MARCH / APRIL 2024 # 116

the Analytical Scientist®

A Century of Innovation

As Scripps turns 100, we shine a spotlight on four of its leading analytical scientists

The Next Big Thing in GC-MS

LECO

EMPOWERING RESULTS

Elemental Analysis | GC Mass Spectrometry | Metallography

Let's Power Through the Perception Problem

Nominate an analytical scientist whose work is positively transforming the world around us

Last month, we asked you to vote on whether the field ought to sail under a new flag – "measurement science" – to boost the reputation of the field. The results are in: a landslide victory (86 percent) for "analytical."

I reached out to Chris Enke for some initial reaction. "Though measurement is an essential and major part of the analytical process, it leaves out a part that is even more central: separation," he says. "The aspect that makes chemical analysis different from physical measurement is that the part we are trying to measure is all mixed up with a dozen to hundreds of thousands of other things. I think the focus on measurement (with great respect to Dick Zare) weakens rather than strengthens the field."

The debate will continue. And even if a rebrand isn't the answer (good news for The Analytical Scientist) the field's perception problem remains. One solution may simply be to shine a spotlight on the analytical scientists whose work is transforming the world around us – for the better. Indeed, this is the approach we are taking with this year's Power List (nominations are now open!).

Consider some of the biggest challenges facing humanity in 2024. From improving our health and wellbeing to clean water and clean energy, analytical science is playing a crucial – but often underappreciated – role. So, we welcome you to nominate individuals in three categories: "Human Health Heroes," "Planet Protectors," and "Instrumental Innovators" – with the latter recognizing that fundamental improvements in analytical methods and technology are the foundation of transformative work in clinical progress, environmental monitoring, and other important applications.

Nominate for the Power List!

And as you flick through this month's issue, you'll find the above themes covered; indeed, they can hardly be avoided. For example, this month's Sitting Down With interviewee, Elena Ibañez Ezequiel, is working towards achieving Sustainable Development Goals related to world hunger with her work in food analysis; Susan Richardson's pioneering research into the environmentally concerning disinfection by-products (DBPs) features in the Mass Spec section; and our cover feature profiling several scientists at Scripps demonstrates how analytical science is contributing to new biological understanding, new diagnostic tests, and new therapies.

Finally, we always ask readers to consider diversity when nominating for the Power List. Interestingly, by my count, this month's editorial content has an almost 50/50 gender split; which, if I'm being honest, wasn't planned (despite my writing this just after International Women's Day) – a testament to the diverse strength and depth of the analytical science community!

James Strachan
Editor

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Ready, Set, Sequence!

Could the rise of nanopore technology cost mass spec its protein sequencing throne?

Now that nanopore based sequencing of DNA and RNA is fully commercialized, there is only one big question unanswered: could the same technology be used to sequence proteins?

Researchers from Nanjing University, China, modified a hetero-octameric *Mycobacterium smegmatis* porin A (MspA) nanopore – incorporating a nickel based sensor and machine learning – to investigate the potential of this specific technology in protein sequencing (1).

Here, we discuss with Shuo Huang, Professor at the School of Chemistry and Chemical Engineering in Nanjing University and corresponding author about his latest nanopore-based proteomics research and the future of this potentially disruptive technology…

What inspired you to explore the possibility of nanopore-based protein sequencing?

Distinguishing and determining all the different amino acids and their post translational modifications (PTM) is the main challenge in nanopore based protein sequencing.

However, with the high resolution of MspA nanopore, this becomes achievable – allowing us to resolve a large variety of epigenetically epigenetically modified nucleoside monophosphates (2) and monosaccharides (3).

For amino acids, we need a different adapter. The NTA-nickel adapter immediately came into our mind, so we decided to focus our research on developing and optimizing this sensor.

Could you describe your sensor?

To the best of our knowledge, there is no previously reported nanopore that contains a sole nickel ion in its lumen. This specially designed configuration appears to be critical to resolving all 20 proteinogenic amino acids along with four PTM.

The nickel adapter at the pore constriction serves to extend the dwell time of each amino acid, when captured by the pore – providing rich identity information. With machine learning, we can more easily find even minor nanopore event feature differences. It turned out to be quite efficient to fully discriminate between events generated by different types of amino acids.

Could this technology replace mass spec?

I am optimistic that it might eventually replace mass spectrometry by being much smaller, more economic, faster, while providing more information. Right now, nanopore protein sequencing has not yet been demonstrated – but the unambiguous discrimination of all 20 proteinogenic amino acids suggests a bright future for it!

References

1. *K Wang et al., Nat Methods, (2023). DOI: doi.org/10.1038/s41592-023-02021-8.*
2. *Y Wang et al., Nat. Nanotechnol., 17 (2023). DOI: doi.org/10.1038/s41565-022-01169-2.*
3. *S Zhang et al., Angew. Chem., 61, 33 (2022). DOI: doi/10.1002/anie.202203769.*

INFOGRAPHIC

The Final Chapter

What books should analytical scientists read? We asked 2023 Power Listers.

Most Popular Books

The Immortal Life of Henrietta Lacks	17%
The Structure of Scientific Revolutions	5.5%
A Philosophy of Scientific Instruments	5.5%

Renã Robinson:

"The Immortal Life of Henrietta Lacks gives a scientist's perspective on mistreatment and unethical use of science and medicine towards the black population. Science, medicine, and engineering fields have suffered from issues described in these books that continue to impact marginalized communities. These books challenge us to think about our science, who it benefits, who it excludes, and how it is conducted."

BUSINESS IN BRIEF

An industry–academia cryo-EM collaboration, product launches from Pittcon 2024 and SLAS 2024, a new multimodal research facility, and more…

- **Max Planck Institute** and **NovAlix** have announced their collaborative effort to accelerate drug discovery research – with experts from both academia and the private sector working on cryo-EM technology.
- **SCIEX** launched the Echo MS+ system at SLAS 2024 – a coupling of acoustic ejection mass spectrometry technology and open port interface (OPI) sampling with either the SCIEX ZenoTOF 7600 or Triple Quad 6500+ system.
- **Bruker Corporation** has expanded their molecular microscopy portfolio with the acquisition of Japanese Raman microscopy developer **Nanophoton Corporation** – with plans to launch more user-friendly microscopy systems with advanced nanocarbon materials.
- Following a decade of research, the **Luxembourg Institute of Science and Technology** (LIST) has announced the commercial launch of magSIMS – a magnetic sector secondary ion mass spectrometry system for nanoscale visualization.
- A new £750,000 UK Centre for **Multimodal Correlative Microscopy and Spectroscopy** (CoreMiS) has opened its doors to environmental researchers in Oxfordshire – fully equipped with emerging spectroscopic and microscopic technologies.
- **Shimadzu** has launched a series of inductively coupled plasma mass spectrometers, ICPMS-2040/2050 – featuring a high-performance quadrupole mass filter, enabling reduced gas consumption and enhanced ionization efficiency.
- The newly released TauSTED Xtend – based on stimulated emission depletion (STED) imaging – holds the promise to extend live cell imaging at nanoscale resolution according to its designer, **Leica Microsystems**.
- **Thermo Fisher Scientific** has launched the Dionex Inuvion Ion Chromatography (IC) system – their latest instrumentation for detection of corrosive contaminants in oil and gas – with improved speed and smaller footprint.

Designer Drug Detection

A new computational framework provides researchers with an efficient process for uncovering new psychoactive substances

Every year, hundreds of new designer drugs emerge on the "gray market," causing avoidable intoxications and fatalities. These drugs are often unregulated through existing legislation, and there is limited knowledge about their effects.

To dig deeper into the issue, researchers at the University of British Columbia, Canada, developed a computational framework that allows for reanalysis of mass spec data from over 12,000 urine samples.

The team discovered new psychoactive substances (NPSs) that were missed by conventional standard-based workflows – including a synthetic opioid called fluorofentanyl.

The British Columbia Centre for Disease Control has implemented the team's software as part of its routine clinical workflows – allowing regular surveys of the entire repository of clinical and forensic mass spec data. Additionally, the team plans to integrate the technology with an AI platform they introduced in 2021.

References available online

Foreign-Language Recommendations

"The Nicomachean Ethics"
by Greek Philosopher Aristotle
(Recommended by Victoria Samanidou)

"L'Encyclopédie du Savoir Relatif et Absolu"
(Encyclopedia of Relative and Absolute Knowledge) by Bernard Werber
(Recommended by Jef Focant)

"La chimica della bellezza" (The Chemistry of Beauty) by Piersandro Pallavicini
(Recommended by Marcello Locatelli)

Popular Science Books

"Genius"
by James Gleick
(Recommended by Gary Heiftje)

"Silent Spring"
by Rachel Carson
(Recommended by Phil Marriott)

"The Gene: An Intimate History"
by Siddhartha Mukherjee
(Recommended by Koen Sandra)

Victoria Samanidou:

"The Nicomachean Ethics is one of [Aristotle's] best known works, distinguishing two types of virtue: intellectual and moral. Science arises from learning, taking time and experience to acquire – with teachers playing a crucial role. Whereas moral virtue is developed through habitual behavior and the responsibility to cultivate it lies within oneself."

Credit: Yannis Tsouflidis

Credit: Images for collage sourced from Unsplash.com and Wikimedia Commons

Firefighting Omics

Intense physical activity increases the risk of respiratory infections, according to multi-omic analysis of biofluids

For some, intense physical activity is a hobby; for those working in firefighting, law enforcement, or the military, it's part of the job – one that can come with health risks. Researchers from Pacific Northwest National Laboratory, USA, set out to quantify that risk using multiomics – and they found that intense physical activity was associated with an increase in respiratory infection risk (1).

In collaboration with the Los Angeles County Fire Department, the researchers collected blood, urine, and saliva samples from volunteer firefighters before and after an intense 45-minute workout simulating real-life wildfire situations of physical stress.

"We used a method that we developed named MPLEx (metabolite, protein, and lipid extraction), which allowed us to perform the three different omics measurements from a single sample," says Ernesto Nakayasu, Senior Research Scientist and lead author of the study. The researchers used LC-MS and GC-MS to quantify the changes of 3,835 proteins, 730 lipids and 182 metabolites in response to intense activity.

The results revealed signatures of energy expense, tissue damage, and a shift in inflammatory response; a decrease in three pro-inflammatory cytokines and an increase in eight antimicrobial peptides. "The biggest surprise was to discover that high-intensity exercise was associated with an increase in susceptibility to respiratory infections. Usually, exercise is associated with protection from such infections, but it turns out that the high intensity has some detrimental effects," says Nakayasu.

One factor potentially limiting applicability of the findings to the wider population is that wildland firefighters are perennially exposed to specific respirable toxic pollutants that may permanently alter their immune system via immunomodulation and gene expression of key metabolic pathways. "Further epigenetics investigation would help to illuminate this potential bias," wrote the authors (1).

According to Nakayasu, there is also potential to use some of the molecules identified as biomarkers of occupation-associated illnesses. "Then we will combine the different biomarkers to make multi-panel assays that can tell us what specific illness the person is suffering from or even predict the likelihood that such an event will occur."

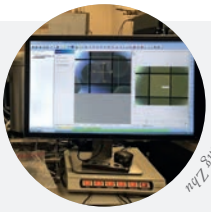
Reference

1. *ES Nakayasu et al., Military Med Res, 10, 48 (2023). DOI: doi.org/10.1186/s40779-023-00477-5.*

An Automated Avenue for Microplastic Detection

An AI–spectroscopic synergy could be the key to identifying microplastics faster and with more accuracy

An AI-based microspectroscopy imaging identification system, PlasticNet, can detect microplastics with high accuracy – and could be used in wastewater treatment and food production plants (1). The tool, developed by researchers at University of Waterloo, Canada, uses a deep learning convolutional neural network architecture to automatically detect images generated by focal plane array (FPA)-based micro-fourier transform infrared (FT-IR) microscopy.



Credit: Ziang Zhu

PlasticNet was able to successfully classify 11 types of common plastics with 95 percent accuracy.

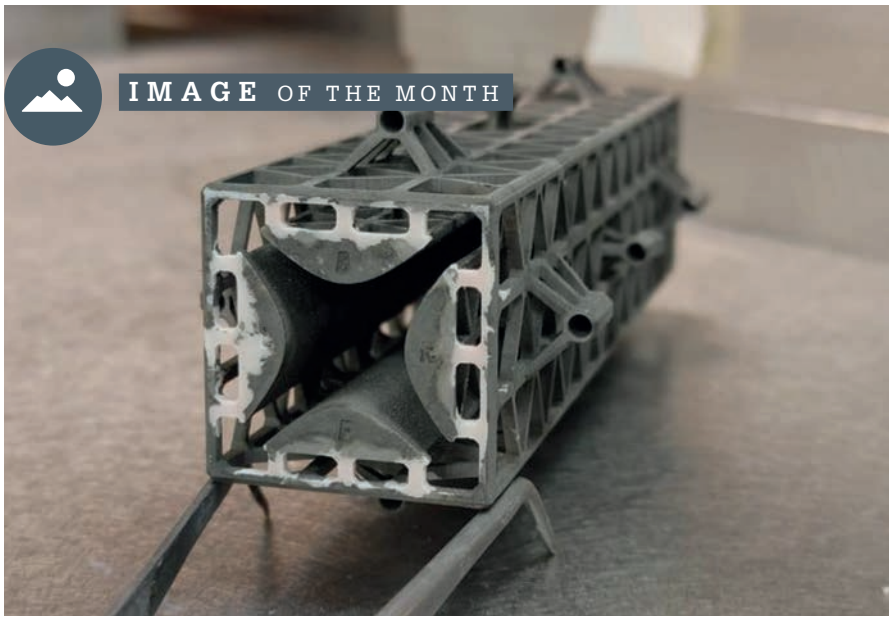
"I was surprised by the efficiency of deep learning in this context," says lead author Ziang Zhu. "With PlasticNet, we received precise and reliable results in a field that is known for often dealing with complex and variable data. It's really opened up avenues for future investigations in environmental science."

Zhu is hopeful that environmental researchers will embrace AI for detecting microplastics – as well as other pollutants and applications.

Reference

1. *Z Zhu et al., ScienceDirect, 337 (2023). DOI: 10.1016/j.envpol.2023.122548.*

IMAGE OF THE MONTH



Go Small or Go Home

Researchers from the Massachusetts Institute of Technology, USA, have used 3D printed components to create a lightweight and inexpensive portable mass spectrometer. The compact quadrupole mass filter pictured above is built from durable, heat resistant glass and could support research in remote areas. "We are not the first ones to try to do this. But we are the first ones who succeeded at doing this," said senior author Velásquez-García in a press release. "There are other miniaturized quadrupole filters, but they are not comparable with professional-grade mass filters."

Credit: Courtesy of Luis Fernando Velásquez-García, Colin Eckhoff, et al

Would you like your photo featured in Image of the Month? Send it to james.strachan@texerepublishing.com

QUOTE OF THE MONTH

"Our analytical expertise is what really enables us to move from observing correlations to understanding causations in metabolic pathways. And that's crucial for our translational goals, as it provides a direct link between metabolic changes and physiological outcomes."

Gary Siuzdak (see page 26)

Painting the Deeper Picture

A combination of deep machine learning and mass spec imaging used to create a 3D map of the rat brain

An integrative experimental and computational mass spectrometry framework for imaging and chemical profiling of single cells – called MEISTER – has been developed by Jonathan Sweedler and his colleagues from the Beckman Institute for Advanced Science and Technology (1).

MEISTER comprises deep-learning-based signals, a multimodal image registration technique that produces coherent 3D reconstruction of imaging MS data, and a computational approach to create and map cell-specific chemical profiles for multiscale integration.

The researchers successfully created a 3D map of the rat brain with high spatial resolution (50-µm lateral and 16-µm sections) – profiling 13,566 single cells and extracting lipid profiles from 11 brain regions. "We envision future endeavors on creating multiscale biochemical atlases, with increasingly powerful profiling technology for metabolites, lipids, peptides and proteins, as well as integrative analysis with other omics data," concluded the authors in their paper.

Reference

1. YR Xie et al., Nature Methods, 21, 521–530 (2024). DOI: doi.org/10.1038/s41592-024-02171-3.

The Easy – and USP Compliant – Way to Modernize Your HPLC Methods

How KNAUER's HPLC Method Converter helps biomanufacturers maximize speed and sustainability, while adhering to US Pharmacopeia (USP) 621 guidelines

Method conversion is the adjustment of chromatographic parameters in response to changes in column dimensions, where correct scaling of all method parameters is critical to maintain sufficient resolution. When pharma manufacturers make such adjustments, they must adhere to the pharmacopeia. The US Pharmacopeia (USP) 621 guidelines define the acceptable range of parameter alterations and calculations in a chromatographic method without fundamentally modifying the pharmacopeial analytical test. But to truly get the most out of method conversion – while staying compliant – can be tricky…

With that in mind, KNAUER has developed an HPLC Method Converter that ensures users are compliant with USP 621, while also aiming to maximize speed and sustainability. We spoke with Ulrike Krop, Team Leader Applications & Academy at KNAUER, to find out more.

Tell us about scaling chromatographic methods…

There are two types: upscaling and downscaling. Upscaling is mostly used in method development for preparative purifications. To save eluent and sample, the method is developed on an analytical system with small columns and then finally transferred to a larger column. Typically, the transfer is linear – the column length is kept constant, and the ID of the column is increased to increase the loading capacity.

Downscaling from HPLC to UHPLC on the other hand is one of the most common and well-known scenarios. The availability of UHPLC columns with very small particles, such as the KNAUER Eurospher II columns with 2 µm particle size, combined with systems with low dispersion, opens up new possibilities. You can speed up your analytical separation by reducing the extra column volume with low dispersion systems, such as the KNAUER AZURA® HPLC 862 bar system or the KNAUER AZURA® UHPLC 1240 bar system – both available with ultra-low dispersion technology (ULDC).

Either way, the final method transfer can be easily realized by using the KNAUER HPLC Method Converter. Indeed, our latest software tool was designed to automatically calculate the suitable parameters according to your new column dimensions and particle size, while being USP 621 compliant.

What are the current challenges with USP methods? Do they need to be modernized?

Most USP chromatography methods were developed a long time ago with long columns and large particle sizes in mind. Now, with all the advances in chromatography systems and columns– with smaller size columns and particles – much faster analysis is possible. It is thus logical to adapt USP parameters and modernize them.

Furthermore, current USP methods might enable a simple and robust chromatographic analysis, but they aren't optimized for efficiency and therefore have a higher environmental impact. That's also why today many users are looking for options to modernize their methods. But so far this has been very limited due to USP constraints, as only minor adaptations are allowed.

The USP and most recently the European and Japanese pharmacopeias have allowed changes to modernize HPLC methods – specifically adjustments in column dimensions and particle size for both isocratic and gradient methods. And now, this must now be realized in the laboratories.

What are the main features of KNAUER HPLC Method Converter?

When we designed our method converter, we were thinking carefully about the customer's key needs: optimizing the method to save time and resources. The KNAUER HPLC Method Converter is a very simple, effective, and intuitive tool, in a modern design.

"The USP describes the process and the calculations for method conversion in detail, but this can be complex – even for experts."

"The software is very easy to use. You just download the free converter and type in your existing method parameters and the new column dimensions you would like to use."

For USP 621 compliant methods, adjustments must be in the range of -25 percent up to +50 percent of the ratio for the particle size and the column length. For many users this ratio is not apparent at first glance and not intuitive. And that's why we decided to include this specific parameter in the KNAUER HPLC Method Converter – you just enter the HPLC method parameters of your original method, choose new column dimensions and particle sizes and you can see immediately whether the change in column dimension is accepted.

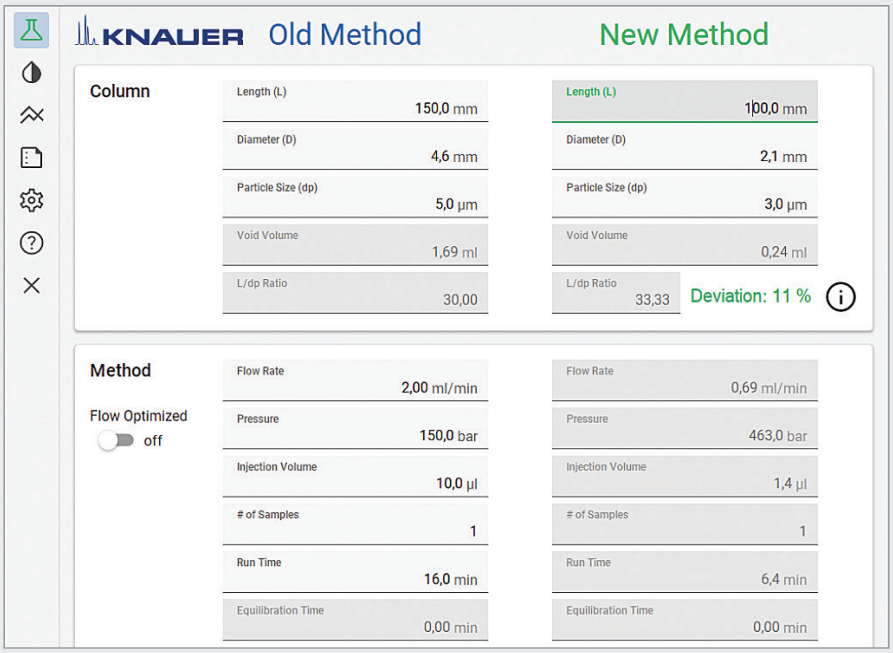
Based on the column parameters, such as particle size, column ID, and column length, this tool adjusts all other method parameters, accordingly, to increase the separation speed. The USP describes the process and the calculations for method conversion in detail, but this can be complex – even for experts. With our software, you can easily calculate method adjustments and improve your methods for higher productivity and a smaller environmental footprint.

Is sustainability an increasingly important driver for conversion to modern methods?
Absolutely. More and more customers are taking this parameter into account when designing and optimizing their methods. The KNAUER HPLC Method Converter supports HPLC users to easily downscale their method. Downscaling means reducing the size of the column, thereby reducing the flow rate and the run time of the HPLC method – with a major effect on solvent consumption and the environmental impact of your analysis.

In one of our recent case studies, we changed the column dimensions from 150 x 4.6 mm ID to 100 x 2.1 mm ID. The flow rate was reduced from 2 ml/min to 0.7 ml/min and the gradient time from 16 minutes to 6.4 minutes. The result? Eluent consumption per run (including equilibration time) was reduced from 48.9 ml to 6.8 ml, and the total run time (including equilibration) was reduced from 24.5 min to 9.9 min. That's an 86 percent reduction in eluent consumption and a 60 percent reduction in time per analysis. And I think that perfectly highlights the environmental and economic benefits of modernizing your methods.

How easy is it to use the software? Do you offer support for customers?
The software is very easy to use. You just download the free converter and type in your existing method parameters and the new column dimensions you would like to use. The new method parameters are automatically calculated and you can even export your data and the graphs.

We don't think customers will need support for the converter, but KNAUER does offer a wide range of support and training for our customers. Depending on your needs, you can choose from our standard HPLC basics and troubleshooting training, software training, or customized training. This can be done online, here at KNAUER in Berlin, or at the customer's site. If you need further support with method development, we are here to help!



In My View

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

Forget Me Not

Poorly understood and rarely emphasized by instrument manufacturers, is a lack of respect for microscopy holding back the microspectroscopy field?

By Brooke Kammrath, Professor of Forensic Science at the University of New Haven and Co-Executive Director of the Henry C. Lee Institute of Forensic Science, Connecticut, USA; and Dale Purcell, Founder and CEO of Chemical Microscopy LLC, Indiana, USA

Headshot of Brooke – Credit: Lindsey Wainger (Platinum CEM). Headshot of Dale – Credit: Brent Russell

Microscopy is the science – and art – of creating, recording and interpreting magnified images; spectroscopy is the science of qualitatively analyzing the chemical composition of physical and biological matter based on light emission, scattering, and absorption (1). Microspectroscopy (MSP) combines the fundamentals of both – enabling the study of microscopic materials through light–matter interactions (2).

Commercially available microspectroscopy instruments have been sold since the mid-1900s – IR microscopes have been staples in pharmaceutical, forensic, industrial and other scientific laboratories for decades.

The ability to correlate chemical and morphological features of samples is key for many MSP applications; for example, UV-Vis MSP has solved numerous problems in a variety of industries – most notably in investigations involving the dyes and pigments commonly researched in industrial chemistry and forensic science.

The ability to see the sample before spectroscopic analysis is another clear advantage of MSP; for example, analyzing microscopically-sized samples ensures that the target is effectively analyzed. In addition, different microscope contrast techniques (for example, PLM, DIC, Phase Contrast) make different characteristics visible in a sample, which can be used to correlate changes in spectral data with sample microstructure. And when using a microspectrometer, smaller areas of analysis – or spot size – are achievable.

Manufacturers are continually making advances in microspectroscopy, enabling novel research. Some of these advances are small incremental improvements (better optics or lasers,

"Manufacturers are continually making advances in microspectroscopy, enabling novel research."

for instance), but there have been other more revolutionary developments in the pairing of microscopy with spectroscopy, such as the recent invention of optical photothermal infrared microspectroscopy + simultaneous Raman (O-PTIR+R) by Photothermal Spectroscopy Corp.

Recent advancements in dichroic mirrors have enabled high throughput spectral analysis and confocality when using different modalities to analyze the same sample. Such advances add new depth to the chemical interrogation of microscopic samples – particularly when using the likes of hyperspectral imaging, particle correlated Raman spectroscopy (PCRS), and morphologically directed Raman spectroscopy (MDRS).

Another trend is the pairing of different techniques with Raman microspectroscopy into instruments capable of simultaneous or tandem analysis on the same sample. Some examples include the combination of FT-IR and Raman microspectroscopy, TERS, AFM-IR, Raman+UV, and Raman+Fluorescence microspectroscopy.

Unfortunately, microscopy, which enables many of the aforementioned benefits and advances in microspectroscopy, is often undervalued. And we'd argue that this lack of respect for the "micro" side of the duo is the biggest challenge facing the field.

One fundamental principle of microscopy that is particularly undervalued in microspectroscopy is the critical importance of sample preparation. There is no post-analysis correction or processing that can overcome poor sample preparation. To achieve optimal MSP analysis, the best microscopic image must be produced. Scientists must put the time and effort into quality sample preparation because the quality of the spectral data is directly correlated with the quality of the image.

Educating individuals about the role, function and importance of good microscopical analysis cannot be underestimated either. It's also important to know that microscopes are not plug-and-play devices. With a benchtop instrument, optics may be set and not controlled by the analyst – but with MSP, the analyst is responsible for aligning the optics through proper set-up of the microscope. Further, there are a variety of microscopic illumination (transmitted and reflected light) and contrast methods, which could greatly improve the information provided by MSP – if the analyst knew how to use them to produce an image.

All of these aspects appear to be poorly understood in the scientific community – and perhaps worse, they are not highly emphasized by instrument manufacturers.

There are several fields that can benefit tremendously from MSP – from additional applications in forensic science, where it is already established, to new areas, such as pharmaceuticals, cultural studies, and nanomaterials. In pharma, MSP could be used to optimize the identification of small domains in complex drug mixtures and determine the conversion of polymorphic forms to study degradation products and aid the development of novel vaccines and other drugs.

But it is crucial to keep in mind current trends, like artificial intelligence. Such technology will undoubtedly make meaningful advancements in MSP – specifically in areas of hyperspectral imaging, mixture analysis, and spectral interpretation.

As research is continuously expanding, and new questions arise, researchers and manufacturers must work together to ensure these MSP instruments are reaching their potential with regard to both quality images and spectroscopic analysis.

"As research is continuously expanding, and new questions arise, researchers and manufacturers must work together to ensure these MSP instruments are reaching their potential with regard to both quality images and spectroscopic analysis."

MSP is more than just a concept. It is already established in forensic science and it is ready to expand to other fields – once we put emphasis on the microscopy aspect and understand its role.

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Blue Is the New Green

Important though it is, greenness can't be the only parameter an analytical scientist must evaluate when deciding whether or not to adopt a proposed method or protocol – and that's why we created the Blue Applicability Grade Index

Credit: Yannis Tsoflidis

By Victoria F. Samanidou, Laboratory of Analytical Chemistry, Department of Chemistry, Aristotle University of Thessaloniki, Greece

Nobody can question the importance of green chemistry – or the fact that an analytical method must comply with a set of criteria so that it can be characterized as "green." Indeed, several tools have been developed to evaluate and prove the greenness of a given method (1–7). But is greenness the only criteria we ought to be taking into consideration before selecting a method?

Of course, protecting the environment and ensuring the operator's safety are top priorities, but there are several questions an analyst must also consider, for example:

- Is a method truly effective if the operator must synthesize the materials on their own?
- How practical is the use of a highly sophisticated instrumentation rarely found in most laboratories?
- How easy is it to construct the devices or equipment that must be incorporated in the method?
- How easily can the analytical scientist deviate from the protocol (especially important for accredited laboratories)?

These questions – and probably many others – demonstrate that greenness is not the only parameter an analytical scientist must evaluate when deciding whether or not to adopt a proposed method or protocol.

On the contrary, I strongly believe that the applicability and practicality of the method are of equal importance. Therefore, it is time to reassess and rebalance method selection so that all relevant factors are taken into consideration.

With this in mind, we – as part of a collaboration between two laboratories: the Laboratory of Analytical Chemistry, School of Chemistry in Aristotle University of Thessaloniki, Greece, and the Department of Analytical Chemistry, Faculty of Chemistry, in Gdańsk University of Technology, Poland – propose a new evaluation tool: the Blue Applicability Grade Index (BAGI). This software, designed by Natalia Manousi, Wojciech Wojnowski, Justyna Płotka-Wasylka and myself, aims to evaluate the "blue" character of a method, which refers to its practicality (8).

"Greenness is not the only parameter an analytical scientist must evaluate when deciding whether or not to adopt a proposed method or protocol."

The color "blue" in our model is inspired by the red-green-blue (RGB) model – which combines a method's cological, analytical, and practical aspects, encompassing the "White Analytical Chemistry" concept (9,10).

Our new index is aimed to complement the available green metrics-based tools, such as complexGAPI and AGREEprep. We have also developed open-source desktop and web applications so that they can be easily used (these are available at: *bagi-index.anvil.app*).

The application generates an asteroid pictogram that describes the applicability and functionality of the analytical method, based on the following 10 criteria:

- the type of analysis
- the number of analytes that can be simultaneously determined
- the analytical technique and the required analytical instrumentation
- the number of samples that can be simultaneously treated

- the sample preparation
- the number of samples that can be analyzed per hour
- the type of reagents and materials used
- the requirement for preconcentration
- the degree of automation
- the amount of sample required.

We think it is especially useful for comparing the performance of different analytical methods, where the aim is to show that one method is more practical and applicable than another by identifying its weak and strong points.

We hope that BAGI will gain the attention necessary to be widely applied in the chemical community – and that blue will be the new green!

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How to Foster an Organizational "Growth Mindset"

Start during the hiring process, make work challenging, engage the "rider" and (especially) the "elephant," and encourage strong empathetic leadership

By Kavitha Parvataneni, Senior Director, Research & Development, Waters Corporation

Without satisfied and engaged employees, entire industries can become inefficient and critical talent can be lost to competitor fields. Strong managers are essential to the functioning of an organization by driving improved employee experiences, maintaining retention, and creating stronger outputs – as many leaders are realizing.

The best managers know that adopting a "growth mindset" is crucial. By enabling and encouraging employees to not only grow, but to stretch their experiences, leadership promotes a culture for exploration, innovation, and curiosity – all vital for fulfillment and retention. All these aspects are especially important in the competitive and ever-changing analytical science industry.

But how can leaders in our field make this a reality? Here, I offer four pieces of advice.

First, consider the growth mindset during the hiring process. From forensics to pharma, analytical science is both broad and highly technical. Managers may be looking for backgrounds in mechanical engineering, physics, and materials science – but these same skill sets are also crucial for people in those management positions. The full team needs to be on the same page – especially when it comes to understanding how to use data science to best support customers.

It can be easy for management to pivot to a new candidate if they feel that an applicant does not fit seamlessly into a specific job description, but the best leaders look holistically at candidates to find the right role for today while also thinking about how the candidate might be able to build a career within the

company. Recognizing the bigger picture (for example, a candidate's aspirations and cumulative skills rather than simply prior experience) leads to smarter and more sustainable hiring processes – and more fulfilled employees.

Second, challenge your employees to keep them motivated. For example, R&D and engineering teams need to really understand the customers' needs and goals – often a big challenge! Empathy and perspective from the customer are crucial here. Being able to connect to the tasks that bring the most value and meaning to the customer is something that, from my experience, really keeps employees energized to do challenging work.

We all have seen how employees can be assigned a set of core tasks based on their past performance and current job responsibilities – often not being considered for more challenging assignments. This isn't good for anyone. Leadership is responsible for helping employees feel supported as they grow and take on new challenges during their development. As yearly goals and objectives are established, quarterly monitoring can support employees in reaching their targets, while also continuing to expand with new stretch goals.

When an employee is promoted, their past work might not be all they need to help them assimilate into their new role, but a culture of open communication and being a champion of an employee through their learning process makes a meaningful impact. Hosting problem-solving workshops, regular training, one-to-one manager check-ins, and team-building activities are tactics to keep employees engaged, focused, and excited in their career development.

Third, "engage the elephant and the rider!" Psychologist Jonathan Haidt's analogy can support leadership with understanding and interacting with employees. According to Haidt, each person has two sides: an elephant (emotional, sympathetic, loyal) and a rider (rational, conscious, data-driven). Leaders must strive to satisfy both aspects of the human psyche; when balanced effectively, employees are then aligned with expectations, engagement, and execution.

"We all have seen how employees can be assigned a set of core tasks based on their past performance and current job responsibilities – often not being considered for more challenging assignments. This isn't good for anyone."

Of course, given that the analytical science industry is filled with data-driven problems that must be logically thought through, the field undoubtedly attracts more "rider-inclined" individuals. Data and project milestones can help motivate teams of such people and deliver results, as well as instilling a leadership style that makes decisions based on facts and collaboration. This concept resonates especially within the R&D space – it is not just a top-down leadership style, but rather a team collaboration to discuss problems at hand and leverage data and analytics to solve them. But everyone has an emotional side – an "elephant" as Haidt puts it – which is sometimes more difficult for leaders and employees in our field to connect with. But we need to because it can help bring purpose to our work – providing the "why." And it doesn't always need to be big picture stuff.

Fourth, encourage strong, empathetic management. Managers are the heartbeat of an organization – a liaison connecting executives and their teams. Strong, empathetic leadership can create the best teams with active listening and a commitment to adjusting for best outcomes. The most effective managers are skilled in their ability to manage (and even exceed) leadership's expectations, while generating excitement for their teams to drive the best outcomes.

Overall, fostering a growth mindset across an organization – or even within a department – is a long-term, ongoing commitment, but one that is important for any successful leader. Many employees might not know how to grow their careers – especially in an industry as complex as analytical science, so mentoring from managers helps provide the tools and opportunities for sequential growth. To see talent flourish under a manager's guidance can be one of the most rewarding experiences personally and helps drive success for the business in growing a company's most important asset: its employees. A commitment to a growth mindset in the workplace is a win-win for all involved.

The Trajan Story: Extraordinary Inspiration from an Ordinary Life

How Trajan's Stephen and Angela Tomisich took inspiration from everyday life back in 2011 to build a global enterprise. Thirteen years later, the company is entering an exciting new chapter with its acquisition of Axel Semrau and the launch of its CHRONOS software.

With Stephen Tomisich, CEO and Managing Director, Trajan Scientific and Medical

Could you tell us about the origins of Trajan?

Trajan Scientific and Medical was founded by my wife, Angela, and I in 2011. With backgrounds in analytical chemistry and biomedical science, and combined experience of over 50 years in the global analytical science industry, we were determined to build a company that could deliver positive impact through science.

The company name was chosen around the family kitchen table – it stems from our daughter's interest in history. Trajan was the thirteenth – and arguably most successful – Roman emperor; building infrastructure and doing social good. The name complimented our focus on enriching personal health through the development and manufacture of scientific tools and solutions enabling extraction of quantitative information from biological and environmental samples. Trajan's purpose is to support science that benefits people; we have a portfolio and pipeline of new technologies that support the move towards decentralized and personalized data-based healthcare.

Trajan has grown rapidly since 2011… Can you share the major milestones and challenges – and your secrets to success?

Our milestones are linked to our acquisition and collaboration strategy as we've built a global enterprise. That's not to say that the signing of an agreement or partnership was the milestone; rather, it is the opportunities gained as we grow and add new capacity, technologies, and reach to our business. Indeed, we're now a global organization of more than 600 people, with manufacturing and operations sites across the US, Australia, Europe and Asia,

With that growth, you have to balance investment. We have consistently reinvested profits back into the business to build infrastructure and the right team to support future growth. Getting that balance right without putting the business under financial stress and dealing with growth pains can be a challenge!

But we've tried to focus on purpose – living by our values. It might sound esoteric, but it isn't, building a team with an aligned sense of purpose and an adherence to values, provides direction and builds momentum.

What does the acquisition of Axel Semrau mean for the future of Trajan?

The acquisition of Axel Semrau gives Trajan full access to the CHRONOS Software, which is the heart of automated workflows developed by Trajan. Offering complete workflow solutions, including automation hardware, special consumables, application specific data analysis software, and a complete range of services, such as training, factory acceptance testing (FAT), site acceptance testing (SAT), and maintenance, allows Trajan to have a greater impact in the areas where we are active. The Axel Semrau portfolio was a direct complement to some of the adjacent Trajan acquisitions, most notably the US-based LEAP and Leap Pal Parts acquisitions. Axel Semrau brings a more in-depth customer

interaction in Europe, while extending our capabilities in key application areas. Having a positive impact on human wellbeing is the fundamental purpose of Trajan business activities and the acquisition of Axel Semrau helps make this vision a reality.

Tell me about CHRONECT; what makes this especially exciting?

The trademark CHRONECT was developed while waiting at a train station after an exciting meeting with a customer in Hamburg. Energized by the enthusiastic customer feedback, the idea of CHRONECT was born. It describes in one word the concept of Trajan workflow solutions. Using the CHRONOS software Trajan CONNECTS different hardware modules, application specific consumables, special data analysis tools, and all the services needed to deliver a complete workflow. This enables our customers to solve analytical problems and generate data more effectively than before. Our slogan "We CHRONECT your lab" means close cooperation with customers, innovative solutions, and brings Trajan's vision "science that benefits people" to the automation business.

Overall, what are your main ambitions for Trajan in the coming years?

We want to continue to build our global team. Angela and I are humbled by the incredibly talented group of people who have chosen to build their careers with us and align to the vision. In short, we want to deliver a positive impact to human health on an ever-increasing scale.

Images supplied by The Scripps Research Institute

SCRIPPS: *a* CENTURY *of* INNOVATION

This year, The Scripps Research Institute is celebrating its 100-year anniversary! Their motto? Turning scientific inquiry into innovative treatments that benefit the world. Here, we shine a spotlight on several leading analytical scientists and omics pioneers at Scripps – and the crucial role their work plays in delivering on Scripps' raison d'etre.

By Frank Van Geel, Markella Loi, and James Strachan

Introduction by John Yates III

The year 1921 proved to be pivotal for medicine. Banting, Best, and McCloud discovered insulin and showed that its absence in the body was the cause of diabetes mellitus. This discovery not only provided the cure for a deadly disease, it also established a new standard for evidence-based medicine and gave the world hope that cures for other deadly diseases could be found. In 1924, the prolific philanthropist Ellen Browning Scripps founded the Scripps Metabolic Clinic to treat diabetes with this new miracle drug. If you have ever been to San Diego, you have certainly noticed the impact of Ellen Browning Scripps' philanthropy – the Scripps name graces institutes, hospitals, roads, and neighborhoods. Two of these San Diego institutions, the Scripps healthcare system and The Scripps Research Institute (TSRI), emerged from the Scripps Metabolic Clinic. In the early days of TSRI, research was focused on immunology under the leadership of renowned immunologist Frank Dixon. The department of molecular biology was later formed by Richard Lerner, who greatly expanded the scientific focus of TSRI after he took over leadership in 1987. Lerner built a chemistry department by recruiting the top chemists in the world; notably, two Nobel prizes have been awarded to K. Barry Sharpless – a founding member of the chemistry department. The creation of the chemistry department at Scripps was a testament to Lerner's belief in chemistry as a central science. Lerner also created world class graduate programs in chemistry and biology; and in 1996 he founded the Skaggs Institute for Chemical Biology, which remains at the forefront of chemical biology research.

During the ten years that followed the completion of the human genome in 2001, there were significant efforts to translate the newly acquired knowledge into cures for diseases and a greater understanding of human biology. When the 10th anniversary of the completion of human genome sequence arrived, the press assessed the impact of the sequence on human health and concluded that it was minor. Making drugs for gene products required knowing something about the protein produced, and many of the genes discovered in the human genome sequence were being observed for the first time. One assessment of currently approved drugs in the early 2000s noted that each FDA approved drug had at least 15 years of research literature behind it. Conclusions by the press were perhaps overly harsh; they failed to appreciate that it took time to assess the sequence information and to discern the best way to parlay this information into the development of therapeutics. There was also a need to identify the disease genes, which meant population studies and then more sequencing. Scripps, with its heavy emphasis on chemistry, biology, and structural biology, is ideally suited to meet the challenge of developing new approaches to drug development to take advantage of genomic information in the coming decades.

In this tribute of 100 years of research at the Scripps Research Institute, four prominent scientists discuss aspects of their research and the Scripps Research ethos. Each of these research areas is steeped in analytical chemistry. Benjamin Cravatt and Christopher Parker describe efforts to develop new approaches to drug development using chemical proteomics, which relies heavily on mass spectrometry (MS). Gary Suizdak has developed MS-based methods to measure and identify metabolites, and his laboratory has built widely used software tools, including the METLIN database. Finally, Mia Huang and her team have been using MS methods to lead the way in glycobiology – a field that has seen an explosion of interest over the last 10 years.

The Scripps Research Institute occupies a small stretch of land overlooking the famous Torrey Pines golf course and the Pacific Ocean – and I'm proud to say that its scientific impact has been as great over the last 100 years as the view from the campus.

John Yates III is Ernest W. Hahn Professor, Departments of Molecular Medicine and Neurobiology, The Scripps Research Institute, USA

A PASSION *for* CHEMICAL BIOLOGY

With Ben Cravatt

What makes Scripps unique?

Scripps is one of the largest nonprofit biomedical research institutes in the world – but people are often confused about its culture and structure, which I think is what makes us unique.

Our main difference from universities is that everyone here is interested in biomedical research – there are no English, Philosophy or Arts departments. We also do not facilitate undergraduate programs like other universities. Instead, we have an independent accredited graduate program in the biological and chemical sciences with an emphasis on research. That definitely shifts our focus on a more science-centered and practical mission.

It is an incredible place to work on interdisciplinary scientific collaborations – the departmental boundaries are almost nonexistent. Take our lab, for example; we are interested in understanding the chemistry of life. Some of the lab members have a synthetic chemistry background, but we also have incredible cell and molecular biologists, meaning we can work at the interface of chemistry and biology through collaboration.

If you distill down the labs at Scripps, many are interested in understanding how proteins function and the biology of disease, using a chemistry-first approach. John Yates, myself, and others have been committed to that field for quite some time, but we are just a small part of this much larger biomedical Institute.

Scripps is certainly much larger and more diverse than just protein science. We have always had a strong footprint in technological advancements. I feel like Scripps has always had a firm commitment – whether it be in proteomics or in other fields like structural biology and synthetic chemistry – to push the boundaries of technologies and methodologies. And we value innovation tremendously here – we are "science changing life" after all!

Where does your Scripps story start?

While I was working as an undergraduate in a laboratory that was operating at the interface of chemistry and biology, I started becoming more interested in that type of multidisciplinary science. I eventually came to Scripps as a graduate student in the early 1990s – it was one of the only programs at that time (perhaps the only program) that had a dedicated commitment to training at the interface of chemistry and biology.

I stayed here as a faculty member, working on the characterization of an enzyme involved in endogenous cannabinoid signaling, which revealed this lipid signaling pathway in the brain – somewhat of a breakthrough in that field. That success helped me launch my own independent lab and, over the ensuing years, I have always tried to integrate synthetic and analytical chemistry approaches to solve problems in biology to benefit human health.

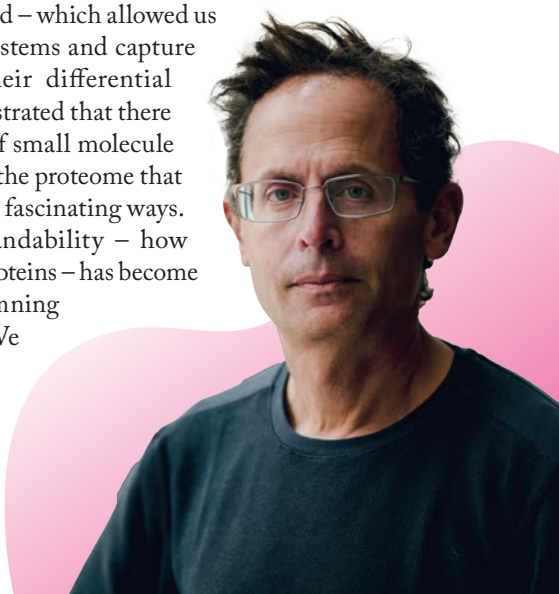
In my graduate career, I could already see the potential impact of mass spec in large scale protein science, and it was pretty clear genome sequences were going to be completed in the near term in the early 2000s. Today, with genome-wide DNA sequencing advances, we now basically know the genetic basis for an incredible number of diseases – but we do not really know the biochemical mechanisms, in many cases, that cause the diseases. Our goal is to fully understand what proteins do in disease and guide the development of chemical probes and, ultimately, drugs. Put another way, our primary goal is not to blindly develop drugs, we know that we need to understand the functions of the proteins in physiology and disease first.

What are some of the main focus areas for your lab?

As our lab started evolving, we began to think about ways to parse out the proteome, based on shared principles of small molecule reactivity and recognition. There was initially this misconception that there are limits to what small molecules could do in their interactions with proteins, but we felt this wasn't true; natural products and other small molecules that have been serendipitously discovered can have very atypical mechanisms; for example, allosteric regulation of proteins through cryptic sites. Our lab approached the problem of systematically identifying first-in-class chemical probes to study protein functions. Sometimes those probes reveal functions of biology that were missed by genetics…

We eventually designed the activity-based protein profiling method – which allowed us to go into biological systems and capture proteins based on their differential reactivities. We demonstrated that there is an incredible array of small molecule binding pockets across the proteome that can regulate proteins in fascinating ways.

The concept of ligandability – how small molecules bind proteins – has become a fundamental underpinning of chemical biology. We have become quite fascinated with the breadth of ligandable



sites throughout the proteome, and we are currently trying to understand how they affect protein function. That is quite a challenging objective when you have hundreds of ligandable sites across proteins that all have different types of functions. To tackle the challenge, we have been trying to come up with new approaches – using mass spectrometry to better understand how proteins participate in binding other biomolecules, such as other proteins, DNA, or RNA.

In the future, protein structure predictions and deep human genetic maps of phenotyptic mutations might allow us to predict how ligands will affect protein function – but we're pretty far away from that right now. The faster the mass spectrometry-based proteomics experiments can be performed, the more data can be acquired. Here, computational approaches could be integrated, so we know exactly what residue is reacting to a small molecule. Such approaches may be too sophisticated from a computational point of view for us, but that's why we advocate for collaborations – within and beyond Scripps.

Why is analytical chemistry crucial at Scripps?

If genome sequences and mass spectrometers existed 20–30 years ago at the level they exist today, someone would have developed activity-based protein profiling and designed chemical proteomic type methods. As is often the case, new technologies drive new biological discovery, and the confluence of those two advances made it a reality – protein science really exploded with mass spectrometry-based approaches and genome sequences provided a near-complete "parts list" of the proteins produced by biological systems. Those two analytical methods have enabled labs like ours to ask and answer questions that wouldn't have been possible decades prior.

Analytical chemistry has been key to our research – and to Scripps' stated aim of turning scientific inquiry into innovative treatments that benefit the world. It enables us to gain more in-depth access to shallow cryptic pockets in the proteome. It has been hard to systematically study those types of principles, but with some of the platforms we have developed, we can now look at thousands of sites in the proteome for interactions with small molecules.

As our platforms have matured, they have been adopted by the biotech and pharmaceutical industry and turned towards more translationally focused research. In fact, there are multiple drugs in clinical development now that have leveraged our lab's activity profiling and chemical proteomic platforms as a way to discover ligands, optimize them, and develop target engagement assays.

I'm excited to see what we can achieve in the coming years at Scripps – and what that might mean for human health.

Ben Cravatt is Professor and Norton B. Gilula Chair in Biology and Chemistry in the Department of Chemistry at Scripps, USA

Supporting *the* Next Generation – Wherever *they* Go

With Ben Cravatt

Each person in our lab learns both the chemistry and biology of what we are doing – including the analytical chemistry of understanding how to run mass spectrometry-based proteomics experiments – so that when they leave the lab, they feel comfortable operating at that interface.

Some of our scientists are more classically trained chemists and want to move into biology; they see the opportunity to join a lab like ours, where they can build on their chemical expertise to solve biological problems. There are also biologists who want to take a more chemistry or pharmacological approach to their science.

Some move on to academia and some go towards biotechnology. I am supportive, regardless of the direction they want to go. I am there to mentor them and help them realize what excites them. And that reflects my number one piece of advice for anyone: follow your true passion.

Chemical Proteomics: REALIZING THERAPEUTIC POTENTIAL

By Chris Parker

Proteomics has been around for a while, but I think it is experiencing a renaissance right now. For a long time, it more closely resembled the Wild West, with each lab having their own unique methods, reagents, software, etc. Now the field has matured and has become really user friendly and easy to practice – to the point where there are now commercial vendors offering standardized software, methods for quantitation, and numerous other tools and reagents for various applications.

The field of proteomics has a strong history and presence here at Scripps – thanks to pioneers like John Yates and Ben Cravatt. Scripps has always appreciated the role of powerful technologies, such as MS-based proteomics, in driving scientific innovation and discovery. Investment in them have greatly benefited folks like me, who are not necessarily technologists themselves, but major users.

My field, chemical proteomics, was really born out of activity-based protein profiling (ABPP) – a powerful strategy for global ligand and protein discovery utilizing proteomic technologies, innovated by Ben Cravatt and Matt Bogyo (Stanford) in the early 2000s. Since then, Ben has trained many academics that now have their own labs and are expanding the web of chemical proteomics in multiple different directions. ABPP has also led to several clinical candidates and is becoming an ever-increasing used discovery pipeline in biotech and pharma.

Most of ABPP strategies have focused on the use of covalent probes, which require a reactive group on the protein to aid in their detection by MS and is often performed in lysates. Our strategy does not require such reactive groups and instead employs photoaffinity probes – probes that can capture transient protein–small molecule interactions upon exposure to UV light. Photoaffinity approaches have long been used to identify the targets of bioactive compounds and to monitor

various other interactions. However, we were the first to realize the potential of integrating photoaffinity probes with the broad discovery concepts of ABPP. Specifically, we've generated specialized libraries of photoaffinity probes that allow us to globally profile the ability of proteins to non-covalently bind to drug-like small molecules, directly in living cells. Upon binding to proteins, we photoactivate the probes to capture these interactions, and then enrich them from the rest of the proteome and then identify and quantify via MS. From this information, we can gather information about the binding sites, binding pocket occupancy and relative affinities, in theory, on any protein and pocket, directly in live cells. This information can be used to understand the activity of compounds or to develop new compounds with novel activity to help elucidate biological functions and explore therapeutic opportunities.

Technology in action

We are now confident in our methods, so are focused on applying them to solve problems of human health. We recently published a study where we use our technology to develop a first-in-class inhibitor for a protein that plays a key role in autoimmune and autoinflammatory conditions – and I think it offers a great example of why our work is so important.

The starting point for this work was the discovery of correlations between people that have autoimmune disease and mutations in this gene, which makes it a great drug target. But the problem was, nobody knew what it did because it is such a complex protein and there is no direct functional readout. With our technology, we successfully developed inhibitors and other chemical tools and used them to dissect the protein's functions and disease roles. I think this is amazing, because we went from not knowing the function to realizing its therapeutic potential.

We are now replicating what we were able to do with this platform to find unique druggable targets in other disease states, including cancer. And it's an understatement to say we are excited about the potential of our technology in these applications.

Chris Parker is Associate Professor in the Department of Chemistry at Scripps, USA

My Path *to* Scripps

Academic research wasn't something I instinctively knew I wanted to do. Scripps is a special place to me for that exact reason; it was here where I realized that I wanted to follow that career path.

I was hesitant to even apply for graduate school – studying for another five years and writing a thesis was very intimidating as a college student. But I was very fortunate to have such a supportive undergraduate supervisor at Case Western, Phil Graner, who gave me the confidence to apply. It was my graduate advisor, David Spiegel, who then introduced me to this modern (at the time) science twist known as chemical biology, where I focused my PhD. David always had a unique perspective as a PhD/MD with a background in synthetic chemistry. He is the one that got me very excited about our ability to design molecules to have specific biological functions.

In graduate school, I was always enamored by Ben Cravatt's work on proteomics and mass spectrometry; I remember emailing him after one of his talks to let him know: "I really want to do a postdoc in your lab, and I have some ideas." So, I proposed the general project area to him – which my own lab is still working on to this day. It was such a privilege working with, and learning from Ben while in his lab. It quickly became evident that this technology has the potential to expand the boundaries of chemical biology and drug discovery but still required a lot of work. I felt we were just scratching the surface, and so I really wanted to dive deep during the next step in my research and career.

Scripps was always the place I wanted to start my own lab – as its culture focuses on research outside of the traditional walls of an academic institute. It is also an amazingly collaborative environment and I get to be surrounded by some of the greatest scientists around, which is a great source of inspiration. My lab continues to expand upon this area as well as develop new chemical proteomic methods, and apply them to develop useful tools to investigate human biology and explore paths for therapeutic intervention.

Postdoctoral fellow Evert Njomen, PhD, at the laboratory bench in the Cravatt Lab.

Nobel laureate and professor of neuroscience Ardem Patapoutian, in the laboratory.

Scripps Metabolic Clinic, circa 1924. *Credit: La Jolla Historical Society.*

METABOLOMICS ORIGINALS

By Gary Siuzdak

Over the years, my team and I have developed novel analytical tools and computational strategies that have been instrumental in deciphering complex metabolic processes. Our primary focus in this area has been on mass spectrometry-based technologies, beginning in the 1990s when we performed what were then the first LC-MS-based metabolomics experiments in a sleep study. These experiments were in collaboration with Richard Lerner (then Scripps president) and Ben Cravatt (now Scripps professor).

Mass spectrometry is indispensable for the high-throughput and high-resolution analysis of metabolites. This technique allows us to quantitatively analyze the chemical composition of biological samples with an extraordinary level of detail. The data we gather are complex and rich, providing us with snapshots of metabolic dynamics that are integral to understanding disease and health. We use both targeted and untargeted metabolomic approaches to analyze biological samples – the latter allows us to discover novel metabolites and unexpected pathways, while targeted approaches let us quantify known metabolites with precision.

Perhaps our most groundbreaking analytical effort in our laboratory (originating with the Lerner sleep study) is the creation of our XCMS-METLIN platform, a data processing approach combined with a comprehensive database to facilitate metabolomic data analysis. In the sleep study, all data analyses and identifications were originally performed manually, a time consuming process, now XCMS-METLIN allows us to deconvolve these studies more rapidly and ultimately in a simpler and more straightforward format, greatly reducing its complexity. In addition, XCMS-METLIN is being designed to further integrate with other omics data, enabling a more holistic view of biological systems. The completion of this tool represents a significant leap forward in systems biology – establishing a comprehensive database of human metabolites, as well as exogenous molecules with a goal of identifying their ability to modulate disease.

Ongoing metabolomic experiments are all performed, like the original sleep study, with high-resolution mass spectrometry coupled with liquid chromatography (LC-HRMS) – to separate and identify thousands of molecules in a single run with high sensitivity and specificity – as well as advanced tandem mass spectrometry techniques (MS/MS via METLIN) to improve our ability to elucidate the structures of new metabolites.

HOW *it* ALL STARTED

I decided to combine my background in chemistry and mathematics – culminating in a PhD to focus on mass spectrometry technologies and pioneering work in the then nascent field of metabolomics.

Today, my scientific career is still dedicated to advancing the field of metabolomics through the development of mass spectrometry techniques and tools.

Our research has provided insights into various diseases, including cancer, neurodegeneration, inflammation, among many others, and contributed to the discovery of the role that endogenous metabolites play in modulating phenotype and treating disease (1). As we celebrate the centennial of Scripps Research, I am honored to have played a part in its history of scientific excellence.

POWER LISTER *Profile:* KIM PRATHER

Kim Prather, Distinguished Professor & Distinguished Chair in Atmospheric Chemistry, Scripps Institution of Oceanography, has been featured on The Power List on four occasions. She focuses on developing and conducting measurements for aerosol chemistry. Asked about her motivation in 2017, she said: "Making a difference for our planet. Our research on aerosol impacts on clouds can help explain why we are seeing a sudden increase in weather-related disasters." She once discovered that dust from 12,000 miles away in Africa (and ocean microbes) affects snowfall over California – her most rewarding moment.

POWER LISTER *Profile:* KURT WUTHRICH

Credit: Kurt Wuthrich in 2022 at Scripps 02 by Cmichel67/CC BY

Kurt Wuthrich, Cecil H. and Ida M. Green Professor of Structural Biology, Department of Integrative Structural and Computational Biology at Scripps, has featured on The Power List on two occasions. Kurt was awarded the 2002 Nobel Prize in Chemistry: "for his development of nuclear magnetic resonance spectroscopy for determining the three-dimensional structure of biological macromolecules in solution."

Looking forward from the original LC-MS-based metabolomics that we performed 30 years ago, our plans in the Scripps Center for Metabolomics have an overarching goal: to significantly advance our understanding of the metabolome and its role in health and disease. We aim to push the boundaries of metabolomics to not only understand disease pathology but also to provide solutions that can be translated into clinical practice.

The driving force behind the research

None of our developments or innovative ideas would have been possible without the present and former scientists in my group – they are the driving force behind these discoveries. Their expertise range from biochemistry to analytics to bioinformatics, creating a fertile ground for innovation. They are not only adept at operating sophisticated instrumentation, but also at developing new analytical methodologies and computational tools to better capture and interpret the wealth of data we generate.

In our projects at Scripps, we work closely with biologists to design experiments that answer fundamental questions about metabolism. Our analytical expertise is what really enables us to move from observing correlations to understanding causations in metabolic pathways. And that's crucial for our translational goals, as it provides a direct link between metabolic changes and physiological outcomes.

One of my favorite stories, beyond the original sleep study, was work performed by Oscar Yanes fifteen years ago. In short Oscar discovered the plasticity of stem cell lipids were a key attribute of stem cells that enable their differentiation into other cells (2), and he even discovered one endogenous metabolite that drives differentiation, neuroprotectin D1. Along the way, Oscar also created a new way of performing LC-MS thus doubling of sensitivity (3). Pretty cool stuff.

Analytical scientists – not only in our group, but in general – are innovators and thought leaders who push the boundaries of what's possible in metabolomics research and beyond.

Gary Siuzdak is Senior Scientific Director and Professor of Chemistry, Molecular, and Computational Biology at Scripps, USA

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AWARDS

6
Nobel prizes

6
Wolf Prizes

2
MacArthur Fellows

4
Power Listers

Source: Scripps Research Institute; Nature index

Pioneering CHEMICAL GLYCOBIOLOGY

By Mia Huang

Scripps enables me and my lab team to immerse in a culture of providing practical answers to real life problems – biomedical in my case. We are focused on developing a molecular understanding of important biological events so that we can open up new therapeutic avenues to treat disease. I feel quite fortunate to be in this position; to exercise creative ideas, train the next generation of scientists, all while being at a place where you can watch talented colleagues (like John Yates, Ben Cravatt, and Chris Parker) excel at their individual jobs and have fun at their work too.

My research focuses on chemical glycobiology. I am interested in developing chemistry-based solutions to reveal how a class of post-translational modifications – called glycans – regulate important biological events.

We are particularly focused on studying the functional roles of glycans that are present on individual proteins; I personally think the interplay of how proteins provide the structural context to present glycans – and how glycans in turn can modify protein structural conformation is quite marvelous.

By gaining more in depth molecular understanding, I hope to open up new therapeutic solutions to treat diseases that are controlled by these glycans. To accomplish our mission, my group is composed of individuals with backgrounds in synthetic organic chemistry, cell biology, and biochemistry.

One current project seeks to discover new cancer biomarkers in the form of differentially glycosylated proteins – these protein glycoforms that we are trying to uncover are proteins that look identical between healthy and diseased cancer cells, but the glycan post-translational modifications on them are sufficiently different. I'm excited about this project – partially because of the magnitude of the problem; finding such "needles in a haystack" is no easy feat. I also like how this problem necessitates the development of new techniques.

I am looking forward to rigorously proving that such unique protein glycoforms exist, and eventually that we can develop modalities to target them selectively.

From measurement to new biology

I think the ability to both detect events and also to assign numbers to our observations – or "measurement science" –

My PATH *to* SCRIPPS

How did I end up at Scripps? Well, as a child, I was very curious about human health and disease; what happens in the body and how I could help alleviate such conditions in patients. So, I wanted to become a physician.

Back then, research-based careers in the Philippines weren't as viable, and I personally had never heard of anyone being a scientist. My idea of a scientist was similar to the cartoon character from Dexter's Laboratory.

Halfway through college as a pre-med student, I received an opportunity to study at the City University of New York, Queens College, USA. There, for the first time, I was engaged in a research project in a laboratory setting – developing materials to combat pathogenic microbes and the growing antimicrobial resistance, and I had the chance to interact with graduate students and scientists. I think it was this experience that forced me to reflect or pause on my intended plans to become a physician – I had realized that I enjoyed being a "lab rat."

I quite enjoyed understanding how microbes survive and what their vulnerabilities might be at the molecular level. Selfishly, I really liked the detective work of solving chemical or biological problems through experiments, and the fact that I could control variables within experiments and assign quantitative metrics to my observations really resonated with me. I thought it was such a privilege to have the time and space to be left alone to think in the lab and come up with solutions. It was an extra benefit that the thing I liked doing could potentially help solve biomedical problems and benefit patients suffering from diseases.

So, after completing my postdoctoral research at Yale and the University of California San Diego, I joined Scripps – where I've been for almost six years.

is an integral part of what we do as chemical glycobiologists. From an NMR spectrum telling us how many and what type of protons and carbons we see in a molecule, to absorbance-based plate reader assays that tell us how much drug dose is required to kill half the given population of cells, analytical science allows us to observe trends in a much more meaningful manner and offers the opportunity to predict upcoming events. Hence, I think much of what goes into being a scientist and having "good hands at the bench" really relates to one's ability to know what is supposed to be detected, if it can be measured experimentally, and if the experiment to detect that particular thing can be done so in a reproducible and quantifiable manner.

For a number of years now, we have been engaged in using mass spectrometry-based glycomics and proteomics to understand the structures of glycans on proteins from cells. We are developing strategies to enhance these analytical techniques to help our hunt for these unique cancer protein glycoforms from cells – these are the "what" we are trying to detect. We know that the ions resulting from these protein glycoforms can be reproducibly detected, which means we can enrich them from the rest of the glycans, proteins, and other biomolecules in cells.

Mia Huang is Associate Professor in the Department of Chemistry at Scripps, USA

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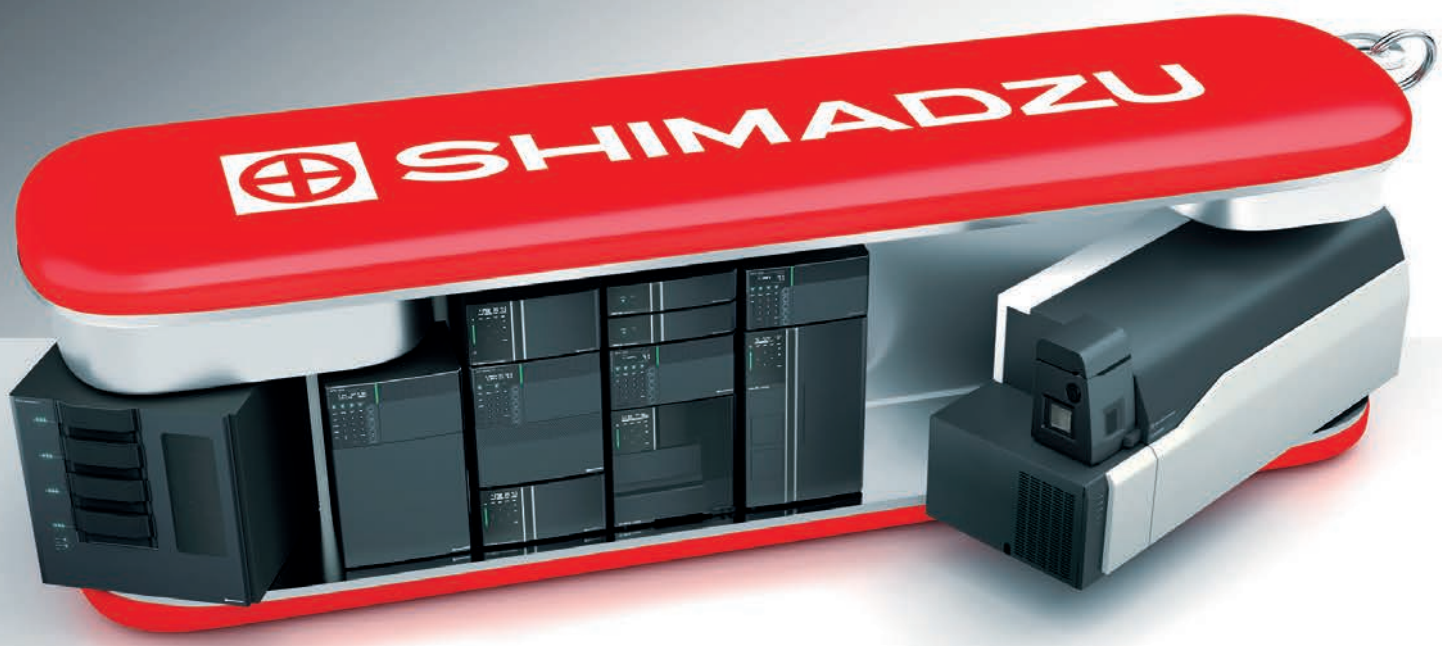

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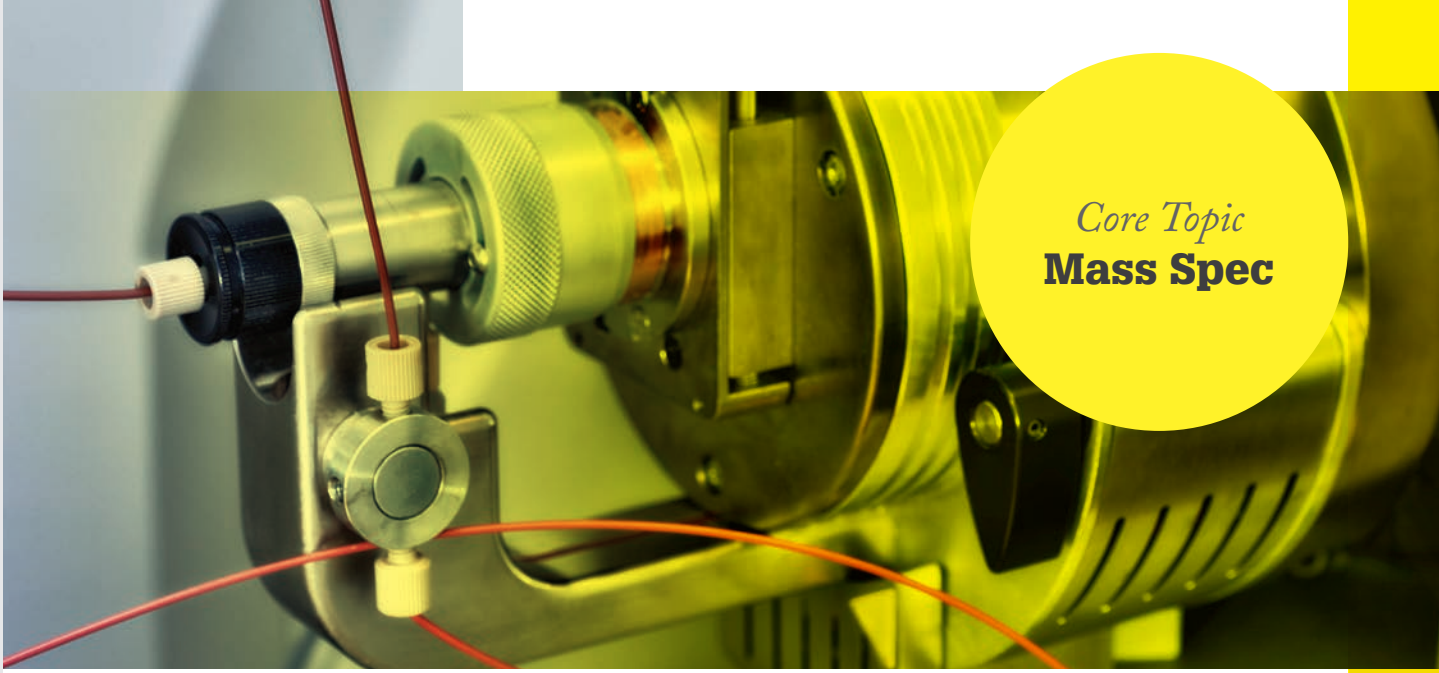

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Core Topic
Mass Spec

The stained Centaur. A stained Centaur marble head that was once decorating the metopes of the Parthenon has now become a puzzle not only for archaeologists, but also for a research team from the University of Southern Denmark. The origin of a thin brown film that covers the artifact has confused experts; was it formed by algae and bacteria or is it the remains of a protective paint the ancient Greeks used? To determine the chemical composition of the stain, the team threw everything at the mysterious film – including LA-ICP-MS, SEM-EDX, μXRD, GC-MS, LC-MS/MS, and optical microscopy – and discovered two distinct layers. The analysis also revealed that the brown stain is composed of proteins from plants, humans, other mammals, including an egg yolk – believed to be a paint binding agent – and animal collagens.

Find the kinase. Kinases are promising diagnostic and therapeutic targets for cancer, but quantifying them in human biopsies can be challenging with current methods, such as immunohistochemistry. So, researchers from the Baylor College of Medicine set out to find an alternative – combining mass spectrometry-based proteomics with their newly developed kinase inhibitor pulldown assay (KiP). The optimized methodology enabled accurate and simultaneous measurement of a 100-strong panel of target kinases.

Bone of contention. In early 2023, skeletal remains were found in a ditch by a country road – leading researchers down a tangled path in an attempt to discover the identity of the unfortunate soul and what befell them. The "who" part of this skeleton mystery was recently unraveled by a team of researchers from across France; anthropological examination determined the victim was female over the age of 60. But how did she die? Hypothesizing a drug-related death, researchers conducted analysis of hair samples using targeted and untargeted liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS). Unfortunately, concrete answers were not forthcoming.

Polluting pollination. Pollination is largely affected – and possibly disrupted – by nighttime pollution, as researchers from the University of Washington recently discovered. Specifically, the team studied the interactions between moths – the main nocturnal pollinators – and the *Oenothera pallida* wildflower, using mass spectrometry. The findings revealed that nitrate radicals in the atmosphere react with the flower's pollination signaling scent, nearly eliminating it.

References available online

IN OTHER NEWS

Researchers introduce MARS: a multipurpose software for untargeted LC-MS-based metabolomics and exposomics, integrated with several adducts and in-source fragmentation detection, to enable in-house building of reference databases.

Researchers from Taiwan develop an electrospray probe mass spectrometry platform that enables point-of-care identification of mushroom toxins for rapid treatment of poisoning.

Researchers combine metabolomics with machine learning to diagnose ovarian cancer with 93 percent accuracy.

The Olsen Lab explores what the Orbitrap Astral can do in proteomics: 48 human proteomes per day "representing 3× higher coverage compared with current state-of-the-art MS."

DBPs: an Underestimated Threat

Why Susan Richardson's recent discoveries about disinfection by-products are (even more) cause for concern

By Jessica Allerton

Back in 2019, Susan Richardson, Arthur Sease Williams Professor, Department of Chemistry & Biochemistry, University of South Carolina, USA, wrote a feature for The Analytical Scientist discussing her work on disinfection by-products (DBPs) – and the threat they pose to our health, wildlife, and environment.

We recently connected with Susan to see where this research has taken her over the past few years, what she's mostly concerned about today, and how environmental analysis can progress in the near future.

What is the biggest analytical challenge in environmental research today – and how do you believe we can overcome it?

Identifying unknown contaminants, whether in drinking water or environmental surface waters, remains as our biggest environmental analytical challenge. It is much harder to identify new contaminants than those we already understand, and they are more likely to be found at very low levels in a sea of contaminants – it's like looking for a needle in a haystack!

Effect-directed analysis (EDA) is a valuable method for pinpointing harmful contaminants causing toxicity effects. However, it takes a great deal of time and effort, which discourages many groups from using it. There are several examples of EDA's effectiveness, such as the discovery of 6ppd-quinone harming coho salmon in the Northwest US (1) and a new algal toxin affecting bald eagles in the Southeast US (2).

Which environmental contaminant are you most concerned about today?

Despite having worked in various now-mainstream areas of environmental analysis, from microplastics to PFAS, I'm still most concerned about DBPs. This is because they're typically found at ppb levels (1,000 times higher than PFAS) and a body of evidence states that they cause serious effects to human health – such as bladder cancer, miscarriage, and birth defects. For example, dibromoacetonitrile – one of the emerging, unregulated DBPs – is carcinogenic in two animal species and often seen in drinking water at ppb levels (3).

What updates can you share about your work with DBPs?

In 2022, we published our new discovery on an important class of DBPs that weren't known before: halocyclopentadienes. We found these DBPs in real chlorinated and chloraminated drinking water using a very sensitive GC-MS instrument (4). I was especially surprised by two aspects of this research. Firstly, this class is the first to be bioaccumulative; secondly, hexachlorocyclopentadiene is now the most cytotoxic DBP known. These six new DBPs were found completely by accident by a PhD student in my lab, Jiafu Li, who spotted the new peaks and figured out what they were. As always with analytical science, important discoveries seem to appear when you least expect them!

Additionally, in a recent Environmental Science & Technology publication, we applied EDA to assess different size fractions of DBPs and determine which are most important toxicologically (5). We discovered that DBPs over 5000 Da molecular weight are not toxic – validating a statement made by a prominent toxicologist at a conference I attended. The most toxic fraction was <1000 Da, challenging the common focus on larger fractions in previous research.

How important is mass spec to your work?

Hugely important! Mass spec is the most important tool in our arsenal thanks to its high sensitivity and ability to handle complex mixtures. For me, it's the most important tool in environmental research because we can use it to identify new contaminants, quantify contaminants, and so on. If NMR was this sensitive and could handle mixtures, maybe we'd veer away from mass spec. But as it stands, mass spec remains on top!

Is there anything missing from the analytical toolbox for environmental analysis?

Some people in the field have started using supercritical fluid chromatography (SFC)-MS. Only time will tell if this fills an important niche. One thing we're missing is an automatic process for testing toxicity of collected prep-LC-MS fractions. As other areas of analytical chemistry begin to use AI, maybe environmental research should take inspiration to push EDA into the future.

Any advice for the next generation of analytical scientists working in environmental analysis?

There's so much to discover and do – newly emerging analytical scientists have a wonderful opportunity to make a difference in human and environmental health. Alongside grasping every opportunity that presents itself, it's crucial that you don't give up! There's always pitfalls, but with collaboration and determination, you will achieve exciting results.

What are your hopes for the future?

I'm hopeful that as the field evolves, we will identify important new contaminants that allow us to draft solutions to minimize human and ecological exposure.

References available online

Machine Learning: A Powerful Weapon in Protein Analysis

Discussing the role of ML in immunopeptidomics – and beyond

By Jonathan Krieger and George Rosenberger

The term machine learning (ML) appears frequently in the news, yet remains poorly understood. There is a general lack of awareness of the crucial role that ML approaches are already playing in the lab environment, particularly their efficacy in managing large volumes of data, exemplified by their use in various omics analyses.

In this article, we explore how ML is advancing mass spectrometry (MS)-based analyses, including those focused on proteins (such as single-cell proteomics) and their interactions with the immune system. Example applications in these areas of research include the streamlining of multi-level data integration and biomarker discovery (1). A promising use of ML lies in its ability to predict protein qualities from primary amino acid sequences. Coupling MS with trapped ion mobility spectrometry (TIMS) allows researchers to "speak the language of peptide sequences" by predicting ion mobilities before acquiring data. The result: simplified analysis and reduced false positives.

The power of TIMS

TIMS is a contemporary evolution of traditional ion mobility spectrometry (IMS) that keeps ions stationary in a moving column of gas, rather than driving the ions through a stationary phase.

An electric field is used to trap the ions, and modification of this electric field allows researchers to elute ions in a mobility-dependent fashion (2). By separating and eluting ions in dense clusters based on their mobility, groups of molecules with shared structural elements are captured at specific times. These structural elements, unique to each analyte eluted, are represented by an acquired collisional cross section (CCS) value, which is highly reproducible across instruments and labs.

Combining TIMS with MS adds a crucial additional dimension to protein analysis and identification, allowing analysts to transition from 3D to 4D proteomics. The result is increased sensitivity, selectivity, and acquisition speed.

A principal challenge in protein analysis is the matching of acquired values to potential peptide matches in existing databases, also known as peptide spectrum matches (PSMs). This process can be complicated by the presence of many potential matches with similar probability scores. Notably, false positives happen when the wrong PSM is chosen. TIMS has been shown to offer a partial solution as using the CCS values acquired increases the number of PSMs, peptides, and proteins identified in bottom-up proteomics analyses, increasing confidence in assignments.

Deep learning predicts CCS

Approaches such as deep learning, a form of ML based on artificial neural networks inspired by the human brain, can be used to predict CCS values from peptide sequences prior to TIMS-MS analysis. The presence of histidine and proline amino acids, as well as general hydrophobicity, are the main drivers of these predicted CCS values (3). Comparing the predicted values with acquired measurements provides us with correlation scores, which can subsequently be used to identify the most likely PSM for a given spectrum. Using ML in this way improves the efficiency of data analysis and reduces the time needed to obtain reliable results.

Existing data already demonstrate the power of these machine-predicted

"A principal challenge in protein analysis is the matching of acquired values to potential peptide matches in existing databases, also known as peptide spectrum matches."

CCS values. In 2021, Yasushi Ishihama and colleagues shared the systematic characterization of CCS values for 4,433 pairs of monophosphorylated and unphosphorylated monopeptides using TIMS (3). Analysis with a ML approach (TIMScore) added over 110,000 PSMs to their published results and doubled the number of peptides observed (reaching almost 100,000).

A transformer model of peptide CCS values has also been applied to ascertain that the accuracy of CCS predictions based on amino acid sequences could be as high as 95 percent for tryptic peptides and 92 percent for phosphorylated tryptic peptides.

Applying TIMS-MS in immunopeptide analysis

TIMS-MS has demonstrated potential in various omics fields, including single-cell proteomics, where (traditionally) hundreds of thousands or millions of cells were needed to conduct in-depth protein analyses. A recent paper detailed the use of TIMS-MS to identify an average of 365 proteins from single primary T cells (these numbers increased to 804, 1116, and 1651 proteins for five-, 10-, and 40-cell samples) (4). So, proteome coverage from these relatively small numbers of cells was sufficient for the study of essential metabolic pathways. And post-translational modifications (PTMs), including phosphorylation and acetylation, were recognizable from samples of just one cell. The approach has promise for the analysis of clinically relevant single-cell samples in the future.

The potential in immunopeptidomics, which describes the analysis of peptides presented to T cells, looks set to be particularly important. In fact, MS-based immunopeptidomics represents the only unbiased method available for the identification and characterization of these peptides (5). Researchers at University Hospital Tübingen, Germany, recently used a TIMS-MS method with HLA peptide prediction for the sensitive and high-throughput analysis of human leukocyte antigen (HLA)-associated peptides. The team more than doubled the immunopeptidomic coverage obtained when compared with previous methods. To be specific, they identified 15,000 peptides from approximately 40 million cells. The hope is that increased knowledge of these peptides will drive the production of personalized cancer vaccines and cell therapies targeting HLA peptides. Notably, the method described could also be leveraged for immunopeptidomic profiling in large patient cohorts and to improve existing CCS prediction algorithms for HLA peptides (6).

What lies ahead?

TIMS-MS adds another dimension to protein analysis, facilitating speed and sensitivity. Combining this powerful technique with ML is allowing researchers to gain increasing levels of insight into complex systems, which could transform key research areas. In the case of immunopeptidomics, this partnership holds promise for the delivery of new biomarkers and the development of improved therapeutics.

In the future, as computing power continues to advance, ML and its associated approaches will continue to develop from this already exciting base. In the field of protein analysis, this may facilitate the faster analysis of more analytes than previously thought possible. Elsewhere, areas such as data-independent acquisition and de novo sequencing also look set to reap the rewards – namely, simplified analysis, increased accuracy, and higher overall confidence in results.

Jonathan Krieger is Head of Research Bruker ProteoScape, Bruker Daltonics; and George Rosenberger is Software Project Manager – Machine Learning for MS-based Omics, Bruker Switzerland AG

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Core Topic
Chromatography

Rare achievements. Rare earth metals have unique magnetic and electrical properties that help power the production of modern technologies, like microchips – thus, increasing their demand. The two main methods of extractions, deposits and recycling of electronic devices, do not provide sufficient quantities. Recently, researchers from the Karlsruhe Institute of Technology, Germany, designed a magnetized chromatography-based method to improve the recycling process of light bulbs for the collection of rare earth phosphors. The authors report "purities of up to 95.3 percent at recoveries of 93.6 percent," thanks to their new technology, which enabled a controlled separation of the phosphor particles.

Monitoring melasma medication. The traditional treatment for melasma – a skin condition distinguished by abnormal hyperpigmentation – relies on multicomponent pharmaceutical creams. Monitoring their active agents can be challenging due to possible interaction with other components during quality control analysis. With that in mind, Mostafa Khairy and his team developed a stability-indicating RP-HPLC-UV assay – for detection of parabens, hydroquinone, and tretinoin in melasma treatment creams. The researchers successfully quantified multiple components simultaneously for the first time using their chromatographic method.

Bone for bone. According to a recent research, chicken broth is more than just a home remedy for a cold; it could possibly delay osteoporosis progression. Scientists from Tsurumi University, Japan, decided to analyze chicken-vegetable bone broth and identify potential agents that could prevent the disease – considering the recognition of bone broth as a superfood. Using ion-exchange chromatography, the team detected two components; hyaluronan and chondroitin sulfate. Both were shown to increase bone mineral and density as well as bone volume and tissue – which are typically depleted with osteoporosis.

SFC advancements. Unlike liquid chromatography, modeling software packages have not been developed for supercritical fluid chromatography – tools essential for the optimization of chromatographic analysis of pharmaceuticals. For the first time, researchers from Freie Universität Berlin, Germany, have advanced a pre-existing linear solvent strength model (LSSM) to improve SFC separation of therapeutic peptides. Complex peptides such as Bac and Tyro were successfully isolated from samples. "This work demonstrates the applicability of currently available modeling software for predicting high-modifier SFC separations with limitations in predicting the peak widths and slight drifts in the retention times," write the authors.

References available online

IN OTHER NEWS

Analysis with gas chromatography–olfactometry and aroma extract dilution of orange juice attributes undesired clove-like off-flavor to 5-Vinylguaiacol (5VG) – a cleaning agent residue.

Post-mortem gas chromatography-mass spectrometry (GC-MS) analysis of aging supercapacitors reveals increased decomposition with doping – paving the way for mitigation strategies to extend the lifespan and performance of electric double-layer capacitors (EDLCs).

PFAS shown to have increased transfer efficiency from maternal blood to human milk the longer the lactation period is, according to analysis with UHPLC/MS.

Researchers monitor circulation of parabens – toxic preservatives found in cosmetics – for the first time in wild boar hair samples using LC-MS.

Impactful Separations at HPLC 2024

What is the societal impact of separation science? Come to Colorado to find out!

By Susan Olesik

Separation science doesn't always get the recognition it deserves, especially given the dramatic impact it has on society – from understanding human biology and developing new medicines, to catching criminals and protecting the environment. There's also a misconception that a meeting of separation scientists has to either be for the experts to network and discuss the niche technical details or a higher-level overview more suited to beginners. Our aim with this year's HPLC meeting is to tackle both of these issues by highlighting the impact of separation science while catering to both experts and interested non-experts.

How? I'll offer an example. We're holding a session on forensics and our keynote speaker will be Bruce McCord, Professor of Chemistry and Biochemistry at Florida International University, USA, who is an expert in forensic science – he worked at the FBI before becoming an academic. He has done a range of interesting and cutting-edge separation science work: analyzing different human fluids to determine a suspect's age, smoking status, drug use, diet, and so on. Not only is his work having a tremendous societal impact, but there's considerable technical finesse involved. So I think Bruce's talk will appeal to both separation science experts and a more general audience.

I'd also like to highlight a couple of sessions on clinical and protein analysis with broad and specialist appeal. Jarrod Marto, a researcher at the Dana-Farber Cancer Institute, USA, is doing a great deal of research on different analytical separations, focused on cancer analysis. He has been able to show how changes to the structure and composition of specific proteins present in humans at very low levels can cause the onset or the proliferation of cancer. In many respects, Jarrod is doing analytical detective work, but the societal impact could be tremendous. We're planning to have a number of such sessions that demonstrate the deep value of analytical separation science and its contribution to society – especially human health.

Let's take another example: the pharmaceutical industry, where separation science is absolutely key with real spectrum of applications – from analyzing complex mixtures of small molecules to separating nanoparticles or nanobodies with the same level of integrity as the small molecules. We want to showcase state-of-the-art separation science taking place in the pharmaceutical industry by inviting speakers from industry – both to share ideas with each other and to hopefully inspire others to take some of what they're doing and apply it in other fields.

Another emerging trend we'll be covering during the conference is AI, which I believe will impact separation science – and it doesn't look that far away. For example, Deirdre Cabooter, Gert Desmet, and Alexander Kensert have recently published an article demonstrating the use of reinforcement learning to select scouting runs for retention time modeling. The use of AI here is compelling because it can be difficult to know where to start when you're selecting mobile-phase conditions to generate a gradient – especially for a large system. Deirdre will give a talk about her work using AI for method development in LC at the event. And that feeds into another main aim of HPLC 2024: to give the 800 expected delegates a glimpse of what they should expect to see in the future in terms of the direction of the field.

"Separation science doesn't always get the recognition it deserves, especially given the dramatic impact it has on society."

In addition to my examples, we have more than 100 people giving talks across three concurrent sessions; we certainly have some excellent keynote speakers, but we are also keen to shine the spotlight on the most interesting submitted abstracts and draw people's attention to further exciting work in the poster session. Finally, you'll be able to sharpen your skills at workshops and short courses on the weekend.

Overall, if you want the chance to meet and share notes with true experts leading the charge using analytical separation science to make important improvements in society, spanning HPLC and electrophoretically-driven technology, then join us in Denver, Colorado – which, by the way, is a spectacular place to visit!

HPLC 2024 will take place July 20–25, 2024, in Denver, Colorado, USA. For more information, visit: hplc2024-symposium.org

Susan Olesik is Dow Professor and Chair, Department of Chemistry and Biochemistry, The Ohio State University, USA

Resurrecting SFC

Has the "game-changer" really fallen into oblivion?

By Stefan Bieber and Thomas Letzel

In 2023, The Analytical Scientist celebrated its 10-year anniversary. Following Caroline West's retrospective looking back on the past 10 years of supercritical fluid chromatography, we couldn't help but notice that SFC has always been a focus for TAS – going all the way back to Issue 01, both with Caroline's piece on "Greening SFC" and Terry Berger's contribution to "The Analytical Entrepreneurs" (his start-up also focused on SFC).

In October later that year, alongside the first Power List, The Analytical Scientist published "Three Gurus of Supercritical Fluid Chromatography," which discussed SFC's potential as a true game-changer in chromatographic separation. One of the interviewees, Eric Lesellier, said:

"It is almost impossible to write an exhaustive list of the benefits of SFC systems. All of the classical separation problems are handled, with the exception of water-soluble compounds. It handles interactions through mobile/stationary phase couplings, it allows coupling of columns for higher theoretical plate number, and it provides the natural concentration of the mobile phase for fraction collection. Of all the benefits, I would highlight isomer separation."

Further, he said: "From a practical point of view, the real challenge for SFC is method development; firstly, because of the many parameters acting on retention and separation, and secondly, because the stationary phase choice is huge, covering all those used in RPLC, NPLC, and HILIC."

The second interviewee, Davy Guillarme, asked: "What about mass spectrometry? Just like RPLC, SFC can easily be coupled with MS with either electrospray ionization (ESI) or atmospheric-pressure chemical ionization (APCI) sources."

Interestingly, one year later, 10 scientists in the "Top 40 under 40" Power List (that's 25 percent, folks!) could be associated with SFC at that time. Notably, Lucie Novakova predicted: "SFC will be a game-changer; we're already seeing new instrumental platforms and stationary phases. Other instrumental development will follow, chiral stationary phases with smaller particles are already on the way."

These interesting findings led us to search for further SFC articles on the TAS website. In total, The Analytical Scientist has published 53 articles that include the keyword "SFC." Over all the years, several scientists published articles discussing the state of SFC within different analytical fields – which we feel is adequate coverage for a media brand that covers the entirety of analytical science. For example, Caroline West featured prominently, with several publications over the years (in 2013, 2016, 2022, and 2023) discussing SFC handling and environmentally friendly performance. More recently, the debate seems to have focused on SFC's excellent chiral separations, as well as the need for "greener" equipment and more basic education.

We appreciate The Analytical Scientist as an advocate for SFC. Nevertheless, having looked back at the past decade of SFC coverage in The Analytical Scientist (and many other media as well), we feel there is a need for SFC users and developers to reemphasize the technique's key benefits.

"We appreciate The Analytical Scientist as an advocate for SFC. Nevertheless, having looked back at the past decade of SFC coverage in The Analytical Scientist (and many other media as well), we feel there is a need for SFC users and developers to reemphasize the technique's key benefits."

SFC is an excellent chromatographic technique, used widely in routine labs and industry, and has excellent hyphenation with electrospray mass spectrometry! It is great to see SFC having become an important technique in certain analytical fields. However, in our perspective, this technique has the potential to change analytics in many other fields, too. With that in mind, we

wanted to highlight several additional applications and solutions that SFC can offer laboratories.

First, the unique characteristics of SFC separations allow for the use of combined stationary phases with different retention modes. The selectivity of such stationary phases is not a combination, but a sequential add-on. This "additive" effect can be achieved by connecting different columns or by small partitions with different selectivity in one column. Several method development strategies are already available for very complicated applications.

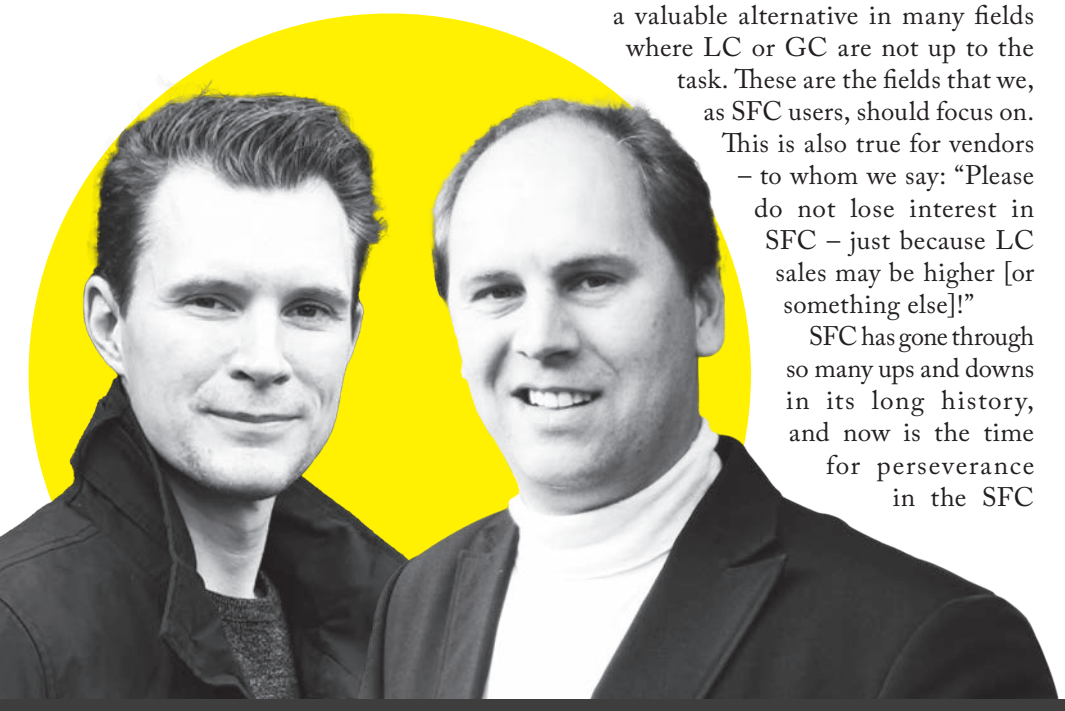
Second, the usage of zwitterionic or silica or other "HILIC" columns allows for the perfect retention and separation of polar and very polar molecules, such as the new class of "regulated" drinking water molecules (PMT and vPvM), while allowing one to handle water-soluble compounds.

Third, SFC in its function as a (polarity-extended) chromatographic separation technique is highly compatible with the mass spectrometric inlet (e.g. the electrospray ionization source) in which the mobile phase has to be removed and the molecular ions have to be transferred into gas-phase. The sensitivity of ESI in SFC is comparable or sometimes even better than in LC. This significantly expands the applicability of SFC.

Last but not least, given that SFC is an extremely versatile separation technique with broad selectivity, as we just have seen, it is also highly compatible with (high resolution, accurate) mass spectrometry. As a result, SFC is perfectly suitable for screening very complex samples, such as in non-target screening (NTS).

Despite these promising applications, if we're honest, SFC will not replace LC (nor GC). Nevertheless, SFC remains a valuable alternative in many fields where LC or GC are not up to the task. These are the fields that we, as SFC users, should focus on. This is also true for vendors – to whom we say: "Please do not lose interest in SFC – just because LC sales may be higher [or something else]!"

SFC has gone through so many ups and downs in its long history, and now is the time for perseverance in the SFC community to ensure it takes a sustainable upwards trajectory.



"SFC remains a valuable alternative in many fields where LC or GC are not up to the task. These are the fields that we, as SFC users, should focus on."

We must prevent a repeat of what Thorsten Teutenberg correctly forecasted in 2016: "It's clear that good ideas do not always end up in the form of real applications – indeed, this is often true whenever a 'new' technology emerges. One good example (or bad example, depending on your perspective) is supercritical fluid chromatography (SFC), which – after its glorious future had been predicted – fell into oblivion for quite some time."

We must do better!

Stefan Bieber and Thomas Letzel co-founded The Analytical Forschungs- (Research) Institute for Non-Target Screening (AFIN-TS GmbH), Augsburg, Germany

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Core Topic
Spectroscopy

Forecasting rocks. On February 28, 2021, the Winchcombe meteorite became the most widely recorded carbonaceous chondrite fall to date. Now, a research team decided to analyze the meteorite aiming to characterize its organic composition – potentially revealing details about the key elements involved in the delivery of prebiotic molecules to the early Earth. Employing high-spatial resolution spectroscopy techniques – to minimize processing of the sample – the researchers identified nitrogen-containing compounds. The authors concluded that the extraterrestrial amino acid found in Winchcombe has also been detected in Ryugu.

Finding nanoplastics. Researchers from Texas A&M University and the University of Notre Dame collaborated to examine plastic nanoparticles in water samples obtained from two open oceans with shrinking surface bubble deposition (SSBD). The technique was originally developed for DNA analysis combining electron microscopy and surface-enhanced Raman spectroscopy and repurposed for this study to enable nanoplastic size and morphology determination – a measure that current techniques, such as gas chromatography cannot provide. The team discovered nanoplastics made of nylon, polystyrene, and polyethylene terephthalate.

Low-energy; large results. Organic semiconductors are a crucial component of several electronic devices. In hopes of determining the binding energies for influencing the behaviors of these materials, Japanese researchers employed low-energy inverse photoelectron spectroscopy. Their research revealed unexpected correlations that could provide applications in bio-related materials. "Given the fundamental nature of our research, we expect long-term and persistent effects, both visible and invisible, on real-life applications," said Hiroyuki Yoshida in the press release.

Gluing history together. Thanks to recent research employing energy-dispersive X-ray spectroscopy (EDX), transmission infrared spectroscopy, and micro-computed tomography (microCT) to analyze Neanderthal stone tools, we now know more about the cultural evolution of ancestors. The researchers discovered ochre-based adhesives – a surprising finding, as such tool making practice has only been recognized in African *H. Sapiens* and not Neanderthals before.

References available online

IN OTHER NEWS

Scientists from Shanghai Normal University design biocompatible protein chromophore-based probes for spectroscopic characterization of fingerprints in crime scenes.

Bullying and victimization leads to decreased glutamate-glutamine (Glx) levels – according to proton magnetic resonance spectroscopy – and a greater risk of psychotic episodes.

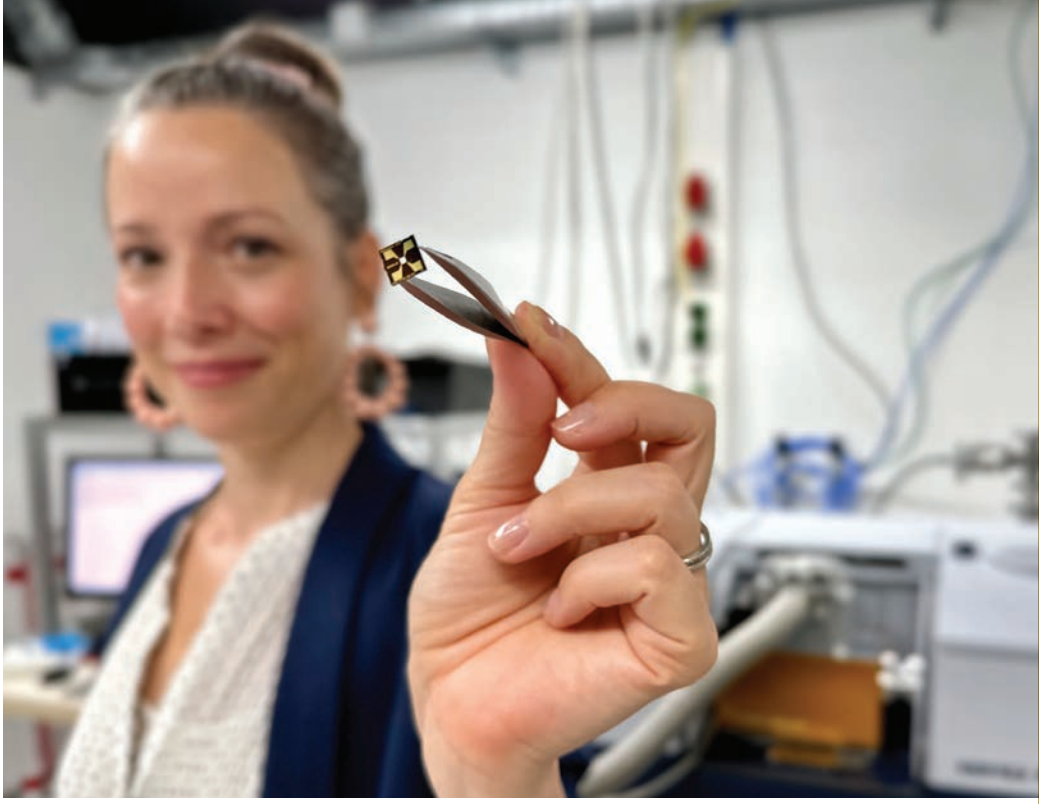
Biologists and physicists from the University of Leeds, UK, collaborate and develop on-chip Raman spectroscopy – incorporating microfluidic techniques – to characterize the development of oesophageal adenocarcinoma cells.

Study demonstrates successful label-free blood typing by AI-enabled Raman spectroscopy – paving the way for future applications in transfusion medicine and blood banking.

Zooming In on Nanoplastics

How increased sensitivity of emerging technologies is improving nanoplastic detection

By Josiane P. Lafleur and Jelena Timarac Popović



Credit: Tatjana Penn / Invisible-Light Labs GmbH

Nanoplastics, a subset of microplastic particles that are even smaller in diameter, are everywhere – from our soils to the air we breathe. Therefore, it is no surprise that researchers have found micro and nanoplastics in various animal species and in human blood (1-5). Polymer-based nanoparticles have a large surface-to-volume ratio, which can increase reactivity and cause interactions with dangerous substances and microorganisms. The toxicity of nanoparticles – alongside their ability to act as carriers for other pollutants – demands that we think cautiously about this issue (6-10).

If all that's not alarming enough, scientists have recently discovered plastics in infants, breastmilk, and placenta (11-13) – a true wake-up call to find solutions.

The size of nanoparticles (1–100 nm) can make sampling and identification a real challenge; for example, sub-microplastics and nanoplastics have sizes below the limit of common microscopy hyphenated with spectroscopy techniques such as Fourier-transform infrared spectroscopy (FTIR), Raman microspectroscopy, and focal plane array (FPA)-FTIR (14). Atomic force microscope-infrared spectroscopy (AFM-IR), transmission electron microscopy with energy dispersive X-Ray spectroscopy (TEM-EDX), and scanning electron microscopy with energy dispersive X-ray spectroscopy (SEM-EDX) are three methods capable of chemical characterization of individual nanoparticles; however, the process is time-consuming, taking several hours to scan the filter's surface.

At Invisible-Light Labs, we're working on a system for nanoplastic analysis by collaborating with external research groups focused on detection of airborne and waterborne nanoplastics. We've come a long way since our initial conversations of the possible applications of infrared spectroscopy in environmental monitoring. The project I'm most excited about is our EIC-funded project NEMILIES (NanoElectroMechanical Infrared Light for Industrial and Environmental Sensing) which allowed us to develop EMILIE. EMILIE uses nanoelectromechanical Fourier-transform infrared spectroscopy (NEMS-FTIR) to provide rapid bulk chemical characterization of nanoplastics and sub-microplastics in the size range of 10–500 nm. Importantly, it uses a perforated nanoelectromechanical membrane as both a filter and a sensing element. This means that after sampling nanoplastics on the nanomechanical membrane, it can be directly transferred to the EMILIE detector chamber for FTIR analysis. With this method, we can achieve the required picogram level detection limits for nanoplastics analysis with minimal sample losses and contamination – we can also determine the absolute mass of the nanoplastics deposited on the membrane (15).

The NEMILIES project could solve several challenges environmental researchers continuously face – namely, by providing more than just the concentration or size distributions of nanoparticles, but instead by providing their physical and chemical properties. Indeed, one important piece of the nanoplastics puzzle is chemical fingerprinting. Without chemical identification, it's very difficult to identify the source of pollution and remediate it. Based on this information, we can understand where the nanoparticles come from, their level of toxicity, their environmental fate, and how they interact with other particles.

As other scientists join our efforts in studying nano and microplastics, we're sure to expand our knowledge for tackling this crisis. I'm excited to see where such technology can go with further efforts.

Josiane P. Lafleur is Managing Director and Head Scientist at Invisible-Light Labs, Austria; and Jelena Timarac Popović, R&D Engineer at Invisible-Light Labs, Austria

the Analytical Scientist

POWER *List*

IT'S TIME FOR THE ANALYTICAL SCIENTIST'S ANNUAL POWER LIST!

This year we are recognizing individuals who are transforming the world around us in the following three categories:

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Introducing NextMinds

Isabelle Kohler explains why she launched a mentoring platform designed for early-career scientists

By Markella Loi

Have you ever thought about adding another string to your bow and starting a new business next to your academic or industry position? Well, Isabelle Kohler – well known for developing mass spectrometry-based approaches for the analysis of drugs and metabolites as Assistant Professor at the Division of Bioanalytical Chemistry at the Vrije Universiteit Amsterdam, The Netherlands – has done just that.

Here, Isabelle – who appeared on our 2022 40 Under 40 Power List – introduces her new mentoring initiative "NextMinds" and reflects on the struggles faced by early career researchers – especially those in analytical science.

Why do you think chemistry students often feel lost when thinking about their career path?

I think that one of the major reasons is because we don't train them well on these aspects during their studies. Of course, they have numerous career events organized (usually by students' associations with guest speakers from the industry), which bring them insights about some of the career paths they can take after their studies (or their PhD), but this is, in my opinion, not enough.

Universities focus on teaching scientific knowledge; we've also started teaching more and more about academic skills at the Bachelor's and Master's level (for example, academic writing, presentation skills, and so on). However, we don't spend much time or energy supporting and guiding students in planning their career – even though I believe it should also be our role, as educators.

Is that why you started NextMinds?

I've now spent 15 years in academia, including 10 years post-PhD. I've been a PhD student myself, and now I'm on the other side of the coin where I'm supervising PhD students. Over the last few years, I realized that many PhD students around me face similar challenges during their PhD – many of which I also had to face. What strikes me the most is that many of these challenges arise from a lack of knowledge or information or a lack of self-confidence.

I'm at a stage of my career when I am now convinced that a traditional academic career as a professor is not what I aspire to do – working 80 hours per week and writing grants that don't come to fruition can be nerve wracking. My power and talent can also be in a different space – helping the younger generation, by combining the knowledge I gathered from the academic world with my empathy and willingness to help, guide, coach, and mentor these young (and not so young) scientists.

"We don't spend much time or energy supporting and guiding students in planning their career."

I believe that there's a strong need for such an initiative – where young scientists can learn from someone who has been through similar challenges and who can bring another perspective. And that's where NextMinds comes in.

So what exactly is NextMinds?

The mission of NextMinds is to provide all the necessary tools and knowledge to early-career researchers (students, prospective PhD students, PhD students, and postdocs) to help them navigate academia and beyond.


Credit: Arian Khoshchin

When I did my PhD before the social media empire, this information was not really available. If you had a great supervisor, they would mentor you – if not, bad luck! You would have to make mistakes to learn.

Today's generation has access to information via social media, but they don't know if it's reliable. With this in mind, NextMinds is active on social media – mainly LinkedIn – sharing free tips not only for academic purposes but also mental health, networking, and soft skills. These tips are also available via weekly newsletter, where I also share personal stories to illustrate the topics I cover.

We're about to launch an e-learning environment, which will feature online courses – covering different topics to help prospective students find a PhD position and prepare effectively for applications and interviews, and a community, where young scientists can interact with each other. We also collaborate with universities to organize workshops, online events, and webinars. In a very near future, we will also offer individual and group coaching sessions.

It sounds like a significant shift away from a traditional academic position…
Indeed, and I find this exciting! One of the aspects I really like with NextMinds is that it allows me to see the direct impact of my work. An academic career does not bring much immediate reward; you know you need to work hard, but the reward is that you will receive even more tasks and need to work harder!

I don't expect to win a Nobel prize with my research. The real impact I see with my work at the university is everything related to teaching. There, I can really see how my endeavors help both people and society. NextMinds goes in the same direction – helping people and society by sharing knowledge. Basically, my mission with NextMinds is to guide and mentor those who may get a Nobel prize!

How has NextMinds been received so far?
Despite only launching the company a few months ago, the initiative seems to be highly valued. The comments I receive from students and professors are incredibly positive. It is definitely rewarding to see NextMinds being embraced so warmly by everyone.

"The real impact I see with my work at the university is everything related to teaching. There, I can really see how my endeavors help both people and society."

I have also received enthusiastic comments from different institutes who would like me to join their consortia, projects, or introduction days, which tells me one thing: we are on the right track and our voice is being heard.

What plans do you have for the company?
I want my work with NextMinds to be an inspiration to many academics (and non-academics) of my generation and younger – people who are seeking more work-life balance and want to have an impact on their peers.

The plan is to have a "NextMinds academic hub," where young academics worldwide and across disciplines gather to learn tips and tricks to navigate academia with a happy mind, self-confidence, a clear goal, and the feeling that they are supported and understood.

And that's why we're trying to take NextMinds to the next level. Our team has been working to build an app so people can easily access our content whenever and wherever they want. We're also hopeful to launch our two first digital courses, *"Unlock Your PhD Position,"* and *"Master Your PhD Application,"* to help candidates craft the best possible applications and choose the best PhD position.

What tips or words of advice can you offer to students and postdocs here?
My first piece of advice is that it's never too early to start preparing for your future. Many young scientists embark on a PhD simply because they love research, but without knowing exactly what they want to do after their PhD. This is fully understandable, but it's important to start looking at possible career opportunities soon after their PhD.

So, get out there and talk to other scientists – especially those at a more senior level and those who work in different sectors: industry, start-up, academia, hospital, education, NGOs, governmental institutes, and so on. The possibilities are endless, but it's important to be aware of them to choose wisely! I always encourage PhD students (and Master's students, if they have this opportunity) to go to networking events to discover all these opportunities. It doesn't need to be a fancy conference – a local university symposium with a few invited speakers from different sectors is already an excellent start.

Enhance Your Non-Targeted Profiling of Polar Metabolites with YMC Accura Triart Diol-HILIC

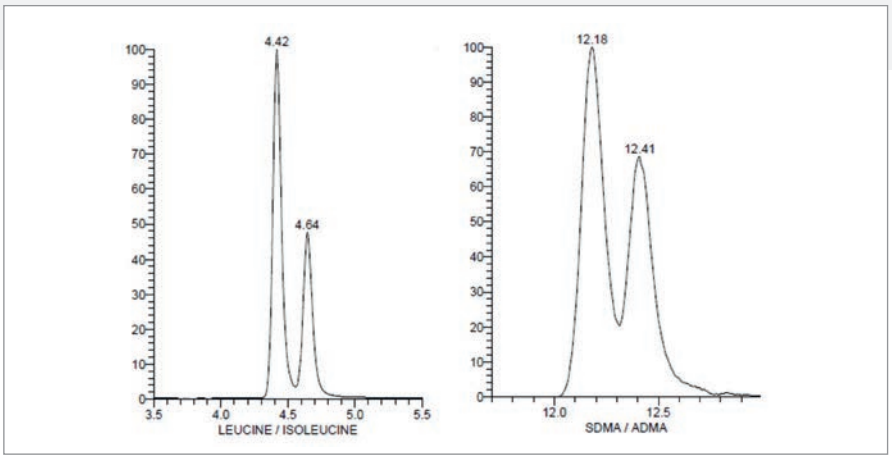

Figure 1: Selected ion chromatograms of leucine/isoleucine (left) and SDMA/ADMA (right) metabolites < 5 ppm found by non-targeted HRMS analysis of human plasma.

This application note shows the non-targeted screening of polar metabolites in human plasma using a bioinert coated YMC Accura Triart Diol-HILIC column, which is essential to achieve the highest sensitivity and chromatographic resolution of endogenous isomers.

Due to the complex matrix, a pre-conditioning step of the stationary phase can be necessary. The conditioning is already achieved after only four runs. Furthermore, an excellent retention stability is provided after conditioning.

The developed HILIC method using a bioinert YMC Accura Triart Diol-HILIC column covers a wide range of polar compounds with an excellent peak capacity. In addition, the method achieves resolution of important critical pairs, such as leucine and isoleucine or ADMA and SDMA. Together with the simultaneous high sensitivity, this method ensures a reliable generation of biological hypotheses.

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

Thinking "In Green"

Sitting Down With… Elena Ibañez Ezequiel, Research Professor, Foodomics Laboratory, Institute of Food Science Research (CIAL-CSIC), Spain

Did you always want to be a scientist?
I was curious, but I wouldn't say I always wanted to be a scientist. I believe my passion for science and research started in the last year of my graduate studies, when I enrolled in the analytical chemistry department of the Institut Quimic de Sarriá (now Ramón Llull University, in Barcelona, Spain). At that time, I had extraordinary professors and supervisors who were able to transmit their passion for knowledge and who made me realize all the opportunities analytical chemistry was able to offer. At that point, I just fell in love with science.

What attracted you to analytical science – and food analysis in particular?
What attracted me most was the potential impact on society's well being. Food analysis has an important relationship with sustainability that can help improve our lives, our cities, and our planet – and that's something I am passionate about. I'm motivated by the potential to help others.

Were there any unexpected turns during your career?
I guess there are always unexpected turns in a professional career, but you must learn from all of them – and I wouldn't be who I am today without having endured challenges and difficult decisions. For example, I remember when I was trying to become a scientist in my organization (CSIC, National Research Council of Spain); at that time (the late 1990s), Spain was not investing in science, so the competition for positions was very strong. After five years as a postdoc (two in the US and three back in Spain), my contract finished and I had to take a university position with no permanent contract. I was already 35 years old at the time. It was difficult, but I was able to manage. Fortunately, I was successful in the end – and became more self-confident as a result.

What achievement brings you the most pride?
I believe I have been able to combine my knowledge in analytical chemistry and chemical engineering for the benefit of society – and I am proud of that. I was able to break all barriers between the two disciplines, which allowed me to truly think "in green" and apply knowledge bidirectionally.

In the past, you've mentioned Karin Markides and Alejandro Cifuentes as inspirational leaders – what lessons did they teach you?
Karin Markides for me was a model of a strong women able to lead two different (and important) laboratories in two places so far apart (Utah, USA, and Uppsala, Sweden). In the 1990s, this wasn't so common. I remember her traveling every two weeks back and forth and being able to significantly contribute to some new and exciting analytical developments in chromatography and mass spectrometry in both labs. Importantly, she was also able to run a family and even had time for friendly dinners at her place!

Alejandro Cifuentes is a model of a self-made leader. I remember him starting a lab from zero and, after few years, becoming one of the most important names in the -omics field. He taught me to never give up, to be confident with my work, to follow an idea (or a dream) and to pursue it with hard work and strong commitment. He opened his lab to me and, from that moment, we became a really strong team – based upon mutual respect, common professional interests, and engaging scientific discussions!

How can we attract more talent to analytical science?
We need to make society aware of the role of analytical chemistry in all aspects of science. We can do that by giving more publicity to scientific papers involving analytical chemistry that have helped solve important issues for society. Perhaps we can use social media more effectively to send the message that there are few important advances in science that aren't connected to advances in analytical chemistry. By better advertising the field, we should attract more talented researchers.

In 10 years time, when you look back on the progress made in food analysis, what do you hope you will say?
Unfortunately, I will probably say that we had the chance to help our world achieve goal 2 of the 17 Sustainable Development Goals (Zero Hunger), but we weren't able to do it. We needed to do more, but, faced with the scale of the challenge, we quit fighting. I hope that I'm wrong. When I look back in 10 years' time, I'd love to say that we made it – we have safer food production, fewer undernourished people, more people accessing healthy food, more food able to prevent diseases, greater equality…

What is your personal mission for the next 10 years?
My personal mission is to keep training young scientists from underdeveloped countries – either in our foodomics laboratory or in their countries of origin. Also, I want to train and enlighten decision-makers in these countries, including governments, communities, companies, and so on. Without a doubt, this is my personal wish and mission for the coming years.

What advice can you offer those following in your footsteps?
Work hard, keep your mind open to new inputs, even from different fields. Be brave and try to think out of the box. Do not forget that you owe a debt to the world and to society, so, work to build a better world for humanity.

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