FACES OF MASS SPECTROMETRY / Chris Crittenden

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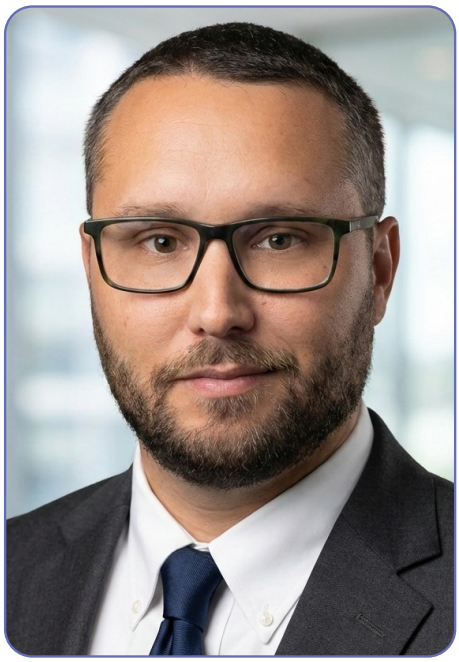

Chasing the Unexpected

Chris Crittenden is a Principal Scientist at Genentech, where he performs advanced tandem mass spectrometry for the structural elucidation of small and synthetic molecules being developed for potential clinical candidates. Chris enjoys this role because it provides the opportunity to study new molecules, contribute to the improvement of human health, and apply innovative mass spectrometry techniques to answer difficult lab questions. While at Genentech, Chris has helped create a mass spec working group for his colleagues that promotes technical training, professional development, and scientific collaboration. He has also helped launch a high school outreach program that offers visiting students a chance to see and learn more about the career of an analytical scientist.

Chris's engagement with these programs highlights his commitment to innovative thinking, professional development, and the spirit of collaboration. Perhaps one reason for this dedication is that Chris has a deep appreciation for the value of mentorship in the sciences. As an undergraduate student at the University of West Georgia and as a graduate student at the University of Texas, Chris had very supportive experiences with his professors and advisors, and he is grateful to them for introducing him to the field and for providing him with the tools and resources that he needed to succeed.

Family life is also very important to Chris; his daughter was born before he started his PhD, and Chris's son was born shortly after he defended his thesis. Chris notes that although obtaining a professional degree while maintaining a family life outside of school can of course have its challenges, it is something that can certainly be achieved!

Did your interest in mass spec develop before, during, or after your PhD studies at the University of Texas?

My journey began well before my PhD. I first found an interest in mass spectrometry in the fall of 2009 during my first semester of undergraduate studies at the University of West Georgia. I consider myself quite lucky to have been given an opportunity by my first chemistry professor—and now long-time friend and mentor—Farooq A. Khan. He encouraged me to get into the lab and learn the basics on an old, broken Thermo Finnigan LCQ mass spectrometer. Alongside two wonderful undergraduate colleagues, J. Brett Kimbrell and Joshua Hite, we were able to get the instrument back to a functional, calibrated state. We even performed early experiments that ultimately led to a peer-reviewed manuscript on the binding of anions to the cyclic peptide valinomycin. I credit Dr. Farooq Khan with my introduction to mass spectrometry and for instilling in me a passion for chasing the unexpected..

Tell us about your work with ion mobility separation in pharmaceuticals.

Let me be clear that ion mobility was absolutely not something I made an active decision to focus on. Rather, I view it as another vital tool in the "bag of tricks" we use for structure elucidation—over the years, it's something we have learned about and found value in; much like we utilize chromatography to separate desired products from impurities or measure reaction completion, ion mobility informs on specific molecular properties that might not be attainable by traditional chromatographic approaches. For example, we have used it to separate atropisomers of divarasib, which were inseparable by our traditional chromatographic techniques but were observed via variable temperature NMR experiments. We also explore a myriad of fragmentation approaches to pinpoint specific modifications on candidate molecules, such as when a synthetic impurity is formed or a degradant is found under stability studies.

How did you come to your current position with Genentech?

Once again, I lean on the sentiment that "I got lucky and was in the right place at the right time." To give some background, my wonderful wife, Shastina Olgesbee, had always said that we could go anywhere in the world after I finished my PhD, except for Florida or California. However, there was an opening in the Structure Elucidation Group within Synthetic Molecule Pharmaceutical Sciences at Genentech that they had been trying

Chris speaking at the ASMS 2024 Breakfast Seminar in Anaheim, CA. (Photo courtesy of Chris Crittenden.)

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to fill for some time. The hiring manager, my first industrial mentor, David J. Russell, reached out to gauge if I would be interested in moving to California after I finished my work in Texas. After going through the interview process, meeting the team, and understanding the day-to-day reality of the role, it was an easy decision. Even my wife agreed that this was a "dream job" for me, and we have settled in nicely in the Bay Area. To be fair, it worked out professionally for her, too; she is a nuclear scientist and now works at Lawrence Livermore National Lab.

What is something you enjoy about working in biotech?

That is an easy answer: the novelty. The first thing that comes to mind is that typically, every molecule we study and work on has never been seen before. Everything is novel when you are at the interface of drug discovery and synthetic chemistry. Furthermore, being a cog in the massive machine of pharmaceutical development, and knowing that the work I do daily aims to improve human health, is a very rewarding aspect of the role.

What are some of the research questions you aim to answer through your work?

First and foremost, I am a "structure elucidation scientist." The question we are always trying to answer is, "Is the structure of this molecule correct with 100% certainty, and if not, what is the structure instead?" We achieve this using two main analytical approaches: NMR and mass spectrometry. The team I am a part of, led by José Napolitano, performs total structural characterization with a myriad of techniques, including through-bond and through-space 2D NMR experiments and many different flavors of tandem mass spectrometry. Because we work in such a unique area of drug discovery, there often isn't a roadmap for solving the structures of these unseen molecules. This absence of a roadmap gives us tremendous freedom to explore collaborations with partners who may possess deeper expertise in a given field, which is a part of the job I really enjoy.

Can you tell us about your own approach, or any "tips and tricks," when it comes to innovative thinking and problem-solving?

Certainly! I often find inspiration for new experiments by talking with other scientists about their interests and challenges, or by attending seminars hosted by internal Genentech scientists or visiting academics. I try to get a sense of the most modern, challenging areas of science—whether based on a specific technology, molecule, or therapeutic area—and use that as a starting point to think about how the technology I know fits into those fields. Additionally, I gain immense inspiration from the annual ASMS conference, seeing the newest cutting-edge mass spectrometry technology and how it is applied across different disciplines. One of the questions I get asked frequently is, "Hey Chris, can we look at this by mass spectrometry?" I love responding with, "I don't know! Let's find out!"

How has mentoring helped to influence you as a scientist?

In my opinion, mentoring is one of the most important aspects of being a scientist. While I come from a heavy mass spectrometry background with excellent mentors, including Dr. Farooq A. Khan and Dr. Jennifer S. Brodbelt, I am surrounded by peers who are experts in many other disciplines. I have learned a great deal just by having conversations in the lab about their expertise and discussing how I can implement my skills to help answer their questions. Conversely, there are many colleagues who do not have a mass spectrometry background, and I take pride in "democratizing" mass spectrometry across our department by

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Chris and his wife, Shasta, in Montréal for New Year's 2025. (Photo courtesy of Chris Crittenden.)

offering training and guidance. I have had the honor of working alongside world-class chromatographers and process-analytical experts who have been in the industry much longer than I have, all sharing the common goal of applying modern mass spectrometry techniques to our hardest lab questions.

As a follow-up, tell us about your involvement in high school outreach.

I have been involved in a high school outreach program that is an internal initiative at Genentech. My former boss, David J. Russell, and I started this program many years ago. Two or three times a year, we host a local high school for a field trip where students spend two hours onsite learning what a "day in the life" of an analytical scientist looks like in biotech. The visit introduces students to a panel of scientists who share their career journeys, followed by a lab tour to see a modern analytical operation. We also provide hands-on demos for NMR and MS/MS. Typically, I run the MS/MS demos, sharing my background and explaining how we utilize mass spec to answer challenging pharmaceutical questions. The visit concludes with a networking lunch for the students, teachers, and scientists.

Tell us about your involvement in your department's MS working group.

About four or so years ago, my colleague Bifan Chen (PhD from UW Madison) and I wanted to give our colleagues a venue to simply come and learn more about mass spectrometry and the proper ways to implement the technique into their projects. What started as a mostly educational venue has turned into quite an impressive group of collaborative research, with working group members floating ideas, sharing raw results, and bouncing ideas off each other. We will also invite guest speakers—either from other departments at Genentech or externally from instrument vendors or academic labs—to share their research and new ideas with this group and engage with us on how to implement such techniques in our line of work.

We understand that outside the lab, you enjoy hiking and baseball. Tell us more about these pastimes.

At home, we have three amazingly chaotic border collies appropriately named Boltzmann, Fermi, and Lotti. My wife and I try to spend our free time hiking in the Bay Area hills with them or sitting on the sidelines, trying to keep them from chasing the soccer ball during our kids' matches. Outside of the lab, you are also very likely to find me at the soccer fields watching my kids play. They are both extremely impressive student-athletes, and I am so proud watching them thrive in school and on the field. I am an avid baseball fan and ex-player too; having grown up just south of Atlanta, I follow the Atlanta Braves very closely. The Braves have always been a big part of my life from literally the day I was born—when I was a baby, I came home from the hospital in a Braves jersey, so my parents didn't really give me much of a say in that matter!