FACES OF MASS SPECTROMETRY / Carlito Lebrilla

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A Penchant for Puzzles

Whether making final adjustments to a mass spectrometry-based tool in his lab, advising one of the startup companies that he has cofounded, or boarding a flight to Europe to meet with collaborators, Carlito Lebrilla is in perpetual motion. He is tireless in his efforts to perfect the technology needed to analyze the molecules and compounds key to understanding nutrition and numerous diseases. While Lebrilla's wheels are always turning, it does not interfere with his ability to remain present in the moment. He is engaged and animated, and his gregarious personality helps him connect with an abundance of research and business partners.

Becoming a pioneering inventor started with putting all of the pieces together. On a memorable day during Lebrilla's postdoc years he successfully reassembled a complex Fourier transform ion cyclotron resonance mass spectrometer and put it to use, inspiring his entry into the golden age of mass spectrometry as an inventor of analytical tools. He is a natural at building machines, but his tenacity and fondness for puzzle-solving brings technological advancements to fruition.

Collaboration with colleagues in other departments at UC Davis has presented Lebrilla with diverse scientific puzzles needing to be solved, and Lebrilla relishes these challenges. Food science, gut microbiomes, and cancer research appear to fascinate him equally. Experience has given Lebrilla the patience to look back at underexplored areas of science before forging ahead, and this has led to the innovation of tools needed to measure bioactive components that have become the focus of many new projects and breakthroughs.

UC Davis has been Lebrilla's hub for over 30 years. He sometimes tells people, "You won't know this in the beginning, but the place where you go will eventually guide your interest in the future."

From the golden age of mass spectrometry until now, Lebrilla has shown no signs of slowing down. It appears that Lebrilla has found his fountain of youth.

How did you get your start in mass spectrometry?

When I was an undergraduate student at UC Irvine, one of the laboratories there was led by Professor Robert Taft. He was doing gas-phase basicities of compounds. I've always liked chemistry from the point of view of studying the physical properties of compounds, so I thought this would be a really cool thing to do. Professor Taft did not have many graduate students, so I pretty much had the run of the lab. We were doing ion cyclotron resonance mass spectrometry on compounds, and that got me really interested. It made me realize I love working with big machines and trying to make them disclose properties of molecules and compounds. Even today, I have a love for big machines, trying to understand them, and making them work on small molecules. I think that is still what sort of drives me.

What are some of your favorite pieces of equipment that you have helped develop?

I got into modifying instruments as a postdoc in Berlin doing mass spectrometry. The instrument that I wanted to start my career was a sector instrument, and it was expensive, so there was a big gap between what I wanted to do and what I financially could do. Then, I went back to UC Irvine to do another postdoc. At that time, Fourier transform ion cyclotron resonance was just starting to be used, and we had solved the problem of figuring out how to take the ionization source from the analyzer. When I got there, there was an instrument that was totally disassembled. I put that instrument together, and we started getting some data. When I started as an assistant professor, I took all the lessons of making that instrument and creating ones similar to it in my lab. When I started my position, it was sort of the beginning of the Golden Age of mass spectrometry.

Why, and how, did you transition from mass spectrometry to the biomedical and analytical chemistry field?

Driving home one day, I heard a congressperson on the radio pleading with his colleagues to put more money into research because of a disease affecting his mother. It made me think about how diseases are not going away. And there's always going to be

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some congressperson or senator saying, "We need more money for this." I started investigating biological compounds to see whether we could actually look at diseases. So, we transitioned from small molecules into now looking at oligosaccharides, carbohydrates, glycans, and glycoproteins. Also, when my mother passed away from ovarian cancer, I said to myself, "There must be a better way of detecting ovarian cancer because now it's always detected too late." That is when we started looking at glycans and glycosylation as biomarkers for cancer. I thought, "Why not develop a blood test for ovarian cancer using glycosylation?" That was another moment that changed the course of my research, but much of what we choose to do is based on personal experience.

How has your work specializing in proteins influenced the field of mass spectrometry?

There has always been an understanding that the polypeptide sequence of the protein was not everything. There were additional modifications that gave it function. This is especially important in human milk consumed by infants because it turns out that a lot of proteins in the milk have this modification. One of the functions of the modification was to block the binding of pathogens to host cells. It turned out milk proteins were changing their glycosylation during lactation as they were blocking different bacteria to protect the infants. One of the other things we found in that study was there were compounds we called human milk oligosaccharides that were being produced in large amounts in breast milk. However, because the infants had no enzymes to break it down, it appeared to have no nutritional value. The question was, why have something more abundant than protein if it has no nutritional value? We worked with nutritionists and microbiologists and found that the oligosaccharides were actually food for a specific type of bacteria, one that the mother was recruiting by feeding it with her milk so that the bacteria could protect the infant. There are certain diseases, such as type 1 diabetes, that are being researched as possibly being caused by the lack of this bacteria in developed countries. These studies led us to our current area of research in the microbiome where we are determining the structures of food. For example, if you if you look at, let's say, a potato, you might say it is made up of "carbs." But what does that mean? There are three or four different polymers in potatoes. Compare that to rice, which has mainly one. If you are thinking about the microbiome, we can ask, are there specific bacteria in your gut if you were raised eating potato? Are your bacteria different than if you were raised on rice? My contention is that the answer is yes.

How might your research on infants and nutrition help people like new parents and pediatricians?

There's a website of testimonials from a company called Evolve Biosystems that we founded several years ago to develop and market the bacteria. Some of the testimonials from there have been amazing. Oftentimes you hear something like, "My child went through several antibiotic treatments because we had a complicated birth. The infant was crying all the time, could not sleep, and was having bowel movements much more often than normal. Then, we administered this bacteria, and it is like we had a totally different baby." In that regard, it is helping parents. Going back to the mass spectrometry, what made all of this possible was the fact that we could characterize these compounds that have been known for a long time, but they could not be analyzed because the tools were not there. Once we could analyze them, we figured out if you take certain bacteria and then look at the supernatant, you could see which compounds would disappear. That is how we discovered the one bacterium found in the gut of a healthy breastfed infant that allowed us then to say, "Wow, this is it. This is the bacteria that eats milk oligosaccharides."

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Are there any particular features of UC Davis that have made you want to stay long term?

Davis is such a big health-focused campus. I realized there were so many problems that mass spectrometry can solve in food, in health, and even in basic fundamental biological issues. I just kept finding new ideas there, which really appealed to me. For example, right now, in our work with food, we look at how diet affects cells, infant development, and brain development. In the end, when you sort of weigh things, there were just a lot of good things happening there. And my collaborators are great, and the students I was getting were also fabulous.

How do you direct the projects and the teams that your students work in?

When students come in, I point them to a general area. I give them a topic that helps them learn and it gives me a gauge of what their interests are. Some of them, for instance, love informatics. Others like to understand how cellular processes work. So, it really depends on the students. Additionally, we learn a lot from our collaborators. As the students are doing their main research, I also have them join our collaborators. That way, they can learn new things that I cannot teach them, and at some point, I set them loose, and they go with collaborators and focus on the kinds of things that they're more interested in. When they're almost finished, I jokingly have a rule of thumb: if you are teaching me more than I'm teaching you, then you should graduate.

What are some of the other countries that you have gotten the opportunity to see through conferences?

I've been pretty much all over Europe. More recently, we started working with collaborators in Southeast Asia in places like Thailand and the Philippines. I'm still trying to get to Africa. We have several collaborations in Africa, where we're looking at breastfed infants and how a mother's milk is affected by diet and other issues. One of the things that we discovered with our collaborators was that stunting in children, a big problem in developing countries, was related to human milk oligosaccharides and the microbiome. It is not just a matter of giving them enough food; it turned out that their microbiome was deficient. We also found that these kids had mothers lacking enough of the human milk oligosaccharides. So, this kind of research into mothers' milk and infant nutrition now has a lot of implications not just in the United States, but in developing countries, too.

What are your interests outside the lab?

ISince high school, I've liked riding motorcycles, and I have an old convertible Porsche that I drive around. We do a lot of camping, and I recently discovered RVing. Instead of sleeping in a tent on the ground, we realized that having your own house in the woods is awesome. It is sort of funny because before COVID-19 I traveled a lot, giving lectures. But now, it has just been a lot of fun going in the RV to Yosemite, or to places like Oregon and Yellowstone. With the RV, you can go places and not have to be in contact with anyone for any length of time, except your family. It really is the perfect social distancing machine.