Pieter Dorrestein reminds us that we are surrounded by a lively and intriguing world, teeming with a diversity of life-forms, all busy communicating in different ways. He enthusiastically describes the ant colony housed in the Klassen Lab, University of Connecticut, and analyzed in the Dorrestein Lab at UC San Diego. The ants diligently carry plant materials into fungal gardens, making use of microbes that convert waste into nutrients. While the ants are building a community the microbes are forming one as well. Such communities are found everywhere from communities in the soil, to plants, to the human gut and the health of those communities also defines the health of the ecosystem, including human health.

When Pieter discovered the power of mass spectrometry, he became not only an observer but an interpreter of tiny organisms that the naked eye cannot see: the microbes, bacteria, and other microorganisms that are constantly communicating with chemicals rather than words.

The Dorrestein Lab is part of the Center for Microbiome Innovation at UC San Diego. In conjunction with his position as professor, Pieter is also Director of the Collaborative Mass Spectrometry Innovation Center and Metabolomics Medicine. In his roles, Pieter strives to understand the chemical language between microorganisms, while also aiming to develop mass spectrometry approaches and tools for data analytics that benefit and enhance the capability of the entire scientific community.

Pieter is known for his community-building efforts within the scientific community. He regularly hosts scientists visiting the Innovation Center, while also delivering workshops in Brazil, Africa, Europe and across North America. Along the course of his career, Pieter realized how difficult it was to find MS-based annotations in reference libraries, so he began to focus on collaborative projects that would make information more accessible and free. This is part of the efforts of his lab to “democratize” science, by leveling the playing field.

His efforts to expand availability of metabolomics data developed into a mission to crowd source annotation. In collaboration with many laboratories, the data informatics and repository developed by the Dorrestein Lab, together with his colleague Nuno Bandeira now has users from over 160 countries that access the ecosystem more than 450,000 times a month.

Pieter believes that public datasets should be easily accessible and informative. It is his hope that accessibility will lead to diagnostic and therapeutic applications that improve “the human condition,” as he puts it.

How did you get your start in the mass spec field? 
While working on my Ph.D., I was studying how Bacillus subtilis and other organisms were making vitamin B1. It turns out this was a very interesting complex interaction of small molecules with proteins, and a lot of these were covalent modifications. This is where I got an opportunity to collaborate with Fred McLafferty, who recently passed away, and that really inspired me. That's really how I learned the power of mass spectrometry, and I wanted to continue to learn top-down mass spectrometry in my postdoc, so I joined Neil Kelleher’s lab. In Neil’s lab, I continued to do top-down mass spec, but it really became middle-down mass spec. But what really interested me was the study of how microorganisms make small molecules using multi-modal biosynthetic machineries. The types of molecules to think about are ones like penicillin, rapamycin, or vancomycin—a lot of the therapeutics that you might be familiar with.

How does your work translate the “chemical language” between cells? 
After becoming an independent investigator at UC San Diego, for the first few years I continued to study how organisms were making these small molecules. But I became really fascinated by the functional roles of these particular molecules in biology. One
thing we know about microorganisms is that they don’t live in isolation—there’s a lot of dialogue going on. What I anticipated is that many of these molecules used as therapeutics, or that have therapeutic potential, may actually be forms of microbial communication. In other words, they give signals that tell another organism, “Okay, now you need to start moving.” Or, maybe, “Now you need to stop growing.” One of the things that I started to do as an independent investigator around 2008 was to grow two or more microbes on petri dishes. We moved the agar onto a stainless steel target plate and then started to look at how different organisms responded to one another by microbial MALDI imaging. That gave us the first insights in terms of diversity of responses based on the chemical cues that each of the microbes were producing.

Have you made any surprising discoveries about the way organisms interact?

I think one interesting example are new bile acids. The first structural elucidation of bile acids happened in 1848, and two Nobel Prizes have been awarded in the field. I know about tens of thousands—or maybe even 100,000 or more—papers that do analysis and structural analysis of bile acids. But here we are now, in 2021, and we have discovered 170 new bile acids already, just in the last year! The real mystery is: why were they not characterized before even though they have been detected thousands of times based on publicly available data deposited by the community?

Has your team discovered any previously unknown microbes that could be used for health advances?

With these kinds of molecules, we’ve discovered that some have antifungal properties and others have antimicrobial or anti-inflammatory properties. So, that’s one aspect of what we’re doing. But it’s also about looking at the human condition, where you can look at the entire organism. For example, we recently discovered microbes that reduce odor and prevent tooth staining in people. As another example, we’ve found that if you isolate microbes from healthy individuals, and then transplant them onto people that have atopic dermatitis, you can reduce symptoms of skin inflammation in people through the suppression of the growth of S. aureus. The inhibition of S. aureus is a direct result of antibiotics produced by microbes obtained from healthy individuals. These are the kinds of things that that we can learn from doing mass spectrometry.

What are some of your current projects?

The tooth staining project that I mentioned is ongoing, and we also have a pretty big project on Alzheimer’s disease, where we’re trying to look at the relationship between diet, microbiomes and cognitive decline. We also have a project looking at small molecules that help to prevent salmonella infection. The other project that I’m really excited about is also related to diet. The project is funded by the Crohn’s & Colitis Foundation. We are looking at how fish digest seaweed; How soil microbes promote plant growth; How citrus can be protected against yellowing disease; How chemistry influences microbial community formation in the international space station; How medications in breastmilk influence the development of nursing infants; How microbes make rocks and many more projects.

It is all about the development of technology to be able to do an untargeted metabolomics readout of a sample. One of the most exciting and impactful projects we have ongoing is the empirical readout of diet patterns in clinical samples. We do this by creating reference data of foods. Each food gives us “mass spec food signatures, so to speak. Let’s say each food has about 2000–5000 MS/MS signatures, which we now can match up to the clinical samples of those same foods. We use a strategy called molecular networking to account for some of the metabolism that might be taking place. With that, we can get information about dietary patterns, and then we can use machine learning to see which dietary patterns improve symptoms of things like Crohn’s disease, along with which dietary patterns worsen those symptoms. We’ve found, for example, that red meats tend to be associated with worse outcomes for Crohn’s disease, although at least for now, it’s all just correlations, and we still need to do the clinical interview studies to validate our findings—that will be the next phase.

Tell us about your passion in promoting diversity within mass spectrometry in science.

It’s partly about “democratizing” science. For example, in the past, you had to buy commercial libraries to use as reference libraries to
make annotations in mass spec data. Even if they were only $1,000 or $1,500, that's still a lot of money for a lot of labs in, let's say, undergraduate institutions. For people in countries that don’t have the kinds of resources that we do in the United States, that creates a large barrier. The other barrier that has existed is the access to the actual data itself, because there haven't always been good data repositories. So, democratizing is about making science accessible and free for everybody to use in the world to promote inclusion, which I really care about.

At UCSD, for example, we have the Collaborative Mass Spec Innovation Center where we house many visitors. When people want to come and visit the lab, they must come for a minimum of three months, because if it's just for a few days, they won't learn very much. We've probably had 100 or 200 scientists come through the Innovation Center (although of course, COVID has put a damper on this). They come from all different places and backgrounds—places like Africa, Brazil, Columbia, Europe, Kyrgyzstan, China, Taiwan, Panama – representing many different cultures. I'm a firm believer that the more diverse your group is, the more creative it becomes. By having people with different backgrounds, we get people who look at the science differently, and we can come up with new ways of thinking and new solutions to the science that's being developed.

I also try to ensure that my lab is generally gender balanced—that's one thing I really pay attention to during the recruitment of postdocs and staff. Another way we’ve promoted inclusion is by giving workshops in different languages. Eight people, for example, have attended our online workshop in Portuguese. We've also given workshops in Spanish, French, and Korean. It turns out that language is a huge barrier in promoting diversity and inclusion in the sciences, even though it's something that we often don't really think about.

Still another way we promote inclusion is related to software. Specific licenses are often needed to inspect data. Recently, we introduced the GMPs dashboard, which basically allows you to look at any public mass spec datasets. You don't need to download special software—you can even upload your own data. Again, this makes the process easy, accessible, and free for everyone, which is key.

Finally, within the context of the lab I promote inclusion and equality. Oftentimes at meetings the same people speak-up, while others just stay quiet. This creates inequality where not everyone has their say. One key to overcome such inequality is to have a round table for group meetings in which everyone gets a turn to talk and to lead the group meeting. This simple structural change has really transformed the introduction of many new creative ideas and also provides a safe approach to anyone to raise a topic, as we are all equal in the round table, including myself. This develops our next generation leaders.

What are your interests outside the lab?

I like to be outdoors, doing activities such as hiking, rock climbing, backpacking, kayaking, and mountain biking. I would say mountain biking is probably the main passion that I have now because it doesn't require as much time as some of my other hobbies. I also spend quite a bit of time gardening.

What excites you the most about your research.

One thing that definitely excites me is the people I work with—they are an amazingly creative team that due to shared respect for one another, really makes a big difference in how they work together. Specific licenses are often needed to inspect data. Recently, we introduced the GMPs dashboard, which basically allows you to look at any public mass spec datasets. You don't need to download special software—you can even upload your own data. Again, this makes the process easy, accessible, and free for everyone, which is key.

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