MARCH 2018 # 62

the Analytical Scientist™

The Cloud Chasers

Meet the scientists striving to bring clarity to the complex (and controversial) world of e-cigarettes.

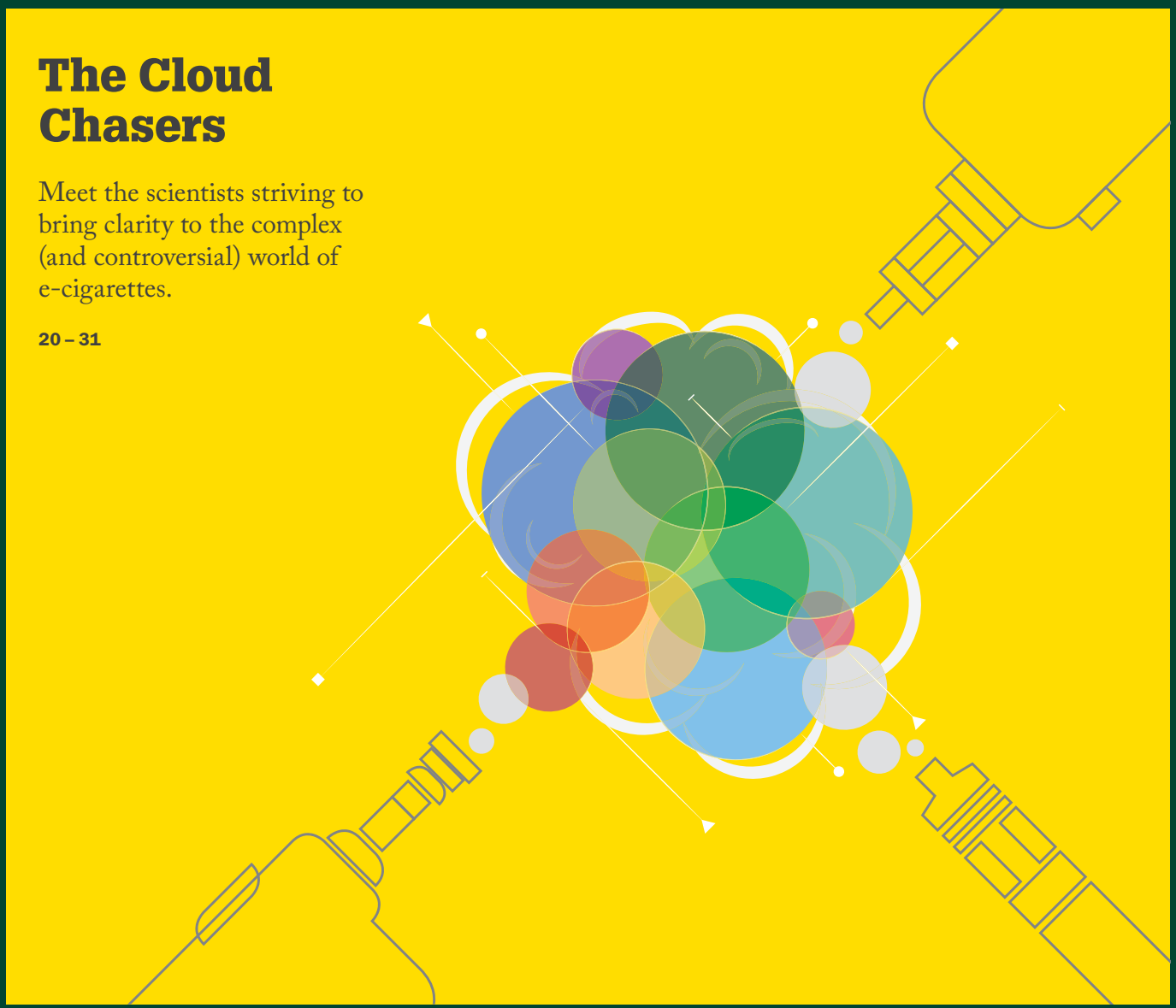

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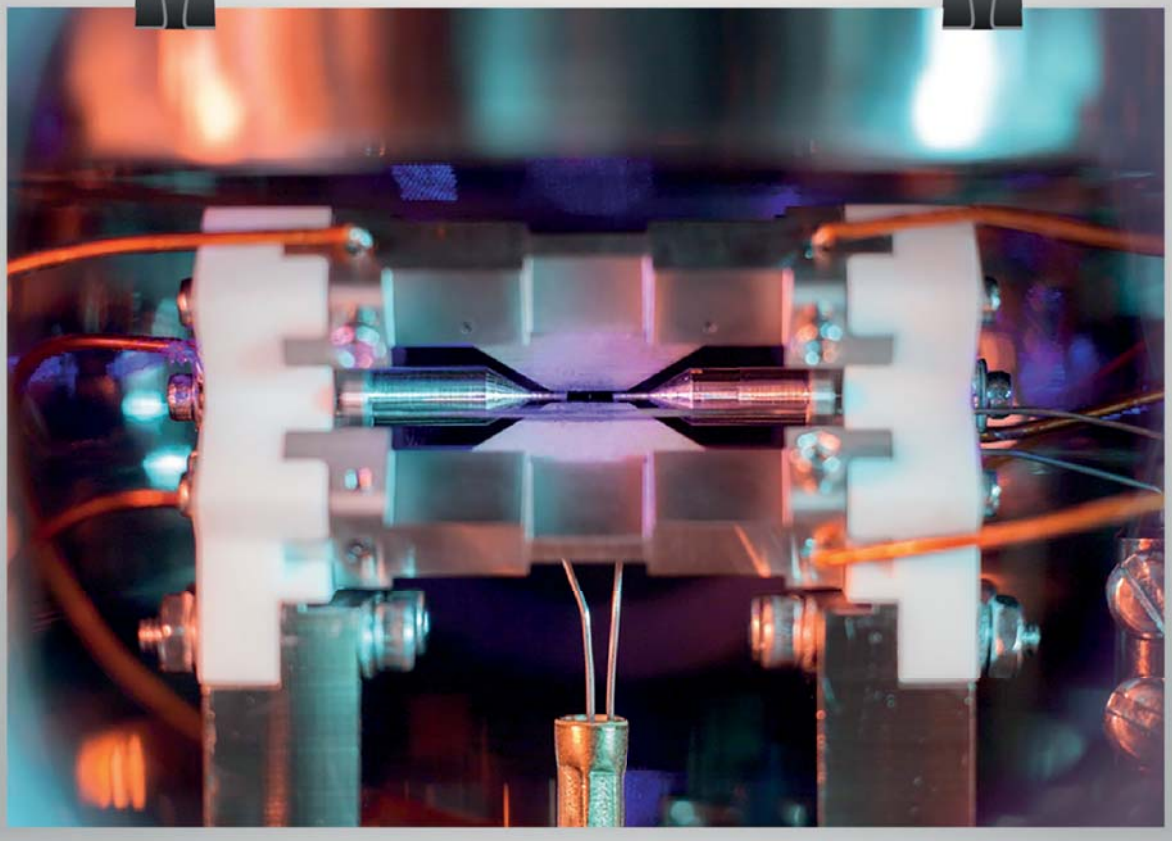
Image of the Month



Small Wonder

I spy, with my little eye... a strontium atom in an ion trap. Electric fields hold the atom in place between the needle tips, while its absorption and re-emission of photons from the blue-violet laser make it visible as a tiny blue dot. David Nadlinger, from the University of Oxford, won first prize for the photograph in the Engineering and Physical Sciences Research Council (EPSRC)'s national science photography competition.

Photograph: David Nadlinger/University of Oxford/EPSRC Photography Competition 2017

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

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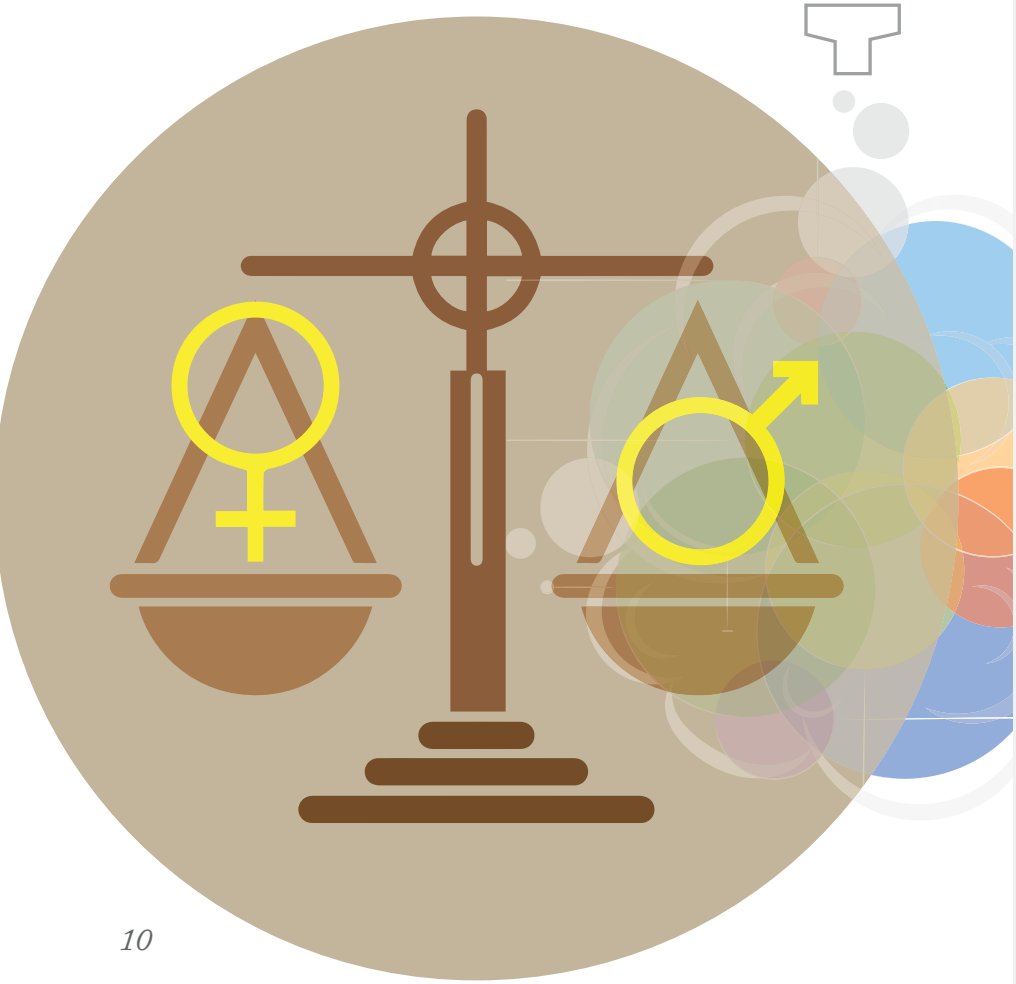

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On The Cover

Complex clouds meet three of the many e-cigarette designs now available to consumers.

Upfront

the Analytical Scientist

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Crowdsourcing Toxicology

Analytical advances are allowing more accurate and sensitive measurements than ever before – but what if we're not looking for the right compounds?

The Cloud Chasers (page 20) explores the fascinating topic of electronic nicotine delivery systems (ENDS) through the lens of analytical science. In particular, I was struck by Hugo Destaillats' comment that vaping is effectively a global toxicology experiment, which presents regulators and organizations with a difficult choice. By banning e-cigarettes, tobacco smokers could be denied a less harmful alternative. (In Japan, where nicotine-containing e-liquids are banned, smokers have turned to 'heat-not-burn' tobacco products, which could prove more harmful than vaping.) On the other hand, public health bodies in the UK have adopted a positive stance towards vaping, which appears (so far) to offer a less harmful alternative to tobacco smoking – a boon to those who have been unable to quit. That said, normalization of vaping could lead impressionable members of the public to underestimate the risks and see it as an entirely 'safe' activity. One thing is clear: there is a desperate need for more and better information on the potential health risks of chemicals of any kind being sucked into our lungs.

For the few academic groups attempting to analyze e-cigarette vapor, challenges abound – not least selecting and making chemical measurements that accurately reflect real-world outcomes (a point underlined by Hans Verhagen on page 17, who argues for the need to find appropriate exposure biomarkers for human biomonitoring studies in food safety).

Several scientists I spoke to raised the ever-pressing issue of "unknown unknowns." With most of vaping based on tobacco smoke, which is different both chemically and toxicologically, we could be missing (a big) part of the picture. Beyond limitations in analytical scope, studies must also attempt to account for the behavior of consumers. For example, when e-cigarettes are used intensively at high temperatures (so-called dry puffing), high levels of dangerous compounds are produced; whereas human vapers typically desist immediately when faced with the resulting acrid taste, the machines used in studies are less particular, skewing results.

How can we be sure that we are measuring the most relevant compounds? Analytical science is by nature collaborative, and assessing ENDS risks is no different. Researchers could stand to gain from working with regulators and public health experts (to understand what data they need to help them draw realistic conclusions), biologists (to determine the best biomarkers), and even psychologists (to assess studies against real-world use). Or perhaps we should just continue with the great global toxicology experiment!

Charlotte Barker
Editor

Upfront

Reporting on research, personalities, policies and partnerships that are shaping analytical science.

We welcome information on interesting collaborations or research that has really caught your eye, in a good or bad way. Email: charlotte.barker @texerepublishing.com

Striving for Balance

Is there gender parity in speakers at a major science conference? It's complicated…

A study examining gender bias at the annual conference of a large scientific society heralds positive changes – but women are still underrepresented in some subspecialties (1). Co-author Jessica Prenni (Associate Professor, Director of Research Core Facilities, Director of Proteomics & Metabolomics Facility, Colorado State University) says the research was prompted by a discussion about how the scientific society could respond to gender inequity with constructive action.

"We realized that in order for change to happen, we need to first better understand where we are right now," explains Prenni. "Our goal was to encourage dialogue on the topic and provide visibility to an issue that impacts all female scientists but that has been historically ignored."

They found that the number of oral session chairs was proportionate to the society's demographics (~70:30, male:female) – something that left Prenni feeling pleasantly surprised. "According to the numbers, our society is actually doing pretty well at maintaining a gender equity."

However, gender disparity was more pronounced in certain technical sub-areas and for keynote speakers and award recipients (see Figure 1). "Your experience can vary based on how you are engaged in the society and which sessions you attend," Prenni adds.

The survey has already had positive results; the society has responded with a new membership form that collects (voluntary) demographic information and an official diversity committee has also been formed to help ensure that things keep moving forward. Prenni has a caveat, however: "Though this result is positive, it is important that as a society we continue to promote change to ensure that we do not become complacent with the status quo."

Reference

1. *E Shishkova et al., "Gender diversity in a STEM subfield – analysis of a large scientific society and its annual conferences", J Am Soc Mass Spectrom, 28, 2523 (2017).*

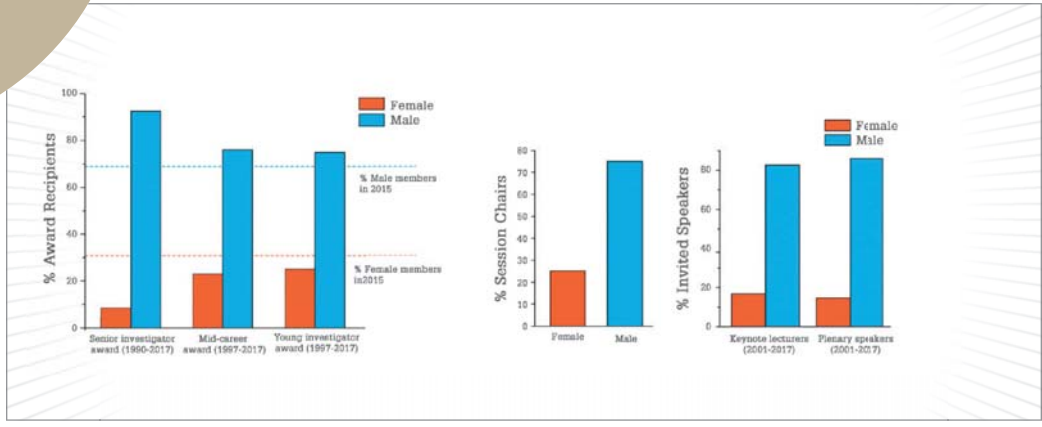

Figure 1. Male and female award recipients, session chairs and plenary speakers.

Materials Science and Mobile Labs

Business in brief: what's going on in analytical science this month?

Products and launches

- Shimadzu has released the C2MAP™-2000, an automated pretreatment module for cell culture media analysis for use with the company's ultrafast LC-MS/MS.
- February saw the introduction of a new MS-based host cell protein detection service from BioPharmaSpec.
- SCIEX has launched the OptiFlow Quant Solution for sensitive biomolecule quantitation.

Collaborations and acquisitions

- Milton Lee, Professor of Chemistry at Brigham Young University, has co-founded Axcend, "a company dedicated to revolutionizing the liquid chromatography marketplace," where he will serve as Chief Science Officer.
- The University of California, Davis, has signed a licensing agreement with SensIT Ventures Inc for an ion mobility mass spec able to identify a broad range of chemicals in environmental samples.
- SEAL Analytical has acquired Dutch lab automation manufacturer, Rohasys BV. Both companies target food and environmental testing markets.

Company updates

- DowDuPont is splitting off into three firms: Dow, DuPont and Corteva Agriscience. Dow will cover materials science, and DuPont will incorporate biosciences and electronic materials.
- Eurofins Scientific continues its spate of acquisitions with City Analysts, a microbiological testing company providing mobile lab services across Ireland.

For links to original press releases, visit the online version of this article at: tas.txp.to/0318/BUSINESS

Raising a Red Flag

How speed is the name of the game, when it comes to beating cheats

University of Waterloo researchers are using coated blade spray for doping analysis, shaving considerable time off the current personal best. German Augusto Gómez-Ríos, postdoc at the Pawliszyn Research Group, tells us more.

How have you managed to speed up doping analysis?

Currently, most methods rely on liquid chromatography (LC) and tandem MS/high-resolution MS. We used a SPME-based technique called coated blade spray to extract the small molecules, enrich them, and then electrospray directly into the mass spec, avoiding the chromatographic step altogether. We also decided to push the limits of the mass spec itself; six months ago, if I wanted to analyze 200 compounds, I needed to electrospray for two minutes (which is still faster than any LC-MS method) but now I can do it at least 10 times faster without dramatically sacrificing the sensitivity.

What are the other advantages of this method?

With our method, you could do the screening of small molecules right in front of the athletes – reducing the opportunity for "modification." For most of the compounds we have tested, we can do an analysis in around 55 seconds per sample, as long as the analysis is performed in high throughput (96 samples per run). We're now looking to work with a company to create fully automatized protocols – without the human factor, we could probably go even faster (less than 15 seconds per sample).

Could this replace conventional analysis?

We're not claiming that our method is a full confirmatory test by any means, or trying to replace what exists. There will sometimes be cases where you have isobars or isomers that have similar fragmentation patterns. In that case, we have to go for differential mobility – ion mobility with tandem MS or high-resolution MS. Our job is to say: "This sample needs a full LC-MS analysis because, potentially, X molecule is present." We are there to raise a red flag, not to accuse anyone.

Do you anticipate any challenges with this method?

It's critical to note that what we have tested so far is mostly targeted – and the challenge is with the drugs that we don't know. Dopers are always ahead of us. We are now trying to see how our technology could be applied to these unknown compounds; for instance, by using this technology together with high-resolution mass spectrometry. Although blade spray is not the most sensitive SPME-MS method, it delivers adequate sensitivity for the tested applications. Besides, its virtue lies in its speed and capability of performing multiple mass spectrometry events from a single device. After all, if you need to detect 1ppb of a given substance, why aim for a sensitivity of 1ppt?

Could this be applied in other fields?

We are developing a method for screening and quantifying pesticides in food matrices, and one of my colleagues already used it for pharmaceuticals in wastewater (1). Our group's main focus is diagnosis, and we published a paper last year on measuring levels of immunosuppressants in whole blood using blade spray (2). It was a great proof of concept, but we still need to show its robustness. Currently, we are collaborating with Vathany Kulasingam at the University Health Network, Toronto, towards the implementation of blade spray in a clinical setting.

Read more about coated blade spray at tas.txp.to/1117/blade

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1. JJ Poole et al., "Rapid and concomitant analysis of pharmaceuticals in treated wastewater by coated blade spray mass spectrometry", Environ Sci Technol, 51, 12566–12572 (2017).

2. GA Gómez-Ríos et al., "Rapid determination of immunosuppressive drug concentrations in whole blood by coated blade spray–tandem mass spectrometry (CBS-MS/MS)", Anal Chim Acta, 999, 69–75 (2017).

Bright and Early

SciX springs across the pond to focus on early career researchers

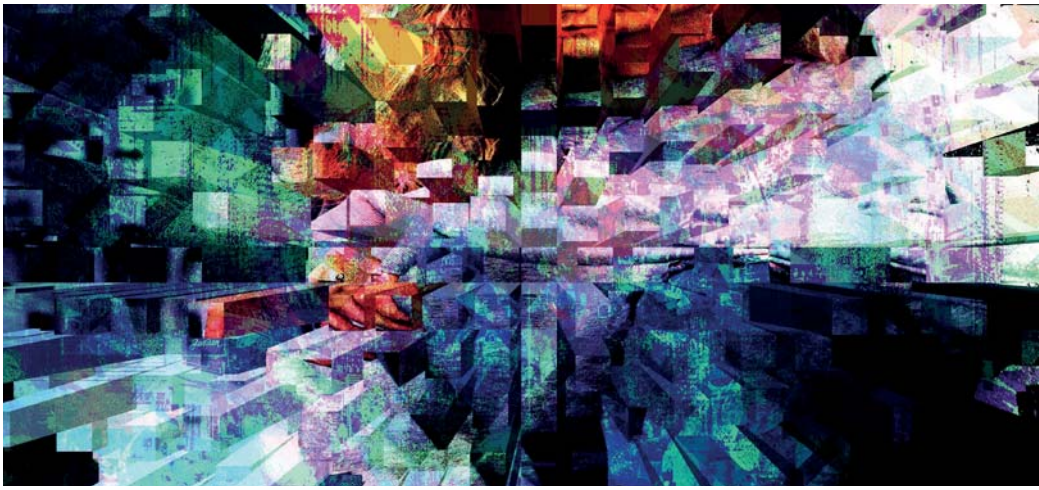
April sees the launch of Spring SciX in Glasgow, UK, a four-day conference building on the success of the established US-based SciX series. Session topics include molecular spectroscopy, biomedical and bioanalytical science and infrared Raman, and provide early career researchers with the opportunity to present their research and vision for the analytical sciences. Kicking off with a plenary speech by 'food fighter' Chris Elliott (Queen's University Belfast), session chairs include Glen Jackson (West Virginia University), Karen Faulds (Strathclyde University) and Sophie Bailes (AstraZeneca).

Duncan Graham, part of the organizing committee, says the idea has been brewing for some time: "Mike George (University of Nottingham) and I had spoken separately to various people at SciX about a possible UK meeting. We had a shared vision and when Mike got the governing board of FACSS (the organization behind SciX) to support the new conference, we decided to make it a reality."

The committee believes that it is important to support scientists in the early stages of their careers. "The parent meeting in North America is large and an excellent conference but we felt there was an opportunity for FACSS to support a meeting focused on early career researchers," says Graham. "Whether in academia or industry, these researchers are the future of science. We want to provide an opportunity for them to contribute to the knowledge base, and to start building networks that will last a lifetime."

Over 200 visitors are expected at this inaugural meeting, and delegates will enjoy a welcome reception hosted by the City of Glasgow Council in the city chambers, an evening poster session, a gala dinner and constant networking opportunities in the exhibition space.

Spring SciX will be held April 17–20 at the Technology and Innovation Centre, University of Strathclyde, Glasgow, Scotland: springscix.org



Pixel Perfect

A spatial gene expression technique for improved tissue sample analysis

Existing gene expression analysis tools, though accurate, are slow and cumbersome to use. Is this trade-off really necessary? Not according to a multidisciplinary group of researchers who incorporated the best of both worlds into a technique that performs on-chip tissue analysis in under two hours: pixelated RT-LAMP (reverse transcriptase loop mediated isothermal amplification).

To find out more, we spoke to Anurup Ganguli, first author of the resulting publication (1) and research assistant at the University of Illinois at Urbana-Champaign, USA.

Why investigate gene expression analysis?

Gene expression analysis has many applications, such as revealing the molecular basis for developmental processes in organisms or helping us to understand the role of differential gene expression in normal and disease conditions. For tissue samples, the spatial localization of gene expression can unravel important insights into tissue heterogeneity, functionality, and pathological transformations – but the ability to maintain this spatial information remains an enduring challenge in tissue sections routinely used for pathology. This very challenge prompted us to develop a simple, rapid, quantitative technique to analyze the spatial distribution of nucleic acid targets across a tissue section.

What does your technique entail?

Our pixelated RT-LAMP approach uses parallel on-chip nucleic acid amplification reactions to provide the distribution of target sequences directly from tissue, without the need for analyte isolation or purification. We do this on a fingernail-sized chip with an array containing more than 5,000 picoliter-volume wells.

We anticipate that this technique, with its ease of use, fast turnaround, and quantitative molecular outputs, will become an invaluable tissue analysis tool for researchers and clinicians in the biomedical arena.

What were the greatest challenges?

The biggest hurdles were automating the tissue microdissection to cut the tissue into 100-micron pixels while preserving the spatial location of each pixel – a process we call "tissue pixelation," loading more than 5,000 wells with 175 picoliters of amplification reagents, and optimizing the protocol to make the RT-LAMP amplification reactions happen in the presence of the tissue debris. In other words, it was all challenging!

What does the future hold?

We hope to use our technique to map genetic mutations in lung, breast, and prostate cancers. We will also work to reduce the size of the wells on the chip below the current 100 microns, which would allow us to examine individual cells at a higher resolution.

With the reactions and biosensing now occurring in picoliter and even lower scales, portability comes as an inherent advantage. However, the true advantage of our technique is the ability to look at the nucleic acid composition of a large region of tissue with high spatial resolution – something no other existing technique can do.

Reference

1. *A Ganguli et al., "Pixelated spatial gene expression analysis from tissue", Nat Commun, 9, (2018).*

Think Fast, Screen Faster

Ten thousand reactions per hour – or else? No problem!

Combinatorial chemistry and other procedures have produced large libraries of chemical compounds – the (re)activity of which need to be assessed. High throughput screening (HTS) is already an important component of the drug discovery toolbox, but could it be improved? R. Graham Cooks, Henry B. Hass Distinguished Professor of Analytical Chemistry at Purdue University, Indiana, USA, certainly thinks so.

Cooks' team has developed an even faster HTS process by coupling desorption electrospray ionization mass spectrometry (DESI-MS) with robotic sampling technologies. "We started with the observation that ordinary organic reactions, carried out in small droplets, are accelerated over bulk rates by several orders of magnitude, depending (inversely) on the size of the droplets – and this is now a well-established phenomenon," explains Cooks.

"When we received funding in 2016 from the US Defense Advanced Research Projects Agency, we set out not merely to perform high throughput screening but to react and screen at high speed." The team ended up using very small amounts of reaction solution in spots separated by about 1 mm on Teflon plates the size of a standard microtiter plate but without the wells, resulting in 6,144 discrete samples rather than 96 or 386. "We found that we could run this set of reactions in about one and a half hours, or at a rate a little over 1 second per spot. We made this our aim when our project manager said – although not in so many words – that she wanted 10,000 reactions per hour, or else!

The fastest current (non-optical) screening methods take about 8 seconds per sample; if Cooks' technique proves to be robust and reliable, it would reduce analysis time for 100,000 reactions from more than a week down to a day.

Now, the team has its sights set on extending the method to bioactivity screening, and also aims to use the approach to improve the design and production of new synthetic molecules.

Reference

1. *M Wleklinski et al., "High throughput reaction screening using desorption electrospray ionization mass spectrometry", Chem Sci, 9, 1647–1652 (2018).*

In My View

In this opinion section, experts from across the world share a single strongly-held view or key idea.

Submissions are welcome. Articles should be short, focused, personal and passionate, and may deal with any aspect of analytical science. They can be up to 600 words in length and written in the first person.

Contact the editors at charlotte.barker @texerepublishing.com

The Road to HPLC 2018 Part V: Emerging Environmental Contaminants

In the run up to HPLC2018, we examine how environmental researchers are reaping the benefits of analytical advances.

By Susan D. Richardson, Arthur Sease Williams Professor of Chemistry, Department of Chemistry and Biochemistry, University of South Carolina, USA; and Xing-Fang Li, Professor of Analytical and Environmental Toxicology, Department of Laboratory Medicine and Pathology, University of Alberta, Canada.

Emerging environmental contaminants will feature prominently at the upcoming HPLC 2018 conference, with presentations highlighting the latest advances in analysis of contaminants, such as per- and polyfluoroalkyl substances (PFASs), nanomaterials, microplastics, artificial sweeteners, 1,4-dioxane, pharmaceuticals, hormones, disinfection by-products (DBPs), sunscreens/UV filters, flame retardants, benzotriazoles, naphthenic acids, algal toxins, ionic liquids, and halomethane sulfonic acids. These contaminants are now frequently found in environmental and recreational waters, as well as in air, soil, sediment, and biota, including human blood (1). The fate of contaminants in the environment is a hot topic because many are transported globally and can transform into chemicals with altered toxicity.

The development of sensitive analytical tools is key for identification and measurement of trace contaminants because environmental samples are inherently complex mixtures. High resolution (HR)-mass spectrometry (MS) is currently the most popular tool for non-target environmental analysis, with quantification limits now commonly at sub- to low-ng/L levels. Mass spectrometer developers continue to improve instrument resolution, with time-of-flight (TOF), Orbitrap, and quadrupole-(Q)-TOF mass spectrometers ranging from 30,000 to >100,000 resolution, a necessity for the determination of molecular formulas for unknown chemicals.

Innovations in chromatography continue to aid analysis, with high performance liquid chromatography (HPLC) and ultra-performance liquid chromatography (UPLC)-MS now commonplace for analyzing emerging contaminants, many of which are highly polar or have a high molecular weight, while gas chromatography (GC) and GC×GC are often used for volatile and semi-volatile contaminants. Innovations in recent years include the coupling of multiple LC and GC columns of different phases to improve separations of complex environmental mixtures. The coupling of C18 and hydrophilic interaction liquid chromatography (HILIC) columns with MS can allow the detection of significantly more compounds than a traditional single HPLC-MS/MS approach. For example, a recent study highlights the identification of more than 600 peptides in drinking water (2).

Ion mobility-MS is also beginning to play an important role in environmental separations. An addition to classical chromatographic separations, ion mobility-MS offers another degree of separation by measuring differences in the cross-sections of molecules, a property

of their three-dimensional shape. Recent applications of ion mobility-MS with HPLC-MS and UPLC-MS include the identification of artificial sweetener transformation products and naphthenic acid ozonation products.

The development of new workflows, software, and library databases is a popular trend to tackle difficult analyses of hundreds or thousands of contaminants in environmental samples. These tools help automate and streamline the identification of compounds, enabling feature detection and tentative identifications in minutes. Though electron ionization (EI)-MS libraries have been widely available for years, electrospray ionization (ESI)-MS(/MS) libraries have yet to be organized for wide application. Fortunately, two commercial MS/MS libraries are now available – NIST and Wiley – which contain >15,000 and >1,200 compounds, respectively. And many open or semi-open MS databases, including the Human Metabolome Database (HMDB), Metlin, mzCloud, and MassBank, are also available. New workflow tools include Metfrag (a metabolomics MS/MS fragmentation predictor), CFM-ID, which predicts MS/MS spectra, and CFM-EI, which can predict EI mass spectra.

Finally, a tool called precursor ion exclusion (PIE) enables the automated detection and identification of low-abundance compounds in HPLC-MS/MS analyses of complex environmental mixtures (because low-abundance compounds are often the most interesting!). This technique overcomes a weakness of data dependent acquisition (DDA) by performing a second MS/MS scan that excludes the high-abundance ions identified in the initial scan. Thus, PIE focuses on lower-abundance ions, which would often be missed in a traditional HPLC-MS/MS analysis.

This is just a snapshot of the exciting innovations happening in the world of emerging contaminants – join us at HPLC 2018 for more from the cutting edge of environmental research.

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Human Biomonitoring Requires Validation

Though human biomonitoring can be an important tool in risk assessment for food and feed safety, suitable biomarkers need to be valid from both analytical and physiological perspectives.

By Hans Verhagen (pictured), Caroline Merten, Arianna Chiusolo, Davide Arcella, and Marco Binaglia, European Food Safety Authority (EFSA), Parma, Italy.

Food safety is at the heart of all: consumers, policy makers, food producers, scientists, and so on. EU Regulation 178/2002 (1) lays down the 'general principles and requirements of food law, establishing the European Food Safety Authority (EFSA) and the procedures in matters of food safety'. Hence EFSA, based in Parma, Italy, is an integral part of the EU's food safety system. EFSA's mission is to contribute to the safety of the EU food chain by providing scientific advice to risk managers, by communicating risks to the public, and by cooperating with Member States and other parties to deliver a coherent, trusted food safety system in the EU (2). EFSA's core responsibilities are the delivery and communication of advice on general scientific assessment priorities, and the evaluation of food and feed products that require a safety assessment before they can be used in the EU market.

EFSA conducts risk assessments using the four steps of the risk assessment paradigm: hazard identification, hazard characterization, exposure assessment and risk characterization. When considering exposure assessment, dietary exposure is most frequently estimated by combining information on the levels in food of a given substances – such as a contaminant, pesticide, a food additive, or micronutrient – with food consumption data from national dietary surveys. A more precise quantification of exposure that is closer to the ultimate health effect can be achieved by using information from human biomonitoring. In particular, biomarkers can be used to estimate internal levels of exposure, which is particularly relevant when we need to assess combined exposure from different routes and sources.

Notably, human biomonitoring can be done on all compounds that are present in foods, either naturally occurring or added, or present as contaminants.

Human biomonitoring is a promising tool to inform risk assessment for human health; for example see recent reflections in the USA (3). EFSA is closely following developments in human biomonitoring, such as the HBM4EU project – a joint effort involving 26 countries, the European

Environment Agency and the EC (4) and the EU Joint Programming Initiative on biomarkers (5).

To date, human biomonitoring data have been used only to a small extent in EFSA. Human biomonitoring for food safety purposes has already been used to inform EFSA risk assessments; for example, bisphenol A (6), cadmium (7), lead (8), methylmercury (9) and the mycotoxin deoxynivalenol (10). For pesticides, EFSA recently commissioned a 'Review of human biomonitoring and its application to exposure assessment for food safety' (11) and a project on 'Human biomonitoring data collection from occupational exposure to pesticides' (12). In addition, a recently published scientific opinion on epidemiology expressly indicated human biomonitoring as a tool to improve the characterization of exposure and therefore contribute to a better use of epidemiological studies in risk assessment of pesticides (13).

We believe that measuring a biomarker in human blood, urine or hair requires a prudent and well thought-out approach. Any biomarker requires validation, as well as standardization and harmonization (14). Analytical validation should follow recommendations such as those under the 17025/2017 (15) or equivalent system, which contribute to the reliability of the results being produced. Physiological validation should follow the scientific justification of the biomarker measured and its response to changes in exposure or effect, such as those used for the scrutiny of scientific substantiation of health claims (16,17).

Next steps for greater application of human biomonitoring into risk assessment for EFSA:

- Human biomonitoring data can be used to "validate" dietary exposure estimates and also to detect health effects;
- Human biomonitoring data are particularly important in exposure assessment and could play an important role in post-market monitoring;
- Human biomonitoring data need to be combined with other data and tools for interpretation in risk assessment, such as information on dietary intake (e.g. from food frequency questionnaires, 24h dietary recall methods);
- Access to individual human biomonitoring data is needed, which requires a data format compatible with EFSA's format for chemical concentration and intake data.

Just measuring substances in blood or urine is a clear waste of energy and resources – and scientifically wrong. The challenge is to measure the right biomarker, in the right place, at the right moment, with validated analytical methods. This brings the scientific areas of analytical chemistry in close proximity to physiology, nutrition and toxicology.

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In Good Company

We speak with KNAUER's owner and CEO Alexandra Knauer in Berlin to find out how a strong focus on corporate social responsibility is good for the company – and great for the soul.

How do you define Corporate Social Responsibility (CSR)?

I know what it is not. It is not a marketing tool – or a trend. To me, CSR doesn't necessarily mean huge, expensive initiatives. We have certainly invested significantly in CSR, but sometimes the simplest actions can have a big impact. We believe CSR should run through every aspect of the business – from designing instruments that use more eco-friendly materials to organizing an annual fun run in the community.

"Responsibility" is the crucial word – putting not just yourself or your profits at the heart of your decision-making, but your employees, your community and your environment. There is so much we can do as companies and as individuals to make things better for everyone – and I believe we all have a responsibility to seize that opportunity. Of course, the 135 people who make up KNAUER cannot save the world single-handedly, but we do what we can.

KNAUER won Germany's "Leading Employer" Award in February 2018 – how did that feel?

It's great to be seen and recognized as a good employer because it helps us to attract the best talents. People these days don't just base their career decisions on salary – they want to know that there is a positive company culture and programs to support staff, such as family-friendly working. Our goal is to make KNAUER such a great place to work that it is difficult for our employees to leave us!

Employees clearly love the company's focus on CSR – what about customers?

Our experience is that our commitment to CSR helps people to remember KNAUER, and to see the company in a positive light. When customers come to visit us, they often tell me how struck they are by the positive atmosphere. Quality and cost of our HPLC instruments and osmometers are, of course, primary factors when making purchasing decisions, but companies also like to work with partners who share the same values; it's the "feel good factor".

What are some of your personal CSR highlights?

A few of our initiatives stand out for me. Business bicycles is a scheme that allows our staff to get a good quality bicycle at a low price. The staff loves it, and it encourages commuting by bicycle instead of car, so it's good for the environment too.

As part of our "Bye Bye Plastic" initiative, we set out to reduce the number of single-use plastic bottles in our headquarters. We worked out that if half of our employees bought a plastic bottle every day, it adds up to around 30,000 bottles every year. Many employees were buying bottles of sparkling water (very popular in Germany), so we have installed a sparkling water machine and provide reusable glass bottles.

Our Kids' Explorer Club is a fun way for us to get involved in the community, and to share our enthusiasm for science with kids. We have dedicated a room at KNAUER HQ as a laboratory for school children (age 10-12), where they carry out fun experiments with our educational HPLC system to learn about how scientists test rivers for pollution or determine caffeine in cola drinks.

KNAUER hosted last year's Humanity in Science Award – why?

Last October, we celebrated our 55th company anniversary. Our long-lasting success in the field of analytical instrumentation makes us both proud and grateful, and to celebrate we wanted to give back to the scientific community. This great award was the perfect opportunity for us to show how much we value the amazing work carried out by scientists around the world for the sake of humanity, and Richard Jähnke was a deserving winner.

Does being a family-owned company give KNAUER a different outlook on CSR?

I believe so. As the owner, I have the freedom to decide which strategy we pursue, and the importance we place on CSR. Of course, it's important for everyone here that we are a successful business and make healthy profits, but I also want our company to be a good place to work as I mentioned earlier – after all, a strong team is critical for business success.

I think it's easier for a family company to look at the long-term – I feel a responsibility to future generations. The nature of CSR is that you are never "done". There are always areas where you can improve, and compromises you must make.

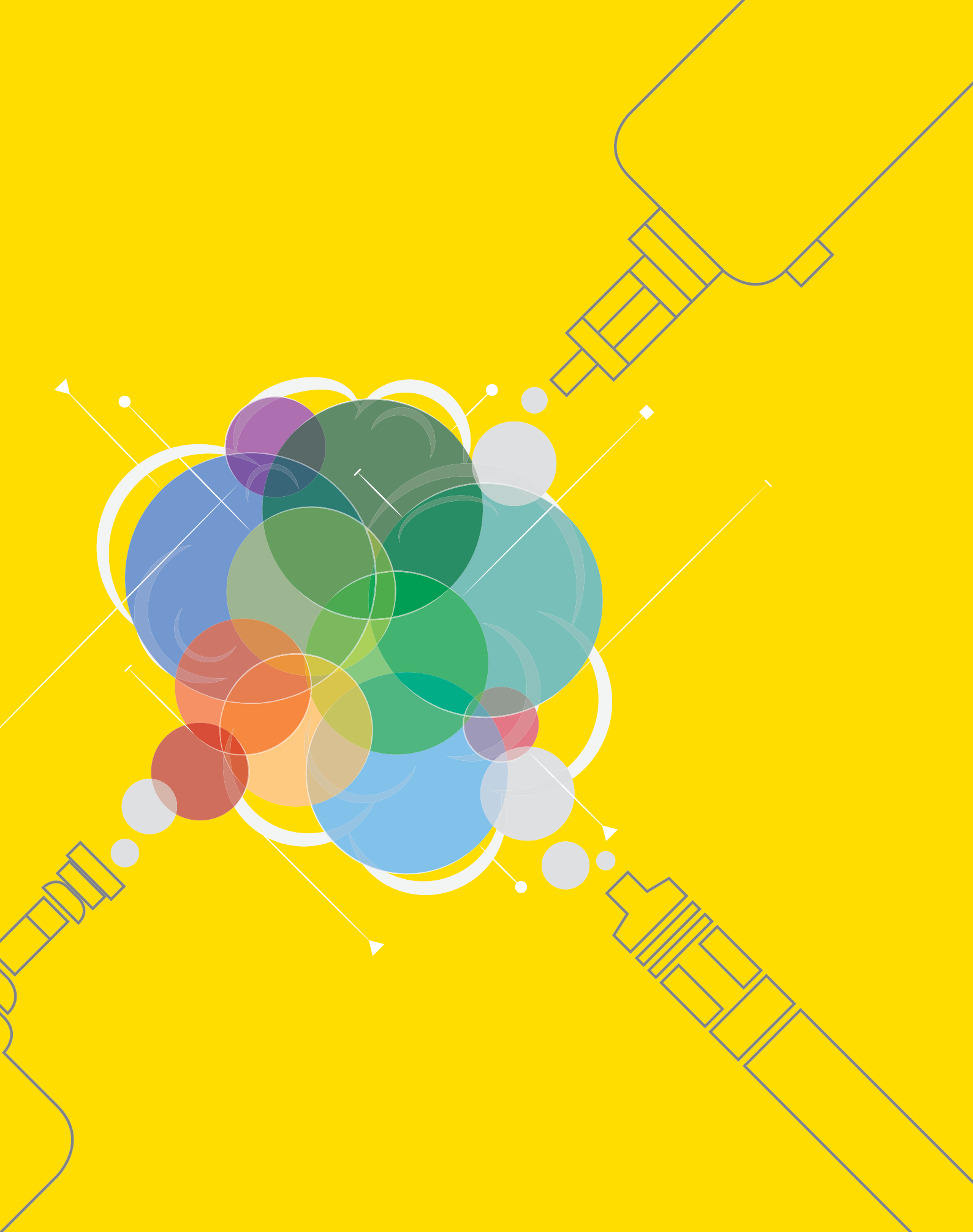
What's next?

We are proud to have recently joined the United National Global Compact movement – the world's largest and most important initiative for responsible corporate governance, which involves more than 12,800 companies and organizations. By joining the scheme, we are pooling our efforts with other companies across the world who share the goal of making business a force for good. We look forward to taking an active role in the Compact and sharing ideas for new initiatives.

The Cloud Chasers

Whether it's the now-ubiquitous e-cigarette or emerging heated tobacco products, the market for electronic nicotine delivery systems is booming. Most scientists agree that vaping is less harmful than smoking tobacco – but with limited regulation in place, how much do we know about what's in the cloud? We meet the scientists tasked with exploring the chemical composition of these complex aerosols.

By Charlotte Barker



Analyzing Uncertainty

Hugo Destaillats is a Staff Scientist at Lawrence Berkeley National Laboratory (LBNL) Indoor Environment Group (USA), where he studies multiple aspects of indoor air quality. The group has studied tobacco smoke for many years, and as the e-cigarette market started to expand in the early 2010s, they turned their attention to the composition of vapor. The uncertainty around the effects of vaping intrigued Destaillats: "Today, everyone agrees that smoking is harmful. With vaping, the evidence is much less clear cut, with scientists and health agencies still debating the health impacts," he says.

Instrumental in the team's e-cigarette research was Mohamad Sleiman, now an assistant professor at SIGMA Clermont (France), who has an interest in developing analytical methods for environmental applications.

What's in the cloud?

"We decided to study the chemical composition of vapor, to predict how it might impact on the user and those around them," says Sleiman. The team were particularly interested in following up on previous reports of potentially toxic aldehydes found in vapor, and wanted to discover how these compounds were formed. They looked at three e-liquids and two devices to see how the technology used would impact on the composition and emission of inhaled and exhaled vapor.

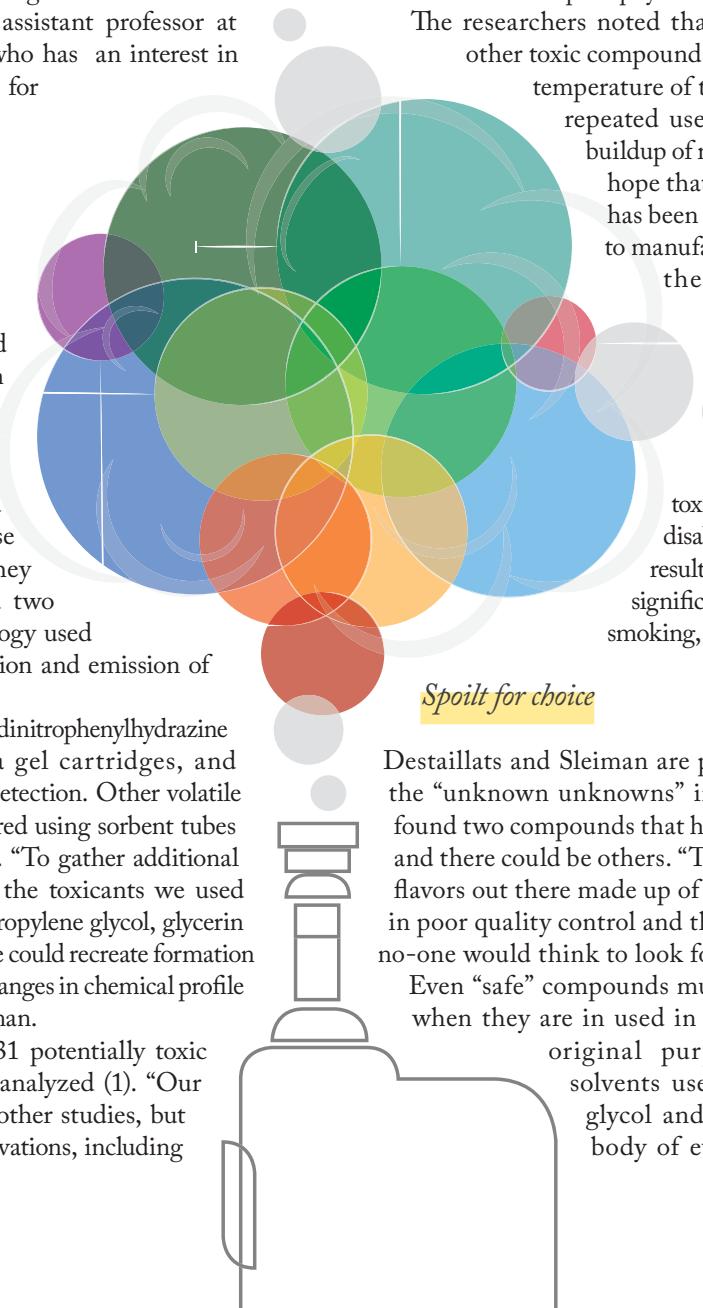
The aldehydes were captured by dinitrophenylhydrazine (DNPH)-impregnated silica gel cartridges, and analyzed by HPLC with UV detection. Other volatile organic compounds were captured using sorbent tubes and analyzed by TD-GC/MS. "To gather additional information on the source of the toxicants we used headspace GC-MS – heating propylene glycol, glycerin and complete e-liquid to see if we could recreate formation of specific toxicants, and track changes in chemical profile with increasing heat," says Sleiman.

The team found a total of 31 potentially toxic substances in the vapors they analyzed (1). "Our findings were consistent with other studies, but we made some additional observations, including two toxicants (one in vapor and one in liquid) that hadn't been previously detected," says Destaillats.

"One novel finding was that propylene glycol and glycerin in e-liquids can undergo thermal decomposition under certain conditions to produce the aldehyde acrolein – a powerful irritant," adds Sleiman. Acrolein can occur at relatively high levels, depending on how the e-cigarette is used, adds Destaillats. High levels of aldehydes are sometimes attributed to unpleasant-tasting "dry puffs", where the liquid burns rather than turning to vapor. But the researchers found that acrolein was also present under conditions mimicking routine use. Detecting aldehydes was a special challenge, says Sleiman "Acrolein is very reactive and easily oxidized, so samples had to be dealt with promptly to avoid degradation."

The researchers noted that emissions of acrolein and other toxic compounds increased as the voltage and temperature of the e-cigarette rose, and with repeated use – presumably a result of a buildup of residue within the device. "We hope that one outcome of our research has been to provide useful information to manufacturers to help them improve the safety of their devices," says Destaillats.

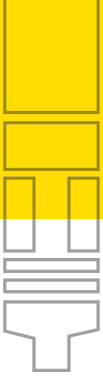
In a follow up analysis, the group carried out a simple health impact assessment for the toxicants they found in vapor, using disability-adjusted life years (2). The results suggested that while vaping is significantly less harmful than tobacco smoking, it isn't without risks.



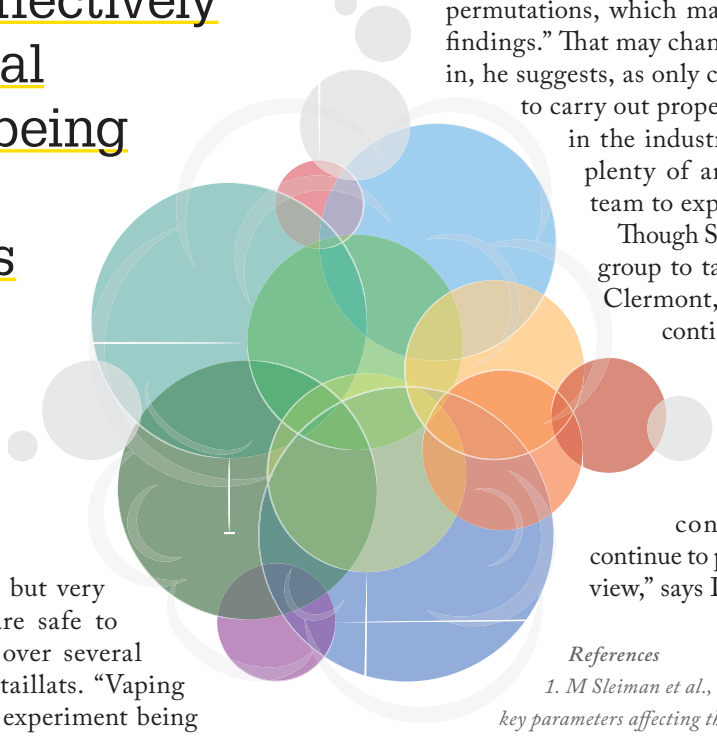
Spoilt for choice

Destaillats and Sleiman are particularly concerned about the "unknown unknowns" in vapor. In their study they found two compounds that hadn't been identified before – and there could be others. "There are hundreds of e-liquid flavors out there made up of a variety of compounds; add in poor quality control and there could be impurities that no-one would think to look for," says Sleiman.

Even "safe" compounds must be regarded with caution when they are in used in ways very different to their original purpose. "For example, the solvents used in vaping are propylene glycol and glycerin – there is a large body of evidence to show that these



> "Vaping is effectively a toxicological experiment being carried out with millions of people around the world."



compounds are safe to eat, but very little to prove that they are safe to inhale in large quantities over several years or decades," says Destaillats. "Vaping is effectively a toxicological experiment being carried out with millions of people around the world – there may be no serious health impacts, but there may be risks that are only revealed with time."

The e-cigarette market and associated technology is evolving rapidly, says Sleiman. "Two conventional cigarettes of the same brand will be virtually identical, but e-cigarettes and e-liquids come in countless permutations, which makes it difficult to generalize findings." That may change as more regulation comes in, he suggests, as only companies with the resources to carry out proper quality control will remain in the industry. Either way, there will be plenty of analytical challenges for the team to explore in the years to come.

Though Sleiman has now left the LBNL group to take up a position at SIGMA Clermont, France, he and Destaillats continue to collaborate on research into vaping and other environmental applications. "As long as electronic nicotine delivery systems (ENDS) continue to evolve, we will continue to provide an unbiased analytical view," says Destaillats.

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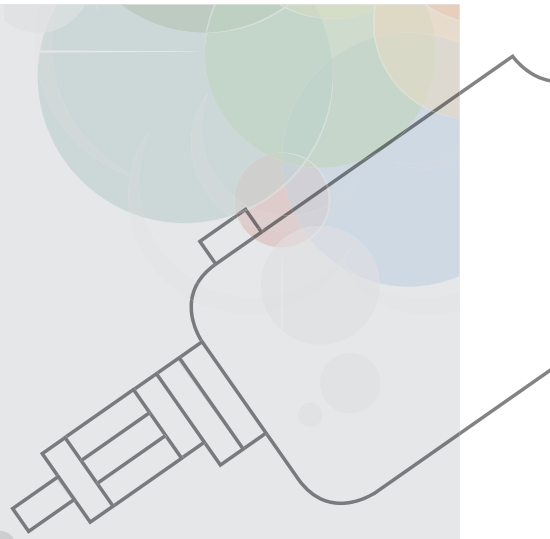
E-Cigarettes Versus Heat-Not-Burn

E-cigarettes heat e-liquid (usually containing nicotine, flavorings and humectants) to vaporize it, before it condenses into a droplet cloud with a similar particle size distribution as cigarette smoke. E-cigarettes are produced by myriad manufacturers and with hundreds of flavors of e-liquid to choose from.

In *heat-not-burn* products, cigarette-like sticks of tobacco and humectants are heated to around 240 degrees Celsius (conventional cigarettes can reach 950 degrees Celsius), releasing nicotine and volatile flavor compounds. These devices are made by tobacco companies, and are currently only available in selected countries.



Industry Insights

Chris Wright, Head of Analytical Science at British American Tobacco (BAT) Group R&D (UK), has worked in analytical chemistry for over 30 years. Starting as a government scientist measuring dioxins in food and human tissues, he later spent 10 years at Unilever, helping to ensure the safety of the company's food and cosmetic lines. Looking for a different analytical challenge, he joined BAT in 2008, despite raised eyebrows from some of his colleagues. "There were people who I had worked with for years who reacted angrily to the move. We all know that the tobacco industry has a checkered history when it comes to ethics and transparency, and I wasn't blind to that. But I saw changes happening in the industry, not least a move away from conventional cigarettes and towards less harmful alternatives," says Wright.

His misgivings were lessened when he met the R&D team at BAT and found them very frank about the dangers of tobacco smoking. "I heard countless statistics about the impact of smoking on health and mortality – there was no shying away from the inherent toxicity of tobacco," he says.

When Wright joined BAT, he says the analytical testing in the industry was still relatively low-tech, lagging behind the prevailing standards in food and environmental analysis. So he spent three years with a small team working to improve the robustness of tobacco and cigarette smoke analysis, before being presented with a new challenge: how to characterize complex aerosols from novel ENDS. "I had always been interested in non-targeted screening of foods, including working with the International Life Sciences Institute on the application of the 'Threshold of Toxicological Concern' concept to food chemical residues. Suddenly, I had an opportunity to do something similar in a new field, with a potentially significant impact on public health," he says.

Attack of the vapors

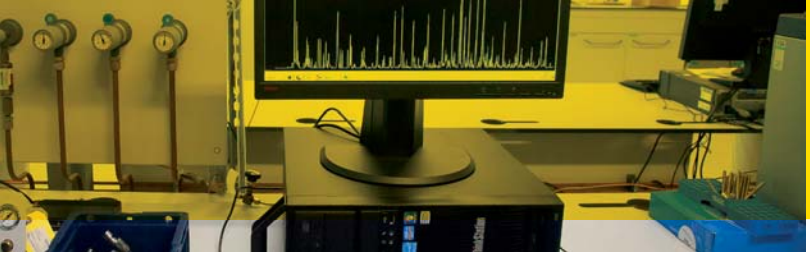
Now, Wright guides R&D on technical standards, selection of analytical techniques, strategic direction for analytical science and investment in analytical technologies. He also works closely with the company's toxicologists to ensure that the department provides robust data for product assessments.

Analyzing aerosols from e-cigarettes or heated tobacco products poses significant challenges for both chemical and biological analyses. The analytical team seeks to answer questions from 'How does this work?' through to 'What substances are formed when…?' to 'How safe is this?'. But, says Wright, "The biggest question facing the team right now is 'How many substances can we detect and identify simultaneously in aerosols?'"

> "I saw changes happening in the industry, not least a move away from conventional cigarettes and towards less harmful alternatives."

E-cigarette vapor is typically analyzed by GC but Wright's team are now introducing HPLC-based techniques. "When we started out, the assumption was that all e-cigarette aerosols were vapor, which would be most easily analyzed by GC. Subsequently, we found that 90–95 percent of an e-cigarette aerosol can be collected on a glass filter pad milliseconds after it is formed – in other words, it condenses very quickly." A few years ago the team acquired two Bruker maXis high-resolution LC-TOF instruments, which are proving a welcome addition to confirm results obtained by GC.

"We are also exploring real-time analytical tools, such as SIFT-MS (Syft), which allow instant monitoring of substances in aerosols



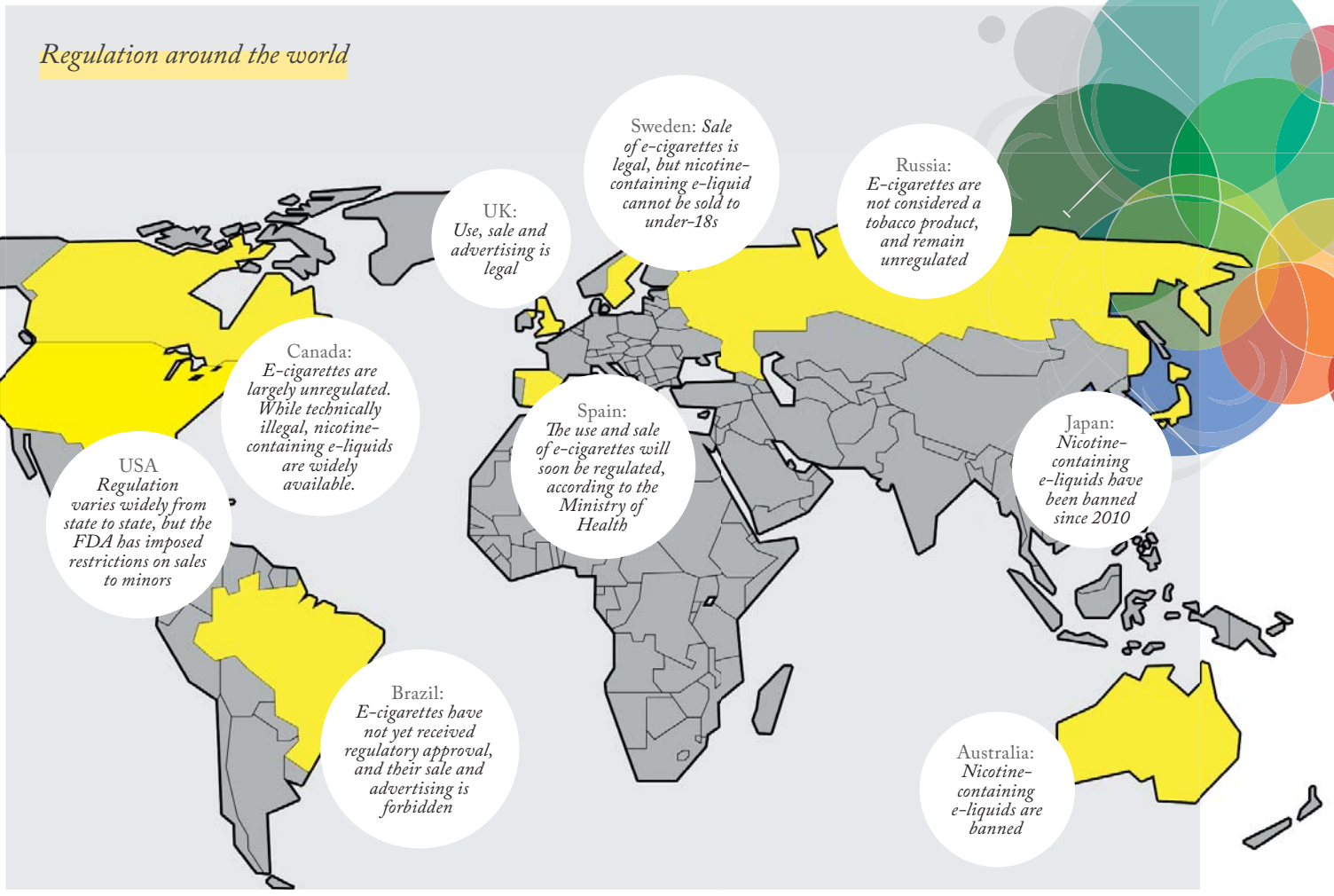
and potentially rapid or at-line chemical characterization," says Wright. Real-time analysis would benefit the product development team in particular, giving them immediate information to make go/no go decisions during early-stage design.

On the biological side, some of the in vitro assays used in toxicology have proved difficult to apply to vaping. "The humectants used in e-cigarettes (such as propylene glycol) absorb water very well, so when added to an in vitro system, they cause dehydration and shock – obscuring some of the toxicology," he explains. "That's one reason why much of research so far has focused on chemical rather than biological screening, but I hope to see more sophisticated biological endpoint testing being applied to e-cigarettes soon."

Another dimension

An ongoing collaboration with Jef Focant at the University of Liege, Belgium has brought multidimensional GC analysis into the company's analytical armory. "I first met Jef over 20 years ago, when we were both working on dioxins. Jef went on to specialize in the emerging area of GC×GC – the only technique we thought would have the chromatographic peak capacity to separate aerosols as complex as cigarette smoke or e-cigarette vapor," says Wright.

Initially, the project was about feasibility, and concentrated on conventional cigarettes. "There had been a few publications from other tobacco companies,



showing some great separations but lots of problems with overloading and dynamic range," says Wright. It's a tall order to catalog every compound in cigarette smoke, not least because of the sheer volume of data generated. So the team focused on data crunching tools that detect differences, rather than analyzing every component. "We made small changes – for example, changing the adsorbents in the cigarette filter – and looked for changes in the smoke chemical profile, which allowed us look at cause and effect on a chemical level, in bite-sized chunks," says Wright. "Our collaboration has generated some very insightful and visually striking data to distinguish even small differences in very complex aerosol samples" (1-4).

Big in Japan

BAT's e-cigarette platform is relatively stable in terms of products and acquisitions, so these days analytical activities focus on managing future commercial and regulatory pressures. Currently, the team spends most of its time on the company's tobacco heating (also known as heat-not-burn) products: Glo. "These products are proving to be a huge commercial success, and it's important that we ensure that they are as safe as they possibly can be," says Wright. The products have proved especially popular in markets like Japan, where nicotine-containing e-liquids are restricted, and where cultural values of discretion and consideration for others make ENDS appealing.

"In a conventional cigarette you get combustion and a lot of pyrolysis, whereas heated products induce something akin to torrefaction of the material, releasing only the more volatile compounds as an aerosol," says Wright. Those volatile components include nicotine and various flavor compounds, but largely exclude the combustion products that are major contributors to the toxicity of conventional cigarettes.

The vapers of the future

Currently, although EU law mandates data reporting, there is no common standard for ENDS and Wright believes there may be products on the market that carry a risk of unexpected and avoidable chemical hazards. Though BAT state that they include only compounds that have a known toxicity profile in their e-liquids, that isn't necessarily the norm in what is a largely unregulated business in much of the world. "I would like to see ENDS become more formally regulated, to provide consistency in technical standards, harmonized methods for sample actuation, aerosol generation and physical/chemical testing," Wright says. "This would provide direct assurance to consumers and regulators that the products that will replace cigarettes have been rigorously designed and that their long-term health impacts have been fully evaluated."

To date, the tobacco industry has focused on comparative risk reduction, but Wright believes more can be done to characterize the residual risk. "Just because a substance appears in lower levels in vapor than in smoke doesn't mean it isn't a health risk. Ideally, we need to set threshold levels for each compound, so that we can concentrate our efforts on those compounds that remain above threshold. To do that, we need sensitive analytical instruments and powerful data analysis software."

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The Human Element

Lion Shahab is a psychologist, neuroscientist and epidemiologist, with a focus on tobacco control: "My interest is in the use of biomarkers as a tool to motivate smoking cessation and investigate the effects of tobacco products and products such as e-cigarettes that are thought to mitigate harms."

"Around 2011, people started approaching our group at University College London about e-cigarettes, which were just taking off at the time," says Shahab. Based on his previous biomarker work, he secured funding from Cancer Research UK for a study examining biomarkers related to various negative health outcomes in users of e-cigarettes compared with smokers, and those using nicotine replacement therapy, such as gum and patches (1).

A lack of evidence

Shahab says that previous studies provided only limited evidence about the harms of e-cigarettes, with some focusing on biomarkers that have only a tenuous link with long-term health consequences. "For example, people have looked at changes in the inner lining of blood vessels, and claimed that e-cigarettes cause cardiovascular disease. The problem is, you see similar changes when you drink a cup of coffee," says Shahab. Then there were the usual problems of extrapolating results from in vitro or animal studies into humans – notably, nicotine itself is far more toxic to mice than humans.

It's also important to note that the risk of a product is not determined solely by its inherent properties, but also by how it is used. Water is safe to drink, but a teaspoon in your lungs could kill you,

> "The risk of a product is not determined solely by its inherent properties, but also by how it is used."

says Shahab. "There was a widely reported study showing that there is hidden formaldehyde in e-cigarettes – the flaw was that the machine used to generate vapor from the product was at a setting that created "dry puffing" – something that consumers avoid at all costs due to the acrid taste," Shahab adds (2). Shahab also points to tobacco industry studies in the 1970s showing that adding perforations into the filter lowered toxin levels. In reality, no such benefit materialized, because human smokers covered up the perforations with their fingers and smoked more intensely, in order to get the same nicotine "hit".

As e-cigarettes have become more sophisticated, there is far more variety in how people use them in terms of temperature, choice of e-liquid, and so on, which makes it difficult to estimate how the aerosols will correlate with actual exposure, says Shahab, "For that reason, my preference is always to study humans."

The lesser evil

In the Cancer Research UK-funded study the team focused on a panel of exposure biomarkers reliably linked with long-term

Quantifying the Risks

Ed Stephens, a research fellow at St Andrew's University, UK, spent a decade studying health implications of heavy metals in tobacco. When e-cigarettes became popular, he quickly saw the importance of determining the chemical composition of the vapor – and giving users a straightforward estimate of the risks. In 2017 he published a paper estimating the relative cancer risk of people who vape compared with smokers or users of heat-not-burn products. We caught up with Stephens to find out more about the study, and his work in the field.

What are the challenges in vaping research?
First, there are no internationally accepted analytical protocols or reference standards in place so no two labs do things in quite the same way - it's effectively a free-for-all. In early 2018, the Tobacco Regulatory Science Program at the NIH plans to release a standard device and liquid formulation that should allow labs worldwide to standardize their analyses. Second, we know little about the speciation of metals in vapour, such as their valence state and molecular species, and this can be a key factor in their toxicity.

What inspired your 2017 study?
I saw that there were many papers in the literature analyzing single components of vapor for toxicity, but very few taking a more comprehensive view. I decided to apply a toxicological risk method that has been previously used in tobacco research to aggregate the impact of the carninogens reported in published studies to date. It involves a number of simplifications, but I was able to calculate a relative cancer risk of smoking tobacco or using various alternative nicotine delivery systems. As expected, smoking tobacco carried by far the highest risk, followed by heat-not-burn, then vaping, then nicotine inhalers.

What's next for your research?
I consider the initial estimates a starting point – I'm now working with toxicologists to address some of the simplifications in the model to create a more comprehensive assessment of disease risk, including health outcomes beyond cancer.

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"E-cigarettes are unlikely to be as safe as standard nicotine replacement, but the study suggests that they are much safer than smoking tobacco."

health outcomes, including tobacco-specific nitrosamines and other carbonyls, and a range of volatiles.

Bioanalysis was carried out at the Centers for Disease Control in the US, using LC and GC MS/MS to measure nicotine exposure in saliva and urine, respectively. Carbonyls were measured using LC and atmospheric pressure ionization MS/MS, while volatiles were analyzed with UHPLC coupled with electrospray ionization MS/MS.

All the products performed equally well in terms of providing nicotine - but compared to smokers, users of nicotine replacement therapy or e-cigarettes had greatly reduced levels of harmful biomarkers. "There was a 95 percent reduction in some biomarkers for e-cigarette users versus smokers," says Shahab. "And that implies that they are likely to have better health outcomes in the long term." E-cigarettes are unlikely to be as safe as standard nicotine replacement – inhaling many e-liquid components (including nicotine) into the lungs causes irritation and inflammation – but the study suggests that they are much safer than smoking tobacco.

The unknown

Though Shahab is confident that vaping is less harmful than smoking, the risks are hard to quantify. One problem with tobacco research is that the health effects may take

a long time to materialize. "If you look at the prevalence of smoking rates in the UK and US, you see a peak in smoking prevalence in the 1950s and 1960s, and then a peak in lung cancer deaths around 30 years later, so there's a huge time lag between exposure and associated health consequences," says Shahab. In addition, while some biomarkers, like NNAL (a nitrosamine metabolite) have been shown in long-term studies to have a close relationship with cancer, for others, the evidence is weaker. Other toxic compounds, like formaldehyde, have no good biomarkers to estimate exposure in humans.

"The other major problem is unknown unknowns", says Shahab. Research into vaping is informed by earlier research on tobacco cigarettes, but the chemistry is very different.

New technology, new risks?

Shahab's latest research is looking at long-term users of heat-not-burn products, like BAT's Glo and IQOS from Phillip Morris International. "Tobacco companies are keen to promote these products, which make use of their existing tobacco supply chains, and they claim that by avoiding combustion, they reduce harms," he says. "So far the research in this area has almost all been carried out by industry, so there is a need for independent verification."

Shahab stresses the need for long-term studies of heated tobacco products, taking into account less than perfect use. "For example, when a stick is replaced some of the tobacco is often left stuck to the heating elements, and I suspect this could lead to the formation of carcinogens over time – but that's something that will only become apparent in long-term studies."

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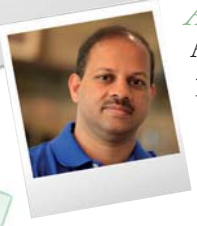
SPECIALIST SNAPSHOT: BIOPHARMACEUTICAL ANALYSIS

Advances in analytical tools and techniques are helping medicine makers understand their biomolecules better than ever before. But that's not to say there is no room for improvement or refinement. We speak with three analytical experts to learn how biopharmaceutical characterization is evolving to meet the needs of the industry – and vice versa.

THE EXPERTS



Anurag S Rathore

Anurag is familiar with both academic and industry perspectives in biopharma characterization. Today, he is Professor in the Department of Chemical Engineering at the Indian Institute of Technology in New Delhi, but he has previously held roles at Amgen and Pharmacia Corp. His main areas of interest include process development, scale-up, technology transfer, process validation, biosimilars, continuous processing, process analytical technology and quality by design.

Koen Sandra

Koen is currently the Scientific Director of the Research Institute for Chromatography (RIC). He is also the co-founder and co-owner of anaRIC biologics, a company that offers a complete range of analytical solutions for characterization, quality control, release and stability testing of biological drugs As a non-academic scientist, he is the author of over 40 highly cited scientific papers and has presented his work at numerous conferences as an invited speaker.

Hermann Wätzig

Hermann has spent his career in academia and is today Professor at the Technische Universitat Braunschweig in Germany. Since 2001, he has been the chair of the pharmaceutical analysis/quality control division of the German Pharmaceutical Society. He is a scientific committee member of Germany's Federal Institute for Drugs and Medical Devices (BfArM) and an expert of the European Pharmacopoeia.

Why is deep biopharma characterization so important for the discovery, development, and manufacture of new biologic drugs?

Anurag Rathore: The importance, as well as significance, of characterization for biopharma arises from the complexity of the product. Biotherapeutics are complex nano-machines, designed to work at a specific rate, for a specific function. This specificity can only be assured if all the parts of the nano-machines are intact and aligned accurately. For this, it is important to first understand how different stresses impact the assembly. Moreover, as it is a product used in bulk (millions of molecules per dose), the range of contaminants and their effect on product function will vary.

Characterization helps define all of the above features in minute detail – and this understanding can then be used in all aspects of development and manufacturing as a signature of the molecule's behavior. In the drug discovery phase, anomalies identified during characterization of a biotherapeutic for a certain target might also help identify treatments for other disorders. Characterization, to some extent, also helps understand and manage the risk involved with manufacturing, and can help alleviate the cost attached to clinical trials. In my opinion, there are very few industries where quality of the product matters so much to the consumers. Ultimately, regulation of this quality comes down to efficient and accurate characterization.

Koen Sandra: Anurag summed that up very nicely. Biopharmaceutical products come with enormous structural complexity. The molecules are large (monoclonal antibodies have a molecular weight of 150,000 Da) and heterogeneous as a result of the biosynthetic processes, subsequent manufacturing steps and final storage. Despite the fact that typically only one product is cloned, the final drug substance or drug product is composed of a mixture of hundreds of variants that differ in post-translational modifications and higher order structure. These different variants can have an impact on function, stability, and efficacy, as well as safety. During development, these characteristics need to be determined in great detail using state-of-the-art methodologies and closely monitored prior to clinical or commercial release. For that, a wide range of analytical techniques and methodologies must be used.

What analytical advances have had the biggest impact in terms of developing biologics?

AR: The field of analytical characterization of biotherapeutics has definitely seen major developments in the last decade; there are two significant advances I would highlight. The first is mass spectrometry (MS). When hyphenated with separation tools such as electrophoresis and chromatography, MS has made it possible to probe the molecular structure of complex biomolecules in previously uncharted ways. Combinations such as LC-MS-MS (liquid chromatography-tandem mass spectrometry) allow us to accurately identify the mass of a molecule to the fifth decimal place and pin-point not only the type but also the exact location of a range of chemical and enzymatic modifications. Even modifications as complex as glycosylation are now being increasingly profiled using characterization tools. If there is a modification that can be separated via a specific mode of chromatography, it can be identified by MS.

The second set of tools that are becoming increasingly promising are surface plasmon resonance (SPR) and biolayer interferometry (BLI). These tools have made it easier to perform binding assays and have significantly boosted productivity. They are gradually becoming the industry gold standard for measuring drug specificity and kinetics.

KS: The enormous advancements in MS and chromatography have had the biggest impact. New mass analysers have been introduced with improved robustness, sensitivity, resolution and mass accuracy, along with powerful software tools to mine all the data. Next to primary structural features such as amino acid sequence and post-translational modifications, we can even study higher order structures using MS (see tas.txp.to/0118/Landmark2). It is important to mention that, despite the many developments in software algorithms, data analysis still requires substantial manual intervention and there is a lack of trained people able to read the spectra.

In biopharmaceutical analysis, MS and chromatography go hand-in-hand. In parallel with MS, many advances have been noticed in chromatography, with the introduction of highly efficient columns with chemistries tailored towards the analysis of biopharmaceuticals and instrumentation capable of successfully operating these columns. Separations are nowadays even performed in multiple dimensions, i.e. two-dimensional liquid chromatography (2D-LC). It does not come as a surprise that instrument and column manufacturers as well as software and consumable providers are extensively focusing on biopharmaceutical analysis. The industry is booming. Looking back to the characterization of the first recombinant therapeutic protein (insulin) in the late 1970s/early 1980s, chromatography and MS were a far cry from the current state-of-the-art. Though fast atom bombardment was used to introduce insulin into low resolution mass spectrometers, today electrospray ionization has become the standard to introduce small peptides and large proteins into high resolution mass spectrometers equipped with a variety of fragmentation modes, providing sequence information and allowing modifications to be detected and localized at very low levels. While HPLC separations were performed on columns packed with 5-10 µm porous particles and pumps operated at 400 bar, one now witnesses the use of sub 2 µm porous and superficially porous particles and system pressures up to 1500 bar allowing rapid resolution of minor structural differences.

There was a time when scientists had to identify all peaks in a peptide map using Edman degradation – a very lengthy task – but now we can easily acquire and process 24 peptide maps a day thanks to the many developments in chromatography, MS and accompanying software tools.

Hermann Wätzig: We are constantly improving our understanding about the quality of the biologics being produced and how aspects such as charge variance and size variance play an important role. UHPLC and capillary electrophoresis continue to deliver better separations. MS, of course, is a much newer technology – and I must admit that the advances in this field continue to surprise me!

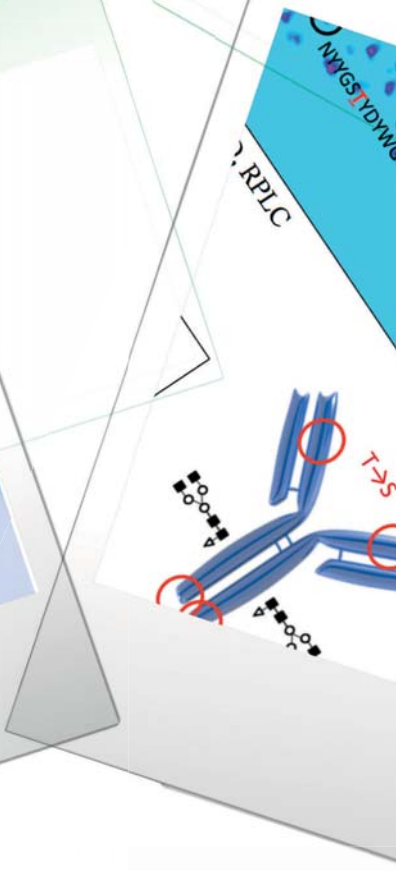
"Looking back to the characterization of the first recombinant therapeutic protein (insulin), chromatography and MS were a far cry from the current state-of-the-art."

How does the characterization of biosimilars differ?

KS: Regulatory agencies evaluate biosimilars based on their level of similarity to the originator. In demonstrating similarity, an enormous weight is placed on analytics – and both the biosimilar and originator need to be characterized and compared in extensive detail. The analytical package for a biosimilar submission is considerably larger than that of an originator. The structural differences highlighted define the number of clinical studies required. When biosimilar developers re-characterize blockbuster products developed 20 years ago using the current state-of-the-art analytical tools, many more details are revealed that pose enormous challenges to position a product within the originator specifications.

What are the biggest discussion points in biopharma characterization? Where are there unmet needs?

AR: We have come a long way in understanding protein molecules as products – but this understanding has also led us to appreciate the limitations of our knowledge. In most cases, these gaps in our understanding are because of current technical limitations, which I am certain will be resolved in the near future. One example is aggregation; there are already established immunogenic effects of the presence of this class of contaminant, making it a Critical Quality Attribute (CQA), but we still need to understand – in greater detail – the



"Better sensitivity is not necessarily what biopharma companies want, but it is a consequence of recent advances in analytical tools."

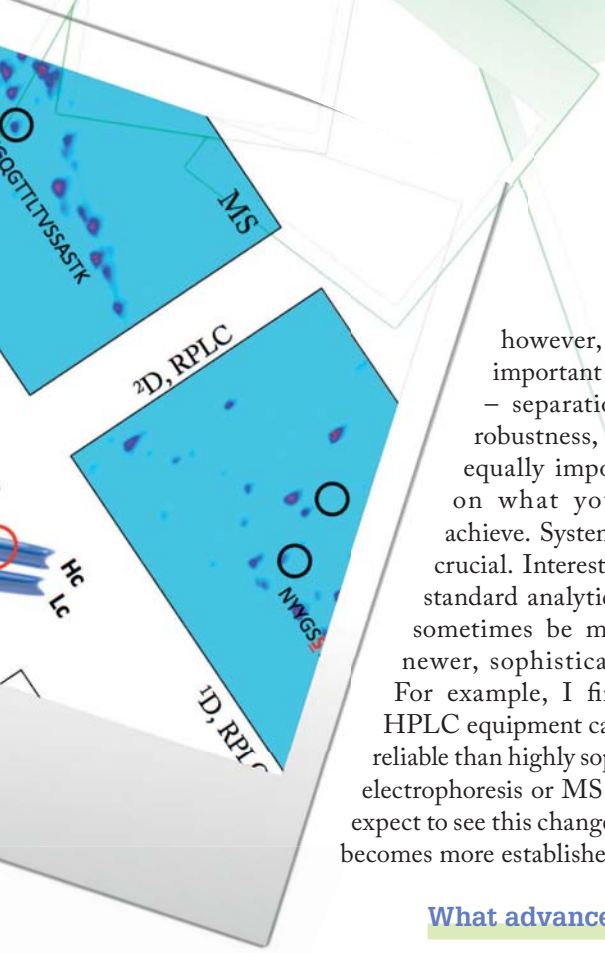
specific effects of individual aggregate species on immune profiles. The mechanism of anti-drug antibody formation is poorly understood; whether the response pathway is generic to aggregates or species specific still needs to be resolved. Understanding this would greatly help in defining specific ranges for this class of contaminants. It would also help in predicting drug behavior more accurately during storage conditions and, ultimately, the quality of the product at the time of patient-administration.

A similar gap exists in our mapping of the glycan profile of complex biomolecules, such as monoclonal antibodies. Given the wide range of possible combinations of glycans that can attach to the antibody backbone, complete profiling of these variants becomes a technical challenge. Moreover, given the acute sensitivity of biotherapeutics to their environment, it becomes even harder to ascertain how true a given profile is and what changes have been introduced because of the analysis itself.

Should sensitivity always be a priority?

KS: Better sensitivity is not necessarily what biopharma companies want, but it is a consequence of recent advances in analytical tools. Today, it is remarkable that we can detect individual host cell proteins (HCPs) at 0.1 ppm levels and product variants at levels below 0.1 percent. In project meetings, we often hear the comment "we don't want to know about all these low level variants!" or "we hope you have not found new liabilities." As analytical scientists, we feel it is our duty to reveal all the details of the molecules we are studying. At the HPLC 2016 meeting in San Francisco, Reed Harris (Genentech) showed an interesting graph plotting the number of modifications revealed in a molecule versus popularity within the project team. When discovering the first set of modifications, the popularity within the team increases substantially. After having shared yet another set of modifications, popularity declines – and at a certain point you are "Doctor Doom" because of the consequences that your findings can have on the timeliness of a project! Sensitivity is important, but in the development of new techniques and technologies, I think our priority should lie in robustness.

HW: Being from academia, my opinion is that sensitivity is always beneficial! Sensitivity allows you to see and understand more – and I think scientists from commercial biopharma should share this view. Sensitivity,



however, is not the only important feature of a system – separation efficiency and robustness, as Koen says, are equally important, depending on what you are trying to achieve. System reliability is also crucial. Interestingly, I think that standard analytical equipment can sometimes be more reliable than newer, sophisticated instruments. For example, I find that standard HPLC equipment can be slightly more reliable than highly sophisticated HPLC, electrophoresis or MS systems, though I expect to see this change as the technology becomes more established.

What advances do you see in the pipeline?

KS: Real-time monitoring of product attributes during manufacturing increasingly looks like the future, but the complexity of biopharmaceuticals makes it a challenge. Various groups within the biopharmaceutical industry have, nevertheless, made enormous progress in real-time monitoring of CQAs directly from the process. In vitro and in vivo CQA monitoring is also on the rise.

We furthermore expect MS, the workhorse in R&D, to find its way into routine environments as a release tool and we have high hopes for 2D-LC, where two different separation mechanisms are combined, with the aim of increasing overall resolution and thereby providing the next level of product detail.

AR: Numerous hybrid MS-based analytical techniques, including ion mobility-MS, capillary electrophoresis-MS, hydrogen-deuterium exchange-MS (HDX-MS), and size-exclusion chromatography coupled to native MS are yet to make their way into routine use. Also, real-time efficacy assessment platforms have been proposed (for example, CANScript technology), which I believe will greatly enhance effective biologic development.

HW: I expect considerable progress to come from automation, particularly sample preparation steps. Less error by dilution or extraction steps will certainly improve analytical precision. Miniaturization also has great potential to speed up analyses, and improve precision by multiple measurements and using the obtained average values as reportable results.

WHAT'S IN THE CANNABIS SCIENTIST?

The last 12 months have been momentous for the cannabis field, with legalization spreading, regulation tightening and science marching ever onwards – and our mini magazine The Cannabis Scientist has been there to tackle the big issues. Here, The Cannabis Scientist presents the people and technology to watch out for in cannabis analysis.





WHAT'S NEW IN CANNABIS ANALYSIS?

It's an exciting time for a growing field, with continuing developments in medical research, regulations, and even molecular tracking of cannabis products. Here are some of the analytical angles we have covered in The Cannabis Scientist.

Taking Research to the Streets

Frustrated by restrictions on studying the acute effects of cannabis in the lab, a team from the Institute of Cognitive Science at the University of Colorado Boulder decided to take their lab to the people. Meet the CannaVan – a mobile laboratory that takes the somewhat incongruous form of a Dodge/Mercedes Sprinter van, modified to include a phlebotomy and assessment station.

tas.txp.co/tcs/cannavan

Cannabis Science: The Next Generation

With market projections for the sale of cannabis at $10billion, and an increasing demand for robust scientific testing, the cannabis industry is looking like an increasingly attractive career choice for young scientists. Tapping into this interest is the Medicinal Plant Chemistry program at Northern Michigan University, which aims to meet the "renewed and enthusiastic interest in medicinal plant chemistry as it relates to the herbal extract market and more recently to the emerging cannabis market"…

tas.txp.co/tcs/nextgen

In Cannabis We Trust

A survey carried out at the Seattle Cancer Care Alliance discovered that 21 percent of their patients use cannabis to help deal with symptoms of cancer – confirmed with GC/MS analysis of urine. And a quarter of those users believe it helps treat the cancer itself – despite lack of scientific evidence. Steven Pergam, Principal Investigator at Fred Hutchinson Cancer Research Center, tells us about the motivation for the survey, and how it might impact patients (and healthcare practitioners) in the future.

tas.txp.co/tcs/trust

THE PROBLEM OF PESTICIDES

As California and other states open up cannabis for recreational use, regulators are clamping down on quality, including strict new standards for pesticide testing. We sat down with four experts to talk about the analytical hurdles that need to be cleared – and the technology required to do it. This is just a taster – read the full discussion at *tas.txp.co/tcs/pesticides*.

Chris Hudalla, Founder and CSO, ProVerde Laboratories, Massachusetts, USA

On the importance of pesticide analysis:
"Pesticide residue analysis is probably one of the most daunting and critical components of testing today. Because there has been a historical lack of regulation, people are using all sorts of pesticides. Plus, even pesticides that are considered safe for ingestion may have a very different safety profile after heating and combustion."

Jingcun Wu, Senior Strategic Scientist, PerkinElmer, Canada

On the analytical challenges in cannabis:
"Because of the diversity of sample matrices and the fact that the sample matrix without analytes is difficult to find, the dilute-and-shoot method is the simplest and most cost-effective approach to reduce matrix effects, although this methodology requires highly sensitive and robust instrumentation."

David Egerton, VP of Technical Services CW Analytical, California, USA

On improving residue analysis:
"The breadth of the pesticides that the California regulations have asked us to detect not only necessitates using two instruments – LC and GC triple quads – but can also create difficulties in designing multi-residue methods. Figuring out a sound chromatographic way to get around the interference created by the cannabinoids would certainly make pesticide analysis – and indeed, many of our other analyses – much easier."

Heather Krug, State Marijuana Laboratory Sciences Program Manager, Colorado Department of Public Health and Environment (CDPHE) Laboratory Services Division, USA

On the future of pesticide testing:
"The biggest challenges from a regulatory perspective are the absence of established tolerance limits for pesticides in cannabis and the lack of any approved registrations of any pesticides specifically allowing use on cannabis – but regulators are working hard to establish appropriate requirements, despite the lack of information available. The key moving forward will be to foster collaborative efforts between testing laboratories, regulators, and researchers to optimize the analytical techniques being used."

ENABLING TECHNOLOGY

2017 saw several exciting new analytical tools specifically designed for the cannabis industry. Here's our Top 3.

G908 3-in-1 Cannabis Analyzer, 908 Devices

Leverages "ballistic" GC and high-performance MS to perform three state-required cannabis tests on one multi-column device: residual solvents, terpenes and total potency.
http://bit.ly/2nAWwXd

Cannabis Analyzer for Potency, Shimadzu

HPLC system to determine levels of 11 cannabinoids, complete with column, mobile phase, certified standards, methods, batches, and reports.
http://bit.ly/2BVrOfM

Cannabis Breathalyzers, Hound Labs and Cannabix Technologies

Legalization of cannabis has led to fears of a spike in road traffic accidents caused by people driving under the influence of the drug, creating demand for roadside testing. Two labs have THC "breathalyzers" under development; the Cannabix Technologies device is based on high-field asymmetric waveform ion mobility spectrometry (FAIMS), while Hound Labs are keeping their proprietary technology under wraps for now.
http://bit.ly/2GJdkDw
http://bit.ly/2GNFBsw

ONES TO WATCH

We present ten influential cannabis scientists – making waves in analytical chemistry, biomedical science and plant biology. Cast your vote online to help The Cannabis Scientist pick our scientists of the year (*tas.txp.to/TCS218/vote*).

Pesticide Pioneer: Reggie Gaudino, Steep Hill Labs

As Chief Scientific Officer at one of the best known testing labs in California, Gaudino is a thought leader and long-time advocate for a more scientific approach within the industry (see *tas.txp.to/tcs/gaudino*). Steep Hill was among the first to speak out about the risk of pesticides in cannabis, and in 2017 highlighted the little-known problem of pesticide contamination in clones (*http://bit.ly/2BTA0gJ*).

Team Effort: Committee on the Health Effects of Marijuana, National Academies of Sciences, Engineering and Medicine

A panel of sixteen scientists who together published the most comprehensive review yet of the health impacts of cannabis and cannabinoids. The report, which reviewed some 10,000 studies, gained coverage in major news outlets worldwide with its balanced view on the benefits and harms of cannabis, covering everything from treating epilepsy with cannabidiol (CBD), to the dangers of driving under the influence of tetrahydrocannabinol (THC). Read the report at *http://bit.ly/2jCIHU9*.

The Auditor: Susan Audino, A2LA

As a lab assessor for A2LA, Audino ensures that cannabis testing labs are enforcing good laboratory standards. Not content with improving individual labs' performance, she is spearheading efforts by analytical standards-setting nonprofit AOAC International to develop consensus standards for testing across the industry. Read more at *tas.txp.to/tcs/audino*.

Gene Genie: Jessica Kristof, Phylos Bioscience

As Vice President of Research and Development at Phylos Bioscience, Kristof has been instrumental in developing the genetic tests offered by the company. The genetic fingerprints of strains have been harnessed to create the Phylos Galaxy, and most recently the Phylos Certified program. If it takes off, the Certified program will allow researchers, growers, suppliers and consumers to know exactly what strain they are dealing with. Read more on *tas.txp.to/tcs/kristof*.

Crucial Collaborations: Chris Hudalla, ProVerde Laboratories

A long career at instrumentation giant Waters Corporation gave ProVerde founder Hudalla not only a rigorous analytical approach, but a wealth of vendor contacts. ProVerde have collaborated with a string of instrument makers in recent years to develop new methods and technology for cannabis analysis. See The Problem of Pesticides (page 40).

Quality Campaigner: Robert Martin, CW Analytical

Martin heads up the Association of Commercial Cannabis Laboratories, a group of 20+ cannabis testing labs who commit to quality standards including integrity, proficiency, reliability and no "dry labbing." Read our interview at *tas.txp.to/tcs/martin*.

Addictive Research: Yasmin Hurd, Icahn School of Medicine at Mount Sinai

Hurd is a Professor of Neuroscience, Psychiatry, and Pharmacology and Systems Therapeutics at the Icahn School of Medicine and Director of the Addiction Institute at Mount Sinai, where her research explores the effects of cannabis in the brain. Her past studies have highlighted the dangers of THC in the developing brain; more recently, she hit the headlines with her work on treating opioid addiction with CBD (*tas.txp.to/tcs/opioid*).

Testing, Testing: Amanda Rigdon, Emerald Scientific

Formerly with Restek, Rigdon joined Emerald in 2016 as Chief Technology Officer, where she recently oversaw the biggest ever Emerald Test (a bi-annual inter-laboratory comparison and proficiency test organized by the company). The test has now also gained the seal of approval from Colorado regulators to act as a third party provider of proficiency testing in the state.

Persistence Pays: Sue Sisley (MAPS) and Marcel Bonn-Miller (University of Pennsylvania)

After a long road to FDA approval, the researchers treated the first patient in their much-anticipated world-first clinical trial of cannabis for PTSD in February 2017, and have so far recruited 32 of the study's planned 76 participants (*http://bit.ly/2yvtj6M*).

Lifetime Achievement: Raphael Mechoulam, Weizmann Institute of Science, Israel

Co-discoverer of THC and CBD in the 1960s, Mechoulam went on to uncover the endocannabinoid system. Now 86, the veteran researcher is still active, publishing several recent papers on the effects of cannabinoids in the body, and speaking at conferences worldwide.

Profession

Leadership
Talent Development
Career Planning

Everything You Wanted to Know About a Career in Chemistry*

(*But Were Afraid to Ask)

Navigating the road from graduate to PhD to first job can be tricky. Entrepreneur and professor Peter Kissinger has mentored hundreds of students and postdocs. Here, he shares ten of the most frequently asked questions – and his wise (and honest) responses. Whether you are a student with an uncertain path or an anxious supervisor with an urge to be supportive, read on...

My professor is not helping me and I am afraid to talk to him/her...

First, remember that faculty are people too. They may be stressed by demands from their formal teaching, travel, search for funding, and family life. Building a relationship between professionals at this level is not simple; a student is transitioning into a colleague, and transitions imply challenges.

Another thing to consider is that faculty often don't engage well with people who do not appear to take the initiative in their own education. Though you may seem to be working for Professor X, you are primarily working for yourself under their guidance. Remember, the PhD is a credential demonstrating independence of both effort and thought. If you do not demonstrate both, you are not a real PhD candidate and that credential is not going to save you.

Many believe that working with a well-established group will help their career; it will not. You will not be viewed as a mini-clone of your professor; instead, you will be judged by what you have done and keep doing. There is no

"In science – as in life – it is not good to put all your eggs in one basket, so consider a portfolio of projects."

way to have a relaxed life in science – resiliency is a requirement, not an option. Graduate school is a transition from being a follower to being a leader and problem solver. The self-motivated win the day, so know yourself and play to your strengths.

I am frustrated. I'm three years into my project and it is not working out.

In science – as in life – it is not good to put all your eggs in one basket, so consider a portfolio of projects. A good cook can get the meat, vegetables, salad and dessert all ready to go at the right time; a good scientist must balance a number of things at once. Changing projects and groups is not that rare. Students often say, "But I'll lose a year!" You will not lose a year. You've already spent it, used it, and (presumably or hopefully) learned from it. When you are 90 years old, a year spent 65–70 years earlier will seem a few minutes.

If your work is delayed, get going on another project, start writing a review article, catch up on reading. Inspiration comes from activities like these. Do not use the delay as an excuse to waste time that you will never get back. We do not want graduate students to be technicians, waiting to be told what to do. Successful people are energetic and resilient. They fail constantly, but get up and try again.

Should I accept a postdoc position?

For many academics, being a postdoc is a point in life with the least threats (no exams, no dissertation) and the least responsibilities (no grants to get, no faculty meetings). Therein lies the danger – you might be tempted to do the minimum. On the other hand, if you are motivated, you can draft new ideas, concentrate fully on research, publish more, help mentor graduate students and get practice at leadership – which always means teaching. A postdoc who doesn't add new skills and new ideas to their repertoire has wasted a substantial taxpayer investment. You should not accept a postdoc position to simply hold scientific territory, but rather to boldly advance and claim new lands.

I've been offered several postdoc positions. Which one I should accept?

A postdoc is too often viewed as a job rather than ongoing education. Postdoc experience is best if you learn something new – and, in return, contribute something unique to the group you are joining. That's both a fair deal and helpful to your career trajectory. Remember too that reputation in science is built over decades; do not assume a good reputation means that

"Classroom learning is overrated by both faculty and students; it simply can't compete with real-world experience."

a professor will be a fabulous mentor today. If you sign on to join a large group without first interviewing that professor and knowing the team, you could be in for a great disappointment.

I've been offered a job, but haven't finished my dissertation yet. Should I take it?

There is nothing worse in a CV than the phrase "completed all requirements for the PhD except the dissertation." You will be in a very precarious position starting a new position without the degree. Your dissertation work will fade into the background, your new environment will be exciting, and it will be extremely tough to concentrate on past research. My advice is to complete the degree in all respects and don't start your career with a reputation for not completing assignments – a good employer will wait.

Should I join the group of a senior professor or someone more junior?

I have no definitive answer. There is satisfaction in helping to build a new research group, but there is also satisfaction in working with a mentor who is away a lot and will not pester you (I thrived under that model). The personalities, size, and fit to subjects that interest you are more important than the maturity of the research group. Ask yourself every day whether what you're doing is going to be relevant to your dissertation, CV, or future career. If not, why are you doing it?

How can I make the leap from my PhD program to industry?

Just do it. Classroom learning is overrated by both faculty and students; it simply can't compete with real-world experience. PhD students have been successful in industry jobs for decades – how is this possible if there were no courses to orient them with industry or government labs? Perhaps because the

basic ingredients for success are largely the same in every occupation. Anyone working effectively in science must be curious, a self-learner, good at working with others, and a good communicator. Respect for others and a sound ethical foundation matter everywhere. That said, there are opportunities to interact with alumni from commercial settings, to take short courses with business schools, and (especially) to read business-oriented publications – take them.

My advisor asked me to help peer review a scientific paper. Should I?
Peer review is the foundation of science, and to participate is a responsibility to the community. It is a means of keeping up with what others are thinking and what they view as important. I served on NIH study sections for 30 years. It was an amazing learning opportunity; I was able to meet people superior to myself from whom I learned so much. Knowing them, dining with them, exchanging ideas with them, and joking with them have been the highlights of my life in science. Some ask, "Why review when there is no pay and no one knows you are doing the work?" Pay is not what makes life purposeful (in fact, if money is your sole focus, it is likely to make you miserable). Helping to review is a welcome opportunity. Do it well, and with respect for the efforts of those you are reviewing.

What advice do you have for a student wanting to start a company?
Don't do it unless you are crazy. If (like me) you are crazy and have tremendous resilience in the face of failure then it is great fun. There are many ways to prepare. Read a lot, write a business plan, and try to meet people who have already set up a business. Take a job in industry and learn

"Anyone working effectively in science must be curious, a self-learner, good at working with others, and a good communicator."

"Learn that whatever you want to do will take three times longer and perhaps five times as much capital as you think it will."

not just that job, but all that is going on around you. Learn how to sell; learn how to inspire people (aka selling); learn how money is raised (aka selling); learn how to listen and follow; learn that whatever you want to do will take three times longer and perhaps five times as much capital as you think it will; learn to adjust your plan in the face of a changing reality. Success is rare – but if you love the process, even a failure will have its rewards.

What are the secrets to success? There are three. (All good things come in sets of three: bears, pigs, blind mice, musketeers, stooges, stages in a mass spectrometer…)

- Discipline (self-control, effort, health, learning, ethics, precise language, listening skills)
- Tolerance (respect that there are different points of view, debate with civility)
- Thrift (spend less than you take in; laugh often, it costs nothing)

To sum it up nicely, simply substitute a technical discipline (for example, chemistry or mass spectrometry) for the word "writing" in this famous quote from Kevin Atchity:

"Discipline is the key to all that follows; it's the bedrock of productive writing. Talent is not a rare commodity. Discipline is. It requires determination more than self-confidence, the commitment of your will to the dream." *Kevin Atchity ("A Writer's Time"; 1986),*

Peter Kissinger is Professor, Brown Laboratory of Chemistry, Purdue University, and a founder of Bioanalytical Systems, Inc. (BASi), Prosolia, Inc., and Phlebotics, Inc. Indiana, USA.

Simple, Rapid Detection of Edible Oil Oxidation Using Direct MS

Process-line or laboratory detection of edible oil oxidation is achieved extremely simply by applying selected ion flow tube mass spectrometry (SIFT-MS). Direct headspace analysis of fish oil using SIFT-MS enables instantaneous quantification of volatile oxidation markers.

By Vaughan S. Langford

Edible oils rich in unsaturated fatty acids offer health benefits, but they are susceptible to autoxidation, which compromises product flavor and shortens its shelf-life. Generally, greater unsaturation in the fatty acid chain means more extensive autoxidation will occur in a given time.

Autoxidation produces volatile aldehydes, ketones, and saturated and unsaturated hydrocarbons, providing sensitive indicators of oxidative status for instrumental methods. Traditional methods for fish oils have targeted propanal, but application of SIFT-MS enables other confirmatory volatiles to be detected simultaneously.

In this study, five 1-mL fish oil capsules ("Giant Eagle" brand, USA) were placed in duplicate wide-mouthed sample jars. Capsules were opened inside the jars, and the contents allowed to drain. Jars were capped immediately (trapping laboratory air) and left on a laboratory bench at ambient temperature for the duration of the tests (diurnal variation from 12 to 25 °C).

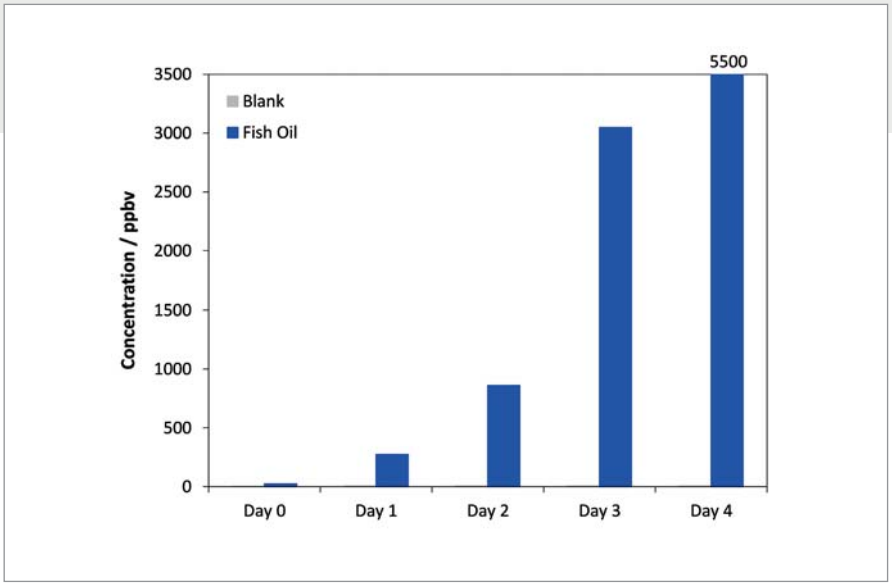


Figure 1. The propanal concentration as measured using the NO^+ reagent ion of SIFT-MS.

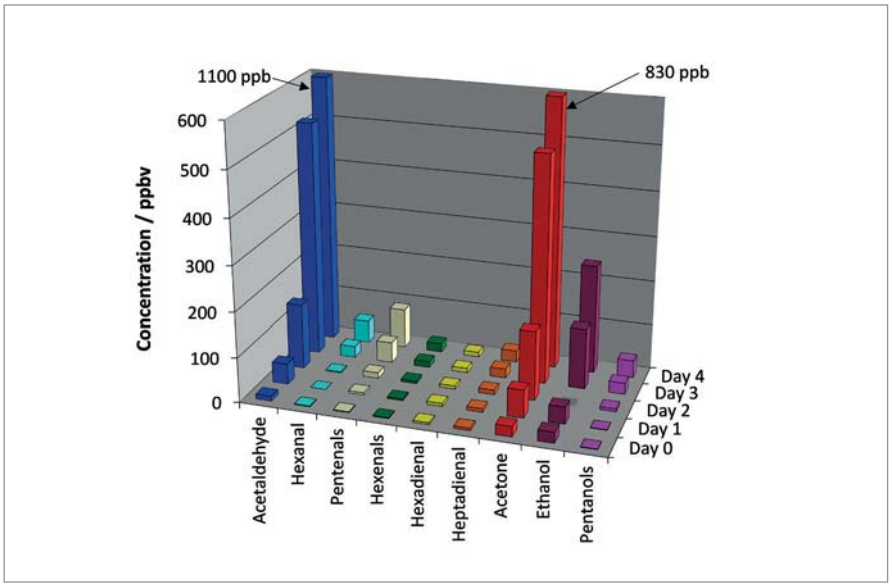


Figure 2. Additional volatile oxidation markers detected and quantified from fish oil headspace.

Figure 1 shows the propanal concentration measured for fish oil samples and blanks over a four-day period. The "Day 0" measurements were made one hour after the samples were prepared (i.e. on the freshly cut capsules) and reveal a significant concentration of propanal in the "fresh" oil (22 parts-per-billion by volume; ppbv). Other volatile oxidation products are shown in Figure 2. The very volatile compounds – acetaldehyde, acetone and ethanol – dominate. Note also that these data demonstrate the selectivity of SIFT-MS ionization: the NO^+ reagent ion resolves isomeric acetone and propanal in real-time.

SIFT-MS very effectively detects early autoxidation of fish oil via traditional (e.g., propanal) and non-traditional marker compounds (acetaldehyde, acetone and ethanol). Simple detection of these polar, low-molecular-weight compounds arises from the unique application of ultra-soft chemical ionization and direct headspace sampling in SIFT-MS. The rapid, high-sensitivity analysis provided by SIFT-MS is ideal for high-throughput quality assurance of fish and other edible oils, both in-process or off-line in the laboratory via autosampler integration.

Faster for Pharma

Sitting Down With... Melissa Hanna-Brown, Analytical Technology & Innovation Lead, Pfizer Global R&D, Sandwich, UK.

What is your current role at Pfizer?
I coordinate Pfizer's pharmaceutical sciences external collaborations in analytical technology, which means bringing in new technologies that can accelerate the process of making new medicines.

You worked in academia previously…
I had a separation science lectureship in the pharmaceutical department at King's College, London. I love teaching – seeing the "lights go on." And I still teach separation science as part of my visiting position at Warwick University. My first role at Pfizer was technology-focused; I worked with the Pfizer Analytical Research Center, collaborating with people like Pat Sandra and Paul Haddad, so my role then was a hybrid between academia and industry. After that, I spent time leading analytical teams and learned more about the business, and now I've gone back to the technology side – but with a new understanding of how that technology is applied.

How did you find moving into industry?
It was exciting, but a big change. I went from having a lot of independence, to having to get "buy-in" from many stakeholders. It was a culture shock at first! I had to learn how to get people on board pretty quickly.

What appealed to you about the analytical side of pharma?
If I find something challenging, then I'll be interested in it. When I was 13, I got a weekend job in a pharmacy and I worked there until I went to university. One day, the pharmacist and I had a discussion on what bioavailability was, and he started drawing pharmacokinetic plots of plasma drug concentration with time and explaining to me what the area under the curve (AUC) meant. He told me some basics about how this was important in the drug development process, and I was intrigued by the measurement aspects and what technology was used to produce this information. I was inspired to look at careers in the pharmacy area, and did a pharmaceutical sciences joint honors degree with chemistry. The problem-solving element fascinated me, and still does – though what fires me up now is finding better and faster ways to solve problems.

What are the biggest challenges in the field?
At Pfizer, our technology strategy includes advanced manufacturing – moving away from the batch concept to a continuous process. The analytical challenge behind that is huge. We're used to doing in-process controls and taking samples away to the lab for testing; now, everything needs to be done online, with analytical sensors, miniaturization and microfluidics all posing particular opportunities.

Another area that affects the whole of pharma is predictive science. How can we be smarter about using knowledge we already have to save time? In chromatography, we're focusing on predicting retention times based on structure, to ensure good starting conditions for our methods.

How well does analytical science serve pharma?
It's always served pharma well, because it has to - analytical science is the glue that holds new drug applications together! We provide regulators with crucial proof about the processes we use to make medicine. Quality, safety and speed are always the drivers. We're being required to make medicines in a shorter amount of time – less than five years from proof-of-concept to development (rather than the 10 or 15 year timelines of the past) – but with the same amount of information. That's why modelling and computational science are increasingly important.

How else has the industry changed?
We've changed the way that we collaborate. Fifteen years ago, there were lots of one-on-one relationships, whereas now you see consortia forming around grand challenges in medicine development. For the pharma industry, that's significant; we now recognize that a great deal of the work we do to develop a medicine is pre-competitive; your IP is in your molecule, so work outside of that and if you can share with other companies and get regulators involved, it speeds up the whole development process. I think that's the way we will continue to work. We're all sharing data so we can build predictive models and do it even faster in the future. Collaboration is essential for innovation.

What are you most proud of?
I'm most proud of – and thankful for – the networks that I have built over the years. It's not the number of connections I've made, but the quality of relationships that I've nurtured that mean the most. Through my strong network, I have gathered mentors around me who I can always rely on for brutal honesty - but in a way that's always constructive.

Is the stigma of going into industry (rather than academia) real?
Students always ask: Will I still be able to do science? Will I be able to publish? You're always going to have to focus on projects, because that's what you are there to do – to get medicines to patients – but although the projects may look very different from what you could be doing as an academic, you are still applying analytical knowledge. I worked on an oncology drug for one of our first accelerated programs in Pfizer, and it was highly rewarding. In the pharma industry, the product of your daily work is actually having a positive impact on people's lives – it doesn't get much better than that.

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