FACES OF MASS SPECTROMETRY

Devin Schweppe

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The Human Connection

Synergistic research endeavors have been prevalent throughout Devin Schweppe's career voyage, made manifest in his quick inclination to acknowledge the work of colleagues. He easily recollects the names of his research partners, highlighting their primary contributions and the continued work that they have inspired. Schweppe's spontaneous practice of recognizing and appreciating other scientists contributes to his receptive, buoyant disposition.

Schweppe became enticed by mass spectrometry while listening to a professor delineate a magnetic sector mass spectrometer in an introductory chemistry class. Recognizing that it can be a clear and stimulating presentation that reels in future scientists, Schweppe has begun to help inspire young people by speaking to them about science and technology, engineering, and math. To help support and amplify diverse voices in mass spectrometry, Schweppe has joined a network of scientists who are actively working to increase diversity and inclusion of underrepresented groups in the field.

Pushing the limits of current proteomics technologies is elaborate work, and Schweppe steadily conveys the importance of streamlining and refining workflow, which has called for joining forces with other scientists. The mainstay of Schweppe's lab in the Department of Genome Sciences at the University of Washington is based on looking for interactions between cells or organisms, analyzing interactions, and quantifying data of interest. The elation in Schweppe's voice emphasizes the notable achievements that have come out of collaborative efforts to improve efficiency in the lab, including the development of a full featured search algorithm, which has proven useful both online and offline.

As Schweppe recounts the joys of pickup games of soccer or flag football after a day of work in the lab, it is apparent that city life suits him. He relishes being where the action is and the camaraderie integral to human relationships both inside and outside the lab. Scientists like Devin Schweppe remind us that it is not only the connections between data and science that matter, but the human connections as well.

How were you introduced to the general field of mass spec?

As an undergrad, I had an awesome introductory chem professor, Charles Lovett. In the intro chem class I took with him, he described a magnetic sector mass spectrometer, and I just thought it was very cool. Toward the end of my undergrad years, he had a project going where we were trying to understand post-translational modifications of these small DNA binding proteins, particularly acetylation. I got a chance at that point to use a mass spectrometer for the first time and try to identify these PTMs from two-dimensional gel slices, which was old school and pretty fun. That really introduced me to the world of protein mass spectrometry. I extended that in graduate school with Scott Gerber at Dartmouth. He let me dig in with both hands to develop and use proteomics and phosphoproteomic workflows. So, I would say Dr. Lovett got my interest going, and then Dr. Gerber gave me the tangible skills.

How does your work in mass spectrometry relate to your work in the Department of Genome Sciences?

The great part about the Department is that it has two main angles. One is very proteomics-focused and the other is very See https://pubs.acs.org/sharingguidelines for options on how to legitimately share published articles. genomics-focused. I think the unifying property of both sides is a lot of technical and workflow development. Much of the groundwork for that, and for getting the Department to focus more on proteomics, was done before my time. Those folks had already established a niche for proteomics in the Department. Our work now focuses on how we can push the limits of current proteomics technologies, or how we can better understand principles of gene regulation or disease progression.

A sign of the times! Devin meeting with lab team via Zoom. (Clockwise from top left): Rose Fields, Devin Schweppe, Chris McGann, and Meagan Gadzuk-Shea.

> *There's a community of diversity within ASMS, and sometimes all of those voices are not necessarily heard. But they do exist and bringing those voices out can help bring others out of isolation.*

Are there any diseases that you hope your work will one day help to cure or to treat?

We often are very disconnected from the bench-to-bedside aspect of the process in technical development for proteomics. But the goal for the lab right now is looking at host pathogen interactions. One thing I got really excited about when I joined Jim Bruce's lab as a postdoc was using chemical cross-linking to try and understand intercellular interactions between human and bacterial cells. I'd like to continue some of that work. The idea is to look for potential interactions that we could perturb or inhibit during bacterial invasion, with a lens toward trying to find those ever-elusive "evolution proof" therapeutics.

Why is your research on mitochondrial function important?

One of our big questions has been whether or not super complexes exist in pole respiring and mitochondria, and how well those structures in mitochondria are represented by the structural models that have come out. In Jim's lab, we were able to identify cross-links between these complexes. With individual structural models, we were able to accurately recapitulate cryo-EM structures. This suggests that those super complexes in the modeled forms actually exist in these whole respiring mitochondria, when they're completely active. As soon as you can identify a cross-link in a given system, you can use that cross-link as a quantitative probe in the future to quantify specific protein complex states. One potential benefit is we now have thousands of protein interaction probes that we can use in trying to profile systems like how super complexes are formed in mitochondria. We can also try to tie that to a disease state. For instance, during dysfunction in the heart, we can look at how proteins in our mitochondria are affected.

What did you discuss as a panelist of "Black People Meet at ASMS" in terms of diversity in science?

The Coalition of Black Mass Spectrometrists, founded by Drs. Christina Jones, Michelle Reid, and Candice Ulmer, provided a phenomenal opportunity at ASMS to create a space to share ideas about how to get anti-racism, diversity, equity, and inclusion into the conversation for the mass spec community. There's a community of diversity within ASMS, and sometimes all of those voices are not necessarily heard. But they do exist, and bringing those voices out can help bring others out of isolation. We pointed out one standing issue in science is involving young students from underrepresented backgrounds who are often very interested in science and technology, engineering, and math. But throughout the process of moving from undergraduate to graduate to postdoc education, the percentage of underrepresented folks decreases markedly. Part of the problem is that underrepresented groups have very few role models and may lack structural support or professional networks. The "Black People Meet at ASMS" helped to highlight, in part, that there are people who can be role models in academia, industry, and government. I think all of us would love to continue that community and make sure people feel heard, seen, and respected.

Are there conferences that you attend regularly or other ways that you get together with colleagues?

The great challenge of 2020 was how to get into spontaneous, fun, and casual interactions. Prior to COVID, I loved going to conferences all over the country and the world, where I could meet excellent scientists and hear really cool stories involving subjects that I would not have necessarily thought about, such as innovative uses for proteomics or mass spectrometers. With the current loss of in-person interactions, one of the big things for me has been using Zoom to recreate the informal conversations with collaborators and other researchers (Figure 1). Another big thing that has blossomed

recently is the emphasis on social media platforms. That is a great avenue for folks to chat in much more casual circumstances and celebrate things that do not necessarily always get out. It adds some levity and lightness to what is often a frustrating and challenging process, where you are feeling like you are to trying to bash your head against the same problem for months or years.

How long have you been using and applying real time database searching platforms in your work?

When I got to Boston to work in Steve Gygi's group, they were trying to extend the RTS idea to a very specific problem in proteomics. One of the previous challenges for the integration of RTS was that there was no super clear benefit of how you were going to get or improve the current state of proteomics. On the other hand, there was great potential for RTS in the realm of sample multiplexed proteomics, where we're going to chemically barcode and mix multiple different samples into one prior to analysis and quantification of the peptides and proteins. The most accurate way to do that was through synchronous precursor selection prior to MS3 scans, or SPS-MS3. For every potential peptide precursor, we have to acquire three scans we have to get a precursor scan, do our data-dependent analyses or acquisition, select precursors for fragmentation and identification using a second scan, and finally do a quantifying scan. When you add that third scan, you can markedly slow down the efficiency of peptide identification. One idea proposed by Steve and Brian Erickson was only triggering that third scan if we knew we were going to have a "good" peptide or protein match. The big question Brian helped address was: could we use a real time database search to actually tell us if and when to trigger the SPS-MS3 scan? Brian showed that nicely with some proof-of-principle work in a binomial scoring algorithm. Through collaboration with Jimmy Eng at UW, I was able to extend this work by bringing in a full featured search algorithm, Comet. Another exciting aspect was that we could use the same exact search platform offline that we used online.

What are some of your interests outside of the lab?

With COVID, outside interests have had to change a lot, just like the conferences. Before COVID, my wife and I would play a lot of soccer in our free time, which I thought was great for getting out of your own head and just doing something low key with some friends. We did that a lot in Boston. We also have done a lot of skiing because that is my wife's family's go-to for winter sports. That is also a good excuse during the winter when you are otherwise discouraged from going outside due to rain or snow.

Have you done any outreach for youth in STEM research?

Clearly, there's an interest for younger folks. We focus on how we can keep that interest going. Part of the problem, I think, is a lack of a clear path to what options are open in STEM. We try to address that by reaching out through local colleges here in Seattle to garner interest in STEM. I had a friend I actually met playing football here, Haley Benjamins, who has a course called STEM 101 at Edmonds College, which is helping to get folks interested in STEM careers. She ran panels where we got to talk to students and answer questions about careers in STEM. It was all about getting folks interested, and also giving them a network they might not have. Now we're trying to figure out how we can expand that outreach over time.