FACES OF MASS SPECTROMETRY / Benjamin A. Garcia

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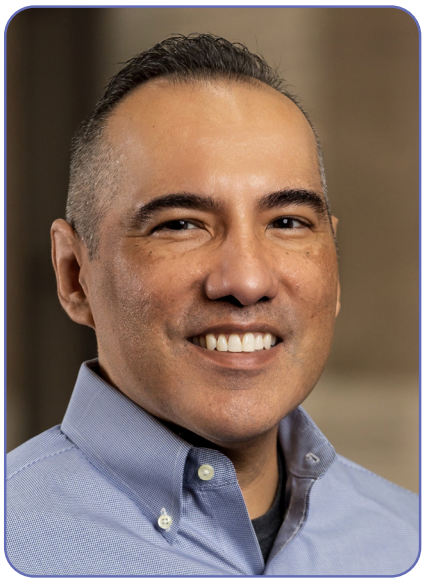

Building Connections that Make a Difference

Ben Garcia is the Raymond H. Wittcoff Distinguished Professor and Head of the Department of Biochemistry and Molecular Biophysics at the Washington University School of Medicine in St. Louis. He previously served on the faculty at Princeton University and the University of Pennsylvania School of Medicine, where he was appointed Presidential Professor in the Department of Biochemistry and Biophysics.

Throughout his career, a fundamental research interest for Ben has been the study of protein and nucleic acid modifications using advanced mass spectrometry techniques. His pioneering work in this field has led to numerous awards and achievements. Notably, Ben received the ASMS Biemann Medal in 2018 for his contributions to the study of posttranslational modifications to histone proteins.

Ben is passionate about promoting inclusive access to resources and opportunities for members of underrepresented minority groups in the science community. He was a founding member of the ASMS Diversity and Inclusion Committee, and he has recently helped with the launch of the Hispanic and Latinx in Mass Spectrometry special interest group.

Commitment to mentorship is another core value for Ben. He is dedicated to helping others navigate the questions and challenges that he too confronted at earlier stages of his career. For younger scientists, Ben emphasizes the importance of staying focused on the research topics they most enjoy. He also recommends taking full advantage of every networking opportunity and reminds us that there are many established professionals who are eager to help the next generation build connections, overcome barriers, and professionally succeed.

How did you get your start in mass spec? How did you come to your current position at Washington University in St. Louis?

I'm originally from Southern California, but I transferred from a community college to Northern California to complete my undergraduate degree at UC Davis. While I was there, I met a professor, Carlito Lebrilla, who was an analytical chemist and mass spectrometry expert. I was very lucky to have been selected for a summer research program that placed me in his lab. That is where I first started in terms of understanding what a mass spectrometer was and can do. From there, I worked for a year in a small biotech company called Sequenom, and I got to learn a lot more about mass spectrometry there. I then met Professor John Yates who came to give a talk at our company. He mentioned to me, "If you want to go back to graduate school, you might want to touch base with my former advisor, Don Hunt, at the University of Virginia. Don Hunt was also suggested by another researcher, Jack Beauchamp, with whom I briefly worked over the summer at Caltech as well. So, I ended up at UVA for my PhD studies, and I worked heavily in protein post-translational modification analysis.

I wanted to continue down that path, so I went onto a postdoc with Neil Kelleher at the University of Illinois. That was a fun time, and I got to extend my training to learn top- and middle-down mass spectrometry. From there, I was hoping to stay in academia, so I applied for a few faculty positions and landed as a junior faculty at Princeton University. I was then recruited to the University of Pennsylvania School of Medicine, which was a scientifically driven decision, as our research was crossing more and more into human health and disease. At UPenn, I co-directed the graduate program in Biochemistry and Biophysics, which, along with other leadership positions, helped to get me ready for my current position as the Head of the Biochemistry and Molecular Biophysics Department at Washington University. In this role, I really enjoy starting programs and initiatives to improve the lives of students and postdocs.

When, and how, did you decide to focus on protein and nucleic acid modification?

When I was starting out working in mass spectrometry, I was looking at the interactions of peptides with oligosaccharides or carbohydrates. Analysis of oligosaccharides by MS was really

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Dave Piston (Head of the Cell Biology and Physiology Department at the Washington University School of Medicine) presenting Ben's department (Biochemistry and Molecular Biophysics) with the Garcia-Piston Cup Trophy for winning the annual softball game. (Photo courtesy Ben Garcia.)

difficult, so I kind of thought, "Maybe there are other things that might be important and maybe easier to analyze." When I finished my undergraduate work at UC Davis, it was the year 2000, which was also the year that the human genome was sequenced. So, that was obviously a very big deal at the time. At first, I sort of naively thought, "Maybe we know everything about the genome now, maybe I should now study all the proteins the genome encodes." In reality though the proteomics field was just getting started. But there were people in the country—such as my advisor at UVA, Don Hunt—who were using mass spec to sequence proteins and very complex biological mixtures.

So, that's initially what got me started in the proteomics field. The nucleic acid work in mass spec is something that has been developed a lot more recently, probably within the past four or five years in my lab. There has been a lot of MS studies performed in the past, including work from the McCloskey lab in the 80s and 90s, and others who have also devoted their careers to investigating nucleic acids such as Pat Limbach and Dan Fabris. However, next generation genomics sequencing techniques besides mass spec have come forward, and most people use those approaches to sequence RNA or DNA. Now, though, there's a resurgence of using mass spec for looking at modifications on these molecules—so, that has intrigued my interest in going back to the future and analyzing nucleic acids by MS.

Which diseases do you hope that your work will one day help to treat or cure?

I think all scientists are hoping that our research—even the most basic science research—is laying out the foundations of how biological mechanisms can operate in normal and disease states. In my lab, however, we do have some applications to specific diseases. We've been very interested, for example, in soft tissue sarcomas, which are cancers. Most are fairly rare, but there's a whole host of them that have mutations to the proteins that we have been interested in for a long time, which are proteins involved in epigenetic regulation. We've been able to identify some really interesting reprogramming of the epigenome using quantitative proteomics in patients with these mutations. We are starting to work with sarcoma clinicians to see if these targets that we have found can be inhibited to reduce tumor burden in mouse models, and we hope to keep progressing in this work to someday begin an eventual clinical trial.

For which achievements did you receive the 2009 ASMS Research Award and the 2018 ASMS Biemann Medal as the first underrepresented minority (URM) recipient?

The 2009 ASMS Research Award was very early on in my independent career. It was awarded to me for methodology we were proposing to identify combinatorial modifications on histones. These modifications impact the function of histones to control gene expression. Therefore, if these modifications' patterns are disrupted, this is when you can potentially have a disease state. But these proteins aren't just modified with one or two modifications at the same time—they have numerous modifications. Our lab has pioneered mass spectrometry approaches using middle-down and top-down proteomics to really understand which combinations of modifications occur together at the same time. The Biemann Medal was awarded as a culmination of a lot of the work we've been doing in the

I never dreamed I'd get this far, but it was all because of the great support from many people around me.

Ben with his daughter, Audrina, at a father/daughter dance. "Audri" is the youngest, at age 11, of Ben's 4 children. (Photo courtesy Ben Garcia.)

lab—not just the combinatorial modification analysis, but also many other advancements in technology and methodology for characterizing these histone modifications and all of the biology and biomedical problems that we have been able to solve with our MS approaches.

What advice would you give to other members of the Hispanic community who are looking to make their mark as scientists?

In mass spectrometry, like in many other areas of science in general, there is currently an issue with diversity. Underrepresented minority (URM) scientists often look at everyone in the field and say, "There really aren't a lot of people who look like me." Even at bigger conferences, it can be hard to find other Hispanic scientists, and the same is likely true for members of other minority communities. While that can be tough, I would encourage other Hispanic scientists, and URM scientists in general, to take advantage of networking at these conferences—as other URM scientists are definitely there, but they're just kind of spread out and harder to find. I would even say that if there are any role model scientists you'd like to meet at a conference, to email them ahead of time and see if you can carve out a short time to meet. If you can't make it to the conferences, try networking through email or social media. Don't be shy to reach out to people whom you know have made it to a higher level that you want to reach in the future—many scientists are very approachable and are trying to help folks whose position we might have been in years ago!

What advice would you give to young scientists beginning their career in mass spec?

Again, it's really all about the networking—even just introducing yourself to someone for 10 seconds might get you on their radar. Then, the next time your name comes up, they might remember, "Oh yeah, I met that person before." But I would also encourage younger scientists to just pursue the specific fields that they have a passion for and not worry so much about what's currently trendy. Being in the fields of mass spec–based proteomics and epigenetics, people often say to me, "Wow, you chose these two fields well for your future career." And that's because they have been two pretty important fields. However, at the time that I chose those fields, they were just emerging, and I really just continued doing the science that I happened to enjoy—I didn't pay attention to what others were saying I should be working on or thinking about. Doing what I love (mass spectrometry), I feel like I've almost never had a day of work in my life—every day in the lab is just a fun time filled with many discoveries.

How has your work in the ASMS Diversity and Inclusion Committee, and in the ASMS Hispanic and LatinX in Mass Spectrometry special interest group, helped to promote encouraging more underrepresented scientists?

I have been very grateful that ASMS was willing, probably around 2015 or 2016, to really have some sit-down meetings with a handful of stakeholders who were wanting to improve and enhance diversity within the Society. That led to a few of us starting the ASMS Diversity and Inclusion Committee, with a goal of highlighting the diversity of the Society. As I mentioned before, when you first walk into a conference such as at the annual ASMS conference, you might not see a lot of diversity—but it's there! So, we wanted to highlight that. The Diversity Committee wanted to keep accurate society demographics and be transparent about them. We also wanted to acknowledge our shortcomings and work as a group to improve them. There have been several individuals who have been involved in the ASMS DEI Committee (past and present) and have worked to highlight diversity in the Society and present it yearly to the ASMS membership. I was the first co-chair of the committee, along with Rena Robinson. Since then, I've rotated out of that position, but I'm really happy to see the committee continuing to be active.

After several years of working on the committee, I thought, "It might be time to bring an even smaller collection of people together, who are specifically Hispanic or LatinX scientists." A few friends who are also Hispanic scientists in the mass spec field started the Hispanic and LatinX in Mass Spectrometry special interest group. We created an evening workshop at the last ASMS conference where some scientists related their struggles and personal journeys to get to where they are now. There was a lot of positive feedback, and from there, it just kind of snowballed—it has been great to see a lot of these efforts really taking off!

Tell us about the session you recently organized to honor Marie Daly, the first African-American female to earn a PhD in Chemistry?

During my involvement in the American Chemical Society Division of Analytical Chemistry, while working with others and brainstorming different things we wanted to do, we felt it was really important to have more diversity sessions at ACS national meetings, as I touched on before. We've been highlighting the diversity trailblazers that have come before us—as the younger scientists might not know the stories behind those pioneers. So, while working with the diversity committee within the ACS Analytical Division, we discussed Marie Daly, and her amazing life and career, as she really overcame so many barriers. And she didn't just earn her PhD and then simply disappear from the scene—she continued to contribute to so many scientific discoveries. For instance, she helped our understanding of the relationships between clogged arteries and cholesterol, and she even helped characterize nuclear biomolecules, such as the histones that I love, which is one of the main reasons I was attracted to her story. Therefore, we felt it was a great time to honor her with the symposium session we had at the 2022 Fall ACS meeting, and I think it was very well received! I also ended up organizing a virtual issue in her honor with the Analytical Chemistry and Biochemistry journals. Hopefully these efforts will help keep her legacy alive and introduce it to a new generation of scientists.

We understand that you act as a mentor in many of your roles; for example, through your work with the ASBMB's Mosaic program. What is something you learned from your own advisors that has informed your approach to mentorship?

I wouldn't have gotten to where I am now if it weren't for the mentors I have been blessed to have along the way. Even as a lowly undergrad, I still had people who were on my side and were promoting and supporting me. Therefore, as I went through the different stages of my PhD and postdoc, I have tried to look back to see if there would be an opportunity for me to mentor someone else coming up in the stages that I had just been through. In my career, I've worked hard to make sure I devote enough time to this—not only with my lab members, but with anyone who is working hard and trying to do all the right things to succeed. I always think about how I might help them and how I could act as an "unofficial" mentor to as many people as possible—you never know how taking the time to help someone might propel them in their career.

I, for instance, was only the second person in my entire extended family to attend a four-year university. I never dreamed I'd get this far, but it was all because of the great support from many people around me. The ASBMB Mosaic program has been fantastic for postdocs who have been awarded a K99/R00 grant and are paired with a faculty member. There are a lot of awardees who are either URM scientists or scientists who come from some kind of disadvantaged background, and they are paired with a mentor who has a similar background. There are many parts of the academic journey that we can help younger scientists through, which they would otherwise have to navigate alone, such as: How do you apply to grad school? How do you apply for fellowships and scholarships? How do you reach out for a postdoc position? How do you apply for faculty positions? Without my mentors I would have really been on my own. It's so important for established scientists to look back and help others coming up behind them.

Do you and your team have any new projects on the horizon?

We definitely have some upcoming work that we're excited about! I think the quantitative proteomics field for a long time has been primarily using bottom-up proteomics—digesting proteins to small pieces. But I think we miss a lot by not looking at the intact protein and their modified forms (proteoforms). Therefore, we want to really push to get back to top-down proteomics on a proteome-wide scale. We have several projects that I think are ideal for this, to look at different combinations of modifications and different processing events that occur on proteins. This will help get a full picture of what's happening at the protein level. We are creating some proteomics experiments to really grasp how modifications mediate protein-protein interactions, to understand the dependency of those protein modifications in mediating larger protein complexes. I think that will help us understand how two proteins come together to form a complex, especially if it's formed by posttranslational modifications.

What are some of your interests outside of the lab?

I have four children—one son and three daughters (Figure 1). So, typically, any time not spent doing mass spec research or working in academia is spent with the family. Our free time revolves around whatever the kids' hobbies are. The girls have always played sports, and I help coach their softball teams. I really enjoy baseball and softball. We have an annual softball game between my department and the cell biology department. The winner gets the homemade Garcia-Piston Cup trophy that's made up of lab junk. My department has won for the last two years, so we have our bragging rights -- AND the trophy --- at the department until at least next year!