JANUARY / FEBRUARY 2023 # 109

# the Analytical Scientist®



Reflecting on progress, standout memories, and future aspirations – as The Analytical Scientist turns…

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# (When) Will a Robot Steal My Job?

*As The Analytical Scientist turns 10, generative AI is born…*
*But what does the future hold for researchers and content creators?*



Those of you who have fantasized about hiring an assistant to draft your emails, grant proposals, and lecture notes – or at least provide you with a decent starting template – may be in luck. Generative AI is here. And I begrudgingly admit that it looks pretty good for some basic tasks.

As for helping solve actual analytical problems? Well, I asked ChatGPT for a practical example: "if an analytical scientist is struggling to reduce heavy metal contaminants in a water purification process using ion exchange and adsorption methods, ChatGPT can analyze the situation and suggest a solution based on its knowledge of past successful cases," it said. "This could include suggesting the use of a combination of nanofiltration and electrocoagulation, which has been effective in removing heavy metal contaminants in other purification processes."

There seems to be some promise, but ChatGPT cannot currently generate references for its claims. And it hasn't been trained on much post-2021 – or indeed any paywalled peer-reviewed data at all. So, there are hurdles to overcome before scientists could use these tools to generate new hypotheses or assist with literature reviews.

But what about us at The Analytical Scientist? One can imagine a tsunami of possibly accurate but possibly dry AI-generated articles flooding the internet. Will that devalue content across the board?

This question (coupled with hopefully tongue-in-cheek comments from launch editor Rich Whitworth about me "not ruining The Analytical Scientist now that we've hit our 10th birthday") got me thinking carefully about what we are trying to achieve. Fundamentally – whether looking back or looking forward – we're all about bringing the analytical science community together. We try to find out how experts feel about trends, what advice or anecdotes they can offer, why they love doing what they do, and what keeps them up at night. Certainly, we want to keep you all abreast of what's happening across the field, but we aim to do that in a very human way.

So, until a robot can connect with people on a personal level, mingle during a conference break, or develop intuition for when to probe and how to decide upon that all-important unscripted final question during an interview, I'm confident we can keep our head above water.

**James Strachan**
*Editor*

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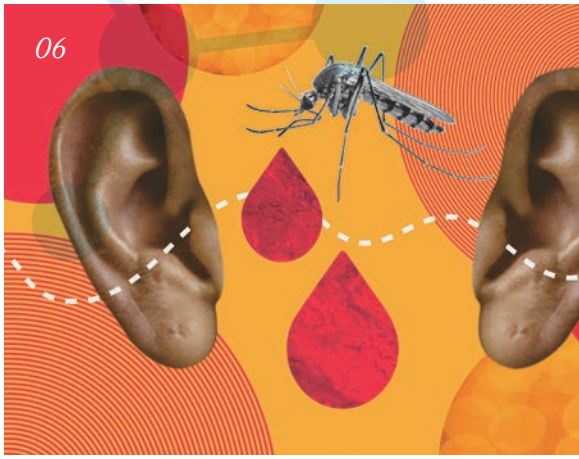


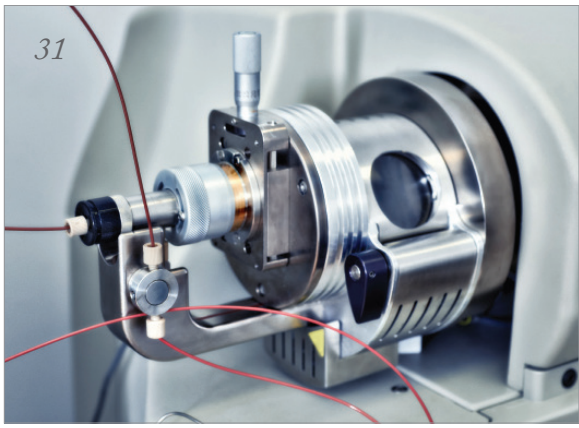




## Upfront



## In My View



## On The Cover


*Welcome to The Analytical Scientist's 10th anniversary issue!*


## Feature



## Core Topics



## Sitting Down With






the Analytical Scientist

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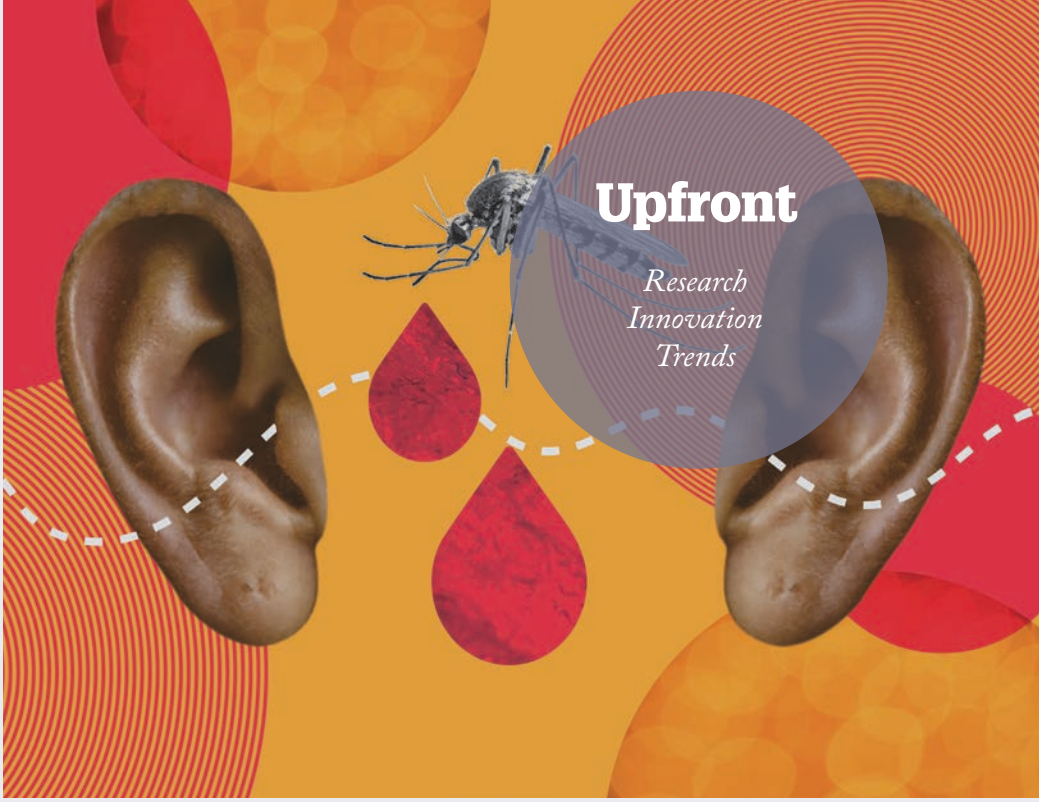


Credit: Images sourced from Pexels.com

# In One Ear, Out the Other

## How a portable NIRS technique rapidly and non-invasively detects malaria

Malaria is still the number one killer of children under the age of five. In 2021 alone, malaria killed 600,000 people – and over 200 million were infected with the disease (1). Malaria can, of course, be treated, but there are barriers to diagnosis. For example, blood tests offer rapid and relatively cheap detection, but some people fear needles and few people like them, which can prevent asymptomatic patients from coming forward for screening. Looking to fill the diagnostic gap for quick, non-invasive, and scalable tools, researchers from Brazil and Australia have developed a smart-phone operated, near-infrared spectroscopy (NIRS)-based technique to detect the presence of the parasites responsible (2).

Participants presenting with malaria symptoms in São Gabriel da Cachoeir, Brazil, were subjected to a 5–10 second scan with the portable NIRS device to collect diagnostic spectral signatures indicating the presence of Plasmodium vivax or Plasmodium falciparum in the ears of patients.

Though spectra were also collected from the arms and fingers of malaria positive and negative individuals, spectra from the ear revealed the most distinct bands. "Our method can screen thousands of people in a day and can successfully identify asymptomatic patients. This way, their treatment can be facilitated, and community transmission will be reduced," says lead author Maggy Lord, School of Biological Sciences, The University of Queensland, Australia.

"[NIRS] is reagent-free, non-invasive, and instantaneous – therefore, it can be used to screen people without the need for drawing blood, specialized skills, or sample processing procedures," adds Lord.

Given that COVID-19 limited the study's population size, the authors are aiming to conduct similar work on a larger scale – and in more areas where malaria transmission occurs – in a bid to develop even more robust predictive models.

Looking further ahead, Lord hopes the new technique will help guide the World Health Organization's epidemiologic approach for malaria control.

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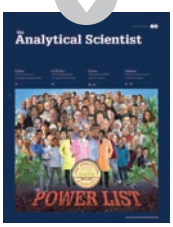
1. *World Health Organization (2022). Available at: https://bit.ly/2UfzJ5E.*
2. *GA Garcia et al., PNAS Nexus (2022). DOI: 10.1093/pnasnexus/pgac272.*

TIMELINE

# All Eyes on the Art

## Parading some of our favorite print covers over the past 10 years

**2013**
*Celebrating the self-effacing giants of analytical science with our very first Power List!*





**2014**
*A magical cartoon showcasing three wizards casting a new sample prep spell…*

**2015**
*Hazmat-suited scientists using miniaturized spectrometers to assess incident severity.*



**2016**
*A deep dive with ocean robot Alvin to solve some of the blue planet's biggest mysteries.*

## BUSINESS IN BRIEF

### A rapid roundup of the month's business news!

- Biosero has announced collaboration and co-marketing agreement with Virscidian for medicinal chemistry applications in drug discovery. The partnership will allow the companies' customers to more easily transfer data between software platforms so that analytical workflows can be automated. This way, more compounds can be tested and rapidly moved into follow up analysis without the need for human intervention.
- Bruker has acquired a majority share in Biognosys. As part of the deal, Biognosys will access Bruker's 4D proteomics timsTOF technology for its proteomics research; in turn, Biognosys will provide deep, peptide-level proteome insights for drug development – with the end goal of opening an advanced US proteomics CRO facility.
- WatersCorp launched Glyphosate-V – a lateral flow strip test for glyphosate detection in a variety of different samples. The new technology can – according to Waters – identify low concentrations of glyphosate in 15 minutes, and requires little technical skill to obtain accurate results. Glyphosate-V could help food and agricultural operations identify and manage raw materials to regulatory compliance.
- Vector BioPharma has entered a collaboration with Instituto de Biologia Experimental e Tecnológica to develop and implement analytical methods that enhance the safety and efficiency of gene delivery. The alliance aims to develop a high-throughput technique for full-to-empty capsid ratio quantification from both in-process and final purified samples.
- Astrea Bioseparations has acquired advanced chromatography column manufacturer Delta Precision. The deal should expand Astrea's range of separation apparatus and purification tools – complementing the company's existing portfolio of bioprocessing resins and reusable columns.

*References available online*

# Breast Cancer Protein Patrol

### Targeted mass spec reveals changes in protein levels up to two years before breast cancer diagnosis

The clinical need for early detection of interval cancers – those that can occur between regular screening sessions – remains fundamental. New research from the Netherlands has led to the development of a quick, minimally invasive proteomics-based diagnostic test for those susceptible to breast cancer.

The researchers drew on the findings of the prospective, multicenter TESTBREAST study, founded by Leiden University Medical Centre's Wilma Mesker and Rob Tollenaar in 2011 to analyze blood-based protein biomarkers in women with a high risk of developing breast cancer. Recently, the first analyses of a subset of TESTBREAST participants were conducted on 30 longitudinal blood samples from six women – three who developed a breast malignancy and three controls.

The researchers analyzed prediagnostic changes in protein levels using targeted mass spectrometry-based proteomics, and found six proteins that showed changes up to two years before diagnosis – suggesting their utility as early indicators of breast cancer onset.

*References available online*

**2017**
*Sniffing out the smell of death with GCxGC.*



**2018**
*Making a wish for the future of HPLC.*

**2019**
*An AI-inspired tribute to the artwork of Kraftwerk's classic 1978 album, "The Man Machine."*



**2020**
*Michelangelo's "The Creation of Adam" amid the COVID-19 pandemic.*

**2021**
*A 3D rendering of the carbonic anhydrase spectrum – an ode to Luis Schachner's MS-based artwork.*



**2022**
*An adaptation of Veemer's "Girl with a Pearl Earring," which formed part of our art analysis feature.*

# Spectroscopy Strikes Gold

**Spectroscopic techniques have authenticated Roman coins – validating the existence of a "new" emperor, called Sponsian**

*Credit: Wikimedia Commons*

In 1713, a horde of gold coins were unearthed in Transylvania, Romania, depicting the face of a mysterious Roman Emperor, called Sponsian – unbeknownst to historical records. The coins were unconventional in style, and their historically mixed motifs meant they were dismissed as forgeries, nullifying Sponsian's identity. This accepted view remained unchallenged – until now.

Researchers from the University of Glasgow analyzed the Sponsian coins after noticing how their crevices were heavily marred with dirt. The team, led by Paul Pearson, University College London, used state-of-the art imaging and non-destructive spectroscopic techniques to image the coins' surface (1). "The coins were first imaged at different wavelengths, and then a high resolution z-stacking microscope that used software to optimize focus was employed," explains Pearson.

Scanning electron microscopy and an energy-dispersive detector revealed clays and other minerals that commonly occur in soil, while fourier-transform infrared spectroscopy further identified oxalates in the crevices – organic compounds typical of soil. Critically, the soil was cemented in place by silica – a process that naturally occurs when a long-buried object is exposed to air. Deep micro-abrasion patterns were also very similar to genuine Roman coins – suggesting active circulation.

"Emperor Sponsian has been written out of history because his existence is solely based on these coins – thought to be fake," says Pearson. "But our analysis indicates this person probably really did exist." By combining evidence from the coins and their provenance, with historical clues and archaeological expertise, Pearson suggests a hypothesis: "Sponsian ruled Roman Dacia, an isolated gold mining outpost, in 260 CE, at a time when the empire was beset by civil wars and the borderlands were overrun by plundering invaders" (2).

Next, the research team plans to investigate the minor elemental composition of the coins, and compare results with known gold from the ancient mines in the Apuseni Mountains of Romania – the possible source of origin.

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1. *P Pearson et al., Plos one, 17 (2022). DOI: 10.1371/journal.pone.0274285.*
2. *University College London, "Ancient Roman coins reveal long-lost emperor," (2022). Available at: https://bit.ly/3WAUkNK.*

# Softening the Blow

**Noble gas mass spectrometer monitors magma activity at volcano site – potentially providing early warning system that predicts eruptions**

In 2014, Japan's Mount Ontake erupted unexpectedly, claiming the lives of 63 hikers. With no preceding earthquakes that might have warned authorities, the event spurred a tragic realization – a method to measure the progression of eruptions was vitally needed.

A team of researchers at the University of Tokyo, Japan, decided to explore whether the ratio of atoms in specific gases released from volcanic fumaroles could provide an indicator of what was happening to the magma deep below (1). Between 2014 and 2021, they measured isotopic compositions of noble gases in six fumaroles at Kusatsu-Shirane volcano in Japan. Noble gas mass spectrometry revealed that changes in the ratio of argon-40 and helium-3 can indicate magma frothiness – which, in turn, can signal the risk of different types of eruptions.

The team is currently developing a portable mass spectrometer for the real-time monitoring, on-site analysis of noble gas isotope ratios in volcanic gas.

*Reference*

1. *T Obase et al., Sci Rep, 12, 17967 (2022). DOI: 10.1038/s41598-022-22280-3.*

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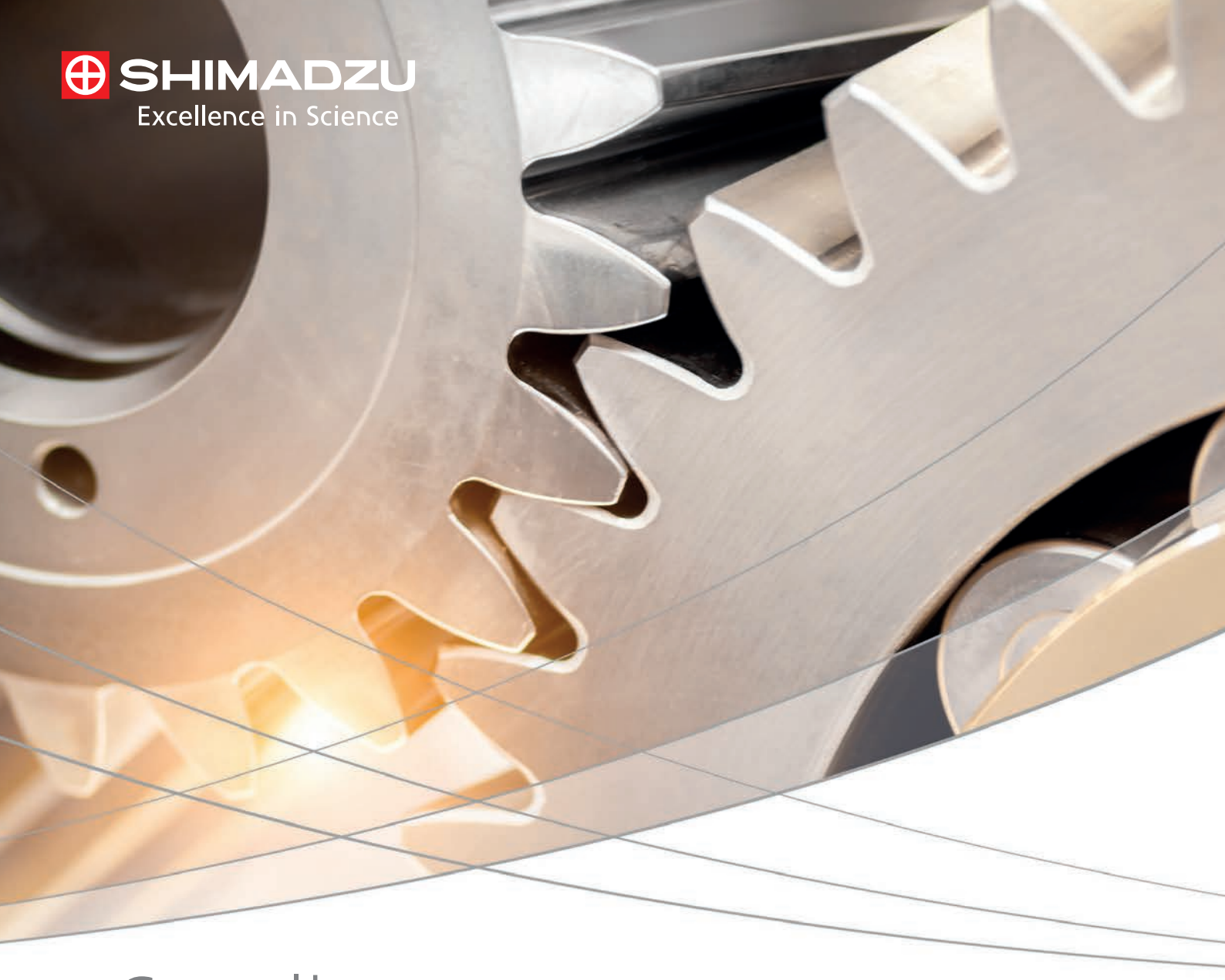

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**In My View**

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

# Greening the Analytical Lab – 10 Years On

**We have seen considerable progress towards greener techniques over the past decade, but we need a concerted effort on the part of analysts and instrument manufacturers to improve recycling and reduce our energy consumption**

*By Caroline West, Associate Professor, Institut de Chimie Organique et Analytique (ICOA), CNRS UMR 7311, University of Orleans, France*

Ten years ago, for the first edition of The Analytical Scientist, I wrote an article on "greening the analytical lab." I focused on supercritical fluid chromatography (SFC) – and pointed to the inherent green features of the technique, such as using lower quantities and less toxic solvents than liquid-phase chromatographic methods. I also acknowledged that it shouldn't be taken for granted – much depends on the way we practice it, as well as the efforts of instrument manufacturers to make the instruments more efficient – especially in reducing solvent consumption.

Unfortunately, where SFC is concerned, my impression is that we haven't made much progress in terms of "greenness" over the past decade. SFC users often talk about the greenness of the technique without bothering to compare the features of their method to other existing ones. Also, because we believe it to be "good enough," we don't investigate green co-solvents (e.g., ethanol), or a less retentive stationary phase to further reduce solvent consumption. It's not all the chromatographer's fault though – current instruments still make it difficult to use columns with smaller internal diameter, which would favor the use of lower flow rates.

Nevertheless, if we consider analytical laboratories in general, we have seen considerable progress towards greener techniques. For example, solvent economy has improved through the adoption of miniaturized techniques and more efficient processes, as well as green solvents, which are now widespread – especially in the field of extraction.

Still, there is room for improvement. For instance, in liquid-phase chromatographic techniques, methanol and acetonitrile are still the most widely used solvents, although they are not the most desirable – in terms of toxicity, for example. Naturally, this is related to their other, more desirable features, such as excellent miscibility to water, low viscosity, and low UV absorbance. Are there other alternatives? The answer is probably yes, but habits are hard to break.

*"The recent spike in energy costs has forced many laboratories to close or switch off instruments for one or several weeks over the winter to save on energy costs."*

Additionally, we should consider the need to improve the lifetime of some consumables (for example, chromatographic columns), the need to re-use or recycle consumables, and the need to improve recycling of solvents. Right now, recycling is essentially non-existent, so all solvents and plastic devices (for example, pipette tips) are simply burnt after use. A whole chain of after-use processes would be required to make better use of our lab trash – but it would also demand that analysts do a better job of sorting waste.

When it comes to energy efficiency, I'm afraid we're in a similar situation to SFC; very little progress has been made in the past decade. Today, this question is more pressing than ever; the recent spike in energy costs has forced many laboratories to close or switch off instruments for one or several weeks over the winter to save on energy costs. With future energy costs uncertain, we must find new ways to improve our energy efficiency without sacrificing analytical quality – which certainly has improved significantly over the past decade thanks to the development of automated procedures that reduce human-induced variance.

We could all play our part in one aspect of instrumental energy consumption – switching instruments off when they are not in use. Admittedly, for some instruments, like mass spectrometers, switching the instrument on and off can be problematic to its function and longevity. But other instruments, such as chromatographic systems, can be easily turned off at the end of a sequence run – especially when several hours separate the experiments. But how many of us actually do that? Often sequences are started before leaving the lab for the weekend and cannot be stopped without an operator coming in over the weekend to push the button. It may seem like a small economy, but many of the modules within a chromatographic instrument use about as much energy idly switched on as when they are operating, running experiments. I'm afraid that at least some of the reason for our lack of sustainability here is that we are a little lazy and not very patient…

Finally, as I pointed out 10 years ago, environmental concerns over solvent economy and energy saving are often not aligned with economic considerations. But given the trends in the energy economy, the two are increasingly aligned. We need – as we did back in 2013 – a concerted effort on the part of analysts to change the way they work while instrument manufacturers need to focus on developing greener solutions.

There's certainly a greater sense of urgency today, so I hope we will look back in another 10 years and marvel at the progress we've made!

# Did SPME Make It into the Clinic?

**Back in 2013, solid-phase microextraction (SPME) pioneers Barbara Bojko and Janusz Pawliszyn predicted that SPME was set to break out of the bioanalytical lab and into the clinic. Well, did it?**

*By Janusz Pawliszyn, Professor, Department of Chemistry, University of Waterloo, Ontario, Canada; and Barbara Bojko, Head of Department, Faculty of Pharmacy, at Nicolaus Copernicus University in Torun, Bydgoszcz, Poland*

Looking back to our 2013 article, we can say that our SPME predictions were broadly correct – at least at the research level. For example, we designed an automated 96-coated-blades system that is compatible with multi-well plates, which we have used in a number of different applications, including biological fluid analysis for range of target metabolites and drugs, as well in LC-MS- based metabolomics.

We have also designed medical devices based on coated fibers for both in-vivo SPME metabolomics and targeted determinations in various organs, involving both animal models as well as human tissues. Initial human trials involving several hospital surgery teams have already been published. And we're confident transplant surgery and oncology both stand to benefit.

In addition, the combination of high throughput and miniaturization has proved powerful in biotechnology – enabling different in vitro analyses, including targeted and untargeted cell line studies cultured as three-dimensional models.

In terms of surprises, we have been pleased to see (when using SPME with matrix compatible coating) a balanced coverage of analytes and low matrix effects compared with solvent

*"Another surprise is the number of ideas regarding new applications of SPME that have come up during our meetings with clinicians – either during projects or at conferences."*

extraction approaches. This observation led to developments in the in-vivo metabolomics area, as well as direct mass spectrometry applications, which are very powerful. One such technique, Coated Blade Spray (CBS), has been recently commercialized by Restek.

These observations also made us realize that the structure and performance of SPME is closer to typical sensor technology, rather than a traditional extraction technique – because the objective of SPME is to equilibrate with the system under investigation, rather than dissolving and/or precipitating sample components to quantitatively remove compounds of interest. But unlike ordinary sensors, SPME has high capacity, which opens the door to applications involving GC-MS, LC-MS, and direct MS readout, which facilitates multicomponent quantification – as opposed to electrochemical or spectroscopic determinations.

Another surprise is the number of ideas regarding new applications of SPME that have come up during our meetings with clinicians – either during projects or at conferences. These conversations highlight the importance of exchanging information and involving end-users as technology evolves.

Reflecting on where we're at today, given the continuously growing number of citations and publications over the past decade – indeed since its inception in 1990 – SPME is still a "hot topic" of research. There are a number of scientists exploring the flexible format of the technology by proposing different types of devices, while others look into new material developments to design high-performance coatings. These efforts have resulted in further fundamental developments and applications addressing critical societal needs.

Perhaps more notably today than 10 years ago (at least for some), SPME is very attractive as a "green" and sustainable tool; it eliminates the use of solvents, it consumes few materials, it uses little energy, it can be used multiple times in high throughput modes, and it facilitates on-site and in-vivo investigation.

Our prediction for the next decade? Well, all these advantages should result in a range of SPME formats becoming available for a range of applications – alongside corresponding method development facilitating broader acceptance among the next generation of analytical chemists who are rightly concerned with sustainability.

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# (Still) Accelerating Food Analysis

**In the very first issue of The Analytical Scientist, we discussed methods to determine mineral oil contamination of foodstuffs – arguing that faster, more environmentally-friendly, and higher resolution methods were needed. Well, did we get there?**

*By Peter Q. Tranchida, Associate Professor in Food Chemistry, Department of Chemical, Biological, Pharmaceutical and Environmental Sciences, University of Messina, Italy; Luigi Mondello, Full Professor in Analytical Chemistry, Department of Chemical, Biological, Pharmaceutical and Environmental Sciences, University of Messina, Italy; and Mariosimone Zoccali, Assistant Professor in Analytical Chemistry, Department of Mathematical and Computer Science, Physical Sciences and Earth Sciences, University of Messina, Italy.*

Mineral oil hydrocarbons (MOH – for example, saturated and aromatic hydrocarbons) – are probably the most abundant contaminants in the human body, with accumulation through nutrition starting very early on; mineral oil derivatives have been found in human milk (1). In addition to MOH, other hydrocarbon contaminants may be found in food, including polyolefin oligomeric hydrocarbons (POH) (2). Over the past three decades, a diversity of food products (vegetable oils, pasta, and so on) have been found to contain petroleum-derived compounds – sometimes at high concentration levels (3). Due to its toxicity, the aromatic hydrocarbon fraction has gained more emphasis and concern.

The analytical determination of such lipophilic food contaminants is, by no means, a straightforward task. Vegetable oils are usually treated with a liquid chromatography (LC) sample preparation step, with the objective of separating the matrix (mainly triacylglycerols) from the MOH (the LC step can also be exploited to perform an intra-class MOH separation). Next, one or more LC fractions are subjected to gas chromatography (GC) – or more recently comprehensive two-dimensional GC (GC×GC) with flame ionization detection (FID – for quantification) and mass spectrometry (MS – for identification) (4). For other foods, we must extract the lipophilic food contaminants using organic solvents (5). In general, on-line LC-GC-FID has been a very popular choice in this applicational field (6).

In our article 10 years ago, we made the case for faster, more environmentally-friendly, and higher resolution methods. I such a respect, one of the first things that still comes to mind when observing the literature, recent and past, is the common use of high volumes of hazardous organic solvents – which we discussed upon in our original article. Having said that, higher resolution methods are now gradually earning space: GC×GC-FID/MS (with cryogenic modulation) – a technique which provides enhanced separation space, selectivity, and signal-to-noise ratios (compared to GC-FID/MS) – appears to be an appropriate choice that is also able to separate MOH and other types of hydrocarbons (for example, POH) (7).

Overall, some progress has been made since 2013, particularly in terms of the development and use of on-line higher resolution methods (e.g., LC-GC×GC-FID/MS) What is probably most lacking today is miniaturization on the sample preparation side – specifically, we need a more environmentally-friendly means of isolating and concentrating the MOH from the food matrix ahead of the main analytical determination through GC×GC-FID/MS. A further drawback is the current operational expertise and instrumental maintenance requirements (especially as far as the LC-GC coupling is concerned); here, the question must be: could the LC step be avoided in some manner? A final general note must be devoted to data interpretation, which can be a highly complex issue – any improvements here are most welcome!

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# 10 YEAR VIEWS

In January, The Analytical Scientist celebrated its 10th anniversary, and we're using the occasion as an opportunity to bring the community together and reflect on the field as a whole. To that end, we spoke with four leading figures and friends of The Analytical Scientist – Graham Cooks, Ruedi Aebersold, David Clemmer, and Jonathan Sweedler – to understand how far the field has come over the past 10 years, what lessons have been learned, which memories stand out, and where we go from here.

By Georgia Hulme and James Strachan

## WHAT HAS BEEN THE DECADE'S MOST SIGNIFICANT DEVELOPMENT IN ANALYTICAL SCIENCE?

### Ruedi Aebersold:

A general trend is the continuous increase in performance and the development of faster, more precise, higher-resolution technologies. There has also been a noticeable diversification of techniques. For example, optical techniques have been pioneered to sequence nucleic acids and reveal how they are organized in the nucleus. Another transformative area has been microscopy – particularly cryo-EM – for structural biology and for tomography measurements on cells and very thin sections.

In the nucleic acid field, there has been significant advancement in single-cell measurements, RNA expression, and DNA analysis in single cells. Exciting progress has also been made in the proteomics field; we are beginning to learn things that you can't discern from bulk analysis, such as how our individual cells are composed. Most analytical papers on the proteome have focused on which proteins are present in a sample and at what concentrations. More recently, we have begun measuring other aspects of the proteome – for instance, proteoforms through top-down MS, how proteins interact, and how they change their shape. These exciting developments, driven by analytical techniques, bring us closer to understanding biological functions.

### David Clemmer:

The broad application of cryogenic electron microscopy (cryo-EM) to image the details of large complex molecules, with resolution that approaches the atomic scale, such as intact viruses, is revolutionary and in the last decade has become routine. Now, we can directly see structural details, and with more sensitivity than ever before. Bioanalytical chemistry has really advanced too, especially in the analysis of genome expression. We have the ability to look at small molecules and lipids. We can see what's happening now (lipids and small molecules), what happened in the recent past (protein and gene expression), as well as what has led us here (genetics and familial history). These factors can be measured very quickly, and to some extent in even single cells, opening a new paradigm for understanding living organisms.

The recent discovery of fast reactions on the surfaces of microdroplets is also revolutionary. Graham Cooks (Purdue), Richard Zare (Stanford), Xin Yan (Texas A&M) and others have opened up the idea that reactions at interfaces can play an incredibly important role – we never knew how fast and how efficient they were and the reactions have transformative potential in other areas of science.

Another advance that has transformative potential was made by Martin Jarrold's (Indiana University) and Evan William's (Berkeley) laboratories; their groups have been pioneering charge detection mass spectrometry, enabling mass measurements of all kinds. Martin and I founded Megadalton Solutions based on the only technology that can quickly determine masses beyond the 10 megadalton regime. Unlike charge induction on an Orbitrap, where you only measure the partial charge of a swarm of ions, Martin's instruments send gigantic ions back and forth through a tube, such that the entire charge of macromolecules and particles is induced as an independent signal. This allows each ion's exact charge to be determined and when combined with mass-to-charge measurements one determines each ion's mass. In collaboration with Subhadip Ghatak's group from our Indianapolis campus, we've been measuring the masses of wound associated exosomes, vesicles that weigh in across the tens to hundreds of megadaltons regime; these measurements provide evidence for other organelles in wound fluid that were unknown to exist extracellularly. Why are they being excreted? Why are they there? The existence of new instrumentation enabling mass measurements of such large molecules allows us to begin answering such questions.

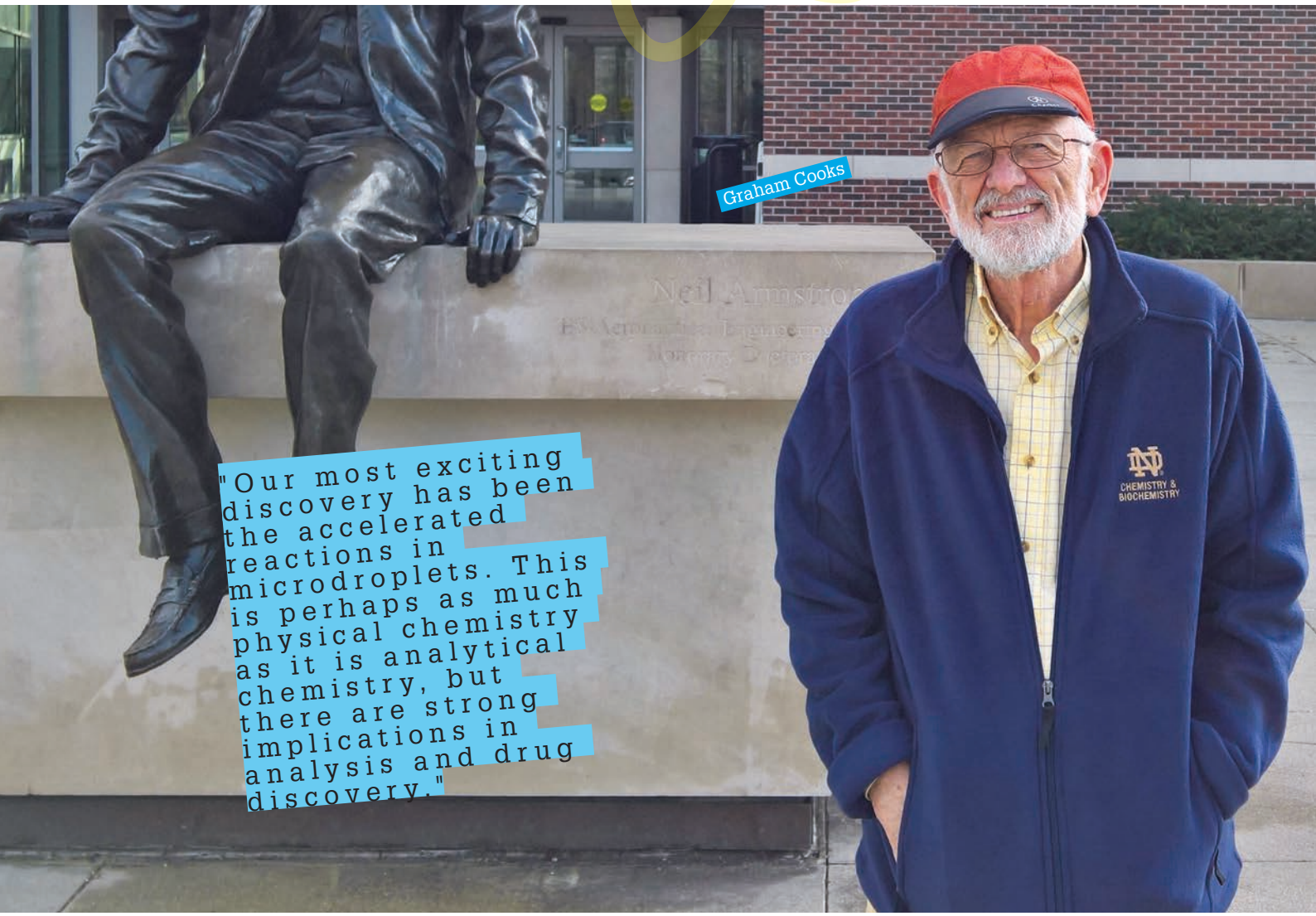
### Graham Cooks:

The evolution of mass spectrometry (MS), and its continuous growth has been the most significant development. I would also add that the emergence of lipid analytics – especially lipid isomer analysis has also changed the face of analytical science. Spectroscopy, especially imaging, optical methods, and the various 2D, second-order methods have come a long way, and microscopy – carried out with various types of laser spectroscopy – has continually gotten stronger for disease diagnosis applications. I also think that the continuing strength of protein MS and ion mobility spectrometry cannot be ignored. Finally, measuring mass, rather than mass over charge, has advanced hugely in the last 10 years, and expanded our access to high mass complexes.

### Jonathan Sweedler:

During the past decade, analytical chemistry has become more internationally balanced in terms of publication authorship in many journals.


Jonathan Sweedler
"More accessible and better curated data repositories should become the norm for all subfields of the analytical sciences."




With my perspective as Editor of Analytical Chemistry and specifically looking at trends in the journal, almost 70 percent of the articles published in 2012 were from Europe and the Americas, with the US comprising 40 percent of our total manuscripts; China accounted for 14 percent. By the end of 2022, this balance had changed. China had the most publications at about 40 percent and the US accounted for about 25 percent. Reflecting this trend, Analytical Chemistry's editorial team now includes an international team of 19 associate editors, evenly divided between Europe, North America and Asia (and it is close to being gender balanced). The movement towards broadening impact for a larger number of faculty from around the world fuels my optimism for the long-term vibrancy of analytical science.

Looking into the topics published, most of the major subfields of analytical chemistry are well represented in terms of the number of published articles. Informatics and data science deserve special mention. Many areas of measurement science now involve multidimensional data, and work with hyphenated disparate data types and very large datasets. Yes, it is now possible to gather literally terabytes of chemical information on a single sample. Fortunately, with the development of new software tools and informatics pipelines, we can deal with this data onslaught. The last decade has ushered in amazing advances for extracting information from these larger and more complex data sets,

from new statistical methods to sophisticated algorithms and machine learning processes, among other computational approaches. These toolsets have proved invaluable to practicing analytical chemists and enable them to manage their data. In addition, better curated and more flexible data repositories are becoming available, although there are still areas within analytical chemistry that either lack such resources or they are not commonly used. More accessible and better curated data repositories should become the norm for all subfields of the analytical sciences.

## WHAT ARE YOUR PERSONAL HIGHLIGHTS OVER THE LAST 10 YEARS?

**Aebersold:**
I was trained as a biochemist, so I always viewed the technological work we did – particularly in the proteomics field – as an avenue to address important biological questions. After fighting with multiple technical issues, we now have robust, powerful proteomic techniques to ask complex biological questions. For me, the highlight of the past few years is that we can transition back to biology to determine the biochemical state of cells and tissues with these new techniques. We can start asking questions about cells in different states, such as how the organization of proteins in various complexes differs. Paola Picotti, the successor of my position at ETH – I'm now retired – developed limited proteolysis-coupled MS, which can measure how a protein's shape changes as a function of cell state. This technique is based on the fundamental principle that the function of a protein is dependent on a certain structure – which can now be tested on hundreds of proteins at a time in a single analysis.

**Clemmer:**
I think the first time that I saw hepatitis B, T3 and T4 mass spectra that Martin Jarrold was measuring really blew my mind. I just couldn't believe that you'd ever see sharp peaks at the right mass! That really surprised me and caused me to reassess what is possible. If you had seen the broad, somewhat ugly, peaks that Martin and our colleague George Ewing made on large water clusters you'd appreciate there was no guarantee that it would be possible to remove salts and residual solvent to an extent that any sharp features would be observed. His group has now shown mass spectra for adenovirus with sharp peaks in the 100 megadalton regime.

I'm also still impressed by what can be done with tiny tips for electrospray ionization. One of my previous colleagues, Lane Baker, really opened up this field when he put one of his nanopores in front of a mass spectrometer. It's embarrassing that I didn't appreciate how profound this was going to be. I think those little tips are going to turn out to be really valuable for trapping things, because such small droplets dry and cool really quickly. My students and I did a back of the envelope calculation a few weeks ago that suggests that the temperature in small droplets can drop by more than 106 degrees per second. This thermal quenching rate is similar to that with cryo EM, where you submerge things into liquid nitrogen, and they cool at a fast rate – allowing structure to be preserved. This suggests that many subtle, transient, structures can be trapped by ESI, and several groups, including ours, in collaboration with David Russell and Art Laganowsky (Texas A&M) are beginning to see this.

**Cooks:**
Our most exciting discovery has been the accelerated reactions in microdroplets. This is perhaps as much physical chemistry as it is analytical chemistry, but there are strong implications in analysis and drug discovery. In 2011, it was first reported that organic reactions in microdroplets occur with accelerated rates – up to 106 times quicker than in bulk. This topic has been widely studied since, and more research has been performed on the fundamentals. We use desorption electrospray ionization (DESI), a fully automated system that completes the three main processes of drug discovery – reaction screening, small scale synthesis, and bioassays. This wasn't on the horizon 10 years ago, and I have been surprised at the speed with which DESI MS is proving useful.

Though it is equally surprising how slowly these applications are being translated to point of care medicine! In part this is because major advances in genomics have driven interest in genomic and proteomic analysis while there has been much less attention paid to small molecule diagnostics. Moreover, medicine is necessarily slow in adopting new techniques. Translation is also slow in the sector that I am most involved in – brain diagnostics - were we take measurements on microsamples, and provide important information on mutations of the brain tumor that should be of immediate value to surgeons. Currently, this information is available from genomics testing but the information is only available after surgery, when it is not of operational value. Although the relationship between the mass spectrometry and medical communities is really close, one would hope to see many more joint publications between surgeons, pathologists, and experts in MS that address actual medical conditions and patient data.


## CAN YOU EXPAND ON WHY YOU THINK FAST REACTIONS ON THE SURFACES OF MICRODROPLETS ARE REVOLUTIONARY?

**Clemmer:**
You think you know about the nature of water, until you start seeing some of these reactions. It turns out that many different types of reactions are accelerated to an unimaginable extent at these interfaces. We measured a three component Bignelli reaction, discovered more than a 100- years ago and requires hours or even days to accomplish in a beaker. We haven't published this yet, in the droplet the reaction turns out to be extraordinarily efficient; our results suggest that even a single reagent molecule of each of the three components in a droplet can condense to make the product over the lifetime of the droplet, which is, at most, milliseconds. The reaction is probably occurring in microseconds, but it's doing it with only the possibility of three reagent molecules in the droplet. From the point of view of chemistry, to control a reaction by controlling the number of molecules down to a single reagent molecule combined with another one in a vessel, in this case a droplet, is unimaginable.

I often have felt that once invented, measurements and instrumentation are somewhat taken for granted and often it is the application that gets that lion's share of attention. I hope analytical scientists get the credit for the findings that are to come with the last decades advancements!

**Cooks:**
I think that accelerated reactions in microdroplets will become a very significant field of science. In terms of what I've been able to contribute? Well, my group really did make some amazing first observations. We've stuck with the research, and passed some of our enthusiasm to other people by exporting students. Although I'm not entirely satisfied with the progress that we've made on the fundamental mechanisms, the contributions that other researchers are making is very pleasing.

For example, chiral selective research and transfer of chirality (based on serine) was something that I became interested in a number of years ago. We worked on the project for 10 years, and found that the serine octamer can enhance chirality and transfer it to various biological compounds, including other amino acids and sugars. It could be that all of prebiotic biochemistry, including making peptides, proteins, and nucleotide RNA, is microdroplet chemistry.

## HAS ANYTHING COME OUT COMMERCIALLY IN THE LAST 10 YEARS THAT YOU THINK IS PARTICULARLY INNOVATIVE?

**Aebersold:**
It is unbelievable what state-of-the-art electron microscopes – such as those developed by FEI and Thermo – can do. In mass spectrometry, there have been incremental improvements at every level, amounting to significant

increases in performance. A decade ago, we would have been happy to detect 3,000 proteins in a complex sample such as a cell lysate. Now, we can detect 8,000 proteins from one tenth of the input material. It has also been 10 years since the data-independent acquisition (DIA) technique to obtain better qualitative and quantitative results was published. The uptake was quite fast and, if you have a large set of samples, it's now the method of choice.

The speed of progress has not surprised me, but the speed of implementation has. Around 20 years ago, it took five to 10 years to go from publishing a technique to see its actual use by the community. Now, uptake is much faster. The DIA SWATH technique was taken up very fast – within about two years – and there were a lot of users. Cryo-EM analysis was applied very quickly, too. The same is true of some nucleic acid techniques – for single cell RNA sequencing, translation was very fast.

What has driven this increase in translation speed? I think these new techniques are phenomenal and address what the scientific community actually needs. If you develop a technique for a niche area, you will not see much translation. If the technique is extremely complicated, such as measuring molecular distances in live cells (which involves engineering cells and having the right light acceptors and donors in close proximity), uptake is slow because the technical hurdles are significant. In contrast, if you know how to run a mass spectrometer for proteins, advancing from DDA acquisition to DIA acquisition is relatively simple.

**Clemmer:**

We did write the IMS-TOF patent, which has been incorporated into commercial instruments. Waters have since licensed those. Dick Smith has taken the IMS into SLIMS to get a really high-resolution ion mobility measurement. And Bruker have also got a new technique called TIMS, which is a nice high-res instrument. And, of course Makarov's (Thermo's) Orbitrap provided an easy approach to Marshall's (Florida State University) revolutionary and incredibly creative FTMS measurements using high-field magnets. But I find myself most attracted to emerging innovations; as an example, Scott McLuckey's (Purdue) ion-ion reactions continue to surprise me. These measurements have the immediate commercial appeal of being able to spread out and resolve ions that are otherwise unresolvable.

In the next decade, the real innovation might be in some of the unexpected chemistry. For example, the widely used electron transfer dissociation method that Hunt's group pioneered is a type of new chemistry that emerges from negative ions interacting with positive ions. But this is only one example. The approach is again a new type of chemical synthesis – but, in a vacuum, and without solvent (making it green). My guess is that Bruce Merrifield, who won a Noble prize for solid-phase peptide synthesis, would be astonished to learn that McLuckey's group was synthesizing these types of molecules in milliseconds inside of a mass spectrometer. It will be interesting to see how new strategies (for example AI approaches) take advantage of the wealth of kinetic and thermochemical data from ion-molecule reactions, acquired over the last forty years and used to train theoretical quantum chemical approaches. Because these measurements are free from solvent, they have a unique archival quality that can be exploited as new methods emerge.


## ARE THERE ANY HARD LESSONS THE INDUSTRY HAS LEARNED OVER TIME?

**Aebersold:**
There are always false starts and things that look extremely promising, but then fizzle away. I think one of the field's hardest lessons was the advent of surface-enhanced laser desorption/ionization MS. Twenty years ago, analytical science was introduced to this as a powerful biomarker detection technology. The machine was simple to use and it was implemented in many hospitals so that clinical labs could run blood plasma samples in large numbers and find biomarkers in bodily fluids. Unfortunately, it did not work – and this set the proteomics field back a few years until newer, more robust methods emerged that had clearly defined and tested analytical boundaries. As a result, proteomics has been particularly good in developing accessible, transparent computer algorithms based on statistical tools that that validate the identity and quantity of observed molecules. Metabolomics, as afield is not quite as far along yet in that regard.

**Cooks:**
There has been a slow increase in the realization that, when we handle complex materials, we do not need to separate out all of the individual components. The universal thought used to be that if you have a complex sample, you can't make a mass spec measurement unless it's chromatographically cleaned up. That's just nonsense – but this lesson has taken a long time to learn. It's not always necessary to separate and purify complex materials to answer questions, including quantitative questions!

## ARE THERE ANY TRENDS YOU SEE THAT ARE SLIGHTLY WORRYING?

**Aebersold:**
I'm worried about the economic environment. A year ago, when money was cheap, there were huge amounts of venture capital to spin out interesting ideas from universities and investors actively sought out new technologies. Now, I know colleagues with very exciting new technologies who are struggling to find funding. Startups need funds to build, maintain, and market new innovations and I worry that this pipeline will take a hit. Many amazing technologies that should reach the market might not.

Another limitation is academic research culture. Often, funding agencies give a lot of research money to whatever they consider translational. They want diseases cured and medicines improved, but that takes time – and analytical sciences are the foundation of those advances. Reduced investment into basic technological advancements will have a detrimental effect down the chain.

**Cooks:**
Within chemistry, analytical science is less appreciated than are the other branches. There are historical reasons; consider that, in the 1950s, the field hit a plateau in development of gravimetric and optical methods, which led to some misconceptions about the long-term prospects of the field. Leading institutions responded to this downturn and, as a result, high quality analytical chemistry in the US at least, became quite restricted geographically. To this day, analytical chemistry is rarely viewed on as a major part of chemistry. For example, many university departments combine physical analytical research.

**Clemmer:**
Yes – I think that analytical chemists, especially those that are involved with advancing new chemical instrumentation are somewhat modest. For example, when

the human genome was sequenced, most of the credit went to the biologists who arguably failed to sequence the human genome with standard techniques. It was really the pioneering work of Jim Jorgensen (North Carolina), Norm Dovichi (Notre Dame) and a few others who first sped the process up. Now that sensitivity, ionization methods, and resolution have all progressed, we have the possibility of looking at the next steps. Finding the double bond in a lipid is a tricky thing to do, but analytical chemists are working hard to advance technology, which will have a big impact on how we think about the cell.

## WHAT EXCITING THINGS DO YOU SEE ON THE HORIZON?

**Sweedler:**
I was optimistic about the field of measurement science in 2013, and I remain so today. My perpetual optimism is driven by the following observations. There has been world-wide growth in educational programs in analytical chemistry and several allied fields, such as bioengineering, environmental science, and applied medical science, with multiple groups in these programs engaging in first-rate analytical research. As a result, many young, innovative scientists are entering the field of measurement science. The hiring of our graduate students remains strong. And finally, in the US, numerous recent national research initiatives have featured measurement technologies. In my opinion, members of our field have lots to be optimistic about in terms of our current status and future potential.

One specific research area that has exceeded my expectation is the chemical measurement of single cells – a focus for me and my group for the past three decades. Progress and accomplishments in this area have greatly accelerated over the past 10 years, with multiple groups making remarkable enhancements to almost all aspects of single-cell mass spectrometry, from characterizing small molecules to proteins, and from improved cell sampling to innovative new informatics tools. In 2013, I had the impression that some researchers found efforts to measure single cells intriguing but not practical or useful. Though single-cell transcriptomics has existed for several decades, studies using this approach have exploded – and the results are transforming many fields of biology and medicine. Perhaps because of the success of single-cell transcriptomics, single-cell chemical measurement has become an exciting goal for many researchers. Publications reporting on cell characterization for a greater range of metabolites, lipids, and proteins have become more common. I expect to see advances in several areas of interest in the

coming years, including understanding how networks of neurons interact, when cancer cells spread, and how cell fate is determined in developmental biology.

Besides reaching a greater depth of molecular coverage, I expect single-cell approaches to gain in throughput so that greater numbers of cells can be measured per experiment, enabling more facilities to offer this measurement. Also intriguing: a few studies have interfaced disparate single-cell measurement approaches, such as vibrational spectroscopic imaging with single-cell mass spectrometry. Just by looking at the number of recent reviews and perspectives from leading journals, single-cell chemical characterization is a field that is definitely going places. I am excited to learn what the next few years bring to this rapidly growing field.

**Aebersold:**

Mass spectrometry has established itself as a technique that can obtain different types of data from proteomes, including the composition, localization, modification, interactions and shape of proteins. I think proteomics will continue to broaden and become more powerful. There are attempts to use the principles from nucleic acid sequencing on proteins, in which billions of proteins are deposited in a flow cell that can then be probed to understand which are present in a given location. This will bring protein analysis to the level of examining single molecules. These approaches got a long way to go, but this is very exciting.

I also hope the new techniques which probe many functionally relevant attributes of the proteome will become more mainstream and widely applied. Proteomics – and, to some extent, metabolomics – has been inhibited by various practical factors. For example, the techniques are considered complicated, largely because they use complicated instruments with a tendency to break down. I see the instruments, computational tools and the technology in general becoming more robust and widely used, which should improve accessibility. More people using a technique means more people having creative ideas and producing interesting results, so I look forward to a broadening of the user base and of the ensuing results.

I think the increase in throughput and robustness will allow us to collect large amounts of data and use artificial intelligence techniques to learn new biology. For example, one of the fundamental questions in biology and medicine is: how does a change in the genome affect a (disease) phenotype? For almost all diseases, the relationship between genomic variants and phenotypic expression is very complicated. With the new techniques we have available, we can start to generate datasets to understand how specific genomic changes affect the cell biochemistry and disease trajectory in patients. This cannot be done in one experiment; we need a lot of data and computational tools. I'm hoping that, within the next 10 years, this area will advance.

**Cooks:**

The emergence of mass spectrometry as a synthetic/preparative method will stand out as a further extension of one of the largest and fastest growing areas of analytical science. Examples are collecting products of accelerated reactions in droplets (organics and nanomaterials) and ion soft landing to make new materials.

**Clemmer:**

I think that analytical chemists are really going to have to step it up. There are enormous challenges in this decade. For example, there is a huge plastic problem, and we're starting to find astroturf in everything – because we made this material that keeps breaking into smaller pieces when decomposing. There also needs to be a global scientific effort to address how to store carbon, and how to slow down the environmental impact of burning fossil fuels. The measurement community has a unique set of skills to solve some of these problems. From the point of view of a chemist, it is unimaginable that we would burn these fantastic molecules. Chemists have worked for years on energy transfer and how to deliver energy back and forth between molecules, and these techniques need to be reimagined and applied globally. Also, I believe analytical science will play an important role in responsible manufacturing – it is important we think about the whole lifecycle of the materials and the products we use. Finally, I think scientists need to be more aware of political, social, and environmental issues, because technology can't solve everything!

# Then and Now

*As part of our 10-year anniversary celebrations, our industry partners discuss developments in their respective fields and reflect on how they've contributed to progress over the past decade.*

Daria Thorp
*President*
*ACD/Labs*

Think back to 2013… What were your main aims and ambitions for the company?

Analytical scientists must combine scientific knowledge with the outputs of multiple instruments to solve complex problems. And while ongoing advances in instrument technology have brought efficiencies, any time saved is often cancelled out by having to retrieve and match data. We aim to change that with our mission to simplify analytical scientists' work through software – which we've been doing since the release of our first ACD/CNMR Predictor for Windows 3.1 in 1995.

In 2013, we released our Spectrus Platform portfolio of applications and technologies to combat inefficiencies through one goal: All Analytical Data… One Software Interface. To this day, Spectrus Processor is widely used to analyze live, interactive NMR, LC/UV/MS, UV, IR, etc., data from numerous instrument vendors in a single interface. With built-in chemical intelligence, the platform streamlines chemical structure confirmation, comprehensive reporting, and database searching.

How has your company made a difference over the past 10 years?

When experimental data is connected to chemical structures and aided by interpretation algorithms, it enables workflows that our users hold in high regard. Our 2022 Structure Elucidation & Verification virtual symposium – accessible online – really brought this home for us, as users from top pharmaceutical and medical device companies shared how this approach empowers their work.

For those concerned with impurities, our tracking and CMC decision support software Luminata uniquely combines chemical reaction handling, batch analytical data management, and modern visualization, and has gained popularity in tightly regulated industries, such as pharmaceuticals, where impurity knowledge is paramount for product performance and safety.

Thinking about the future, what excites you most?

Organizations are increasingly investing in standardization and digitalization of analytical chemistry knowledge – often aided by ACD/Labs' expertise. In addition to optimizing data quality and integrity, having knowledge that is both human- and machine-readable grants scientists access to the data and insights of their colleagues and predecessors, while also enabling machine learning and AI.

Of course, software cannot replace human talent and expertise, but it can empower scientists. Removing tedium by automating routine data processing and analysis allows chemists to focus on challenging cases and innovative science, which increases overall productivity.

And finally, a decade after launching Spectrus Platform at Pittcon 2013, we are excited to present our next stride forward at Pittcon 2023: our new generation of browser-based analytical data processing software, Spectrus JS.

ACD/Labs

*www.acdlabs.com*

Thomas J. Tague Jr
*Applications Manager*
*Bruker Scientific*

What has been the most significant development in your field over the past 10 years?

Fast tissue imaging using infrared and Raman spectroscopy has added a lot of scientific value. Now, we can analyze tissue samples for disease, such as cancers, with extreme accuracy and cost effectiveness. Hospitals and clinics can now look at biopsies and diagnose disease within 24-hours without the time-consuming staining and counterstaining steps. This simply wasn't possible 10 years ago. Our technology in particular is easy-to-use, and people with minimal scientific training can run some of these tests.

What made this possible?

The incorporation of very fast translating devices, and new types of spectroscopic sources has made fast tissue imaging possible. In our system, we use an array of quantum cascade lasers to rapidly image important areas of tissue. The number of spectra is hundreds of millions, and this can be done in 15 minutes because the new source is so bright that the signal-to-noise ratio eliminates the need for co-averaging of multiple scans – one scan is sufficient.

How would you say your company has made a difference over the past 10 years?

We've solidified ourselves as the leader in scientific instrumentation and imaging in the life-science world, with specialists visiting from state-of-the-art hospitals around the world interested in implementing our tools – some already are. For example, St. Jude Children's Research Hospital, USA, recently began using one of our imaging systems for cancer detection in children. This work, using infrared, Raman, and MALDI imaging to analyze tissue samples and diagnose disease, has had a real impact.

Thinking about the future of life sciences... What excites you most?

Disease detection will continue to forge ahead, as will state-of-the art, tailored treatments for cancer. We have the tools to make a difference in these areas. And given the significant proportion of our revenue we spend on R&D, I'm excited to see where we can innovate over the next decade.

Are there any other trends that excite you?

We have also seen the emergence of machine-based AI in the past few years, which is allowing the scientific community to manage images that are many gigabytes in size. Instead of taking weeks to analyze data sets, it can be done in mere minutes by just using more careful, adaptive algorithms. We have formed a team to employ machine learning AI-based algorithms to handle large datasets, for example. But the field as a whole is still in its infancy – so I'm excited to see what this will allow us to do in another 10 years.

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Lukas Maerk
*CEO*
*IONICON Analytik GmbH*

Think back to 2013… What were your main aims and ambitions for the company?

The cornerstone for our success today was set back in 2013 with an R&D breakthrough: we introduced the first PTR-TOF instrument – which we developed and built entirely by ourselves. This allowed for perfect component matching, flexibility in the design, and a lower price tag for our customers. It was robust, user friendly, and powerful. But 2013 was only the starting point for many new technologies and PTR-TOF products...

What has been your company's most significant innovation over the past 10 years?

Before our company was founded in 1998, chemical analysis was done offline, required laborious sample preparation, and took hours. We disrupted this process completely. PTR-MS trace gas analyzers sample the air in real time, do not require sample preparation, and provide immediate quantitative results. Introducing the new PTR-TOF series in 2013, we made this technology available for many cost-sensitive routine applications, reducing the complexity of earlier products and increasing sample throughput significantly.

How has your company made a difference over the past 10 years?

Our PTR-TOF instruments have been part of some groundbreaking discoveries, and thinking about what our customers have achieved in these years is genuinely humbling. For example, our instruments were used in the CERN CLOUD chamber studies, which have changed how we understand the world's climate. Our mobile and robust trace VOC analyzers have contributed to monitoring the melting permafrost VOCs in the tundra, and, as airborne analyzers, tracking oil and natural gas production emissions in the US aboard NASA's flying laboratories. Decision makers across the globe rely on IONICON PTR-TOF data gathered from urban air quality network installations. Our analyzers cover many locations, from the greater Shenzhen area, where a dozen PTR-TOF 1000 instruments are monitoring the air 24/7, to one of our most advanced CHARON PTR-TOF 10k analyzers, which is on a discovery mission in the New Delhi smog.

Turning to the semiconductor industry, our systems are used to monitor production processes, cleanrooms, and wafer transport containers (FOUP), contributing to chips that are readying the world for the decades to come.

Our 10th anniversary coincides with your 25th…

Indeed! While we are glad to be part of your story, we are very proud of our successful and sustained growth through all these years. Like you, we have ambitious plans for the future; but most importantly, I want to thank our customers and (our now more than 50) employees, who make my world brighter each day.

25 YEARS
THE WORLD'S LEADING PTR-MS COMPANY

IONICON

*www.ionicon.com*

Harald Fischer
*Marketing Director*
*WITec GmbH*

What has been the most significant development in your field over the past 10 years?

In our field of Raman microscopy, correlative imaging – the integration of multiple techniques to acquire data from a sample – has really flourished.

By itself, Raman is a powerful analytical method that can characterize materials in a sample, as well as identify molecular allotropes and polymorphs, determine their orientation, purity and crystallinity, and detect their strain states. With the same optical setup, research-grade Raman microscopes can also record photoluminescence spectra for materials and life-science applications. Correlative Raman microscopes enable the integration of these capabilities with other complementary approaches through a modular hardware and software architecture.

Are there any examples you would like to highlight?

Certainly. Atomic force microscopy combined with Raman imaging can illuminate relationships between structure and chemistry, while also acquiring data on sample adhesion, stiffness, viscosity, and electrostatic potential. Raman can also be combined with optical profilometry to investigate roughly textured, curved, and inclined samples by keeping the surface in constant focus. These topography-guided analyses are especially useful in looking at pharmaceutical tablets in whole form, raw materials, and any experiments with long measurement times that may require compensation for changes in temperature or humidity.

Raman imaging and scanning electron (RISE) microscopy brings vibrational spectroscopy into the vacuum chamber of a scanning electron microscope (SEM), producing structural and chemical insights at the nanoscale. Software-facilitated overlays of Raman images on SEM scans can deliver comprehensive insight to researchers looking at novel 2D materials, battery materials, semiconductors, polymers, and geoscience samples.

Taken together, these combinations have enhanced the utility and versatility of Raman microscopy, while also broadening its appeal to a wide range of application areas.

Which specific advances and innovations has your organization achieved?

In addition to developing correlative Raman microscopy systems, we leveraged the research-grade white-light microscope from the WITec alpha300 to create a tool for automated Raman-based particle analysis. Our ParticleScout option has many advantages over competing methods for vital research in environmental science and pharmaceutical development. Its sub-micron resolution and ability to investigate aqueous samples set it apart, as does its integration with our Raman spectral database software, TrueMatch.

How has your company made a difference over the past 10 years?

We're most proud of bringing Raman microscopy to an ever-growing number of disciplines and types of facilities. What was formerly a specialist favorite has gone mainstream and WITec's products have played a central role in this development.

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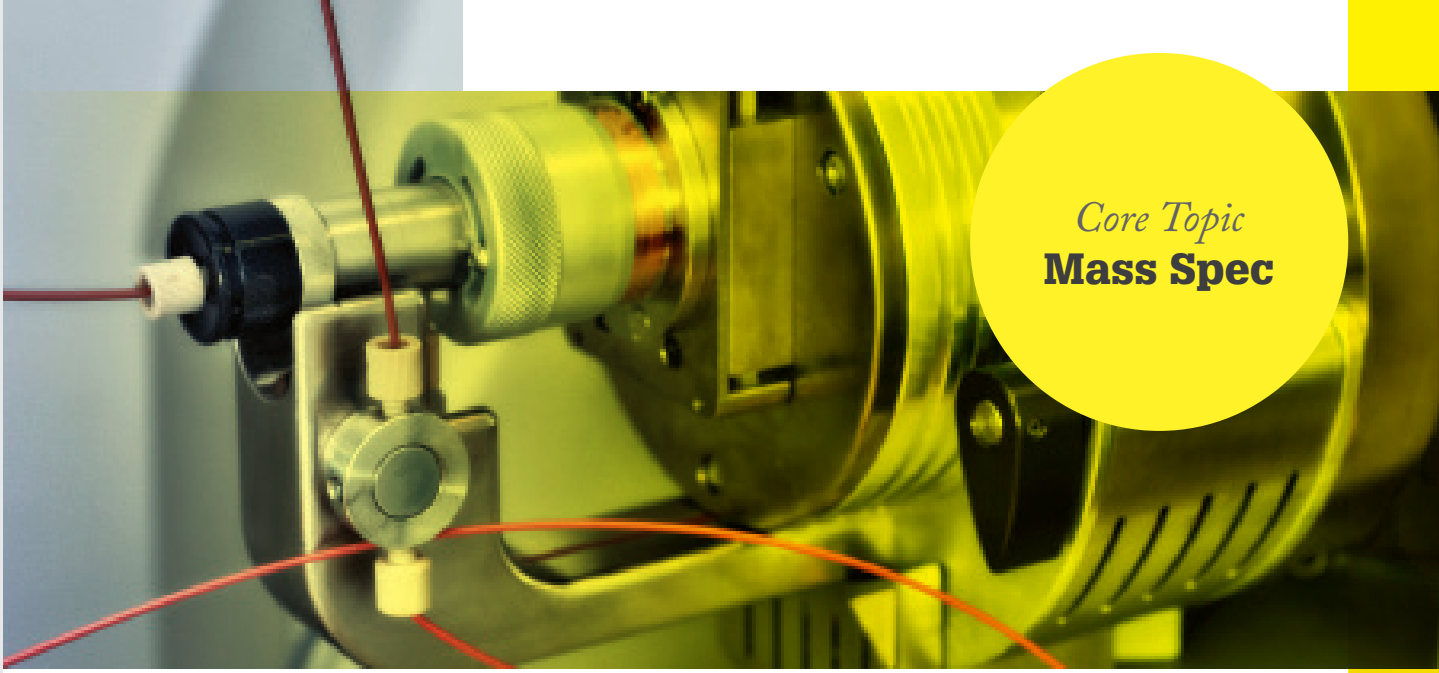


*Core Topic*
**Mass Spec**

Space spec. Researchers from the University of Maryland, USA, have unveiled a new miniaturized version of the Orbitrap analyzer – specifically tailored to the needs of NASA space missions. They paired this miniaturized technology with laser desorption mass spectrometry (LDMS), enabling in situ characterization of organic content and chemical composition of planetary materials without requiring extensive sample processing. This combination could aid astrobiology missions – particularly those focused on life detection objectives and progressive exploration of the lunar surface. According to the press release, this new device "boasts the same benefits as its larger predecessors but is streamlined for space exploration and onsite planetary material analysis."

The power of iDEMS. In an effort to study DNA methylation in more detail, researchers developed a new, highly sensitive mass spectrometry-based method – dubbed iDEMS (thankfully shortened from "isolation of DNA by 5-ethynyl-deoxyuridine labeling for mass spectrometry"). The method revealed that DNA methylation levels increase steadily after replication – outpacing cell division – and that hydroxymethylation is perpetually asymmetric between sister strands in favor of the parental strand. These findings offer a step towards answering long-standing questions about DNA modification propagation. According to the press release, the authors hope that iDEMS can be used for "profiling methylation and hydroxymethylation dynamics in different cellular contexts" – including aging and cancer evolution.

Deep breath. Pulmonary arterial hypertension (PAH) – a rare disease of the lung arteries – can result in excess scar tissue and thickening of lung blood vessels. In an effort to explore the origins of the resulting increased biomass, researchers used multi-isotope imaging mass spectrometry (MIMS) to examine the key contributors. MIMS is a new imaging modality that merges in vivo stable isotope tracer methodology with nanoscale secondary ion mass spectrometry – and this is the first time it has been used in the study of lung disease. The results? "Closer investigation of proline and glucose in human PAH may uncover opportunities to inhibit biomass formation, prevent obstruction of lung arteries, and decrease the chance of heart failure for PAH patients," said first author Bradley Wertheim in a press release.

*References available online*

## IN OTHER NEWS

*UHPLC-MS/MS reveals 10 biomarkers of non-small cell lung cancer that could aid clinical detection – especially at early stage.*

*Noise-robust deep clustering of biomolecular ions improves interpretability of mass spectrometric images.*

*Combination of electrospray ionization-mass spectrometry (PESI-MS) and machine learning shows promise in pancreatic tumor diagnosis.*

*Laser-based plasma mass spectrometry used to assess strontium-calcium ratio in teeth of Homo erectus – revealing dietary strategies.*

*Rapid evaporative ionization mass spectrometry (REIMS) accurately identifies mosquitoes age and species – with important implications for public health and risk of pathogen transmission.*

# Ten Year Views: With Ron Heeren

**Imaging mass spec in molecular pathology, high throughput metabolomics, the broad availability of high-performance tools… Ron Heeren discusses mass spec innovation over the past decade.**

## What has been the most significant development in analytical science over the past 10 years?

Looking back, one of the things that really stands out is the broad availability of high-performance analytical tools. Ten years ago, if you wanted to do something like high-resolution mass spectrometry analysis, you had to go to a specialized lab that had all this equipment – an FT-ICR, and maybe one or two Orbitraps – now it's commonly available. The ease of availability of these high-performance technologies has revolutionized analytical science as a whole.

It also means that we can now start to look at very different and detailed applications of analytical science. If I project that onto my own field – the field of molecular imaging based on mass spectrometry – it has become so easy to generate lots and lots of data, images, and mass spectra. Of course, this can pose new challenges (in data analysis, for example), but the technological developments have been tremendous and it is incredible to be part of that.

## Which application areas have seen the biggest impact?

The biggest impact is clearly in healthcare. The COVID crisis is a perfect example – we could only do such a huge amount of screening because of the availability of high-end analytical technologies. Similarly, food sciences and material sciences have also benefited from these developments.

In my opinion, this is the strength of analytical science – but also its weakness. Analytical instrumentation research is often not recognized as a field in itself – it is seen as an enabler to other sciences. I think that is something that we really need to be aware of. We need to invest in talented analytical scientists that have the competences to build, modify, and change analytical instrumentation – the innovators of the future, so to speak. As an academic society, we also need to appreciate that we need to invest in the growth of technology, instrumentation, and method development – and not only in the application of these developments. The emphasis must be placed on curiosity-driven analytical instrumentation research.

## Are there any specific mass spec innovations that stand out to you over the past 10 years?

Some innovations that stand out are molecular pathology with imaging mass spectrometry, high throughput metabolomics, lab-on-a-chip, the intelligent knife, and intraoperative diagnostics as a whole. There are many, many examples but this is the type of innovation I follow closely and continue to promote. These advances changed the world and they lead the next generation of analytical scientists.

High-resolution mass spectrometers are also up there (Orbitrap and MRMS technologies come to mind here). These mass spectrometers have revolutionized the way we do things and, as I noted above, the fact that they are now so readily available is amazing. The capabilities of the time-of-flight instruments in mass spectrometry really stand out to me; in fact, both time-of-flight and ion mobility spectrometry have come a long way the past 10 years, enabling such rapid analysis that we can now generate thousands of spectra a minute – which has really helped us to push the imaging field forward.

From a diagnostic perspective, the speed at which we can do these types of studies is just mind- boggling – and the best is yet to come. There are some major breakthroughs that are just beyond the horizon, and I can't wait to witness them!

## Were there any surprises over the last 10 years?

Here, I'll focus on surprises in imaging mass spectrometry. Ten years ago, I would not have thought that we would now be capable of doing high-throughput, high-resolution, accurate mass analysis in a pathological setting. I estimated that it would take at least another five years, but we're doing it now! And we're doing so much more than I had expected. We've introduced ion mobility into imaging mass spectrometry, and completely new instruments that do rapid screening of tissues in pathological settings. Back in 2013, I never would have thought that this would be possible – let alone routinely! The imaging mass spectrometry field has progressed significantly faster than I initially gave it credit for.

**Is there anything on the horizon that worries you?**

I mentioned this briefly in a previous question, but I think the perception of analytical science is going to be really important going forward. I think that, as analytical scientists, we need to keep an eye on the image of analytical science and ensure that it is recognized as its own individual discipline – rather than one that enables others. The Analytical Scientist is a perfect example of how to do exactly this. I also think we need to educate the next generation of young scientists to ensure that they enthusiastically pursue a career in analytical sciences.

Another worry is the fact that we are producing more and more data – and we need to find ways to connect the dots. I think – and hope – that AI can be incredibly useful, but we will need better collaboration between bioinformaticians and analytical scientists. A great analytical scientist is not necessarily a great bioinformatician; and a great bioinformatician is not necessarily a great analytical scientist. We need to invest in teams.

**What are you most excited about?**

I'm most excited about our ability to see single cells in complex tissues – and understand how these cells metabolically interact with their environment. This capability can be turned to a number of questions, for example, studying immune cell communication, mindboggling and unbelievably exciting! I'll definitely be investing most of my time on this area in the next couple of years.

**What's your favorite memory from the past 10 years?**

I think one of my best personal memories is seeing my young colleagues shine. There's nothing better than seeing somebody give a lecture at a big international conference, and show off what they've picked up in the environment that we've created. Seeing my group at IMSC in Maastricht was truly amazing. It was extremely fulfilling to see how well they fit into the mass spectrometric landscape – and it really showed that we made an impact on so many people's lives. I also loved seeing what a great community we've created. It showed me how important human connections are in analytical science. We were devoid of those connections for two years (during the COVID-19 pandemic) and, when we reconnected, it was like a family coming back together again. That feeling was indescribable.

Science thrives on human interactions and we need to remember how important they are.

# Conquering the Human Proteome

**The Human Proteoform Project needs a US$1.3 billion moonshot to transform our understanding of protein-based disease**

*By Margot Lespade*

Neil Kelleher has previously discussed the many merits of top-down proteomics and how they will enable "the earlier and more precise detection of all human disease." He is currently the Walter and Mary Elizabeth Glass Professor of Molecular Biosciences, Professor of Chemistry, and Professor of Medicine (Hematology & Oncology) at Northwestern University, Evanston, Illinois, USA. He is also the Director of the Chemistry of Life Processes Institute at Northwestern and Director of Northwestern Proteomics. Here, he answers our questions about challenges facing the proteomics field, the Human Proteoform Project and which areas will benefit most.

**Tell us a little about the current state of proteomics…**

First, I think it's important to mention the Human Genome Project – a great collaboration between labs across the world that resulted in the mapping and sequencing of all the genes in the human genome. Essentially, it allowed us to decode the instructions for life in the world of DNA.

However, in the world of proteins – for reasons I'll go into later – we haven't quite reached that level. The biggest difference between these two worlds is that one has had a "moonshot" project, whereas the other has not. In my opinion, the time has come for us to focus on protein biology. I hope that, within the next eight to 12 years, the ability, scale, and economic efficiency of our technology will meet the challenge our biology presents at the protein level.

**What is the most exciting thing happening in proteomics today?**

Single-cell proteomics is definitely up there! It means you can perform analysis via direct cell imaging. You can take an organ or a part of a tissue at microscopic levels, image it at single-cell resolution, and examine the proteins found there. It's now possible to interrogate dozens of different proteins using antibody-based imaging technologies, so that's one really cool development!

Other exciting things that come to mind include the Human Protein Atlas, which is a Sweden-based program that aims to map all human proteins, and the US$600 million Human Biomolecular Atlas Program (HuBMAP) out of the National Institutes of Health. HuBMAP is now approaching the mapping of 30 tissues in the human body at single-cell resolution. What makes this so exciting? It means we're only a few years away from being over the hump and on the downward slide toward completion!

Single-cell proteoform analysis is also becoming possible in a few labs. Notice the wording here – proteoforms, not proteins! That is also going to become very important, because we are getting another level of molecular precision that will help to bring order to the world of human proteins.

**What major challenges is the proteomics field facing?**

I would say one of the major issues we face at the moment is funding. Essentially, we want to devise technologies that put genomics and proteomics on par with one another. In genomics, we can now do easy, inexpensive single-molecule DNA sequencing – and that's because of the "moonshot" Human Genome Project. That is the level of investment we need in proteomics.

There has been a big push in the private sector in the last two years, with a particular focus on investment in single-molecule proteoform sequencing (SMPS). In fact, a few billion dollars have been promised over the next couple of years. The big question is – will there be a breakthrough in protein sequencing or single-molecule proteoform analysis in the next few years? Right now, there are 10 to 12 companies that stood up with significant or early-stage venture capital investment, many of whom have come out of the genomics world wanting to nail down the world of proteins – so I think the future looks promising.

**Tell us about the Human Proteome Project and the Human Proteoform Project. How do they differ?**

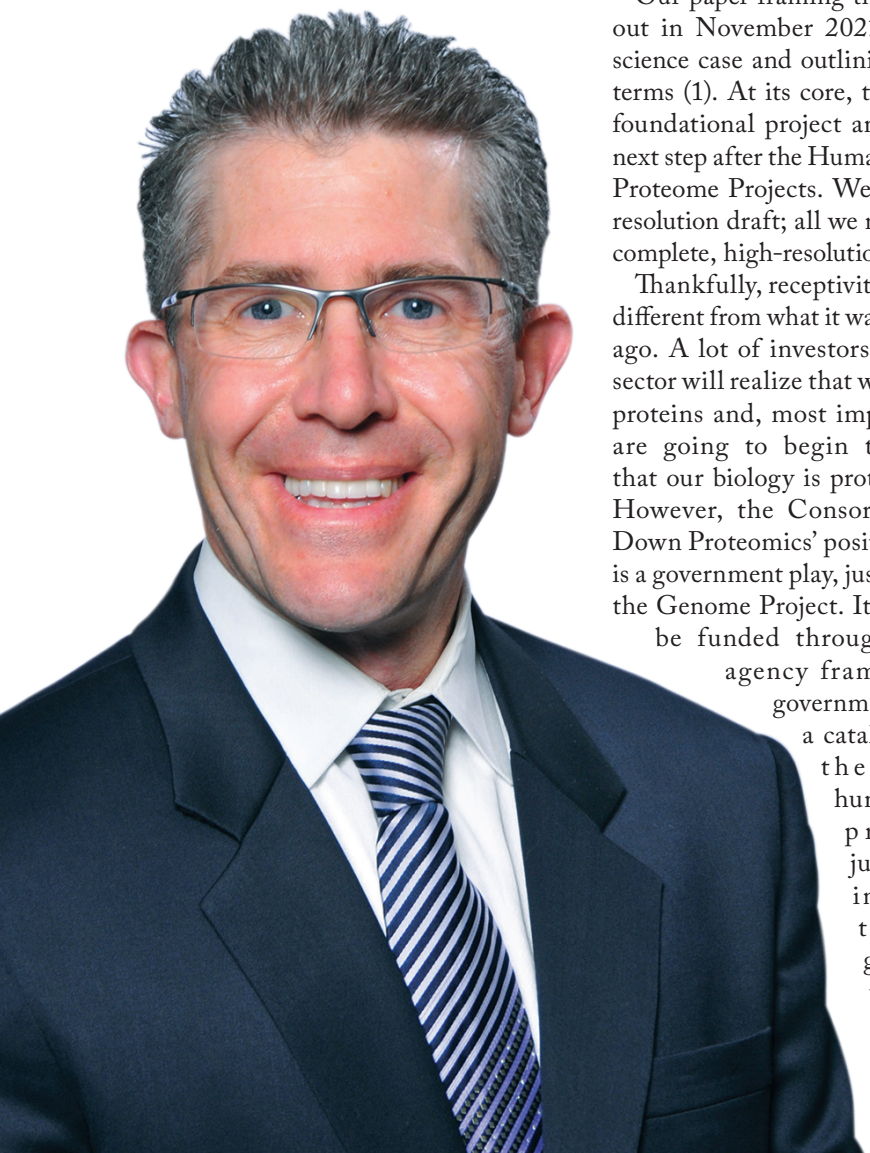
The variety of words – proteins, proteome, proteomics, proteoforms – can be challenging, but there is an important distinction between these projects.

The Human Proteome Project was conceived all the way back in 2002 and found a home in the Human Proteome Organization (HUPO), which is very similar to the Human Genome Organization. HUPO has articulated two major versions of the Human Proteome Project over the years since. The first was rearticulated in 2010 and relaunched aggressively in 2012. Then, two groups with back-to-back Nature papers in 2014 did a large amount of that project, covering about three-quarters of all human proteins using bottom-up proteomics with peptides as the unit of measurement. In some sense, the Human Proteome Project is a little out of date today as, essentially, a low-resolution draft of the human proteome.

On the other hand, the Human Proteoform Project is more specific and uses top-down proteomics with different measurement philosophies and units of measurement. The project states that we must systematically discover proteoforms as they exist in all human cell types and body fluids, providing complete and absolute molecular specificity. The aim is to create a map of the human proteome at proteoform-level specificity.

**What is your role within the Human Proteoform Project?**

Well, you know when you have a wedding and the dance floor is open… I was one of the first people to start dancing. You could say my role is chief instigator! I'm also the founding president of the Consortium for Top-Down Proteomics.



**Where is the project at the moment?**

The Human Proteoform Project is not currently funded. At the base, we would probably need about $1.3 billion over 10 years; $130 million a year would allow us to begin aggressively and then bring in disruptive technologies later. There are three phases to the project and we haven't even launched the first. But we've articulated the project and we're actively seeking a worldwide consortium of like-minded scientists to participate.

Our paper framing the project came out in November 2021, making the science case and outlining the general terms (1). At its core, this project is a foundational project and the obvious next step after the Human Genome and Proteome Projects. We have the low-resolution draft; all we need now is the complete, high-resolution version!

Thankfully, receptivity today is quite different from what it was 10 to 15 years ago. A lot of investors in the private sector will realize that we can sequence proteins and, most importantly, they are going to begin to understand that our biology is proteoform-based. However, the Consortium of Top-Down Proteomics' position is that this is a government play, just like it was for the Genome Project. It can absolutely be funded through established agency frameworks. The government can then be a catalyst to provide the definitive human reference proteome – just like it did in 2002 with the reference genome – and then everybody can feast on that information. That includes patients and advocacy groups, as well as companies and academic institutions discovering disease mechanisms and biomarkers. The project would vastly improve efficiency for basic and translational biomedical research.

So that's the case for spending $130 million a year. The arguments in favor have always existed, but I think it's important to think about receptivity, timing, the arc of history, and when the technology can be put in place to do it.

**Is there a particular application area that you think might benefit most from the Human Proteoform Project?**

Proteins and proteoforms are involved in all human disease; there is not a single human disease that does not involve proteins. So it's that fundamental.

That said, I think neurodegeneration will be a key area to benefit from this project. We have yet to apply the planet's best technologies to protein-based diseases such as Alzheimer's, Parkinson's, amyotrophic lateral sclerosis (ALS), upper motor neuron disease, and frontotemporal dementia. All of these disorders involve proteins going bad.

When we eventually have the right technology, regenerative medicine will also benefit majorly from the Human Proteoform Project. Unfortunately, we don't currently have the tools to meet the scale of the analytical challenge. So, to me, the question is – how are we going to get there? Are we going to do it slowly? Or are we going to invest in a moonshot to get it done in the next decade?

*Reference*

1. *LM Smith et al., "The human proteoform project: defining the human proteome," Sci Adv, 7, eabk0734 (2021). DOI: 10.1126/sciadv.abk0734.*

# The Art of Listening

**Calling for all women's voices to be heard is certainly welcome, but we mustn't forget the other side of the coin: Listening!**

*By Anne K. Bendt*

Our main aim with Females in Mass Spec (FeMS) – a community-led initiative to create a network of support for women in the field of mass spectrometry – was to create a truly useful resource. Organized loosely via a website, a monthly newsletter, and a LinkedIn group, we have grown into a buzzing international initiative – a network of close to 2,000 members, spanning academia, hospitals, governmental agencies, and industry. And I am very pleased to report that 10–20 percent of our members are men. At events, I sometimes joke, "Look around you. This is how us women typically feel!" It's fun to flip the perspective, creating awareness and sensibility for shifted group dynamics. We all benefit from hearing different voices – trying to understand different perspectives and challenges, whether they are gender-specific or not.

During our recent FeMS workshop – on 29th August 2022 at IMSC, Maastricht, Netherlands – I was amazed at how many men showed up and actively contributed to the discussions. The workshop was centered around mentorship and advocacy in the workplace. Naturally, navigating the complexity of mentorship relationships is of relevance to all of us regardless of gender.

Over the past 30 years, I have been lucky to be both a mentee and a mentor, by and for people of various genders. And yes, I have experienced differences between genders – and thankfully so; we can learn so much from each other! It is in exactly this spirit that FeMS was founded. We wanted to build a global network for women working in the mass spec field, as well as their supporters.

In the workshop, we wanted to learn from a panel of established, mid-career and late-career scientists about how they navigated their career so far. We wanted to share tips and tricks for self-advocacy; for example, in situations where there is potential to be overlooked for promotions. True to the FeMS spirit of being inclusive, we invited both male and female panelists from diverse geographical and scientific backgrounds.

One question in particular, raised by a participant, comes to mind: "What do I do if I am up for promotion and have demonstrated all required achievements for said promotion, but am being told to wait, as the more senior man ahead of me needs to go first?" Jennifer van Eyk, Director at Cedars Sinai Precision Biomarker Laboratories, USA, had a reply ready. "Don't let them stop you. Don't stay quiet. Claim what's yours," she said. "If you have any doubts about your dossier being 'ready' or good enough – send it to me, I will check it, and vouch for you!" This is exactly the kind of encouraging nudge (well, strong push!) we sometimes need and which can be provided by established mentors, sponsors and supporters – regardless of gender.

I very much enjoyed their stories and learned a thing or two about how I could become a better mentor myself. Mutually agreeing on expectations and then holding each other accountable is certainly something I want to focus on more.

Another question – this time posed by a male professor – stuck with me: "What can I do as a male boss to encourage junior female students and co-workers to challenge me and give critical feedback?" My answer: Actively listen. Sometimes, we simply don't hear the things we need to hear. If our discussion partner expresses concerns or challenges in a way that we are not used to, it is all too easy to turn a deaf ear. And I suspect this problem happens more frequently for those women who are typically quiet – or from cultures in which 'questioning the authority' is not necessarily encouraged. I am so grateful for this professor's openness to ask this question – he proved to be a role model in his willingness to learn, change, and become a more inclusive boss.

Overall, I am thrilled to see how our FeMS activities are received and acted upon by the whole mass spec community – regardless of gender. After all, everyone's voice counts – but we only truly benefit if we listen.

*Anne K. Bendt is a Principal Investigator at the National University of Singapore*

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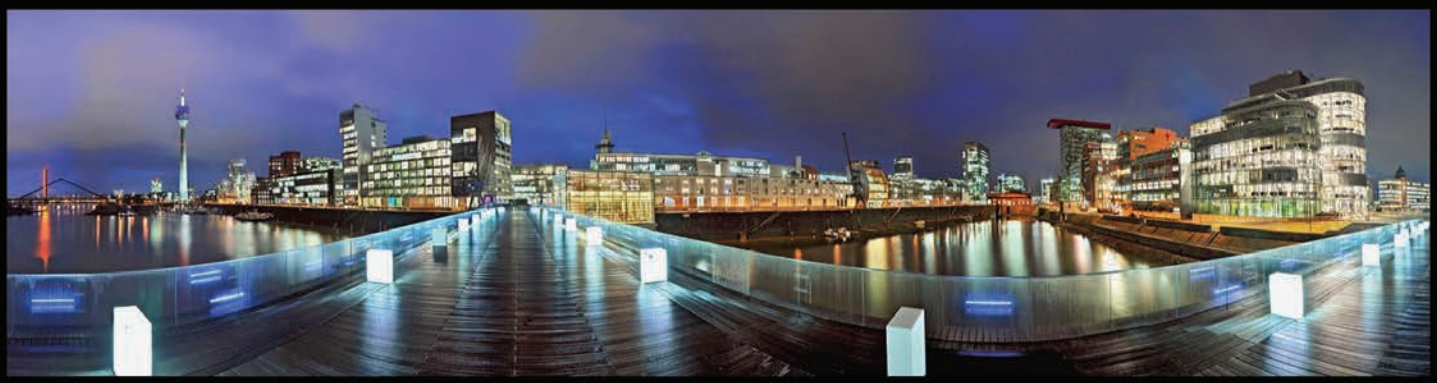

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*Core Topic*
**Chromatography**

Probing problematic pesticides. Broad-spectrum insecticides – called neonicotinoids (NEOs) – are rapidly replacing traditional organophosphorus and organochlorine-based insecticides. Some studies have already reported adverse effects of NEOs on mammalian health – but the relationship between NEO exposure and toxic effects on the human liver remains unclear. And that's why researchers have recently attempted to examine the link by quantifying eight commercialized NEOs in human bile using ultra-performance liquid chromatography combined with triple quadrupole mass spectrometry. The results indicate that neonicotinoids – particularly dinotefuran and nitenpyram – were not completely degraded in the liver and were found at high frequencies and concentrations in bile. According to the press release, these neonicotinoids are "likely to be reabsorbed by the intestine and enter the circulatory system, eventually accumulating in the liver and causing hepatotoxicity and enterohepatic circulation disruption."

Sweat it out. Cystic fibrosis is caused by a defective cystic fibrosis transmembrane conductance regulator (CFTR) gene. The absence of the CFTR protein in patient sweat glands leads to a notable side effect known as aquagenic palmoplantar keratoderma (AKP), which spurred researchers to analyze sweat from CF patients. Using LC-MS/MS, they discovered that 57 proteins were differentially expressed between the patients and controls. The CF sweat proteome was characterized by 25 upregulated and 32 downregulated proteins. According to the authors, the sweat proteome could eventually be used as the basis of a diagnostic tool for CF and potentially reveal treatment options for AKP.

Bare bones. The bone proteome (or osteo-ome, if you prefer) is a rich source of information for forensic studies. But forensic biomarkers based on the bone proteome are typically assessed using skeletal remains from human taphonomy facilities (controversially also known as "body farms" – yes, they exist), which use accelerated methods to clean the bones. UK-based researchers decided to investigate one such technique called maceration, which uses water and heat to de-flesh the bones. On comparing the proteomes (determined by LC-MS/MS) of untreated and macerated (three different protocols) bovine bones, the researchers revealed clear distinctions between proteomes, as well as lower protein abundances with increasing maceration time. The authors recommended the introduction of a standardized method to minimize protein degradation – and to avoid maceration completely where possible.

*References available online*

## IN OTHER NEWS

*Gas chromatography–isotope ratio mass spectrometry analysis of Pliocene-era leaf waxes could help predict future climate conditions in Southwestern North America.*

*UHPLC combined with panel testing demonstrates that the perceived intensity of chilli sauces depends on what they are eaten with, as well as the capsaicinoid content.*

*Astrea Bioseparations acquires chromatography column manufacturer Delta Precision (both based in the UK).*

*Rapid LC-MS/MS method quantifies lenvatinib in dried blood spot samples – with promising preliminary clinical validation results.*

*Solid-phase microextraction paired with GC-MS reveals 38 aroma compounds in crystal malt – which plays a crucial role in flavor and color of beer.*

# Ten Year Views: With Peter Schoenmakers

**Peter Schoenmakers discusses the decade's developments in chromatography, concerns for the field, and future predictions**

Over the last 10 years, what has been the most significant development in chromatography?

Overall, I think that chromatography-mass spectrometry is the most significant development. In the past, they were two fields that were not connected, but now, they form a mutually beneficial relationship with lots of synergy. When I took over from Hans Poppe 24 years ago, there was not a single mass spectrometer in the group, and now we have more than half a dozen. Mass spectrometry has developed fantastically. And chromatography has progressed from a very hands on process to an extremely advanced tool with very sophisticated measurements: It does more, and it works better.

What has made these developments possible?

During my career, many scientific developments originated from scientists in academia. Now, a lot of good contributions come from instrument companies, who play a much bigger role in the development of science. Unfortunately, most people do not make the effort to publish – especially if they work within larger companies. This lack of transparency is a pity, considering that it is important for analytical scientists to know what's in the black box.

What has been the most important innovation, in your opinion?

I don't think that liquid chromatography (LC), gas chromatography (GC), or UHPLC have changed fundamentally. The liquid chromatograph itself, as a unit operation, has also not changed much – in practice, yes, but, fundamentally, no.

The major changes are in coupling and combining. Hyphenation techniques are very different nowadays. Hyphenation is maybe too narrow, but combining two instruments – such as two separate separation systems or a simple but automatic preparation system with another separation tool are well known.

Two-dimensional separations are not going to be as big as LC-MS or GC-MS – but they are relevant and challenging. Specifically, it is exciting how we can now couple different techniques – John Phillips' work on two-dimensional gas chromatography (GC×GC) was revolutionary.

What drives these innovations in chromatography?

Around 70 years ago, GC became popular because the oil industry needed more complex separations. This pursuit ultimately led to GC×GC. In addition, pharmaceutical and life science applications drove LC, and two-dimensional LC innovation. As you can see, innovation in chromatography is driven by societal needs and industry's demand for higher separation power. Such a need still exists, even when combining chromatography with mass spectrometry.

What are your concerns for the field?

Instruments are getting more complicated, and education – even in basic chromatography – is a big issue. We are starting to see more mistakes in analytical science because of a lack of education. We need people to understand what they're doing; although we do our best to train enough people, there are already too many vacancies. This issue has less impact on routine analysis, where we have control procedures, but it is having an important impact on non-routine work, such as problem solving. Moreover, as analytical science is an engine for innovation, we should be able to produce correct data from complex and unknown samples.

What are you most excited about?

I am most excited about young, enthusiastic scientists that understand analytical science and have the opportunity to do things that I've never been able to do. I see many assistant professors that are doing great things, and I meet smart and motivated students during poster presentations in conferences – which gives me a lot of confidence. I'm positive about the next generation.

Overall, where do we go from here?

I see two directions. Firstly, we haven't seen the end of building complex instruments that take sophisticated measurements. Secondly, I think that we will be doing more of our own medical testing. We can already conduct insulin tests, pregnancy tests, and COVID-19 tests. Twenty years ago, we believed that everybody would be able to measure their own biomarkers, but this process is slower than I expected.

In forensics, processes are much faster. Forensics is a good field to do on-site measurements and so it's exciting for us. They go to the waste containers to find evidence of drug use, and we develop simple measurements for the identification of products and solvents.

In the next 10 years, we will move to simple on-site "do it yourself" measurements – both in the field and in the clinic – and at the same time build new, even more sophisticated analytical instrumentation for the laboratory.

# Power List Perspectives on Chromatography

**We asked last year's Power Listers about current challenges facing separation science, plus predictions for the future of the field**

Ken Broeckhoven: Chromatography seems to have reached a limit in separation power without implementing drastic technological changes to instrumentation and column technology. Although 3D printing technology seems promising, it will probably be at least a decade before it becomes feasible to print high-performance columns.

However, I expect to see more work towards user-friendly miniaturization in chromatography. This will resolve certain fundamental issues (such as viscous heating), but will also improve compatibility with emerging technologies such as 3D printing, which can't print large-volume structures with high resolution.

Katelynn Perrault: One of the big shifts I think we will see over the next five to 10 years is a reduction in our reliance on helium in the world of gas chromatography. I've been having a lot of trouble sourcing helium and, when it is available, the costs increase exponentially each year. I would love to see a shift to more sustainable approaches to gas chromatography involving the use of different carrier gases that can be generated in the laboratory. There is already a large national funding focus on reducing and recovering helium in other instrumentation areas, such as NMR and FT-ICR, but I think we'll see this translate to GC instruments soon because we are significant consumers of this resource. Luckily, gas generators have come a long way and are reliable, clean, and can produce the high flow rates required for use in chromatography. I am curious to see the distribution of gases used by laboratories in the next five years and how it differs from what we see now. I personally don't think I'll ever purchase another GC instrument without the capability for hydrogen carrier gas use and a hydrogen generator!

Martina Catani: When it comes to the adoption of GC×GC, I think the biggest challenge we face is implementing software approaches that have high user-friendliness and don't require extensive training to operate. GC×GC is still viewed largely as a research technique, even though it is used more and more in routine analysis in industry. Complex software, data analysis, and statistical approaches have the tendency to make the technique more elusive. Ultimately, GC×GC is meant to make complex mixture analysis "better" – more efficient, more comprehensive, and more accurate. Simplified approaches in software and data processing will help accomplish this goal across more applications. The balancing act here is to improve usability without making software too "black box" or rigid with respect to user control. It is a challenging task, but I think we are moving in the right direction.

Justin Godinho: As a chromatographer, I believe the biggest analytical challenge is the increasing complexity of biopharmaceuticals. Characterization of large therapeutic proteins, including monoclonal antibodies, antibody drug conjugates, bispecific antibodies, and coformulations, offers a rich and challenging set of analytical chromatography hurdles.

I believe there will be increased demand for simultaneous characterization of large proteins and their supporting sample constituents. Currently, a series of separation techniques is required for complete analytical characterization. We have seen some research shift toward innovative methods to elucidate multiple critical quality attributes simultaneously. I also expect greater adoption and drive toward multidimensional separation technologies and MS-based instrumentation in quality control settings to safely deliver well-characterized molecules to patients with fewer, more comprehensive analytical tests.

James Grinias: As a field, we continue to strive for "greener" analytical methodologies that reduce energy consumption and the use of toxic solvents. Within LC, multiple compact instruments have been commercialized that reduce solvent usage 100- to 1,000-fold compared with standard benchtop instruments. I am optimistic that, in the future, routine chromatographic analysis may be performed at a scale that reduces solvent consumption.

Furthermore, compact LC instrumentation that uses capillary-scale columns has a flow rate 1,000 times smaller than traditional high-performance LC (HPLC). Though many consider LC columns "less robust," modern advances have brought them closer to what a typical HPLC user may be familiar with. HPLC is a frequent choice for routine analysis and I believe that scientists should scale down their systems for a greener alternative. Although changes are often met with resistance because of the need for revalidation, the reduction in solvent and power consumption from using these compact instruments would be worthwhile. Continued improvements in column quality and instrument performance will hopefully help this vision become a reality.

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*Core Topic*
**Spectroscopy**

Hot new technique. The first triage of a burn injury is crucial in forming successful clinical treatment plans. However, accuracy rates of burn depth evaluation are currently around 60-75 percent, suggesting that the most appropriate treatment is not always given. With this in mind, researchers from Stony Brook University, New York, USA, have employed a neural network model that uses terahertz time-domain spectroscopy (THz-TDS) to non-invasively triage burns. The new technique was combined with a handheld imaging device, named PHASR, to rapidly image in vivo burn injuries using THz-TDS. Results showed an average accuracy rate of 84.5 percent when estimating burn severity, and predicted the outcome of the wound healing process with an accuracy rate of 93 percent. Researchers hope that – with further testing – the handheld device may be integrated into point-of-care settings for clinical burn assessment.

Spoiler alert. Beer spoilage bacteria are a constant nag for breweries, and existing methods to identify culpable bacteria are often time-consuming. Enter researchers from China, who employed label-free, surface enhanced Raman spectroscopy (SERS) to detect harmful microbes throughout the brewing process. An aluminized chip was paired with SERS to enhance signal strength, which the researchers used to successfully identify eight bacterial species responsible for beer spoilage. Machine learning algorithms suggested that accuracy rates were all above 90 percent – confirming the ability of SERS to classify and identify bacteria in beer.

Joining forces. A group of researchers from China have developed F-GIBS, a dual technique that combines filament- and plasma-grating-induced breakdown spectroscopy (FIBS and GIBS) to improve sensitivities for trace metal detection in liquids. In the study, strong nonlinear interactions of filaments were combined with different plasma gratings, and fluid jets were created to analyze aqueous solutions. Further, no random filament breakups were noted when the nonlinearly coupled filaments entered the fluid jet across the air-aqueous interface. Overall, F-GIBS spectral line intensities were much greater than when FIBS and GIBS were used in isolation.

*References available online*

## IN OTHER NEWS

*Miami Miller researchers receive NIH grant for the study of spectroscopic MRI, and its role in detecting – and potentially eradicating – glioblastoma.*

*MR spectroscopy successfully identifies pseudoprogression to differentiate between necrosis and recurrent brain tumors.*

*UK researchers use 1H-NMR spectroscopy-based metabolic profiling to demonstrate how rectal swabs have the ability to analyze gut microbial functionality with similar effectiveness to fecal sampling.*

*ATR-FTIR spectroscopy – combined with machine learning – identifies urine protein that allows early detection of diabetic kidney disease.*

*Novel, non-destructive SERS-based nanoprobe allows stress signal molecules to be monitored in endogenous plants, which could improve disease management.*

# Ten Year Views: With George Chan

**George Chan discusses the decade's developments in analytical atomic spectrometry, concerns for the field, and future predictions**

Could you give us a brief introduction to analytical atomic spectrometry? What falls within its scope?

It is logical to refer to analytical atomic spectrometry as analysis for elemental (atomic) information based on the principle of either electromagnetic radiation (optical spectrometry), or charged particles (mass spectrometry).

On the optical spectrometry side, techniques are typically classified according to their working principles – absorption, emission and fluorescence – with a wide variety of atom reservoirs and excitation sources. The wavelength range is vast, spanning from x-ray to near-infrared, although only a subset is used in almost all cases.

On the mass spectrometry side, there is also a wide range of ionization sources coupled to different types of mass spectrometers, and often, the same atom reservoir can be used as an excitation source in optical, and mass spectrometry. There are also some "hybrid" techniques that use optical transitions to achieve selective ionization – followed by detection of the charged particles. In addition, sample introduction techniques, instrument hardware, data handling, processing and reduction techniques – specific for use with the spectrometric methods – all fall within the scope of analytical atomic spectrometry.

What has been the most significant development in atomic spectrometry over the past 10 years?

There have been several significant developments. I think that the ChemCam instrument – which was installed on the Mars Curiosity Rover and landed on Mars in 2012 – is the most significant. ChemCam combines a high-resolution remote imaging camera and a laser induced breakdown spectroscopy (LIBS) system to characterize the elemental composition of rock and soil samples on Mars. Although the development of LIBS is not new (it can be traced back to the 1960s shortly after the laser was invented), LIBS was still more like a laboratory research tool at the start of the 21st century. Sending a LIBS-based instrument to Mars shows the analytical community how advanced, capable, and reliable the LIBS technique and hardware is. The success of ChemCam, of course, is driven by the needs of a special mission, but advancement of the technology, and reliability of lasers and photodetectors are the keys to its success.

What have been the most important commercial developments over the past decade?

Array detectors are indispensable tools in optical spectrometric measurements – but they are not without their drawbacks. One limitation is that registered "detector counts" can not be readily reverted back to the number of photons or photoelectrons (for various reasons). Although some modern array detectors can be used in a photon-counting mode, the dynamic range is then greatly reduced as a pixel is temporarily "dead" after a single photon hits it – a phenomenon similar to detector dead-time in ion-counting mass spectrometry. An array detector with read noise significantly less than one electron only became available two years ago. In particular, the readout noise of the ORCA-Quest qCMOS camera from Hamamatsu is reported to be 0.27 electrons rms. This low level of read noise makes counting of multiple photoelectrons on a single detector-pixel possible. Although the global reset time of this camera is not yet fast enough to match the typical timescale of LIBS measurements, I consider it an important innovation in detector technology.

**Do you have any concerns for the field?**

My major concern involves the continuation and transfer of experience and knowledge to the next generation. There are several reasons for this concern. Firstly, without dispute, the academic community of analytical atomic spectrometry has been shrinking for the past 20 years. In almost all cases, retired faculty members specializing in analytical atomic spectrometry have been replaced by someone specializing in another area. As a result, there are now only a small number of active research groups that can transfer knowledge in atomic spectrometry to the next generation.

Secondly, the focus of many research programs has shifted from fundamental understanding and instrument development to method development and applications (for example, metallomics, speciation, forensics, environmental). A natural consequence of a heavy focus on applications is a de-emphasis on fundamental theory and mechanistic studies. Experience, knowledge, and expertise in the field of atomic spectrometry are often lost and not transferred to students or technicians.

Another concern is the potential harm that may arise from the ever-increasing computation power available for data mining, pattern recognition, and chemometrics. These are powerful tools, but there is also a danger of giving users a false impression that training in reading and understanding spectral data is old fashioned and no longer important.

A similar situation involving a lack of knowledge transfer to the next generation was noted about a decade ago in the field of nuclear science and engineering. To combat this problem, the US Department of Energy initiated several university consortia with generous support to ensure that a strong pipeline of new technical talent would be available in the future. I hope that someone with vision and power will see that a similar situation is developing in many other disciplines, including, but not limited to analytical atomic spectrometry, and take action before it's too late.

*"Experience, knowledge, and expertise in the field of atomic spectrometry are often lost and not transferred to students or technicians."*

**What are you most excited about?**

In short, the joy of working with good people is what excites me most about the spectroscopy field. I also like the intellectual challenge of solving difficult problems with my expertise. In particular, I like to conduct fundamental studies that explain new experimental observations and also explore novel applications with new tools. I am fortunate enough to continue conducting fundamental research even though my current position is not at a university. How? Well, some applications require fundamental characterization before methods can be formulated – one example is my project exploring the use of LIBS for optical isotopic analysis of uranium. We need fundamental details of the uranium LIBS plasma and an understanding of the behavior of the various uranium emission lines.

In some other situations, fundamental research is performed through collaborations with my friends at universities. For example, my collaborators and I submitted a manuscript in December 2022 on characterizing a plasma-based ambient desorption-ionization source using temporally resolved monochromatic imaging spectrometry. It was a fun project, and the idea of writing this work up for submission developed from a casual chat with Carsten Engelhard, University of Siegen, and Jacob Shelley, Rensselaer Polytechnic Institute, at a conference this past October. The data was not new, but we now have a different and better explanation compared with when we originally collected the results.

**Overall, where do we go from here?**

Development is highly funding-driven. I can see there will always be a need in analytical atomic spectroscopy for elemental and isotopic analysis. In addition, there will be a demand from users and stakeholders for techniques and instruments that, compared with current tools, are smaller, easier to use, while providing higher sensitivity and faster analysis times. The question is whether there will remain a sufficient supply of well-trained analytical spectroscopists for ongoing development.

*George Chan is a Chemist Research Scientist/Engineer at Lawrence Berkeley National Lab, USA*

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# Ten Year Views: With Duncan Graham


**Duncan Graham discusses developments in SERS over the past decade, and where he thinks the field will take us next**

## Reflections on the past decade…

The surface-enhanced Raman scattering (SERS) field has certainly come a long way since PhD student Jim McQuillan reported an enhanced intensity Raman spectrum in 1973. The field really took off in 1977, when two papers attempted to understand the enhancement in the Raman scattering from the roughened metal surfaces, inspiring thousands of subsequent studies.

In 2012, there were approximately 1,250 papers published in the SERS field. Notably, among the total articles published in 2012, only 1.9 percent and 5.5 percent covered medicinal applications and biochemistry, respectively. Fast forward to 2022 and we find that over 2,350 papers were published. We still see that chemistry dominates, but the materials aspect of SERS has dropped to 19 percent. Interestingly, medicinal applications jumped to 2.3 percent and biochemical use of SERS went up to 9 percent. And so I would say the most significant development in the last 10 years is the realization that SERS is useful for biological, biochemical, and medical applications – linking to an increase in portable Raman spectrometers.

In 2012, there were 50 articles published containing the words "SERS" or "assay," but, in 2022, there were 108. This increase is driven by the combination of SERS with lateral flow assays. In light of the COVID-19 pandemic, colorimetric lateral flow assays became incredibly important. These assays are simple to convert by adding a Raman reporter and interrogating the lateral flow device with a portable Raman spectrometer. Benchtop Raman spectrometers can also be used to analyze lateral flow strips – although this may not be in the spirit of lateral flow assays, which are designed for point-of-use and rapid response.

I'd also add that there have been significant industrial developments to Raman spectrometers. The high-end microscope systems are highly valuable for research but, in terms of translating this growth of SERS for non-experts, Raman spectrometers need to be made more accessible. Firstly, they need to be within laboratory budget parameters in terms of research; secondly, they must be easy to use with software that doesn't require interpretation by an expert spectroscopist.

## The decade(s) to come…

The SERS field continues to be buoyant and there are a number of ongoing research projects that are extremely interesting. My main concern is that those beyond the spectroscopic community are limited in their awareness of SERS as a technique that can be used when other methods fail to fulfill the required measurement criteria. There are many examples of this in literature, and the concern is whether the end user base is open enough to use SERS to its full potential. We are still without a large-scale SERS application that transforms the end user base.

I am most excited about the integration of AI with SERS data. SERS data has got a reputation for being variable – although this can be controlled and minimized. The integration of AI with data processing will advance the presentation and interpretation of data beyond what is currently possible. Of course, there needs to be caution in terms of overreliance on AI, but steps are being taken by researchers to integrate this capability into the SERS community. Advances in this area would really help with the reliability and presentation of data for non-experts of SERS.

In the future, I hope we will see SERS applied in several new and unique ways – such as non-destructive, real-time analysis of multiple species simultaneously at ultra sensitive concentrations and in a quantitative manner. If this can be achieved, we'll see greater advances in SERS from the research laboratories into the hands of the end user – ultimately benefiting society. SERS is finally being acknowledged as a promising technique – one that is going to deliver on several meaningful applications. But we need to continue with the strong research base and the integration of researchers working with industry partners to overcome the barriers that are in place for translating research into commercial reality. The pandemic has proved that working collaboratively, rather than competitively, provides results. Collaboration will benefit the whole spectroscopic SERS community – as well those beyond.

*Duncan Graham is the Associate Principal and Executive Dean of the Faculty of Science, University of Strathclyde, UK*

# RP Analysis of RNA Markers Using a Bioinert Column

Clean and reliable oligonucleotide standards – such as RNA markers – are necessary for various analytical methods. RNA markers are fragments of a certain size and used in gel electrophoresis to estimate the size of other RNA fragments.

The irreversible adsorption of oligonucleotides on metal parts is a major issue for RP-LC analyses, as standard equipment and column hardware are made from stainless steel. To overcome these challenges, bioinert systems and columns – such as the recently introduced YMC-Accura Triart columns – are beneficial. These columns have a bioinert coating on all surfaces, including the frits, to prevent any unwanted ionic interactions.

RNA markers from 100–1000 bases can be separated using a YMC-Accura Triart Bio C4 column at pH 7 and 80 °C. All seven peaks are very well resolved and show excellent and reproducible recoveries from the first injection; while a standard column would require pre-conditioning and provide much lower sensitivities.

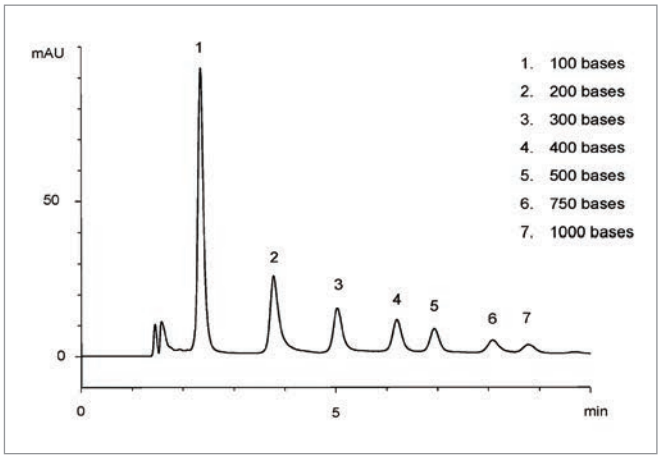


Figure 1. Analysis of 7 RNA markers using the bioinert YMC-Accura Triart Bio C4 column.

*Full method details can be accessed here https://ymc.eu/d/brDou*

# "The Orbitrap Man!"

**Sitting Down With…**
**Alexander Makarov,** Director, Global Research LSMS, Thermo Fisher Scientific, Bremen, Germany; Professor of High-Resolution Mass Spectrometry, Utrecht University, The Netherlands; and Fellow, Royal Society, UK

Thinking back to your childhood, did you always want to be an inventor?

Strangely enough, yes! I know it sounds odd but, even at the age of seven or eight, I tried to invent a device to collect wheat. As a city dweller in Siberia, I had not really seen much wheat nor many collection devices – but that happened to be my first idea. I also attempted to invent different kitchen utensils for my mother. Unfortunately, she was not too pleased with my proposals, because my ideas were not very practical and did not really address the need for safety or cleanliness.

However, one great thing I had in my childhood was a special journal for budding engineers. In this journal, there was a section, called something like "the patent office of young engineers," where they invited children to submit invention ideas. I wrote to this journal several times and, interestingly enough, I always received an answer. It could take up to three months – but they would usually send me a long response, with both positives and constructive criticism. And, of course, in the majority of cases, these ideas were already long-invented by proper adult engineers – but I kept doing this until I grew up myself.

How did you become interested in mass spectrometry?

Even as an adolescent, I had this idea in my mind that I didn't want to explore nature – but instead create a "second nature." In a sense, this is what I'm doing now – though, at the time, I wasn't thinking in those terms. Initially, I actually wanted to create what is now known as a 3D printer – a concept that didn't exist at the time. So, I started to look for an institute where this might be a possibility.

When I arrived at the Moscow Physics Engineering Institute, I asked if they had this type of instrument – that could build objects atom by atom, molecule by molecule. They said no, but that they had the opposite: technology that takes objects and breaks them down to a molecular level and analyzes them. So I decided that if I could not do assembly, I would do disassembly! And that is how I ended up in mass spectrometry – it seemed to be the closest to my idea at the time.

There were various groups dealing with molecular analysis and I really wanted to be involved. Eventually, a professor of mass spectrometry gave me a chance – despite my limited knowledge – as well as some literature on analyzers and ion sources, and a laboratory position as a technician. My first assignment was to repair a leak in a vacuum pump, which is how I started working with older students – one of whom co-invented mass cytometry (now at Standard BioTools) – who showed me what high voltages were, how mass spectrometers worked, and so on.

I was then diverted in a different direction by another PhD student working on a spark ion source – his analyzer was delivering too low performance, so he asked me to look for alternatives, and that's when I started to learn about all different mass analyzers. Eventually I found an analyzer with hyper-logarithmic potential from Lidia Gall's group and attempted to realize it with a spark ion source. And so, when the need arose for Orbitrap technology, I was already well equipped for taking the next step.

How does it feel to be a superstar in the world of mass spec technology?

In principle, it sounds great doesn't it? When you step into an elevator and people start whispering or simply being recognized as the "Orbitrap man." But on the other hand, I realized I shouldn't get carried away; these things are just superficial. More importantly, people really take your word for truth. You have to be careful with what you say – and what you promise – because expectations are high.

When I found myself in this position for the first time, I naturally suffered from imposter syndrome, especially because so many colleagues contributed to the Orbitrap success. For the new generation of scientists, the Orbitrap is something that has always existed.

Do you have further ambitions for the Orbitrap analyzer?

First of all, I want to bring the Orbitrap story to completion. Essentially, I want to make it an analytical technique for every laboratory – something that could be considered a commodity. And we are getting there already! There is currently a five-digit number of Orbitrap instruments working 24/7 around the globe; in most big and medium cities, there will be one or more somewhere – in labs or in a university. Although these instruments still provide industry-leading performance even after 17 years of development under competitive conditions, it would be great to see Orbitrap technology go from a high-end technique to a routine method, especially in clinics and biopharmaceutical industry.

If you weren't a scientist and inventor, what would you be doing instead?

I am really interested in all types of unusual theories, particularly theories relating to history – where you can examine the question "what if?" – leading us to imagine what could have happened if certain events had happened differently. A book that specifically impressed me was Jared Diamond's "Guns, Germs, and Steel", where he explores why history went the way it did, and why Eurasian and North African civilizations have survived and conquered others and not vice-versa. So if I wasn't a scientist, maybe I would be studying history – or maybe even working as a tour guide!

As someone with a significant innovation under your belt, what are your views on innovators?

I would say that not many people are capable of true innovation. And a large number of simple "doers" – who just do what they are told – cannot replace a single person who is able to innovate, although they are really needed when innovation gets scaled up. So, if you find one of these innovators, you really need to protect them and fight for them; they are very difficult to replace!

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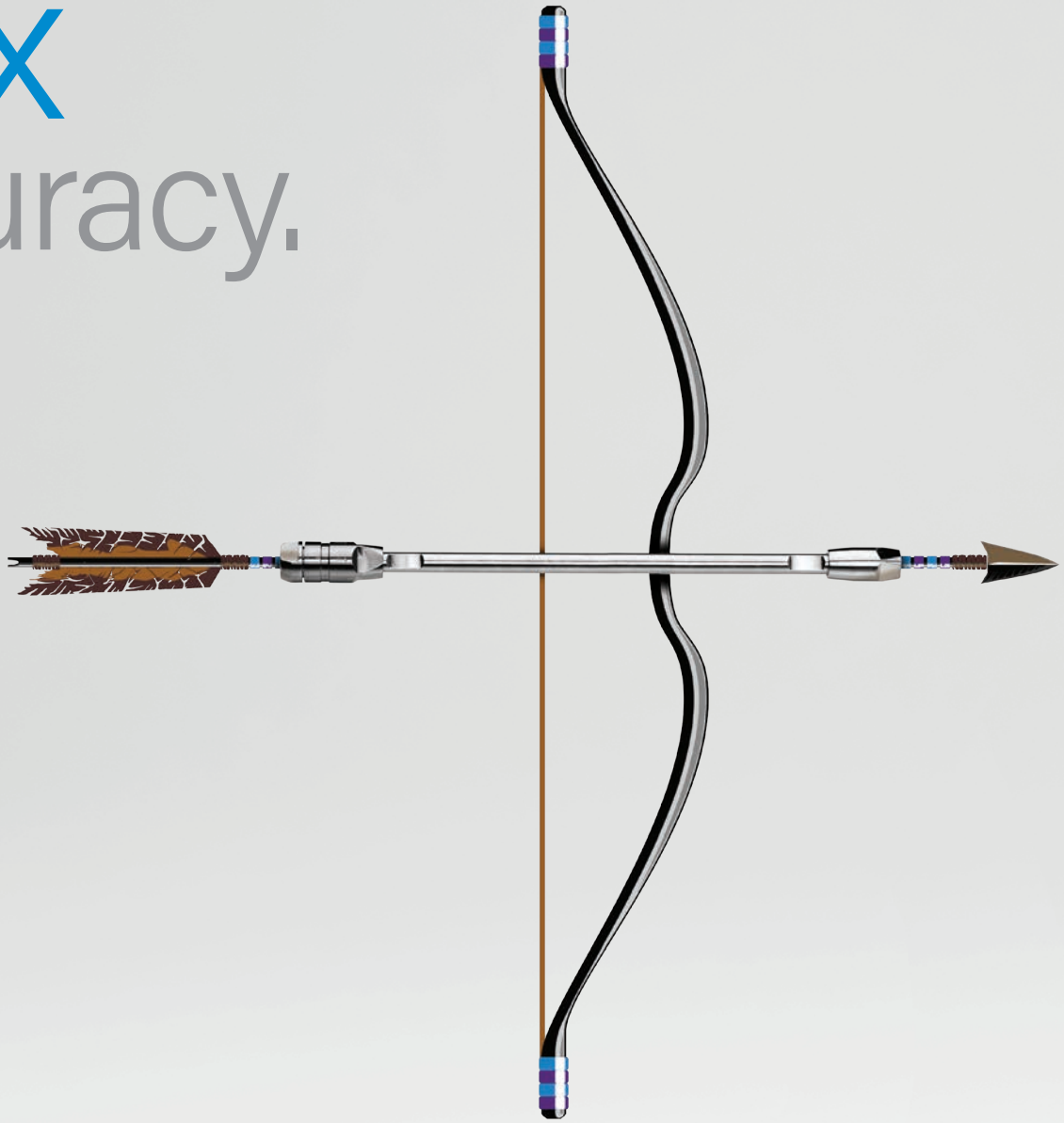

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