Advantage Business Media

# Laboratory EQUIPMENT®

INNOVATIVE SOLUTIONS FOR LAB PROFESSIONALS

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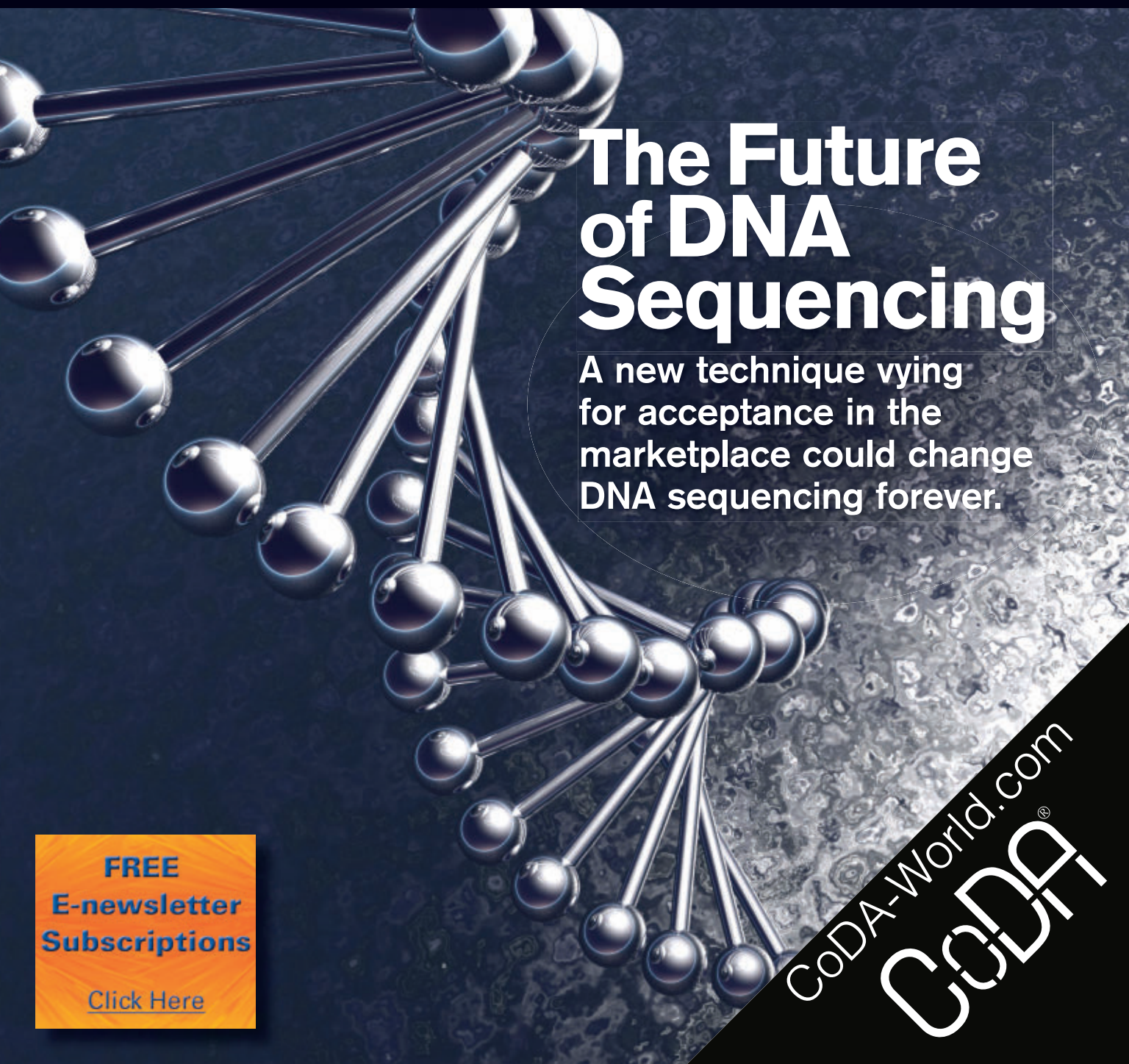
May 2018



# The Future of DNA Sequencing

A new technique vying for acceptance in the marketplace could change DNA sequencing forever.

## Exclusive Online News

### Discovery of Interstitium Fluid: Does it Upend Human Biology?

A new look deep into the workings of the human body provided by a mix of the latest technologies has produced a potentially startling revelation: there is a heretofore unknown network of fluid and collagen bundles running throughout the body. The interstitium, described by some even as a "new organ," acts as both shock absorber for vital organs, and also as a medium for transferring vital fluids. It could even hold the secret of pathologies, such as the spread of cancer.

### Lasers Could Detect Chemical Weapons, Toxic Events

A laser tool could scan the air, revealing the presence of chemical weapons or other toxins, according to researchers from the University of Central Florida. The infrared lasers detect traces as small as one ppb, and the dual-comb spectrometer uses a pair of subharmonic optical parametric oscillators. The platform supplies Fourier transform spectroscopy, and the oscillators are pumped by two phase-locked thulium-fiber combs. Essentially, the lasers are able to detect the minute vibrations of single molecules.

## Science Milestones

*It happened in May*

### *Oldest university unearthed*

*On May 12, 2004, the discovery of what was believed to be the world's oldest seat of learning, the Library of Alexandria, was announced. A Polish-Egyptian team had uncovered 13 lecture halls featuring an elevated podium for the lecturer. Such a complex of lecture halls had never before been found on any Mediterranean Greco-Roman site.*

### *Submarine nuclear power plant prototype test*

*On May 31, 1953, the land-based Mark I prototype submarine power plant began to produce power in significant amounts. This was an experimental unit, built in Arco, ID, to gain experience for operating the Mark II unit in the world's first nuclear submarine, the* Nautilus, *launched Jan. 21, 1954.*

# @@@On the Web

## LaboratoryEquipment.com

### Old Brain Makes New Neurons, Study Shows

The traditional belief was that the process of aging in the brain is largely a story of deterioration and decline. Key to this narrative is the theory that new neurons are not manufactured past youth. But a recent study of the brains of the dead indicates that's not entirely correct: the brain does indeed make new cells through the course of life. However, the cells made by older brains may not form as many connections.

### Great Pacific Garbage Patch Has Four Times the Mass as Previously Believed

The Great Pacific Garbage Patch covers more of the Earth's surface than many countries. A "gyre within a gyre" of ocean currents collects plastic in a huge man-made maelstrom of fishing line, laundry baskets, toys and bottles, floating halfway between Hawaii and California. The mass of the plastic within the Patch is actually at least four times, and perhaps 16 times, greater than previously believed—and it continues to grow, according to a study published in *Scientific Reports*. The new estimate is due to bigger pieces that were unaccounted for in previous estimates.

**Read more exclusive online news at:**
**www.LaboratoryEquipment.com**

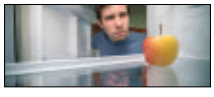
## News From Our Sister Sites

### *FBI, Harvard Scientists Get Nuclear DNA from Ancient Egyptian Mummy Head*

FBI and Harvard scientists succeeded in sequencing a degraded mitochondrial genome and pieces of nuclear DNA from an Egyptian mummy's head—a breakthrough that could have implications for the toughest, most degraded forensic samples. The 4,000-year-old genetic data even contained some traces of nuclear DNA, which helped allow scientists to determine whether the head was of a prominent ancient official or his wife.

**Forensic Magazine, *www.forensicmag.com***

### *Hunger Over Chronic Pain*



Researchers at the University of Pennsylvania identified 300 neurons responsible for prioritizing hunger over chronic pain in laboratory mice, a discovery that could offer targets for novel pain therapies. The research explains how focusing on hunger can help animals survive in the wild after a debilitating injury. The study examined the pain responses of laboratory mice that hadn't eaten for 24 hours. The hungry mice responded to acute pain, but interestingly, were less responsive to inflammatory pain than their counterparts.

**Animal Lab News, *www.alnmag.com***

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## Cover Story



## Features



## Departments

# *Harassers (Rightfully) Will Not Receive Federal Grants*

**Michelle Taylor**
Editor-in-Chief
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advantagemedia.com

Although always a topic of concern, 2017 and the beginning of 2018 have seen increased media coverage of sexual harassment in nearly every industry, from Hollywood and collegiate/professional sports all the way to the scientific research community.

And now, the primary funding agency of basic science research in the United States is taking a hard stance on the subject.

After a 60-day public comment period, the National Science Foundation (NSF) just initiated a policy that requires institutions to disclose when grantee researchers are found to have violated harassment (not just sexual) policies, and/or are put on leave pending investigation. It's an extremely rare move for a funding agency; but, it follows some high-profile cases that rained down on the industry recently—one specifically involving NSF-funded fieldwork.

Late last year, Boston University found one of its professors, David Marchant, had violated campus policies during research expeditions to Antarctica starting 20 years ago. In a piece published by *Science*, two of Marchant's former graduate students describe being pelted with rocks while urinating, being called vulgar terms, encouraged to engage in sexual activity, and even threatened with blocking access to research funding in the future. In supporting documents and interviews, several other women who worked with Marchant during the time period reported similar disturbing treatment. Marchant denies he engaged in inappropriate behavior.

Still, the scandal hit hard, especially after a 2015 decision that saw UC Berkeley astronomer Geoffrey Marcy, one of the world's foremost experts on planets outside of the solar system, found guilty of sexually harassing students over nearly a decade.

NSF's new policy includes a term and condition that requires grantee organizations to report findings of sexual harassment, or any kind of harassment, regarding a principal investigator (PI), co-PI, or any other grant personnel.

"This…will make it clear that NSF may take unilateral action as necessary to protect the safety of all grant personnel, to include suspending or terminating an award or requiring the grantee to replace or remove personnel," reads NSF's statement.

The notice indicated that NSF expects awardee organizations to establish and maintain clear standards of behavior to ensure harassment-free workplaces—including activities at all research facilities, field sites and offsite conferences and workshops, the latter two proving to be the most vulnerable, especially for young female researchers.

I think it's absolutely impressive that NSF stood up and took a hard stance on such a critical issue. It's a much needed—and appreciated—step in the right direction. But as with most things, there's still some work to do.

For one, the policy makes it clear that the onus falls on the awardee institution, but what if that organization does not begin or complete an investigation in an adequate and fair manner?

In the Marchant case, two of three woman attempted to speak out about the harassment, only to be met with roadblocks. One claims Boston University told her not to take action because of Marchant's "sizable reputation and funding," while the other says a requested meeting with NSF never materialized. The third woman says she was afraid for her career if she spoke up against Merchant, who she claims threatened her pathway to success.

So there's obviously more that needs to be done, but it's manageable. Some experts have proposed routing funding directly to students or postdocs, or even specific academic departments, to avoid career impediments and increase reporting. While NSF has not commented either way if that's a route it may take, it's always a possibility.

Even with the roadblocks that linger, it's meaningful for a funding organization like NSF—who has admittedly had problems in the past—to take this first step toward ensuring a harassment-free workplace.

Money talks—especially when it comes to research grants. In this case, NSF quite literally put its money where its mouth is.



Laboratory EQUIPMENT

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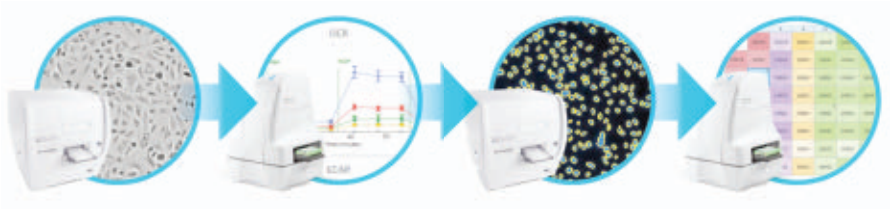
## Integrated Metabolic Analysis, Imaging Platform



Agilent Technologies' and BioTek Instruments' new integrated solution combines cellular metabolic analysis and imaging technologies. The solution integrates the Agilent Seahorse XFe96/XFe24 Analyzers with the BioTek Cytation 1 Cell Imaging Multi-Mode Reader. This creates a standardized approach for comparing XF data sets, improving assay workflow, embedding images into WAVE software, and applying normalization values to Seahorse XF measurements. The ability to incorporate high-quality imagery within Agilent Seahorse XF WAVE software adds another dimension to the data. Now researchers can toggle between XF data, brightfield images and fluorescence images in a unified software experience. Referencing the images while analyzing XF data provides evidence and guidance on how to limit variability and improve the reproducibility of XF assays. Applying a cell count-based normalization value ultimately makes interpreting Seahorse XF data and finding relationships among the data easier. The Agilent Seahorse XFe Analyzers simultaneously measure the two major cellular energy-producing pathways—mitochondrial respiration and glycolysis—in live cells, in real-time. These measurements help scientists better understand the connection between cellular physiological processes and genomic and proteomic data. The BioTek Cytation 1 Cell Imaging Multi-Mode Reader can be configured for fluorescence and high contrast brightfield cellular imaging with up to 60x magnification, and has a wide variety of potential applications.

▶ **BioTek Instruments, Inc. and Agilent Technologies Inc.**
www.biotek.com, www.agilent.com
888-451-5171, 877-424-4536

# Hot Products

## Microplate System Reduces Contamination Risk

The 96-well Multi-Tier Microplate System from Porvair Sciences and sister company JG Finneran is a unique device providing analysts with the convenience of an ANSI/SLAS microplate footprint, but loaded with inert glass vials. Minimizing the risk of extractables leaching out into samples, the system accommodates a range of vial volumes so it can be used for a breadth of applications. The microplate system is formed of sections that can be clipped together to produce a vial holder suitable for 0.5, 1, 1.5, or 2 mL sample vials. The base plate has a vented bottom to allow uniform transfer of heat or cold to each of the vials, and the secure fit of the vials permits use with shakers and vortex mixers during sample preparation. The entire unit can be capped with a pierceable cap mat to prevent contamination and evaporation, making it ideal for use in high throughput chromatography laboratories.

▶ **Porvair Sciences Ltd.**
www.porvairsciences.com
800-552-3696

## Lab Coat Wicks Off Splashed Chemicals

The new Workrite CP lab coat is a cutting-edge, first-of-its-kind coat designed to provide comfortable, affordable protection against inadvertent chemical splash. Made with Milliken ShieldCSR, a proprietary chemical-splash protective technology, this lab coat provides protection against dangerous acids, oxidizers and polar organic solvents by repelling liquid and resisting penetration, and wicking off small amounts of splashed chemicals. The lab coat offers a more comfortable and cost-effective alternative. Unlike other disposable lab coats and chemical-splash aprons, this lab coat is lightweight and breathable. Additionally, it offers excellent durability and resists chemical and colorant stains, allowing it to last longer than disposable lab coats, as well as many traditional white coats.

▶ **Workrite Uniform Co.**
www.workritefrcp.com
800-521-1888

## Automated Sample Prep System Handles Complex, Simple Needs

Teledyne CETAC Technologies' SimPrep automated sample preparation system is designed to automate the sample preparation process for environmental, mining, pharma, clinical and soil laboratories. It utilizes the company's ASX-560 or ASX-280 autosampler, and a high-precision dual syringe pump with flexible, simple software. Both the autosampler and syringe pump have proven to be robust, fast, accurate and precise solutions. The unit is a labor-saving system for the complex to simple sample preparation needs found in today's labs—which saves on the bottom line of the laboratory. It can completely eliminate manual sample preparation steps performed on a daily basis.

▶ **Teledyne CETAC Technologies**
www.teledynecetac.com
402-733-2829

# The Future of DNA Sequencing

*A new technique vying for acceptance in the marketplace could change DNA sequencing forever.*

*by Michelle Taylor, Editor-in-Chief*

Three decades ago, DNA profiling was used for the first time in the United States, successfully tying a rapist to his crime. In Orange County, Florida in 1987, Tommy Lee Andrews was convicted of rape after DNA tests matched his DNA from a blood sample with that of semen traces found in the rape victim.

This changed everything—from police investigations and forensic laboratories to the criminal justice system as a whole.

Since DNA analysis became commonplace, it has held a prominence in the criminal justice system akin only to fingerprints. In that time—much like the rest of technology, regardless of industry—DNA has benefited from advanced innovations, such as the ability to use a wet vacuum collection system to pull microscopic trace DNA, or the advent of DNA software that can easily interpret mixtures once considered too complex to understand.

And now, the DNA industry looks posed for another revolution with the uptick of massively parallel sequencing (MPS), also referred to as next-generation sequencing.

"[MPS] is not something that is going to be coming, it's already here. It's current," said Richard Guerrieri, forensic research leader at Battelle, a non-profit R&D institute that manages multiple national laboratories.

*Scientists with Battelle Memorial Institute worked on a 19-month project to assess the feasibility of massively parallel sequencing as a forensic technique. Photo: Battelle*

Currently, capillary electrophoresis (CE) stands as the industry-standard for DNA analysis. But like all technology, it has its limitations. For example, if a forensic analysist wants to examine the Y-chromosome, the X-chromosome and single nucleotide polymorphisms (SNPs), each requires a separate amount of DNA—which, given the sample, is sometimes not possible—as well as a separate amplification and assay, increasing time, cost and efficiency.

That being said, CE has still proven to be exceptionally effective—as long as there is a suspect, or a match between the DNA sample and a national database. Without a suspect or match, the analysis stops and law enforcement is confronted with the beginnings of a cold case.

This is where MPS can play a role, overcoming select technological hurdles.

MPS is a high-throughput approach to DNA sequencing in which miniaturized, parallelized platforms are used for sequencing 1 million to 43 billion short reads per instrument run. The technical paradigm is built upon sequencing via spatially separated, clonally amplified DNA templates.

With MPS, forensic analysts are no longer limited to one type of marker at a time. Instead, an analyst can multiplex a number of them, say 20 autosomal short tandem repeats (STRs), 20 YSTRs, along with 100 SNPs standing at the end of the ancestral or phenotypic characteristics. Even if law enforcement doesn't have a suspect or match, this extended ancestral or phenotypic information may provide some investiga-


*A lab worker swabs a mobile device at Battelle's forensic lab during its feasibility study of MPS. Photo: Battelle*

tive or intelligence leads to build upon.

In fact, according to data obtained by *Laboratory Equipment* and sister brand *Forensic Magazine*, that is one of the most desirable capabilities of MPS technology for end users.

In a recent reader survey on the forensic applications of MPS, respondents that are already using the platform, or plan to use it in the near future, indicated autosomal STRs and YSTRs as the top two marker sets they intend to analyze. Multiple types of SNPs as well as mitochondrial DNA (mtDNA) were also indicated as target marker sets for MPS, although to a lesser degree than STRs by a median of 19 percent.

## Feasibility study

Of course, technological advancements are only as good as those who use them. To that end, in 2015, the National Institute of Justice awarded Battelle a 19-month applied research project to evaluate the feasibility of MPS. With the overall goal to perform an objective assessment of the technology for forensic DNA testing labs, the project was split into two phases: 1) conduct the sequencing using commercially available products, and 2) evaluate and assess the fundamental elements of MPS analysis.

To do so, Battelle partnered with eight very different labs, in terms of size, mission and affiliation. This was done intentionally to evaluate if MPS could fit into all laboratories, regardless of capabilities. The eight labs included: Armed Forces DNA Identification Laboratory, Bureau of Alcohol, Tobacco and Firearms, California Department of Justice, Federal Bureau of Investigation, Harris County Institute of Forensic Sciences, National Institute of Standards and Technology, New York Office of the Chief Medical Examiner, and North Carolina State University.

There were four workflows to evaluate, one featuring Illumina products, two featuring Thermo Fisher Scientific products, and a final hybrid workflow featuring Promega, Illumina and Battelle products.

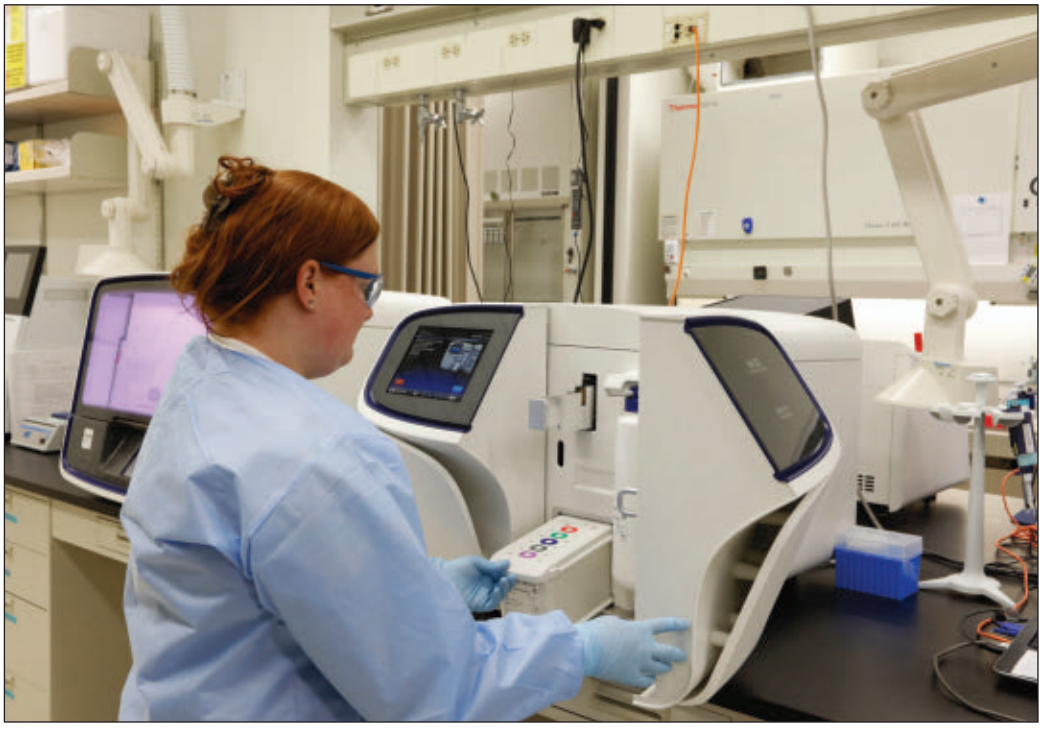
Each partner lab chose up to 12 non-probative casework samples to analyze, working on at least two of the four workflows. Some labs chose more classic forensic casework, such as bloodstains, while others chose specialized casework, like touch DNA samples or bones from WWII and the Korean War.

Overall, there was full concordance between MPS and reported CE data. All the partner labs and the different workflows were consistent and accurate, and there were no incorrect detections of DNA down to the level of single alleles. Sensitivity, accuracy, precision and reproducibility were all proven in the study, leading Guerrieri to conclude that "technical readiness was established, and the collective view is that MPS technology does have immediate value as a resource, especially for selected forensic applications."

Beside concordance with established methods, one key takeaway from the project was the increased level of information available through sequencing technology.

For example, MPS proved especially effective on bone samples from the Korean War.

"Because the amplicons are much smaller in sequencing, you're consequently able



*Battelle scientists worked with a number of next-generation sequencing systems, including Thermo Fisher Scientific's Ion S5 (pictured). Photo: Battelle*

to accommodate samples that have been subjected to environmental abuse, resulting in degradation," Guerrieri explained to *Laboratory Equipment*. "DNA degrades from the outside in, and so fortunately if you have amplicons that are smaller, those regions are more protected from degradation."

While the partner lab was successful using CE on the bone samples, MPS generated two to three times the amount of data.

In fact, Guerrieri sees the identification of human remains, missing persons and cold cases as areas where sequencing technology can really make a difference.

"Whether you couldn't tease a profile out of that sample, or the suspect wasn't in the national database, sequencing now has the capability and potential to solve some of those cases," he said. "The possibility of bringing closure and resolution to something that has lingered for 25 years or longer, that to me is the big objective."

According to *Laboratory Equipment's* recent reader survey, Guerrieri is right on target.

Survey respondents overwhelmingly confirmed that cold cases and missing persons/unidentified human remains were the top two applications where MPS could provide the greatest impact and value for their specific laboratory and/or agency.

Those two applications were following by degraded casework and sexual assault casework. Ancestry and phenotypic prediction for investigative purposes and sample biopsy matching were also indicated as possible MPS applications, but to a much lesser degree.

In July 2016, Ohio's Bureau of Criminal Investigation began the process of implementing MPS, and just last month they went online with services for the entire state. Thus far, the bureau has used the sequencing technology for missing persons cases and unidentified human remains. This is a step up for the state, which had to previously outsource its missing persons cases to a lab based in Texas, causing time inefficiencies.

Additionally, one of the partner labs in the project, the Armed Forces DNA Identification Laboratory, has been using MPS technology for the last 12 months on selected cases dealing with bones, tissues and missing persons.

Another area this "extra information" can prove useful is in dealing with mixtures, a hot topic in forensic science currently. While conventional methods for analyzing mixtures are limited to identifying the length of alleles, sequencing can show the construction of the bases that make up the units of alleles. Thus, even if two or three people in a mixture have the same length, MPS can tell them apart.

However, Guerrieri said there is more work that needs to be done with mixtures in general.

"There's a lot of interest recently in trying to deconvolute mixtures, and the idea of using probabilistic modeling to further distinguish mixtures and the resulting information. That same approach can be successfully applied to this sequence-derived data, and I think it will actually be more effective," he said.

## The strategic roadmap

Like any new technology, there are still some kinks to work out as MPS moves forward—including acceptance in the laboratory. After all, the advancement won't serve much purpose if lab technicians fail to use it.

While an overwhelming majority of forensic laboratories surveyed in *Laboratory Equipment's* reader survey have not purchased an MPS instrument and have no plans to do so in the next year (84 percent), one-third of the respondents are at least interested in pursuing the technology, even going so far as initiating planning/implementation activities over the next 12 to 24 months.

For those that are interested in MPS but are not pursuing it at this time, cost is the dominating factor—both in terms of setup/operation costs, as well as training/validation costs.

On a marker-to-marker basis, MPS is actually less expensive than CE, but that would predicate a lab using every marker, every time, which is obviously not practical. In terms of time, MPS does not currently fit as the sole DNA method at a busy crime lab. For instance, it takes six to eight hours to obtain 20 CODIS markers from a DNA sample currently. MPS technology would produce 10 times the data, about 200 markers, but would take at least 24 hours to do so.

Forensic research leaders at Battelle said there are a few key technical areas in which further knowledge and advancement would be beneficial, including thresholds, how noise and remnant sequences

of alleles may be related, and the effects of high-level multiplex amplification.

But according to Guerrieri, one of the more prominent issues going forward is the need for larger population databases.

"Because you have more information, more alleles, more forms of genes that are being expressed, it would be a benefit to build the databases to be even larger for frequency determinations," Guerrieri explained. "Now that you have more information, it would make sense to expand those databases on a technical level. In doing so, that gives you a better idea of how rare or how common some of those sequence variants can be."

Indeed survey respondents considered the use of existing DNA databases (35 percent) and population databases (27 percent) as main challenges for the implementation of MPS for forensic DNA analysis (more than one option was selectable so percentages will not equal 100).

Battelle's partner labs NIST and North Carolina State University have completed work in this area already, and intend to share their population data with the community soon.

The main challenge identified by survey respondents, however, was legal acceptance and legislative enactment, chosen by almost half of the readers.

There are several other forensic laboratories, not affiliated with the Battelle/NIJ project, that teamed up to conduct their own internal validation of MPS, which was submitted to the FBI for approval in September 2017. The FBI is currently assessing the submission for potential acceptance into the national database.

Once the process is completed, and it is indeed approved, Guerrieri believes it will be a turning point for sequencing.

"After the [Battelle] validation study and this second one get accepted by the FBI, I think there will be a lot of activity," he said. "Now you can use sequencing technology to take advantage of the 15 million profiles in the national database."

Of course, there is a downside to all of this extra information MPS can provide—where do you store that additional data? Survey respondents identified both data management and data storage as core hurdles in the implementation of the technology.

Of those laboratories that perform MPS or intend to soon, 52 percent said they use internal servers, 27 percent use external servers and 21 percent use instrument manufacturer-provided cloud services.

"The expansion of servers is definitely an area that requires attention," Guerrieri said. "Some labs have been exploring the possibility of using the cloud, but there are security concerns with regard to that, so those labs, especially on the federal level, have been making adjustments to internal storage capabilities. This is not a game breaker, though, because it can be done in increments. You can expand gradually, and in a conservative matter."

In the meantime, Guerrieri said forensic laboratories at all levels should do a self-inspection with regard to their mission and how they could possibly use MPS technology now and in the future. No matter what conclusion these labs arrive at, Battelle's feasibility study made one thing evident:

"Going forward, it's clear the method is reliable and is shown to be validated," Guerrieri said.

## Laser Diffraction Particle Analyzer Measures Wide Range of Sizes

Beckman Coulter Life Sciences' LS 13 320 XR laser diffraction particle analyzer delivers fast, accurate and reproducible high-resolution measurement and analysis, eliminating complex procedure setups and reducing the time required to process liquid or dry samples. It uses polarization intensity differential scattering technology to analyze material at multiple wavelengths and polarities to deliver a highly accurate picture of the sample material. It can detect multiple peaks within a heterogeneous sample, and measure the widest possible range of particle sizes, from 10 nm to 3,000 µm. The analyzer is suitable for diverse environments, from food and beverage quality control and industrial manufacturing to small molecule and biopharma applications. It incorporates 127 laser diffraction detectors for analysis of particles larger than 0.4 µm, and an additional six for smaller particle analysis. A high number of detectors enable resolution of subtle size differences. **Beckman Coulter Life Sciences** www.beckman.com, 800-742-2345

## Microplate Decontamination System for RNA Labs

Designed at RNA researchers and lab managers, the Phoseon Technology's KeyPro KP100 is a standalone decontamination system that saves time and money. The system provides validated, simple, fast decontamination of microplates and preparatory slides, utilizing the company's patented SLM LED technology. Complete inactivation of laboratory contaminants, including the hard-to-kill RNase A, can be accomplished in under five minutes. The combination of UV LED technology, combined with a simple touchscreen interface seamlessly integrates into existing workflows. The decontamination system is targeted for use with compatible microplate and preparatory slides commonly found in laboratory environments. It provides increased repeatability through the use of stored protocols for different equipment categories. **Phoseon Technology** www.phoseon.com/life-sciences, 503-439-6446

## Inverted Confocal Raman Microscope Speeds Workflow

WITec's alpha300 Ri inverted Raman microscope combines the advantages of data acquisition from below with the established merits of 3-D confocal Raman imaging—a powerful and versatile technique that can chemically characterize samples nondestructively and without labeling or other specialized preparation. The inverted beam geometry of the microscope delivers many advantages in sample access and handling. Specimens in aqueous environments, such as cell cultures, can be examined more effectively. Standardized liquid sample holder formats can be quickly and easily mounted and measured. **WITec** www.witec.de, +49 0 731 140 70 0

## DMA Can Run Multiple Commands in Single Procedure

TA Instruments' Discovery DMA 850 dynamic mechanical analyzer features frictionless air bearing supports, providing high force sensitivity to 0.1 mN and a wide continuous travel range of 25 mm. A linear optical encoder ensures stable, accurate, high-resolution displacement measurement across the full travel range and enables displacement control of 5 nm. The analyzer can sequence any combination of instrument commands within a single experimental procedure. This includes the combination of stress- and strain-control in a single experiment, as well as transient, oscillation and more measurement types in back-to-back steps. This new capability may be used to execute a full series of measurements on a single specimen, or to apply a mechanical history to a specimen before measurement. New DirectStrain and intelligent autoranging test controls help eliminate the guesswork involved in selecting test settings that will be successful when testing over a wide range of temperature and stiffness. These user-convenience features help to provide the best data, every time. **TA Instruments** www.tainstruments.com, 302-427-4000

## Automated Workstation Meets Rigorous Regulatory Requirements

Tecan's Fluent Gx Automation Workstation was designed specifically to provide the advanced process security features required for regulated applications in clinical, GCP, GLP, GMP and QC facilities. This latest model combines the powerful liquid handling and workflow benefits already familiar to Fluent users—fast and precise processing, high on-deck workload capacities and intuitive operation—with a suite of software features needed to comply with rigorous regulatory requirements, including FDA 21 CFR Part 11. The Fluent Gx Assurance Software provides full sample tracking capabilities and secure electronic records, together with a LIMS interface, multi-level user management, and electronic signature options to ensure compliant and audit-ready operation. This is further enhanced by a number of software utilities to simplify system management. **Tecan** www.tecan.com, +41 0 44 922 81 11

## Segmented Flow Analyzer Boasts High Reproducibility

SEAL Analytical's AA500 segmented flow analyzer (SFA) features an auto start-up/shutdown, as well as new software. It was developed to incorporate feedback from users of the company's AutoAnalyzers, which can run several parameters simultaneously on large numbers of samples. Delivering high levels of performance and reproducibility, the SFA provides maximum sensitivity by ensuring that the reaction always goes to completion, and with a digital true dual-beam detection system with real-time referencing, high reproducibility and low detection limits can be achieved. **SEAL Analytical** www.seal-analytical.com, 262-241-7900

## Acid Digestion Fume Hood for Corrosive Environments

HEMCO's HDPE Acid Digestion Fume Hood is engineered specifically for extremely corrosive operations involving dissolution procedures for element analysis. UniFlow Acid Digestion Hoods feature a completely chemical-resistant hood construction with a welded one-piece HDPE interior fume chamber, including hood walls, ceiling, worksurface, and rear drain trough. The exterior is also chemical-resistant. **HEMCO Corp.** www.hemcocorp.com, 800-779-4362

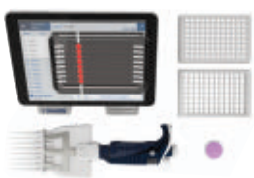
## Anhydrous Solvents Deliver Low Water Levels

ROMIL's Hi-Dry anhydrous solvents deliver low water levels of 50 ppm (0.0050%) or less, with many products routinely manufactured to below 5 ppm (0.0005%) using coulometric Karl Fischer analysis to ensure specifications are met. All Hi-Dry solvents are supplied in packaging designed to maintain the anhydrous state achieved during purification. The amber glass bottles are oven dried to remove all traces of moisture before filling under inert dry nitrogen and sealing with a tamper-evident, screw-on HiDry cap. The cap's double seal design features a PTFE wad and self-sealing septum, helping to maintain chemical purity. **ROMIL Ltd.** www.romil.com, +44 0 1223 863876

## Lab Labels Ensure Proper ID, Use

Brady Corp., has developed new dissolvable paper (B-403) identification labels, sterilization-indicating polypropylene (B-7425-AC) labels and mini GHS labels. These three new materials make important processes throughout a lab environment easier and help ensure that they are completed properly. The B-403 material dissolves completely in warm water in 30 sec, leaving no adhesive residue behind, making it ideal for temporary identification labels. The B-7425-AC material displays "STERILIZED" for proof of sterilization when the material has been exposed to autoclave conditions at 250.7 F (121.5 C) for 10 min. **Brady Corp.** www.bradyID.com, 888-250-3082

## 'Smart' Devices Ensure Verifiable Data

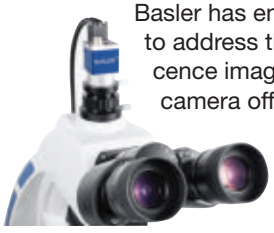


Gilson's Gilson Connect is a cloud-connected platform that powers a product line of Bluetooth-enabled, smart liquid handling devices designed to help scientists achieve verifiable science. The first smart products include the TRACKMAN Connected and PIPETMAN M Connected. These new lab instruments give scientists the ability to record and track pipette performance data in real-time and transmit them to sciNote, a free, open-source electronic lab notebook (ELN). **Gilson** www.gilson.com, 800-445-7661

## LIMS Enables Easy Scheduling of Reports, Personnel and More

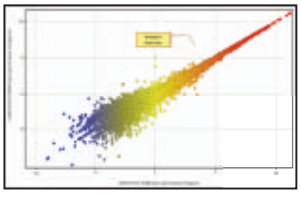
Matrix Scheduler is an optional module for the Matrix Gemini LIMS from Autoscribe Informatics. Users can automatically schedule reports, worklists, registration of samples and more. In this way, activities can be managed more efficiently and significant savings in staff time can be made. An easy-to-use interface allows flexible scheduling in a number of ways, based on dates, times, days of the week and other parameters. Examples include daily and yearly, as well as many other combinations. Period schedules can also be set, such as "every 5 days, 19 hours and 7 minutes." Multiple jobs, such as sample/batch registration, can be scheduled to save personnel time. Staff holidays can be specified to ensure tasks are not scheduled then or at other times when personnel are not available. **Autoscribe Informatics** www.autoscribeinformatics.com, 508-457-7911

## Microscopy Cameras Enhanced for Fluorescence Imaging



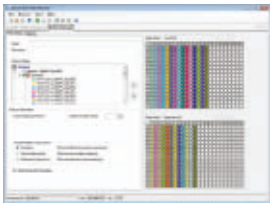
Basler has enhanced its PowerPack for Microscopy to address the challenging requirements of fluorescence imaging. The Microscopy Ace 2.3 MP Mono camera offers a resolution of 2.3 MP combined with high sensitivity thanks to its large pixel size. The Microscopy Ace 5.1 MP Mono scores with an ideal balance between high resolution (5.1 MP), large pixel size and low noise level. An important factor in fluorescence applications is the use of low light emissions to reduce the risk of photo bleaching the sample. These cameras provide high quantum efficiency and sensitivity to take images even in low light. Besides suitable frame rates, both cameras deliver a high dynamic range for recording the differentiation between subject and background. **Basler** www.baslerweb.com, +49 4102 463 500

## Bioinformatics Platform Updates to Address Next-generation Sequencing



The latest version of Strand Life Sciences' bioinformatics flagship product, Strand NGS v3.1, addresses recent challenges in next-generation sequencing (NGS). The first change is large-scale RNA-Seq data analysis. Current cross-cohort RNA- and small-RNA-Seq studies span tens of replicates and batches across hundreds of samples, sometimes conducted across several different institutions. For such studies, this software includes confounding variable analysis to eliminate technical effects, including batch effects; the t-SNE plot; profile and heat-map plots of gene-body coverage; and several other notable visual enhancements. The second feature is support for Unique Molecular Identifiers, or UMIs, for DNA-, RNA- and small-RNA-Seq. **Strand Life Sciences** www.strand-ngs.com, 800-516-5181

## Liquid Handlers Feature Compliance Software for Regulated Environments



Labcyte's Echo 21CFR11 Compliance Manager software is integral to the company's new line of Echo Acoustic Liquid Handlers intended for pharmaceutical companies and laboratories developing and running bioassays. The software is designed to simplify deployment in regulated laboratories that must comply with the 21 CFR Part 11 regulations established by the U.S. Food and Drug Administration. The software seamlessly integrates with Echo liquid handlers to control who can view, create, edit, approve, archive and delete data that is generated by the systems. Using advanced proprietary verification algorithms, the software also detects any data tampering to give users confidence in the integrity of their data. **Labcyte Inc.** www.labcyte.com, 408-747-2000

## Data Analytics Software Helps Find 'Hidden Gems'

Sartorius Stedim Biotech has released a new version of its SIMCA and SIMCA-online data analytical solutions, offered by its subsidiary Sartorius Stedim Data Analytics, formerly known as Umetrics. SIMCA, an established advanced data analytics and visualization program, makes it possible to combine and analyze data from all sources to isolate, understand and act on the hidden gems that hold the secret to better decision-making and greater business success. The software's multivariate data analysis engine enables companies to swiftly detect and analyze deviations from normal operating conditions by modeling an idealized process. Once this model is transferred into SIMCA-online, it serves as a valuable reference for current production. **Sartorius Stedim Biotech** www.umetrics.com, +46 90 184800

## ICP Software is Easy to Use, Intuitive

SPECTRO Analytical Instruments has released the SPECTRO ICP Analyzer Pro software package for the latest models of its SPECTROBLUE and SPECTRO ARCOS ICP-OES analyzers. The software delivers a greatly improved and more-intuitive experience plus ease and speed for the rapid retrieval and processing of results with total traceability. Natural, streamlined workflows are backed by ultra-fast data processing. Recalculations, even of large amounts of data, are up to 1,500 times faster. Modules and plug-ins are customizable to each user's skills and needs. Displays show only essential information, and mouse movements are minimized. **SPECTRO Analytical Instruments GmbH** www.spectro.com, +49 2821 8920

## Raman Microspectrometer Features High Sensivity, High Spectral Resolution


Designed for routine research, CRAIC Technologies' Apollo II Raman microspectrometer is reliable, robust and powerful. It features high sensitivity, high resolution, a broad spectral range and rapid sampling times. The state-of-the-art instrument enables scientists and engineers to measure the Raman spectra from microscopic samples or microscope sampling areas of large samples, such as semiconductors. **CRAIC Technologies, Inc.** www.microspectra.com, 310-573-8180

## Spectrometer Delivers High Throughput, Low Stray Light


Ocean Optics' Ocean HDX spectrometer has a back-thinned CCD array and a new high-definition optics design to deliver an exceptional level of spectral performance for a compact UV-Vis spectrometer. At the heart of the spectrometer is its optics design, which uses a combination of optimized optical bench components, specialized materials and precision engineering to maximize optical resolution, increase throughput, reduce stray light and maintain thermal stability. **Ocean Optics** www.OceanOptics.com, 727-733-2447

## Handheld Material ID System for First Responders

Metrohm's new handheld Raman material identification system, the Mira DS, safely identifies illicit substances and explosives without the need for direct contact with the material in question, making it an ideal solution for police, hazmat teams, bomb technicians and military personnel. The system provides powerful mixture-matching capability for identifying the hazardous materials in street drugs and explosive formulations. **Metrohm USA** www.metrohm.com, 866-638-7646

## UV-Vis Spectrophotometers Boast Flexibility, Options

Industrial QA/QC technicians, instructors and university researchers seeking robust UV-Vis spectrophotometers that are accessible, automated and network-ready can now choose from a flexible range of options with the Thermo Scientific GENESYS UV-Vis spectrophotometer family. Regarded for reliability, accuracy and reproducibility, these spectrophotometers are designed to meet today's expectations for advanced technology in a compact, robust package. **Thermo Fisher Scientific, Inc.** www.thermofisher.com, 781-622-1000

# Mass Spectral Library *Gets Automation Upgrade*

*NIST has updated its popular spectral library with a hybrid search function designed especially to help with the nation's opioid crisis.*

*by Michelle Taylor, Editor-in-Chief*

When chemists need to identify the molecular components of a sample, they turn to mass spectrometry. After blasting said sample with electrons—shattering the molecules into fragments—the technique sorts the fragments by their mass, ultimately producing a mass spectrum. Then, the mass spectrum is run against a database in search of an identifying match.

But what happens when a researcher can't find a match, or a match is just one inert group away but doesn't register on the hit list due to its initial differences? This is increasingly becoming a problem for laboratories, especially those in the forensic industry who are left to deal with the growing opioid crisis.

Last year, NIST (National Institute of Standards and Technology) released the latest version of its widely used Mass Spectral Library, adding molecular fingerprints from more than 25,000 compounds, bringing the total number to over 265,000.

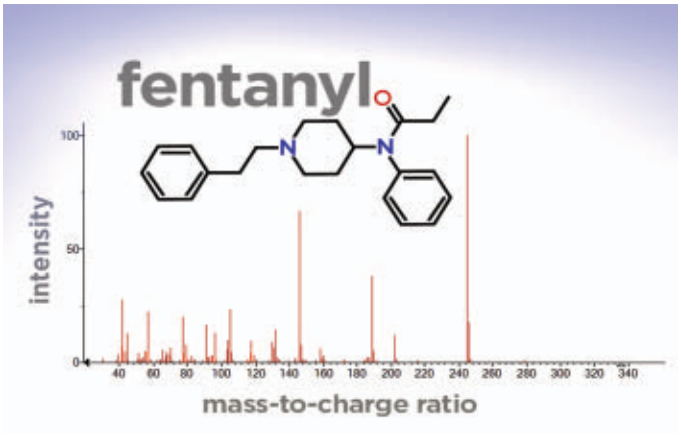
This June, at the American Society of Mass Spectrometry (ASMS) conference in San Diego, NIST will present four posters on its upgraded library and—more importantly—its brand new Hybrid Similarity Search, which makes it significantly easier to spot designer drugs and their analogs.

## Hybrid similarity search function

Illicit chemists are constantly cooking up new forms of designer drugs, each with a slightly different chemical structure, to stymie law enforcement and provide users with an enhanced high. There's perhaps no better example in recent memory than fentanyl—a powerful opioid, intended as pain medication, that is fueling the nation's opioid crisis. Fentanyl, which can be 50 times more potent than heroin, became the most widely used synthetic opioid in 2017.

To control fentanyl, chemists need to identify it. But that can be a hard task with the many kinds of fentanyl analogs that exist, many of which are not in the chemical and/or mass spec databases yet. This is where NIST's hybrid search comes into play.

The search function can reliably identify compounds—even if they are not in your library—that differ from your library compound by one chemical group that doesn't affect the fragmentation. So, if you search for one compound, you will find all the compounds that have a similar chemical structure. Thus, if you have even one fentanyl in your library, you can theoretically identify hundreds of analogs using the search function. More often than not, the difference between an original designer drug and an analog is just one inert group, like a methyl group or a hydrogen with fluorine.




*The mass spectrum for the synthetic opioid, fentanyl. Photo: NIST*

"With the hybrid search, we use two different kinds of peaks within the mass spectrum—one for the ions and one for the neutral losses," explains Stephen Stein, the NIST research chemist who oversaw the development of the search algorithm. "By combining them together, you can use both criteria to do the matching and find spectra in the library. As a result, you are finding a lot more compounds, especially compounds where the molecule you are looking for differs from a library compound by one inert structural unit. That could appear either in the ion or the neutral loss. Wherever it appears, it will find the compound in the library by having that additional information."

The method works for a large fraction of drugs of abuse, including synthetic marijuana, bath salts and other designer drugs. But, it's not limited to the forensic industry. The search function can be used as a general tool for finding analogs of other compounds, which are present in nature, in urine, in biological samples, etc. According to Stein, the method finds applications in diagnosing medical conditions, identifying environmental pollutants, developing new fuels, cutting-edge metabolic research and the flavor and fragrance industry.

"If you use it, it finds all the same hits it would find if you didn't use the hybrid search, but it adds to the hit list everything else that matches with the mass," Stein told *Laboratory Equip-*

*ment*. "It links them together so whenever you do a mass spectral library search, you get more information that allows you to reliably identify the compound."

The search function also informs which peaks are shifted in the mass spectrum, and which are not—alerting researchers as to where a modification is located in a specific molecule. This can help define the structure, as well.

But Stein wouldn't recommend using the function without an analyst's judgement on its reliability. After all, libraries don't identify compounds—people do.

"When you get a hit list, it always needs a manual confirmation," Stein said. "Compounds' spectra are too variable, they can be too similar, or there could be an analytical problem. In all cases, a human needs to look at a couple hits in the library and make a decision based on that."

Humans are the ones that fuel NIST's rigorous quality control measures for the Mass Spectral Library. According to Stein, his team first tries to obtain the highest-quality original spectrum "because there's no substitute for that." Every spectrum is then critically evaluated by at least two people. If they agree, the spectrum gets added to the library. If they disagree, the spectrum is either resolved with a third-party, or is completely left out of the library if a high level of confidence cannot be reached. The last stop for a spectrum includes running it through various software methods that match consistency with structure or chemical formula. If a spectrum passes all these tests, it's added to the archives.

"We just want the compounds to give [scientists] good, confident identification when they find it in the lab," Stein said.

## More tools for forensic analysts

The NIST spectral library is used by scientists in virtually every industry—clinical, environmental, food, fragrance, energy, etc. As Stein points out though, forensic scientists have another tool at their disposal—one he believes is underutilized, especially in relation to the opioid crisis.

AMDIS, as it's called, was developed at NIST with the support of the DoD to reduce the effort involved in identifying compounds by gas chromatography mass spectrometry (GCMS), which is often the method of choice for forensic scientists given its reproducibility factor.

The program extracts the spectrum of each component in a mixture analyzed by GCMS or liquid chromatography mass spectrometry (LCMS), and identifies target compounds. AMDIS is an integrated set of procedures for first extracting pure component spectra and related information from complex chromatograms, then using this information to determine whether the component can be identified as one of the compounds represented in a reference library. The library could be your own, it could be NIST's, or it could be one of a third-party.

Be it targeted or untargeted analysis, Stein leans toward the use of a large, comprehensive library.

"One interesting thing about a big library is all the compounds that could masquerade as false positives are probably in a big library. So, you can show the uniqueness of your spectrum only by searching against a large library," he said.

## Additional upgrades

Although the library upgrade is still new, NIST postdoc and mathematical statistician Arun Moorthy is already working on improvements to the search algorithm. He told *Laboratory Equipment* he is busy deciphering a way to automatically estimate the molecular weight of compounds by conducting a hybrid search at multiple masses.

When the right mass is hit, the score will go up—indicating a reliable match to the researcher. It's an automation function that will negate one of the only drawbacks of using the hybrid search function—having to guess the molecular weight.

After work on the molecular weight estimation is completed, Stein said they will turn their attention to the hit list.

"We want to improve the distance between the correct hit score and the highest incorrect hit," Stein said. Doing so will allow researchers to be even more confident in their mass spectrum analyses.

NIST has been publishing its Mass Spectral Library since 1989, with the latest update coming last year. At ASMS this year, NIST will be giving three poster presentations on the application of the hybrid search to various research areas, including metabolomics, proteomics and forensics, as well as a fourth presentation detailing mass estimation.

# Managing the Growth *of Scientific Data*

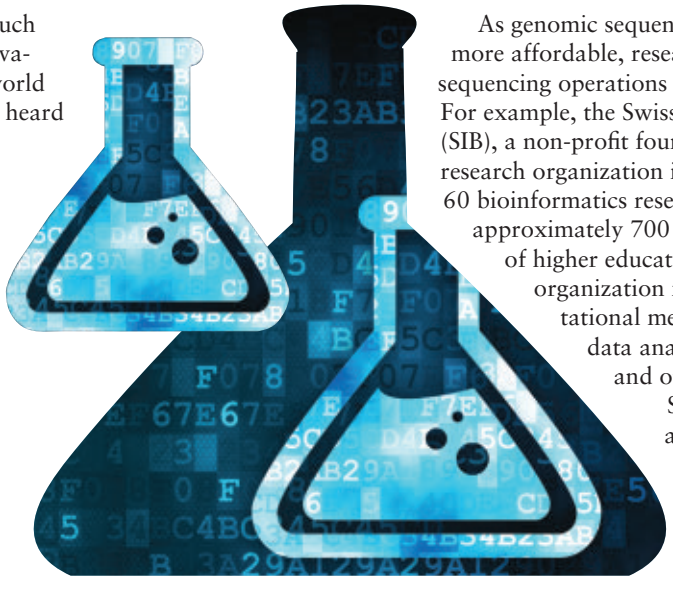
*The ability to collect and analyze more data is essential to breakthrough discoveries, but it doesn't come without challenges.*

*by Mark Pastor, Director, Product and Solution Marketing, Quantum*

Data drives the digital world. Much has been written about the pervasiveness of technology in the world and the promise of big data. We've all heard the mantra.

All speculation aside, the growing volume of data is a fact, and one that can't be ignored. International Data Corporation (IDC) estimates the amount of data in the world will reach 163 trillion gigabytes by 2025. Every industry—from transportation to manufacturing, healthcare to consumer products, financial services to research and development and all the others—is looking for new ways to harness and use this growing volume of data.

Scientists understand that data is the fuel that powers insight, discovery and innovation. The Institute of Cancer Research (ICR), for example, says big data analytics plays an important role in the discovery of cancer drugs. Scientists are analyzing vast amounts of data—from patient samples, genomic sequencing, medical images, lab results, experimental data, pharmacological data, and many other sources—to help in their efforts.



*Data powers insight, discovery and innovation in the sciences—even when there's an excess of it.*

According to Bissan Al-Lazikani, head of data science at ICR, more data is better.

"The more data we are gathering," he says, "the more patients we are profiling, the smarter the computer algorithms: the better we are becoming at discovering drugs for cancer."

## Large-scale growth

According to Illumina, a manufacturer of DNA sequencing solutions, it cost $300,000 to sequence a human genome in 2006. Today, with their high-end sequencers, the cost has dropped to $1,000 and with their new generation of machines it could eventually drop to as little as $100.

As genomic sequencing has become faster and more affordable, researchers are running more sequencing operations and generating more data. For example, the Swiss Institute of Bioinformatics (SIB), a non-profit founded in 1998, is a leading research organization in Switzerland. Comprising 60 bioinformatics research and services groups and approximately 700 scientists from Swiss schools of higher education and research institutes, the organization is a leader in applying computational methodologies and large-scale data analysis to genomic, proteomic and other bioinformatic research. SIB supports projects from active research teams (about 300 currently) at their six different sequencing centers. The organization handles about five separate projects in a week. Data grows rapidly with sequencing runs generating up to 30 terabytes a week.

In another example, GWDG (Gesellschaft für wissenschaftliche Datenverarbeitung mbH Göttingen), a computing center shared by the University of Göttingen and the Max Planck Society, has seen data volumes steadily grow over the years. Today, the center supports some 40,000 users engaged in research and training, manages billions of files, and stewards about 7 petabytes of data.

For research organizations, the ability to collect and analyze more data is essential to finding breakthrough discoveries. But handling more data has its challenges.

## Operating at petabyte levels

Data is not stagnant. It has a lifecycle; it grows and ages. In addition, it must be managed. Once data is created, it must be stored, accessed for computational analysis and collaboration, archived for future use, and protected at every step against the risk of loss. As the amount of scientific data at research insti-

tutions grows, these tasks become more difficult.

High performance is important in research. Faster computing power means more data can be analyzed in less time, which can accelerate the research process. Storage infrastructure plays a significant role in the performance of computing environments. High performance requires an infrastructure capable of fast I/O operations without bottlenecks. When storage capacity reaches the multiple petabyte level, maintaining high performance access is a challenge.

Another factor essential at research institutions is collaboration. Technology has made it possible for hundreds of scientists to work together on projects and to share information. But scientists may not use the same client operating platforms or reside in the same locations. Some may use Linux while others use Mac OS or Microsoft Windows. Some may connect to the storage infrastructure via a SAN while others connect via LAN or NAS. Sharing access to data files and research results requires a storage infrastructure that not only supports simultaneous access to data files but also multiple access methods and different operating systems.

*To build a storage infrastructure capable of handling the growing volume of scientific data, research institutions must find ways to blend different storage technologies together.*

As storage size grows, data backup procedures must change. When data reaches the petabyte level, traditional data backup operations are no longer able to handle the volume. Still, data must be protected against hardware failures. Installing secondary storage arrays for the purpose of data replication is one way to backup data. But that can be an expensive solution.

## Multiple storage tiers

To build a storage infrastructure capable of handling the growing volume of scientific data, research institutions must find ways to blend different storage technologies together. High-performance storage, like flash or high-speed disk, is needed to meet high-performance computing requirements. But at any given time, only a subset of data is active and needs to reside on high-performance media. Storing inactive files on the same media is unnecessary and expensive.

A better approach is to implement multiple tiers of storage. In a multi-tier environment, total storage capacity is broken into different forms of media. There is high-performance disk or flash storage for active files—those files that are part of an active project or are undergoing computational analysis. The remainder of the capacity consists of tape or cloud storage.

Some research institutions have successfully realized this approach. GWDG, for example, uses a multi-tier storage infrastructure. Of the 7 petabytes of data managed by the organization, only 2.5 petabytes reside on disk. The remaining 4.5 petabytes are stored on tape. Since tape storage is more economical than disk, this approach allows GWDG to deliver the performance and capacity needed at a lower cost to the organization.

The process of data management is the key to getting the most benefit from a multi-tier storage environment. As previously mentioned, data has a lifecycle. On average, about 70 to 80 percent of data files stored are not actively used. As files age or become inactive, they should be moved off of higher priced storage and archived on a lower cost media.

With a complex storage environment, data management can be cumbersome. Fortunately, data management processes can be automated. Policies can be established at the file level, and the movement of files into archive can be done without the researcher even being aware of it. Managed this way, data files look the same from the researcher's perspective regardless of where they are stored. As a result, files remain visible and accessible when they are needed.

Data management in a multi-tier storage environment also helps ensure data is protected. Leveraging multiple tiers, policies can be established so that critical data sets are copied to another disk array or to another form of media. That way data is protected and preserved, so it can be restored quickly in case of a hardware failure and the research process is not affected.

More scientific data is helping researchers to uncover new discoveries. But as more data is generated and data storage environments become larger, research institutions must pay attention to how they manage the growth of their storage infrastructure in order to deliver the best performance possible in the most economical way.

EXPERTS *Explain*

# Crafting the Future of Science with Advanced Artificial Intelligence

*by*
*Reza Sadeghi,*
*Managing Director,*
*Dassault Systèmes*
*BIOVIA*
*www.3ds.com*

The sciences are on the verge of a revolution: new technologies are constantly emerging that are fundamentally changing the ways in which we carry out experiments and process the results. Broader trends like the Internet of Things (IoT) and big data have placed unprecedented amounts of data in the hands of researchers. While this helps provide greater context to research, simply improving access to data will not solve the scientific and engineering problems industry, academia and even governments hope to tackle today. There must be a paradigm shift in the way future science is carried out. This future will need to ask different types of questions: rather than ask, "what happened?" or "what will happen?" when designing an experiment, researchers will need to ask, "how do I make it happen?" This will require a widespread embrace of advanced artificial intelligence (AI)—specifically "prescriptive" analytics.

As the challenges researchers face grow more sophisticated, so too must their approaches to solving them. Whether it is a biopharmaceutical firm hoping to understand the multiple mechanisms that lead to cancer, a specialty chemicals firm exploring the molecular interactions that make up self-healing polymers, or an aerospace company attempting to develop lighter, stronger composite aircraft, research methodologies must evolve. The multifaceted nature of these questions is stretching the limits of what physical experimentation can accomplish alone.

Consider epigenetics, which explores phenotypic outcomes due to variations in the amount of gene expression rather than changes in the genetic code. Introducing more or less copies of a protein directly impacts a complex signaling system of thousands of proteins and ligands within a single cell, which in turn affects nearby cells, tissues, organs and, eventually, the entire organism. The combinations of potential experiments a scientist could consider are astronomical, raising an important question: "what do I test next and how do I execute that test?"

This question creates a problem for research, especially within industry. The pace of discovery is accelerating, placing strains on laboratory and knowledge resources. Physical experiments are costly and time consuming, and researchers are feeling the pressure to prune the discovery process from a branching maze into a straight line. While widespread adoption of technologies that support broader trends such as IoT and big data have helped, augmenting these traditional approaches by providing researchers with new and more tools to manipulate data can uncover hidden trends and interactions. The majority of these tools have previously had diagnostic or predictive applications, seeking to explain "what happened in my experiment?" or "what will happen if I do this experiment?" These tools have begun to grow more automated, assessing data as it comes in to help guide future experimentation. An example of this approach is automated dashboards, which can run statistics on new data, predict values for new inputs and visualize the results. These tools have helped streamline the research process, but still fall short when it comes to answering the question, "what do I test next?" To achieve this, these tools must evolve.

## Prescriptive analytics

At their core, traditional analytics are limited in scope to answering the specific question their creator sought to answer. This hampers the true potential of these analytical approaches, as these creators are in turn limited by their own minds. They don't know what they don't know. This presents a problem: how do scientists know what questions to ask if they don't know to ask them? Advanced AI provides a promising solution in the form of "prescriptive" analytics. This is the next logical step in AI-based prediction: it asks, "what should I test to make this happen?" This approach allows machines to go where scientists cannot: by assessing more potential experimental outcomes, the scope of consideration for what a scientist should test grows substantially. Effectively, prescriptive analytics screens future experiments based on existing experimental outcomes, suggesting only the most promising approaches for scientists to verify at the lab bench. Achieving this cognitive level of computing ultimately requires a shift to pursue scientific knowledge as a digital conti-

nuity where discovery and research is an evolving and adapting continuum.

The goal of prescriptive analytics, then, is to evolve the decision-making capacity of a given researcher. However, this evolution requires consistent, timely inputs to ensure that the decision logic of the application remains both relevant and actionable. Tools such as data lakes and IoT can support this approach: a data lake aggregates data together while IoT provides more sources for this data in real time. These tools simplify the timely collection and aggregation of data for researchers to use. However, this alone leads to the previous problem of simply having more data; the challenge is determining what to use and how to use it to generate actionable insights.

*Big data and analytics can help researchers better craft the future of scientific exploration and discovery.*

Again, AI provides different approaches that can help support the development and maintenance of prescriptive models. Semi-supervised learning methods, such as active learning, can interact with data sources to label new data as it comes in. For example, consider a formulation development project for a thermoplastic that has a high tensile strength but low modulus: an active learning approach would look at existing formulations that meet the project's criteria to determine the likelihood that a new formulation could meet those criteria. It can then iteratively suggest new formulations to test, adjusting its methodology throughout subsequent generations as new data becomes available. This approach thus uses new data to refine existing models to ensure that the model's "decision logic" is up to date, and allows the shift from the previous diagnostic and predictive questions of, "what happened?" and "what will happen?" to prescriptive foresight: "how can we make it happen?" There are existing tools that automate this process; incorporating such technology into an active learning environment helps streamline the managing of these models throughout their lifecycle.

Prescriptive analytics supports decision-making in other ways as well, especially within search functions. In a way, it becomes a Netflix for scientists, suggesting related items for researchers to consider. For example, if a scientist searches for a particular experiment within the organization's electronic lab notebook system, it can suggest related experiments carried out by colleagues for the researcher to read. This also applies to literature searches, suggesting related journal articles and thus expanding the potential pool of information available to the researcher. All these potential applications combine to evolve the decision-making of the researcher and expand the scope of consideration for an accelerated time to discovery.

## Knowledge-driven decisions

This concept could be extended to think beyond raw data alone: these prescriptive models could utilize the results of existing models as inputs to generate new "models of models." This would allow researchers to take on more complex questions. In the biopharmaceutical industry, a prescriptive model could suggest small molecule drug candidates that simultaneously optimize multiple parameters, such as maximum target affinity and synthesizability while minimizing hERG-related toxicity. In polyolefin catalyst design, such models could propose new structures for catalysts that minimize synthesis cost and reaction temperature, while maximizing product specificity and catalyst lifetime. In the end, however, these approaches will not take the place of physical experimentation; instead, they will augment the existing work that researchers do, guiding their decisions to ensure work at the bench has the highest likelihood to succeed.

This would create a feedback loop with the lab, where researchers would validate the results of models with physical experimentation, which would generate data to inform future models. This feedback loop would thus accelerate research, gradually pruning off R&D dead ends and helping each researcher answer the question, "what do I test next?"

The pace of discovery is accelerating, and the next generation of AI will provide enhanced experiences that allow scientists to truly think outside the box. By expanding a researcher's scope of consideration, researchers can begin to more effectively ask the questions that they did not know they needed to ask. Prescriptive analytics brings together the benefits of existing technologies and helps to unlock their true potential. Automating these processes also improves the overall benefits these approaches offer to an organization, allowing each researcher the ability to become a sort of citizen data scientist, continuously guiding their projects with increasingly sophisticated analytical techniques. The future of science is one of knowledge-driven decisions where data, both from virtual and physical experimentation, becomes the fuel that accelerates toward discovery.

# Science in Action: *Visualizing and Designing New Biotech Labs*

*Laboratory architects have introduced innovative ideas to the biotech marketplace as the next generation of research and researchers continues to mature.*

*by Brian DiLuiso, Partner, E4H*

Today's workplaces have been strongly influenced by the trend to provide modern comforts to employees. For example, architects are adapting plans to accommodate increased access to daylight, more flexible spaces that encourage idea sharing, and a variety of environments that can accommodate different personalities in the workplace.

Some of these trends are finding their way into the biotech workplace—enhancing the work environments of the front office and lab space at the back—while maintaining regulatory compliance.

## Transparency

Of the many design innovations architects are bringing to biotech offices and labs, one of the most impactful is the ability to provide transparency between non-classified spaces (offices, corridors) and research and product manufacturing. By bringing researchers and scientists forward to the "front of the house" and making them visible, venture capitalists, investors and regulators can observe work being done and witness breakthroughs occuring. Glass walls around research spaces can also be a positive solution for giving regulators and auditors access to observe laboratory operations—without the need for them to gown up every time they want to inspect or review highly secure spaces where research is underway.

It's not a perfect analogy, but in many ways, this change in biotech company work spaces mirrors changes in restaurant design, where today, more high-end eateries make chefs and their crews visible for patrons. Diners take pleasure and inspiration in seeing where their meals come from, who is preparing them and how.

We see that same sense of excitement from biotech stakeholders who today can visit a prospective portfolio company and witness researchers and technicians harvesting cultures, working with raw materials and using automated technologies. It's one thing for a company executive to tell investors about progress on a new autoimmune disease treatment: it's more powerful when the CEO can tour guests through a facility showing what researchers may be looking at in real time through the lens of a microscope. This is science in action.

The stakes are very high when it comes to transparency and allowing access to sensitive information. It has to be done carefully and is not for every biotech or pharmaceutical company. There are limits, of course, to how much companies can safely expose to public view, particularly in this era of heightened concerns about intellectual property protection.

*The trend of transparency in laboratory workspaces in the past few years has lead to an abundance of glass walls. Photo: E4H*

## Maximizing real estate spend

Another trend driving innovation in biotech space design is the steadily increasing cost of real estate, particularly in the research hubs where the best talent and the best companies want to be, such as Boston, New York, Seattle and San Francisco. Whether it's renovating an old urban structure or building new, biotech companies are looking to architects to help manage and maximize their real estate investment.

Utilizing Smart Facility Design principles, architects can maximize workflow and create environments that are economically and environmentally sustainable. One leading example is the transition from stick-built, drywall-and-stud construction to modular environments, where prefabricated structures are created offsite and assembled quickly at their destination. For example, creating a modular cleanroom in a controlled shop, testing its systems and

pre-commissioning it before bringing it to the site for installation provides cost and scheduling efficiencies. It allows builders to adhere to timelines, and bring in painters and floor installers as modular rooms arrive. Studies by Research and Markets project that modular construction for pharmaceutical and biotechnology facilities will grow by an annualized rate of about 9 percent between now and 2030—doubling every eight years on average. More than 80 percent of this modular construction will go to serve biologics manufacturing, 5 percent for other manufacturing, and 12 percent for research and development spaces. R&M predicts that 65 percent of modular/prefabricated construction for biotech/pharma will be to create new facilities, the other 35 percent expansions of existing sites.

In addition to modular construction, real estate spends are being maximized by designs that incorporate adaptable and multi-use spaces. Instead of creating rooms and areas that are dedicated to a sole function, many companies are opting for spaces that can serve multiple purposes.

### Multiple spaces for multiple personalities

When it comes to office space, it's no secret that there's an ongoing debate about open floor plans versus traditional office layouts. However, it's important that amidst the trend to attract millennial talent with open floor plans and foosball, architects do not lose sight of the unique culture of each biotech company they design for. Design needs to account for the many types of personalities in an organization. Some executives and scientists perform better in quiet space with doors that can close. Others prefer flexible spaces for spontaneous collaboration, and still others want to gather in a "corporate living room" to have an informal conversation. Ultimately, architects should look to the company founders for inspiration and to ensure the culture they created and seek is captured in any new design. A workspace that caters to many different personality types will help invigorate and retain talent.

What I've learned as an architect is: one size does not fit all. It's critically important before we even begin to draw schematics that we do the work to understand the culture of the companies and organizations we are building for. The workplace has to work for all workers, in all generations, and for both extroverts and introverts. An obsessive insistence on an open workplace makes no more sense than does an obsessive insistence on making sure every employee has an office with a door that closes. The reality is, we need a mix of both, and almost all people working in a biotech environment will want and need both public and private spaces at different times in their work week.

The pace and promise of innovation in biotechnology have never been as exciting and challenging as they are now. For architects and designers, it's a great time to work with biotech laboratories and researchers as they move toward the next generation of research.

# Combination of Techniques *Proves More Effective in Drug Testing*

*While single methods have their own unique challenges, combining and supplementing with complementary approaches can ensure a more complete analysis.*

*by Michael Menz, Frank Steiner and Ian Acworth, Thermo Fisher Scientific, Inc.*

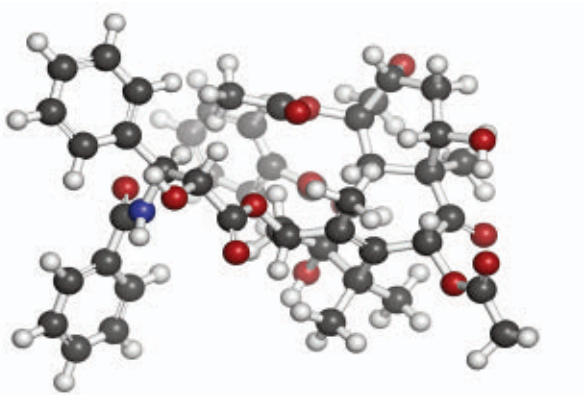
The chemistry behind every medicine that goes to market has a significant impact on how it is made. Not only does an in-depth understanding of molecular makeup provide information about how a drug can react within the body, but it also supports quality control to ensure that the drug is exactly what it is supposed to be.

All medicine requires quality analysis, whether new to the clinic or a time-tested treatment. Along with confirmation of the (obvious) regulated amount of active ingredient, inclusion of product-based related compounds and process-based impurities can cause issue with overall drug efficacy, safety and stability. Unwanted impurities that could arise throughout the drug development lifecycle are a key concern across formulation and manufacturing, pushing companies to follow regulatory guidelines and constantly improve upon current analytical methods so that only safe and effective drugs go to market.

When investigating pharmaceuticals, such as those involved in the treatment of cancer, quality and attention to side effects can direct drug analysis. Cancer treatments in particular are wide-ranging and generated in many forms, from traditional chemotherapies to innovative immunotherapies that are targeted to a specific cancer type. As one of the most researched disease classes, cancer and cancer therapies are a potent example of the importance of progressing drug quality analysis to encompass different types of drugs that can result in finding unknown impurities.

Cancer is the second leading cause of death, with one in six deaths contributed to the disease, worldwide. Projected estimates of cancer incidence suggest that the number of new cases is expected to rise by approximately 70 percent over the next two decades. Given the unfortunate increase in cancer prevalence across the world, substantial energy in the cancer community is focused on improving older treatments and investigating novel therapies.

Quality and purity monitoring in the final drug formulation of both old and new cancer treatments is of the utmost importance. Questions must be asked regarding whether any additional substances affect the drug's activity or increase potential negative side effects. Evaluating the chemistry behind each treatment is a key part of the process that allows pharmaceutical companies to be sure that a drug is effective and safe.



*The chemical structure of paclitaxel, a cancer chemotherapy drug. Atoms are represented as spheres with conventional color coding: hydrogen (white), carbon (grey), nitrogen (blue), oxygen (red).*

## There's something about impurities

Typical methods applied to cancer drug quality assessment, including ultra-high performance liquid chromatography (UHPLC) combined with ultraviolet and visible (UV/Vis) detection, aim to provide an overall view of drug components while still being specific and sensitive enough to detect low abundance impurities. While UV/Vis detection can easily identify some impurities and other compounds present in a sample, challenges arise with selectivity and identification of impurities that do not have inherent chromophores or vary in response factors (such as extinction coefficients). These cases bring a level of uncertainty to impurity analysis that cannot be tolerated when quality checking a drug.

In addition to ensuring accurate identification of impurities, testing and monitoring approaches must also conform to the International Council for Harmonisation of Technical Require-

ments for Pharmaceuticals for Human Use (ICH) guidelines. These guidelines outline reporting, identification and qualification requirements for impurities in a drug, specifically advising on those impurities potentially arising from degradation products of the drug substance, ranging from catalyst byproducts in manufacturing to interactions with packaging materials. Furthermore, the ICH guidelines propose threshold values for the control and quantitation of impurities based on the maximum daily dose of a substance in the final product.

In regard to manufacturing, the ICH recommends the use of less toxic solvents in the manufacturing process, in case of solvent integration into the drug, and sets pharmaceutical limits for residual solvents in drug products. By providing a consistent global policy for limiting impurities both qualitatively and quantitatively in drug products and ingredients, these guidelines can help direct how current approaches can be upgraded to exceed recommendations. However, if current approaches overlook compounds due to method inadequacies, the guidelines cannot be met, and analysis could result in potential inclusion of impurities that affect the efficacy and safety of the drug, as well as the health of the patient.

## More comprehensive analysis

In order to gain insight into how current methods might be improved for quality drug assessment, researchers compared the commonly used UHPLC-UV/Vis approach to an alternative detection method, charged aerosol detection (CAD), in evaluating impurities in the chemotherapy drug paclitaxel. Applying CAD to impurity detection could help overcome some of the obstacles met with UV/Vis detection, since CAD response does not require a chromophore for detection and can provide a uniform response independent of chemical structure. It was hypothesized that applying both detection methods could utilize the strengths of each, providing a more comprehensive profile and more universal response across all types of compounds.

In this study, calibration measurements of paclitaxel and two known compounds associated with the drug were assessed. When testing impurities for pharmaceutical applications, calibration standards are useful to quantify and confirm the identity of a known compound. However, calibration standards in early drug discovery are not always available, creating additional challenges with certain analytical methods. To accommodate this, CAD was used to allow for a single calibration and enable comparison of known compounds to unknown impurities.

A stock solution of paclitaxel and the two related compounds was generated for use as a calibration standard measurement. A series of dilutions based on the stock solution were analyzed in three consecutive runs with blank injection runs between each dilution to reduce carry over. This generated a single calibration curve, where all three standards displayed similar linearity. Highly similar linear calibration is key to ensure proper quantitation of known compounds as well as accurate relative quantitation of unknown impurities. Detector response was also evaluated with UV detection and CAD to determine the relative differences in each method. The inherent sensitivity in UV detector response to chemical structure was highlighted in the results, in which data showed a variable response among the three analytes measured at similar concentrations. CAD response in these circumstances remained consistent across the three analytes, indicating an independent response from chemical structure. Given the linearity of calibration and uniform response, these measurements demonstrated the ability of the UHPLC and CAD system to apply directly to drug assessment and comparison of unknown compounds in a sample to a single calibration.

*Combining multiple high performance techniques can improve the overall view of drug components and impurities.*

Since CAD response is known to be affected by mobile phase composition, an inverse gradient compensation was implemented to assess the ability for uniform response across a typical drug gradient elution. This turned out to be an important addition for CAD response, as results without gradient compensation demonstrated an underestimation of compounds prior to active pharmaceutical ingredient (API) detection and an overestimation of compounds after the API due to the changing organic composition within a gradient. However, with gradient compensation, a more uniform response of detected analytes over the course of the gradient elution is noticeable, which minimizes quantitation errors.

Comparison of CAD with inverse gradient compensation to UV response suggests that a combination of both methods offers a more universal response and the most comprehensive evaluation of a sample, detecting and allowing measurement of all impurities and related compounds present in the sample.

UV detection can identify volatile compounds in a sample unidentified by CAD, while CAD can detect compounds lacking a chromophore that cannot be determined by UV detection. By combining these two detection methods with UHPLC, improved identification and measurement of pharmaceutical samples overcomes challenges inherent to each, as well as confidently meets ICH guidelines to ensure the safety of a drug.

## The future of impurities testing

Pharmaceuticals, such as paclitaxel, are analyzed to ensure that the level of impurities in the final drug product are at a safe and consistent level by accurately measuring the compounds and implementing removal processes downstream from the analysis. Additional testing of the combined approach on different drug samples would further qualify UHPLC-UV-CAD as a valid method for impurity analysis.

Analytical methods applied to detect impurities within a therapeutic drug, for cancer or other diseases, should have both the selectivity to separate impurities from each other and the sensitivity to quantify low levels of analytes. Given that single methods each have their own unique obstacles that make them less effective to use alone, combining and supplementing methods with complementary approaches can overcome individual challenges to ensure that a complete analysis for impurities can be performed on any drug.

# ISS Resupply Reinvigorates *Microgravity Research*

*A capsule of supplies recently arrived at the International Space Station, providing much needed scientific equipment for continued research on materials, biology, food and more.*

*by Laura French, Associate Editor,* Forensic Magazine

With a fiery blast of orange and a plume of smoke behind it, the SpaceX Dragon capsule, carried by a Falcon 9 rocket and containing over 5,800 lbs of supplies, set off on its resupply mission to the International Space Station on April 2.

Two days later, NASA astronaut Scott Tingle and Japan Aerospace Exploration Agency astronaut Norishige Kanai captured the Dragon capsule using the space station's robotic arm, and welcomed its vast array of cargo into their lab and temporary home.

Included in CRS-14 were upgrades for the station's carbon dioxide removal system, high definition camera components, a new printer for the astronauts, and an array of new research equipment for the orbiting laboratory and its six current crew members to continue their studies both of space and Earth from afar.

In its unique position above Earth's atmosphere, in low earth orbit where gravity is about 10 percent less than on Earth's surface, the astronauts have a special opportunity to study the reaction of various materials—and even living things—in an extraterrestrial environment. This research may one day form a foundation for human inhabitance in outer space—and in the nearer future, will help astronauts visiting the station live and work more comfortably and efficiently.

## Planting modules and veggies

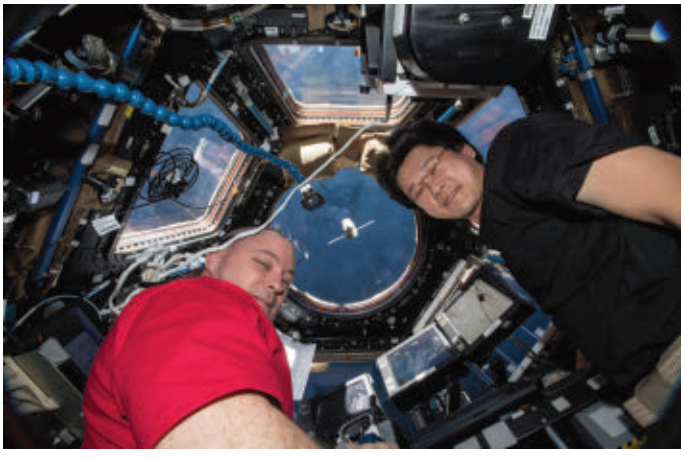
As would be expected, the vast majority of food astronauts eat on the space station comes from Earth, but research is underway to study the growth of plants in space, which could possibly become a food source for long-term space inhabitants.

Astronauts have already been using a vegetable production system known as Veggie to grow salad-type plants on units called "pillows"—water is injected into the pillows with a syringe, light is provided, the seeds take root, and the plants grow. However, previous Veggie operations have revealed that some plants fare better than others, as the microgravity environment has an effect on how water is distributed to each plant. New units supplied by CRS-14 will seek to solve this problem through a new design: the Passive Orbital Nutrient Delivery System, or PONDS.

"PONDS units have features that are designed to mitigate microgravity effects on water distribution, increase oxygen availability and provide sufficient room for root zone growth," explained Veggie project manager Nicole Dufour, of NASA's Kennedy Space Center.

Engineers and scientists at NASA and Tupperware developed these units, designing the system to distribute water throughout the unit to each plant with the aim of uniform growth. Seven of these units arrived at the space station on April 4—four opaque models that will remain closed as the plants grow, two models with clear windows and removable covers so the astronauts can monitor the plants' growth, and one clear model that will be used to further observe the hydrodynamics in the unit in microgravity conditions, using videography. Each of these units will be used to grow "Outredgeous" romaine lettuce, which has been grown through the Veggie system previously.

Observing how plants grow in extraterrestrial, microgravity conditions—and seeking out ways to improve this growth—is valuable not only because it can enable astronauts to grow their own fresh, nutritious food, but also because it expands the possibilities of future long-term space inhabitance for astronauts and civilians alike.



*Astronauts Scott Tingle (left) and Norishige Kanai watch the SpaceX Dragon cargo craft arrive from inside the seven-windowed Cupola moments before capturing it with the Canadarm2 robotic arm. Photo: NASA/Johnson Space Center*

## Space drugs

Another experiment enabled through this resupply mission is the Comparative Real-time Metabolic Activity Tracking for Improved Therapeutic Assessment Screening Panels investigation—a study using a new method to track the metabolic activity of cells and the effects of five therapeutic compounds on those cells in microgravity.

Previous research has found that microgravity can alter the way drugs interact with human tissue, and has opened up the possibility of drug discovery and development in space—which can even result in more effective and less expensive medications. This experiment will investigate the use of autobioluminescence to track metabolic activity in microgravity in real-time, without having to destroy the tissue sample.

A synthetic luciferase gene is combined with human embryonic kidney cells, which emit a certain amount of light correlating to their metabolic activity. By observing this bioluminescence, researchers will track the effect of the five compounds on the tissues. Samples on Earth will be compared to samples on the ISS to further assess the impact of microgravity on this process.

This research, in addition to assessing the potential of drug development in space, can also lend insight into emergency medical treatment for astronauts on missions.

## Materials in space

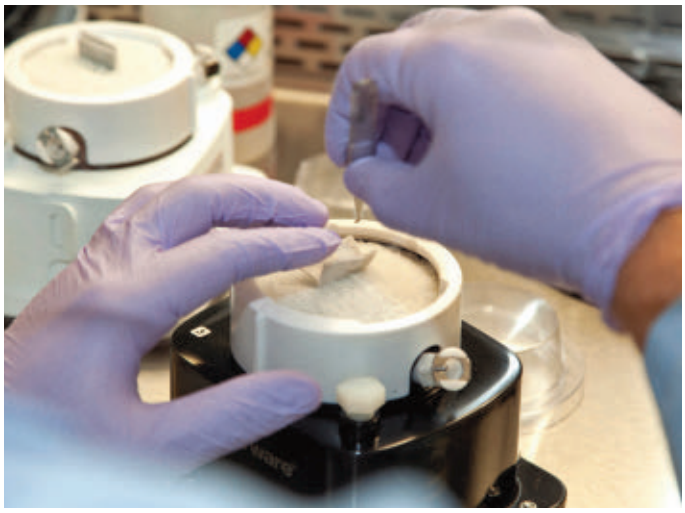
Testing a variety of materials in space has been one long-running objective of the International Space Station's research—since 2001, the ISS has been working on a project called the Materials International Space Station Experiment (MISSE), beginning with MISSE 1 and 2 that were attached to the outside of the station on Aug. 10, 2001. The objective of these missions was to observe how different material structures, coatings, electronic components and more would fare on the exterior of a spacecraft, exposed to various types of radiation, highly reactive atomic oxygen, thermal cycles and an ultra-high vacuum environment.

With the arrival of CRS-14, ISS scientists received new MISSE samples—and the new MISSE-FF (Flight Facility) that will allow for closer monitoring of the tested materials than ever before. While the previous MISSE missions—MISSE 1 through 8—mostly involved planting the materials outside of the station and retrieving them after a long period of time to see how each fared, this facility includes components called MISSE Sample Carriers (MSCs) that provide monthly images of the materials to the researchers, as well as on-demand data.

Additionally, the MSCs do not require the astronauts to leave the space station to plant or retrieve them. The MSCs are attached via one of 12 "slots" on the MISSE-FF, and can be retrieved using the same robotic arm—the Canadarm 2—used to bring in the Dragon capsule. Scientists control the MSCs remotely from Earth—the ISS astronauts simply need to load and later retrieve them, and prepare them to be returned to Earth for further study.

Once the samples are sent back to Earth, researchers can observe any erosion that may have occurred to the palette of materials—the results to inform engineers designing future spacecraft. The MISSE-9 samples include 138 different materials, which will be left in orbit for about a year. In addition to the overall effects of different space conditions like radiation and temperature on the materials, this experiment will also look at how flight orientation—the position of the materials relative to the direction of the station's movement—affects the materials.

"We will fly some of the same materials in different orientations as the same material can react differently in each flight direction,"



*Seeds are planted in the veggie Passive Orbital Nutrient Delivery System (PONDS) units inside a laboratory at the Space Station Processing Facility at NASA's Kennedy Space Center in Florida. Photo: NASA/Daniel Casper*

said Kim de Groh, senior materials research engineer at NASA's Glenn Research Center, when explaining the experiment.

## Thunderstorms from above the clouds

In addition to its novel microgravity and thermospheric conditions, the ISS is also in a unique position to observe Earth from above. The Atmosphere-Space Interactions Monitor (ASIM) supplied by CRS-14 will do just that, tracking Earth's upper atmospheric lightning patterns to strengthen scientists' understanding of the atmosphere and potentially provide insight into the planet's climate. The ASIM observatory will be installed on an external platform on the European Space Agency's Columbus module of the ISS.

Upper atmospheric lightning is different from most lightning observed from Earth's surface during normal thunderstorms—these transient luminous events involve electrical discharges in the stratosphere and mesosphere, high above the altitude of typical storm clouds. This lightning can take a variety of different forms, including sprites, large electrical discharges in the mesosphere; blue jets, which discharge up from the tops of clouds into the stratosphere; and ELVES (Emissions of Light and Very Low Frequency Perturbations due to Electromagnetic Pulse Sources), large concentric light rings occuring in the lower ionosphere.

The ASIM will monitor these phenomena using its cameras, photometers, X-ray detectors and gamma-ray detectors to observe the processes of these different luminous events and possibly help scientists understand their role and impact on other atmospheric processes and the climate. Overall, these observations will help build a more comprehensive atmospheric mode that can be applied to climatology, meteorology and environmental studies.

## What goes up must come down

SpaceX's Dragon capsule is scheduled to return to Earth in May, bringing back approximately 3,500 pounds of research material as well as additional hardware and supplies. CRS-14 will also return with Robonaut 2, a robot that has helped ISS crew members with various tasks since 2011, and is in need of repairs.

# *Perish Not Publish? The Lack of Female Authors in Journals*

**Ione Fine**
*Professor of Psychology*
**University of Washington**
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"Publish or perish" is tattooed on the mind of every academic. Like it or loathe it, publishing in high-profile journals is the fast track to positions in prestigious universities with illustrious colleagues and lavish resources, celebrated awards and plentiful grant funding. Yet somehow, in the search to understand why women's scientific careers often fail to thrive, the role of high-impact journals has received little scrutiny.

One reason is that these journals don't even collect data about the gender or ethnic background of their authors. To examine the representation of women within these journals, myself and Alicia Shen, a psychology Ph.D. candidate, along with our colleagues Jason Webster and Yuichi Shoda, delved into MEDLINE, the online repository that contains records of almost every published peer-reviewed neuroscience article. We used the Genderize.io database to predict the gender of first and last authors on over 166,000 articles published between 2005 and 2017 in high-profile journals that include neuroscience, our own scientific discipline. The results were dispiriting.

## Female scientists underrepresented

We began by looking at first authors—the place in the author list that traditionally is held by the junior researcher who does the hands-on research. We expected over 40 percent to be women, similar to the percentage of women postdocs in neuroscience in the U.S. and Europe. Instead, fewer than 25 percent first authors in the journals *Nature* and *Science* were women.

Our findings were similar for last authors, the place typically held by the laboratory leader. We expected the numbers to match large National Institutes of Health grants—30 percent are awarded to women, comparable to the proportion of women tenure-track faculty in neuroscience. But it was half what we expected—just over 15 percent of last authors in *Nature* and *Science* were women.

Our study, published online and highlighted in a letter printed in *Nature*, focused on neuroscience. We made our code accessible, and we're thrilled that students in other fields are already beginning to examine the gender breakdown of bylines in their own disciplines.

One thing our data mining study doesn't reveal is why women are so seriously underrepresented. But a large literature review suggests gender bias almost certainly plays a role.

## Bias in the publishing pipeline

One place bias occurs is when scientists themselves undervalue the scientific contributions of women. One analysis found that women are more likely to be the person performing experiments. Despite this, they are more likely to be in the less prestigious middle author position. Anecdotally, many laboratory leaders have observed that male students tend to be more proactive about negotiating their position in the author list than women.

Bias can also influence the reviewing process. Researchers at the Ohio State University found that, when reviewers are randomly assigned to evaluate scientific work ostensibly submitted by a female or a male author, they rated the work written by male authors as having higher rigor. An analysis of peer-review scores for postdoctoral fellowship applications in Sweden revealed a system that was "riddled with prejudice"—women were given lower competence ratings than men who had less than half their publication impact. Bias may be particularly strong when expectations are high—qualities like "brilliance" are far more likely to be attributed to men. This may be why we found the proportion of women authors was negatively correlated with journal impact factor.

Finally, bias occurs within the editorial process. *Nature*, in a series of editorials spanning more than a decade, has observed that its editors are less likely to ask women to write commissioned pieces.

Do women fail to "lean in"? Female authors may be less likely to submit to high-profile journals. Success rates for elite journals are low—for instance, in *Nature*, less than 10 percent of submissions make it into print. In many fields, the publication delay associated with a failed submission means there's a high risk of being scooped by another research team. If a female scientist estimates her chance of success more conservatively than a man, for whatever reason, she will be more likely to play it safe.

## Holding journals accountable

Scientific publishing is staggeringly profitable: in 2017, Elsevier reported profits of over $1.2 billion. These companies rely heavily on the scientific community, both as authors of the journal content they are selling and as reviewers. Given the profit they make and the outsized influence they wield over scientific careers, it seems obvious that journals have a moral and perhaps even legal responsibility to make sure the process is equitable.

We believe journals need to take full responsibility for ensuring social equity across the publishing pipeline: encouraging women to submit, ensuring that women receive fair reviews, and enforcing equity in the editorial process.

There are some obvious first steps. The scientific community should demand that journals collect data about gender and ethnicity for article submissions and acceptances, and these data should be publicly available. That way researchers can choose to avoid (or even boycott) journals with a poor track record. Researchers should insist that reviewers be given more specific review criteria—such as requirements to explain their ratings of significance and impact, as well as their assessment of scientific quality. Finally, it is past time for journals to adopt mandatory double-blind reviewing.

While the representation of women authors may not have changed over the last decade or so, the attitude of the scientific community has transformed. These days there is an overwhelming consensus in our scientific community that scientific talent is not gendered. Universities, funding agencies, conference organizers and individual laboratory leaders around the world are all working to resolve this problem. It is time for the journals to "lean in." LE

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