FACES OF MASS SPECTROMETRY / Francisco Fernandez-Lima

Kristin Elise Phillips, Health and Science writer at the University of Texas at Austin

November 2018

Improving Mass Spectrometers

During a phone conversation and while describing how to squeeze sailing into an intense schedule, ***Francisco Fernandez-Lima*** *betrayed a bit of his personality by spontaneously inviting a complete stranger to visit Miami.*

Francisco (Fernandez-Lima insists on first names J) grew up surrounded by the sea in Havana, Cuba where he studied nuclear physics at what is now the Instituto Superior de Tecnología y Ciencias Aplicadas. It is this background that gives him the edge as a developer of new mass spectrometry (MS) technology.

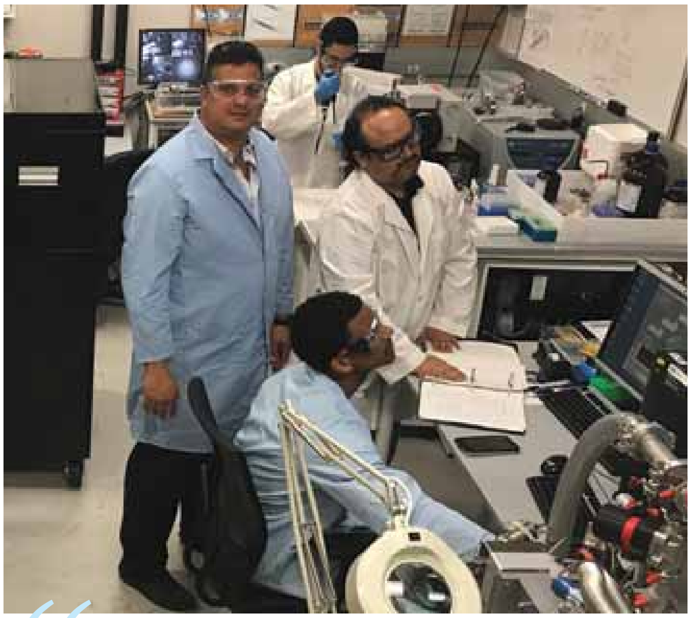
"My background started with physics and then slowly merged into chemistry and biology," Francisco –now an Associate Professor at Florida International University (FIU) – explains so rapidly that words compete to be heard. "Mass spectrometry is a perfect bridge between medicine, biology, chemistry, and physics."

After building mass spectrometers as a doctoral student of Enio Frota da Silveira at Pontifícia Universidade Católica do Rio de Janeiro [Fernández-Lima, F.A., et al., Applied Surface Science. ***217****, 202-209 (2003)], Francisco truly began to incorporate chemistry and biology into his research as a postdoctoral fellow in the research groups led by Texas A&M professors David H. Russell and Emile A. Schweikert. He spent a total of five years in Texas, the last two as a K99 NIH fellow. At FIU since 2012, Francisco has quickly distinguished himself through his groundbreaking research, receiving numerous awards including an Emerging Investigator Award from the Florida Section of the American Chemical Society (2017), and a National Science Foundation CAREER Award (2017). In 2015, he was an invited contributor to the "Emerging Investigators" Focus Section of the Journal of the American Society for Mass Spectrometry (JASMS).*

What are you developing for mass spectrometry instrumentation?

It has been an interesting journey. There is a point where the instrument can be the limiting factor in research. We don't have a natural way to increase molecular detection while working with biological problems at the cellular level, so the options are to improve the resolution, sensitivity, and ionization yield of the instruments, or their coupling to orthogonal analytical techniques.

For example, we have been working on the development of a trapped ion mobility spectrometer (TIMS) in collaboration with Bruker Daltonics colleagues Dr. Mark E. Ridgeway and Dr. Melvin A. Park [Fernandez-Lima, F.A., *et al., Int. J. Ion Mobil. Spectrom.* **14**, 93-98 (2011)]. This work started in 2011 when I was a postdoc in Texas; I already had a very well-defined idea of the type of instrumentation that I wanted in my laboratory at FIU. Over the last five years, we have been working very intensively to improve the hardware, acquisition protocols, coupling to different MS analyzers (e.g., TOF and FT-ICR) and potential applications. We have the highest reported mobility resolving power (R ~400) [Adams, K.J., *et al., Int. J. Ion Mobil. Spectrom*. **19**, 69-76 (2016)], which is five or six times larger than any other commercial instrument. The TIMS technology became available in the form of TIMS-q-TOF MS in 2016 and is being now mainly marketed for proteomics research, but it can also be used for forensic, environmental, metabolomic, and lipidomic research, and structural biology. The versatility of TIMS-MS allows for its use in pretty much any field that requires the separation of complex mixtures by their isomeric and mass content. Some of the recent applications we have researched using HPLC-TIMS-TOF MS include opioid detection in urine, and metabolites in blood – with better sensitivity than traditional MRM analysis [Adams, K.J., *et al., Int. J. Mass Spectrom*. **427**, 133-140 (2018)].



"I see the importance of not taking everything for granted."

What challenges have you faced on your career path?

I was trained in a research environment that did not have a lot of money. Back when I was a Ph.D. student in Rio de Janeiro, we custom-built TOF mass spectrometers from the ground up. So, starting there to where I am now, I see the importance of not taking everything for granted. I tell my students that they have access to the best instruments in the world and they should produce like they have the best instruments in the world.

We still need better, faster and more sensitive and reliable MS instruments. There are a lot of things that we couldn't do 20-40 years ago because the technology was not there. You listen to the old folk stories that they could smoke a cigar while a machine analyzed one spectrum. Now we can get millions of spectra in the same time frame, and the challenge is how to account for the biological diversity and complexity.

What is the current research focus in your lab?

We have three main areas of research in my group.

The first is mass spectrometry imaging (MSI). Our focus is on 3D single cell ultra-high-resolution mass spectrometry. MSI is natural when you work with biological surfaces. MSI allows the mapping of the molecular components without the need for labels; during MSI we can learn about how the function and structure relates to chemical composition. One recent application of 3D-MSI focused on the delivery of drugs inside cells because drugs that reach the target preferentially are less toxic [Vanbellingen, Q.P., *et al., J. Am. Soc. Mass Spectrom*. **27**, 2033-2040 (2016)].

The second area of research is the huge niche of structural biology, with emphasis on the interaction between proteins and cofactors. We look at systems that are dynamic—like membrane proteins or intrinsically disordered proteins—that can be better tackled by MS when compared to traditional techniques (e.g., XRD and NMR).

The third focus is on the separation and characterization of complex mixtures, with applications in environmental analysis like dissolved organic material [Benigni, P., *et al., Anal. Chem*. **87**, 4321-4325 (2015)], petroleomics like crude oils and transformation products [Benigni, P., *et al., Environ. Sci. Technol*. **51**, 5978-5988 (2017)], forensics like explosives [McKenzie, A., *et al., Analyst*. **140**, 5692-5699 (2015)], proteomics like peptide biomarkers [Garabedian, A., *et al., J. Am. Soc. Mass Spectrom*. **29**, 817-826 (2018)], metabolomics such as metabolites in blood, and clinical analyses like opioids in urine [Adams, K.J., *et al., Talanta*. **183**, 177-183 (2018)]. During complex mixture analysis the main challenge is the separation and identification at the molecular level, which usually requires the identification of thousands to millions of compounds in a single analysis.

What do you enjoy outside of the lab?

In my lab, we are hands-full: at any time, I have a lot of undergraduates, six to eight graduate students and a couple of postdoctoral fellows. It is always a challenge to find the time to do everything. But I have learned that, if you get a job where you have everything that you need, you can be fortunate with the few moments that you can spare outside the lab over the weekend. I was raised on an island, so I enjoy being close to the sea. Miami is a really nice place with natural attractions and weather that is a privilege. I don't need to go far to appreciate the ocean: I can easily go to the Everglades, to a beautiful sandy beach, for a nice scuba dive or enjoy sailing the Florida Bay.

What are your future plans?

I'm still learning. My goal as a scientist is to use the tools that we have to improve the state-of-the-art and provide better solutions to clinical and medical problems. The work in our lab benefits greatly from collaborations. We have collaborators from clinicians to people who synthesize new molecules, and we—by measuring compounds and providing the final characterization—are that last link that confirms whether the hypothesis is true. This work makes you realize where the analytical needs are and where we need to improve the mass spectrometry technology.

I enjoy working with students. FIU is a minority-serving institution, so many of our undergraduates are first generation college students. I take this very close to my heart and am glad that they have the opportunity to work in a lab that is at the top of the world.