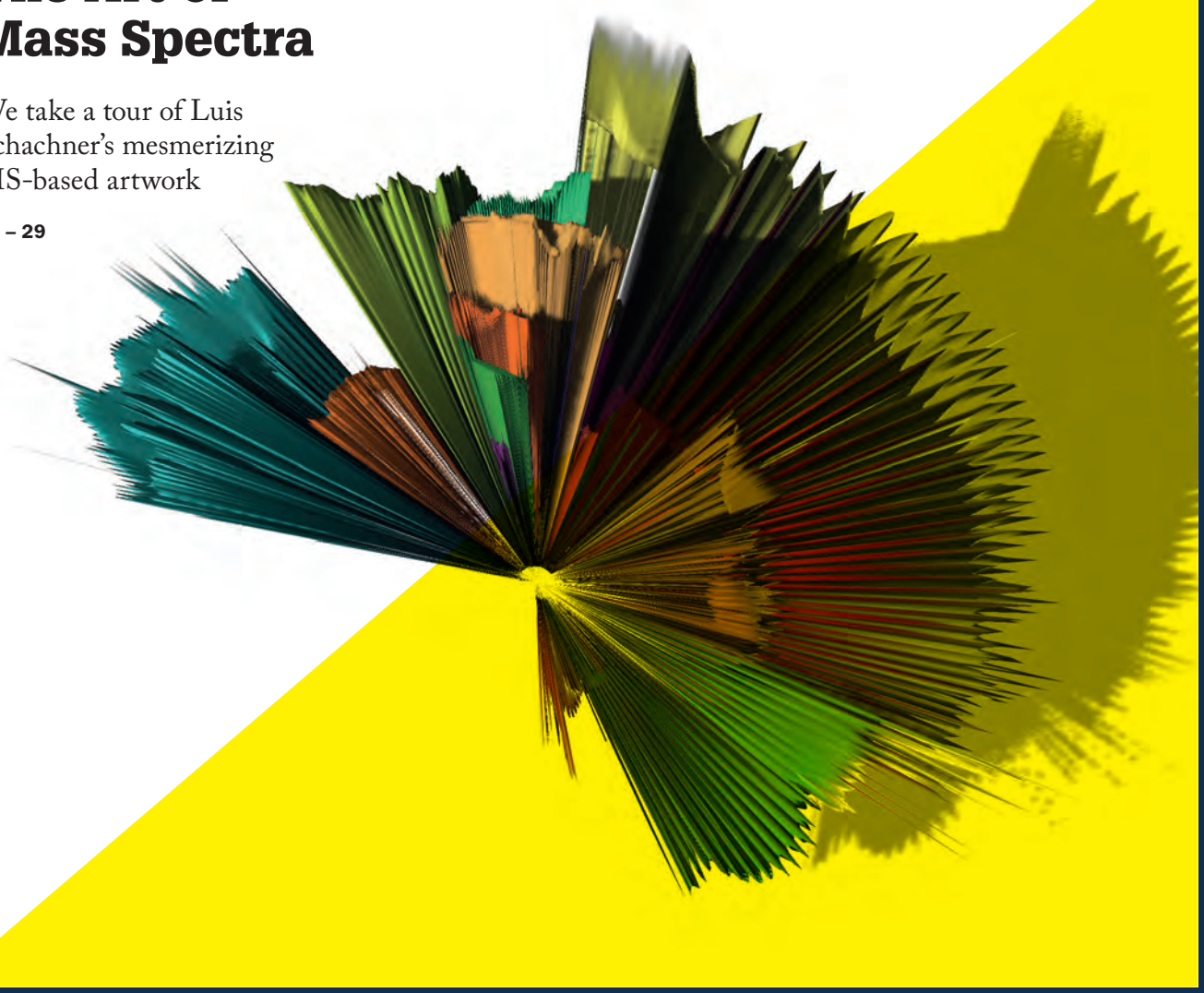
MAY 2021 # 97

the Analytical Scientist®

The Art of Mass Spectra

We take a tour of Luis Schachner's mesmerizing MS-based artwork



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The Beauty of Mass Spectrometry

May is MS month at The Analytical Scientist

As you flick or browse through the pages of The Analytical Scientist this month, you'll notice that mass spectrometry takes center stage.

Luis Schachner (page 16) sees literal beauty in mass spectra, morphing the characteristic lines to connect the worlds of art and science – and telling stories in the process. But Schachner's work also highlights how widely MS is being applied (need I say more than mouse stool proteomics?). And so I'd say the real beauty of MS lies in its adaptability.

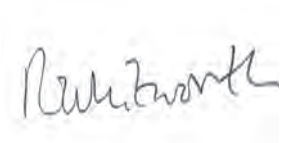
When it comes to the clinical application of MS, this adaptability (or perhaps the complexity that allows it) is truly put to the test; it's fantastic to explore samples from multiple angles with all the bells and whistles on offer – but what if you want a straightforward test that gives the "right" answer every time? You may remember a 2017 article called "Taking MS into the Clinic," which shared the story of two clinicians – Neil Dalton and Charles Turner – who worked towards the routine implementation of MS-based screening for newborn hemoglobinopathies (1). It took them 16 years.

With that in mind, I'd like to point you to Perdita Barran's work on developing a rapid MS-based test for SARS-CoV-2 in just four months (page 30). I think the words of Jenny van Eyk best sum up the feat: "I remain in awe of the UK team's work in bringing an MS-based protein test to [National Health Service] clinical chemistry laboratories [...] There's so much that needs to be considered when you are translating a new marker test to a clinical lab – it's almost unbelievable that they managed to do it in such a short window of time."

Given the challenges, where are we heading? Maarten Dhaenens says, "I can see a future where there's an MS sitting in a clinic, running a test for COVID-19 perhaps, and then something from oncology comes in, something from hematology after that... And the MS is measuring them and spitting out a semi-automated report for the clinical biologist. It would be truly amazing, but I think it's entirely possible."

It's not the first time I've heard this vision of the future – and each year we seem to edge just a little closer. For Dalton and Turner, the road to the clinic demanded a great deal of time (and effort). For Barran, driving the project over the line so fast required high levels of collaboration and a great many passionate people. In both cases (and despite the challenges), the resulting success offers a tantalizing glimpse of Dhaenens' vision. MS in the clinic? It's inevitable.

Rich Whitworth
Content Director



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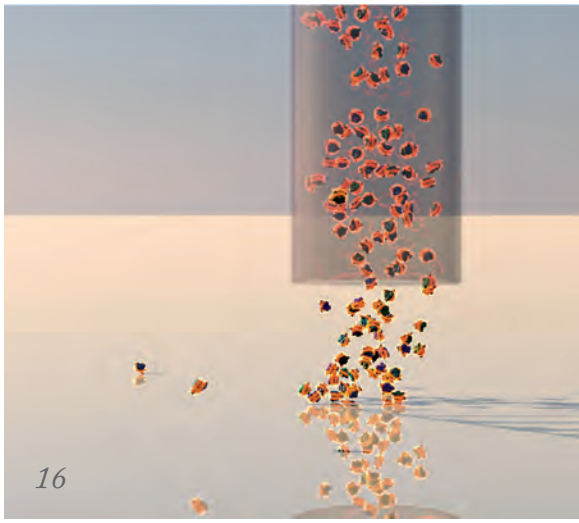
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On The Cover

A 3D rendering of the carbonic anhydrase spectrum, from our cover feature on Luis Schachner's work.

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Inside the Honey Pot

How lipid residue analysis is revealing our ancient connections with honeybee exploitation

Medicine, sustenance, preservative, cosmetic, sweetener – honey has played many different roles in human history. Today, this amber nectar is still vital to our economy, with around 1.6 million tons produced annually. However, aside from some Paleolithic rock art depicting bees and honeycombs, there is little evidence of humans' exploitation of the honeybee.

Recent lipid residue analysis has revealed the presence of beeswax in Neolithic vessels from Europe (1), but less is known about other areas of the world – for instance Africa, where collecting honeybee hive products (including honey, beeswax and pollen) is still crucial to the cultures and livelihoods of local communities. Now, researchers from the University of Bristol and Goethe University have discovered direct chemical evidence of ancient honey hunting by analyzing prehistoric pottery fragments from West Africa dating back some 3,500 years (2).

The team initially set out to study general diet and subsistence among the Nok people of West Africa – a culture known for their large-scale terracotta figurines and early iron production – through excavation. However, acidic soils meant organic material was hard to come by, so they instead turned to lipid residue analysis of the excavated potsherds. This involved grinding up small pieces of pottery and analyzing the lipid biomarkers via GC-MS.

They expected to find evidence of common foodstuffs, such as meat and dairy. "Imagine our surprise when our analyses revealed that one-third of Nok vessels (over half in the Early Nok phase) contained a complex series of lipid biomarkers comprising *n*-alkanes, *n*-alkanoic acids, and fatty acyl wax esters that denote the presence of beeswax," says lead author Julie Dunne. The researchers believe the beeswax residue could be a proxy for the cooking or storage of honey or could come from the heating of wax combs used for other purposes. Some pots even showed the presence of both meat and honey, suggesting its use as a preservative in some instances.

"Our work has revealed the antiquity of honeybee product exploitation in the Nok culture, an area where we know very little about what foods the people were eating," says Dunne. "There is lots of potential for future research, and we'd like to further investigate human exploitation of honeybee hive products in Africa and its geographical extent."

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2. *J Dunne et al., Nat Comms, 12, 2227 (2021). DOI: 10.1038/s41467-021-22425-4.*

TIMELINE

Koji Nakanishi

Exploring some of the key events in the life of this spectroscopy pioneer

Born in Hong Kong on May 11th 1925, Nakanishi gained his PhD in Chemistry from Nagoya University in Japan, and in 1969 joined Columbia University in the US where he would later become chairman of the chemistry department

His research covered everything from structural and bioorganic studies of bioactive compounds, to the development of spectroscopic methods like circular dichroic spectroscopy, the NMR nuclear Overhauser effect, second derivative FTIR and UV difference spectroscopy

BUSINESS IN BRIEF

Our round up of the latest business news – from product launches to validated workflows for drinking water analysis

- Thermo Fisher Scientific recently validated a new disinfection by-products application workflow, which uses IC-MS/MS to analyze nine haloacetic acids in drinking water samples in just 35 minutes. Not only is it faster than the previous US EPA Method 557 workflow, it is also simpler to use and eliminates sample preparation steps (1).
- At the recent Experimental Nuclear Magnetic Resonance Conference, Bruker announced the launch of a number of new systems to increase the accessibility of chemical analysis via magnetic resonance spectroscopy. In particular, this included the Fourier™ 80 FT-NMR benchtop spectrometer for multinuclear gradient spectroscopy (2).
- Waters and Genovis have teamed up to co-develop efficient workflows for the characterization of critical quality attributes in biotherapeutics, such as antibodies and other protein-based drugs. The workflows will be based on the Waters BioAccord LC-MS system, Andrew+ pipetting robot and Genovis SmartEnzymes (3).
- Agilent's InfinityLab LC/MSD iQ and Ultivo Triple Quadrupole LC/MS systems have recently received the ACT seal of approval from My Green Lab – a nonprofit organization dedicated to improving the sustainability of scientific research – demonstrating their reduced environmental impact (4).
- SCIEX has announced that Joe Fox, who joined the company in 2011, will take over from Inese Lowenstein as President. Fox will focus on continuing SCIEX' legacy in quantitative LC-MS, and will also oversee the launch of new technologies later in the year (5).

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3. *Waters (2021). Available at: https://bit.ly/3xoDMfY*
4. *BusinessWire (2021). Available at: https://bwnews.pr/2S1Az5M*
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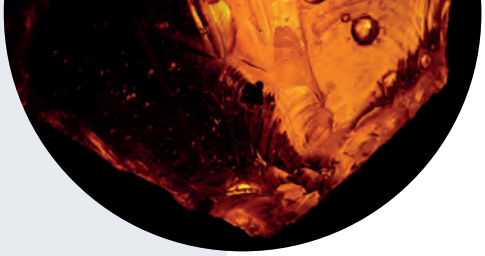


Amber Alert

Could fossilized resin be the antidote to antibiotic resistance?

For centuries, people in Baltic nations have used ancient amber from now-extinct pines in the *Sciadopityaceae* family for medicinal purposes – but the science behind amber's therapeutic effects has, until recently, remained a mystery.

To solve it, scientists ground commercially available samples into a homogeneous semi-fine powder before filtering, concentrating, and analyzing them by GC-MS. Dozens of compounds (including abietic acid, dehydroabietic acid and palustric acid) were identified and then tested against nine bacterial species.

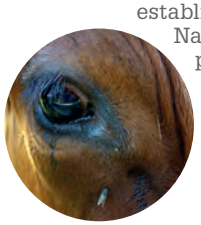
Interestingly, scientists found that these compounds were active against Gram positive bacteria, such as certain *Staphylococcus aureus* strains, but not Gram negative bacteria – suggesting that the composition of the bacterial membrane is important for the compounds' activity. The findings indicate that abietic acids and their derivatives may be an untapped source of new medicines – and a potential answer to our drug resistance problem.

Reference

1. *ACS Newsroom (2021). Available at: https://bit.ly/2QIqs5k.*

Overall, his research group determined the structure of over 200 biologically active natural products, including ginkgolides (from the ancient ginkgo tree), insect hormones, antibiotics, and the human eye pigment involved in macular degeneration

His group also synthesized more than 100 analogs of retinoids and his research in this area helped us better understand animal vision and phototaxis



He received a number of awards throughout his career, and in 1996, ACS and the Chemical Society of Japan established the Nakanishi prize in his honor

He was also an amateur magician who frequently entertained his audiences and fellow chemists at various events

Tough Mother (of Pearl)

Researchers invent new optical technique to nondestructively analyze the nanoscale nature of nacre

Hyperspectral camera used to record the spectrum of nacre. *Courtesy of Mikhail Kats.*

Nacre, or mother of pear, is one of many natural materials of interest to researchers because of its extraordinary strength – but studying the structure of this iridescent substance is experimentally challenging. Existing methods result in the sample being destroyed, and are also hard to scale to large sample areas – an important factor for studying nacre, because it is typically not uniform across a given shell.

Now, Pupa Gilbert and Mikhail Kats of the University of Wisconsin-Madison have developed an all-optical technique to overcome these challenges. The technique they came up with – eventually called hyperspectral interference tomography (HIT) – is based on hyperspectral imaging, in which every pixel on an image contains a full reflectance spectrum (in this case, in the visible and near-infrared). By taking angle-dependent and polarization-dependent hyperspectral measurements of the shells and mapping the results to a computational model, the team were able to predict the reflectance spectra of possible nacre structures.

"HIT has several major advantages over existing techniques for structural characterization of nacre and other layered biominerals," says Kats. "One, it is nondestructive, so it can easily be used on precious samples, such as ancient nacre; two, because it does not require any cutting or additional sample preparation, it is very fast, enabling the measurement of many points on the sample and across many samples; and three, it is inexpensive and portable, not requiring electron microscopy or X-ray facilities."

Though the team made several interesting discoveries during their experiments, the technique's real value here lies in how it could be used in the future. "We believe that HIT of ancient nacre could provide a more comprehensive view of climate history, because nacre encodes the environmental conditions in which it was formed," says Kats. The technique could also be of value for the characterization of other layered biominerals.

Reference

1. *J Salman et al., PNAS, 118 (2021). DOI : 10.1073/pnas.2023623118.*

Lowering Chromatography Costs

An old technique – resurrected and repurposed for modern bioprocessing

Though useful in the treatment of various chronic illnesses, the price of many monoclonal antibodies negatively impacts their accessibility. "Every year, individuals and insurance companies spend upwards of US$100 billion on antibodies, with costs to treat a single patient often exceeding $50,000," said Andrew Zydney, Bayard D. Kunkle Chair, and professor of chemical engineering at Penn State, in a statement (1) . The reason? Affinity chromatography, the process used to separate a desired antibody from a solution, relies on chromatography columns that can cost up to $10 million each.

Aiming to lower the cost of these much-needed medicines, Zydney and his colleagues applied a 70-year-old protein purification method used for plasma processing to the development of antibody drugs (1). The team added zinc chloride and polyethylene glycol to separate a target antibody in solution – a cheaper, time-effective alternative to conventional practices. This progress has left the team hoping that the process can be scaled up to help patients access these medicines at affordable prices.

Reference

1. *AL Zydney et al, Biotechnology Progress (2020). Available at: https://doi.org/10.1002/btpr.3082*

IMAGE OF THE MONTH

Mural Mysteries

Researchers at the University of Costa Rica have developed two new software-based multispectral imaging techniques to aid in artwork conservation studies. In the first ever study on *Musas I* and *Musas II* (above), by Carlo Ferrario, the new techniques were not only able to reveal details about the artist's creative process and color palette, but also able to assess the conservation state of the paintings and seek signs of possible biodeterioration. In the image above, we can see six different views of the paintings, spanning visible light, infrared, infrared false color, UV fluorescence and UV reflectance. The final images show locations where samples were taken. Importantly, this work could help conservation efforts in tropical climates and provide important information to help slow down decay in these regions.

Reference: M D Barrantes-Madrigal et al., Scientific Reports, 11, 8560 (2021). DOI: 10.1038/s41598-021-88066-1

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QUOTE OF THE MONTH

"There are going to be more pandemics coming our way – with the help of MS we should be able to respond much faster next time, or more immediately, as new variants come out."

Jenny van Eyk, Director of the Advanced Clinical Biosystems Research Institute and Precision Biomarkers Labs at Cedars-Sinai Medical Centre, Los Angeles, California, USA.

In Sheep's Clothing

Peptide mass fingerprinting confirms sheepskin was the material of choice for historical legal documents – and reveals interesting details as to why...

Though historic legal deeds are abundant in British archives, they are also largely neglected as a resource. "However, these documents are fantastic biological archives, through which millennia of animal genetics, breeds, farming, craft and trade can be explored!" says Sean Doherty, lead author of a recent paper exploring the use of sheepskin parchment in early modern legal deeds.

To find out more about the animals used for their production, Doherty and his team analyzed over six hundred documents using "ZooMS" (zooarchaeology by mass spectrometry) or, for the uninitiated, peptide mass fingerprinting – in this case, using a MALDI-TOF instrument (Bruker Daltonics) and an open source MS software tool (mmass.org). They found that almost all were made of sheepskin.

Great – but why? Doherty believes it could be because of its unique structure, which means any attempt to fraudulently alter the text would leave behind a large blemish on the surface.

Reference

1. *S P Doherty et al., Herit Sci, 9, 29 (2021). DOI: 10.1186/s40494-021-00503-6*

In My View

Experts from across the world share a single strongly held opinion or key idea.

GC×GC 2021: Great Science Virtually Guaranteed

An online GC×GC symposium may not be the ideal substitute for our beloved face-to-face meeting, but it's definitely better than the alternative

By Phil Marriott, Professor in the School of Chemistry, Monash University, Melbourne, Australia

In The Analytical Scientist's recent feature, "The Show Must Go On?," I expressed my feelings of loss at the cancelation of a face-to-face ISCC/GC×GC meeting for the second year in a row. Though a virtual conference is admittedly less than ideal, the members of the GC×GC organizing committee and I simply could not face the alternative: no meeting at all.

Three linked facts drove our collective decision to offer GC×GC-18 as a virtual symposium: i) we have not met as a GC×GC Symposium community since 2019; ii) we had originally hoped that missing the 2020 iteration meeting in person would allow us to reconvene in 2021 rather than relying on a virtual platform – but how wrong this would turn out to be!; and iii) we could not imagine waiting until 2022 before gathering as a community of GC×GC enthusiasts to celebrate our science. So, a virtual event it was!

To organize a relatively broad coverage of GC×GC in the short time available (we pushed the date of the meeting to a slot vacated by the ASMS meeting), we decided it was best (or most time-efficient) to work with largely invited presentations. We believe we have a good balance across a spectrum of key applications and technology in GC×GC – but you can visit the website (gcxgc-symposium.com) to confirm this! And to maximize the number of presentations and to offer an alternative to poster-style presentations, we have planned brief burst oral talks – but of only five minutes each. For PhD students today, this is not an unusual format. An increasing number of meetings use a similar model, such as the increasingly popular '3 Minute Thesis' or 'PechaKucha' presentations. Only the burst presentations will be held as parallel sessions. Other presentations

"Though a virtual event necessitates a number of changes to the traditional format, it was important for us to maintain as many key elements of the GC×GC series of symposia as possible."

are of a more traditional 15-20 minutes, organized as applications or technology sessions. We will also have a number of keynote state-of-GC×GC lectures. To fast-track the organizational aspect, the Multidimensional Chromatography Workshop – previously held in Toronto, and now in Liege – has agreed to host the meeting on their virtual platform (thank you!).

Though a virtual event necessitates a number of changes to the traditional format, it was important for us to maintain as many key elements of the GC×GC series of symposia as possible. So it is our pleasure to include the GC×GC Scientific Achievement Award and the John B Phillips Award – and, this year, it will be double the honor (and double the award lectures) because both the 2020 and 2021 awards will be presented. The award winners and their lecture titles can be found on our website, but I'd like to announce here that the Scientific Achievement Awards go to Hans-Gerd Janssen (2020) and jointly to Jack Cochran and Frank Dorman (2021). And the John B Phillips Award goes to Pierre-Hugues Stefanuto (2020) and Katelynn Perrault (2021). A GC×GC workshop will be presented, and manufacturers/conference supporters will have 15 minute Sponsor's Corners to share their developments and new offerings.

In short, if we'd not gone virtual for 2021, then there would have been no Symposium – in my view, an unacceptable situation. I think there is uniform agreement that GC×GC should and will revert to face-to-face meetings – when appropriate to do so. The Analytical Scientist recently canvassed opinions from GC×GC users on the pros and cons of GC×GC as a virtual meeting, and I think it is clear that most in our field feel the same way. There are certainly some benefits to virtual meetings, particularly for scientists who cannot travel to a conference but can attend online, so maybe some hybrid model will emerge in the future. But, for me, the opportunity to have (scientific or peripheral) conversations over dinner, to peruse posters then quiz their authors, and to visit exhibitor stands (and pick up yet another "favorite" pen) is simply invaluable.

What's in Your Capsids?

Are your capsids full, half full, or empty? We need better analytical techniques to tell us the answers to these crucial questions in the development of gene therapies.

By Lori Stansberry, Senior BioPharma Marketing Manager at Thermo Fisher Scientific

It's just over 30 years since the first approved gene therapy procedure was performed – and I'm sure we're all amazed at how the field has progressed since then. The FDA expects approvals for cell and gene therapy products to reach around 20 per year by 2025 (1). A key component enabling the growth of the field of gene therapy is recombinant adeno-associated virus (AAV) vectors. There have been three recombinant AAV-based gene therapies approved for commercial use so far (2), and there are hundreds of active clinical trials worldwide for a variety of diseases.

As development of gene therapies increases, there is a growing demand for accurate and efficient techniques for characterizing AAV vectors. Many existing methods for analyzing AAV vectors, particularly for determining the full/empty capsid ratio, are labor-intensive and time consuming. Analytical methods using anion exchange (AEX) chromatography, however, are supporting the analysis of AAV capsids and could be a key technology for further advancing gene therapies.

Viral vector characterization is essential for assuring product quality. Critical quality attributes (CQAs) include viral potency, identity, quantity, process residuals (i.e., Triton and deoxiribonuclease), aggregation, empty capsids, capsid protein content, and product safety. To meet purity requirements, the proportion of empty, partial, and full AAV capsids must be determined. Unsurprisingly, full capsids are required for therapeutic efficacy; empty capsids, which do not contain genetic material, or partial capsids, which contain only a fragment of the genetic material, are simply by-products of AAV production and can negatively impact product efficacy and safety – potentially producing adverse reactions, such as an immunogenic response in the patient.

There are various analytical methods for characterizing capsid levels in the laboratory, including transmission electron microscopy (TEM), analytical ultracentrifugation (AUC), charge detection MS, and UV spectrophotometry. The two main methods are TEM and AUC. TEM involves a sample vitrified by rapid freezing to preserve the structure of a biological specimen. When imaged, there is a clear difference in structure between full and empty particles. The AUC method distinguishes and quantifies the different AAV capsids either by density (sedimentation equilibrium) or mass (sedimentation velocity).

As AAVs are relative newcomers in gene therapy, the industry has not yet decided upon the most effective method of analysis. Certainly, existing methods for determining the full/empty ratio of AAV capsids have limitations; for example, TEM provides direct visualization and counting of the empty and full particles, but quantification heavily relies on image quality and field selection.

And although AUC has excellent resolution and is highly accurate, it often requires a dedicated facility and specially trained analysts, who must spend hours on data interpretation. Moreover, AUC also consumes hundreds of microliters of valuable samples.

In short, TEM and AUC are both low throughput – and neither is readily scalable.

In my view, AEX chromatography is a useful technique for the analytical toolbox. When genetic material is

"Historically, use of the AEX method for separation of empty, full, and partial capsid was less than optimal due to analysts narrowly exploring anion exchange column chemistries."

encapsulated in the capsid, the surface charge on the particle changes. This physiochemical difference between full and empty capsids makes them ideal for analysis with AEX chromatography methods. AAVs are also small (20-25 nm) and suitable for both traditional and monolithic columns.

The AEX chromatography method requires only several microliters of material – clearly a real benefit when gene therapy samples are so precious. Furthermore, no sample preparation is needed, which simplifies the analysis and increases throughput.

Historically, use of the AEX method for separation of empty, full, and partial capsid was less than optimal due to analysts narrowly exploring anion exchange column chemistries. For example, a user may begin method development with a column that would be recommended for nucleotide analysis because this would work well for characterizing genetic material inside the AAV. However, this same column chemistry may not be best suited to separate empty, partial, and full capsids. Today, chromatographers have learned they need to search across multiple column chemistries to find the solution that provides the best resolution for empty/ full capsid separation.

Right now, AUC provides the better resolution, but I believe that ongoing developments with AEX column chemistries and chromatography systems make it a technology to watch for the future. Chromatography systems are already up and running in the QC environment for other processes and specialist expertise is not needed. Also, chromatography lends itself well to automation opportunities, opening the door for high-throughput capsid analysis, ultimately providing a more cost-effective way of speeding up product development and reducing time to market.

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Ethics or Profits?

Lab shopping not only destroys trust in the industry – it also puts consumers in harm's way

By Joshua Swider, Co-founder & CEO, Infinite Chemical Analysis Labs, California, USA

California: Home to some of the best cannabis in the world. From the Emerald Triangle's premium flower to solventless hash rosin, the industry has quickly evolved from backyard experiments to an artisanal craft. Before any products can hit the dispensary shelves, they must undergo state-mandated quality and safety testing. Producers have 36 labs to choose from to conduct the analysis, but not all labs are created equal. Some labs have prioritized quality analytics, while others have prioritized profits.

Clearly, there is an incentive for companies selling cannabis concentrate or flower to find the lab that will report the highest THC concentration – higher THC equals more profit. This has left the industry vulnerable to the practice of "lab shopping." It's not difficult to find a lab that's willing to boost numbers to gain more business (or so I've been told). I've lost count of the number of times people ask me to bump potency up with the promise of money or "earning the account." One request we get from producers more than you would believe is to guarantee their flower always tests over 30 percent THC. I value ethics over profits. However, not every lab in the industry does. When I refuse to ensure over 30 percent THC, the grower has no problem calling the next lab on the list.

Lab shopping is not only unethical in that it misleads consumers – it also hinders the industry. I have clients who will test a concentrate sample and get 87 percent THC during R&D, then take it to another lab that will report a 95 percent THC at compliance. This leaves me with two choices: I can start inflating numbers to earn a company's business or continue to provide precise, quality analytics and potentially miss out on millions of dollars in revenue.

It comes down to scientific as well as personal integrity and ethics. Lab operators should ask themselves why they are in this industry: is it public safety and science, or is it to make money at the public's expense? As chemists, we don't spend time and effort earning degrees to fudge potency results for someone to sell their product at top dollar. If consumers knew the rampant nature of THC inflation, they would have zero confidence in results posted by most labs. If people cannot have confidence in potency results, how can they have confidence in the accuracy of safety tests?

The current regulations set for testing pesticides are another massive contributor to lab shopping. The 66 analytes we are required to test for are split into two different categories: 45 belong to Category 2 and have an action limit for the maximum amount allowed before causing a sample to fail. If any amount of the other 21 pesticides (Category 1) are detected, it will result in a failed batch.

The only analytical requirement for Category 1 pesticides by the California Bureau of Cannabis Control is that the laboratory must quantify them above

"It comes down to scientific as well as personal integrity and ethics."

100 parts per billion (PPB). This is when the quality of a lab (and its analytical scientists) really comes into play. If a lab has done its job and created a method that is as sensitive as possible for consumer safety, it will be the best lab for the public and the worst lab for its clients. For example, one lab might have a limit of detection of 30 PPB, but another has a limit of 75 PPB. A sample with a pesticide concentration at 50 PPB would fail at the first lab and pass at the second. This problem is not new – it has been discussed for years, yet it remains in the regulations. We've unknowingly participated in many blind spiked sample studies by clients, where a contaminated sample was sent to multiple labs. The results prove that other labs are missing category 1 and 2 pesticides over action levels or required LOQ.

Misreporting pesticides is harmful to consumers and creates an unequal playing field in the lab industry. Current Category 1 pesticide testing regulations allow cannabis companies to work with a lab with less stringent standards than competitors. Instead, regulators need to assign action limits to all pesticides. California regulators should conduct a blind study to reveal how well cannabis is currently being tested – and how much danger they are exposing residents to under the current system. Until then, consumers will continue to be at risk of buying products that advertise inflated potency values or, worse, fail to meet the safety standards for consumption.

The Safe Hands of ICP-MS

Anna Cousens, Global Analytical Business Development Manager at Almac Sciences, discusses ICP-MS analysis and the importance of getting it right in drug development

Almac Sciences – part of the Almac Group – provides integrated services from development to commercial scale for API and finished products and employs over 170 highly skilled analysts working in GMP/ GLP environments across the UK, Europe, and US. We spoke to Anna Cousens, Global Analytical Business Development Manager, about inductively coupled plasma MS (ICP-MS) and its importance in drug development.

What is ICP-MS and why is it important to drug development?

ICP-MS is a spectroscopic analytical technique with applications in the detection of metals in drugs. It is one of many different analytical techniques in use in the industry to ensure that all drugs on the market are safe to use, manufactured to a high standard, and free from impurities. ICP-MS is a relatively new technology that came into mainstream use three years ago, when new US Pharmacopoeia regulations were implemented regarding limits on heavy metals in pharmaceutical products.

The US Pharmacopeia is considered the gold standard of pharmaceutical testing. It covers a wide range of analysis, but chapters <232> Elemental Impurities – Limits and <233> Elemental Impurities – Procedures specify limits and analytical procedures for elemental impurities in drug products. These new chapters came into force on January 1, 2018, and prompted updates to ICP-MS analysis in the industry.

How did the updated regulations drive changes in the market?

These regulations impacted how CDMOs and pharma companies performed their analyses. In the last three years, there has been significant activity in this space as manufacturers sought to comply with the new regulations. Because any pharmaceutical product sold in the US needed to be in compliance, the changes were felt across all drug delivery platforms from tablets and capsules to vials, injectables, and even devices. In addition, the regulations had repercussions for suppliers because the final product manufacturers performed risk assessments to see where elemental impurities could originate. This led to a significant increase in the number of requests to API, raw material, and excipient suppliers and manufacturers for information about their procedures.

Essentially, the entire industry had to update their testing regimens to include the new ICP-MS standards. Some companies with very low risk of elemental impurities performed a risk assessment that limited the amount of testing required, whereas others had to completely rethink their approach and develop and validate new ICP-MS methods for their entire product portfolio. With increased demand in testing, equipment sales to finished product manufactures, big pharma, and CDMOs grew exponentially.

How did Almac react?

Almac invested heavily in both equipment and staff, employing team leaders with experience in method development and validation, purchasing state-of-the-art equipment, and qualifying that equipment for GMP use. This included an Agilent 7900 and a Thermo iCAP RQ.

Over the last five years, Almac has developed a wealth of experience, performing 57 validations (phase I to commercial release), offering QC support for more than 30 APIs, and analyzing approximately 60 different test articles – including drug substance/API, excipient/drug product, and raw materials.

We have robust methods in place to support our existing clients – and new clients can also leverage our library of methods.

What is next in this space?

The pharma world is constantly evolving. Even now, new guidance is being issued on nitrosamines, which – although not as widely applicable as the heavy metals limits – will be the next big analytical challenge.

With its 20 years of experience in LC-MS, Almac is already working to adapt to these new changes and has methods in place to support clients in this area. LC-MS equipment is managed by Almac's spectroscopy team, a 30-strong group of employees who manage an extensive range of equipment (including 2D LC-MS/MS equipment, GC-MS, and NMR) that is fully GMP-compliant. The team has extensive knowledge of not only the equipment and our library methods, but also structural interpretation and data processing to ensure the correct experiments are run for each project.

Despite the ever-changing pharma landscape, our team has the experience and knowledge to help our clients navigate key drug development challenges.

ALMAC

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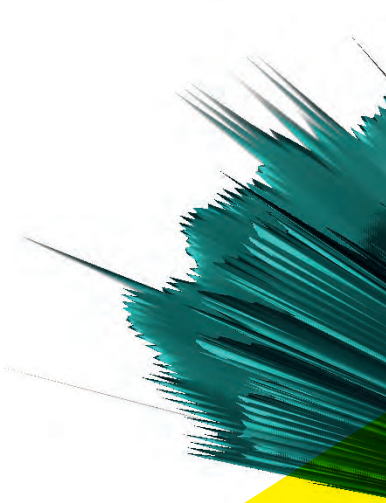
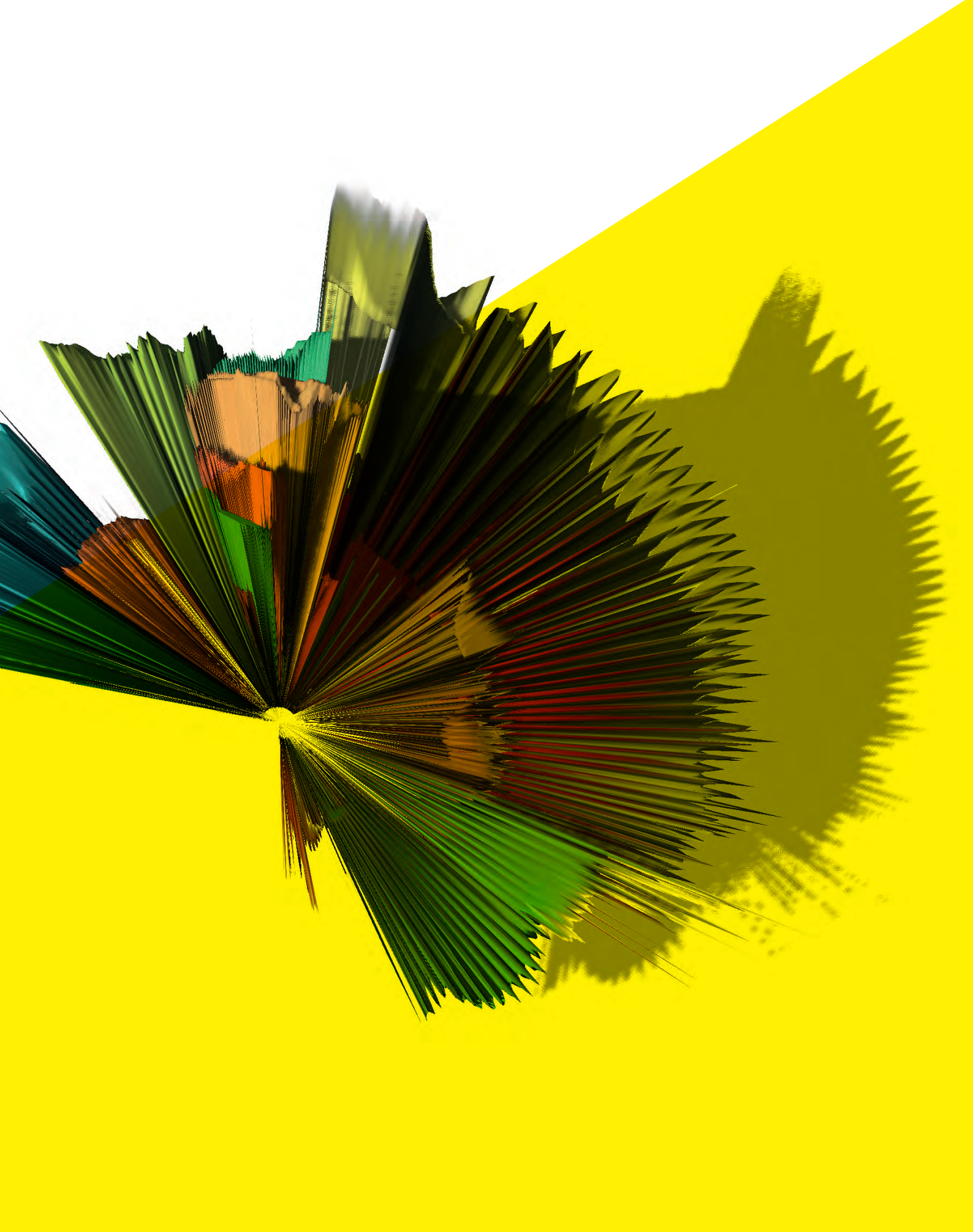
The ART of MASS SPECTRA



Luis Schachner produces mesmerizing artwork from mass spectra to spread messages about leading research and the quest for equity in science…
Welcome to his gallery!



TELL US A BIT ABOUT YOUR SCIENTIFIC BACKGROUND...

I was born in Venezuela and came to the USA for college, where I was determined to study International Relations and make a positive difference for my home country. But my first encounter with scientific research led me down another path entirely.

I discovered the research world by accident. My summer internship ended unexpectedly during my freshman year and the only job I could find was in an environmental engineering lab. There was something really special about working on the experiments there. I was working with my hands and troubleshooting problems. Everything felt like it was falling into place, and – a few twists and turns later – I found myself doing a PhD in analytical chemistry. I'm completing that PhD right now at Northwestern University near Chicago, Illinois, focusing on the application of MS to structural biology and protein systems.

WHAT WAS IT YOU LOVED SO MUCH ABOUT SCIENCE? AND HOW DID THIS TRANSLATE INTO SCIENTIFIC ART?

I was excited by how easy it was to collaborate with others through technology and answer many scientists' questions about their favorite systems. By my second year, I had over 30 active collaborations across multiple departments. As you can imagine, my PI wasn't too keen on this, so I had to dial it down a bit. But it felt like I was doing science with friends and I had so much fun, often inviting my collaborators to join me as I analyzed their samples on the instrument. Research felt more meaningful this way.

I only became aware of the "art multiverse" when I attended an art and meditation festival in the American midwest. It was around that time that I had discovered mindfulness and was really enthusiastic about it. But I had this sense of: "I'm present. Now what…?" After meeting all sorts of artists, I had an empowering feeling that, when I was present, I could start flowing with my imagination and create without judgment. I wasn't conscious of this then – or how I would relate it to science – but that was the beginning of an amazing journey.

"Along the way, I've been inspired over and over – by both scientific and artistic discoveries."

WHERE DOES YOUR ARTISTIC INSPIRATION COME FROM?

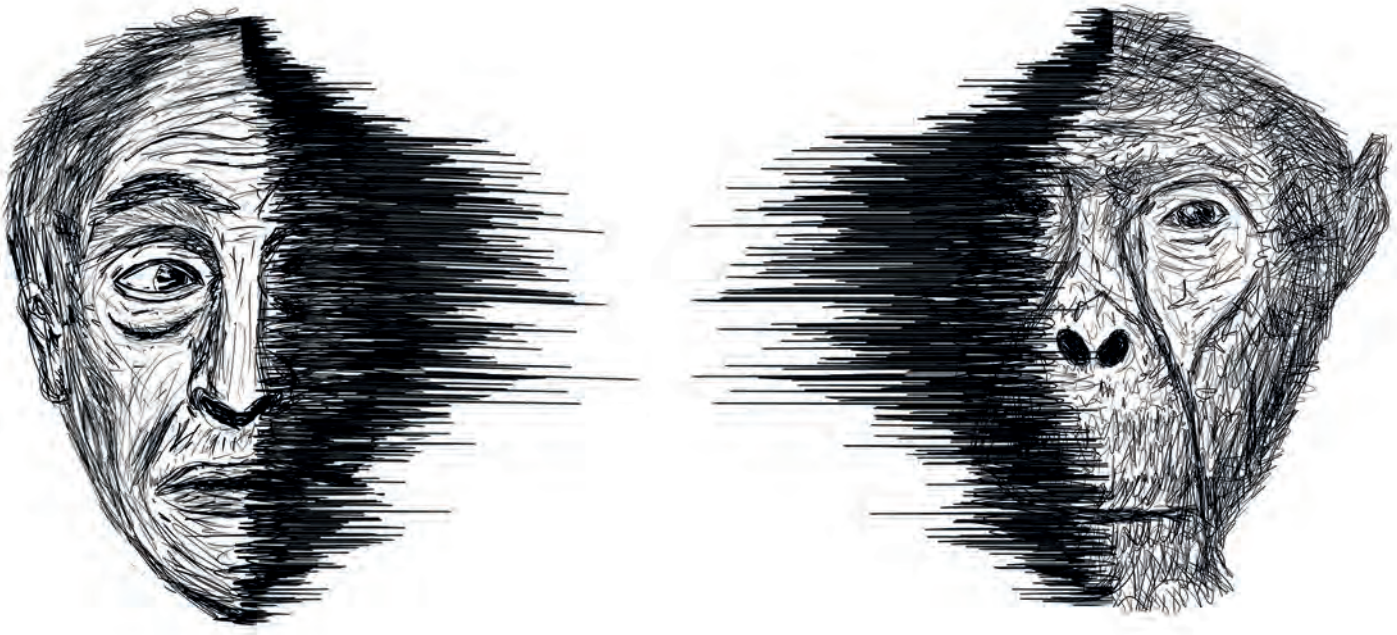
That's a great question, because it's definitely something that I struggled with as I started my art journey. I would look at the blank canvas and be totally overwhelmed. Overwhelmed then quickly became overthinking – and then my mind would freeze completely. One day a colleague approached me while I was analyzing a spectrum; she said that I could see things in the data that others can't. I was inspired by what she said. I decided to start with the data, rather than the (intimidating) blank canvas in front me. Extracting and manipulating the data then triggered my inspiration.

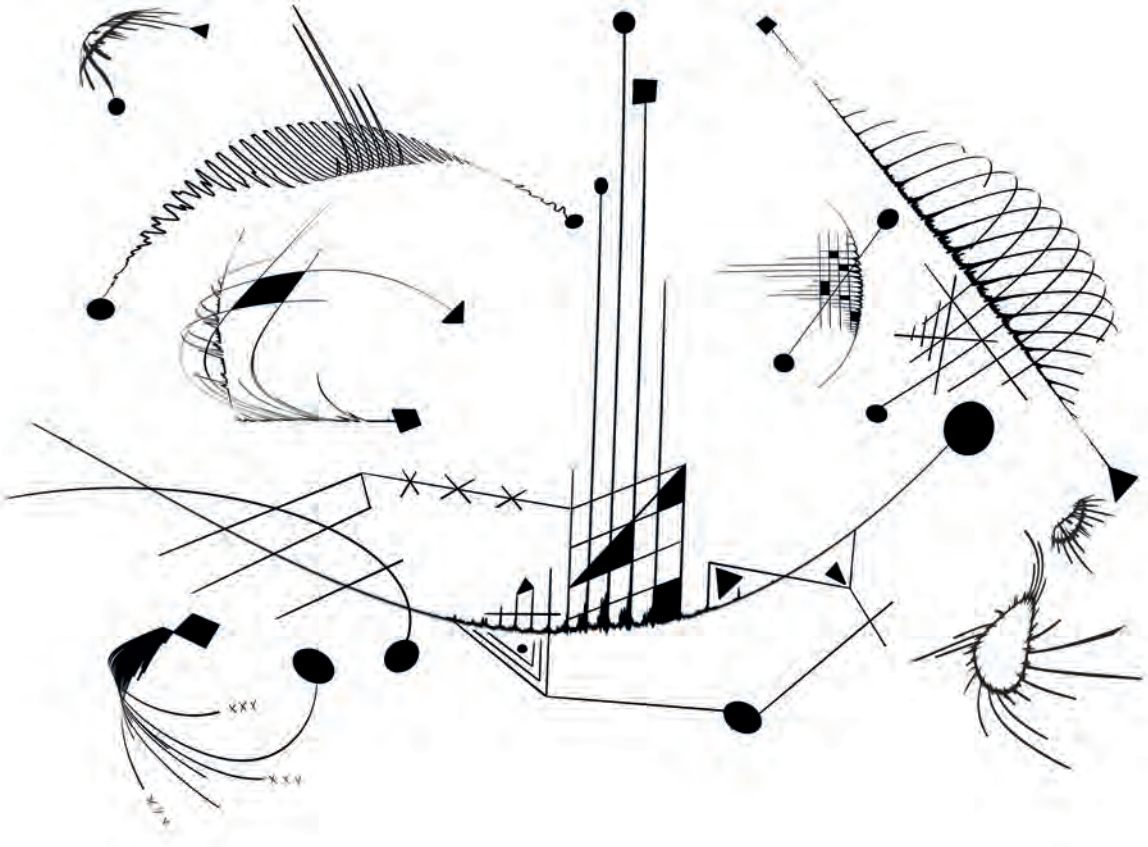
Along the way, I've been inspired over and over – by both scientific and artistic discoveries. My vision now is clearer: to play with spectra in subjective ways, and also to create art using increasingly accurate representations of data. Part of this will involve moving my art into three dimensions, which should allow me to create actual shapes that represent the parameters and constraints of the data. I'm learning to code now so that I can do that.

THE FIRST PIECE OF YOUR WORK THAT I SAW WAS A BLACK WOMAN SKETCHED WITH THE GC-MS SPECTRA FOR MELANIN. HOW DID THAT COME ABOUT?

I collaborated with two colleagues, Danté Johnson and Raquel Shortt, who represent the black community in MS. We became friends at conferences and they loved my art portfolio. By the time Black History Month came around, the three of us were brainstorming a way that we could combine my passion for art with the need for powerful messaging about increasing the number of Black researchers in science. We wanted to start important conversations about representation, diversity, and equity (see April's Image of the Month: Portrait of a Black Researcher).

One of the key ideas we had was using spectra for the hair. I had used spectra to create hair in my previous works; for example, in my drawing of Ronald McDonald using high-density lipoprotein spectra. But that's a tale for another time.





TOP:
The loss of self, as experienced by both man and monkey, symbolized by Alzheimer's amyloid beta protein spectrum. With the ability to anticipate danger, humanity fears losing one of its quintessential qualities: the mind. Neurodegeneration is also a painful process for the family and loved ones who witness it. The juxtaposition of man and monkey evokes two reflections. First, the evolutionary lens reminds us that a man with Alzheimer's does not lose his humanity. Second, we notice that the man is looking toward the monkey expectantly, inviting us to reflect on the use of non-human primate models in Alzheimer's research.

BOTTOM
"Lost in the Mass Spec Universe." Proteins' spectral signatures create unique shapes and geometries that have a life of their own. Inspired by Miró, I created a window into this alternate spectral dimension where there is no limit to how the data is imagined or depicted.

Beautiful afros and wonderful, thick hair are really prominent in Black culture, so we opted to draw a Black woman with hair comprising GC-MS traces for melanin. I think the result speaks for itself.

We're now working on other projects with the same aim, including some doodles of Henrietta Lacks, a Black woman whose immortalized cervical cancer cells were taken without consent and are still used in medical laboratories around the world to this day.

I LOVE THAT CONCEPT! WHAT OTHER EVENTS DO YOU CELEBRATE WITH YOUR ART?

I'm working on a couple of others right now – one for Women's History Month, and another for trans representation. Then there are a handful of general celebrations in the field, too. The other day, I even saw some scientists post about an MS application that allowed them to differentiate between grain-fed and grass-fed beef. I'm not exactly sure why, but I found this very exciting (in spite of the fact that I'm in the process of becoming vegan). I immediately dropped everything I was doing and started drawing a steak. I even used their mass spectra to mimic the marbling of the meat. Once I finished, I sent the drawing to the researchers in question.

"I'm very curious, and I love to share that curiosity with people who share my passion for research."

It's great because I love to share my excitement with the people doing this great work. Together, we create this continuous cycle of creativity and joy. And that's a wonderful thing, because the scientific community – as supportive as it can be – can tend to take things very seriously. I'm very curious, and I love to share that curiosity with people who share my passion for research.

HOW DO PEOPLE REACT WHEN THEY RECEIVE AN UNEXPECTED PICTURE – FOR EXAMPLE, A GC-MS STEAK – FROM YOU?

They love it. It's quite special to connect with a student who's really excited about their work, so when I up the ante by appearing out of nowhere with a drawing of a steak in the context of their research, I think they find it gratifying. And it's a lovely experience for me, too. I love connecting with enthusiastic researchers and grad students. It's another amazing example of how we can create and maintain a community through our appreciation for MS.

HOW LONG DOES A "STANDARD" DRAWING TAKE TO CREATE?

I guess that depends on how long it takes to make a given drawing as stunning as it needs to be. The steak took me 30 minutes, but that was a quick one because I was really excited about the meat. In any case, the first step in my process is to study the raw data, noting the thoughts and images that come to mind as I do so.

That process is apparent in another piece I made for another scientist on Twitter. The scientist in question had commented on one of my posts to say that she really wanted her own drawing. Once I noticed that she was a fellow analytical chemist, I did what any budding artist would do: I looked

Van Gogh's Starry Night, incorporating the mass spectrum for Prussian blue, a staple pigment used by some of the world's most famous artists from the 18th century onward.

at the spectra from her own microplastics research and used them to draw the first image that came to mind – a fish skeleton. Once I had that clear vision, it took me around 45 minutes to bring the drawing to life.

The melanin piece that I worked on with Danté and Raquel took me around two hours after I discovered a neat trick to transform the spectral lines into curls for the afro. With an additional week or so of minor edits and new iterations with my collaborators, it was ready to share. One thing I am learning on my artistic journey is to let go of my perfectionism!

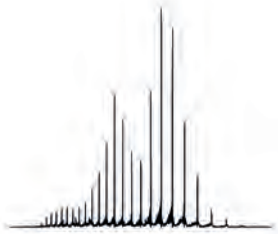
CAN YOU TELL US A LITTLE MORE ABOUT YOUR ARTISTIC JOURNEY SO FAR?

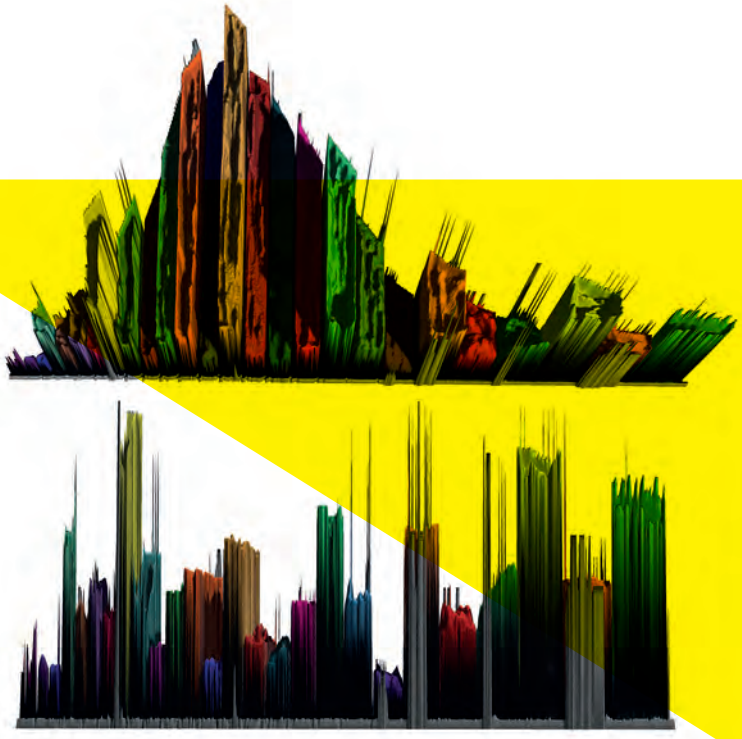
Well, I should start by saying that I don't have a particularly artistic background. I empowered myself to learn (putting in lots of practice on my iPad) over the couple of years following the art festival I mentioned earlier. As I started to wrap up my PhD projects and began writing articles for publication, I started referring to my scientific figures as art. I would even joke with others that, to me, a mass spectrometer was an instrument with which I was making molecular art in the form of spectra!

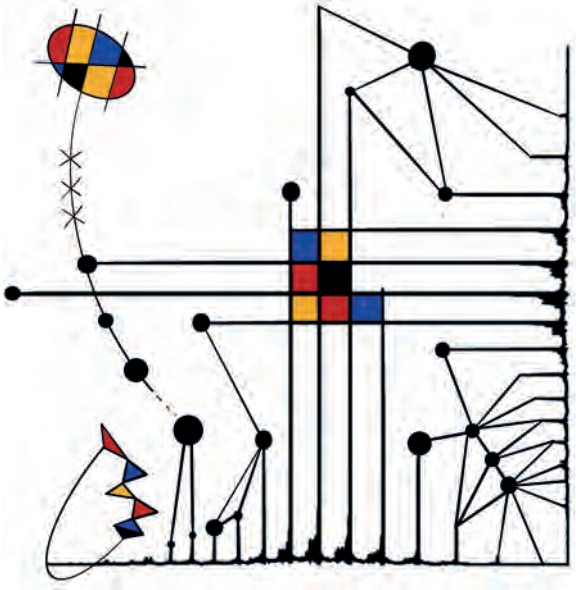
During this process, I also became slowly more conscious of this strange boundary between data visualization in science and art. At times, I found this boundary became much more blurred than we might first imagine. Consider it for yourself… At what point does data visualization become art? And at what point can art become a form of meaningful data representation?

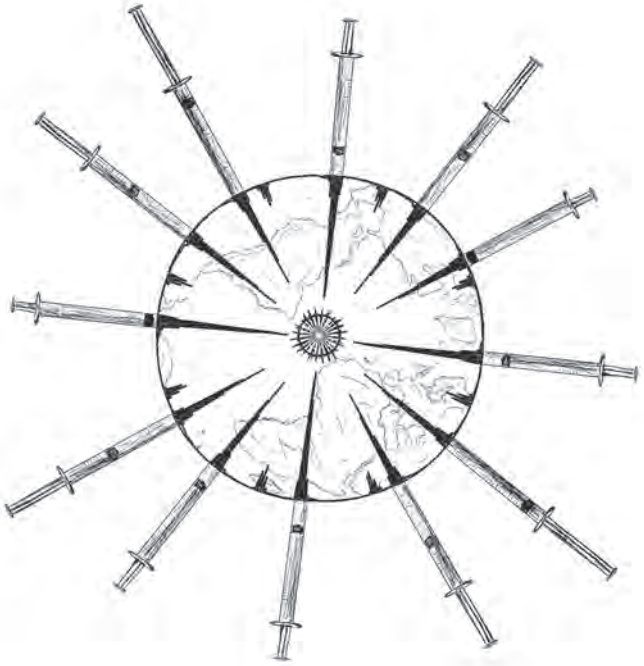
I found myself existing somewhere between these questions. Plus, MS is a very special technique – not only

"One thing I am learning on my artistic journey is to let go of my perfectionism!"









TOP LEFT:
The native mass spectra of synthetic (left) and endogenous (right) nucleosomes transformed into artistic representations that highlight the order in human design and the chaos of biological diversity. The drawing of the Golden Gate Bridge is an example of the artificial and repeating structural elements used in architecture which maps neatly onto the spectral signature of a synthetic nucleosome, a biochemically defined single species with mathematically precise charge state distributions. The endogenous diversity of nucleosomes – due to differences in DNA and histone modifications – produces an undecipherable spectral signature that, like the man's mustache, reflects the beauty and messiness of biology.

TOP RIGHT:
A cityscape formed from a 3D extrusion of the mass spectrum for carbonic anhydrase.

BOTTOM LEFT:
"Data intersections." The parallel lines in spectra only intersect through a lens of subjectivity and artistic intent. Inspired by Miró and Piet Mondrian, I created nodes and intersectionality that symbolize the ways analytical scientists make associations across data sets and "connect the dots" to theorize about the nature of our physical universe.

BOTTOM RIGHT:
Antibody spectra injecting vaccine into the RBD domain of the COVID-19 spike protein spectrum. The RBD domain facilitates SARS-CoV-2 binding to human ACE2, mediating cellular invasion and subsequent illness.

"I'm really proud of the melanin drawing and how it was received by the community, and also my progress with 3D modeling and animation – the possibilities are endless!"

because of the massive community surrounding it but also because it brings together disparate disciplines around the study of atoms and molecules. At the annual ASMS meeting, you'll see biologists, geologists and food chemists connecting around MS. Maybe this interface is the reason that I felt such kinship with the data it produced. I didn't want to portray that data accurately at first, mind you. I just wanted to play with the spectra!

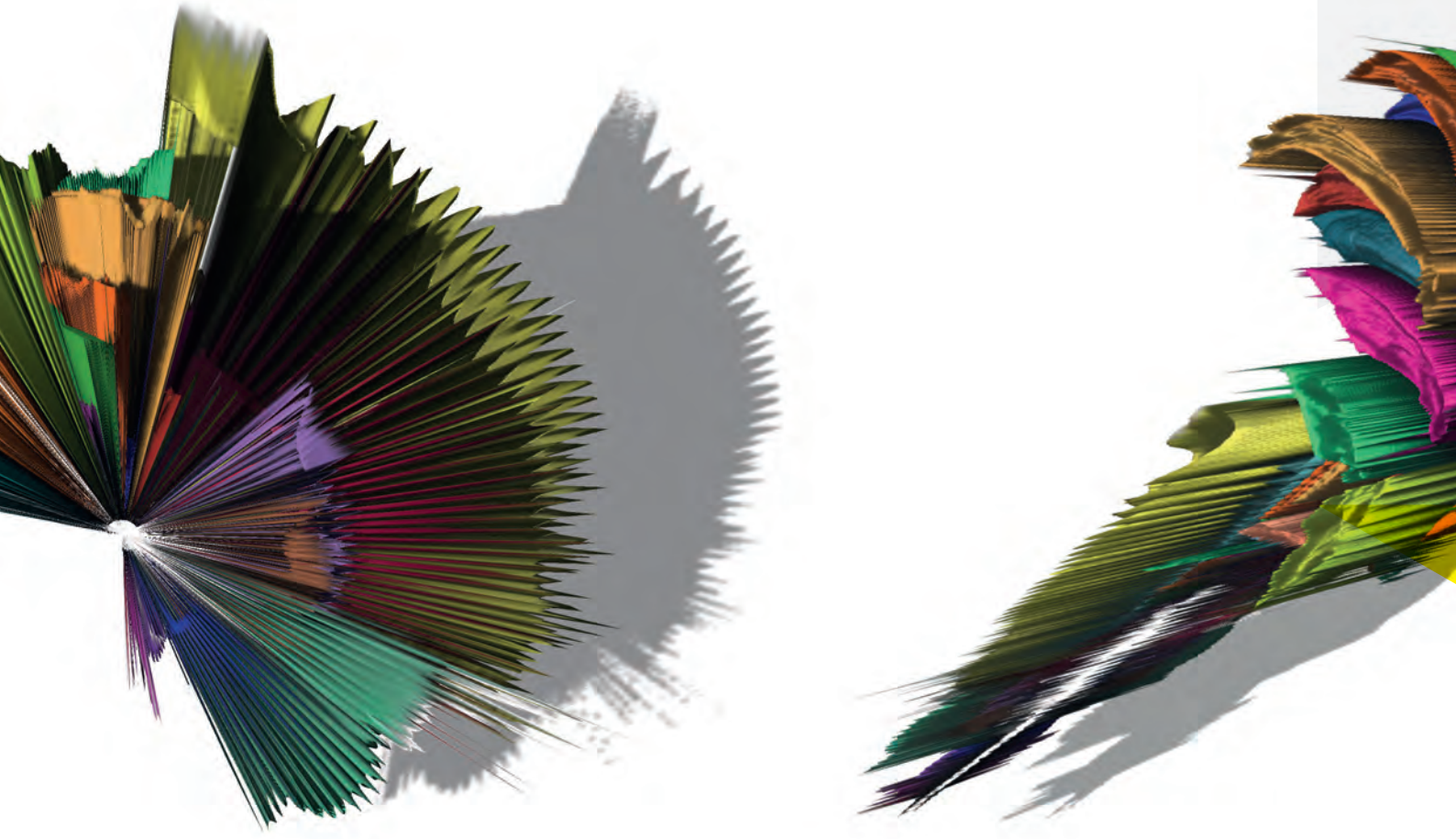
ANALYTICAL SCIENCE MUST BE AN AMAZING FIELD IN WHICH TO EXPLORE ABSTRACT CONCEPTS AROUND DATA VISUALIZATION...

Absolutely. Analytical science is a great medium for my art. Why? Well, because it's analytical science! There's not much out there that celebrates the amazing data we gather. Don't get me wrong; we are always talking about what our data mean, but we don't spend time just looking at and admiring our data. In a way, the mass spectrometer records the spectral essence of molecules, and it often produces unique patterns and experiences. One of the main drivers behind my love for MS is the shapes and parallel lines that it produces… I love parallel lines! Moreover, by changing the conditions inside the instrument, we can interact with the ions directly. The mass spectrometer thus transduces our will into the molecular universe; the whole process is phenomenal.

WHICH PIECES OF ART ARE YOU PARTICULARLY PROUD OF?

I'm generally happy with all of it. I'm really proud of the melanin drawing and how it was received by the community, and also my progress with 3D modeling and animation – the possibilities are endless! The nucleosome is my favorite subject at the moment. I studied it extensively during my PhD, and I'm playing with lots of ways to depict it in 3D space using all of the structural data available. I even made a drawing of a sea urchin using the 601 DNA sequence, which is vital for nucleosome biochemistry and was discovered in sea urchins. So many little discoveries have made my research possible, and I want to honor them as I go.

I have also been interested in learning about the role of analytical chemistry in the conservation of fine art. For example, Prussian blue is a deep blue pigment made of iron-cyanide crystals that revolutionized the art world in the 19th



"I'm actually writing (or rather illustrating?) a picture book for scientists based on different data collections – but I'm also planning to add an element of augmented reality to it."

century. At the time, blue paint degraded easily and did not have much depth. I used the mass spectra of Prussian blue to draw my interpretations of paintings that first made use of it like "The Great Wave off Kanagawa" by Hokusai, and others by Van Gogh and Hiroshige, to commemorate the ways in which mass spec is contributing to art around the world.

WHAT ARE THE MAIN PROJECTS YOU'RE WORKING ON NOW?

I'm actually writing (or rather illustrating?) a picture book for scientists based on different data collections – but I'm also planning to add an element of augmented reality to it. The idea

3D renderings and transformations of the carbonic anhydrase spectrum. Carbonic anhydrase is a robust protein and easy to work with. For this reason, it serves as a great model system to test new technology and method development. I wanted to artistically celebrate this enzyme, which interconverts carbonic acid with water and carbon dioxide, and highlight its extraordinary role in analytical science.

is that a scientist (or non-scientist) would have a physical book with my drawings and the scientific and human stories behind them. But then they would also be able to scan the images with their phone to bring a 3D version to life so that they can interact with the data much more dynamically. Progress is good so far; I'm getting close to having a full version to share with the American Society for Mass Spectrometry soon. I think they'll like it.

I also have a physical gallery exhibit in the works. I'm preparing a showing based on molecular and spectral perspectives on plastic. The aim is to expose the meaning of plastic, from its monomer building blocks all the way up to the complex structures that they come together to form. I'm planning to have 3D-printed sculptures, augmented reality exhibits, canvas… all to show that plastic allows us to turn our dreams and visions into reality thanks to its malleable and versatile nature. I'm also collaborating with an artist who specializes in gamified, interactive experiences. For this, we are building an augmented reality game around the exhibit, where the audience acts like PETase – a bacterial enzyme that "eats" plastic – to clean up plastic litter in a virtual scene using their phone. We want to place the exhibit in the context of the human experience, but also create a sense that "plastic" is an idea and that there are many ways to engage with it.

I also prepared a set of drawings for the 420 holiday. For the uninitiated, this is an annual celebration of all things cannabis on April 20. My aim here is to showcase the amazing MS research happening in the cannabis space right now (for example in quality control) to produce some cool pieces that can communicate the

importance of this research. I want to dispel stigma around this research area and normalize conversations about cannabis.

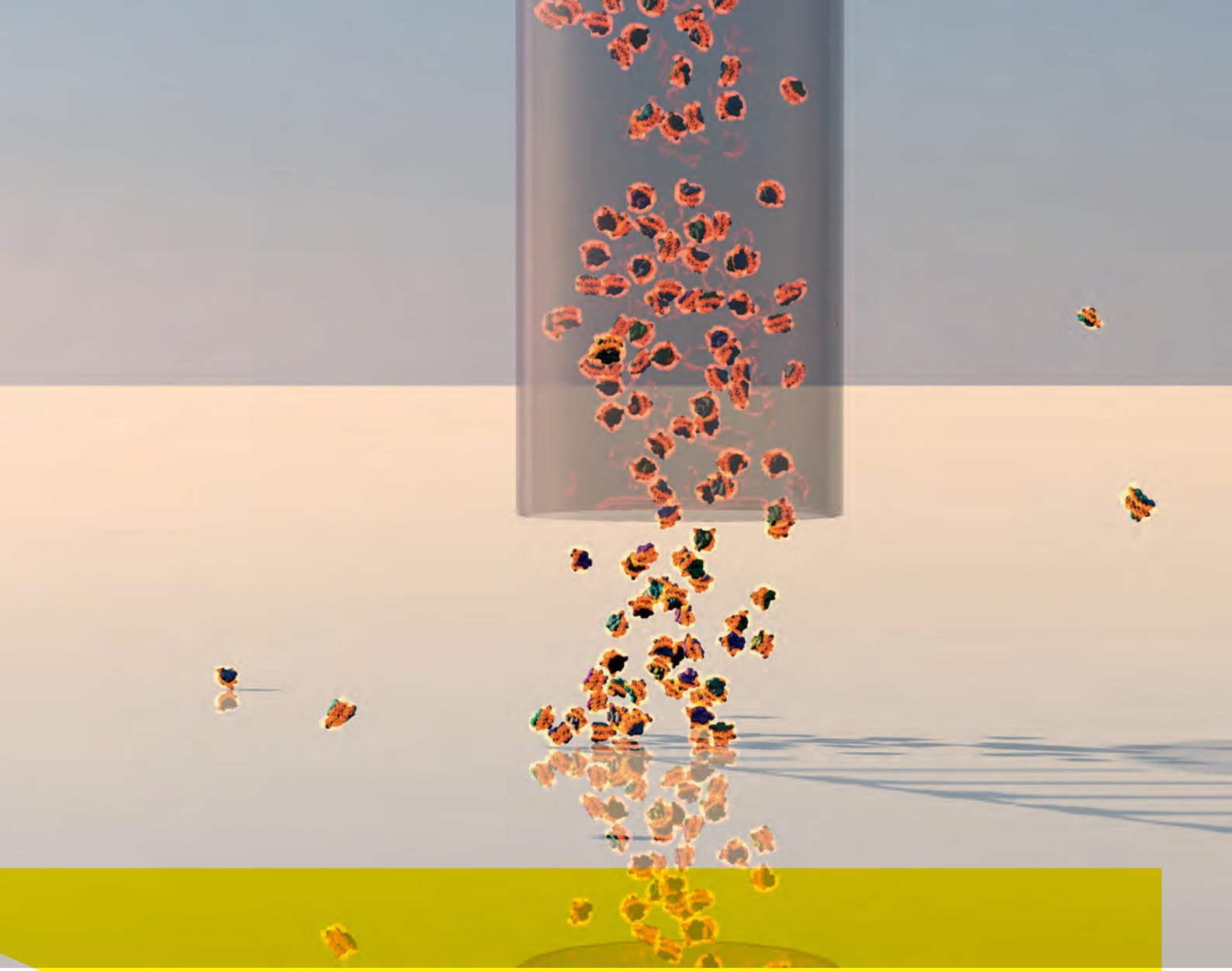
DO YOU HAVE A VISION FOR THE FUTURE OF ART AND SCIENCE INTERSECTIONS?

With the current expansion in digital art and animation, there are many opportunities for science storytelling to become more artistic in structural ways. Imagine science conferences that also hold a space for a curated exhibit of the participating scientists' art. Or a journal that publishes great science but with a strong emphasis on art, animations and beautiful figures.

Artists and scientists share lots of great qualities. I envision the two worlds coming together in playful and productive ways to creatively address the shared needs of our communities.

"Imagine science conferences that also hold a space for a curated exhibit of the participating scientists' art."

To see more of Luis' artwork, check out his Instagram (@luis.schachner) and Twitter (@ArtSpectrometry) accounts.



LEFT:

A still from a video celebrating the LC-MS run of a mouse's stool proteome in a multiple sclerosis model (Gonzalez C et al., Sci Rep (2019)). Poop is an ancient part of the human and animal experience and analytical scientists are currently researching its composition in the hopes of finding connections to health and disease. In collaboration with Carlos Gonzalez, we wanted to create a 3D LC-MS "temple" that commemorates the mass spec research about our poop. Visualizing the chromatographic peaks with these dramatic, earthy textures evokes a greater-than-self, ancient importance. The video ends with a comedic salute to the poop taboo and the ways analytical science is unafraid to explore where no one has before!

ABOVE:

Studying nucleosome particles by MS, with a shadow forming their representative spectrum. During my PhD, I studied nucleosomes extensively using MS and wanted to create a 3D scene that represents the moment the nucleosomes leave the infusion capillary and reach the mass spectrometer. 3D animation is a great opportunity to reimagine the publicly available structural models for protein and DNA as media that can be turned into art.

PUTTING MS *to the* (COVID-19) TEST

Can MS hold its own as a diagnostic tool in the fight against a pandemic?

When we talk about the power of MS testing, it can be easy to overlook (or forget) the challenges involved in translating a promising approach to the clinical lab. And, in the context of COVID-19, MS already has strong competition: real-time RT-PCR offers impressive sensitivity and specificity and lateral flow tests are tough to beat on speed and cost. So is there any room for MS in the fight against this pandemic – and those of the future?

Leading mass spectrometrists think so! And despite the hurdles ahead of translation (from training personnel to proving the robustness of the tests themselves), Perdita Barran and her team at The University of Manchester, UK, managed to achieve the feat in just four months within the National Health Service (NHS). Here, Perdita offers us a unique insight into the project's journey from academic to clinical labs. We also speak to Maarten Dhaenens and Jennifer van Eyk (both external advisors on the project) about the diagnostic value of MS and its impact beyond coronavirus testing.

WEIGHING *Viruses*

How clinical MS can be mobilized for national testing

By Perdita Barran, Professor of Mass Spectrometry, The University of Manchester, UK

When faced with limited access to coronavirus tests at the height of the pandemic, I was inspired to repurpose my laboratory – and mass spectrometers across the UK – to assist with national testing. Over the past six months I have acted as a Scientific Advisor to the UK Department of Health and Social Care. And now a network of eight academic labs in the UK have joined forces with twelve clinical laboratories based in the NHS (backed by government and industrial funding) to deliver a rapid and sensitive MS test for coronavirus. Here's how we did it…

Mobilizing MS

The first key challenge with our pilot was to develop a method that was robust enough to be readily adopted by the NHS. Thankfully, NHS staff already perform more than 750,000 MS-based tests per year on new-born babies alone, along with further tests for diagnosing other metabolic disorders and for therapeutic drug monitoring. We wanted to tap into this world-class capability that had already been established within our labs.

When the pilot started, we had three clear criteria:

i. the method should have clinical utility (in other words, it can be performed in a routine hospital laboratory),
ii. the assay could be widely adopted (which necessitated viral deactivation upon sampling)
iii. the lab-based test should be compared with RT-PCR assays in terms of its specificity and sensitivity.

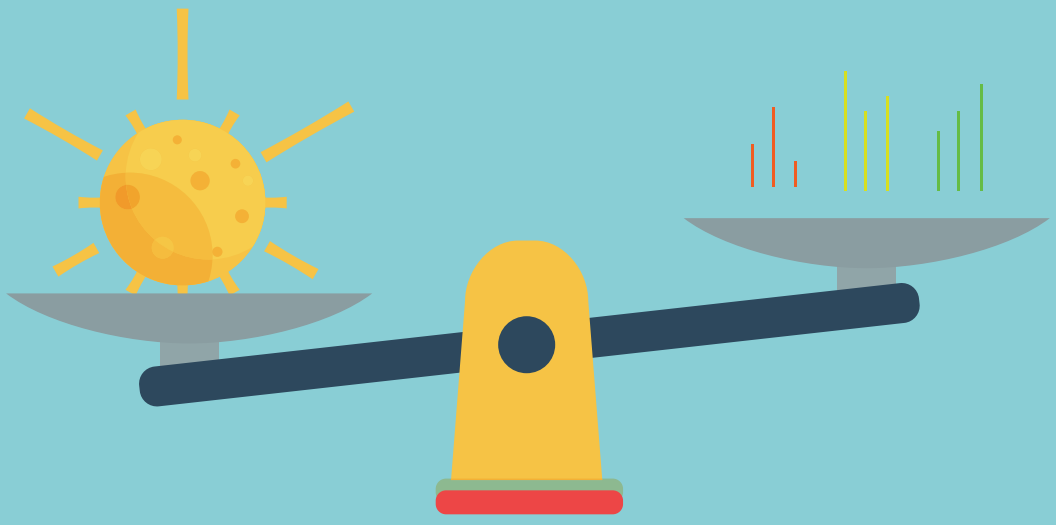
Following a period of consultation with academic groups who had already signed up to the COVID Mass Spectrometry Coalition, eight laboratories with strengths in proteomic analysis and method development were selected to take part – we called these the 'Pillar 1 labs.' They had to be willing to act, have strong links to hospital laboratories, and have experience with translation. Trials began with recombinant forms of viral proteins establishing limits of detection and quantification with proven methods. The work of Maarten Dhaenens at the University of Ghent, which involved some of those academic labs, was compelling. He had shown that quantitative proteomics performed on LC triple quad platforms was able to detect the presence of peptides from the spike and the nucleocapsid protein at levels that were commensurate with PCR Ct values of 25 – the stage at which symptoms can be mild or non-existent. Also of interest were the MALDI methods developed by Ray Iles of MapSciences, and two academic labs were chosen accordingly for their expertise with MALDI instruments.

> *"The first key challenge with our pilot was to develop a method that was robust enough to be readily adopted by the NHS."*

Handling live virus severely limits the type of laboratory and the staff that are available to perform such assays. Because of this, we started thinking about different methods of viral inactivation that were compatible with MS. We considered heat and UV exposure, but only organic solvents were suitable for the deployment of mass testing. Fortunately, robust tests performed at Public Health England's testing labs in Porton Down helped us decide on the best approach, and volunteers at the Manchester Institute of Biotechnology (MIB) set about filling 30,000 falcon tubes with our deactivating solution. We decided to consider two different methods of sample acquisition. The first method was identical to the one used ahead of RT-PCR – an oral nasopharyngeal swab that could later be added to the deactivation solution. The second, which was also being used elsewhere in test development, collected saliva via a funnel that fitted into the sample tube. Each participant in our pilot would be asked to provide a saliva sample as well as being swabbed twice – one for the MS test and one for a comparator RT-PCR test.

Finding samples

Test packs at the ready and methods being developed, we needed a source of samples. But that proved much harder than we had anticipated. Eventually we found the indefatigable



Rick Body – an emergency care consultant who was leading an NIHR research program called FALCON, which had been set up to enable trials of new tests. Rick applied for an ethical amendment to allow samples to be collected for MS, and, in early November 2020, we started to receive samples from patients who had been admitted to hospital with COVID-like symptoms. The number of hospital collecting sites grew and again the MIB volunteers, led by the marvelous Kat Hollywood, dug in and made up boxes of swabs, saliva funnels, and collecting tubes, as well as boxes for the hospitals to post samples on to the P1 academic labs. Students at the MIB and staff at Manchester Foundation Trust Hospitals also took part to boost sample numbers. As we neared the end of the P1 process at Christmas, we had received a total of 285 samples by this route; the positivity rate was just over 10 percent.

Though several of the P1 labs had shown that LC-MS/MS could detect a few 100 attomoles of protein, 285 samples split 8 ways was not enough for the pilot labs to prove the validity of a new test. We were therefore very grateful for the suggestion from Ed Blanford (Head of Test Validation for the Pillar 2 test labs) that he could send the FALCON study coordinators a list of names of people who had tested positive and agreed

to provide material for research into new tests. This was a lifeline; again, the MIB team swung into action; more packs were made up and sent out to people at home who had tested positive. With the new variant came a rise in people testing positive and by mid-January we had received enough samples.

The final transfer

At this stage, we had shown that MALDI was not sensitive enough to compete with the LC-MS/MS methods; in fact, even the LC-MS/MS methods were struggling to reach the technical limits of detection with background from other proteins in the samples. We decided to try a capture method, where digested peptides specific to the nucleocapsid protein bind specifically to antibodies tethered to magnetic beads. The results from this were electrifying. The specificity of the assays shot up which in turn increased sensitivity. A harmonized method and SOP for samples from both saliva and swab was developed. The method, which is enabled by reagents from SISCAPA, can be automated; the inject-to-inject time on the MS is currently only 3 minutes – meaning at least 480 samples can be run in a day on each MS.

Swabs outperformed saliva, with sensitivity and specificity of 97 and 98 percent, respectively, for samples where the Ct value is 27 or less (600 samples). For saliva, the variation in the background protein levels means that "positivity" is not as clear cut, although the sensitivity is again above 80 percent.

"We all hope that the fantastic vaccine rollout will allow most people to have immunity from severe infection, but none of us know what the virus will do next."

The P1 labs have now handed the method over to 12 clinical MS laboratories, which are geographically spread across the UK. These labs will now seek accreditation for the method from UKAS and then be ready to test the population.

The role of MS as we learn to live with coronavirus

Now that an MS-based test has been developed and deployed in the NHS, what can we do with it? This new capacity could be used to monitor levels of infection in regional outbreaks, in hospital inpatients, and for surveillance studies in different populations, for example, at schools or workplaces. The fact that the virus is deactivated directly after sample collection makes the entire process much simpler; samples can be directly transported to labs for a diagnostic screen.

The method is robust to sample pooling (which enables many people to be screened in a single assay), and we are also able to detect mutated regions of the virus from the non-captured material.

We all hope that the fantastic vaccine rollout will allow most people to have immunity from severe infection, but none of us know what the virus will do next. Therefore, we will continue to need to test people and to monitor vaccine resistance; MS could well have a role to play here.

The investment into the MS test has enabled the deployment of 12 new mass spectrometers into the NHS for a six-month period. Existing staff are learning how to run this assay and I am sure they will continue to make improvements. The long-term effects of the pandemic will necessitate increased diagnostic capacity for COVID, long-COVID and for many other diseases in a population who have avoided visiting their GPs or had test appointments delayed. The very same instruments and capable staff will be able to meet this increased need for accurate and robust analysis of infection and disease.

This government-funded program is an outstanding real-world example of an MS test being translated from academic labs to clinical laboratories across the country. And we have done it in four months. Necessity is indeed the mother of invention; this pandemic has driven so much collaborative and novel science. The entire process also demanded creativity, perseverance, and a willingness to work together to pool resources – as well as the need to compromise.

As for the future, I am optimistic that this will be the first of many such rapid deployment actions. The unique collaborative links that have been formed between academic and clinical labs, gratefully supported by industry, will continue to grow through this pandemic and for future diagnostic challenges.

A WORD *from the Wise*

Maarten Dhaenens and Jenny van Eyk tell us about the value of MS as a diagnostic tool, and its impact beyond coronavirus testing

You're both involved in your own work related to COVID-19. Could you tell us more about that?

Maarten: My lab was actually involved in our own consortium, similar to Perdita's, called CoV-MS, which was looking at developing a short-term addition to the COVID testing toolbox. With my PhD student Bart Van Puyvelde, we were initially only aiming at the discovery phase – we wanted to see if we could detect some proteins related to SARS-CoV-2 in patient samples. But that ended up going so well that before we knew it, we were looking at how it could work in a clinical setting. We got it to a really promising point, but essentially there were too many hurdles to us moving it into the clinic. And that's why I admire Perdita's work so much – what she managed to do really is an impressive feat!

Even though our initial project didn't continue as such, we have continued to work in this area. We had already been talking to SISCAPA, who were building peptide antibodies that essentially act as tweezers to fish out whatever it is you need to measure. Because our strength is really in academic optimization, we've been helping to build different protocols with SISCAPA – and that is actually what the NHS protocol is built around. At the moment, while Perdita has used this ingenious method to inactivate the virus, we are still trying to discover whether we can create an SOP that is perfect for the clinic and will work with any background – because we think we have a better chance of convincing clinical labs to give it a chance in Belgium in this case.

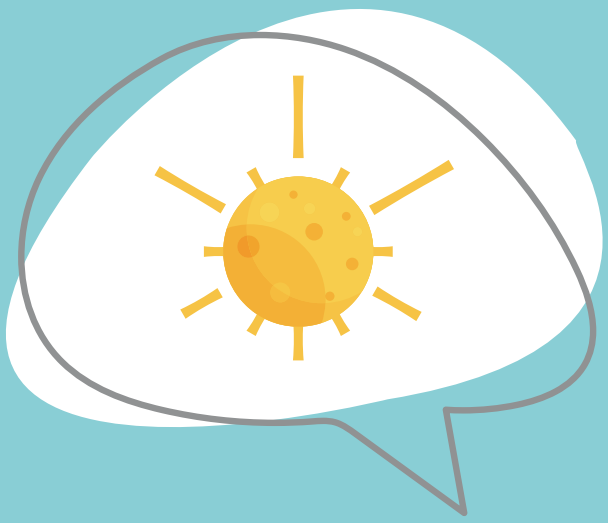
Jenny: My group has been involved in quite a few projects related to COVID-19 with a large number of collaborators. Of interest is a study of multi-systems inflammatory condition (MIS-C) in children, as well as other plasma studies focused on identifying mortality biomarkers. We've also been involved in the analysis of cells expressing different SARS-CoV-2 proteins – in fact, we are about to analyze the California variant (Cal20.C) and look at whether or not there is an underlying difference in the mechanism of infection. The final thing we've been working on is using remote blood sampling devices to look for COVID-19 induced seroconversion post-infection. We've then been analyzing those patients to figure out what the proteomic influences are in that process including those influences in COVID-19 long-haulers. So quite a lot!

> *"I would meet with the team pretty much weekly to help troubleshoot and provide guidance to the team because there was such an urgency to this project."*

How did you initially get involved in Perdita's project?

Jenny: I got involved at the stage where the UK team had already started to generate some of the data – the infrastructure was already in place but they were trying to figure out which methods or instruments were best to pursue. As one of the external advisors on the project, I would meet with the team pretty much weekly to help troubleshoot and provide guidance because there was such an urgency to this project. We were mostly used as part of the decision-making process for the technical and analytical concepts that had to be decided. Of course, it was a unique situation brought about by COVID-19, because advisory boards do not usually meet this regularly. It was a super interesting process to be involved in and it was extremely productive.

Maarten: While we were working on our own test, we got to a point where we had to look for people with access to triple quad MS instruments and who were used to working with them. That's when I sent out an open call to anyone who met the requirements, and we got to work with lots of instrument vendors and academic labs that had more expertise in certain areas than we did. This actually worked pretty well and we got a good idea of what the instrumental capabilities were around the world. It was at this point that Perdita really got to work



on a similar (but much bigger) effort in the UK and managed to get funding from the NHS. So we kind of linked up at that point, and I helped to advise on certain aspects – it was perfect timing really because our project in Belgium was not destined to move into the clinic.

Why is it important to have MS testing for COVID-19 at all?

Jenny: The power of MS lies in multiplexing and the ability to quantify multiple proteins simultaneously, providing better analytics and additional clinical insight. Originally, the test was developed to improve COVID-19 testing capacity in response to a lack of reagents, but its ability to adapt to different variants will also be incredibly useful. Expanding this idea, we could see development of an assay comprising multiple tests for SARS, flu, and lots of other diseases that could be run simultaneously.

The other reason is simply to show it can be done! That is, to show it is possible to efficiently and effectively develop and deploy a protein clinical MS assay. Certainly, there are going to be more pandemics coming our way – with the help of MS we should be able to respond much faster next time, or more immediately, as new variants come out.

> *"The power of MS lies in multiplexing."*

On top of this, there's of course examples where MS can overcome analytical interferences or issues where antibodies don't give you a correct concentration value. But my main interest lies in remote blood sampling devices, where patients can take their own blood sample at home, send it to a clinical laboratory for analysis and then the assay results reported to their physician for clinical decision making. I think this is a really crucial area in healthcare where MS can help.

Maarten: I'd agree with Jenny. For me, multiplexing is the most exciting aspect of MS. It's simply a more versatile technique. With PCR, you need to synthesize a very specific nucleotide sequence. With MS – at least in routine tests – we are using simple chemical reagents. The information we can gather is also much broader. In theory, we should be able to tell patients exactly what variant they have, and even look at other viruses while we are there. If people feel sick at the moment and take a COVID test, they either get a positive or negative result. With MS, we would be able to tell them whether they have the flu or something else – we could even be looking at things like cancer and Parkinson's. Perdita is again leading the way on the latter!

The other argument for MS is that it tells us exactly what is in our sample, as opposed to PCR which inflates the signal. And so, with MS, the risk of contamination is a lot lower. If we truly mobilize the power of MS, we will be much more prepared for future pandemics.

What are some of the challenges in translating such tests to clinical labs?

Maarten: Aside from having to convince doctors, I think the biggest challenge for MS is that it's still too sensitive to the matrix. With PCR, you amplify the RNA and that's the only signal left to be seen. With MS, we see everything – and that has both advantages and disadvantages. I like to use the metaphor that with MS we are trying to find tiny specks of gold in a riverbed – there's a lot of sand that needs to be filtered through, and we need to have the right size holes to find what we are searching for.

Aside from this, the diversity of instrumentation is a major hurdle. With PCR, it doesn't really matter which vendor you're using. With MS, every clinical lab has a different LC, a different buffer system, a different instrument, and different software. Trying to convince people to develop an assay specifically for each vendor is a challenge. In this work with the NHS, they've managed to navigate the issue pretty well because they looked at the performance of different platforms in the P1 Phase and then naturally evolved towards the ones that out-performed others. Then, if a clinical lab doesn't have those specific instruments, you can provide them with SOPs that are detailed and tailored to their set up.

The final challenge, of course, is that we are constantly competing with RT-PCR. The first question everyone asks is: "So you're more sensitive than PCR?" No, of course we're not because PCR detects just one molecule. The next question invariably is: "So you can run more samples than PCR?" Sorry, but no, we cannot look at 1 million patients a day. However, there are all these other amazing benefits that could really have a significant impact on the way we monitor health in the future.

Jenny: I think people still underestimate just how challenging it is to translate these new tests to the clinical lab. The tests need to be so much more rigorous because, all of a sudden, people's lives are at direct risk – and that's not a typical problem when working in an academic lab. So you need to know exactly where every chemical is coming from, looking at every reagent that has its own SOP, and you need to produce the same results every day. Even something as simple as changing pipette or reagent brand, which you might assume to be okay in an academic setting, you absolutely need to

make sure it will be okay in a clinical chemistry environment.

I remain in awe of the UK team's work in bringing an MS-based protein test to NHS clinical chemistry laboratories. To me, what's so incredible is how they've managed to bring together so many research labs in the discovery phase, additional labs in the clinical phase, while working with industry to develop an assay so quickly and to make key decisions in unprecedented time. There's so much that needs to be considered when you are translating a new marker test to a clinical lab – it's almost unbelievable that they managed to do it in such a short window of time.

How is the situation different in the US and Europe?

Maarten: I think it's almost a cultural thing. When I talk to doctors in Belgium, they hear 'mass spec' and immediately get skeptical. In the UK, there are a lot of clinical labs that are used to using MS already, so you're already halfway there. Also, because every test is now benchmarked against RT-PCR, which works very well for what it's supposed to do, people aren't really looking for an alternative. Unless there was another shortage in reagents, people wouldn't really turn to MS instinctively for this testing. So we need to get it as easy to use as possible to see a change in attitude.

Jenny: There's a unique culture in the UK for collaboration, but I think there's another important point to stress here: you can only collaborate and produce work like this if there is a technical and scientific foundation on which to build. You can have all the collaboration in the world, but if you don't have the right support, funding, and expertise already in place, such impressive and rapid developments are not possible.

With this NHS project, the UK team managed to bring together discovery labs who were experienced in proteomics already and were willing to pivot in this new direction, and they also had the clinical labs who had the technological capabilities and were experienced in running such tests.

What about the impact beyond COVID-19?

Jenny: My view is that every place a clinician has to make a decision, there should be a quantitative biomarker assay available to help them make that decision; that's our focus as biomarker development researchers. If we manage to address this chasm between academic and clinical labs, I think this is definitely something we could see more of in the future.

I do also think remote blood sampling devices will become more commonplace in the future. We've seen it this year with COVID-19 where, particularly in the US, we've managed to adapt very quickly to telehealth. We were doing it already in some areas, but imagine how amazing it would be to be be able to send a blood sample device to the patient, and then they have a video call with a clinician who's already received their blood biochemistry data! This is where I see MS and protein assays opening up a lot of clinical usefulness. It could even help solve healthcare challenges such as the lack of available healthcare in underrepresented communities or provide resources in countries where there are fewer physicians.

> *"Imagine if you could do 100 patients in three minutes – that's the perfect way to monitor any future outbreaks of coronavirus, through population screening"*

Maarten: We are currently working on pooling samples. Imagine if you could do 100 patients in three minutes – that's the perfect way to monitor any future outbreaks of coronavirus, through population screening. We could pick it up as soon as one patient gets infected. It's not proven yet, but I'm excited to see where it goes.

I'd also like to mention multiplexing again. I can see a future where there's an MS sitting in a clinic, running a test for COVID-19 perhaps, and then something from oncology comes in, something from hematology after that… and the MS is measuring them and spitting out a semi-automated report for the clinical biologist. It would be truly amazing, but I think it's entirely possible. Once we get the SOPs sorted, I don't actually think it will be that hard to convince doctors to make the switch once we show them that one MS can replace all these different tests. They would get their return on investment in a matter of months.

Just like with mRNA vaccines, which were sat there for a long time but suddenly had a huge push from COVID-19, MS needs time to develop in this area. It's impossible to be the best right away. I think we're at the earliest stages of MS being used as a diagnostic tool in the clinic, but the promise is so large that we need to continue trying.

Solutions

Real analytical problems
Collaborative expertise
Novel applications

Lipids on the Brain

Kim Ekroos, President of the International Lipidomics Society, shares how high-resolution ion mobility MS is transforming research into the lipidomics of neurodegenerative diseases

Lipids represent the most diverse set of molecules in human biology, with extremely heterogeneous underlying chemistry. For a long time, lipids were largely overlooked in research – but it has become increasingly clear that they have a significant role to play in human health and disease. As analytical tools have become more advanced over the years, we have seen the lipidomics field boom. However, there are still many questions about the exact role this huge diversity of compounds plays in the body.

High-resolution ion mobility MS (HRIM-MS) offers researchers an exciting insight into the structural details of lipids and the impact of altered metabolite pathways on the pathogenesis of many diseases. Measuring such alterations and understanding the pathways involved is crucial to fully understanding cellular metabolism. Here, Kim Ekroos takes us through his work in the field of lipidomics and explains how an emerging HRIM-MS technique based on structures for lossless ion manipulation (SLIM) technology is enabling him to dissect the metabolic glycosphingolipid map in Parkinson's disease (PD).

What's your background in this field?

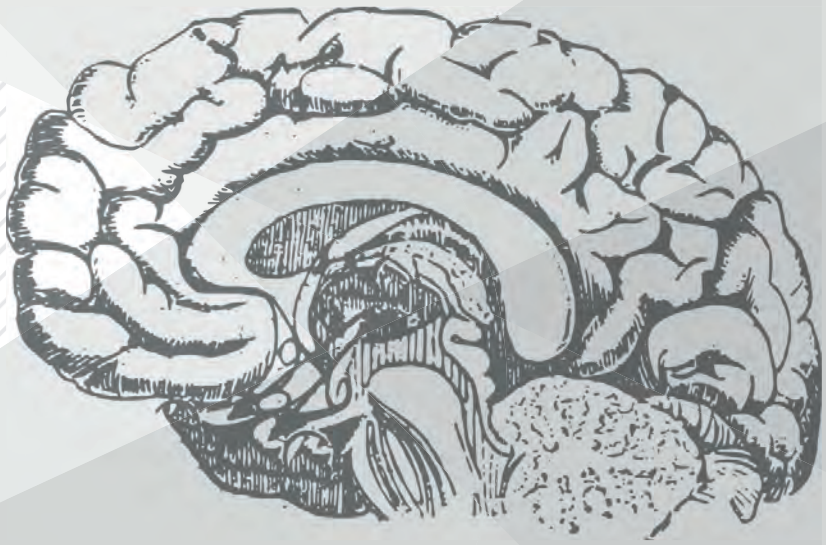
I have been working in lipidomics for over 20 years now. After receiving my PhD in biology from the Technical University in Dresden, Germany, in 2003, I continued to work in lipidomics, both in academic research and industry – with CROs, pharmaceutical companies, and eventually running my own business. My expertise includes high-throughput technologies for the accurate assessment of lipidomes enabled by advanced MS, automation, and software tools focusing on the discovery of diagnostic biomarkers for clinical applications. I am pleased that the work I do has had a great impact on the development of the field as a whole, enabling the discovery of the first lipidomics-based biomarkers in clinical diagnostics, for example. I am also a co-founder of the Lipidomics Standards Initiative and President of the International Lipidomics Society.

"We can generate much more in-depth and quantitative details from our analysis with HRIM-MS."

How did you first get interested in SLIM technology?

I was aware that Richard Smith of Pacific Northwest National Laboratory had been working on SLIM because I was also involved in developing another ion mobility technology at the same time. I knew something was being created but not much more than that. Then, a few years back, I was attending a lipidomics meeting in Singapore when I met Melissa Sherman – CEO of MOBILion Systems. We started discussing the fact they were commercializing Richard's SLIM technology and how that could beneficially serve the lipid community. It was really good to meet with her and find out more about this new ion mobility technology – I immediately saw its potential to provide a much needed analytical option to advance lipidomics research. Our initial work on brain ganglioside measurements proves this; we can generate much more in-depth and quantitative details from our analysis with HRIM-MS.

Tell us more about your exploration of glycosphingolipids and Parkinson's Disease (PD)...



As part of my work with MOBILion, I helped establish a collaboration within our industry networks that aimed to identify alterations in the metabolism of selective glycosphingolipids in specific brain regions that contribute to the early onset and progression of PD. Our international team includes the research group of Shane Ellis at the University of Wollongong in Australia, Ron Heeren from the Maastricht MultiModal Molecular Imaging Institute (M4I) in the Netherlands, and Nathan Hatcher, a principal scientist at the Department of Neuroscience at Merck. I play a consulting role in the project and it is great to be able to work with such a strong, global network.

Glycosphingolipids are natural cellular fats and part of the PD epidemiology. They are components of cellular membranes that fulfil multiple functional roles, from cell structure and transport to signaling. However, the contribution of glycosphingolipids to PD is not yet fully understood. Our research builds on several technical developments made by the group at M4I in the fields of MS imaging and lipid analysis. And it includes the use of MOBILion's SLIM-based HRIM instrument to identify alterations in the metabolism of selective glycosphingolipids in specific brain regions that contribute to early PD onset and accelerated progression rates.

Any initial findings?

HRIM-MS is helping us to finally look deeper into more complex samples; for example, looking at glycosphingolipids in selective brain regions which have not been well described before. Mutations in the GBA1 gene – the most prevalent genetic risk factor for PD – results in accumulation of glucosylceramide and glucosylsphingosine. However, we do not know the breadth of alterations in glycosphingolipids and how this contributes to PD. We are now combining MS imaging with stable mass isotope precursor labeling methods that allow us to track the synthesis and breakdown rates of glycosphingolipids in different brain regions, in real-time, as well as using the HRIM-MS technology to study how larger, more complex glycosphingolipids are altered in PD.

What are the next steps in your research?

In October 2020, we were really thrilled to have been awarded a grant from The Michael J Fox Foundation and its partner, the Shake It Up Australia Foundation. Their support means we

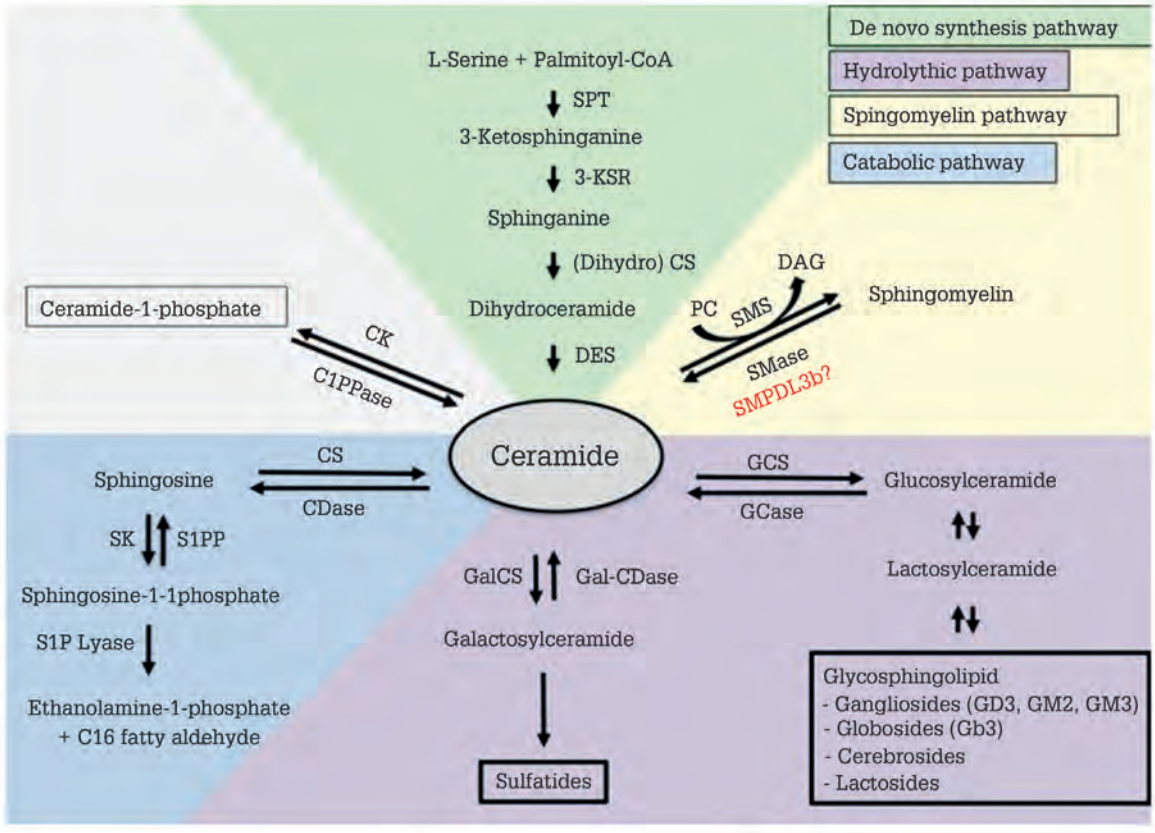


Figure 1 - Generalized schematic of sphingolipid metabolic pathways.

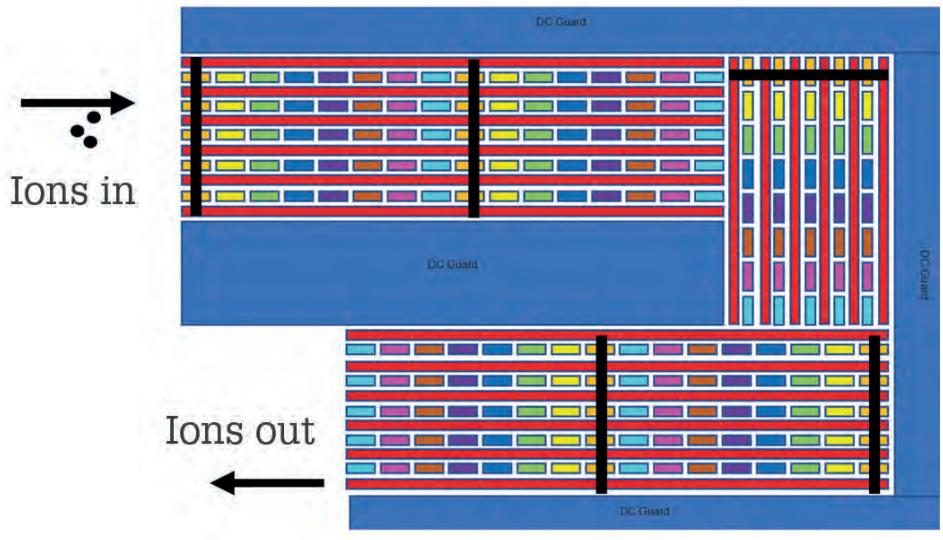
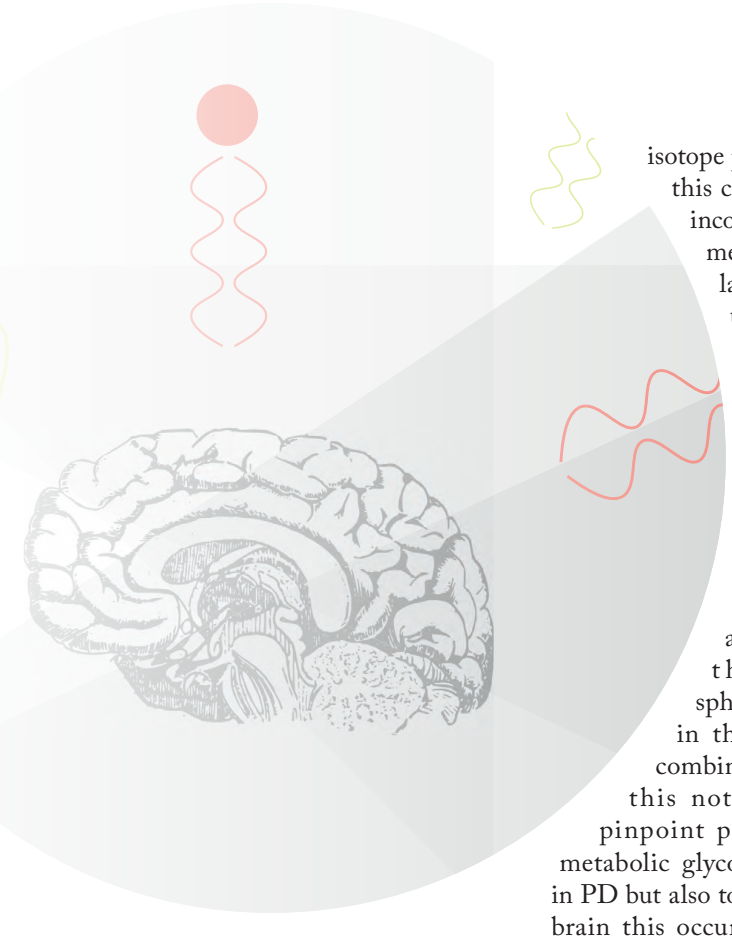


Figure 2 - Schematic of the PCB used for SLIM-based HRIM-MS.



can now run experiments that have never been done before – identifying the ways in which glycosphingolipid metabolism can be restored in PD. With the other organizations involved in the project, we are looking at matter in the brain and how that is dynamically changing. When we add stable mass isotope precursors to cells – in this case to mice – they are incorporated into the lipid metabolism. Clearly, the labeled precursor has a unique mass, so we can distinguish between the endogenous unlabeled and newly labeled lipids. In this way, we can carefully track the turnover rate of newly synthesized glycosphingolipids, allowing us to extract the properties of sphingolipid metabolism in the greatest detail. In combination with imaging, this not only allows us to pinpoint potential underlying metabolic glycosphingolipid defects in PD but also to localize where in the brain this occurs. We are using the most advanced MS imaging techniques from Shane Ellis' lab, enabling us to carry out in-depth identification of glycosphingolipids and other lipids and correlate this to the properties of sphingolipid metabolism.

"By using HRIM-MS technology, we've calculated that we can obtain a fifteen-fold gain in throughput."

How does HRIM-MS compare with other technologies?

HRIM-MS provides a level of detail on really complex glycosphingolipids that is difficult to access with other technologies. Importantly, there are many different isomeric species, which cannot be separated by MS alone. Other separation methods have been used to measure glycosphingolipids, including thin layer chromatography and hydrophilic interaction chromatography (HILIC) – but they are not only laborious but also insufficient to fully separate the very complex glycosphingolipid kingdom.

By using HRIM-MS technology, we've calculated that we can obtain a fifteen-fold gain in throughput – a significant reduction in how much time we spend on analysis!

At the same time, we have higher selectivity and are able to separate isomers; something that we are not able to do with reversed phase or thin layer chromatography – and not completely with HILIC either. Crucially, we do not sacrifice quality with HRIM-MS; rather, we are able to precisely quantify all monitored lipid species. In this respect, it is truly bringing something new to the table – opening up a new level of detail in our analyses. And that has also allowed us to "think" further.

What do you hope to see for the future of HRIM-MS – and lipidomics research?

If we look at what is done in clinics or in the pharmaceutical industry today, LC is often found in front of MS analysis. However, LC is typically complicated, brings issues to the measurement, and causes difficulties in the whole workflow. In HRIM-MS separations, 13 meters of path length (in a component that is around 35 x 45 cm!) allows the separation of molecules that have very minor differences. Ion mobility separations are also based on fundamental principles that differ from LC; several characteristics of ionized molecules – size, charge, shape, and structure – come into play at once; in short, HRIM-MS can separate and identify molecules that other instruments fail to detect, while providing a deeper level of structural information.

HRIM-MS represents an opportunity to work with a truly new technique – the benefits of which are reflected in our results to date. And so, I would love to see a reduced dependency on LC… Let's simply get rid of that unnecessary complexity!

Spotlight on... Technology

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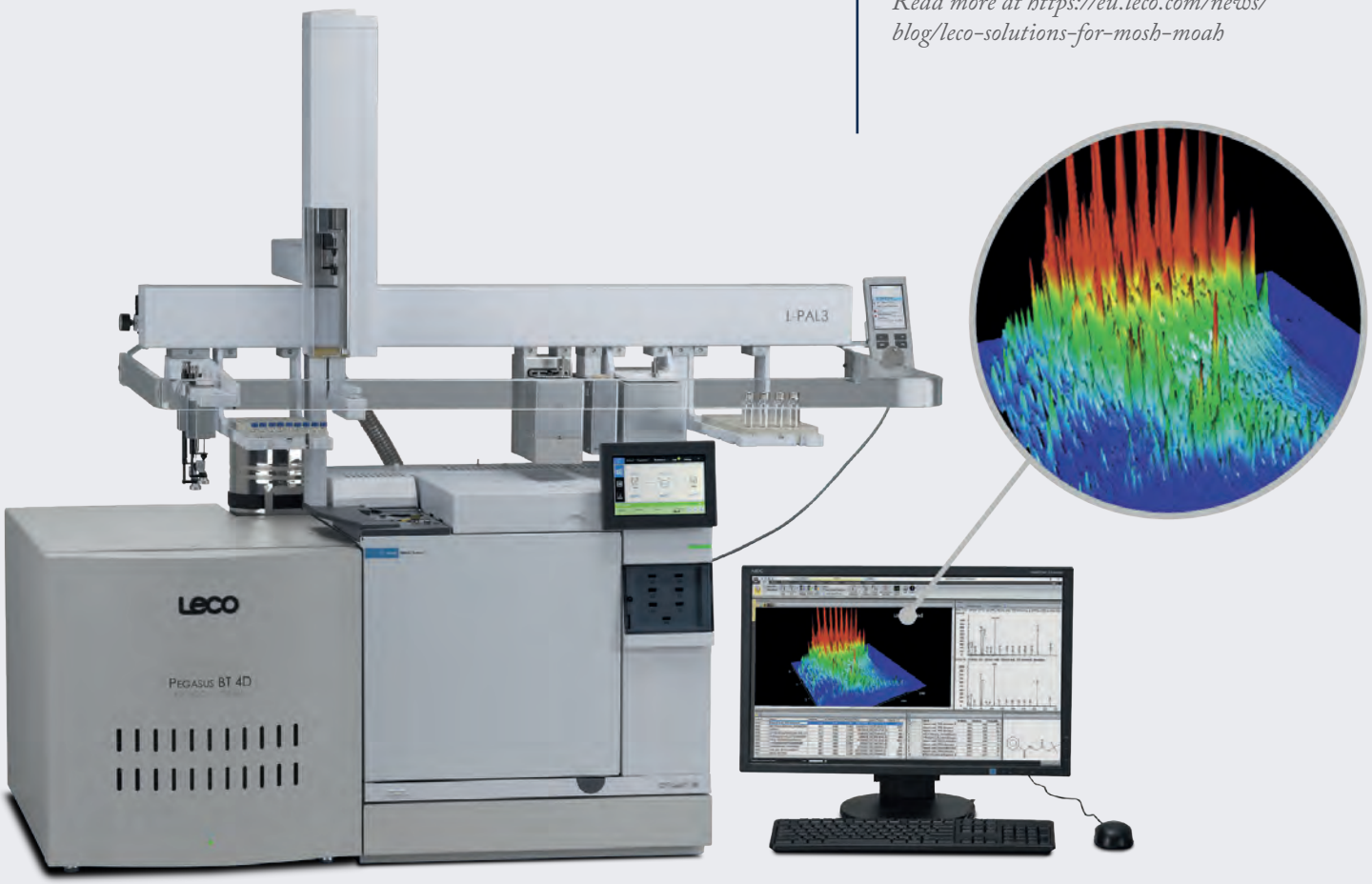

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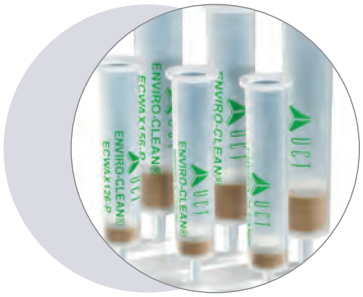

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Interrogating Metabolism

Sitting Down With… Timothy Garrett,
Director of Experimental Pathology and Associate Professor, Department of Pathology, Immunology and Laboratory Medicine, University of Florida, USA.

Can you tell us about your current role?

Since 2019, I have been an associate professor at the University of Florida, where I am also Director of high-throughput metabolomics for the Southeast Center for Integrated Metabolomics (SECIM) and Director of Experimental Pathology. My interests cover both research and clinical work in several areas, including cancer, rare diseases, and diabetes. My lab comprises 12 scientists, including graduate students and post-docs grappling with complex problems and new fields of research. I often think my job is just to facilitate their work! We are asking fundamental questions: what drives human metabolism? Why does it sometimes fail? How does it change throughout the course of a disease? And how can we better characterize disease so that we can make a diagnosis earlier – or more accurately? By understanding how health may be disrupted, we will help find better treatments.

Much of your work is focused around MALDI MS. When did you become aware of this technique?

My interest in MALDI MS began as an undergraduate in Jonathan Amster's lab at the University of Georgia, working on the characterization of bacterial proteins. MALDI fascinated me: such a simple technique, and yet it generates so much information from such tiny samples. Not only did I fall in love with the technique, I also fell in love with the instruments themselves – how to operate them, fix them, and tinker with them to make them better. Right now, we are pushing MALDI to its limits in metabolomics and lipidomics; we are analyzing populations of metabolites and lipids, and applying informatics to determine which ones are important in disease.

How does your research connect with clinical labs?

It may be easiest to demonstrate this with an example. Recently, a clinical pathologist asked for help with a female patient who had symptoms similar to the lysosomal storage disorder, Fabry disease. Interestingly, this is an X-linked condition typically found in males. To investigate her lipid metabolism for defects, we needed to develop a new diagnostic approach, with careful attention to experimental design. It paid off – we found a defect in a non-obvious enzymatic pathway, completely different to those defects typically seen in male Fabry patients. We can't actually declare the patient to have Fabry disease, because our technique is not yet validated as a diagnostic. Our work does, however, suggest ways of better managing these patients, and, as it is MS-based, it is easy for labs to adopt. Ultimately, it may lead to significant improvements in our ability to diagnose and develop new therapies that target the enzymatic defect we identified.

What most satisfies you about your work?

I'm most proud of having built a resource – the SECIM center – that helps address difficult clinical questions both locally and nationally. And it's immensely satisfying to see our work fundamentally affecting patient care. For example, our method of assessing the immune system of transplant recipients, specifically pediatric kidney transplant patients, allows us to predict organ rejection before development of clinical symptoms. And that can improve healthcare management of these children after validation studies are completed. We're always proud to see our systems solving clinical problems.

Is your technology applicable to COVID-19 research?

Yes. We are developing an MS test that both rapidly diagnoses COVID-19 and also identifies the causative strain. This ability to identify multiple variants – or multiple viruses – in a single assay is a real advantage of MS; PCR, by contrast, is designed to detect only single analytes. We are also collaborating with partners on a multi-omics analysis of the effects of different COVID therapies. The aim is to understand how drugs might affect SARS-CoV-2 infections and prevent the spread of this disease.

What impact has the pandemic had on analytical science?

COVID-19 highlighted the importance of analytical science for diagnosing, monitoring, and tracking infections – and reminded us of its critical impact on public health. But it also taught us that large-scale testing is expensive and slow to implement. It crucially exposed our heavy reliance on reagents – for PCR tests, for example – and we should not forget how limitations in reagent supply forced us to be selective regarding which patients we would test. In a pandemic, these resource constraints are not national, but global. The development of MS-based tests, or diversification of analytical systems in general, will help us address reagent constraints in the future. Having the staff and technology to run mass screening programs is of little use if you have run out of reagents! Overall, then, the pandemic has emphasized the need for investment in faster, cheaper, and simpler analytical technology.

What are your plans for the future?

For me, it's exciting to see how MS can solve problems associated with virus detection – and not just SARS-CoV-2. I want to know how we can harness the power of MS to understand symptoms and to understand when and why one person might be sicker than another. Now, we are looking at how to make testing faster – using techniques like paper spray ionization we could get a diagnosis in 30 seconds, with no sample preparation. And subsequently – by running the same paper sample through MS, we could gain a full metabolite profile. Combining technologies that permit both rapid diagnosis and also deep metabolomics analysis is very promising. For all these reasons, I am very passionate about continuing virus research in my group – but seeing MS reach its full potential will take time!

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