AUGUST 2018 # 67

the Analytical Scientist™

Behind the Scenes at the Museum

A close-up look at the Met's cutting-edge art analysis.

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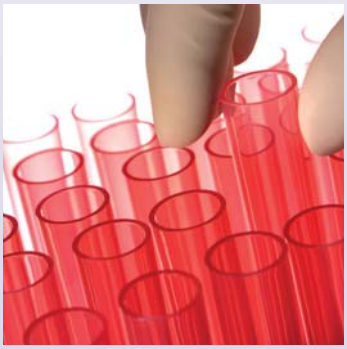
- **Neuroscience: Monoamines and metabolites analysis**

- **USP/EP Pharmacopoeias: Antibiotics analysis**

- **Food/Beverage: Sugars, Lactose-free products analysis**



- **Clinical: Catecholamines, Metanephrines and FDG analysis**

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Image of the Month

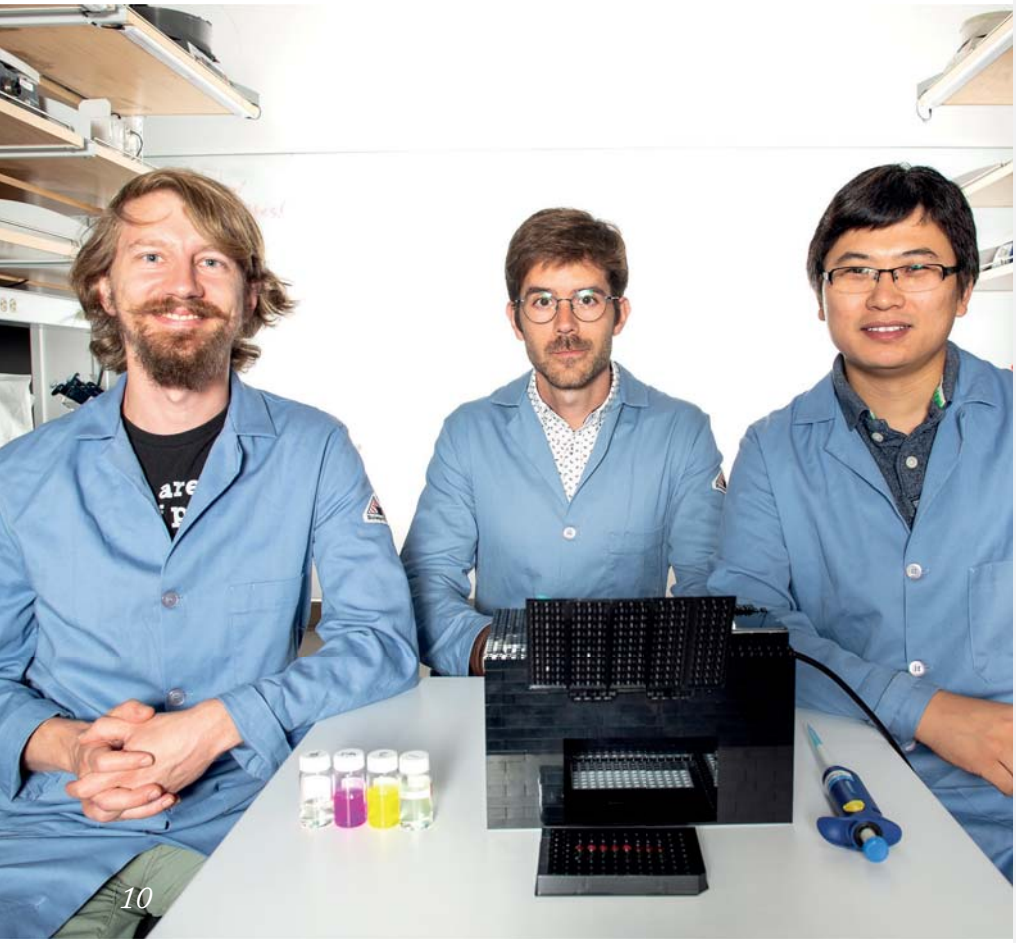
Sweet Success

Microelectrodes can be used to measure electrical signals within organs such as the brain, but the hard materials microelectrodes are usually made of can cause problems when transplanted into the body. Bernhard Wolfrum and team successfully inkjet-printed microelectrode arrays (MEAs) onto a variety of soft materials, including gummy sweets, in the hope of one day developing better sensors for biomedical applications (1).

Reference: N Adly et al., "Printed microelectrode arrays on soft materials: from PDMS to hydrogels", npj Flexible Electron, 2, 15 (2018).

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

Contents



10

On The Cover

This ancient Egyptian faience hippopotamus, known as William, has become an unofficial mascot of New York's Metropolitan Museum of Art (page 20).

Upfront

the Analytical Scientist

ISSUE 67 - AUGUST 2018

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The Humanity in Science Award recognizes and rewards scientific breakthroughs that aim to have a real impact on humankind's health and wellbeing.

HUMANITY IN SCIENCE AWARD

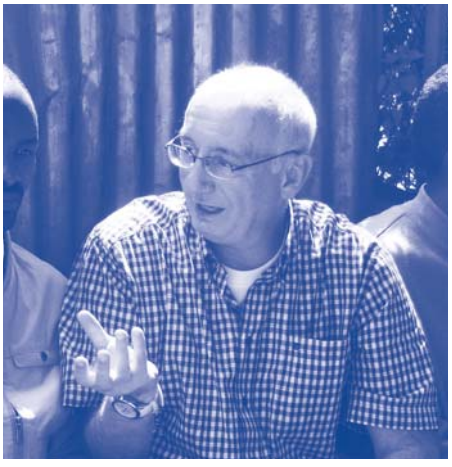
the Analytical Scientist

2015

Peter Seeberger & Andreas Seidel-Morgenstern, Directors at two collaborating Max Planck institutes in Germany, developed an innovative process to manufacture the most effective drugs to treat malaria from plant waste material, air and light.

2016

Waseem Asghar, Assistant Professor at Florida Atlantic University, developed flexible sensors for the rapid and cost-effective diagnosis of HIV – and other infectious diseases – in point-of-care settings.



2017

Richard Jähnke, Global Pharma Health Fund (GPHF), developed and continuously improved GPHF Minilab – a "lab in a suitcase," enabling resource poor countries to rapidly identify substandard and falsified medicines.

Nominations will open soon for the 2018/2019 Humanity in Science Award

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The Force That Binds Us

The secret to true scientific innovation? Creativity.

We've had a run of showcasing the importance of creativity in science recently. From last month's article on curiosity to the behind-the-scenes feature on The Met Museum in this issue, the link between art and science has never felt stronger. As someone of a creative bent myself (I started an art degree, have performed in my fair share of Shakespeare plays, and am still pretty nifty with a paintbrush) I approve.

Can good science be considered an art form? As Zoltan Takats said in our Curiosity feature, the key difference between art and science is that "science is systematic – whereas you could argue that good art isn't!" (tas.txp.to/0718/curiosity) Anyone comparing a mass analyzer, say, with a mid-career Jackson Pollock would no doubt agree. But just as there is method in the "madness" of Pollock's paint-splattered canvases, there is inherent creativity in the development of new and innovative technologies. And both artist and scientist often demonstrate an unshakeable commitment to their work, particularly when encountering hurdles or opposition – consider Alexander Makarov's twisting tale of the Orbitrap's early development (tas.txp.to/1013/orbitrap)…

Of course, creative thinking is only the start, as Makarov himself points out: "It's one thing to have a scientific curiosity that everybody loves, it's quite another to deliver something to labs, where it matters." But for the scientists on page 10, a creative approach – constructing an instrument exterior using pieces of LEGO – allowed them to deliver a low-cost nerve gas sensor that can be easily transported and reconfigured. Brianna Cassidy, one of the women smashing the "grass ceiling" in our latest issue of The Cannabis Scientist (www.theanalyticalscientist.com/thecannabisscientist) says her love of art and knack for creativity prepared her to tackle the complexities of analyzing this still-controversial plant. And, for the skilled scientists in our cover feature, a love and respect for art drives them to employ the latest analytical tools in their investigations of what they refer to as "products of human legacy".

Is it possible, as Federico Carò says on page 26, that combining art and science can help young people relate to science, technology, engineering and mathematics (STEM) subjects? Well, the STEM to STEAM movement (where art is added to the mix) is certainly growing in popularity – even Sesame Street is jumping on the bandwagon (1).

Conventional wisdom used to hold that people were either left-brain or right-brain thinkers – scientific or creative. But, in fact, as we see in every issue of The Analytical Scientist, creativity is as much a part of good science as it is good art.

Joanna Cummings
Deputy Editor

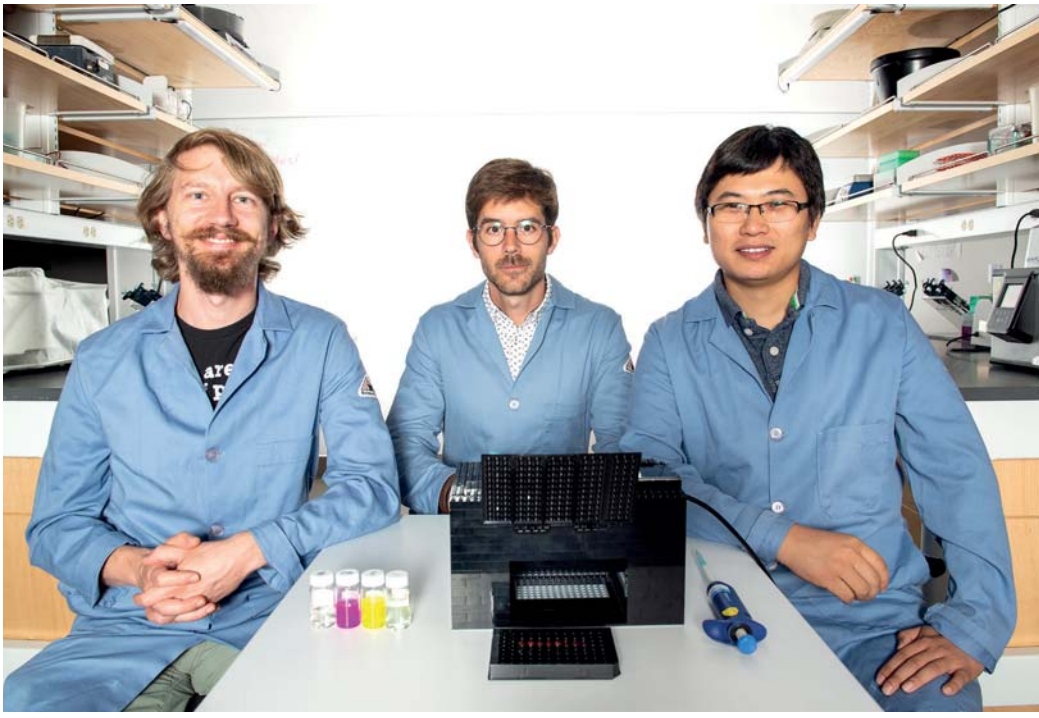
Reference

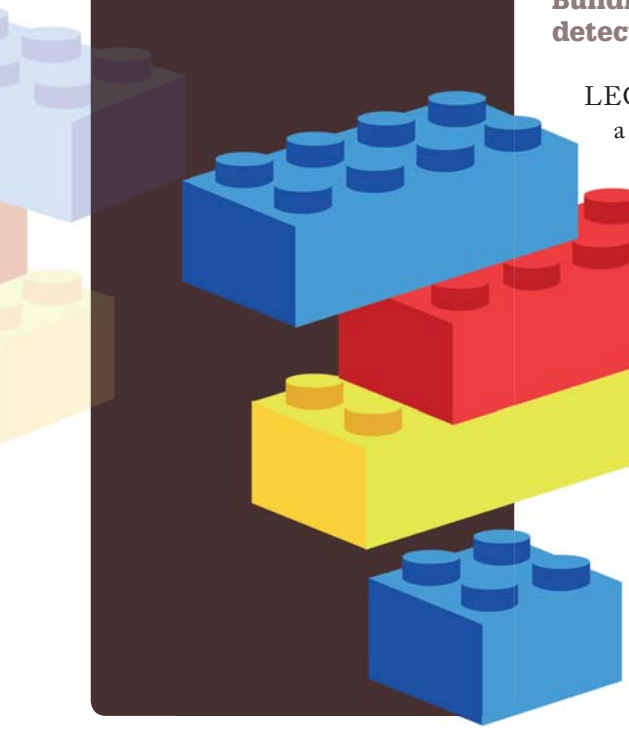
1. *https://ind.pn/2HqHSOj*

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





Toy Story

Building a nerve agent detector, brick by brick

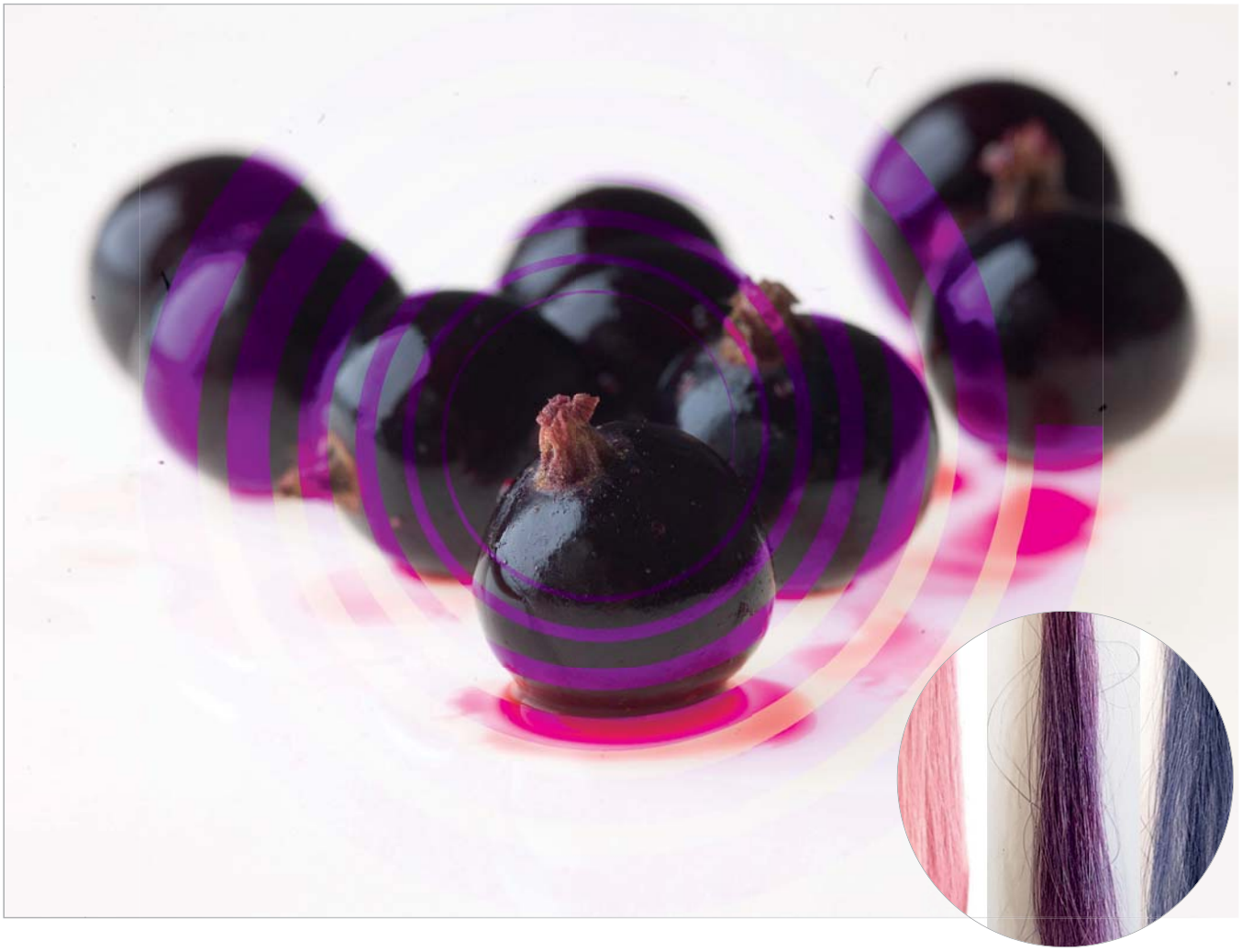
LEGO claims: "You can build anything." And now, an international team from the US and China are testing that motto to the limit. The researchers have housed a sensor in a box made of the toy bricks, in an attempt to create an improved (and portable) nerve agent detector.

Nerve agents are very much on the map since the Novichok 'outbreak' in Wiltshire, UK. The fact they are highly toxic, yet odorless and colorless, makes them a particularly formidable foe – requiring sensitive instrumentation to detect. Current detection methods, such as UV/Vis-, fluorescence spectroscopy or circular dichroism spectropolarimetry, tend to be costly and difficult to transport.

This detector's modest exterior belies the sophistication within; by combining a smartphone, digital photography and fluoride/thiol self-propagating protocols for fluorometric signal amplification, the researchers were able to determine analytes at levels comparable with more traditional techniques. Both easy to construct and to reconfigure, the LEGO exterior can also be dismantled for easy transportation – and costs a lot less than a 3D printed device. Just don't step on it with bare feet…

Reference

1. *X Sun et al., "Photography coupled with self-propagating chemical cascades: differentiation and quantitation of G- and V-nerve agent mimics via chromaticity", ACS Cent Sci, [epub ahead of print] (2018).*



Currant Affairs

Why dyeing your hair with blackcurrant cordial leftovers could be better for your health – and the planet

Amidst consumer concerns about irritants, carcinogens and environmental impact, the search has been on for alternatives to synthetic hair dyes.

Researchers from Leeds, UK, decided to look to the humble blackcurrant; specifically, the fruit waste left over from the manufacture of popular British cordial, Ribena. As blackcurrant skins contain high quantities of anthocyanins – water-soluble pigments responsible for vivid blue and purple hues in plants and flowers – they seemed a "natural" choice.

The blackcurrant skin anthocyanin was combined with aqueous solution before being applied to hair in various concentrations; for comparison, extracts were also applied using a typical hair dye formulation. The hair samples in both instances were then measured using reflectance spectrophotometry. The team discovered that the anthocyanins and hair fibers were a winning combination; not only was an intense (and comparable) color achieved, but the dye remained stable after multiple washes (1).

The best bit? The UK's consumption of blackcurrant cordial is so high that access to biodegradable raw materials is unlikely to present a problem – potentially making this a truly sustainable alternative to commercial hair colorants. So feel free to drink and be merry – for tomorrow we dye…

Reference

1. *PM Rose et al., "Application of anthocyanins from blackcurrant (ribes nigrum l.) fruit waste as renewable hair dyes", J Agric Food Chem, 66, 6790–6798 (2018).*

From Microscopy to Milk Analysis

Business in brief: What's going on in analytical science?

Products and launches

- Zivak Technologies has launched the Zivak Multitasker, a UHPLC system that uses robotic arms to simplify and speed up sample preparation.
- Agilent has announced that handheld Raman system Resolve is now being used by the UK Border Force for the detection of hazardous materials through opaque packaging.
- Waters has acquired exclusive rights to Desorption Electrospray Ionization (DESI) technology for all mass spectrometry applications from Prosolia and the Purdue Research Foundation (PRF). Waters will also provide Purdue University with a TOF-MS to continue to advance research applications of DESI technology.

Collaborations and acquisitions

- Thermo Fisher will acquire Gatan, the electron microscopy supplies manufacturer, by the end of 2018. Thermo's Dan Shine said that this, and their recent acquisition of desktop scanning electron microscope manufacturer PhenomWorld, will lead to a more integrated system for their customers.
- Agilent is expanding its biopharma consumables portfolio with the recent acquisition of ProZyme, leading provider of glycan analysis reagents, kits and standards.
- Agilent will also be working with Grabner Instruments to develop an innovative FTIR-based mobile testing solution for the petroleum industry.
- After collaborating on a high-end FT-NIR dairy analyser, Bruker has acquired Lactotronic BV, manufacturer of analytical instruments for the dairy industry, including the MIRA™ Milk Analyzer.
- bioMérieux is providing biotech company Deinove with 250 strains (130 species) for screening of antibiotic and antifungal activities, as part of a new collaboration to discover antibiotics. Deinove's genetic and metabolic technology platform will allow them to accelerate large-quantity analysis of the strains.

Company and people updates

- Merck KGaA, based in Durmstadt, Germany, has opened a new OLED Technology Center in Shanghai, China. The Center will also function as a collaborative working space for the company and its customers.
- SCIEX has donated $17,500 to the World Cancer Research Fund's ongoing research into links between nutrition and prognoses in cancer survivors. An additional $6,500 was donated by their parent company Danaher Foundation.
- Students from Cornwall, UK have won the AS Schools' Analyst competition from the Royal Society of Chemistry. Their college will receive £3,000 to spend on analytical chemistry equipment, while the students each took home £100.

For links to original press releases, visit the online version of this article at: tas.txp.to/0818/BUSINESS.

A Bloody Good Solution

The secret to better polymerization might be close to your heart

What? Researchers from Australia have shown that the chemicals found inside red blood cells can act as a catalyst for the synthesis of plastics.

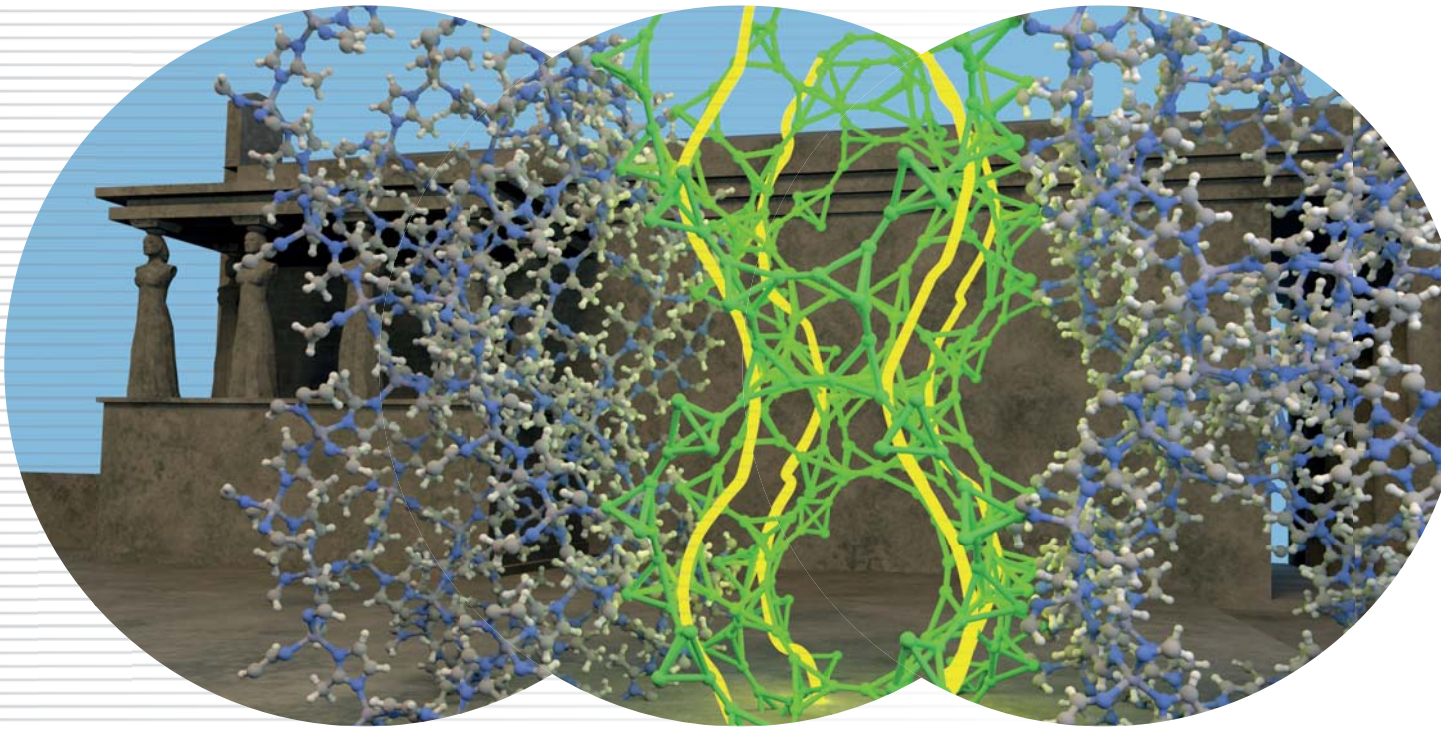
How? In one of the more unexpected concoctions we've seen, Greg Qiao and his team from the University of Melbourne combined sheep's blood and N,N'-dimethylacrylamide, before adding the enzyme glucose oxidase and leaving the mixture in a sealed vial. They then analyzed the mixture at intervals using proton nuclear magnetic resonance (1H NMR) and size-exclusion chromatography (SEC), discovering that "smooth polymerization" was observed in under 45 minutes (1). Polymerization is triggered when glucose oxidase produces hydrogen peroxide – releasing hydroxyl radicals from the heme group.

Why? The researchers hope the technique could one day allow improved in vitro cell engineering.

Reference

1. *A Reyhani et al., "Blood-catalyzed RAFT polymerization", Angew Chem, [Epub ahead of print] (2018).*

Photo by George Rex.



Support Network

"Chemical caryatids" improve the stability of metal–organic frameworks

Metal–organic frameworks (MOFs) are a diverse range of materials with a variety of analytical applications. In our June feature, Victoria Samanidou noted their usefulness in several sample pretreatment approaches, including SPE, dispersive SPE, magnetic solid phase extraction, SPME and stir bar sorptive extraction – "and with many others likely to be included in the future," (tas.txp.to/0618/MOFs). However, MOFs do have a weakness – they can be vulnerable to changes of pressure or temperature. If a material is not sufficiently mechanically stable, these forces cause pores to collapse or the material to break.

"Compared with other nanoporous materials, MOFs are relatively mechanically weak," says Berend Smit (École polytechnique fédérale de Lausanne). "There are MOFs that are very strong and some that have such a low density that they are more like solid foams – sufficient mechanical stability in MOFs cannot be taken for granted." To help tackle the problem, Smit and Lev Sarkisov (University of Edinburgh) set out to get a better understanding of MOFs – and, in particular, zeolitic imidazolate frameworks (ZIFs) – at the molecular level.

They discovered that functional groups on the organic lipid molecules can either enhance mechanical stability through nonbonded interactions or weaken it by destabilizing bonding networks (1). The researchers further deduced that by controlling these functional groups – which they termed "chemical caryatids", in reference to the supporting columns for structures in ancient Greece – they could strengthen MOF structure and thus improve performance.

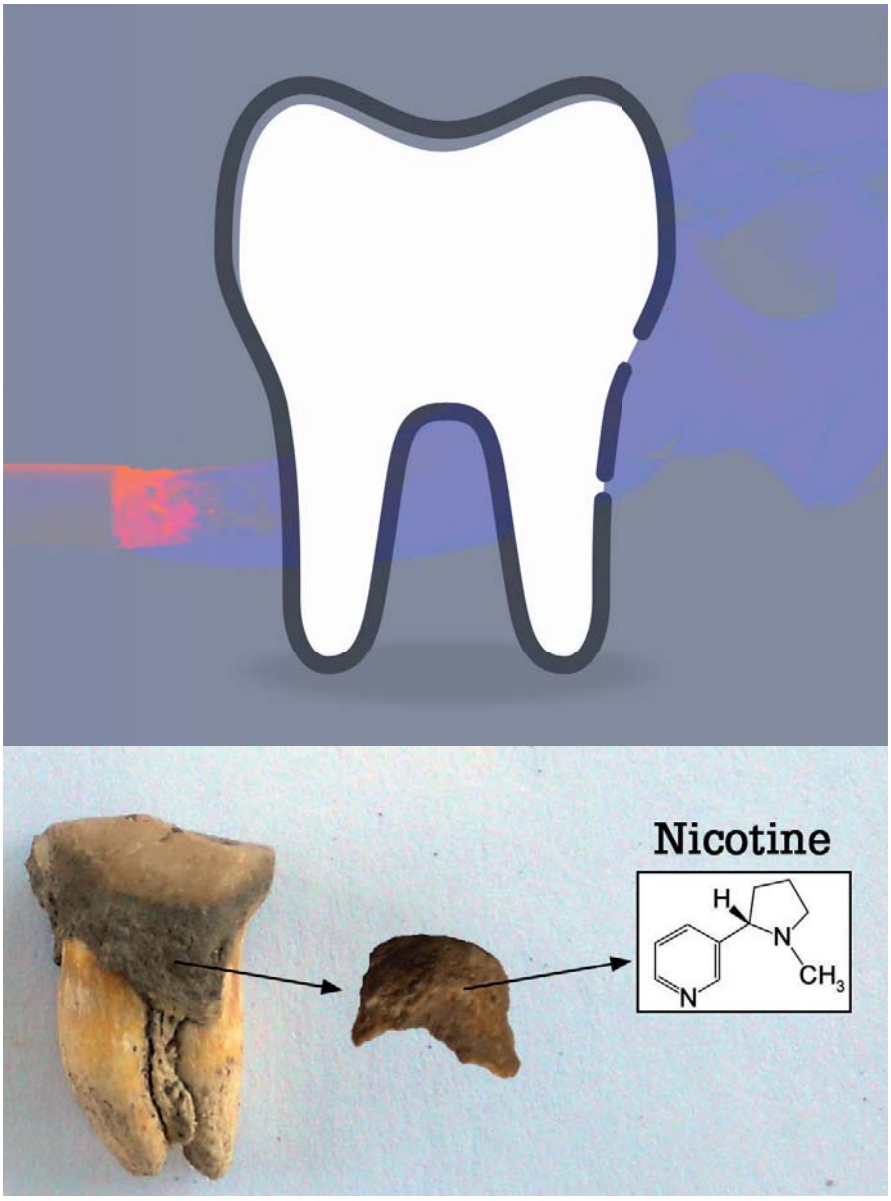
The researchers went on to develop software to predict the effect of different functional groups on MOF mechanical stability. Improving mechanical stability of materials at the early stages of a project will be a big time-saver for researchers, Smit adds. "Before our work, assessing mechanical properties was trial and error – there was a danger of discovering at the very end of a project that the material cannot be used because it collapses as soon as one handles the materials."

Reference

1. *SM Moosavi et al., "Improving the mechanical stability of metal–organic frameworks using chemical caryatids", ACS Cent Sci, [epub ahead of print] (2018).*

The Tooth Will Out

LC-MS reveals the smokers of ancient societies – and it may not be who we thought



In an attempt to track early tobacco use across the Americas, a group from Washington State and University of California, Davis, have identified nicotine residue from the teeth of ancient tobacco users for the first time.

"Plaque has largely been ignored by archaeologists in the past because the amount of plaque on the teeth tends to be small – and it simply wasn't possible to analyze such small samples," explains anthropologist and first author of the paper, Jelmer Eerkens (UCD). But improvements in instrumentation that offer greater sensitivity have helped to solve this problem (at least for ancient plaque), even allowing characterization of proteins, bacterial DNA and plant fibers. In this case, researchers used ultra performance liquid chromatography-mass spectrometry (UPLC-MS; Waters Corporation) to analyze dental plaque (or "dental calculus") from eight individuals across three archaeological sites in Central California to determine the presence of nicotine, caffeine and atrophine.

One interesting discovery: nicotine was found in the calculus of a middle-aged woman. Eerkens believes this tells us something about women's roles at the time. "When anthropologists interviewed Native Californians in the late 19th and early 20th centuries, they recorded that it was mostly or exclusively men, especially those who practiced healing or doctoring, who used tobacco," he says. "Judging by our findings, there must have been women healers and doctors as well – they just weren't recorded by the mostly male anthropologists who happened to mostly interview men."

The work underscores the value of carrying out archaeological tests like these, he adds. "While the science of archaeology has some of its own biases, it can serve as a means to tell the stories of under-reported or under-represented communities." They are now working with several indigenous communities to identify a range of medicinal plants other than tobacco, and are also looking for older plaque samples (from 5,000 to 10,000 years ago) to see if they can trace how far back people were using tobacco in this region.

Reference

1. *JW Eerkens et al., "Dental calculus as a source of ancient alkaloids: Detection of nicotine by LCMS in calculus samples from the Americas", J Archaeol Sci Rep, 18, 509–515 (2018).*

Real-Time Tumor Analysis

Look out! Here comes the SpiderMass

How can we make cancer surgery more efficient? At the moment, there's approximately a half-hour waiting time built into the procedure so that pathologists can inspect the excised tissue to make sure all the cancerous matter has been removed. Now, a research group from France is adding to a growing list of mass spectrometry-driven tools that aim to speed up the process.

"We started by developing a technology to enable in vivo mass spectrometry analysis to target applications for medicine," says Isabelle Fournier, Professor of PRISM Laboratory at Université de Lille. "In our first prototype, we demonstrated that we could perform in vivo analysis with mass spectrometry without being invasive – using the system, SpiderMass, to analyze our skin (1). The technology we developed is based on using the endogenous water of biological tissues as a MALDI matrix." They dubbed the process Water Assisted Laser Desorption Ionization – or WALDI. Initially, the system was used to detect lipids and metabolites – but, in a recent study (2), the researchers expanded their remit, using SpiderMass to detect and analyze peptides and proteins from cancer biopsies in real time.

Fournier says, "The advantages of the technology are to enable easy analysis of various raw samples without any preparation. The samples can be easily screened dynamically by moving the [SpiderMass] handpiece above the surface of the sample." But biopsy tissue isn't the end of the line for SpiderMass. Fournier and her colleagues also hope to analyze peptides and proteins noninvasively in vivo soon.

The team believes that such real-time technologies are a big clinical step for diagnostics and prognostics. With use by pathologists at the bench, in the lab, or directly in a surgical theatre, the process is relatively flexible. Plus, there's room for improved accuracy and further adaptability. Fournier explains, "For diagnostics, the system will rely on the creation of databases of molecular profiles that will be used to build up classification models that can be interrogated in real-time."

A bonus to the technique is the speed at which the team expects it to be clinically ready – less than a year. "We recently moved a prototype to the vet surgery room for testing," says Fournier. "We plan to finish our POC in the next few weeks – although we are currently testing the [in vivo] surgical applicability of the system using lipids and metabolite profiles, but not proteins yet."

References

1. *B Fatou et al., "In vivo real-time mass spectrometry for guided surgery application", Sci Rep, 6 (2016). PMID: 27189490.*
2. *B Fatou et al., "Remote atmospheric pressure infrared matrix-assisted laser desorption-ionization mass spectrometry of proteins", Mol Cell Proteomics, [Epub ahead of print] (2018). PMID: 29653959.*

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

Embracing Analytical Scientists Everywhere

Whether it's disseminating expert knowledge, exchanging thoughts on the latest tools and techniques or dancing like Ewoks, SciX is a special conference to attend.

By Karen Esmonde-White, Senior Marcom Specialist, Kaiser Optical Systems, Inc., Ann Arbor, Michigan, USA.

The SciX Conference holds a special place for me. It is where I met my husband, earned my first student poster award, and found a supportive professional analytical chemistry community. And this year is even more special because I am serving as Program Chair for the first time. I feel lucky to work with a passionate, dedicated, world-class team that includes over 120 program chairs, including Mark Henson as General Chair, Mike Carrabba as Exhibits Chair, Rob Chimenti as Workshops Chair, and Garth Simpson as Awards Chair.

The event will be held at a new location for 2018: the Marriott Marquis in Atlanta, Georgia – a unique venue that allows SciX to expand its technical program, offer new workshops, and enable new networking opportunities.

The SciX conference is known for the strength and diversity of its technical program, and this year is no exception. The joint meetings of SciX 2018 will contain 130 sessions covering all fields of analytical chemistry. We are pleased that this year's program will also incorporate the International LIBS 2018 conference.

For 2018, we have a special focus on analytical chemistry's role in addressing the environmental impact of microplastics, with a number of dedicated sessions and a keynote address from Matthew Savoca of the NOAA Southwest Fisheries Science Center and Hopkins Marine Station at Stanford University. Savoca will speak on the analytical challenges of identifying microplastic debris and understanding their effect on marine wildlife.

Education is a central mission of the Federation of Analytical Chemistry and Spectroscopy Societies (FACSS), and the SciX conference supports this goal through the technical program and by offering short courses. Taught by experts in the field, introductory, advanced, and/or hands-on technical short courses will be offered onsite encompassing the areas of Raman spectroscopy, LIBS, entrepreneurship, process analytical technology (PAT), STEM education, and chemometrics. I highlight two exciting offsite workshops that will be offered for the first time this year: hands-on forensics analysis (offered in conjunction with MVA Consultants) and Quality Control Testing of Beer (to be held at Sweetwater Brewery). Notably, space is limited for all workshops.

By design, SciX is a great conference for students. We feature daily student poster awards, special conference hotel rates for students, the opportunity for travel grants, networking events, scientific receptions, and even a free lunch! There are also volunteer opportunities for students to increase their involvement in the conference and earn discounted registration. Additionally, in recognition of our long-standing relationship with scientists in Puerto Rico and in support

of rebuilding efforts after Hurricane Maria, we are offering complimentary registrations for SciX 2018 for students enrolled at any Puerto Rican university.

The Exhibits feature the latest in instrumentation from leading vendors in the analytical sciences. Lunches are provided for attendees in the Exhibits hall, with the "What's Hot" sessions assembled by Exhibit Chair Mike Carrabba to learn about the latest products vendors have to offer.

Lastly, SciX is about bringing people from the exhibit floor to the dance floor. The theme for Wednesday night's all-inclusive Gala event is: "The Great Science Fiction Exchange." After a long day of exchanging scientific facts, come put your knowledge of lasers and quantum physics to more entertaining use as SciX warps into an alternate dimension for one night only. Dress up as your favorite science fiction character and add your distinctiveness to our collective, or just dance like an Ewok as we assemble the armada to party like the Second Death Star just blew up! Resistance is FUTILE. So say we all!

SciX 2018 will be held at the Atlanta Marriott Marquis October 21–26 in Atlanta, Georgia, USA. Visit www.scixconference.com, to learn more and to register.

Another Man's Treasure

Got an obsolete but working instrument sitting in the basement of your institution? There are students across the world who are in need.

By Kym Faull, Director, Pasarow Mass Spectrometry Laboratory, University of California, Los Angeles, USA.

A few years ago, a scientist from the University of Bornova in Izmir, Turkey, came to do a sabbatical at UCLA. We had a couple of old GC/MS instruments sitting in the basement – they were both in working condition but we had discarded them for a newer, better system. I casually said he could have them, and in due course the instruments were shipped to Izmir. Months later, I visited the Turkish university, and managed to get one of the instruments working. I was amazed to find that the students in the lab had previously never even seen a mass spectrometer, let alone used one. I trained a couple of them in how to use it, and though I afterwards lost touch with the professor, I was told that the instrument ran for several years – helping in their research and to introduce their students to mass spectrometry and GC/MS in particular.

It occurred to me then that this could be done on a larger scale. Institutions, universities and pharma companies are constantly replacing their analytical equipment with more sensitive versions – why not make the old instruments available to countries who need them for research and teaching? For the past two years, I have conducted a workshop at ASMS, discussing the lack of instrumentation in many labs around the world. At this year's workshop, a scientist from Cameroon confirmed that he'd never seen a mass spectrometer as a student, only read about them in books. That lack of contact puts such students at a huge disadvantage; without experience, they struggle to compete for post docs and positions in other countries. The situation hardened my commitment to try and find a way to repurpose discarded instruments from the USA.

It's worth noting at this point that I am not the only one to have had this idea. Getting something like this off the ground is a real challenge, but Giles Edwards, at the Recycling Organization for Research Opportunities (RORO), has been very successful (particularly in finding homes for Waters equipment throughout West Africa, India and Pakistan), as has Seeding Labs, an organization in the US headed by Nina Dudnik.

I've contacted every MS company in the US, but they are loathe to make obsolete equipment available for legal reasons, even though it should be a simple matter of signing the right paperwork. The long and short of it is: finding a home for an instrument is easy; finding the instrument is the problem. Last Christmas, we acquired a mass spectrometer for a three-day course at the Congo Basin Institute, Yaounde, Cameroon, which some students traveled over 600 km to attend; however, to their disappointment – and mine – we couldn't get it working because it was in poor condition and not repairable. My hope is to find one soon, get it operational, and run another class over the 2018 Christmas break.

I'm focusing on mass spectrometry because that's my field, but the same argument applies – and the same need exists – for any superseded but working analytical equipment: centrifuges, chromatography systems, NMRs, and so on. So, whichever field you work in, whether you are a CEO or an academic like me, please consider this a call to action: look at what instruments are lurking in basements and storage units, and ask yourself: couldn't they be put to better use?

Resolution Revolution

Can GC×GC be considered a super-resolution technique?

By Philip Marriott & Yada Nolvachai, Australian Centre for Research on Separation Science, School of Chemistry, Monash University, Victoria, Australia.

We posed the question above at the Riva del Garda ISCC/GC×GC symposium in May – perhaps somewhat rhetorically given that the audience was made up of committed GC×GC researchers. Today, "super-resolution" is a term apparently reserved for the Nobel prize-winning spectroscopic technique that is defined by achieving spectroscopic imaging at wavelengths less than those of light. This feat is accomplished by a combination of the "blinking" of fluorescent emitting centers – for instance, located along a fibril – and the mathematical localization of the center of the emission, which effectively reduces the dispersion of the light and centers it better on the emitting moiety. In this way, a biological feature comprising the emitting centers can be defined with much greater precision.

So, does GC×GC qualify as a super-resolution technique? We define the separation power of GC in terms of peak capacity – the total analysis time/peak width measure. Or, in other words, how many peaks can be fitted in the chromatogram. For example, if we consider the limit for well-resolved peaks to be separation by 4 σ (the width at baseline), then we might fit 400 peaks in the total chromatogram. If we relax (reduce) the peak width measure for defining separated peaks, then we can fit in more peaks. There is a natural limit to how small the peak separation measure can be before we are unable to distinguish neighboring peaks, which is exacerbated as peak response magnitudes become increasingly different. For a regular (non-MS) GC detector, we rely upon peaks being adequately resolved.

For GC×GC, we use a second column, decoupled and independent from the first. The total resolvable peak number is often quoted as being the product of peak capacities on each dimension – ${}^1n_c \times {}^2n_c$. If ${}^1n_c$ = 400 and ${}^2n_c$ = 25, then total resolvable peaks will be 10,000. When modified by the sampling of first dimension peaks, it will actually be about 8,000, but still significantly expanding upon the 1D GC peak capacity capability. In addition to total capacity, the manner in which GC×GC presents data as 'structured retentions,' grouping similar compound classes in a structured manner, is informative.

However, peak capacity is not everything. We argue that for a technique to be considered super-resolution, it is important to consider the ability to provide peak localization and, ideally, identification. Localizing a peak in 2D space depends on the detector used. A flame ionization detector (FID) generates a peak defined by its dispersion in both ${}^1D$ and ${}^2D$, given, for instance, by its width at baseline in each dimension. The peak maximum in ${}^2D$ (known as ${}^2t_R$) is readily obtained, but marginally decreases for each successive modulation due to the incrementing oven temperature. Defining the peak in ${}^1D$ is somewhat less clear, due to the discrete modulation period sampling employed.

Some years ago, we reported a method to predict the ${}^1t_R$ value based on fitting a Gaussian distribution to the modulated peak profile, which allows a better characterized ${}^1t_R/{}^2t_R$ set of peak coordinates – something that has been picked up by other users. With a reliable set of peak coordinates in 2D space, a better-defined peak apex plot can be generated (the apex plot is defined as a plot that presents just the 2D peak coordinates; to do this precisely, accurate identification of the coordinates is needed). The peak apex plot clearly offers considerably greater peak 'capacity' than those of classical definitions based on peak widths at baseline, as the peak apex should be 'definable' to a much narrower width – although the magnitude and uncertainty of the apex plot is not normally stated.

Mass spectrometry detection further refines the total peak identification that is possible. If based on the total ion chromatogram, the consideration is effectively the same as for FID. But if a unique extracted ion is available for a compound, then the compound corresponding to that ion can be further isolated from other compounds that might be located with very similar 2D coordinates. Using the approach of precise prediction of the ${}^1t_R$ value, and locating the ${}^1D$ and ${}^2D$ peak ${}^2D$ apex, it is possible to obtain a truly ultra-high resolution GC technique. Does this mean we should be able to call it "super-resolution"? I believe so.

The GC community has accepted the high resolution provided by capillary GC as the gold-standard in separation of volatile compounds. By adding a suitable second dimension in GC×GC, the expanded separation power provides a degree of chemical resolution that is unprecedented – in essentially the same time. The addition of mass spectrometry further enhances the ability to isolate the response of individual compounds. The resolution provided is simply 'super'.

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This hippopotamus statuette (known as “William”, and the unofficial mascot of the Met) dates from 1961-1878 BC.

MEET THE MET

Conservation science not only demands a multitude of complex analytical techniques, it also requires collaboration and skilled communication between scientists, conservators, art historians and archaeologists. We step behind the scenes at The Metropolitan Museum of Art, New York, to meet three scientists who are studying the art of the past – and driving art analysis into the future.

How important is it to understand the art that you study?

Elena Basso: A basic knowledge of humanities disciplines, such as art history, archaeology, artistic techniques and conservation theory is usually a requirement for a conservation scientist. My own background is in geology, but I also acquired a good knowledge of art, archaeology and conservation. From the beginning of my career, I understood that communication with archaeologists, art historians, curators and conservators was key, and I have endeavored to find a common language.

Julie Arslanoglu: Scientists who enter the field of cultural heritage science may not be required to have a degree in conservation or art, but they need to gain that knowledge, as the preservation of art depends on understanding the materials, the cultural or art historical significance, and the expected appearance of an artwork. Artworks are carefully crafted and considered products of the human legacy, and the materials used, although critical to their preservation, are not the only aspect that our work sheds light on. Our ability to answer questions about provenance, origin, or use is essential to the deeper understanding and contextualizing of artworks.

Federico Carò: I agree with Elena and Julie. For our research to be meaningful, it is necessary to have strong collaboration with art historians, curators, and conservators. We, as scientists, need to know how to communicate with other staff at the museum to gather the information we need, as we work on objects from disparate cultures and times. In addition, we need to have a deep knowledge of the traditions, techniques, and materials used to fabricate works of art.

Tell us more about how the team works together...

JA: The scientists of the Department of Scientific Research (DSR) have individual expertise in the identification and study of different materials. Since most artworks are composites of different materials, all of our work is in collaboration, because one technique and one scientist rarely has the solution.

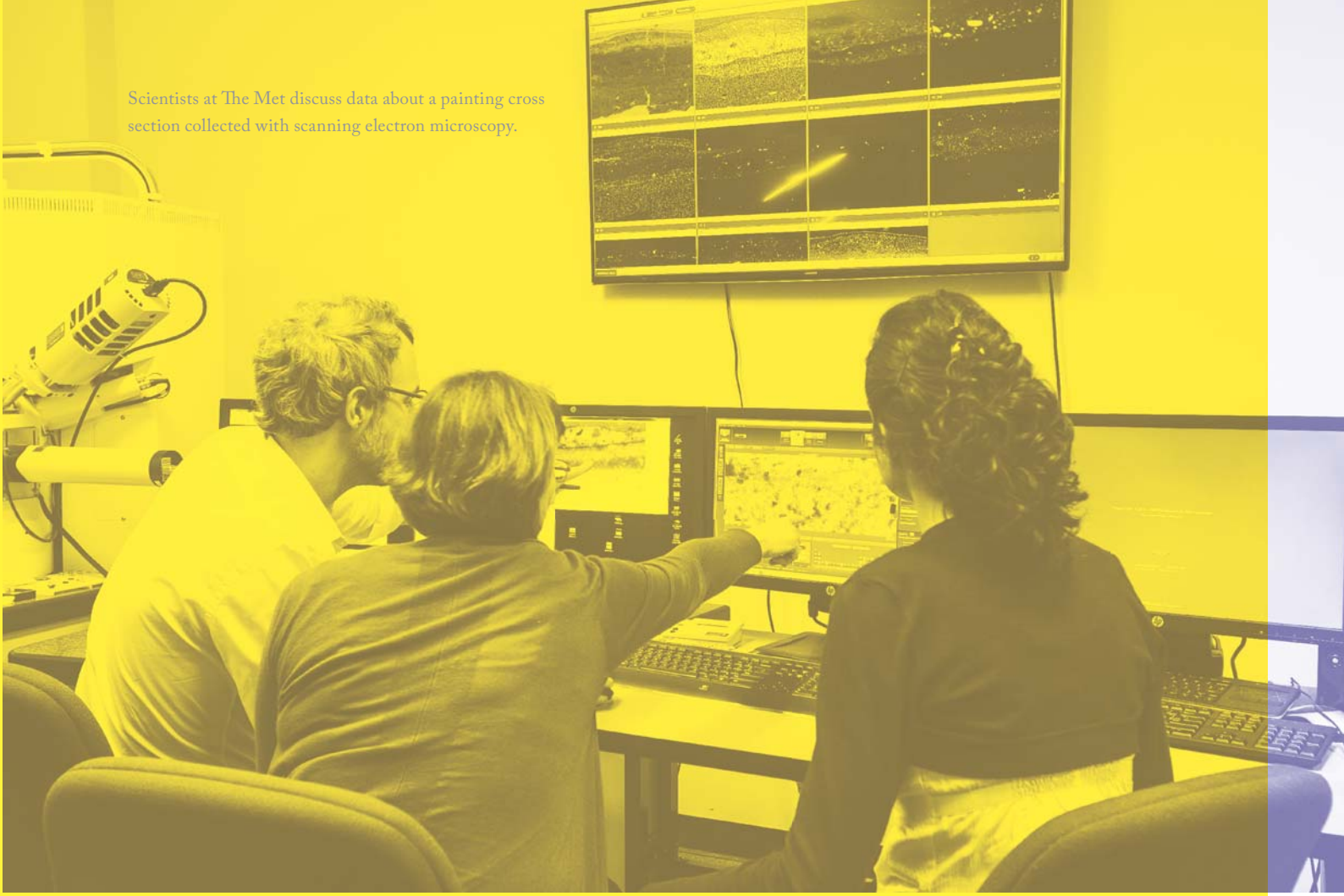
EB: Exactly – one single object may raise several questions, such as its material characterization, evaluation of the state of conservation and analysis of previous treatments, or how it should be displayed and stored.

FC: Our research group also includes three scientists working specifically on preventive conservation – monitoring the museum's climate and making sure that all the building and construction materials employed in the museum pose no harm to the works of art. The group is also developing an innovative, reproducible test for approving materials for use in the galleries and this may replace the qualitative test (known as Oddy test) now commonly used in museums.

"Our ability to answer questions about provenance, origin, or use is essential to the deeper understanding and contextualizing of artworks."

What analytical techniques do you use now, and what new tech would help move things forward?

JA: For the study of organic materials, we currently have: Fourier-transform infrared spectroscopy (two Bruker instruments – one coupled to a microscope and the other a portable instrument), a GC-MS (Agilent) equipped with a pyrolyzer (Frontier Lab), an HPLC system (Waters) and a plate reader for ELISA (SpectraMax). Mass spectrometry has become a crucial analytical tool as its sensitivity allows us to be far more precise in our characterizations, permitting animal and plant speciation as well as degradation evaluation and stability prediction that has not been possible before. Through New York University, we have access to a Bruker matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) instrument. Ideally, we'd like to acquire a system in-house that we can set to our specifications and also apply MS/MS and high spatial resolution imaging, in order to examine molecular interactions at interfaces of multi-layer structures. LC-MS would also be a powerful tool for our work. It provides complementary information to MALDI-TOF MS and excels at the analysis of smaller molecules, such as dyes.



Scientists at The Met discuss data about a painting cross section collected with scanning electron microscopy.

TEAM EFFORT

Federico Carò, Research Scientist, Department of Scientific Research
With a PhD in Earth Sciences, Federico oversees the investigation of inorganic materials employed in archaeological objects and works of art (pigments, glass, ceramic, metals, rocks, semi-precious and precious stones, etc.). He also investigates inorganic compounds that might manifest as a result of weathering and/or past conservation treatments. He works in direct collaboration with the museum's curators and conservators on a wide range of research projects relating to exhibitions, specific conservation treatments and broad art-history investigations.

Julie Arslanoglu, Research Scientist, Department of Scientific Research
Julie joined The Met in 2006 and focuses on the analysis of organic materials used in artworks from the entire collection, primarily paintings and works of art on paper, ranging from ancient Egyptian to modern and contemporary art. She works with curators, conservators, and her scientific colleagues to answer questions about paints made with oils, acrylics, protein and gum binders, varnishes, adhesives, and the changes that occur as these materials interact and age. She also develops and improves analytical approaches with collaborators for the study of these materials, primarily with mass spectrometric and immunology-based techniques.

Elena Basso, Research Associate, Department of Scientific Research
Elena, who only joined the team in November 2017, works mainly on inorganic materials used in art and archaeology, characterizing ceramics, glass, plasters, stones, metal alloys, pigments, and their degradation products. Together with Associate Research Scientist Federica Pozzi, she is committed to the Network Initiative for Conservation Science (NICS), an ambitious program established by The Met to provide scientific support to those museum partners in New York City who are not equipped for scientific analyses.

Fragment of a painted mummy shroud,
late 2nd-3rd century AD.

FC: I have access to both invasive and non-invasive techniques that include traditional approaches, such as petrographic microscopy or Bragg-Brentano X-ray diffractometry (XRD), and more innovative techniques such as electron backscattered diffraction (EBSD) within a scanning electron microscope (SEM) or scanning X-ray fluorescence spectroscopy (XRF). State-of-the-art instruments that can be operated non-invasively, such as micro XRD diffraction units with large 2D detectors would benefit my research, as I would be able to characterize crystalline phases in a large variety of archaeological objects and works of art that, because of their uniqueness, cannot be sampled.

What is the most exciting project you've worked on recently?

EB: We work on objects from all over the world, dating from prehistory to the present day. One of the most challenging but rewarding projects involved the analysis of an Egyptian stone sculpture from another museum. We determined the cause of intense cracking on the sculpture, and we were also able to indicate the most likely location where the stone was quarried.

JA: We have recently identified two unique families of plant-based polysaccharides, one of which contains two species, in a Roman Egyptian painted mummy shroud (2nd–3rd century A.D.). Because of the extremely low amounts of organic materials in the sample, we could never have achieved this with more traditional chromatographic approaches. This discovery opened the conversation among Egyptian experts about materials for image production, as the literature has maintained that ancient Egyptians used only one specific species of Acacia gum.

FC: I learn something new and exciting every time I investigate a new work of art. The diversity in technologies, techniques, and materials means almost every investigation is a fresh intellectual and scientific challenge. Right now, my colleagues and I are investigating the provenance of turquoise used in artifacts from ancient Egypt. This research is particularly satisfying because we are validating a fully non-invasive XRF procedure to gather meaningful chemical information from small turquoise artifacts that can't be sampled for other analyses, such as isotopic or trace element analysis. We can then use the data to help reconstruct trends of procurement, manufacture, and trade of turquoise stone during millennia of Egyptian history.

What inspires you?

EB: Ever since I was a child, archaeology and science have been my two passions. At university, I learned about archaeometry, an emerging field of science that applies scientific techniques to the analysis of archaeological materials, combining both of my interests. I was intrigued by how we could start from a small fragment of an object, and unravel how, when and where it was made.

"What drives me is my wonder at the amazing things that humans have created and cherish."

JA: What drives me is my wonder at the amazing things that humans have created and cherish, that still exist after a lifetime of travels, commerce, storage, and sometimes anonymity. The challenging, complex questions about materials (which ones were chosen, and why and how, along with why and how they have changed) drives my curiosity – both as a scientist and as an admirer of human expression.

FC: I am passionate about my work, and consider myself a very lucky scientist! I am particularly inspired by the strong, but sometimes invisible, connection that exists between technical and material choices and the artistic effect/product of artists and artisans. I enjoy discovering through scientific investigation that specific artistic results were achieved because of an intimate knowledge and skilled use of the available materials. This is valid for modern artists as well as for ancient civilizations.

How has the field of conservation advanced in the last couple of decades?

FC: Conservation, as well as scholarly research in the field of the arts, increasingly relies on scientific research. For instance, we are seeing a constant increase in the proportion of art history and conservation fellowships that require some kind of scientific investigation as part of their research.

EB: My perception is that conservation professionals have become more aware of the importance of scientific support for conservation treatments, which has resulted in larger investment in conservation science. This in turn allows scientific departments in museums to acquire state-of-the-art equipment and carry out cutting-edge research. Scientists and conservators working together definitely contributes to advancement in both fields.

JA: The field of art conservation has become much more sophisticated in its understanding and incorporation of the science behind observed phenomena. Scientific research has begun not only to provide material identification but also propose mechanisms and conditions for the changes that are observed in artists' materials. These scientific advances have helped provide more non-invasive techniques for the evaluation of artworks as well as guiding cleaning and structural conservation, for example, treating water-sensitive modern oil paintings, and in the species characterization of biological-originated materials.

What are the hot topics in heritage science?

FC: Conservation science relies increasingly on non-invasive techniques. The visual, synoptic presentation of large amounts of multi-layered data has the potential to increase the number of works of art and archaeological objects that can be investigated (to include those that can't be sampled, for instance) – and it allows a larger community of scholars (conservators, curators, and art historians) to access and properly interpret the results from scientific analysis. In addition, the improvement in the sensitivity of certain analytical instruments (for instance the development of laser ablation SERS) allows us to obtain information from very small amounts of material, something not possible a few years ago. Conservation scientists are continuously working with colleagues and peers from other research fields to adapt innovative analytical techniques to the study of artworks.

JA: At a minimum, non-invasive imaging techniques, such as scanning macro-XRF and multi- or hyperspectral imaging, provide a visual map for understanding similarities and differences of the surface of an object; at best, they can provide molecular information about the composition. The ability to create a "picture" of elemental distributions or organic components (such as the binder for a paint) is powerful; art historians, curators and conservators can use the information to guide interpretation and conservation treatment.

Does the public understand the value of conservation?

FC: I believe the value of conservation and science is generally underestimated. We need to make research in this field more visible, and to include the results from investigations by scientists and conservators in exhibitions and in the permanent galleries. There is an idea that the public find science boring, but in reality people enjoy discovering scientific facts about works of art, and are inspired when looking at objects from a different perspective. Combining art and science can also help young visitors to discover and relate to STEAM (science, technology, engineering, arts and math) topics.

"Our analyses provide another way to access and appreciate art, helping visitors to understand how an artwork was created and how its meaning and value has changed over time."

EB: People go to a museum to enjoy art, but also to learn. I think the majority of people are conscious of the importance of conservation, but relatively unaware of the contribution of science to this area. When I talk to people about my job, their first question is always: "Oh, so you deal with authentication?"

JA: Informed collectors are very knowledgeable about the value of conservation – and some are quite aware of the contribution of science to the conservation of their collections. When it comes to the general public, our analyses provide another way to access and appreciate art, helping visitors to understand how an artwork was created and how its meaning and value has changed over time.

What are the unique challenges of this field?

EB: I came to the museum from academia. At the university, I worked on medium- and long-term projects, dealing with large samples (up to 3–4 cm) – which allowed me to perform every kind of analysis I could think of and collect huge amounts of

Senior Research Scientist Silvia Centeno performs micro-Raman spectroscopy directly on a photograph from the Museum's collection.

MOTION PICTURES

A long-term collaboration between The Met and Bruker Corporation puts new tech to the test

The Met and Bruker have embarked on a ten-year collaboration to improve upon the instrumentation used for heritage science analysis. The Met's ambition is two-fold: to set up a mobile lab for the Network Initiative for Conservation Science (NICS), a new program established by The Met to support research at other museums in New York City, as well as to incorporate high performance mass spectrometric and X-ray diffraction equipment into the scientific department.

So how does the partnership work on a day-to-day basis? "We identify the challenges that we encounter– such as very limited sample, contaminated and degraded materials, and the need for a non-invasive approach – and work with Bruker to advance analytical technologies and methods," says Research Scientist Julie Arslanoglu. For example, NICS scientists were given the opportunity to test a prototype of the Bravo handheld Raman spectrometer for the non-invasive analysis of artworks, and the equipment was modified based on the team's critical review, before being launched to the market. Met scientists have also evaluated highly sensitive instrumentation such as UltrafleX MALDI-TOF-TOF with imaging for the analysis of microsamples from artworks.

"A collaboration of this nature has the potential to advance the field of heritage science," says Research Scientist Federico Carò. "The recent introduction of XRF scanners, such as the Bruker M6, has already radically changed the way we approach the study of art objects with relatively flat surfaces," he says. "In a few hours, it is now possible to collect high-resolution data from an artwork without the need for sampling – allowing us to map the distribution of materials at and below the object's surface, identify compositional changes and later additions or retouches, and plan a representative and minimally invasive sampling campaign, if necessary."

data. When you work in museum conservation science, the methodology remains more or less the same, but the approach is different. Data need to be collected and delivered in a short time, because results can impact on the choice of a conservation treatment. The sample size drops down to a few mm (if you are very lucky!), or even a single fiber or scraping from a surface.

JA: Working with extremely small, very materially complex samples, we often only have one chance to obtain an answer. Sampling artworks is not something that is done without careful consideration with conservators and curators but it is necessary when we can't answer the question with a non-destructive technique. Furthermore, the materials in artworks age over time, and the molecules interact with the atmosphere, light, and many different inorganic and organic materials. It is critical that our analytical methods are robust, reliable, and reproducible.

FC: As Elena and Julie said, the main analytical challenges relate to the very small samples – if any – we have to work with. Thus, highly sensitive, non-invasive analytical instruments would be ideal in our field.

How would you like to see the field develop?

JA: The study of the materials of art spans from the atomic to the macro scale, and advances are being made worldwide with the goal of understanding, monitoring and predicting chemical interactions. The ability to correlate many types of data about an object is a key development in our immediate future, as is predictive modelling of material behavior and degradation. These advances are incredibly challenging; however, fundamental research is required because we are modelling very complex systems.

EB: Science is often perceived as an "elite" discipline, so I would like to see more effort to make science accessible to everyone. Museums organize many activities for adults and kids – my hope is to include more science.

FC: I agree. I believe that we should strongly support and publicize scientific research, and keep proving the importance of science and scientific knowledge in our everyday life, including in the field of the arts and culture. As a scientist working in a museum, I do feel responsible for preserving our cultural heritage for future generations, and helping disseminate knowledge about ancient practices and materials to the public.

Learn more about the work of the museum at www.metmuseum.org.

Roses, by Vincent Van Gogh, oil on canvas (1890).

The Damascus Room, dated A.H. 1119/A.D. 1707.

One of the Met's scientists loading a MALDI plate with samples.

IN SERVICE TO OUR SMALLEST PATIENTS

Clinical laboratories serving pediatric wards face unique challenges and pressures. Find out how Great Ormond Street Hospital labs are evolving to face the future.

With Simon Heales

When you work at one of the foremost hospitals in the world, there's an expectation that you're always moving forward. Nowhere is this truer than at Great Ormond Street Hospital (GOSH) – a facility that serves an exclusively pediatric population, and one that provides the most difficult diagnostic and treatment challenges its staff have ever encountered. How do the labs at GOSH tackle these medical mysteries? By recognizing the unique needs of their patient population – and by working together across disciplines and specialties.

STILL A HOSPITAL FOR SICK CHILDREN

As pediatric pathologists, we provide the voice that children don't have. Children often can't tell doctors what's wrong with them, so the doctors rely on pathology services to provide that information – even more so than in any other setting. What makes GOSH unique is that our doctors receive tertiary and quaternary referrals – and that means the whole team must take on the most complex of medical problems. That's why I often say that there is no "routine" in our routine service. In fact, I try to avoid the word altogether. Instead, we call ourselves Pediatric Laboratory Medicine – emphasizing our focus on children's health.

I believe the doctors here understand that they would be somewhat at a loss without our services – so we're lucky to have the scope to host a range of different specialties. For instance, we have a center for lysosomal storage disorders and other enzyme deficiencies; we have areas to deal with hematology, immunology, microbiology, histopathology, and much more, all at a highly specialized level. And though it's certainly specialist work from an outside perspective, it doesn't always seem like that to us – unusual is our normal!

That said, it's not all esoteric – and we actively avoid change purely for the sake of change. Not everything needs to be updated just because it can be; if something already works really well – an enzyme assay, for instance – there's no point in spending months trying to automate it; some assays work better manually, and we use quite a lot of them. But, at the same time, we're investing significantly in mass spectrometry, because we can use that technology to analyze a wide range of metabolites in a single sample and get a very fast response. We feel very strongly about embracing state-of-the-art technology, but it must be adopted appropriately.

We also focus heavily on translational research here; I'm a biochemist by background, but as Head of Clinical Service for Laboratory Medicine, I also oversee hematology, immunology, microbiology, histology, and every other diagnostic specialty. I can see how closely they work together, and how much they might benefit from working even more closely. And that's what drives our desire for a "combined omics" approach to diagnostics and monitoring.

DEFINING COMBINED OMICS

Right now, in most hospitals, laboratory specialties are somewhat in silos. There is certainly crosstalk, but at GOSH, we're pushing for a completely integrated service. Instead of individual specialties, we want to develop our labs by technology – enzyme assays here, flow cytometry there, mass spectrometry over there – and share those technologies among all disciplines. We also want to have a unified specimen reception; at the moment, laboratories tend to have different specimen receptions depending on their disciplines, but a single receiving site would give us better control over preanalytical conditions. We want all of our specialists to have carefully controlled samples and unfettered access to tests and devices – but, even more importantly, we want to make sure that we're sharing our knowledge base as well as our tools, so that we can begin talking to – and understanding! – one another more effectively.

With the rise of genetics in the laboratory, we've found that our workload has only increased. When genetic analysis first came on the scene, my colleagues said things like, "We'll have to retrain as geneticists, because biochemists won't be needed." That couldn't be further from the truth! We need functional assays more than ever. Each time we find a new variant of unknown significance (VUS), we have to ask – is it functional? Answering that question requires enzyme assays, metabolite profiling, and other biochemical tests. It's the crux of "combined omics" – the integration of genomics, proteomics, metabolomics, and other omic disciplines.

> "With the rise of genetics in the laboratory, we've found that our workload has only increased."

The Trust is investing heavily in electronic patient record systems; we no longer want just a chemistry report, a microbiology report, a pathology report… Instead, reporting scientists will be able to pull results from different areas to develop an integrated report. In my opinion, such integration is the most comprehensive – and therefore best – option for our patients, and everything we do here, we do for them.

TRANSITIONING TO COMBINED OMICS

Pathology services across England are moving to a standardized hub-and-spoke model. We are currently in discussion with our network partners to explore closer working opportunities but pediatric pathology is a specialist service, so we need to ensure that the model works for our patient population and does not compromise patient safety. If you have a 120 µL blood sample from a newborn baby, you have to do all of your testing on that volume; the last thing you want to do is have to request a second blood draw. When dealing with a very sick neonate, you can't start sending samples off-site to non-specialist laboratories because that's not what's right for the patient.

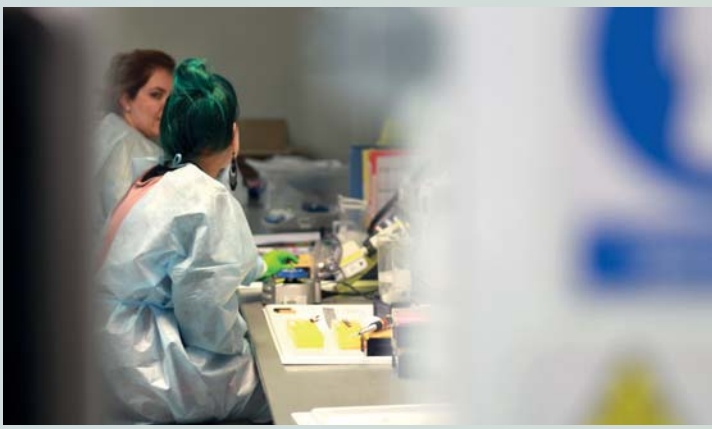
We're very fortunate here because the hospital, as a whole organization, is actively engaged with the lab. Not every hospital is like GOSH; when I talk to colleagues in similar positions, they often appear quite worn down by their roles – as if they're fighting a never-ending battle. On the other hand, I often feel like I'm being actively pushed to make positive changes for the lab. GOSH is a research-led hospital where scientific advancement is embedded into the working lives of our staff and the patients and families we treat and see. We're looking into implementing measures like generic consent, which would allow us to use excess tissue and blood samples for future research. It's especially valuable because we have the opportunity to use samples from a patient, conduct research,

PROTEOMICS

Our MALDI mass spec system – called Bonnie Tyler(!) – has made a massive difference to our protocols. For instance, whenever we received a new blood isolate, we used to take up to three days to identify the pathogen(s) involved and get an antibiogram – a summary of antibiotic susceptibilities. With Bonnie, we can take a positive blood culture, spin it down to get a pellet, identify the pathogen(s) in four hours or less, and begin treating the patient with more appropriate antibiotics based on species identification immediately, rather than just providing general recommendations based on a Gram stain.

We received a lot of support from our colleagues in biochemistry for this first venture into using proteomics – it was a very new thing for microbiology, after all. Our experienced biochemists helped us to understand what our results meant and what we could do with our new tools. Now, we've expanded to other types of analyses.

Currently, if we want to test for carbapenem-resistant Enterobacteriaceae, we have to take a sample, plate it, look at the pathogen's antibiogram, and then, if it looks resistant, perform follow-up testing in infection control. Final confirmation can take three weeks! And during that time, the affected patient must be isolated, receive special cleaning, go last on the list for investigations and operating theaters; in general, it really impacts on clinical care. To avoid that, we're introducing a new method that uses proteomics to look at enzyme cleavage of the antibiotic. In only two hours, we'll be able to get that confirmed result – sparing the patient weeks of disruption. I think it's clear how important that rapid proteomic result is to improving patient care!

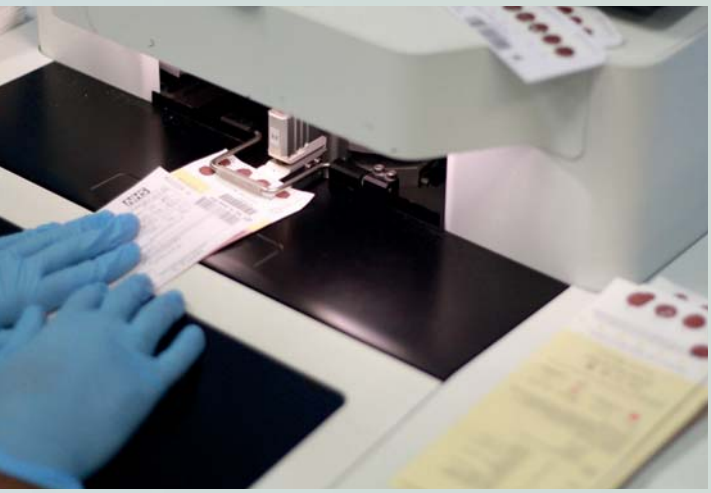


NEWBORN SCREENING

Tejswurree (Preetee) Ramgoolam and Helen Aitkenhead

The dried blood spot assay is a very simple test – just a pinprick for a drop of blood, and then we can perform nine different assays. It's normally done at five days old; a midwife takes the sample, puts it through the post, and we receive it within a day via a special registered address. Upon receipt, we label the sample and put it into the Panthera blood spot punching machine, which automatically evaluates the quality of the spot – and, if it's good enough, punches it in four different places for the nine assays. One of the punches is for the five inherited metabolic diseases (medium-chain acyl-CoA dehydrogenase deficiency, phenylketonuria, maple syrup urine disease, glutaric aciduria 1, isovaleric aciduria, and homocystinuria); the other three are for cystic fibrosis, congenital hypothyroidism, and sickle cell anemia. We perform our cystic fibrosis and hypothyroidism testing via automated immunoassay, which takes 1–3 minutes per sample. Because of the length of time per sample, we prepare and load all of the samples during the day, and run the assays overnight. When we come in the next morning, we can check all the results.

We also have three tandem mass spectrometers – two for metabolic disease testing and one for sickle cell anemia. Using tandem mass spec for screening is very reliable and has the advantage of avoiding the detection of asymptomatic sickle cell disease carriers. With HPLC, the detection of such carriers is unavoidable and leads to unnecessary follow-up testing and referral for genetic counseling.



"If we do not continue to move forward, we're doing our patients a disservice by looking at every result in isolation."

and then potentially take the results of that research directly back to benefit the same patient. I think that's what lies ahead for us – and hopefully for other institutions, too.

It's really important to get buy-in from all staff. In science, it can be hard to get people working together across the bench – let alone across the building. It's not the only challenge, though; once you have your staff on board, you have to work out how to implement change without compromising service; and how to ensure that everything is not only fit for purpose, but kept to an ISO standard as well. I think aspects of our work here make it easier to move to combined omics and to provide greater opportunities for our staff group. If we do not continue to move forward, we're doing our patients a disservice by looking at every result in isolation. Our highly specialized pediatric investigations will certainly benefit from a more integrated approach.

COLLABORATING TO IMPROVE CARE

I'm the Head of Laboratory Medicine at GOSH, but I'm also the Head of the Neurometabolic Unit at the National Hospital next door – so we've been working in partnership for quite a while, with a number of joint contracts and other arrangements that allow free movement between the two organizations. We're scientists at heart – and scientists are often good at networking and collaborating!

Here at GOSH, we compare ourselves to institutions like the Mayo Clinic, the Children's Hospital of Philadelphia, and Toronto's Hospital for Sick Children. Like them, we're hoping to become a sort of pediatric laboratory medicine supermarket, offering a broad range of specialist tests to other providers who may lack the facilities themselves. We have a great network

with those institutions; we're constantly in touch with them for consultations, second opinions, and advice. What we haven't done yet is share operational details – aspects such as funding, organizational structure, and increasing efficiency – but it's something I hope to investigate in the future.

I never hesitate to raise the profile of laboratory medicine to the wider Trust to highlight why we exist and our essential role in patient care. The training of the next generation is also embedded within our strategic plan. It will be news to no one that pathology is struggling to recruit graduates. With limited resources for recruitment and retention, we need to come up with new ways to attract new graduates and train them in our highly specialized areas. At the moment, there's a traditional training route to which all new NHS scientists must conform – but we've got to look at ways to customize training to suit different educational and career needs.

Industry partnerships also help us move forward. In my own interest area, metabolic disorders, we have healthy relationships with the companies that produce treatments – enzyme replacement therapies for lysosomal storage disorders, for instance. We collaborate with those companies to develop new assays in the laboratory, and the collaboration benefits the companies because it means that more patients are diagnosed faster and progress to the treatments they provide. More importantly, because the longer diagnosis is delayed, the worse the outcome in metabolic disorders, the collaborations allow us to identify patients in need of treatment so that we can improve or even save their lives.

PREVENTING PREANALYTICAL VARIATION

Preventing preanalytical variation is a key priority here at GOSH, and one I think is under-recognized in pathology and laboratory medicine – Carolyn Compton raised the issue wonderfully in "Garbage In, Garbage Out" in The Pathologist last month. We're working on a number of initiatives to prevent preanalytical error; for instance, the Trust invested in a dedicated member of staff for one year initially to reduce preanalytical error.

The staff member will focus on the development of practice, policy and procedures to reduce preanalytical error rates for

HISTORICAL INVESTIGATIONS

The histopathology department here at GOSH has records going back to post-mortems in the 1850s and archived material dating from about 1900. It's all FFPE (Formalin-Fixed Paraffin-Embedded), which means it's stable and safe indefinitely at room temperature. Recently, we went back to the archival material, cut fixed sections, removed the wax, and put it through mass spectrometry to see what proteins were present – and what anomalies existed in them (1).

Because our tissue archive is so huge, we can look back and see how disease has changed through time. So if you look through our records in 1900, a large number of children were affected by infectious diseases, such as tuberculosis – and, with the advent of antibiotics, we see a huge reduction in the number of children affected by infectious disease. And as children then began to live longer, cancer and chronic illnesses became more prominent.

Reference

1. *A Virasami et al., "Molecular diagnoses of century-old childhood tumors", Lancet Oncol, 18, e237 (2017). PMID: 28495283.*

clinical samples. They will be an integral part of the laboratory quality management team and, within this structure, will oversee the implementation, development and coordination of improved preanalytical quality processes.

They will provide leadership and direction on quality improvement processes linked to the collection and delivery of samples and will advise on sample quality issues, developing a team approach and encouraging sharing of best practice to meet the requirements of a patient-focused service, which is vital for our children and their families.

Getting the right samples to the right place at the right time isn't as "sexy" as new tests and fancy machines, but getting the basics right is truly important. The last thing any hospital, parent or child wants is for their sample to end up in the wrong department. Eliminating preanalytical variation is very dear to our hearts, so we're working hard to achieve that goal.

A MOVE TO MASS SPECTROMETRY

At GOSH, what we have right now is a virtual facility – with machines distributed around the department. We have just acquired a new system, and we're planning to acquire more as we increase our test volume and move toward more quantitative assays.

We use mass spectrometry a lot – newborn screening, vitamin D assays, metabolic analyses – which is why we are so eager to expand and improve those facilities. Mass spectrometry is powerful and relatively cheap (aside from the initial system purchase), so we want to move as many tests as possible onto that platform – appropriately. As I mentioned, not every assay needs to be conducted via mass spec – but many can and should be. For instance, we measure glycosaminoglycans in urine to diagnose and monitor lysosomal storage disorders. At the moment, we use two-dimensional electrophoresis, which takes quite a long time; with a mass spectrometer, you can do it all in a single run, and it becomes fully quantitative instead of just semi-quantitative.

We're also running more enzyme assays on the mass spec. Instead of running one long assay that yields a rate of change, we can perform up to 10 different enzyme assays on a single dried blood spot – we add all the different substrates, incubate, and then have the mass spectrometrist separate out the products. It's a great way of doing lots of enzyme assays at once – and it uses the skills of the scientist in new ways. I anticipate that mass spec will develop in many other areas – histopathology (where they're already looking at proteins from embedded blocks), immunology (for instance, by looking at cytokines), microbiology… For these applications, I consider the use of mass spec a no-brainer.

A WHISTLE-STOP TOUR OF

GOSH PATHOLOGY

ENZYMOLOGY

Derek Burke

In this laboratory, industry-funded posts complement our research. One of our staff members, Jonathan Lambert, has just finished a PhD on Fabry disease – both the diagnosis and the disease mechanism – that was funded jointly by his academic institution and by an industry partner. Now, another industry organization has provided two years of funding for him to set up an enzyme assay for asparaginase, which will be used in leukemia for treatment efficacy monitoring. We never expected this laboratory to be working on leukemia – but because we do enzymology so well, the company wanted to recruit one of our enzymologists. And we benefit as well: when Jonathan's grant finishes next year, his assay may be rolled out into the NHS as a diagnostic or monitoring test for leukemia patients. It's a good relationship.

We strongly emphasize the importance of translational research at GOSH; you might set up a new enzyme assay to use as a diagnostic tool – and, if it works, it will be in clinical use very quickly. Everything we do here, we do for our patients and our doctors, so the impact is immediately visible.

You can't talk about GOSH – and especially about the enzymology lab – without talking about newborn screening. Our program is the biggest in the country, screening about 130,000 babies each year.

MICROBIOLOGY

Elaine Cloutman-Green

We have quite an interesting way of approaching microbiology here at GOSH. We're trying to incorporate new rapid diagnostics, while simultaneously looking at new combined omics approaches to aid clinical interpretation. When we began to look at bacterial whole genome sequencing, for instance, we quickly realized that we couldn't look at that data in isolation. Genetically, the profiles were showing antimicrobial resistance (AMR) – but, when we conducted sensitivity testing, that's not what we saw. To clear up the confusion, we sent our samples for LC-MS/MS to look at proteomic expression profiles, and compared that data with our sequences to see what additional information we could glean and how essential it might be. What did we find? It turned out to be key, which is why we're now exploring how to use tools like MALDI-TOF MS for rapid CRE expression diagnostics. It's easy to miss things by looking at either DNA markers or expression profiles alone, so we are always trying to pair the two together. We really need to know what's functional to make reliable clinical decisions about patient treatment.

The AMR work is just one example of why it's important to have different tools and disciplines working together. I might sequence a viral genome alone – but then I go to immunology and ask what they've learned about the patient, because it definitely affects my interpretation. You can't do the clinical interpretation without understanding the overall disease process. With all of the data now available to us, interpretation is more complicated than ever. When you're designing clinical decision-making algorithms to handle big data, it's important to make sure that the final report can be fully understood by the clinical teams on the ward. From five million base pairs to a single page – that involves quite a bit of skill!

One thing that helps is to speak with the clinicians themselves. I ask, "What is it that you need from me? What information will change your management of the patient?" I can give them 101 different pieces of information, but that isn't helpful (and can even get in the way); all they really need are the few pieces that will affect the patient's diagnosis, treatment, and ongoing care. Best of all, we have everything we need on-site – so if a patient needs a test immediately, we can all pull together to optimize our use of a tiny sample and deliver rapid results in time to provide crucial treatment.

HISTOPATHOLOGY

Toby Hunt

Histopathology is the study of changes in tissue, which can have immunological, metabolic, oncological, or infection-based causes. We deal with a pediatric population – from fetal to about 16 years of age – and there are nuances to the pathology of those patients that you wouldn't necessarily see in an adult. To give you an example – consider the development of a kidney. A fetus may have a kidney, but because it has not completely finished its growth phase, there will be differences in its appearance to that of an adult kidney. To the average pathologist, it might look unusual or even pathological – but actually, for patients at that stage of development, it is the norm. Another classic example is the thymus; in a fetus or newborn, there's a prominent thymus to permit T cell maturation – but in adults, the thymus is atrophied or even completely absent, because it's no longer required. If you have a specialty service, you need specialty support. And there are a number of subtleties that our pathologists need to be aware

of to best serve a specialty population like ours.

In the Department of Histopathology here at GOSH, we take in two types of samples: neuropathology and "surgical pathology" (almost anything other than neurological). In short, we accept everything – brain, heart, lung, renal, tumor biopsies of all sorts… Because we are a tertiary referral center, our patients will have seen a general practitioner; the GP will have referred them to a hospital; the hospital will have undertaken its own investigations and then, if the issue is too obscure or too complex, the patient comes to us. In other words, we have to try to make a diagnosis where others could not – likely because they didn't have the same level of exposure to the condition or tumor, or to pediatric pathology as a whole.

In histopathology, we use a machine called a microtome to cut thin section of tissue. We then use these slices to visualize the cells that make up that tissue so that we can understand and report on a disease process. Unlike many other hospitals, when a sample comes to us, we use almost 100 percent of what we get; because our patients are so young, our samples are often very small. Much of the material we receive is fresh, not fixed, because of the investigations we undertake. If an adult hospital receives a tumor biopsy (for instance, from a breast tumor or prostate core), they put it into formalin, the formalin goes off with the sample in it, it's given its individual accession number, popped into a processor, cut, stained, and the resulting images interpreted. When we receive a tumor biopsy, we take a portion of that fresh tissue, immediately produce imprints (by dabbing the tissue onto a slide so that cells adhere to the glass), and send the slides for cytogenetic testing. If the sample comes from the brain, we may also do a brain smear, which involves producing a monolayer of cells on a slide for interpretation – something that we turn around very quickly so that we can offer surgical guidance. Are tumor cells present in the sample? Is it an aggressive tumor type? What form of resection or other treatment would be best?

We then subdivide the remaining material into pieces and freeze some of them prospectively, in case a future test is able to give us an answer that our current ones cannot. Many of the tumors we see are rare – some come into the laboratory only once every few years – so we always try to retain some material for future investigations. Every sample is a new challenge, so we prepare ourselves to run every test that is currently available – and those that may become available one day…

Finally, we fix the remaining tissue to run what adult pathologists might consider more "routine" histopathology. The gold standard for looking at tissue is, of course, hematoxylin and eosin staining – a pattern that is recognized by all trained pathologists. Beyond that, we also do special stains. For instance, we have a special stain for acid-fast bacilli (like those that cause tuberculosis). We can tell you whether or not a patient has the disease – but what we can't tell you is whether or not that pathogen exhibits drug resistance. And that's when we need to communicate with microbiology, who can add the next piece of the puzzle and tell us (and the clinician looking after the patient) which antibiotics are most likely to be effective.

Neurometabolic disorders are a good example of our approach to testing. When we receive a skin or muscle biopsy to test for metabolic disorders, we conduct a batch of tests; most of those must be performed on fresh or snap-frozen tissue because the techniques we use are dependent upon the enzymes present. As soon as you take that material away from the body, it begins to break down. So we perform enzyme histochemistry, which indicates whether or not an enzyme of interest is present in the tissue. We send some material to other laboratories for biochemistry or other analyses (such as enzymology). We section some material and send it for electron microscopy. Why? Because no one test can stand in isolation. Microscopy might reveal enlarged mitochondria or storage granules in the tissue – but why are the mitochondria enlarged? What's in those storage granules? We need enzyme histochemistry to reveal the actual biochemical deficiency. But what causes that deficiency? Is it a genetic condition? Our colleagues in the genetics department can tell us that – either by finding the genes for a known disorder, or by examining the entire exome or genome to identify a new genetic condition. It's clear that none of us can do our jobs without the others; we all have to work together to figure out what is going on.

We are also involved with evaluating "new" histopathology techniques, such as micro-CT for visualizing small specimens, mass spectroscopy to evidence the presence of particular proteins within formalin-fixed, paraffin-embedded (FFPE) material, and DNA sequencing of historical archival material (see "Historical investigations").

FLOW CYTOMETRY

Sarah Inglott

Our flow cytometry laboratory performs diagnostic and monitoring analyses as well as translational research and academic collaborations. On the diagnostic and monitoring side, we analyze peripheral blood and bone marrow, solid tumor, and spinal fluid samples. We assess children with suspected hematologic malignancies for leukemia-associated phenotype (LAP) markers. We can then monitor their progress through treatment, track their minimal residual disease, and conduct follow-up testing for potential relapse. We also monitor chimeric antigen receptor T cell (CAR-T) therapy patients for treatment response and potential relapse of disease. CAR-T cells target a specific epitope, typically CD19 or CD22 in B cell leukemias or alternative epitopes in solid tumors. But following a period of successful response to therapy,

there is always the potential for relapse – and the relapsed disease can then evolve to stop expressing its target epitope. This loss of expression affects the way we have to analyze the resulting disease; gating strategies have to change, which involves using different, potentially non-lineage-specific markers. We can do this down to two cells in a million where phenotypic aberrances are pronounced. Detecting returning disease at such low levels allows for changes in disease management and therapy with greater effect than waiting for relapse to become clinically frank.

In addition, we run biomarker tests for diseases such as neuroblastoma. It's a cancer, prevalent in pediatrics but nonexistent in adults – and it has a very poor prognosis. We want to work out how to detect it at low level, or when it has infiltrated into the bone marrow (as this alters the disease staging and treatment). We also monitor the efficacy of CAR-T therapies that might improve outcomes for neuroblastoma patients.

RAPID RESPONSE

Simon Heales

Our "rapid response" laboratory operates at a high throughput 24 hours a day, seven days a week. We refuse to call it a routine laboratory, as I said, because there's nothing routine about it. One key difference between this and an adult lab is the much smaller sample volume. We have to be highly proficient at conducting tests on very small amounts of sample, because children simply have less blood to give.

The other significant difference is that children are not just small adults – at least in terms of their biochemistry – and so it's vital that we understand those differences and remain child-focused. For one thing, changes happen faster and have a greater effect, so even more than in adults, speed is always of the essence. In some of the disorders we work with, rapid diagnosis can prevent irreversible brain or organ damage – or even death. Adults are often at the other end of the spectrum; diseases like Alzheimer's or Parkinson's move slowly and may not have effective interventions.

The speed required in our work is just one more way in which pediatric pathology is completely unique. We're working on puzzles that no one has previously attempted to solve, and we're trying to do it as rapidly, comprehensively, and collaboratively as possible.

THE ART of Writing

Publications are vital to building your profile, but for many scientists it's less of an art and more of an afterthought. Here, we present a straightforward guide to preparing papers and posters that will get you noticed.

By Paul R. Haddad, Emily F. Hilder and Frantisek Svec

Over the years, we have presented the "Scientific Writing and Publishing" course at a number of analytical science conferences across the world. The origins of the course lie in discussions between the editors of several major journals in the field about the common mistakes made by authors, especially young scientists. Here, we distill the course into a straightforward guide to creating journal articles and posters that are clear and concise – but that also catch the reader's attention.

THE WRITE STUFF

How to prepare a manuscript for publication.

Before you type a single syllable, ask yourself: are my results suitable for publication?

Publications are one of the important outputs of any scientific researcher. Results that stay "in the drawer" and are not shared with the community are of little value to you or others. Publishing papers and presenting at scientific meetings serves not only the outside community, but your own career, especially when you are starting out. Defending a PhD thesis with no published papers is exceedingly difficult at best, and your publication record is scrutinized by granting agencies when reviewing project proposals.

Clearly, publishing your work is of utmost importance. But first you have to be sure that your research is sufficient. The first and most important question is whether you have discovered something new and interesting. Good journal editors and peer reviewers will quickly see through attempts to publish papers that present only an incremental development, such as separations of different compounds using a well-known method, or jumping on the bandwagon of a hot topic to publish a "me too" paper. You should also spend some time thinking about the major challenges of the work you carried out and whether you solved a difficult problem. If the answers to all these questions are "yes," then it is time to grab a coffee, settle down at your desk and...

Select a journal

Once you have decided to write a paper, the next step is to select the journal in which you want to publish. All journals are not created equal. It is critical to make sure that your research lies within the scope of the journal, which is typically found in the "Instructions for Authors" on the journal's website. It is also a good idea to look at a few current issues of that journal to get a feel for the type of research that is being published. Submitting a manuscript to a journal that covers a completely different field is a total waste of time. Several major publishers helpfully provide tools to help match your research to a journal from their portfolio (1–3).

A frequently mentioned parameter used to differentiate journals is the impact factor (IF), which indicates how often papers published in that journal are cited over a defined period. Publishing in high IF journals contributes to the personal prestige of the author and improves the image of their institution, so a spot in one of these journals is much sought after. However, journals with a high IF are often highly selective in the manuscripts they choose to publish and their rejection rate is usually very high. Plus, some of these journals favor certain topics. After all, how many chromatographic papers do we see in Science or Nature? Remember that the impact of the work you publish should prevail over the impact factor of the journal in which it is published. Therefore, you should choose a journal that is read by a large number of people in your own field.

Great on paper

Each journal has specific requirements for submitted manuscripts, which should be read by all authors before they start writing. Many authors have the impression that the journal editors will correct their poorly formatted manuscript to make it publishable, but editors handle hundreds of manuscripts each year (the vast majority of which are formatted incorrectly). Improper formatting will instead lead a submitted manuscript to be immediately returned to the authors for reformatting, causing a delay before the article can even be processed.

While writing, authors should always keep in mind the potential readers. For example, though the use of abbreviations makes the writing faster (and the manuscript slightly shorter), too many abbreviations make the manuscript difficult to follow and can cause readers to lose interest. A particularly common error is the use of abbreviations in the title or abstract. Who would understand the title "Development of an analytical method to quantify PBDEs, OH-BDEs, HBCDs, 2,4,6-TBP, EH-TBB, and BEH-TEBP in human serum"? Most readers would not care to read even the abstract. A better title would be "Development of an analytical method to quantify polybrominated diphenyl ethers flame retardants in human serum."

Choosing the right keywords is also important, as these are typically used in literature searches. A keyword such as "Ultra-high performance liquid chromatography-Q Exactive hybrid quadrupole-Orbitrap high-resolution accurate mass spectrometry" is completely useless. Instead, consider what keywords you would use when searching for your paper in PubMed or similar databases.

Figures are an important part of any manuscript, but there are a number of pitfalls for the unwary. As some journals restrict the length of a printed paper, too many authors try to condense their manuscript by combining several figure panels into a single figure until each panel is so small that it is difficult to see the details, rendering them next to useless. A better approach is to show only the most important figures in the published paper and include all other figures in the electronic Supplementary Information. Despite the obvious importance of graphics, authors continue to submit completely inappropriate, uninformative and unnecessary figures.

Finally, don't forget the references. It is easy today to generate a large number of references using computerized databases. Thus, manuscripts including more than 50 references are becoming commonplace. Unfortunately, not all authors read the references that they cite and it is not uncommon to find some that are completely irrelevant to the paper, which is unlikely to leave editors or reviewers with a favorable impression. Also, avoid including an excessive number of self-references – you are more likely to irritate than impress. Authors should also keep in mind that each journal requires a specific format for references. It is sometimes possible to recognize where a manuscript has been submitted previously just from the format of the references, immediately telling the editor that this manuscript has been rejected previously. So be sure to re-format the reference list before submitting to a new journal.

MANUSCRIPT MISTAKES

Ten of the most common errors made by authors:

1. *Submission of papers that are clearly out of scope*
2. *Resubmission of a rejected manuscript (to the same or different journal) without revision*
3. *Not sticking to the format required by the journal*
4. *Typos and grammar errors*
5. *Overzealous use of (undefined) abbreviations*
6. *Poor selection of keywords*
7. *Plagiarism, especially of small parts of a paper*
8. *Too many figures*
9. *Poor legibility of figures*
10. *Too many references and excessive self-referencing*

POSTER HASTE

How to create and present an eye-catching poster.

For most young scientists, the first opportunity to present work to the scientific community comes in the form of a poster presentation at a scientific meeting. Posters are a unique and important form of scientific communication because they allow direct and personal communication between the presenter and the audience. However, there are some major challenges associated with poster presentations. First, poster sessions at major conferences are often crowded and very limited on time, so the primary challenge is to attract an audience by preparing a poster that is arresting, visually appealing and scientifically exciting. Second, a poster must be able to convey its major findings in 1–2 minutes through a logical and clear layout and focused interaction between the poster presenter and audience.

Attracting an audience

A primary feature of poster sessions is that attendees can be selective about which posters they will read and discuss with the presenter. So how can you get people to stop at your poster rather than walking by? These five points will help you to stand out:

1. Posters are a visual communication tool, so graphic design is essential. Think about the overall impact of your poster in terms of layout, photographs, figures, schematics, and so on, to convey information without words. Suitable use of color throughout the poster is also essential. If you have a colleague or friend (whether or not they are a scientist) who is skilled in graphic design, it is a good idea to get their opinion and feedback on your poster layout.
2. A clear and logical layout is also essential. Start with an informative and brief title and then include clearly delineated sections showing background, aims, experimental, results, conclusions, references and acknowledgements. The logical flow of the poster should be immediately apparent so that the reader can easily move from one section to the next in the correct sequence. To assist this process, each section should be numbered and you might also wish to include arrows to guide the reader to each successive section.
3. Include a photograph of yourself (as the poster presenter) in a top corner of the poster so that you can be easily identified amongst the crowds of people at the poster session.
4. Don't forget to carefully check the poster size requirements for the particular conference that you are attending. Poster boards vary widely and it is your responsibility to ensure that your poster fits on the board provided. Avoid landscape formats as most poster boards will not accommodate this format. The safest approach is to use a portrait format printed in A0 size. Laminating your poster improves its durability but the resulting shiny, reflective surface can be hard to read.
5. Legibility is the chief concern, so keep text to an absolute minimum. Given that most posters are printed in A0 format (841 mm wide × 1189 mm high) and are viewed from a distance of approximately 1 m, a good way to check legibility is to print your poster on an A4 sheet and hold it 25 cm from your nose. If you can read the A4 version easily from this distance then your A0 poster will be easily legible from 1 m.

Getting your message across

Once you have managed to attract an audience for your poster (remembering that the audience will normally be one person), you must be ready to engage with that audience in a friendly and open manner.

1. Ensure that you attend your poster at the designated time. Most conferences will assign each poster to only one or two poster sessions so the audience will expect you to be present at your poster for the entire designated time.
2. Prepare a 1–2 minute overview of the aims and major findings of your poster and be ready to guide the audience through your poster. When someone stops at your poster you can ask politely "May I give you a 1 minute overview of my work?" People will rarely refuse this offer as it is generally faster than trying to read the poster themselves. This oral presentation must be focused and clear and you should rehearse it carefully. The audience can then extend the discussion, or move on to the next poster.
3. You may wish to provide an A4 copy of your poster for people to take away and read in more detail later. It is also useful to have an open envelope at the bottom of your poster (many conferences provide this) so that people can leave their business cards to request further information or a reprint of your poster.

POSTER PITFALLS

Five of the most common mistakes in preparing and presenting posters:

1. Poster will not fit neatly on the poster board
2. Poster is illegible from a distance of 1 m
3. Poster looks boring or has too much text
4. Poster presenter is not in attendance at the designated session
5. Poster presenter takes too long to explain their work

ONCE MORE WITH FEELING

How to navigate the review and revision process.

For many authors the details of peer review are opaque, making the process confusing and disheartening, particularly for young scientists. Read on as we attempt to demystify peer review and equip you with the tools to participate constructively as both author and reviewer.

Submission

Most journals use similar online submission platforms, structured to guide authors through the submission process. Just as it is important to format your manuscript to meet the journal's specific requirements, it is essential that the journal's instructions are followed concerning the information and files required. Without this information it can be difficult or impossible for a manuscript to be reviewed fairly, and a lack of information can also delay publication if the manuscript is ultimately accepted.

Authors should be aware that most journals now undertake an electronic check of the manuscript for plagiarism – a process that will identify any sections of text that have appeared in previous publications or on the internet. If the overlap with previously published work is considered to be excessive, the manuscript will be rejected. Take extreme care to avoid plagiarism as this is considered completely unacceptable – even if you are "borrowing" your own words from previous work.

Why is the cover letter important?

In addition to providing the core documents, including the manuscript text, figures and any supporting information, a critical and often underappreciated aspect of the submission process is the cover letter or justification statement. Almost all journals receive many more manuscript submissions than they can reasonably publish. Each journal will also have a defined target audience and thus will consider not only the novelty of the work but also the fit and interest for their target audience. For this reason, it is very important that the authors carefully consider the aims and scope of the journal and provide a strong justification as to why their work will be of interest to readers; most journals now require the authors to submit a cover letter and/or justification along with the manuscript. Rather than a chore, it is an opportunity for the authors to communicate directly with the editor and explain why their work is novel, what contribution it makes to the field and how it fits within the scope of the journal. Editors will not reject a manuscript because the cover letter is bad. However, a cover letter that piques the editor's interest may accelerate the editorial progress of your paper.

Nominated reviewers

Many journals ask authors to recommend possible reviewers, which is an important opportunity to contribute to the fair review of your manuscript by appropriate experts in the field. By suggesting inappropriate reviewers, you send a clear message to the editor: you are not familiar with the literature in your field or not confident in your work. Here are some general guidelines for choosing appropriate reviewers.

Inappropriate reviewers are:

- Editors of the journal (or editors of other journals)
- The top scientists in the world
- Your research collaborators
- People from your own institution
- A group of reviewers drawn solely from your country
- People without a publication record in the field

Appropriate reviewers include:

- People who publish actively in the field, especially in the journal
- People whose work you have cited and discussed in the Introduction of your manuscript
- Members of the advisory board of the journal where you submit your manuscript

Though authors may be asked to recommend potential reviewers, the editor will ultimately decide who will review a manuscript. The reviewers will provide both a recommendation on whether the manuscript should be published, and comments supporting this recommendation. It is a common misconception that the final decision by the editor will always directly follow the recommendations of the reviewers. Editors certainly do rely on reviewers to provide expert advice on manuscripts and their suitability for publication, but the final decision will be made by the editor, who must balance feedback from multiple reviewers.

For each manuscript that you submit for publication, a number of other scientists will give their time to review and provide feedback. To allow this system to continue, it is critical that if you publish in the scientific literature, you also actively support the peer review process. For younger scientists, providing high quality and timely reviews is an excellent way to increase your visibility. And it also provides a very effective way to engage with editors and experts in your field. In our experience, young scientists are often very well informed in their area of specialization and can be very effective reviewers. A recent editorial explaining how to prepare a helpful review gives some helpful tips for novices (4).

Responding to reviewer comments

One of the most challenging aspects of the publication process is that you must open your work to critical feedback – and this feedback is not always positive. Remember that all authors, even the most senior in the field, must respond to criticisms of their work. Read the reviewers' comments dispassionately and don't take offence – after all, the reviewers have taken time to read your manuscript and provide suggestions to improve it. In many cases you will be asked to address the feedback from the reviewers and revise your manuscript accordingly. Be sure to address all comments, including any specific instructions from the editor and/or editorial office. We suggest preparing a document that lists each reviewer's comment, your response to that comment, and what specific changes have been made in the manuscript, each in a different color font. If a particular reviewer's comment is not clear you may request clarification through the editorial office.

In some cases, you will receive a decision that your submission has been rejected for publication. Though never welcome news, rejection is something that almost all scientists experience in the course of their career – including the authors of this article! In some cases, the editor will reject a manuscript without review – sometimes referred to as a desk rejection – but it is not necessarily a reflection on the quality of the research. Rather, the rejection may be based on other factors, such as the manuscript being presented in the incorrect form or written in poor English that prevents proper understanding of the work.

When a manuscript is rejected following peer review, remember that you have received the benefit of the reviewers' time; don't ignore the advice they have given. If you choose to submit your manuscript elsewhere you should revise the manuscript appropriately before resubmission and never resubmit the manuscript unchanged. The scientific community within a specialized area can be small, and it is very likely that the same reviewers may see your manuscript again. We suggest that when resubmitting a previously rejected manuscript to a new journal, you should declare the history of the previous submission in your cover letter and also include the reviewers' comments and your response showing how you have addressed these comments. This makes the new editor's job much easier and in many cases will greatly speed up the review process – it may even result in your manuscript requiring no further review.

FIVE TIPS FOR BETTER WRITING

The Analytical Scientist editorial team give their top tips for better writing in any context.

1. Be concise.

2. Don't use unnecessarily complicated language.

3. Avoid cliché and hyperbole. (Approach "paradigm shifts" and "holy grails" with caution.)

4. Be your own editor. Go back to a piece of writing a day or two later – you'll find it is much easier to spot any mistakes.

5. Write something, even if it's bad. Getting the thought down on paper, in any form, is often the hardest part.

PARTING WORDS

Getting a manuscript published in a good journal is never easy; most journals have high rejection rates. There is no secret recipe for success – just some simple rules, dedication and hard work. Authors should remember that editors are very busy people, so it is in everyone's interests to make the editor's job as straightforward as possible. Authors should cherish their work and take the greatest care in preparing their manuscripts properly. Finally, authors must expect some of their submissions to be rejected. Rejection is a statistical inevitability – the important thing is to understand why the article was rejected and incorporate this knowledge into future submissions. Success will come if you persevere.

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Profession

Leadership
Talent Development
Career Planning

Those Who Can, Teach: Anna Donnell

Continuing our series of interviews with innovative educators, we find out how new tools are bringing a fresh approach to chemistry teaching at the University of Cincinnati.

Anna Donnell is Assistant Director of the Center for the Enhancement of Teaching & Learning (CET&L) at the University of Cincinnati, Ohio, USA. During her time at the university, she has taught as an adjunct in the Department of Chemistry and consulted with other faculty members to redesign its courses, with projects ranging from the creation of a robust laboratory course assessment strategy to the incorporation of a tablet to allow freedom of movement during classroom activities.

What motivates you to teach?

I've always loved figuring out how the world works and helping others do the same. My passion for science started at a young age and developed alongside my enjoyment of teaching others. In my role as an educational developer, I not only get to teach faculty about evidence-based pedagogies, but I also work closely with faculty in a range of disciplines to incorporate evidence-based practices into their teaching. Many new faculty are surprised that CET&L exists as a resource and welcome new ideas for making their courses more engaging, inclusive, and active.

What motivates your students to learn?

For many students, an experience or person piques their interest and causes them to want to learn more. We can work to motivate students by relating chemistry to the world around us and by getting to know our students, but we also need to work to keep students motivated and continue to support them through graduation and in their careers. I was lucky to be educated and mentored by several inspiring female teachers who made chemistry relevant, but, perhaps more importantly, they also gave me a bit of a push and the confidence to continue to study chemistry and pursue my PhD. They continue to mentor and support me, and I have become a mentor for some of their students as well!

What is the best approach to teaching analytical chemistry?

I approach the subject from a very practical, hands-on, real-world point of view. Creating active learning opportunities during class where students can apply knowledge to real-world situations is not only motivating, but develops skills that they will use when they graduate. Students enjoy connecting what they are learning in the classroom to their local community or to issues that affect their daily life. I often try to incorporate applied chemistry through videos, current events, and literature to engage my students.

What is your biggest challenge in teaching?

Today's students are juggling far more than just their coursework. Most of my students are working part-time jobs and

"I was lucky to be educated and mentored by several inspiring female teachers who made chemistry relevant to the world around me."

they need to develop time management skills to attend to both areas of their life while trying to feel connected to the college community. To overcome this challenge, I am very purposeful in the work that I have my students do outside of class, and I also communicate how what they do outside of class connects to what we are doing in class. I want students to feel like these assignments matter and that I respect their time.

What valuable skills are graduating students lacking?

Communication skills, often classified under "soft skills", are continually recognized by employers as highly desired but not necessarily well developed in students. Partly because these skills sit outside the content of the class, they often aren't directly addressed. In addition, large class sizes may limit communication-based activities, such as presentations. We can provide a variety of ways for students to practice their communication skills, even in large classes, such as group activities, projects, and "low-stakes" (or informally graded) writing assignments.

What impact has technology had on the way you teach?

The benefits of technology far outweigh the potential for distraction. Efficiencies in students working together in groups and streamlining some of the logistics of teaching, such as turning in assignments and grading, have made life far easier. For group projects, I use a file sharing tool called Box – everyone has access through their university username, there is technical support through our Help Desk, and I can monitor groups' progress at any time rather than waiting for groups to turn in the final assignment.

How do you see the future of new technologies in education?

Educational technology is rapidly evolving and expanding; however, we can't count on our students knowing how to use it. The notion that students are "digital natives" assumes that students can figure something out because they've been exposed to technology their whole lives. In reality, students don't want to have to keep learning new technologies for each course they take, it's exhausting and hard to keep track of which tool you are using for which class.

"Do you want more students to participate? Do you want to figure out a better way to grade a particular assignment? Do you want to know what students retain from pre-class reading?"

I work with faculty members to figure out the simplest tool that students are familiar with that meets the pedagogical goal, rather than start with the flashiest new tool out there. Our first step is to see if a university-supported tool fits their needs because that guarantees that all students have access, students may be familiar with the tool already, and there is technical support. Our next step is to identify resources for students on how to use the tool. This takes the burden off the professor so that they can focus on the activity or assignment, rather than answering technical questions about the tool. Often, the simpler the tool, the better.

Could you give an example of a course you've helped redesign?

Over the past few years, I've worked to redesign our Analytical Laboratory course. A major component involved developing new experiments that incorporated real-world applications. I developed an experiment to detect arsenic in sinus wash and tap water using inductively coupled plasma–mass spectrometry (ICP-MS), which continues to be one of the students' favorite labs. Students can bring in their own tap water sample and are eager to test water from their homes and locations around the city. I also developed a robust rubric and peer evaluation form to aid in grading the laboratory reports and monitoring how students work in groups. Both of these tools have resulted in more consistent grading and fewer group dynamic issues.

What advice would you give to teachers who want to incorporate new techniques into their teaching?

First, I would start with your goal. Do you want more students to participate? Do you want to figure out a better way to grade a particular assignment? Do you want to know what students retain from pre-class reading? From there, I would look to see what others have done so you don't have to reinvent the wheel. There is a great deal of literature out there and plenty of resources on active learning, assessment, course design, inclusive teaching, and so on. Your institution may have a Center for Teaching and Learning that can also help you find strategies that fit your goal. Finally, start small. Try to incorporate one new strategy in the next course you teach; gather feedback from students and reflect on how you think it went to help you make adjustments for next time.

Antibiotic Analysis by HPLC-ECD According USP/EP Monographs

Analyzing aminoglycoside and macrolide antibiotics in bulk products and pharmaceutical formulations.

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With the increasing demand in product quality and safety assurance for antibiotics, sensitive analytical methods are required. HPLC with electrochemical detection (HPLC-ECD) is the best analytical platform that fulfils all the criteria including sensitive impurity profiling, and the detection of by-products at low cost of operation and ownership (unlike LC/MS).

To guarantee ease of use and reliable results, Antec Scientific has developed a dedicated Antibiotics Analyzer that can be used for any type of aminoglycoside or macrolide antibiotics analysis.

ECD-PAD: the ideal detection

Both categories of antibiotics (aminoglycosides and macrolides), as well as most relevant impurities and by-products, contain one or more carbohydrate moieties on each molecule. This makes the use of pulsed amperometric detection (PAD) the ideal analytical technique, not only for the analysis of the antibiotic itself but in particular for the sensitive analysis of impurities and by-products. The preceding separation can be based either on reversed phase HPLC with post column addition of sodium hydroxide or the use of high performance anion exchange chromatography (HPAEC).

Two types of electrochemical flow cells are available: The FlexCell with easy exchangeable gold (Au) working electrode for routine use and the SenCell with integrated Au electrode and a stainless-steel auxiliary electrode, which is a requirement in some EP/USP monographs.

Figure 2. ALEXYS Antibiotics Analyzer for aminoglycosides and macrolides antibiotics analysis, based on RP-HPLC or HPAEC with PAD (3 or 4 steps) detection. Inserts: (A) FlexCell (routine use) and (B) SenCell (in case of EP/USP requirement). Sensitivity FlexCell 100 nmol/L, SenCell 10 nmol/L.

Figure 1. Salmonella typhi, a Gram-negative bacterium causing typhoid fever, which is treated with the macrolide antibiotic azithromycin.

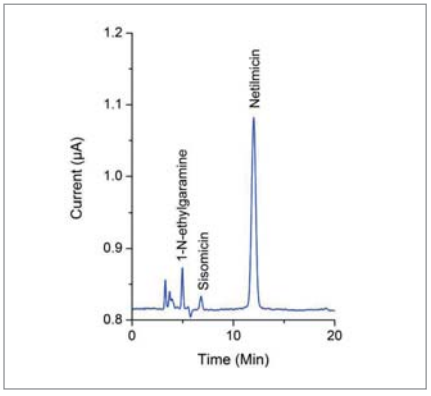

Figure 3. 20 µL injection of a standard consisting of 10 µg/mL netilmicin sulfate CRS (CRS - Chemical Reference Substances), 10 µg/ml sisomicin sulfate CRS and 8.2µg/ml 1-N-ethylgaramine sulfate CRS in mobile phase. ALEXYS Antibiotics Analyzer.

Example: netilmicin sulfate analysis according EP 8.1

Netilmicin is a semi-synthetic aminoglycoside antibiotic synthesized by alkylation of sisomicin (1-N-ethyl derivative). It is an effective antibiotic used against a wide range of gram-positive and gram-negative bacteria. Netilmicin is available as injectable and ophthalmic pharmaceutical preparations.

During the synthesis of netilmicin, by-products are formed at low concentrations such as 2'-N-ethyl and 6'-N-ethyl derivatives of sisomicin (alkylation products) and 1-N-ethylgaramine (hydrolysis product). UV detection is not suitable for the detection of low levels of netilmicin and its impurities because they have a weak UV chromophore. However, pulsed amperometric detection (PAD) can be successfully utilized as described in the European Pharmacopoeia 8.1 (2014). A chromatogram recorded under the required conditions is shown in Figure 3. The separation of netilmicin and its major impurities, i.e., sisomicin and 1–N-ethylgaramine, are based on RP-HPLC followed by post column addition of NaOH solution upfront PAD detection, and it meets all the system suitability criteria of the EP method.

Conclusions

With the ALEXYS Antibiotics Analyzer the EP criteria for composition and impurity analysis in commercial netilmicin formulations are easily fulfilled. Comprehensive, scientific product applications are available for aminoglycosides such as: amikacin, framycetin, gentamicin, kanamycin, lincomycin, neomycin, spectinomycin, streptomycin, tobramycin to name a few. In addition, macrolide antibiotics such as azithromycin, clarithromycin, erythromycin, and roxithromycin can also be analyzed by the ALEXYS Antibiotics Analyzer.

Protect and Serve

Sitting Down With… Michael Breadmore, Professor, Australian Centre for Research on Separation Science (ACROSS), School of Physical Science, University of Tasmania, Australia.

You are perhaps best known for your work on detecting explosives...

Our explosives detection system – GreyScan – is now in production through a technology translation company called Grey Innovation.

The ability to rapidly analyze solid samples isn't only useful for airport security. We are already working on adapting the technology to detect bacterial contamination in meat processing facilities. And we have had discussions on how it could be used for identifying houses formerly used for illicit drug manufacture (for example, meth labs), where the resulting drug residues could have ongoing health impacts. Many think that it will eventually become a requirement for houses to be tested before sale.

Was it a challenge to get the technology commercialized?

We had funding from both Australian and US national security organizations for the initial development, but once we were ready to move to the next phase, the funding dried up. Luckily, a company who were involved in fabricating parts of the instrumentation saw the potential and offered to license and commercialize it. Our priority was getting the instrument into airports as soon as possible, so it was the ideal solution for us, and I believe if we had spun it out and tried to do it on our own, we would still be working on it. Ultimately, we hope the technology will go global. I may not get rich but I will smile every time I go through an airport and get scanned with our technology!

You've had first-hand experience of an explosion…

Yes. I was filling up my car at a gas station when I heard a huge bang and felt a shockwave. I saw that the truck at the next pump was on fire, and found the presence of mind to carefully replace the nozzle and walk away from the flames. People were trying to talk to me but I couldn't hear them – the explosion had temporarily deafened me. I later found out that I was just two car-widths from the explosion and police at the scene couldn't believe I had walked away with just bruising. If the shrapnel had hit my head instead of my leg – or if it had been sharp enough to pierce the skin – I could have died. I consider myself incredibly lucky. Forty-eight hours later I was in Amsterdam, presenting our work on explosives detection at a major conference!

What are the overarching themes of your research?

Most of my work revolves around making analytical technology and methods portable, whether for on-site analysis or remote collection of samples. We look at everything from one measurement at a single time point, through to continuous, autonomous measurements in field-deployed systems. When you are developing new technology in the lab, it is easy to lose sight of the end user's needs. For example, if you develop a technique that performs separations in a few milliseconds, but it takes three hours to extract the molecules, it's not of much practical use. We are trying to integrate and streamline entire workflows – not just one small part.

We try to span the whole range, from focused solutions right down to fundamental chemistry. If we want to continue to make new scientific advances, we have to be willing to ask different questions. For example, we have known about electrophoresis in liquids for over 100 years, and in gases for 50 years. Recently my lab has been trying to establish whether we can do the same in solids. It's taken three years but we think the answer is yes. I'll admit there's no practical application right now, but who knows what it could be used for in future?!

You have strong views on education – what needs to change?

As an Australian Research Council Research Fellow for 14 years, I was not required to teach, but I did, because I enjoy engaging with students. However, I think there needs to be an overhaul of university teaching. Methods of communication have moved on and we must move with them – why spend hours memorizing things that you could look up in 30 seconds online? And if all we are offering is lectures that you could just as easily watch online, why attend university at all? To me, lectures are an old-fashioned way of learning and it's time we moved on to newer and better teaching methods. I hope to implement the "flipped classroom" concept in my teaching, and replace lectures with labs. I'd also like to move away from written exams and toward practical skills assessments. I think we'd get a better idea of students' capabilities in analytical science by giving them 10 compounds and challenging them to separate, identify and/or quantify them, rather than setting 10 exam questions.

You have appeared twice on The Power List. What response did you receive from the analytical science community?

The University was thrilled when Emily Hilder and I were both recognized, and I got a lot of congratulatory messages. The article was also posted to the Australian Research Council website, and people from all over the country left comments saying how pleased they were to see Australian researchers being recognized internationally. It was humbling to receive so many well wishes from strangers.

What is your greatest motivator?

Ultimately, I want to make a difference – to my students, my field or society as a whole, whether that involves keeping airports safe, developing a new blood test, or protecting the environment.

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