines proteomics, next generation sequencing, cryo-electron microscopy, and cellular and molecular approaches to characterize ubiquitin's role in translation control. Specifically, we focus on understanding how K63 ubiquitin impacts ribosome structure and function, regulates the reprogramming of translation, and supports cell viability in response to stress. We developed a proteomics method to identify and quantify the precise ribosome sites modified by K63 ubiquitin, which provided multiple insights into how ubiquitin impacts translation (5). Furthermore, other types of ubiquitin linkage, like K48, also accumulate in response to stress, and we are interested in understanding how those different systems regulate multiple aspects of protein dynamics and cellular health. Most of our research has been developed using budding yeast as a model organism; however, K63 ubiquitin also modifies ribosome proteins in human cells and we are very excited to use all the molecular knowledge produced in yeast to understand how this system is regulated and supports cell viability in higher eukaryotes.

What did you learn during your training that prepared you for being a group leader?

I had an incredible opportunity to join a young laboratory as a postdoc, which helped enormously in my preparation to become a group leader. My mentor, Christine Vogel, was very transparent and honest about the joys and challenges of the profession and I learned a great deal by witnessing firsthand how she navigated her own tenure process. Christine was instrumental in developing my grantsmanship and understanding of different funding mechanisms. She supported my attendance at many career development workshops and coached me in applying and interviewing for faculty positions, for which I am forever grateful. The job of a group leader requires multiple management skills and Christine is a great communicator and very diplomatic when dealing with a variety of management issues in the laboratory, which made me realize mentoring is an individualized process and we must detach ourselves from a "one size fits all" model. This does not mean trainees should not be held accountable for their careers, but we have a mission and responsibility to be attentive, sensitive, and provide the best support possible to nurture their talents and aspirations.

The website for your group has an excellent section dedicated to diversity and inclusion. What challenges need to be overcome to stop certain groups from being marginalized in science?

We need to create a culture where every member has the responsibility to participate in and contribute to developing a more equitable space if we truly believe that science should be based solely on merit. We must understand that shying away from actions toward equity helps perpetuate all the inequalities in the system, preserving the privileges and benefits of select groups. Unfortunately, being aware of our implicit biases does not prevent us from acting on them (6). We also need to foster a climate that is inclusive and respectful of all differences, where everyone can have a fair shot and perform to the best of their abilities. But, unfortunately, the weight of fixing the culture currently falls disproportionately on people from underrepresented groups. As faculty, we advance our career with our scientific progress, our teaching commitment, and service. However, faculty from minority groups are the ones expected to put in the work and come up with solutions to improve the issue of underrepresentation, a burden that should not be carried only by already disenfranchised groups.



Gustavo Silva and his mother Marlene Simões. Image courtesy of Ivan Prates.

But it is also important to understand that most of us are trained exclusively as scientists for decades and that we would benefit tremendously from training and supervision from experts to become aware of our biases, to implement mitigation strategies, to become equipped to promote equity, and to become knowledgeable enough to answer questions like: How do we judge candidates' success and potential during any selection process when they come from very distinct environments and possibilities? How do we provide fair treatment and equal opportunities? How do we effectively mentor individuals from different backgrounds? How do we develop and foster the cultural capital and professional networks required to succeed in this career?

Although individual efforts have been a powerful source of transformation, structural changes must be attained to level the playing field and provide equal opportunities to all scientists who are impassioned and devoted to a career in the sciences. For example, I am particularly excited about the Black Think Tank initiative we are leading at Duke to connect black faculty on campus, enhance community-building, provide mentorship and resources, and foster multidisciplinary research across schools.

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