Technology Networks

The Scientific Observer

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Failing Faster Succeeding Sooner

Technologies That Are Accelerating Drug Discovery

How Collaboration and Curiosity Make for a Successful Scientist

Towards the Lab of the Future

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Falling Faster, Succeeding Sooner: Technologies That Are Accelerating Drug Discovery

Anthony King

EDITORS' NOTE

Welcome to issue 25 of *The Scientific Observer*, the monthly online magazine brought to you by *Technology Networks*.

The "lab of the future" concept promises to revolutionize how scientists spend their time in the lab and accelerate research practices across scientific industries, including drug discovery and development. Ninety percent of therapeutic candidates never make it to market, adversely impacting patient's lives and costing the pharmaceutical industry billions of dollars. Emerging and rapidly developing technologies, such as artificial intelligence (AL) and machine learning (ML), are already impacting the drug R&D landscape. This month's feature article sees science journalist Anthony King investigate how these technologies can help compounds fail *faster* and fail *better*, reducing the time and money invested into pharmaceuticals that ultimately would not reach patients.

While automation and AI are praised as "good news" for the pharma industry, the speed at which these platforms are evolving creates challenges in their widespread adoption. In *Towards the Lab of the Future,* Joanna Owens interviews researchers across the life sciences to discover how they are creating research environments that they can can grow with and update.

Amid what feels like a period of rapid evolution and change in science, it's important that we continue to champion the *people* at the heart of research – not just the technologies. In this month's issue of *The Scientific Observer*, immerse yourself in the fierce passion and fervour that Dr. Birgit Schilling expresses when asked to talk about her career and her love for "the beauty" in chemistry. In our interview, she is open about the qualities she believes make for a successful scientist. This, and much more in issue 25.

We hope you enjoy exploring this issue of *The Scientific Observer*. *Subscribe* to make sure you never miss an issue.

Have an idea for a story?

If you would like to contribute to *The Scientific Observer*, please feel free to *email* our friendly editorial team.

CONTRIBUTORS

Anthony King

Anthony King is a freelance science writer based in Dublin, Ireland. He reports on a variety of topics in chemical and biological sciences, as well as science policy and health.

Joanna Owens, PhD

Joanna is a freelance science writer, covering all biomedical topics with a focus on oncology, pharmacology and drug discovery.

Masha Savelieff, PhD

Masha Savelieff is a professional freelance scientific writer with medical, biomedical and chemical research and writing experience.

Molly Campbell

Molly Campbell is a senior science writer for *Technology Networks*.

Kate Robinson

Kate Robinson is an assistant editor for *Technology Networks*.

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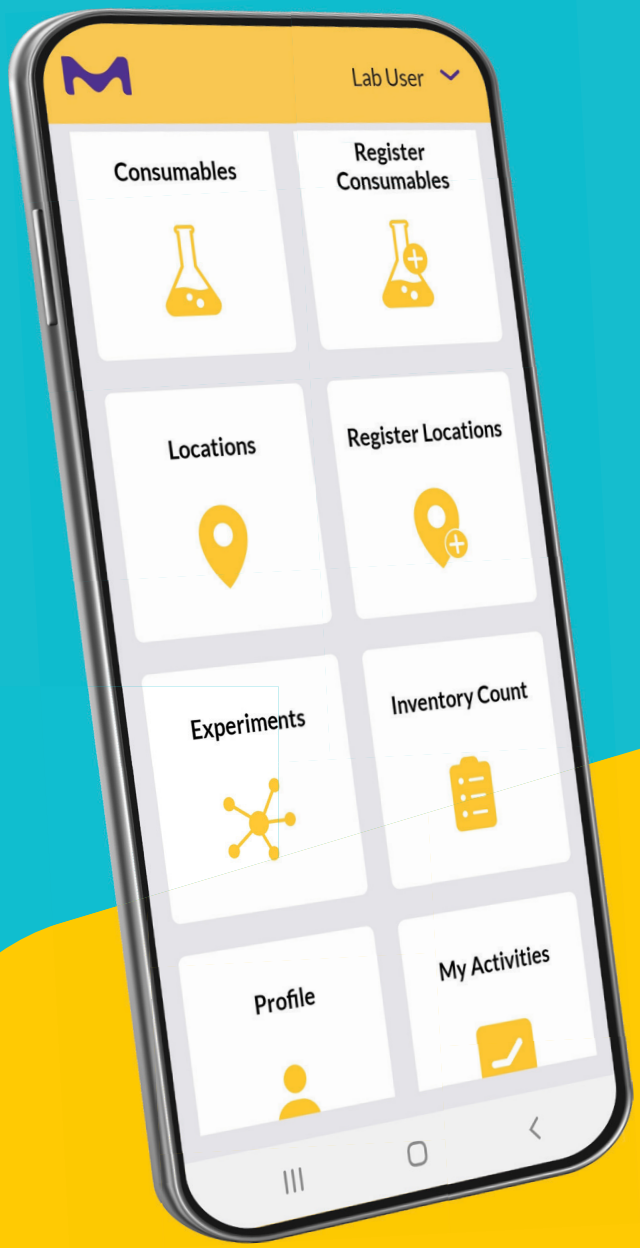

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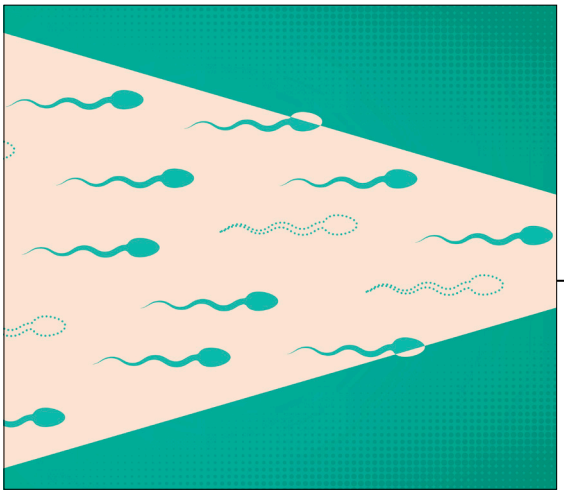
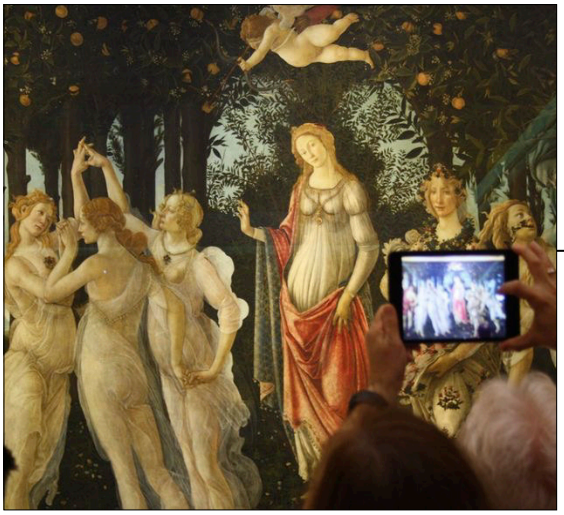


GENETIC DISCOVERY COULD ENABLE NON-HORMONAL MALE CONTRACEPTIVE

MOLLY CAMPBELL

Washington State University researchers have identified a gene – *Arrdc5* – that is expressed in the testicular tissue of mammals, which they suggest could be a promising target for male contraceptive development.

JOURNAL: *Nature Communications.*



THE EGGSTRAORDINARY MYSTERY OF PROTEINS IN RENAISSANCE PAINTINGS

MOLLY CAMPBELL

An interdisciplinary team of researchers propose that Italian Renaissance masters – artists such as Sandro Botticelli and Leonardo da Vinci – added protein to their oil paintings to prevent wrinkling and issues with humidity.

JOURNAL: *Nature Communications.*

THIS ELEPHANT PEELS BANANAS JUST LIKE HUMANS DO

RUAIRI J MACKENZIE

A new case study of an unusual elephant in Germany shows that, given the right circumstances, elephants can learn the complicated movements required to peel a banana like humans.

JOURNAL: *Current Biology.*

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HAVING A POSITIVE ATTITUDE TO AGING COULD HELP REVERSE COGNITIVE DECLINE

RUAIRI J MACKENZIE

A new study suggests that people who have more positive attitudes towards aging are 30% more likely to recover from a state of cognitive decline thought to precede dementia.

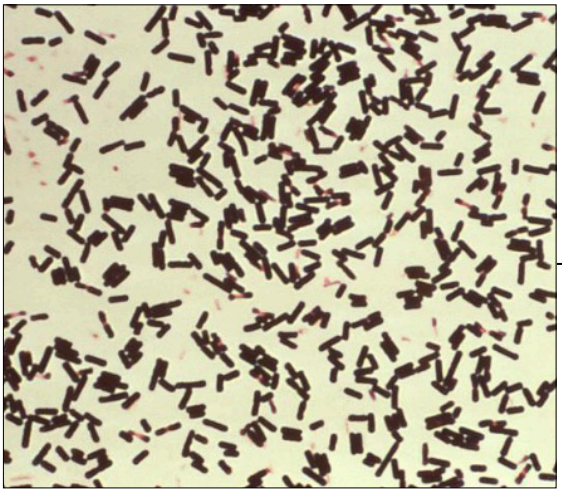
JOURNAL: *JAMA Network Open.*

COMBINED AND PROGESTERONE-ONLY CONTRACEPTIVES HAVE A SIMILAR RISK OF BREAST CANCER

SARAH WHELAN

A new study has found that both combined and progesterone-only hormonal contraceptives are associated with a similar relative increase in breast cancer risk of around 20–30%.

JOURNAL: *PLOS Medicine.*



GUT BACTERIA TOXIN LINKED TO ONSET AND RELAPSE OF MULTIPLE SCLEROSIS

SARAH WHELAN

Researchers suggest that the onset and relapse of multiple sclerosis (MS) may be initiated by a toxin from gut bacteria.

JOURNAL: *Journal of Clinical Investigation.*

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iStock. Dr. Birgit Schilling.

How Collaboration and Curiosity Make for a Successful Scientist

MOLLY CAMPBELL

Dr. Birgit Schilling studies the molecular mechanisms that underlie aging processes, and is particularly passionate about research that could lead to novel therapeutic interventions for human aging or disease. At the *Buck Institute for Research on Agingin* Novato near San Francisco, CA, she leads her laboratory in the use of modern proteomics technologies – such as data-independent acquisition – to fulfill these research goals. Key project examples from her lab include investigating the dynamic role of post-translational modifications (PTMs) during cell signaling, specifically in the context of metabolic diseases, neurodegenerative diseases, cancer and aging.

Dr. Schilling studied chemistry at the University of Hamburg in Germany and she also studied as an undergraduate student in Southampton. After completing her PhD in Germany, she started a postdoctoral fellowship in 1998 at the University of California San Francisco (UCSF). She has worked at the Buck Institute since 2000, where she is also the director of the Mass Spectrometry Technology Center. Dr. Schilling has a long-standing scientific track-record in developing mass spectrometry (MS)-based methodologies for quantitatively analyzing complex samples. She is incredibly well respected in her field and has collaborated with many scientists across the globe.

Dr. Birgit Schilling is a professor and director of the Mass Spectrometry Technology Center at the Buck Institute for Research on Aging.

Technology Networks champions diversity in science and embraces the opportunity to learn from women in science about their journey – the challenges they may have faced, how their research focuses evolved and the advice they may offer young scientists eager to follow in their footsteps.

We recently had the pleasure of interviewing Dr. Schilling, who talked about the "beauty in the chemistry that generates life", why science careers can be hard and the importance of knowing when to change direction.

Molly Campbell (MC): What inspired you to pursue a career in science?

BIRGIT SCHILLING (BS): I was always fascinated by the natural world around me and how one could use science to try to explain natural phenomena. I studied chemistry, and I really liked the logic and elemental understanding of what is around us. Most of all, I really love the multi-disciplinary aspects of science, and how chemistry, biology, physics and medicine all inform each other and often yield wonderful collaborations between scientists from different backgrounds. Science is highly collaborative, which I cherish, and those collaborations can be national and international.

What intrigued me when I studied chemistry is how nature has brought forward fascinating chemical structures and molecules that "operate" and manifest life, and often show "healing" power. Quite a few pharmaceutical drugs are based on natural products, and in some cases these structures are synthesized and further optimized to generate therapeutics that become medical interventions for disease treatments – this is also referred to as "natural product chemistry". There is a beauty in the chemistry that generates life.

MC: Why did you decide to focus your research on aging, specifically?

BS: The aging process of life – how an organism develops, grows and ages – is a fascinating field of research. We are interested in "healthy aging", meaning to extend what we call "health span" so that humans have a longer span of health throughout their life.

Interestingly, aging is closely related with many age-related diseases, so a better understanding of aging will help to tackle age-related diseases. Aging is also something that we all will face, but understanding the complexity of this biological process is important to implement interventions – in lifestyle (exercise/diet) or pharmaceutically. Connecting aging mechanisms with, for example, neurodegenerative brain diseases, such as Alzheimer's disease – but also other devastating diseases, such as cancer – is interesting from a scientific standpoint and will contribute to the development of further interventions.

MC: As a woman in science, have you faced any barriers in your career journey?

BS: That is an interesting question. I have always been a "strong" person. When I studied chemistry in my college years, there were so few female students, it was really surprising. But what counted was the science and I could usually easily connect and interact with anybody. We were good friends supporting each other – it did not matter whether we were men or women. So that was not a problem.

Throughout my career, I was focused on my scientific work and would try hard to showcase the skills and passion that I had. I wanted to be "measured" based on that – the good science I could contribute and the fact I was a good collaborator. I did not get too much pushback, and when I did, that was just not the direction I would pursue, I would re-orient myself.

There are so many opportunities, if one thing does not work out, I would look for other directions, or if I cared a lot for something that led to me facing obstacles, I would try to really show what I can do and convince those around me with my good work.

Being a scientist is not always easy because sometimes experiments are challenging, but when things go well, it is so rewarding.

I found great supporters that would help me move forward – but I also put in a large amount of work to make my case! I have found many scientists do support each other when they collaborate well, and when they see how valuable the work of the other person is.

MC: What qualities and values do you think makes for a successful scientist?

BS: Curiosity, persistency, enthusiasm and a fascination with learning something new every single day – imagine that! What is also important is having a keen eye for understanding a scientific observation: many people may observe the same thing, but it is the right interpretation of an experimental outcome that sometimes reveals the most interesting scientific results.

Being a scientist is not always easy because sometimes experiments are challenging, but when things go well, it is so rewarding. Finding the right collaborators, the right projects to engage in, showing persistency but also knowing when to change direction are incredibly important.

I think being a team player is key and being open to embracing the joy of collaborating. Also, recognizing how technology can help scientists is very important, in addition to finding the "right" place to do your fun science.

Something to ask yourself if you are thinking of being a scientist is: do you love nature – plants, animals, humans, microbes or other? Are you interested in understanding how life works? We can use science to help, for example, in human diseases, or for other scientific purposes. An overall appreciation for the complexity of life is a good quality for scientists to have.

MC: Can you talk about women in science that have inspired or supported you?

BS: This is an interesting question – until I was >30 years old, there were no women in science who had inspired me. My history teacher in high school, who is a woman, really inspired me with her strength and knowledge and other interests outside of her school work (travel and photography).

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In my college years, there were no women professors in Chemistry (in Germany at the time). When I was an early postdoctoral fellow, I met Dr. Catherine (Cathy) Costello, who is an amazing scientist and professor at Boston University. She was so kind as to give me a ride from an Asilomar Mass Spectrometry conference back to San Francisco Airport. During the journey, we talked about many things, both within and outside of science. That was so important to me – to experience how somebody can be such a highly respected and successful scientist, admired by many (myself included!), but also be a kind person with so much generosity on a personal level.

Other women scientists who have really supported me are Dr. Jennifer Van Eyk at Cedars-Sinai in Los Angeles and Dr. Ileana Cristea at Princeton. At the Buck Institute, I am so lucky to work with Dr. Judith (Judy) Campisi and Dr. Lisa Ellerby, who both are dear colleagues. We do *great* science together and we support each other.

I also know a lot of male scientists who I admire greatly, and who have helped me a lot in my career. I usually look at the person (man or woman) – and then I connect with them as a person and a scientist. It is the connection that generates a great scientific colleague – somebody who I support and who may support me.

MC: What advice would you give to someone that wishes to pursue a career in science?

BS: Follow your dreams. If science is what you like to do – then go for it. It is hard at times – but also greatly rewarding.

Dr. Birgit Schilling was speaking to Molly Campbell, Senior Science Writer for Technology Networks.

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Towards the Lab of the Future

JOANNA OWENS

In the lab of the future, researchers will be freed from manual, repetitive experimental tasks, as automated tools and artificial intelligence-powered robots carry out protocols, collect and analyze data and design subsequent experiments, freeing up time for humans to focus on interpreting what the results mean and addressing the bigger scientific questions.

The lab of the future will bring together a range of different technologies, all digitally connected and seamlessly integrated. These innovations will be involved in every step of the research cycle, from managing a lab's supply chain of scientific products and reagents – handling samples, chemicals and equipment – to sharing data within and across organizations.

But the timescale for realizing this vision is slower in some research sectors than others. In this article, we look at the barriers preventing more widespread adoption of automation and digitization, and the opportunities they could bring.

AUTOMATING THE ACADEMIC LAB

Anyone who has worked in a lab will be familiar with the repetitive, manual nature of many experiments, and there seems ripe opportunity for using automation to free up researchers' time. But for academic labs, adopting automation can be daunting and cost-prohibitive, and isn't helped by structures for funding and impact assessment.

"I think the vision of the lab of the future differs in academia and industry because we have different outputs," says Dr. Ian Holland, an engineer who moved from the automation industry to a lab focused on tissue biofabrication at the University of Edinburgh and has written about the "automation gap" in academia. "Academic labs tend to carry out a wider range of work and there's considerable protocol

variability, whereas industry uses standardized protocols for highly focused, repetitive applications, which are more amenable to automation. Academic labs cannot afford to invest in off-the-shelf technologies that aren't more flexible to suit their needs. So, although there is appetite for the improved efficiency that automation brings, the route to the lab of the future for academic labs is less clear."

There is a shared vision though, which is a world where scientists spend more time doing science and automation carries out the manual tasks. "It's not good having highly educated people carrying out manual tasks, and I think that happens too much in academia. I'd like to see more manual tests done by machines and let scientists do more science," says Holland.

BARRIERS TO ADOPTING AUTOMATION

The short-term nature of academic research funding does not lend itself to investing in large-scale technologies for modernizing the lab, says Holland, and although investment in major infrastructure such as robotics will improve efficiency, it is difficult to directly relate that to an increase in the output of research papers – the main metric used to measure a lab's success – making the investment hard to justify.

This is a problem also experienced by Professor Ross King, at Cambridge University, who has been working for several decades on "robot scientists" – semi- or fully autonomous robots that automate simple forms of scientific research, from setting new hypotheses to automatically designing and running efficient experiments to discriminate between them. This futuristic type of research seems to divide funding panels, who have tended to take a conservative view, and existing university structures don't lend themselves to the collaborative, interdisciplinary nature of the work required. "I think it's slowly changing, and we're getting traction in different areas, especially now these ideas are being taken up by the pharmaceutical industry," says King.

Another challenge for academic scientists is a skills gap, because automation and robotics requires an understanding of mathematical models, machine learning and engineering – expertise not every lab has easy access to. And although automation brings efficiency, it also brings with it new challenges, such as how to manage large amounts of data.

This is where having the right expertise can help, as Prof. Ola Spjuth, from Uppsala University in Sweden, explains: "We have a big focus on trying to automate our entire cell-based screening and profiling methods in the lab, and this generates a lot of images. This scale of data can scare a lot of researchers, but we have a background in managing big data and using high-performance computing clusters here, so we see large amounts of data as valuable. We're also not the typical life scientists in that we take an engineering approach and have a multidisciplinary group with experimentalists, data scientists and engineers."

USING AUTOMATION AND AI TO IMPROVE EFFICIENCY AND REPRODUCIBILITY

Spjuth took what he calls an unconventional strategy to automating the lab in that they did not go out and procure entire robotic installations from vendors, instead choosing to buy individual equipment components and build the system themselves using an open-source approach. "It's a lot more challenging than buying something off the shelf, but we have full control of all steps in the protocol, and we wanted a research environment that we can grow with and update."

So far, the main efficiency gains have not been the envisioned capacity increase from using robots able to work 24/7. "We are getting there," says Spjuth, "but our system still needs a lot of human support, and steps such as cell culture are too expensive for an academic lab to fully automate right now." The major gain, he says, is in reproducibility – every experiment is carried out in exactly the same way.

In fact, alongside efficiency, reproducibility appears to be one of the main drivers for automating research processes. One of the goals of King's work on robot scientists is to improve the scientific method. "Machines in some ways already do better quality science than humans because what they do is recorded, explicit and clear," says Ross. "Human beings are often unintentionally sloppy about what they do in experiments, and there's a huge problem with scientific reproducibility because experiments are so susceptible to human error. Just like games on computers have improved over the years, we think that in science, the machines will keep progressing. Ultimately, they'll be as good as humans at science, and maybe even better."

King has already developed two prototype robot scientists, Adam and Eve. Adam was designed to carry out functional genomics in yeast, assigning functions to the genome that was sequenced back in 1996. Eve specializes in early-stage drug design, using artificial intelligence to find compounds to treat specific diseases.

"The way compound screening used to be done in industry was you would make an automated assay to tell you if a compound was likely to be good or not, and then you'd screen a large compound library – maybe one million compounds – and find a small number of hits to take forwards. Then you'd start again with another assay and library," explains King. "But actually, that's a missed opportunity, because you've learned something during the screen and you could use that insight to decide what to do next." By using quantitative structure-activity relationship (QSAR) models and accumulating biological knowledge, Eve was trained to find hits using only a small fraction of the compounds in a library – speeding up the process and make it more cost effective.

Now, King is working on the next iteration of the robot scientist – called Genesis – as part of the Nobel–Turing AI scientist grand challenge. The challenge is to develop AI systems capable of making Nobel-quality scientific discoveries autonomously at a level comparable, and possibly superior, to the best human scientists by 2050.

Genesis is a scaled-up robot scientist with thousands of micro-chemostats – tiny bioreactors where nutrients are continually added to cells and metabolic end products are continually removed. These will enable Genesis to run more sophisticated experiments in parallel. "We need an AI system to plan so many experiments and especially hypothesis-led experiments, rather than just altering a component and seeing what happens," says King. "Here, the robot is saying 'I think change Y will do X to this model, and then it conducts the experiment to see if the hypothesis is true."

MOVING TOWARDS A DIGITIZED LABORATORY

In addition to adopting robotic solutions to improve efficiency and reproducibility in the lab of the future, many researchers are moving towards digitizing their labs, switching from paper-based systems to informatics solutions such as laboratory information management systems (LIMS) and electronic notebooks (ELNs). LIMS enable researchers to keep track of data associated with samples, experiments and instruments efficiently, as well as actively manage lab processes, while ELNs digitize note taking and can automate the data review process. Guidance on good records and data management practices from the World Health Organization (WHO) recommends that hybrid systems – a combination of manual and electronic systems – should be replaced by fully digitized systems at the earliest opportunity.

Adopting informatics solutions such as LIMS can offer laboratories several benefits, including helping to improve performance, maximizing quality and ensuring compliance requirements and regulations are met. They can also remove repetitive, laborious steps in workflows and reduce human error. The time savings can empower scientists, allowing them to focus on more complex and meaningful work.

Despite the benefits offered, barriers to adopting these solutions and digitizing a laboratory remain. The cost of subscriptions, new equipment and software, as well as time to implement the solutions, can be prohibitive for many laboratories, particularly in academia. "Accessibility is also a huge barrier. Many academic laboratories aren't set up for the digital capture of laboratory information, both from a hardware and software perspective," Dr. Samantha Kanza, senior enterprise fellow at the University of Southampton, told *Technology Networks* previously. Problems with outdated equipment and software compatibility can further limit the adoption of digital technologies. In addition, "The lab can often be a hostile place for technology," said Kanza. Space for using laptops or tablets may be limited, and researchers may be concerned about spills and accidents occurring. Even things such as removing gloves to type notes rather than jotting them in a notebook can be seen as prohibitive.

However, the continuing advancement of technologies is likely to reduce these barriers and encourage greater adoption of digital solutions in the lab of the future.

"Much like smart homes have become commonplace in today's society, so will smart labs. Users will be able to control their laboratories by voice using smart lab assistants, all of the laboratory systems will be seamlessly linked together and users will have multiple options to record their data via voice, tablets, phones or computers if they wish," envisaged Kanza.

TAKING SMALL STEPS TOWARDS THE LAB OF THE FUTURE

It might be another two decades before fully autonomous robots are designing and conducting experiments in the lab, but it's never too early for academic labs to start their journey towards automation, says Holland. "As an engineer in a biology lab you can see the potential opportunities to use technology to improve processes. However, I think too often in academia, researchers strive for a magic machine that does everything. But that is never how you develop automation as an engineer, you build prototypes that carry out each part of the process."

Holland advocates starting small, by automating something simple such as fluid dispensing that can bring substantial gains in efficiency and reproducibility. In the tissue biofabrication lab, just making this change has reduced a protocol from 25 to 5 minutes, freeing up time for other tasks.

Another advantage of adopting automation early is it can help researchers looking to translate discoveries from bench to bedside. "The earlier you can include automation in your process and start thinking about that, the better chance you have of convincing people to invest in your product, because they can see it will be easy to scale up quickly."

In Spjuth's lab they are hoping for additional collaboration with other researchers working on their own robotic and automated solutions for the lab, sharing protocols and code. "With major advances in technology such as 3D printing and people now sharing code for these and other applications, it is becoming possible for researchers to do much more independently. The do-it-yourself movement is advancing and that means you can build your own microfluidic chips and microscopes, and as prices for robots come down there is an opportunity for many biological labs to adopt some sort of lab automation."

However, an important consideration as this movement advances, notes Holland, is sustainability. "There is already a real problem with automated processes generating high amounts of waste – a machine generating millions of waste pipette tips, for example. I think this needs to be considered more and certainly in the design stage, both from an environmental perspective and to ensure supply chains can meet demand."

FAILING FASTER, SUCCEEDING SOONER

Technologies That Are Accelerating Drug Discovery

ANTHONY KING

Most drug hopefuls fall flat. Approximately 90% of drug candidates fail clinical development, costing hundreds of millions to billions of dollars. That's a gargantuan waste of resources thrown into compounds that never reach patients.

Drug discovery scientists at university labs and in big pharma, along with patients and governments, want more winners. One solution is to have drugs fail faster, fail earlier and fail completely – while it sounds contradictory, this could reduce costs and efforts invested into compounds that ultimately never make it onto a patient's prescription.

Researchers now have some helpful levers that they can pull to fail *better* and boost success rates. One is laboratory automation, where automated technologies take the place of human hands in manual and time-consuming tasks, making the research and development of possible drugs quicker and easier. A second is artificial intelligence approaches (AI), which divulge patterns in the myriad sand grains of data available, such as linking nebulous data patterns to the intervention of a potential drug compound, that no human could realistically wrap their head around. Both are being combined with an array of innovative techniques in the world of drug R&D to open new treatment avenues, which we'll explore in this article.

IN SILICO METHODS FOR EARLY COMPOUND EVALUATION

The early stages of drug discovery benefit most from AI right now, says Professor Andreas Bender. "There's lots of machine learning in early-stage ligand discovery, but the problem is al-

ways translation to the clinic," meaning taking the research from laboratory to patient bedside. An analogy for ligand discovery is finding a key that fits and turns a lock, usually a protein involved in a disease. How the key and lock interact is pure physics and chemistry, and this is something that algorithms and computers handle well. There are treasure troves of public data that can be reached into, such as ChEMBL, a curated database of bioactive molecules with drug-like properties.

Bender taps *in silico* computer methods, essentially experiments performed via a computer simulation, to evaluate compounds early on. Such calculations can instantly reveal that a compound's chemical structure will lead to its rapid clearance from the body, meaning dosing will be a problem in patients. "Despite having huge amounts of data, predictive models are always fallible. You need experimental data to validate," says Professor Miraz Rahman, medicinal chemist at King's College London, UK.

But biology gets messier as you move towards humans, which is why the big hurdle is often Phase II clinical trials, when a drug is tested to see if it carries efficacy and can make a difference to patients' lives. Often the information fed into an algorithm to try to improve on patient efficacy comes from lab animals , but the algorithm usually does not know about underlying conditions that impinge on the results from the animals, such as the age, genetics or sex of the organism. This situation is set to improve. "Experimental datasets will increase over the next 5 to 10 years probably," says Miraz. "This will enrich AI models and will likely make the success rate significantly higher." That is not to say machine learning cannot help now.

AI CROSSED WITH FOLK MEDICINE

Bender investigates natural compounds believed to have medicinal qualities for their influence on the formation of blood vessels, known as angiogenesis. He used machine learning to identify such plant compounds from texts online, where they are often described as molecules of interest in folk medicines. Such botanical products might prep the pace of blood vessel formation and benefit heart attack patients, or they might choke off blood supply to hungry tumors, helping cancer patients. "We tested the compounds to see if they had an effect on blood vessel formation," recalls Bender, who collaborated with colleagues in China. Zebrafish embryos – less than a week old – were placed in trays with 96 wells before varying doses of the compounds were added to each well. Zebrafish embryos are transparent, and automation in the lab allowed each embryo to be imaged using a microscope and the data fed directly into an algorithm. This revealed which compounds, and at what dose, influenced angiogenesis. "You get good bang for your buck and quite a lot of return from your time and effort," Bender comments on the pairing of AI and automation in this context. It's an approach that is well established, and advances at this stage in drug discovery can help move compounds closer to use in patients.

When combined with automated and cell imaging and other laboratory techniques, AI can also make great inroads in identifying patient subgroups that might benefit the most from a specific treatment. This has been most notable for cancer patients, where researchers have developed successful treatments of patients by pinpointing drug targets on their tumors. This tailored approach requires an in-depth understanding of their individual disease, something machine learning can assist with. For example, clinical data and computer tomographic images have been combined to identify which patients with colorectal cancer are likely to also develop metastatic liver cancer, and how best to treat them. Beyond cancer, there is also hope that machine learning can aid the discovery of drugs for central nervous system diseases, as noted in a recent review.

Conversely, in the 1990s, high-throughput screening of compound libraries pinpointed many interesting candidates, but after testing and moves towards patients, the approach turned out to be largely disappointing in terms of patient impact. Lack of disease understanding was often to blame. "If you poke in the dark, you will reduce your chances of success," says Bender. Instead, AI works best if there is a working hypothesis on how to treat a disease, as well as relevant data to feed into an algorithm; then, *in silico* predictions can deliver testable hypothesis which, followed by experiment, can then identify disease-modifying compounds.

BEATING DRUG RESISTANCE

One area of drug R&D that has particularly struggled is the discovery of new classes of antibiotics. Microbes that are resistant to existing drugs are deemed one of the top global public health threats facing humanity by the World Health Organization. With effective antimicrobials, medical procedures such as cesarean sections, hip replacement, cancer chemotherapy and organ transplantations will become far riskier. "Globally, recent data indicates that close to one million deaths per year are due to these types of infections,"

"You get good bang for your buck and quite a lot of return from your time and effort," Bender comments on the pairing of AI and automation.

says Dr. Jose Bengoechea, a professor of biomedical sciences at Queen's University Belfast, UK. Bengoechea has just embarked on a project funded by the Medical Research Council in the UK that will use AI and machine learning to find new ways of turning off microbial defenses against antibiotics.

Previously, AI has been tapped to identify how microbes gained resistance in healthcare settings such as hospitals. Often this relies on sequencing genomes of the microbes. But Bengoechea's new project seeks previously unknown protein targets on a troublesome bacterial species, *Klebsiella pneumonia (K. pneumonia)*. This is a common bacteria found in the environment and naturally inside and outside the human body, but some strains can cause pneumonia, wound infections and blood infections in hospital patients, which are difficult to treat with standard antibiotics.

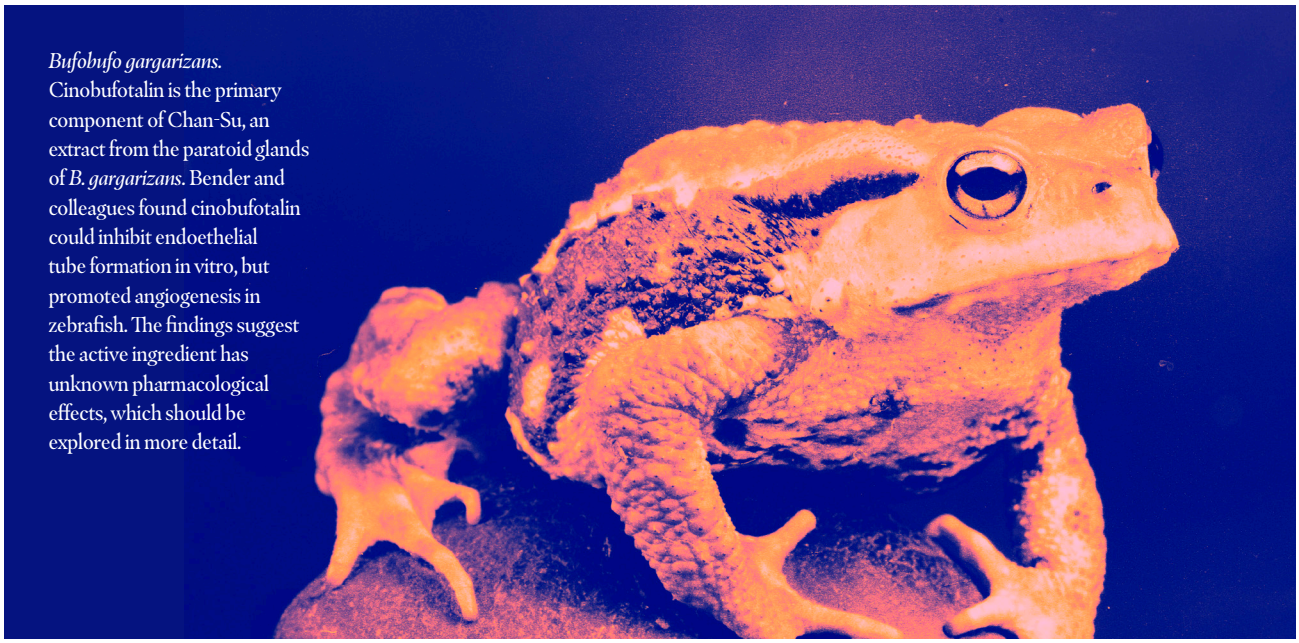
As part of his project, Bengoechea seeks new ways to block mechanisms of resistance in bacteria by combining AI and lab experiments. "This will allow us to make discoveries faster than traditional approaches," he says. He explains that the problem with traditional approaches is that they keep turning up the same drug targets: "We are getting the same hits all the time." AI brings the opportunity to discover new ways to make *K. pneumonia* susceptible to existing antibiotics and our own defenses, which will be cross-checked with existing drugs. "We will interrogate libraries of drugs that already have received approval," says Bengoechea, "dramatically cutting the cost and time it takes for a drug to be tested in patients." Results can then be checked in lab experiments. If AI, coupled with other experiments, succeeds in reducing the defenses of *K. pneumonia,* the lab will explore whether the strategy can be deployed against other troublesome organisms resistant to our antimicrobials.

FEWER ANIMAL TESTS, AND MINI-ME CANCERS

Newer approaches that lean on AI and automation can reduce the reliance on animal testing in drug discovery and developments. In principle, animal tests have not been accepted for cosmetics in Europe for some time, while recently the US removed the rule whereby tests on two animal species were needed before drugs could go to human trials. "I see this as a step forward, because the bar is so low," says Bender. "Animal tests are not sufficiently predictive." Results from drug tests on rats and mice often differ from each other, never mind from people, and it is an oft used quip that we have drugs that cured many diseases in mice, but failed where it matters – humans. Now, in a move away from animals, many scientists tap previous experiments for running *in silico* tests, coupled with new lab experiments that don't involve rats, mice or guinea pigs.

For example, an anti-cancer compound might be added to cells in a dish or mini-organs (organoids) in 96-well or 384-well plates. An automated imaging system tracks changes to the mini-organ or monitors what happens inside of the cells, to see if expected changes occur. Once upon a time, potential cancer drugs were mostly tested on human cancer cells by applying them to immortalized tumor cell lines organized in single layers on a dish or suspended in a flask. One of the most famous is HeLa, a prolific line of cells that originated from cervical cancer cells taken from a US woman – Henrietta Lacks – who died of cancer in 1951. Biologists could keep these cells alive beyond a few days in the lab, and experiments using them contributed greatly to medical advances. However, a problem is that such cells adapt to life in the lab. Worse, perhaps, layers of cells are not the same as the 3D milieu of cells in most human tumors, so that cell lines do not mirror real-life cancer – and there is *lots* of variation within tumor types.

This is where organoids enter the story. Cancer organoids are tiny three-dimensional (3D) tissues that can be grown in a lab from patient tissue obtained



Bufobufo gargarizans. Cinobufotalin is the primary component of Chan-Su, an extract from the paratoid glands of *B. gargarizans*. Bender and colleagues found cinobufotalin could inhibit endoethelial tube formation in vitro, but promoted angiogenesis in zebrafish. The findings suggest the active ingredient has unknown pharmacological effects, which should be explored in more detail.

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When combined with automated and cell imaging and other laboratory techniques, AI can also make great inroads in identifying patient subgroups that might benefit the most from a specific treatment.

during surgery or biopsy. They are predicted to revolutionize our understanding of patient-specific tumors "If you want to find a drug that works for a patient's tumor, then you make sure the organoids you are testing are as close as possible to the patient," says Dr Alice Soragni, who heads a lab at the University of California, Los Angeles, that uses organoids to better understand rare cancers. She seeds 96 well plates with organoids taken directly from patients at surgery. Handling error and variabilities in techniques are kept to a minimum because of automation use and how the organoids are placed into the wells as a ring.

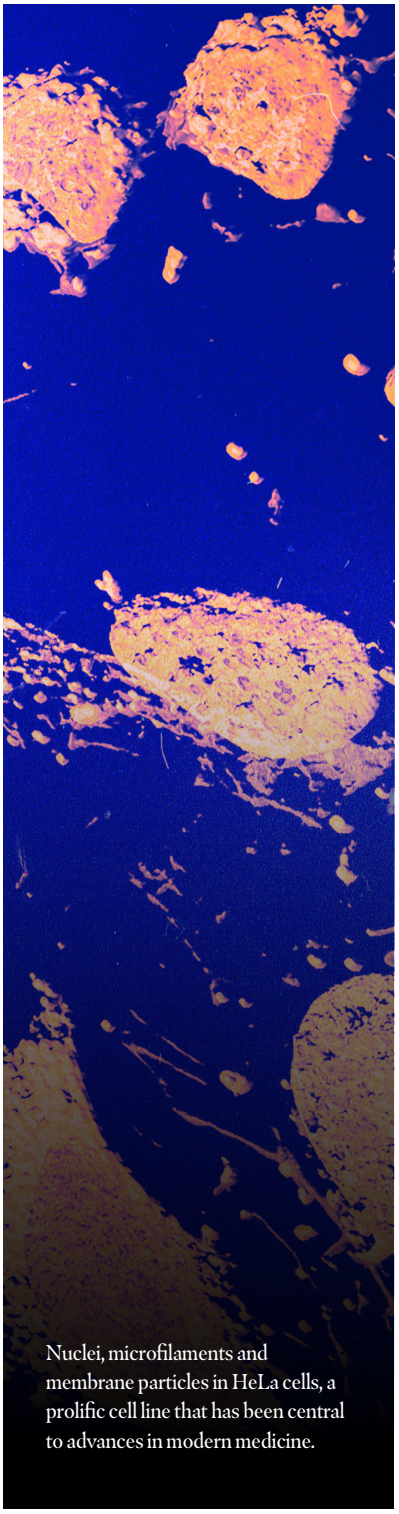
Once the "mini tumors" are in place, Soragni hits the button on an automated system that monitors them while they are exposed to different doses of off-the-shelf drugs over several days. In one set-up, she can use an imaging technique called interferometry that allows her to weigh and image the cells in real-time, to see how they are responding to a treatment.

The Soragni lab is now also printing cells from patients with rare sarcoma tumors, embedded in a support matrix. "This is a high throughput platform powered by machine-learning based tools," Soragni explains, "which allows us to extract as much information as possible from the images." Her team seeks to leverage machine learning tools to link tell-tale characteristics of tumor organoids, which would not be picked up by eye, to their response to therapy.

Organoids – tied with automated approaches – are making headway in other areas too. In a Chinese study, researchers profiled the chromosomes of 84 pancreatic cancer organoids to analyze their response to hundreds of chemicals and five chemotherapies. Meanwhile, scientists in Germany developed a human midbrain organoid to screen 84 drugs, pesticides and other chemicals for toxicity. Their fully automated set-up identified a flame retardant and a pesticide as toxic to dopaminergic neurons through analyzing microscope images. These neurons, which release the neurotransmitter dopamine, are of interest partly because their deterioration is the hallmark of Parkinson's disease.

Back in California, Soragni is also interested in a genetic condition, neurofibromatosis type 1, which causes tumors to grow under the skin of patients. The tumors do not spread or become cancerous, but they can cause a patient pain and distress. Surgery is one option, but Soragni has obtained patient tumor samples to grow into organoids in a quest for treatments. She is testing existing drugs on these patient-derived organoids to try to help these patients. "Automation makes this possible, because manual screening would be technically challenging, time consuming and labor-intensive, and could also suffer from operator issues," explains Soragni, referring to the fact that individuals in a lab can vary in their techniques and introduce variability. "Once you have automation, everything becomes not only faster but also more robust and easier," she adds.

She is excited about the vistas that lab automation and organoids open in terms of discovering new drugs, but also in trying them out against tissue from an individual patient. "We don't even need that much information about the tumor per se," enthuses Soragni. "We can take a tumor, shower it with different drugs and let the tumor tell us what works best." The ultimate beneficiary of AI and automation should be patients, with newer therapeutics brought to market that are more tailored to them as individuals, boosting effectiveness and diminishing side effects – the right drug for the right patient.



Nuclei, microfilaments and membrane particles in HeLa cells, a prolific cell line that has been central to advances in modern medicine.

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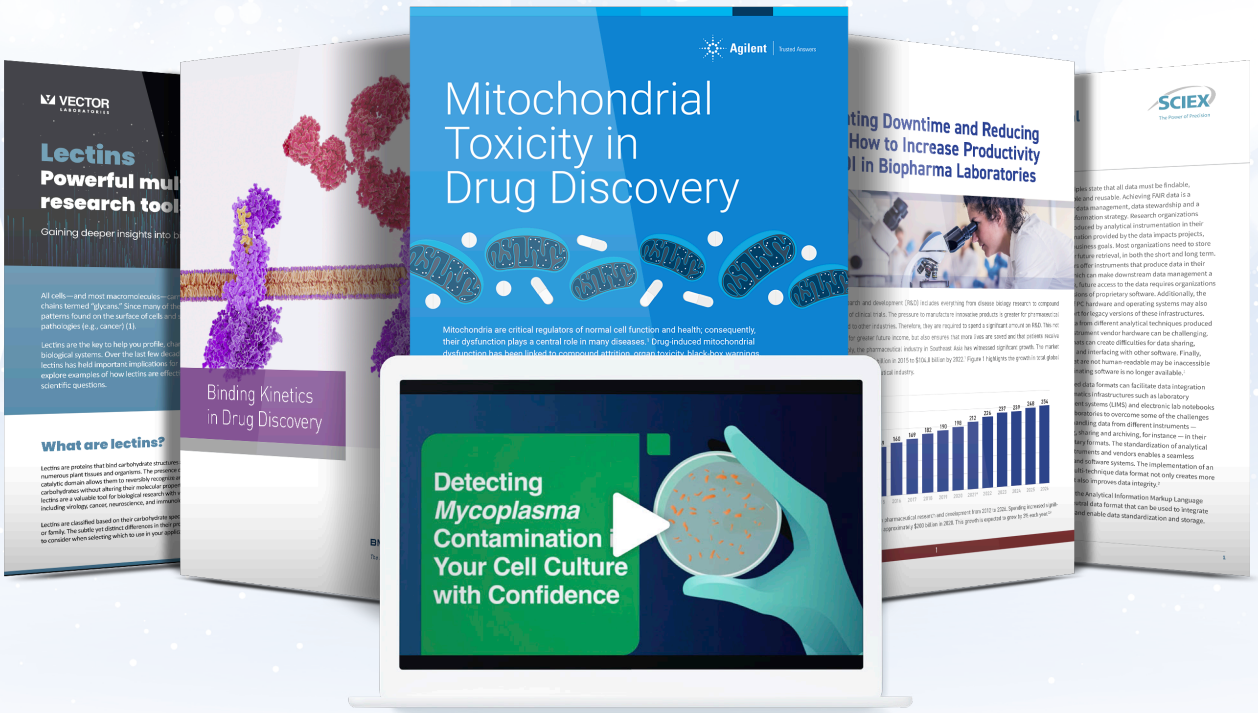

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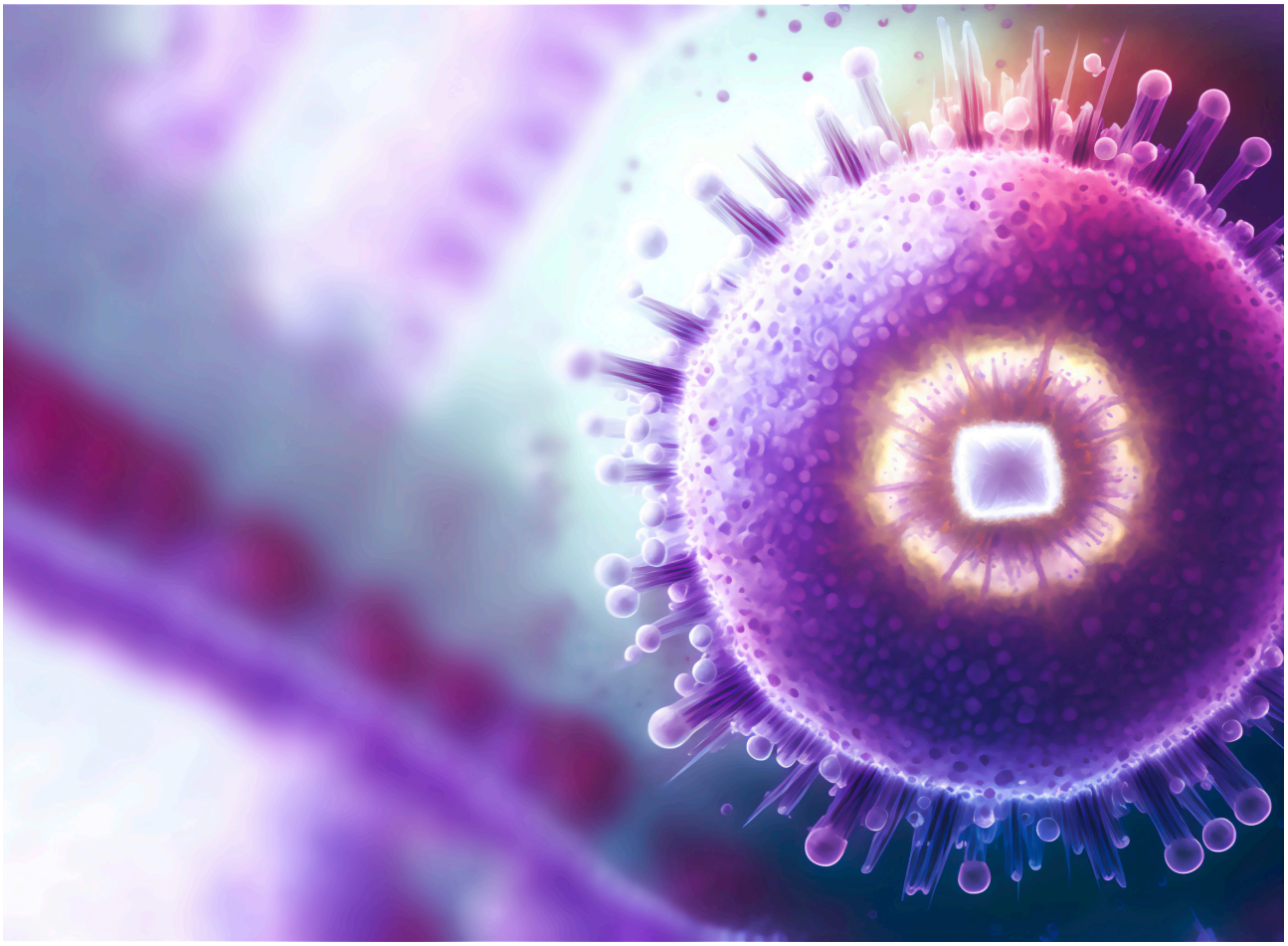

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Viral Evolution: Changing Priorities Under Environmental Cues

MASHA G. SAVELIEFF

Human host–virus co-evolution has been occurring for hundreds of thousands of years, since the dawn of modern humans. The evidence of human viral infection is even imprinted in our DNA, where, for example, remnants of retroviruses from previous infection can be observed. Today, host–virus evolution continues, shaped and molded by environmental cues that apply selective pressures on the mutating virus, favoring the variants that are the most fit to survive in the shifting landscape. Sometimes, mutations that help a virus survive some situations, e.g., within a host during chronic infection, exact a toll on fitness under different circumstances, e.g., between host transmission. Thus, changing host conditions dictate viral evolution.

This article will describe this everchanging scenario for two viruses, human parainfluenza virus (HPIV) and human immunodeficiency virus (HIV), to highlight some of the selective pressures on rapidly mutating viruses.

HUMAN PARAINFLUENZA VIRUS (HPIV): A SIGNIFICANT RESPIRATORY VIRUS

HPIVs are enveloped, single-stranded RNA viruses belonging to the *Paramyxoviridae* family. There are three HPIVs, 1, 2 and 3, the last accounting for most infections. Of the children under 5 years old hospitalized for fever and/or serious respiratory infection in the United States, 4 to 14% have been attributed to HPIV infection. It is also a significant respiratory virus in immunocompromised patients, such as transplant recipients and older individuals.

"Currently, we don't have effective vaccines or therapeutics against HPIVs," explained Anne Moscona, professor and director of the Center for Host–Pathogen Interaction at Columbia University Department of Pediatrics. Moscona investigates the impact of the environment, or host setting, on HPIV viral evolution and fitness. "The single-stranded RNA genome of HPIV3 tends to mutate

rapidly because its polymerase lacks a repair function. Thus, HPIV3 adapts to its host, be it a human *in vivo* or culture *in vitro*," Moscona elaborated of the virus's dynamics.

HPIV ENTRY INTO HOST CELLS: IT TAKES TWO TO TANGO

HPIV viruses enter host cells via the concerted effort of two viral surface glycoproteins, the receptor-binding protein hemagglutinin-neuraminidase (HN) and fusion (F) protein. "HN has four roles. First, it stabilizes pre-fusion F, preventing premature activation. Second, HN mediates binding to host receptors that display α2–3 or α2–6-linked terminal sialic acids; the strength of this interaction is called avidity. Third, once engaged to the host receptor, HN triggers F, meaning it induces structural changes to F, causing it to pierce and initiate fusion with the host membrane. Lastly, HN cleaves the receptor, disengaging from it. As you can see, it is a tightly orchestrated process," described Moscona.

Given the closely regulated nature of the interaction between HN and F, mutations at key residues introduced during viral replication alter host entry dynamics. Specific mutations will be advantageous, disadvantageous or neutral to the virus, depending on the host conditions. "HPIV3 variants that are fit, i.e., have advantageous mutations, *in vivo* during acute infection have lower HN avidity for host receptors, which allows the virus to attain the lower respiratory tract and deeper lung tissues before attempting to infect. Fit variants also ensure HN does not prematurely trigger F, otherwise the virus will "activate" before it contacts with host cells, meaning F protein will not pierce the host membrane nor initiate fusion and the trigger will have been wasted," elaborated Moscona.

"In contrast, *in vitro*, the virus immediately contacts with cells in culture, so premature activation is not a concern. In this scenario of persistent infection, higher HN avidity for the host receptor and enhanced F triggering become an advantage, which promotes cell-to-cell spread. Thus, the host conditions dictate viral evolution. Mutations that are normally disadvantageous during acute infection *in vivo* in a human can become advantageous *in vitro* in persistently infected culture."

HPIV IN IMMUNOCOMPROMISED HOSTS: A PERSISTENT SCENARIO *IN VIVO*

A different scenario arises in immunocompromised patients versus patients who clear an acute infection. An immunocompromised host does not quickly or properly clear HPIV3 due to impaired immunity, which permits the virus longer residency in the lung and the opportunity to establish a persistent infection. "During its extended time in the lung, the virus evolves, and the same principles of fitness apply. Advantageous mutations flourish," explained Moscona. To identify the advantageous mutations, Moscona and her team, in collaboration with Alex Greninger at the University of Washington, examined HPIV3 evolution in two immunocompromised patients by sequencing the virus from patient nasal swabs or bronchoalveolar lavage. Mutations consistent with higher HN host receptor avidity and enhanced F triggering emerged.

"Mutations that favored persistent infection *in vivo* in an immunocompromised host mirrored mutations that helped the virus spread *in vitro* in culture, namely the H552Q mutation in HN, which we identified in an earlier study. Given time to evolve in the lung, the virus gained mutations that helped it survive within the host by spreading cell-to-cell, as it does in culture. This contrasts with mutations that would instead help HPIV3 transmit from host-to-host, such as lower HN host receptor avidity and more controlled F triggering, which is needed to allow virions to traverse the respiratory tract without activating," elaborated Moscona.

It should be noted that one of the two study participants also received DAS181 treatment, a sialic acid cleaving drug that strips host cells of their sialic acids, which is under investigation as a human therapeutic for lower respiratory tract parainfluenza infection in immunocompromised patients. Treating cultures *in vitro* with DAS181 has been found to favor the emergence of the fusion-promoting H552Q mutation in HN. So, the selective pressures that elicited the H552Q mutation to HN *in vitro* in culture have effectively been replicated in the host. Despite the small numbers and confounding factors in this study, the emergence of the same mutations in immunocompromised hosts and in culture, i.e., H552Q mutation to HN, is interesting and raises important therapeutic considerations. "It is suggestive that persistent infection in the lung may also promote HPIV3 HN's H552Q mutation. This is a correlative finding and further study is needed, but it does raise concerns about this form of host-directed DAS181 therapy, and I would suggest closely monitoring immunocompromised patients treated with this drug for the emergence of fusion-promoting mutations," explained Moscona.

Moscona further added that it is important to consider that viruses rapidly and deftly adapt to their environment, evolving to fit the host setting. So, if the host setting changes, so too will the virus, evolving to survive that change. "Host-directed therapeutics – be it DAS181 that cleaves sialic acids from the host, or other therapeutics that alter host receptor molecules, membranes or innate immune pathways – will all provide a selective pressure for the virus to evolve!" Moscona concluded. "Viral evolution under selective pressures is of particular concern in immune compromised patients with long-term persistent infections, at least for this group of paramyxoviruses. Treating persistently infecting viruses will require a strategy that prevents cell-to-cell virus spread once infection has been established. It may also be that antivirals that directly target the virus, as opposed to those that target the host, may be advantageous."

HUMAN IMMUNODEFICIENCY VIRUS (HIV): A CONTINUED HEALTH THREAT

HIV is an enveloped, single-stranded RNA virus belonging to the *Retroviridae* family. Once the virus penetrates a host cell, its RNA genome is reverse transcribed into double-stranded DNA, which integrates into the host genome. HIV is subdivided into two types, HIV-1 and HIV-2, the former leading to more

progressive illness. Nevertheless, both HIV types contribute substantially to the global burden of disease and are responsible for acquired immunodeficiency syndrome (AIDS). Despite significant advances in managing infection and transmission, there were 38.4 million people living with HIV worldwide in 2021, along with 1.5 million new cases and 650,000 AIDS-related deaths. Among people living with HIV, 28.7 million had access to antiretroviral therapy (ART).

"ART has vastly improved quality-of-life and survival prospects for people with HIV," explained Ana B. Abecasis, professor of Global Health and Tropical Medicine at the Institute for Hygiene and Tropical Medicine, University Nova de Lisboa, Portugal. "Widespread ART use has also reduced the risk of HIV transmission in communities, which has led to a decline in HIV infection rates. Unfortunately, despite progress, obstacles remain to eradicating the virus, due to, among many other reasons, the development of drug resistance among HIV strains, which mutate rapidly."

HIV YIN AND YANG: WITHIN-HOST EVOLUTION AND BETWEEN-HOST TRANSMISSION

To eradicate HIV, it is essential to understand the dynamics of within-host viral evolution versus between-host viral transmission, in order to implement appropriate strategies. "Within-host HIV-1 evolution is dictated by selective pressure, for example, from host immune responses or ART. Random mutations may confer an advantage to HIV-1, for example by helping it evade the host immune system or circumvent ART inhibitors, e.g., protease inhibitors, which allow the virus to establish a chronic infection. At the same time, mutations that are favorable under certain selection pressures may incur costs, such as impaired replication, which would lead to lower viral load and potentially reduced transmissibility," Abecasis elaborated.

Although between-host transmission was previously thought to occur mostly by chance, studies increasingly suggest that selective pressures also operate. "The contribution of selective pressure on viral transmission is supported by multiple lines of evidence," Abecasis outlined. "First, several studies have shown that certain HIV-1 strains favorably spread between hosts. Infectiousness is especially higher in HIV-1 variants that more closely resemble ancestral strains, which suggests that contemporary, highly evolved strains within the host can be less fit for transmission. Second, specific structural characteristics in viral envelope proteins may predispose to transmission, again indicative of selective pressure on host-to-host spread." Thus, between-host HIV-1 transmission may be determined by both stochastic and selective pressures.

Overall, within-host HIV-1 evolution is a balancing act against virus transmission. Mutations that favor chronic HIV-1 infection may be detrimental to transmission dynamics; nevertheless, mutated viruses do transmit, which has important treatment implications.

HIV DRUG RESISTANCE: WITHIN-HOST DEVELOPMENT AND BETWEEN-HOST SPREAD

Among the HIV-1 mutants that can transmit between hosts, drug resistance is one problematic viral characteristic. "In HIV-1, we distinguish acquired drug resistance (ADR) from transmitted drug resistance (TDR). The former, ADR, is drug resistance that occurs in treated individuals, through within-host HIV-1 evolution, which accrues mutations that help it evade ART-mediated selective pressures. On the other hand, TDR is defined as drug resistance that occurs through infection of the host with a viral strain that already harbors drug resistance mutations," Abecasis elaborated on the distinctions between the two modes of drug resistance.

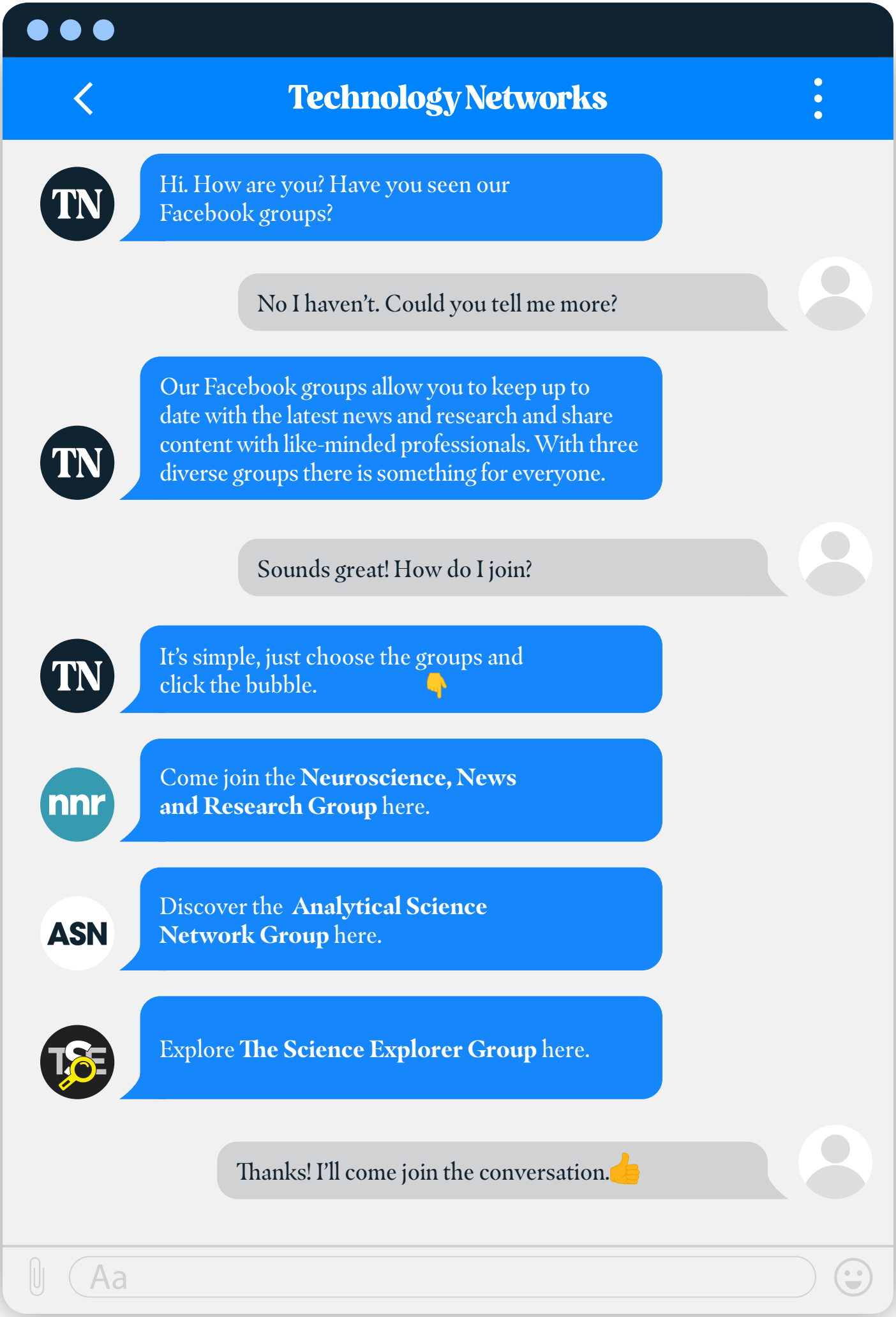
Abecasis studies trends in ADR and TDR in various populations, including in Europe. In Portugal, Abecasis is involved with BEST HOPE, a cohort of newly diagnosed HIV patients in Portugal. "It is important to monitor trends in ADR and TDR because they are undesirable and problematic," Abecasis explained of her research interests. "The main cause of ADR is low adherence to treatment by patients. It is possible to mitigate ADR by using antiretroviral drugs that have a higher genetic barrier, meaning they do not induce drug resistance with ease."

TDR is also problematic, especially for patients that contract an HIV-1 variant harboring resistance to first-line drugs. In this instance, the patient cannot take the recommended first-line therapy because it will be ineffective against the resistant strain. The patient must instead settle on a second-line treatment regimen, which may be more expensive, with more side effects and may also be less convenient in terms of dosage and number of daily pills. "Our work and work by other groups have shown that many TDR mutations have been circulating and transmitted between patients for a long time. Using antiretrovirals with higher genetic barriers should reduce TDR rates. However, we suspect that this is not the case in some parts of Africa where patients' adherence is very low."

Furthermore, Abecasis' research has shed light on risk groups for TDR. "Our transmission cluster approach allows us to identify risk groups for TDR. In a recent survey of 820 patients in Portugal with newly diagnosed HIV-1 infection between 2014 and 2019, we found 89 had TDR. Unexpectedly, TDR was more likely during heterosexual transmission compared to transmission in men who have sex with men, although previous studies found TDR more likely in the latter population."

Overall, ADR and TDR surveillance can help public health by identifying clusters and reevaluating strategies for encouraging adherence to ART. It can also identify risk groups to target public health campaigns.

Overall, the examples discussed here demonstrate how human host–virus co-evolution occurs by considering both host conditions and viral mutations. Rapid viral evolution generates a variety of mutations that will help the virus flourish or perish in the host, depending on the host conditions. Mutations that help the virus are favored, shaping viral evolution. Changes to the host, for example, when treatments are administered, can exert selective pressures on the virus, altering priorities and favoring different mutations.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Where Is ICP-MS Making a Difference?

KATE ROBINSON

Inductively coupled plasma-mass spectrometry (ICP-MS) is an analytical technique that allows sample identification by ionizing, separating and detecting analyte components. ICP-MS can analyze almost all elements of the periodic table, is very sensitive, can be used on small sample volumes and is suitable for high sample throughput. The technique can be used across a broad range of applications, a few of which we will explore here.

SHORT-LIVED VOLCANIC LANDMASS OFFERS SOME MICROBIAL SURPRISES

In a study published in *mBio*, researchers discovered a unique microbial community that metabolizes sulfur and atmospheric gases on Hunga Tonga Hunga Ha'apai (HTHH), an island created by a submarine volcano eruption in 2015.

The island's emergence allowed the first-ever comprehensive study of microorganisms on this type of island system at such an early stage of ecosystem development. Soil samples were collected from HTHH and returned to the lab for DNA extraction and sequencing. The researchers used lithium borate fusion ICP-MS to measure the composition of trace elements in the sediment. The study authors believed they would find organisms observed when a glacier retreats or other typical early colonizer species – but instead, they discovered a unique group of bacteria that metabolize sulfur and atmospheric gases.

"One of the reasons why we think we see these unique microbes is because of the properties associated with volcanic eruptions: lots of sulfur and hydrogen sulfide gas, which are likely fueling the unique taxa we found," said Nick Dragone, Cooperative Institute for Research in Environmental Sciences (CIRES) PhD student and lead author of the study. "The microbes were most similar to those found in hydrothermal vents, hot springs like Yellowstone and other volcanic systems. Our best guess is the microbes came from those types of sources."

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COULD EGG POWDER HELP TO COMBAT MALNUTRITION?

Results of a study published in *Frontiers in Nutrition* show that egg powder could have the potential to improve the nutritional situation of children in deprived areas.

"Studies show that adding one egg a day to complementary food can help reduce the incidence of underweight in older infants by 74%, as well as counteract the so-called "stunting" effect," says Veronika Somoza, director of the Leibniz Institute for Food Systems Biology at the Technical University of Munich (LSB).

However, eggs aren't usually readily available in areas where malnutrition is part of everyday life. Compared to pasteurized whole egg, the powder form is easier to store and transport, and can be easily added to food. Despite the widespread use of the powder, little was known of its nutritional quality. Researchers from LSB set out to determine the nutrient profiles of industrially produced, pasteurized whole egg and the egg powder processed from it. The analyses show that the powder contains lower amounts of essential fatty acids, but still provides many vitamins, essential amino acids and important trace elements.

"ICP-MS measurements were carried out to examine the overall mineral composition of both products concerning nutritional quality and safety, as well as to compare possible losses of nutritive elements or concentration of potentially toxic non-essential trace elements during spray-drying" the authors write.

MICROPLASTICS MAY BOOST THE TOXICITY OF OTHER POLLUTANTS

A study published in *Environmental Science & Technology Letters* suggests that microplastics can aid in transforming pollutants into a more harmful form.

Heavy metals such as chromium (Cr) can easily attach to microplastics. When on the surface of microplastics, Cr can take on different oxidation states, and while Cr(III) is relatively safe, Cr(VI) is toxic and could harm aquatic life. To investigate how the oxidation state of Cr bound to microplastics may change when affected by UV filter molecules (a common organic contaminant found in products like sunscreen), a research team from Hong Kong Baptist University and Hong Kong Polytechnic University created mixtures of Cr and polystyrene microplastic (PSMP) particles both with and without benzophenone-type UV filters. The team used liquid chromatography-inductively coupled plasma-mass spectrometry (LC-ICP-MS) to determine the abundance of Cr(VI). The research found that microplastics could aggregate even more Cr in the presence of a UV filter, and the oxidation state of Cr was higher in the mixtures containing the filters. When exposed to mixtures containing the filters, microalgal growth was inhibited.

"Results showed that Cr uptake by PSMPs was remarkably higher when UV filters were present. This enhanced affinity was attributed to the formation of Cr–UV filter complexes together with multilayer sorption on PSMPs' surfaces" the authors write.

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ORIGIN OF EARTH'S VOLATILE CHEMICALS REVEALED BY METEORITES

Research from Imperial College London (ICL) has uncovered the origin of Earth's volatile chemicals.

Volatiles, such as zinc (Zn), are elements or compounds that change into vapor from solid or liquid states at relatively low temperatures. They include the six most common elements found in living organisms, and water. Nucleosynthetic anomalies are variations in the abundance of isotopes in Solar System material. By measuring these anomalies, it is possible to constrain the origins of material that formed Earth.

In the study, published in *Science*, the team measured the relative abundances of the 5 different isotopes of zinc (Zn) in 18 meteorites of varying origins. Zn isotope measurements were conducted on a multiple collector-inductively coupled plasma-mass spectrometer (MC-ICP-MS). The researchers found that around half of the zinc on Earth came from asteroids originating beyond the asteroid belt that includes the planets Jupiter, Saturn and Uranus.

"This contribution of outer Solar System material played a vital role in establishing the Earth's inventory of volatile chemicals. It looks as though without the contribution of outer Solar System material, the Earth would have a much lower amount of volatiles than we know it today – making it drier and potentially unable to nourish and sustain life" said Mark Rehkämper, professor of isotope geochemistry, ICL.

LAST THOUGHTS

While there are some challenges associated with ICP-MS, including undesired interference, expensive instrumentation and user training requirements, it is an effective technique for the detection of a wide variety of analytes and can be applied to many different areas of study. For more educational resources, events, news and products related to ICP-MS techniques and applications, explore our ICP-MS topic page here.

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