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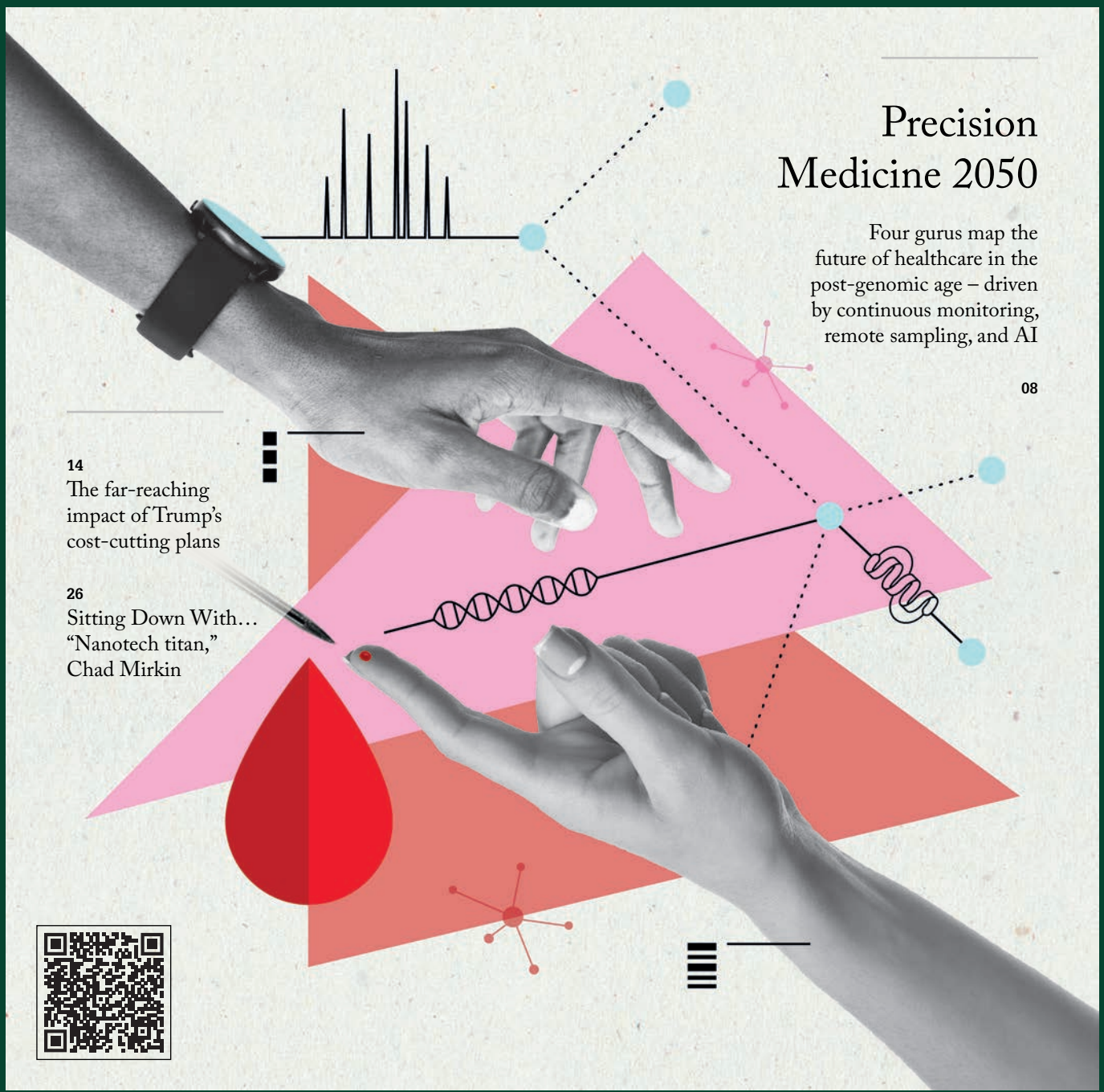

Precision Medicine 2050

Four gurus map the future of healthcare in the post-genomic age – driven by continuous monitoring, remote sampling, and AI

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Still Showcasing the Extraordinary

With (analytical) science under siege, we need to ensure the field's transformational efforts are appreciated

When we asked Erin Baker in January for her thoughts on the future of analytical science, she couldn't wait to talk about all the exciting developments taking place. However, just a few months later, the future makes her "almost ill to even think about." Erin is of course alluding to the US government's recent cost-cutting plans and their impact on the field – which we examine on page 14. The feature paints a fairly bleak picture of the "diminishing of American science" (as John Yates put it) resulting from actions that Lloyd Smith describes as "reckless, destructive, wanton."

Our response? We juxtapose "Analytical Science Under Siege" with our cover feature that imagines a world where continuous monitoring, remote sampling, and AI-powered tools analyze your entire molecular profile to predict risks and guide personalized treatments. Elsewhere, we explore analytical science's role in flighting nuclear terrorism (page 24) and assessing pollutants in Ukraine's war-ravaged environment (page 6). And in this issue, we sit down with Kavli Prize winner and nanotechnology pioneer Chad Mirkin, whose work has the potential to bring about a new age of synthesized materials.

In other words, we're doing what we've always done: showcasing the extraordinary endeavors of those analytical scientists transforming the world for the better – in an effort to restore some balance in the science community in terms of recognition and prestige for our field. This now seems more important than ever.

James Strachan,
Editor

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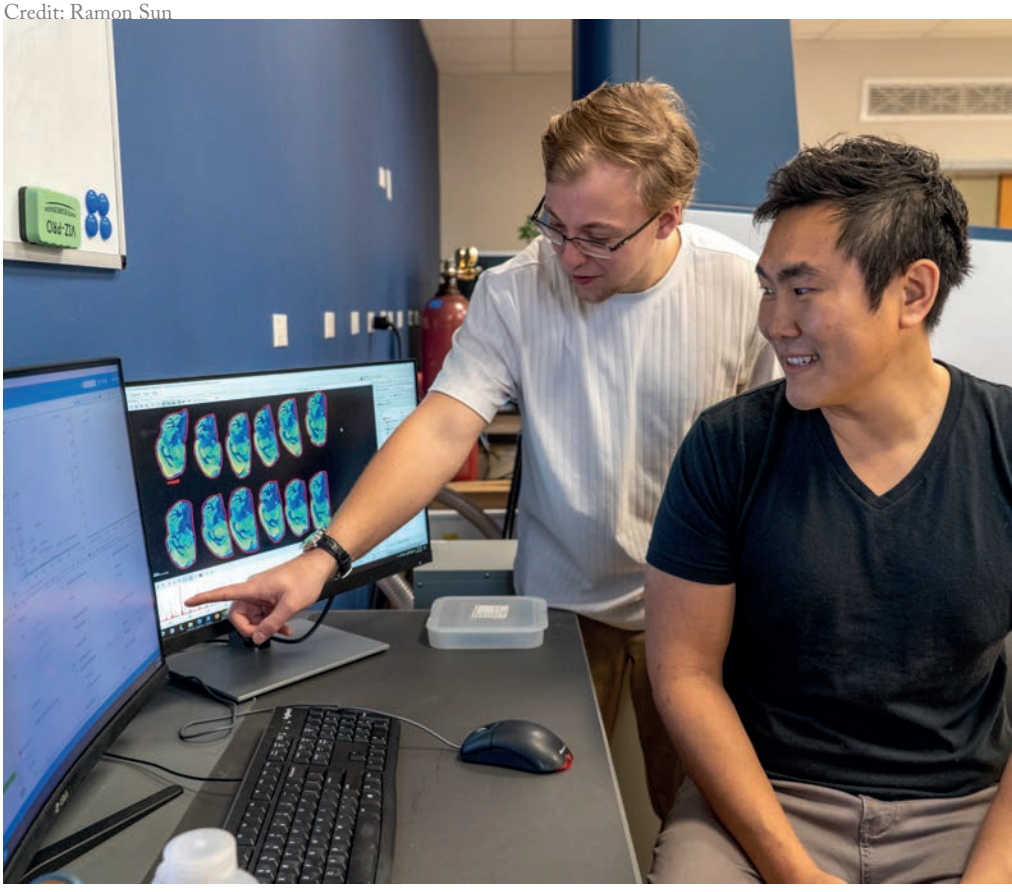
"Western Diet" Fuels Lung Cancer

Spatial metabolomics reveals that glycogen accumulation – exacerbated by high-fat, high-fructose diets – accelerates lung cancer

Credit: Ramon Sun



A study from the University of Florida has identified glycogen as a key metabolic driver of tumor growth in lung adenocarcinoma (LUAD), thanks to a next-generation spatial metabolomics platform (1).

The team, led by Ramon Sun, Associate Professor and Director of the Center for Spatial Biomolecule Research (CASBR), mapped out the precise locations and roles of glycogen – once thought to be a passive energy store – within intact tumor tissues. They found that glycogen accumulates uniquely in LUAD cells, is correlated with tumor grade, and drives disease progression.

"We were especially surprised to find that glycogen is uniquely accumulated in tumors and that its buildup is induced by a diet high in fat and sugar," says Sun. "More importantly, eliminating glycogen synthesis specifically in cancer cells significantly blunted tumorigenesis in vivo."

Sun, trained in cancer metabolism and biochemistry, was inspired by the challenge of doing something different. "I wanted to fundamentally change how we study metabolism," he says. "That led me to matrix-assisted laser/desorption ionization (MALDI) imaging and spatial metabolomics. My goal was to tackle the most pressing problem in in vivo metabolism: resolving the metabolic microenvironment with spatial and cellular resolution."

Sun's spatial metabolomics platform, developed in 2020, combines large scale MALDI mass spectrometry imaging with isotope tracing and 3D anatomical registration.

"Our platform is designed to help biologists address key challenges in metabolism," says Sun. "Unlike static mapping, we visualize dynamic fluxes across intact tissue volumes and connect them to anatomical and cellular structures. This approach translates MALDI imaging from a tool for analytical chemists to one broadly usable by biologists."

The platform allowed the researchers to simultaneously assess glycogen and cellular metabolites, uncovering a direct relationship between glycogen levels and elevated central carbon metabolites essential for tumor growth.

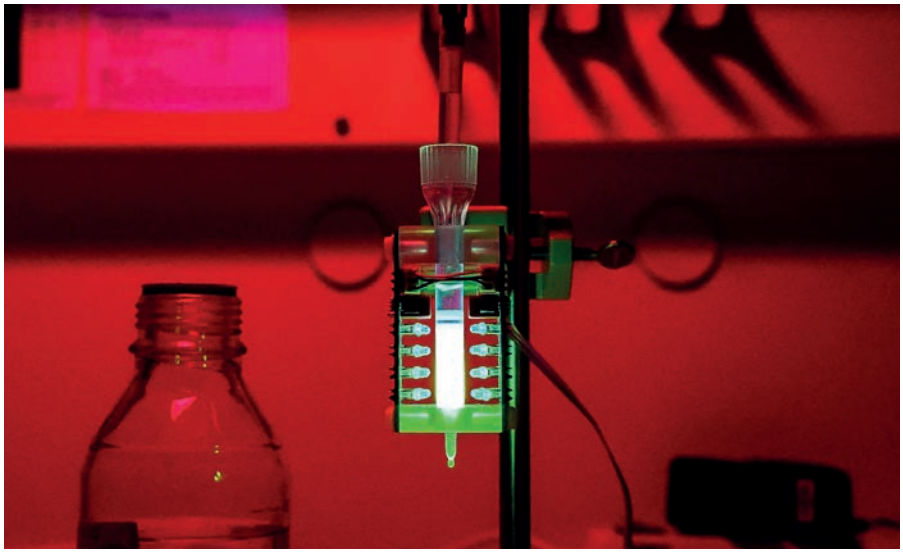
The team also found that increased glycogen promotes accelerated tumor progression in a LUAD mouse model. But when unable, due to genetic modification, to synthesize glycogen, the same cancer mouse model did not form mature tumors – further confirming the role of glycogen metabolism in LUAD.

"When paired with the right genetic and molecular biology methods, spatial metabolomics can help uncover new insights into health, disease, and many of life's unresolved mysteries," says Sun. "It is a powerful hypothesis-generating tool, it enables us to ask the right questions in biology."

The researchers are now applying spatial metabolomics to study brain tumors, liver cancer, Alzheimer's disease, and rare diseases such as Ewing sarcoma and Pompe disease. "We are integrating spatial metabolomics with AI, engineering, molecular biology, mouse genetics, and human research," says Sun. "Our goal is to re-examine long-standing diseases through the new lens of spatial metabolism."

References

1. *HA Clarke et al., Nat Met (2025). DOI: 10.1038/s42255-025-01243-8.*



Lighting Up Protein Purification

A team at the Technical University of Munich (TUM) has developed a photochemical protein purification method that avoids the harsh elution steps of traditional affinity chromatography. By integrating a genetically encoded light-sensitive amino acid, azobenzene-lysine tag (AzoK – or "Azo-Tag") into target proteins, the researchers achieved reversible protein binding and release using mild ultraviolet light – without requiring chemical reagents. The chromatography column used in the study had a diameter of less than 1 cm, but the team anticipates that the system could be adapted for larger-scale purification in industrial settings.

Reference: P Mayrhofer et al., Nat Comm, 10693 (2024). DOI: 10.1038/s41467-024-55212-y.
Credit: Sabrina Bauer / TUM.

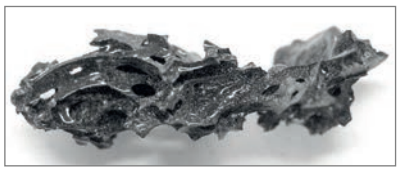
QUOTE *of the month*

"Without analytical science, there is no means to develop new measurements. Without measurement, there is no way to assess new technologies. Simply put, a reduction in support for analytical science means a reduction in support for progress across all areas of science, technology, and medicine."

Kevin Schug (See page 16)

How Vesuvius Turned a Man's Brain to Glass

Spectroscopic analysis reveals how extreme volcanic heat vitrified the brain of a victim in ancient Herculaneum



Credit: Pier Paolo Petrone

The first known case of a human brain preserved as natural glass formed when the victim of the 79 CE Vesuvius eruption was exposed to extreme heat before rapidly cooling, according to a new study. The researchers used spectroscopic techniques to confirm that the glassy material found inside the skull of an individual from Herculaneum was formed through a process of high-temperature vitrification.

The study (1) examined fragments of the material recovered from the skull and spinal cord of a man believed to have been a guardian at the Collegium Augustalium, a public building in Herculaneum. Unlike typical forms of organic preservation, such as mummification or saponification, the remains showed characteristics consistent with vitrification, a process in which material transitions into a glass-like state.

"This is the only known case of preserved vitrification of human tissue as a result of cooling after heating to very high temperatures," the authors wrote.

Reference

1. *G Giordano et al., Sci Rep, 5955 (2025). DOI: s41598-025-88894-5*

Ukrainian Science's Fight for Environmental Safety

Ukrainian scientists studying the environmental impact of the war welcome global collaboration

By Modest Gertsiuk, Researcher, Institute of Environmental Geochemistry, National Academy of Sciences of Ukraine, Kyiv; and President of the Chromatographic Society of Ukraine

A large-scale war is underway in Ukraine in which the Ukrainian people defend their sovereignty, territorial integrity and security. For millions of Ukrainians, this war means a tragic loss of loved ones, loss of homes, and migration to safer shores. The war continues to destroy cities and other settlements, energy networks, infrastructure, and we also see the deterioration of the state of chemical and environmental safety – a direct result of military operations and the destruction of enterprises, warehouses, agro-industrial complex facilities, hydraulic structures, sewage systems, and treatment plants. During these events, hazardous substances migrate into and pollute the environment, posing a danger to the health of the population. One example of such devastation is the destruction of the Kakhovka Dam and the Dnipro Hydroelectric Power Plant dam.

The study of the impact of military operations on the state of chemical and environmental safety is one of the priority areas of research for Ukrainian scientists, including those in the laboratory I head. These studies involve analyzing contamination in areas affected by hostilities and emergencies resulting from the destruction of various facilities. They also focus on tracking contamination dynamics, understanding chemical transformations of anthropogenic substances, and identifying patterns of hazardous substance migration and decomposition. This work often relies on extensive analyses of surface water and soil samples. Although Ukraine has a network of state and municipal laboratories conducting such tests, the range of substances they monitor is limited. Given the current situation in Ukraine, it is critical to assess a broad array of potential pollutants in the environment. This requires new methods of analysis and modern equipment.

Our laboratory applies its expertise in environmental pollution analysis to meet these challenges. However, funding for scientific research in Ukraine has been drastically reduced, as resources are diverted to maintain state functions and provide social protection. Under these conditions, Ukrainian scientists, using their own capabilities to the maximum, try to develop contacts with other laboratories and scientific institutions, participate in projects financed on a grant basis in order to expand research and obtain good results.

The development of contacts and cooperation between Ukrainian scientists and specialists working in control laboratories and enterprises with their counterparts abroad is one of the main tasks of the Chromatographic Society of Ukraine, which I head. Since its establishment, the Society has constantly held international conferences, in which both Ukrainian scientists and specialists and their foreign colleagues participated. These conferences considered the development of new methods of analysis and their application, problems of chemical and environmental safety. The geography of the venues for these conferences in Ukraine was quite wide: Kyiv, Sevastopol, Precarpathia, Transcarpathia. However, in the conditions of the pandemic, and now the war, the holding of these conferences was suspended.

The Society also publishes a scientific periodical, *Zurnal Hromatograficnogo Tovaristva* (Journal of the Chromatographic Society), ISSN 1729-7192, DOI:10.15407/zht. Articles are published in Ukrainian and English, covering new chromatographic and chemical analysis methods, their applications, and the work of scientists and research institutions in chromatography. In 2021, a special issue highlighted the research directions and achievements of Ukrainian chromatographic centers.

We are confident that studying the environmental impact of military actions will contribute significantly to devising strategies to mitigate chemical contamination, protect the environment, and ensure public safety. Nevertheless, we welcome collaboration with other labs – especially those with the capacity for joint analyses. Addressing the environmental impact of war requires a systemic approach, involving not just Ukraine, but the global scientific community.

The HALO® Effect

Tim Langlois, President of AMT, celebrates two decades of cherishing quality and driving innovation for the HPLC community

Please give us an overview of Advanced Materials Technology – and the 20-year milestone…
Advanced Materials Technology (AMT) was founded by me and Joe DeStefano back in May 2005. AMT gave both of us an opportunity to fulfill our ambitions of starting a business that used our knowledge of liquid chromatography and silica chemistry to develop products that were both innovative and commercially successful. A combination of the resulting products, a dedicated team of employees focused on quality, lifelong connections within the HPLC community, and a strong network of knowledgeable column distributors around the world have helped make AMT a 20-year success.

Can you take us back to the development of the AMT's SPP column – what inspired the innovation?
After establishing the company, we hired our friend and former colleague Dr. Jack Kirkland – an HPLC pioneer whose name will be familiar to most in the field. He worked with us on several different silica particle projects, one of which was the design of a small-particle superficially porous particle (SPP). Although SPP is more common nowadays, AMT had to overcome the task of placing nanoparticles on the surface of a non-porous micron size bead in an orderly fashion. To put that in perspective, around 75 of these non-porous beads equate to the thickness of a human hair, while around 15,000 nanoparticles add up to that same width. Under magnification our SPP looked like a halo, inspiring the brand HALO®.

One of AMT's key innovations is Fused-Core® Technology. Can you explain how it works and how it improves chromatographic performance?
Fused-Core® Technology involves a particle composed of a solid core, surrounded by a thin layer of porous silica thermally fused onto the core at high temperature. Columns packed with such particles have been chromatographically proven to provide improved separation performance over totally porous particle columns. Why? Because the distance sample molecules travel inside Fused-Core® particles is comparatively shorter than that with totally porous particles.

Can you give us an overview of AMT's full product line?
The HALO® product line spans a diverse range of products to meet market demands, ranging from capillary (<1 mm inner diameter) to preparative columns (>10 mm inner diameter). AMT was founded for solutions of small molecule separations, which now comprise 15 chemistries, but we continue to innovate with our HALO® BIOCLASS line of columns to ensure we remain at the forefront of bioseparations. These columns offer the necessary particle and pore morphology for the analysis of proteins, peptides, oligonucleotides, and glycans.

More recently, AMT has come to the market with application-specific columns to address shortcomings of environmental LC separation methods. The HALO® ENVIROCLASS line includes solutions for PFAS and PAH, joining the other small molecule chemistries for the analysis of additional environmental concerns, such as pesticides, mycotoxins, and herbicides.

How does AMT ensure that its columns continually meet high standards of quality?
Quality and customer satisfaction are paramount to the success of AMT. After all, without a satisfied customer that's willing and able to purchase the "same" column for years to come, our business ceases to be successful. Perhaps most importantly, we create all parts in-house – from the start of the silica particle to the finished column – to ensure successful separations every time. With relentless quality, and process control from the beginning of the silica synthesis to the end column, AMT is committed to Quality (with a capital Q)!

As AMT celebrates its 20-year milestone, what's next for the company?
We've just finished a major expansion and facility upgrade to prepare ourselves for the next 10 years (and beyond) of increased business. Our new product pipeline is very healthy, with separation products addressing challenges in aforementioned "hot" areas, including oligonucleotide separations and short-chain PFAS analysis. More recently, our developments have focused on helping separation scientists improve their chromatographic performance against basic analytes, prevalent in the pharmaceutical industry. This includes both a high pH and high temperature stable phase, as well as positively charged surface chemistry.

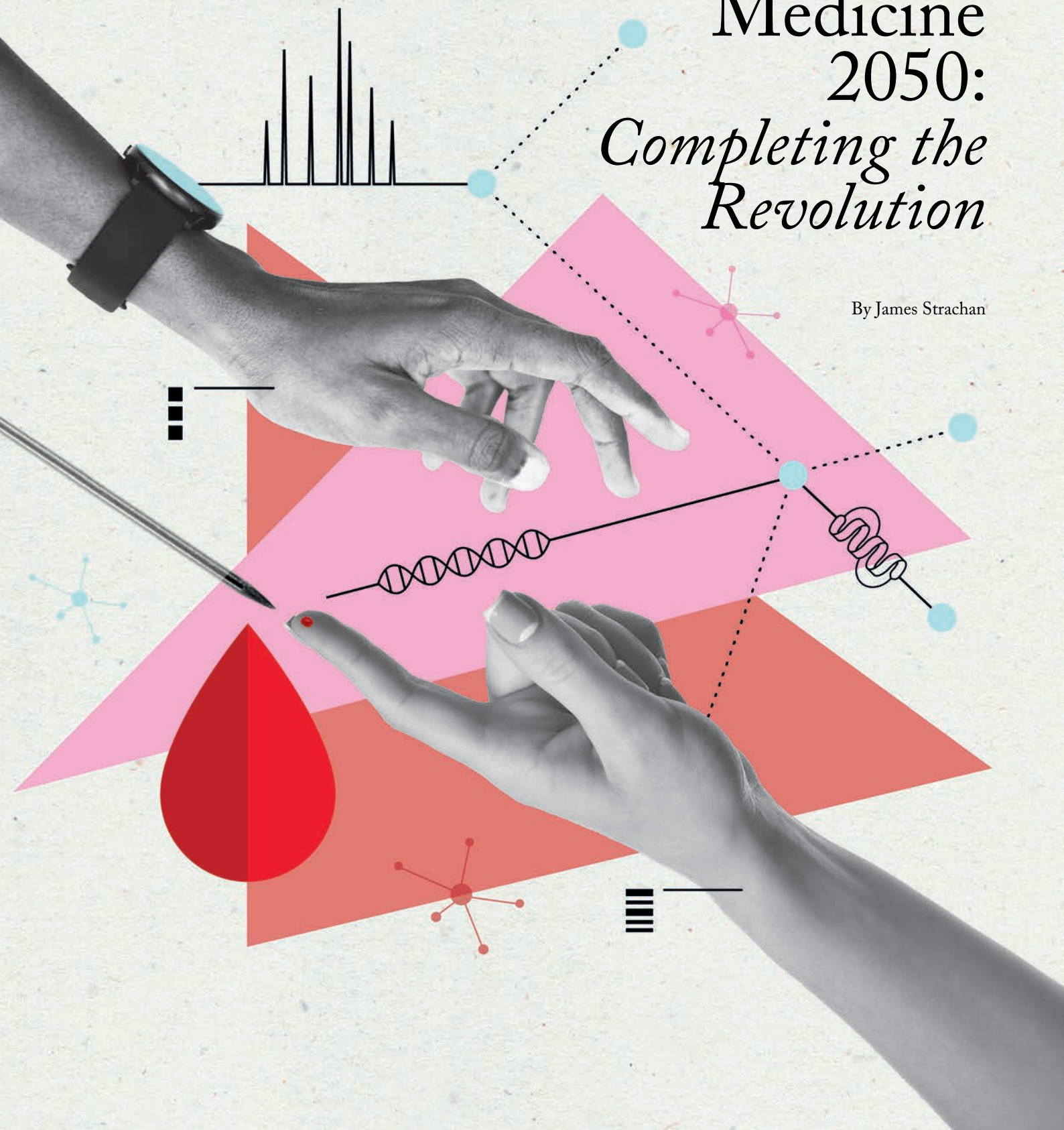
I'm very proud to say that the team at AMT is still applying technical expertise to produce new technologies – just like we did 20 years ago! A quick browse through our latest catalog shows different particle sizes, pore sizes, including the first 1000 Å, bonded phases, and more. As we go forward, we'll continue to develop and introduce new technology to the separations community.

Oh – and I should add that we are now the only SPP manufacturer who can claim 20 years of manufacturing history in sub-3 micron SPP products!

HALO® advancedmaterialstechnology

Precision Medicine 2050: *Completing the Revolution*

By James Strachan



In April, 2003, the International Human Genome Sequencing Consortium gathered at the White House, alongside President Bill Clinton, to announce that the Human Genome Project was complete – two years ahead of schedule and $400 million under budget. Much of the media coverage at the time focused on the coming new era of medicine – a shift from one-size-fits-all approaches to more personalized and predictive care.

Today, although genomics has delivered clear benefits – cancer genome sequencing, for example – it is hard to argue that we are truly living in the promised new era. It has become increasingly apparent over the past two decades that in order to fundamentally change how we diagnose and treat disease, we'll need to transcend the genome – to the proteome and beyond.

Here, our four experts – Ying Ge, Neil Kelleher, Lingjun Li, and Mike Snyder – imagine a world where continuous monitoring, remote sampling, and AI-powered tools analyze not just your genome, but your entire molecular profile, including all proteoforms, to predict risks, guide personalized treatments, and even prevent diseases from developing at all. What would it take to make this vision a reality? What role will analytical science play? And can we get there by 2050?

Has the Human Genome Project lived up to expectations?

Neil Kelleher: The Human Genome Project moved the needle in all sorts of ways. At the time, launching a $3–3.5 billion, 10-year project was highly controversial, whether you were talking to scientists, science enthusiasts, or the general public.

But now, more than 20 years later, I think it has proven its value. The advancements in the medical community that have stemmed from the Human Genome Project are undeniable. Today, when people talk about genomics, they have a much deeper understanding of what it means. Cancer genome sequencing, genetic assessments, and personalized medicine have all evolved far beyond where they were before the project.

Mike Snyder: I think the Human Genome Project held great promise, and in my opinion, it has delivered – though perhaps more slowly than many expected. However, the fundamental idea that we can sequence human genomes and make risk predictions has proven to be valid.

In my own case, for example, my genome predicted that I was at high risk for type 2 diabetes. As some readers may know, I conduct extensive deep-data profiling on myself and a group of individuals. During this process, I actually developed diabetes. Because my genome had indicated a higher risk, I was already on alert, which allowed me to catch it early and get it under control.

Beyond individual cases, the Human Genome Project has been foundational for basic research. Our understanding of biology and human health has expanded dramatically in ways that wouldn't have been possible without having the genome sequence as a reference. But it is just the tip of the iceberg. The genome provides useful information, but it doesn't tell the whole story.

Lingjun Li: The Human Genome Project has certainly brought major advancements, particularly in understanding gene mutations and their role in disease. Mutations in genes like RAS, for example, have been implicated in different cancer types. But while the genome provides a blueprint for biology, it's the proteins and protein complexes that actually carry out the functions in a cell.

Many factors influence how genes are expressed, including protein translation and post-translational modifications. For instance, phosphorylation plays a major role in regulating protein function, and in our lab, we also study proteination and other modifications that alter protein structure and activity. These modifications can serve as critical biomarkers that aren't always evident from just looking at the genome.

There's also proteoforms to consider – the idea that a single gene can give rise to 20, 30, or even more different protein variants. This adds another layer of complexity to biology that isn't captured at the genetic level.

When did we fully realize – if indeed we have – that we'd need to go beyond the genome?

Li: I think the concept of the proteome really started gaining attention around 1995 when the term was first coined. At that time, people were beginning to understand the complexity of post-translational modifications (PTMs) on a global scale, but the ability to study them in depth was still quite limited.

A major turning point came with advancements in analytical science, particularly in mass spectrometry. The improvements in sensitivity, throughput, and chemical specificity allowed us to start mapping site-specific modifications in proteins and truly appreciate the molecular complexity of the proteome.

A lot of what we've learned in the past two decades has been enabled by technology – better instrumentation, improved sampling techniques, and more powerful computational tools for data analysis. These advancements have not only transformed proteomics but also helped expand other fields like metabolomics and glycomics, which focus on different layers of molecular regulation.

Kelleher: I think there's still a significant gap between DNA-level biology and how diseases actually manifest. Some conditions – monogenic diseases like sickle cell anemia – are relatively straightforward in terms of their genetic basis. We're already seeing FDA-approved treatments targeting these types of diseases. But complex diseases? Well, they're complex for a

Meet the Experts

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Neil Kelleher is Walter and Mary E. Glass Professor of Molecular Biosciences; Director, Northwestern Proteomics; Director, Chemistry of Life Processes Institute; Northwestern University, USA.

Lingjun Li is Vilas Distinguished Achievement Professor of Chemistry and Pharmaceutical Sciences, Charles Melbourne Johnson Distinguished Chair in Pharmaceutical Sciences, School of Pharmacy and Department of Chemistry, University of Wisconsin-Madison, USA.

Mike Snyder is Stanford W. Ascherman Professor of Genetics, Director of the Center for Genomics and Personalized Medicine, Stanford School of Medicine, USA.

reason. There's a huge gap between genetic information and how traits and diseases actually express themselves.

Many of us in the proteomics community – whether protein biochemists or geneticists who have pivoted toward protein-level biology – recognize this gap. There's a growing consensus that we need a systematic, standardized approach to proteomics, similar to what was done with genomics. Proteins are distinct from other molecular players like metabolites or RNA, and yet, unlike genomics, we still lack a fully standardized framework for understanding them at the proteoform level.

What are the main health challenges that could – or should – be tackled with precision or personalized medicine?

Ying Ge: In clinical practice, we have long relied on a "one-size-fits-all" approach – treating patients with the same medications and dosages, regardless of individual differences. That's a problem because people have different genetic, biochemical, and physiological profiles, and a single treatment isn't going to be equally effective for everyone. This is where the concept of personalized medicine emerged – the idea that each person is unique and should have an individualized treatment. While the idea of personalized medicine is compelling, it's not yet practical to develop a completely unique treatment for each individual. Hence, precision medicine comes in – a more feasible strategy that involves grouping patients with similar characteristics and treating them with tailored therapies.

A great example from my own research – our PNAS paper looked at obstructive hypertrophic cardiomyopathy (HCM) patients (1). It is a fairly common genetic heart disease and a leading cause of sudden cardiac death in young adults. While HCM is known to be caused by mutations in sarcomeric protein genes, these genetic differences alone do not reliably predict clinical outcomes. So, we used high-resolution mass spectrometry-based top-down proteomics to comprehensively characterize sarcomeric proteoforms in septal myectomy tissues from obstructive HCM patients. We observed a complex landscape of sarcomeric proteoforms shaped by combinatorial PTMs, alternative splicing, and genetic variation in HCM. Surprisingly, we found a shared pattern of altered sarcomeric proteoforms across these patients, regardless of their specific mutations. It was really the direct evidence showing that proteoforms can better reflect patient's disease phenotypes than their genotypes. This is how analytical chemistry contributes to precision medicine – helping identify biochemical differences that standard genetics or clinical markers might miss.

Snyder: I would say it applies to everything. We should be able to build predictive models to assess individual risks for

various conditions. I like to think of health and disease as being influenced by many factors – your DNA is one of them, and an important one, but it's only part of the picture. Environmental factors, lifestyle, diet, activity levels – all of these also play a crucial role.

We should be able to build personalized models that incorporate all these elements. Our lab is doing a lot of work in this space, particularly in glucose control. It turns out that glucose responses to food are highly personal – some people spike to bread, others to pasta, others to potatoes. The microbiome plays a role, as does genetics, but neither tells the full story.

Proteomics is another important window into health. While genomics and transcriptomics provide valuable insights, proteins and metabolites are often much closer to an individual's actual health state. Advances in proteomics have been driven largely by mass spectrometry and capture-agent-based technologies, and now the combination of both is extremely powerful for profiling health.

What's even more exciting is that remote health monitoring is becoming increasingly feasible. We've developed microsampling assays that allow people to provide just a tiny drop of blood – about 10 microliters – from a finger prick, which can then be mailed in for analysis. From that one drop, we can now profile 7,000 analytes, including proteins, metabolites, and lipids.

This is the foundation of Iollo, a company we spun off. We can analyze these blood samples and provide insights on 600 metabolites, which reflect various health areas like oxidative stress, inflammation, and heart health. It's a simple, scalable way to provide in-depth health profiling remotely.

Li: Longitudinal tracking of global proteomic changes could be hugely valuable for early disease detection and preventive medicine.

In our research, we've been working on Alzheimer's disease biomarker discovery, looking at cerebrospinal fluid (CSF). However, since spinal taps are invasive and not ideal for routine clinical use, we're also investigating blood-based markers – in plasma or serum – to see if they correlate with CSF findings. Blood-based assays would make long-term, global proteome monitoring much more feasible for clinical applications.

Another major aspect of this is tracking post-translational modifications (PTMs) over time. We've been particularly focused on glycoprotein and glycation changes – which are known to be highly relevant to aging and disease progression. Many diseases, including neurodegenerative disorders, are age-related, so distinguishing normal aging-related changes from early disease markers is crucial.

If we could monitor a person's proteome longitudinally, we could build a baseline for what's "normal" for them and detect subtle deviations that indicate early disease risk. Right now, when we analyze proteomic changes, it's often difficult to separate the effects of aging, sex, diet, and lifestyle from actual disease-specific changes. But with long-term, global-scale omics tracking, we could pinpoint specific markers that truly reflect disease progression, rather than just general physiological variation.

What barriers must be overcome for analytical science to deliver a precision medicine future?

Li: When we talk about translating discoveries into clinical settings, there are a few key challenges. First, in biomarker discovery, we often use high-end mass spectrometry in academic labs to identify potential markers. But for these biomarkers to be clinically useful, we need large-scale validation in diverse patient cohorts. This requires robust, reproducible, high-throughput methods that are also affordable enough to be used in a hospital or diagnostic lab – which is very different in an academic research setting.

Right now, ELISA assays are widely used in clinical diagnostics because they are simple, scalable, and cost-effective. But translating mass spectrometry-based discoveries into clinical practice requires methods that can bridge the gap – such as triple quadrupole mass spectrometry or multiple reaction monitoring

(MRM)-based assays, which are more targeted and reproducible than discovery-based proteomics.

Another challenge is making mass spectrometry itself more clinically viable. There are emerging technologies, like mass spectrometry-based point-of-care devices (e.g., the MasSpec pen), which could make real-time, in-clinic proteomic and metabolomic analysis a reality. But for widespread clinical adoption, we still need to simplify the workflows, reduce costs, and improve automation so that these technologies can be routinely used in diagnostics.

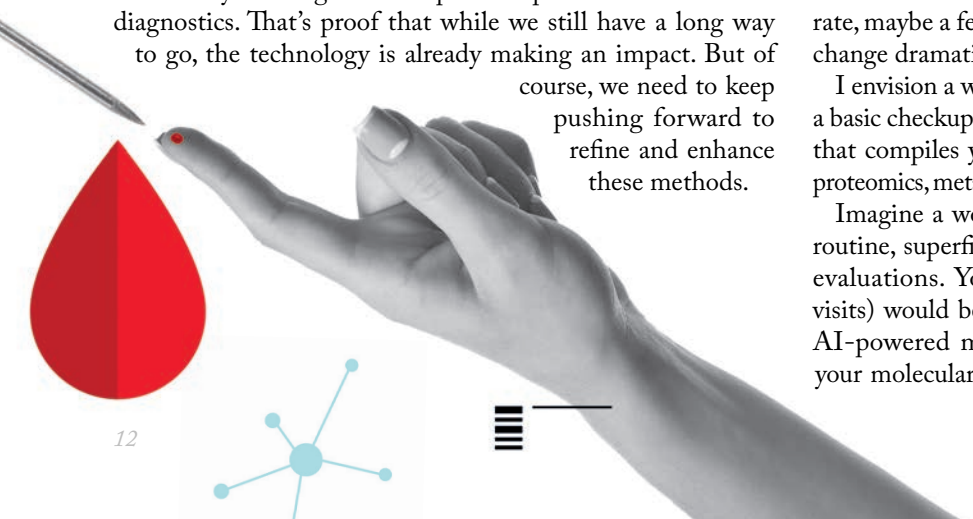
Kelleher: What we need is regularization – a structured, standardized approach to defining proteoforms: the precise molecular versions of proteins that stem from our 20,300 genes. If we start by defining these proteoforms, we can then develop cost-effective technologies – similar to next-generation sequencing – to track proteins with complete molecular specificity. That means we'd finally be able to see, at the protein level, what drugs are doing and how diseases are progressing in a way that genomics alone cannot provide.

That's the next step – some would say the obvious step. We need a Genome Project for proteins: a high-resolution reference proteome – not just fragmented glimpses where different technologies measure partial sequences of proteins, creating ambiguities and inference problems. Incomplete molecular information leads to knowledge gaps. And that's what we aim to close with the Human Proteoform Project – the proteomic equivalent of the Human Genome Project.

Ge: Yes – right now, personalized proteomics isn't fully achievable because of limitations in throughput and proteome coverage. In genomics, we've reached a point where personal genome sequencing is widely accessible. But sequencing the full proteome – including all proteoforms – is still a major challenge. Hopefully, one day, a personalized proteoform project will be a reality, but we're not there yet.

That said, we don't need to wait for all the challenges to be solved before applying current technologies. We can use existing technology to tackle biological and clinical problems now, while simultaneously working on improving the tools.

I've been impressed by how clinical chemists and pathologists are already starting to use top-down proteomics in clinical diagnostics. That's proof that while we still have a long way to go, the technology is already making an impact. But of course, we need to keep pushing forward to refine and enhance these methods.



Assuming we overcome the hurdles, describe your dream scenario for how precision medicine could look in 2050.

Li: In a dream scenario, a visit to the doctor (or even an at-home health check) could involve a simple drop of blood or another biofluid sample, and within minutes – AI-assisted diagnostic tools could analyze your health status and prescribe personalized treatments tailored exactly to your biology.

Imagine a system where continuous health monitoring is effortless – perhaps through non-invasive wearables, or small, routine biofluid tests that allow real-time tracking of health markers. If early signs of disease appear, customized interventions – whether it's medication, lifestyle changes, or preventive therapies – could be immediately recommended based on your unique molecular profile.

The ultimate goal would be to replace the reactive "treat the disease" model with a proactive, preventive healthcare system. Instead of waiting until a disease reaches critical stages, precision medicine could identify risk factors early, allowing early intervention – potentially preventing diseases from developing altogether.

Snyder: When it comes to biochemical testing, I see a combination of different sampling frequencies emerging. There will be continuous monitoring – this is useful for tracking specific biomarkers in real-time, like glucose, cytokines, or lactate. Then there's frequent but less invasive sampling – finger-prick devices that instantly analyze a small panel of key markers (maybe half a dozen or up to 20 analytes), done weekly to track overall health trends. And finally, deep profiling at longer intervals will be key – micro-sampling done every few months to get a very comprehensive biochemical profile, measuring thousands of molecules at once. This would provide high-resolution insights into multiple wellness categories, disease risks, and metabolic health. The deep sampling would be particularly powerful because it gives a broad view of your health, rather than just focusing on one or two markers at a time like continuous monitors tend to do.

Ge: Right now, when you visit a doctor, the amount of real-time data collected is very minimal – blood pressure, heart rate, maybe a few blood tests. But in the future? That's going to change dramatically.

I envision a world where you walk into a clinic, and instead of a basic checkup, you're greeted by a large dynamic digital display that compiles years of your personal health data – genomics, proteomics, metabolomics, microbiome – and more, all in real time.

Imagine a world where your annual exams wouldn't just be routine, superficial checkups, but comprehensive, data-driven evaluations. Your longitudinal health data (from previous visits) would be analyzed continuously to detect early trends. AI-powered machine learning algorithms would compare your molecular profile to millions of other patients, grouping

individuals into precise molecular subtypes rather than just broad disease categories.

One idea that excites me is the concept of "Molecular Twins" – something I first heard Jenny Van Eyk present in one HUPO conference. The idea is that as soon as you show early signs of disease, your data would be matched to another patient with a similar molecular profile. If that "molecular twin" responded well to a certain treatment, doctors could apply the same approach to you – dramatically improving the efficiency and success rate of personalized treatments.

In 50 years, I believe this will be routine. Cancer detection will no longer rely on late-stage diagnoses because we'll have the tools to track its emergence at the molecular level. We won't be "blind" to disease progression; we'll be able to intervene much earlier. Diseases that are currently "invisible" will become detectable, predictable, preventable, and treatable before they take hold.

Kelleher: In 20 or 30 years, here's what I imagine: you'd take a small blood or skin sample, and from that, you'd get a detailed readout of your lifestyle, disease status, and biological health – all from single-molecule proteoform sequencers that are cheap and accessible, much like what's happened with next-gen sequencing (NGS) in genomics.

The genomics revolution has been incredible for human health. But to truly enable next-gen proteomics, we need a high-resolution reference set of about 50 million proteoforms, covering all cell types and body fluids. That's a fundamental requirement. Once we have that, the impact will be massive. In 20 years, we'd start seeing clinical uptake of these proteomics technologies. In 30 years, precision medicine would be fully integrated into healthcare systems.

We've already seen this timeline play out in genomics – look at Epic Systems and other health IT platforms. They're increasingly able to handle genomic data, and we're seeing genetic counselors working directly with patients. Doctors are regularly ordering genetic tests to guide treatments. The same will happen with proteomics.

If you think back to the late 1990s, that was when we really started skiing downhill toward the Human Genome Project's completion. If we start the Human Proteoform Project now, we could finish it in about 10 years – taking us to the early 2030s. Then, it would take another decade to develop and scale next-gen proteomics technologies. And finally, the clinical uptake would follow – just like it did with genomics – but faster, because we've already built the infrastructure. But long before 30 years, proteoform data will become essential in drug development, R&D, and pharma pipelines. It will be a must-have data type in research, well before we see full-scale clinical adoption.

Reference

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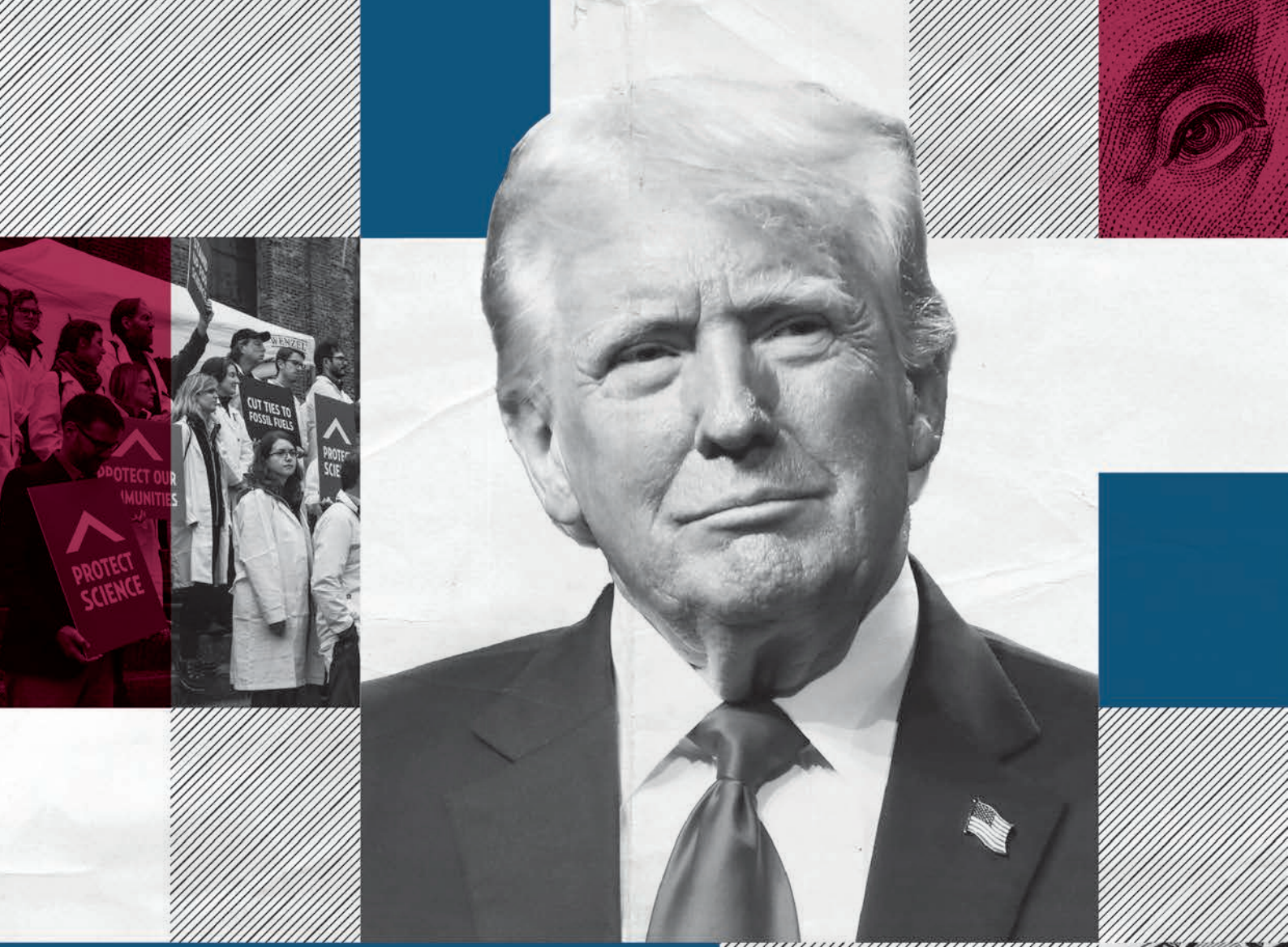

Analytical Science *Under Siege*

The US government's recent cost-cutting measures have created a tidal wave of uncertainty for scientists of all stripes. But, in the face of adversity, perhaps comes an opportunity for the analytical community to dig in and collaborate.

By Henry Thomas

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The 47th President of the United States, Donald Trump, launched his second term in office by announcing a series of effective-immediate "executive orders," centered on international relations and a crackdown on initiatives related to diversity, equity and inclusion (DEI) (1). Such moves were not unexpected, but few anticipated the speed – and scale – of what happened next.

A few days later, an internal memo was issued by the National Institute of Health (NIH) referencing an immediate – and indefinite – ban on travel. Then, on February 7, the NIH announced the introduction of a 15 percent cap on indirect costs for both new and existing research grants (2). Around the same time, the newly formed Department of Governmental Efficiency (DOGE) – chaired by Elon Musk – instructed the National Science Foundation (NSF) to freeze funding for new research and cut staff numbers by as much as 50 percent to meet daunting financial targets (3).

Despite claims from NSF president Sethuraman Panchanathan that the agency is "continuing to advance the scientific enterprise" as usual, independent analysis of NSF's publicly available database has suggested they have awarded up to 50 percent fewer grants compared to this time last year (4). More recent reports have suggested that DOGE is considering the termination of over 200 active grants, in addition to the axing of 1,000 places on the NSF's prestigious research fellowship program for graduate students (5).

How has the analytical community responded to these recent developments? What are the immediate, imminent, and speculated repercussions? And is there any room for optimism? To get a grasp on the situation, we reached out to several past Power Listers and US-based leaders in the field to hear their thoughts and perspectives on the rulings. The general consensus? Well, as Lloyd Smith, W. L. Hubbell Professor of Chemistry, University of Wisconsin, succinctly put it: "Disaster."

Feelings of surprise, confusion, and fear were ubiquitous. "It seems surreal," says Susan Richardson, Arthur Sease Williams Professor of Chemistry at the University of South Carolina.

"I have never experienced anything like this in my professional career," adds Kevin Schug, Shimadzu Distinguished Professor of Analytical Chemistry at The University of Texas at Arlington.

Pulling no punches, Richard Zare, Marguerite Blake Wilbur Professor at Stanford University, says: "If one sought to devise a plan to destroy science in the United States, it is hard to imagine a more effective strategy than what is presently in full operation."

Uncertainty abounds

One consequence of the US government's cost cutting measures is that many institute and faculty heads feel unable to commit to new endeavours. "The situation is extremely confusing – made worse by the uncertainty surrounding what's *actually* happening versus what our administration *wants* to happen," says Schug. "This disconnect adds yet another layer of complexity, making it very difficult to predict outcomes."

"Frankly, it's driving people up the wall," says ASMS President and UCLA Professor Joseph Loo, who goes on to describe the current mood at his institution. "Graduate students are losing support from training grants. Hiring freezes for new faculty and staff are in place. Some departments have begun to reduce the number of new graduates they recruit. Other department chairs have taken it further and told their faculty to reduce spending on everything – including instruments and lab supplies – in case the cuts come to fruition."

In particular, the uncertainty surrounding current grant applications is one of the most pressing issues. Schug suggests the only option for current applicants is to "try to ensure your proposed science avoids topics currently considered 'taboo' by this administration" – especially anything related to DEI or "misinformation" (6). In fact, there's evidence to suggest that even those who have avoided such topics have had their proposals flagged and denied nonetheless. Following an investigation into the publicly available NSF grants, it has been speculated that some applications have been rejected simply for the inclusion of "DEI-coded" terms – regardless of their original context (7). One application, for example, is thought to have been rejected due to its use of the word "diversify," in reference to plant biodiversity.

Although NIH grants are awarded for four years, the funding is on a year-by-year basis, which is different from NSF and other grants that are funded upfront. "As a result, NIH can withhold the next year's funding (and by the looks of things, they are)," says Richardson. "Of course, this not only affects the research, but also sadly the graduate students who are typically living paycheck to paycheck on a small stipend."

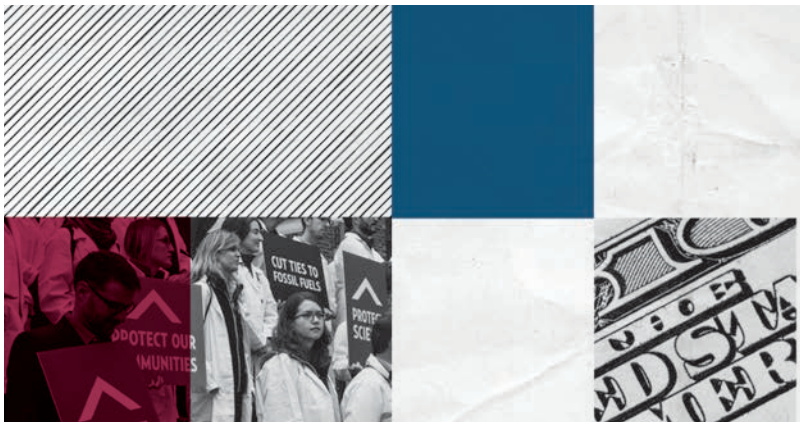
The NIH's decision to reduce "indirect costs" from 50 to 15 percent is also set to have significant consequences. Loo states that these cuts represent "a huge loss of funds that essentially 'keep the lights on' and support all of the support personnel required for scientific research."

"They are an essential and integral part of the University financial model," adds Smith.

John Yates, Ernest W. Hahn Professor at The Scripps Research Institute, points out that research grants include travel money for researchers to attend conferences. "If even that one item is cut or restricted in NIH funding, it would interfere with information sharing, the development of future collaborations – and would devastate the conference industry and the cities that depend on that business."

A generation stifled?

One sentiment shared by many is the sympathy felt towards junior scientists and students – especially those facing layoffs. "What hurts in particular is watching the next generation of young, excited scientists, keen to make a real impact on the world,



"I would hate to be a young scientist at the beginning of their career."

made redundant – often while still in their probationary periods," says Erin Baker, Associate Professor at UNC Chapel Hill. "They are the ones who have been training on the latest and greatest techniques – the ones we hoped could use these skills to develop new treatments and find cures for important diseases, especially those which cause harm to so many of our loved ones."

"It is uncertain whether [scientists] will be able to continue to support our graduate students as we have in the past," says Richardson.

"Today, the uncertainty in the actions of the government and their effects on scientific research and education have caused frustration and anxiety among the students, the faculty, and the institution leadership," says Loo. "I would hate to be a younger scientist at the beginning of their career."

Yates also notes that industry depends heavily on PhD analytical students, highlighting the long-term impacts the layoffs could have on science more broadly. "The American scientific board of HPLC recognizes that industrial jobs are so attractive for American LC trained students that very few seek academic jobs," he says, "so a reduction in the number of analytical graduate students will profoundly impact industry and will further diminish the number of analytical scientists in academia to train future generations."

Any room for optimism?

Unfortunately, any damage to analytical science is likely to have a lasting effect on many industries. "Without analytical science, there is no means to develop new measurements," says Schug. "Without measurement, there is no way to assess new technologies. Simply put, a reduction in support for analytical science means a reduction in support for progress across all areas of science, technology, and medicine."

"Analytical scientists are expected to pay careful attention to detail and to generate reproducible results," says Baker. "Are these really the qualities we want to eliminate from our workforce, and our population?"

So, amid the confusion, speculation, and anxiety that so many are presently experiencing – is there a glimmer of hope at the end of a long and narrow corridor of uncertainty?

As Schug points out, the views of the administration aren't necessarily in line with those held by the wider American public – especially scientists – which he feels is widely appreciated abroad. "Much of the rhetoric I have encountered from voices outside the US understand that these decisions to pursue certain policies are solely that of the US administration," he says. "With this in mind I don't see my personal relationships with foreign colleagues eroding, only the mechanisms through which we might interact. Luckily, such mechanisms can always be restored if lost, and my hope is that personal relationships will not be damaged in the interim."

Moreover, counter-moves to the recent rulings are already in full swing, with a number of lawsuits already in progress (8). "I want to believe in the rule of law, and most of the actions being taken are violating long-standing law," says Yates. "Traditionally, congress has supported the NIH and NSF on a bipartisan basis because researchers in every state receive funding and congressional reps are proud of their NIH and NSF funded researchers. Let's hope these representatives fight for their constituents." Yates is however worried that "even if the current proposed changes in funding are blocked or rescinded, the current administration will look for another way to cut NSF and NIH budgets."

Loo believes that the adversity may – out of necessity, above all else – actually *encourage* collaborations between research groups. "Of course, I'm sure that wasn't the original intention of the funding cuts, but the consequences might be for more labs to share the pain, but also to share the gain." Choosing optimism in the face of adversity, he implores members of the scientific community to "be resilient and focus on things that we can control, like the experiments in the lab."

Ultimately, it appears to be very difficult to forecast what the rest of the year – let alone the remainder of Trump's second term – may have in stock for the analytical science community. But, as Erin Baker puts it: "Science cannot start to move forward again until order is restored, chaos is removed, and our researchers and thinkers are no longer under attack."

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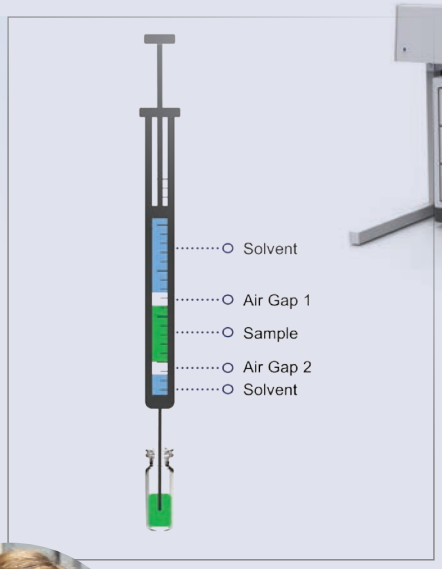

A Liquid Handling Solution for the Modern Lab

How the new KNAUER Liquid Handler LH 8.1 meets the demand for precision, high throughput, and sustainability

As analytical processes become more complex, achieving consistency is increasingly challenging. At the same time, laboratories seek to minimize manual steps while maintaining accuracy, driving demand for automated sample preparation. Sustainability is also a growing priority in HPLC and other analytical workflows, with a focus on reducing solvent and sample consumption.

The new KNAUER Liquid Handler LH 8.1 is designed to address these evolving needs, integrating automation, precision, and modularity for improved liquid handling. In this interview, Juliane Kramer, Senior Application Scientist Analytical at KNAUER Wissenschaftliche Geräte GmbH, discusses how the LH 8.1 enhances ease of use with its modern, intuitive software.

How does the LH 8.1 differ from a traditional autosampler, and what advantages does it offer?

The KNAUER Liquid Handler LH 8.1 is a fully customizable XYZ autosampler, meaning its syringe tower moves in all three dimensions for maximum flexibility. Though its primary function is sample introduction into an analytical instrument, such as an HPLC system, it also offers highly customizable settings to accommodate a wide range of sample types, concentrations, and volumes.

Compared with traditional autosamplers, which may have fewer adjustable parameters, the LH 8.1 provides greater versatility across applications. It also features a sandwich injection mode – an advanced technique that prevents sample loss and peak broadening.

Sandwiches in liquid chromatography… Tell us more.

It may sound a little strange, but sandwich injection is a key feature of the LH 8.1 that ensures precise sample delivery. In this mode, the sample is trapped between air gaps and transport solvent plugs, preventing peak broadening during the injection process. The result? True zero sample loss.

High-throughput analysis is crucial in many laboratories. How does the LH 8.1 optimize cycle times?

One way to optimize cycle times with the LH 8.1 is to configure it according to your specific needs, such as optimizing module combinations and ensuring wash and method steps are as efficient as possible. The LH 8.1 also features "overlapped injections," which allow the instrument to optimize sequence runs by enabling the next run to start before the current one is finished. For high-throughput applications, sample capacity is crucial. When paired with a robotic cooler, the LH 8.1 can accommodate up to six sample racks, holding up to 390 sample vials per cooler. With the long rail version (887 mm), up to four robotic coolers can be integrated, expanding the total sample capacity to 1560 x 1.5 ml vials or 24-well plates.

Can the LH 8.1 adapt to different LC system configurations?

Yes! The LH 8.1 is highly flexible and compatible with various liquid chromatography systems and chromatography data system software packages. Such flexibility is essential for high-throughput labs, where configurations and setups must be adaptable for different analyses.

What types of laboratories and industries will benefit the most from integrating the LH 8.1 into their workflows?

The LH 8.1 is ideal for contract laboratories or, more generally, laboratories where high throughput is essential. Common applications include clinical and environmental – but really, the LH 8.1 is also suitable for any workflow that requires direct injection into the mass spectrometer.

How have (analytical) scientists reacted to the LH 8.1?

The system has already been showcased at exhibitions and conferences, where industry professionals have welcomed the arrival of a genuinely new and modern liquid handling solution.

For laboratories considering an upgrade, what would you say is the best reason to choose the LH 8.1?

The main reason is undoubtedly sample capacity. It is the best solution for storing thousands of samples in cool conditions and analyzing them automatically without any further user intervention. Additionally, its customizable injection workflows provide a flexible and efficient alternative to conventional autosamplers.

For laboratories looking to enhance throughput, precision, and sustainability, the LH 8.1 represents a cutting-edge liquid handling solution.

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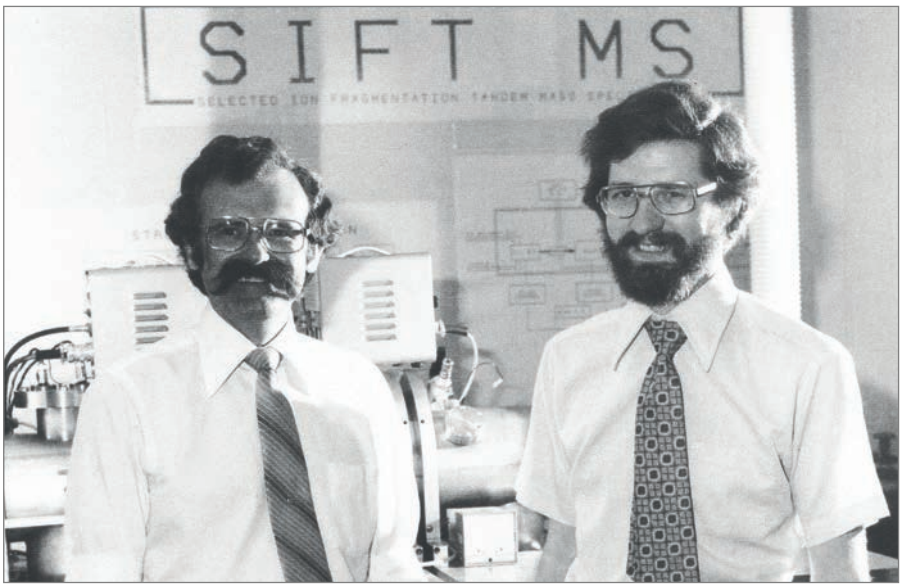
MASS SPEC

Let the Problems Lead: Lessons Learned with Chris Enke

After pioneering in the electrochemistry and electronics fields, Chris Enke co-invented the triple quadrupole mass spectrometer in the late 1970s. Today, Enke is still pondering solutions to big problems. Here, he shares his lessons learned.



You never know where an after-show dinner with a colleague may lead…

My career wasn't exactly planned. I always enjoyed science and teaching. But electronics was my first love. I originally attended a liberal arts college and planned to transfer out to get my electrical engineering degree. But I ended up falling in love with chemistry as well. So electrochemistry – using electronics in chemistry – was just perfect for me. But when the top universities had filled their electroanalytical positions and I struggled to find a placement for an excellent graduate student, I decided to move into computers.

I had one of the first laboratory computers, which I used to automate instruments – not just the data collection but also the instrument itself. My reputation in this area grew and I started to think about making an automated analytical instrument. I wanted to have both the separation and identification – or at least certain aspects of both – under computer control.

Rick Yost had just joined my group and chose this project. We were puzzled about what kind of separation method we could use and Rick mentioned this thing called the quadrupole mass spectrometer – which seemed like a good fit. The next question was what to use for identification. Here again, mass spectrometry seemed like a good option. The problem was that we needed to fragment the ions that we had selected to get the characteristic spectrum for identification, which is where we were stuck.

We consulted with Graham Cooks, who was an expert in metastable ion fragmentation found in double-sector mass spectrometers. We outlined our goal of separation, fragmentation, and identification, but we could not come up with an efficient fragmentation method using quadrupole analyzers. Graham, undeterred by the poor efficiency of high energy fragmentation, implemented the concept on his sector instruments and opened up the analytical potential of tandem analyzers.

Looking for inspiration, we went to ASMS in Washington, USA (1977), where we bumped into an old friend of mine, Jim Morrison. Back in his room after a nice dinner, he told us about his experiments with photofragmentation between quadrupole analyzers – which he hadn't yet published. I thought perhaps we could use photoionization. And he said, no – it's just ridiculously inefficient. In fact, it's so inefficient, he said, that I have to use synchronous demodulation to sort the fragments from the noise. And I said, what noise? You have the second quadrupole to pass only fragment masses, right? I realized that Jim's noise was the fragmentation process we were looking for!

At the time, nobody believed you could have low energy fragmentation. To figure out what was going on, Rick went to work in Jim's lab. We eventually proved that there was low energy fragmentation, it's just that the fragments scattered. And because Jim had a third quadrupole set to pass all ion masses, between his selector and analyzer, the scattered ions weren't disappearing into the pumps. That was the key breakthrough that led to the development of the triple quadrupole mass spectrometer. Jim was a co-inventor on the low-energy fragmentation patent.

Never underestimate serendipity; but you still have to persist in the face of skepticism

I've always thought that you have to throw some balls in the air and some you catch and some you don't. I've had plenty of ideas that don't work. And with the triple quadrupole, there was so much serendipity

– Rick having suggested quadrupoles, our informal chat with Jim Morrison, the funding…

We faced a lot of skepticism. Really, we had no experience (we weren't mass spectrometrists!) and no equipment. And even when we published the paper with Jim Morrison on low energy fragmentation, we still didn't know completely what was going on. In fact, some tried to prevent the paper from being published.

And prior to meeting Jim, we'd submitted many proposals, and basically, we were told: you're nuts, it'll never work, and who are you anyway? We ended up getting funding from an unusual place: the Office of Naval Research. They weren't interested in the mass spectrometry. But I had realized that our lab computer wasn't fast enough to control all aspects of running a mass spec – especially scanning and detecting. So I had the idea of incorporating a network of microprocessors that had just come on the market (I called the idea "distributed intelligence"). This was the aspect of the project that hooked in the Office of Naval Research. If it wasn't for that, I don't think we'd have ever gotten funding. But we persevered – and the rest is history.

Follow the problems

Some scientists are motivated by the possibility of having a real-world impact. For me, I'm not sure exactly how it happens, I find myself thinking about problems that I might be able to solve, which often opens up new avenues and further problems. In fact, I'm still thinking about some of the problems that arose from our work back in the 1970s.

For example, after we invented the triple quad, I got interested in time-of-flight because I thought it could help solve some of the problems associated with generating a full three-dimensional map from the triple quad. But then I realized there's a detection problem with time-of-flight – achieving adequate ion focusing to generate meaningful results. As a result, the early TOF-MS instruments were displaced by quadrupole analyzers. This problem has been addressed with modern electronics, pulsing schemes, and ion-beam collimation techniques. We developed a tandem TOF instrument using photo fragmentation. But I started working on an alternative solution: distance-of-flight mass spectrometry (DOF-MS).

"I think innovation comes from imagination. And imagination is wondering why – and using all of your background, resources, and experience you have to answer your question."

In DOF, ions of different mass-to-charge (m/z) are separated by the distance they travel in a given time after acceleration, where different methods of ion focusing and detection are used. DOF-MS can provide wider dynamic range and increased throughput, compared with TOF-MS. In fact, DOF-MS might help us to achieve simultaneous MS/MS – which people have been trying to do for a long time.

I'm still working with Steve Ray, State University of New York at Buffalo, USA, on the challenge of inexpensively achieving the thousands of simultaneous detectors required. Intrigued by its application to complex mixture analysis, I looked into the way component responses of complex mixtures were distributed. This work involved Luc Nagels in Belgium and Alex Gundlach-Graham. My paper on Using the Response Distribution to Compare and Optimize Untargeted Analysis Techniques has recently been accepted by the Journal of the American Society of Mass Spectrometry (1).

I think innovation comes from imagination. And imagination is wondering why – and using all of your background, resources, and experience you have to answer your question. And, in fact, my philosophical work tells me that there isn't one answer to why a particular law works. Just because an explanation makes sense, doesn't mean it is necessarily correct. And when you think about it, it's our explanations, not our laws or observations that end up getting changed…

Listen to your students!

All of the students and postdocs I've had over the years have influenced my thinking and research direction. I've already mentioned the impact Rick Yost had; but I had no interest at all in electrospray ionization before my student Calin Znamirovschi started working in that area – which ended up opening a whole new field for me. Nadja Cech conceived the experiment that demonstrated the relationship between response factor and surface activity in ESI. And early in the triple quadrupole days, I had a student who said we really ought to be working on a way to analyze proteins. There wasn't any mechanism for doing that at the time, but he was absolutely right.

I've had some wonderful students over the years – 69 people did their PhDs with me. Many have gone on to have great careers in academia, industry, teaching, and elsewhere. They all brought something unique. So if there's one final piece of advice I'd like to offer, it would be: listen to your students!

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CHROMATOGRAPHY

Pushing the Limits of Liquid Chromatography – Ten Years Later

In 2015, we gathered a group of experts to ask: have we reached the limits of liquid chromatography? Our experts returned a resounding "no!" – as they did two years later in the follow-up piece. However, ten years on – and with HPLC 2025 just around the corner – we feel the time is right to revisit our provocative question: are we still pushing the limits?

With Fabrice Gritti, Principal Consulting Scientist, Waters Corporation, USA; Gert Desmet, Full Professor and Department Head, Vrije Universiteit Brussel, Belgium; and Martina Catani, Associate Professor, Department of Chemical, Pharmaceutical and Agricultural Sciences, University of Ferrara, Italy

When you look back over the past 10 years, has HPLC innovation lived up to expectations?

Fabrice Gritti: Yes, I believe HPLC innovation has lived up to expectations – though not through breakthroughs in resolution, selectivity, or throughput, which have remained relatively stable (notably, UHPLC celebrated its 20th anniversary last year). Instead, the last decade has seen HPLC evolve in response to the analytical challenges posed by complex biomolecules such as monoclonal antibodies (mAbs), mRNA, adeno-associated viruses (AAVs), and lipid nanoparticles (LNPs). This growing demand has catalyzed significant advances in column and system technologies.

The most impactful development of the past decade has been the emergence of fully bio-inert systems and columns, designed to overcome issues like sample loss and resolution degradation caused by metal-analyte interactions. Manufacturers have introduced metal-free hardware, new surface chemistries, and specialized columns – such as robust SEC columns with ultra-wide pores (up to 2000 Å for LNPs) and slalom chromatography columns tailored for large DNA/RNA molecules. These solutions have dramatically improved the analysis of sensitive compounds and accelerated innovation in biopharmaceutical research.

Gert Desmet: I would say the past 10 years were evolutionary rather than revolutionary, but that doesn't take away from the fact that steady improvements were made nonetheless. For example, the uniformity of commercially available particles has improved significantly, and new microfluidic techniques are being developed to improve this further still.

Martina Catani: The HPLC landscape over the past decade has been shaped by three core advancements, in my opinion. Firstly, UHPLC instrumentation evolved through innovations in plumbing, particularly with corrosion-resistant materials and metal-free flow paths that broadened biopharmaceutical applications. Concurrently, hyphenated techniques like LC coupled to high-resolution mass spectrometry, as well as comprehensive two-dimensional liquid chromatography (LC×LC), became indispensable for complex separations in proteomics and metabolomics – driven by the growing need for biomarker discovery and personalized medicine. Secondly, automation has been improved thanks to AI-driven software integration and optimization, reducing errors and streamlining method development. Finally, sustainability emerged as a priority, marked by eco-friendly practices, such as reduced solvent consumption, novel mobile-phase formulations, and miniaturized systems like nano-LC.

So, has HPLC peaked?

Desmet: It is undeniable that research on HPLC columns and instruments is declining, especially in academia, and that most of the significant strides forward have already been made. However, nobody saw the core-shell revolution coming (and I really mean nobody, because their advantage turned out to be much bigger than can be explained based on their presumed advantage: the reduced intra-particle diffusion distances). So who's to say we won't get surprised again? Indeed, there is still room for improvement: about 50 to 60 percent of the band broadening in our columns is today still wasted to omissible eddy-dispersion.

A few years ago we were close to a new breakthrough when Agilent researchers worked on core-shell particles with radially-only oriented mesopores, showing a 33 percent decrease in plate height compared to the "normal" core-shell particles. Unfortunately, the material never made it to the production and commercialization phase. However, if someone can solve the impediments, we may just be in for another unexpected revolution in particle technology.

Gritti: Although certain aspects of HPLC, like particle size reduction and packed column performance, may have reached practical limits due to physical and chemical constraints, the technique has not peaked. About 15–20 years ago, discussions at international conferences predicted a lower limit around 1.5 µm for the particle size, due to challenges with pressure, heat dissipation, and system dispersion. Those limitations still hold today, making further gains in speed and performance from smaller particles unlikely. Similarly, major breakthroughs in column selectivity are rare, aside from some promises in mixed-mode HPLC. However, many other areas – such as bio-inert column and system design, advanced detection methods, automation, hyphenation, data handling and processing – continue to evolve rapidly.

The history of HPLC reminds us that while core principles are bound by physics, innovation often thrives in novel surface chemistry, system hyphenation and integration and application expansion.

What are some of the hottest trends in HPLC today?

Gritti: In addition to the development of improved columns and systems designed to meet the needs of application chemists working on the characterization of complex biological systems discussed above, which I would say is the hottest trend, another major trend is the rising importance of artificial intelligence in chromatography, particularly for system diagnostics and predicting compound retention based on molecular structure in untargeted metabolomics, proteomics, and lipidomics. Although still in its early stages, this approach holds significant promise due to the vast amount of data being generated in these fields.

Desmet: I agree that the evolution towards the analysis of ever larger molecules is, for sure, the hottest trend. At the other end of the spectrum, I also find the quest for sensitive single-cell proteomics and robust clinical proteomics very interesting and promising.

Catani: I agree with Fabrice and Gert. I would also add that many efforts are also given to the development of sustainable separation methods, for instance by designing novel adsorbents to be used in pure aqueous mobile phases or by exploring the possibility of replacing common organic modifiers with greener ones.

Is AI having an impact on the HPLC field today?

Desmet: Not yet – at least as much as it could have or should have. Because, with the number of HPLC practitioners without a strong separation science foundation growing bigger and bigger, it seems natural to compensate by making the instruments more intelligent. However, so far most AI and machine learning efforts are still limited to the academic groups, often focused on developing better retention time prediction models. This work has yet to led to new products for the users community.

Could machine learning be used to take control of instruments and propose new, better gradients by reviewing the results of the past gradient runs? That would certainly be interesting. Some work in that direction has been done at the University of Amsterdam, in Belgium in Brussels and Leuven too, as well as in some vendor companies, which is good news. (I happen to know some of them will report on this at the upcoming HPLC conference...)

Catani: I believe that AI holds transformative potential in chromatography – to accelerate method development and enhance analytical precision, but I agree that its application is still limited to a research stage now. Recent HPLC symposia have highlighted machine learning's ability to predict optimal chromatographic conditions, such as mobile phase composition and gradient profiles, by training algorithms on minimal experimental data, leveraging molecular properties like polarity and solubility. This approach drastically reduces the time traditionally spent on trial-and-error optimization. AI-driven tools could also address complex peak deconvolution, automating integration tasks that require manual intervention, thereby improving reproducibility and throughput.

In the decade to come, what might the next "HPLC gamechanger" look like?

Gritti: Looking into the decades ahead, I believe the next HPLC game-changer will be the integration of artificial intelligence across nearly every stage of the workflow – from sample preparation and method development to data handling and processing. Process development for large-scale bioreactors will also benefit significantly from AI and hybrid modeling approaches (e.g. digital twins), helping to reduce both costs and carbon footprint.

Moreover, I believe that generative design – combining fundamental principles of physics and chemistry with the vast amounts of data generated today – will drive the discovery of new 3D column structures, enhancing both speed and resolution. These innovations could become accessible to HPLC users once 3D printers capable of producing at 1-micron resolution across large build volumes are widely available.

Desmet: In the area of column technology, I still expect a lot from new particle morphologies. I already mentioned the possibility of core-shell particle with radial-only oriented pores to produce columns with a reduced minimal plate height of 1; but other particle formats – such as spiky particles, for example, which would generate a

drastically lower hydrodynamic resistance than conventional spherical particles – could one day emerge and surprise us all.

I also expect some important breakthroughs from the pillar-array column technology. Whereas particle packed columns have clearly reached their limit in terms of size reduction, the development of pillar array columns still only in its infancy and is far from reaching its fundamental operation limits. Nor has it already fully exhausted its potential to increase flow rate ranges.

Then there's the design of our instruments. In the not too distant future, I expect to see the emergence of radically novel instrument lay-outs. This would allow columns to be installed as a simple cartridge – like we do in our printers or coffee machines – which have enough intelligence on-board to operate fully autonomously.

Overall, are you optimistic about the future of HPLC?

Desmet: Sure, as long as the ion-suppression problem of MS detection does not get fundamentally solved, chromatography will remain the key technology to analyze and quantify complex samples. And given that the fundamental performance limits of the technology in terms of speed and efficiency have not been reached yet – by far – I am quite confident we will continue to witness new breakthroughs in the future.

Gritti: Absolutely. HPLC will always remain a force to be reckoned with. It is one of the most sensitive analytical techniques available, capable of detecting subtle differences in free energy, approximately 25 J/mol using recycling chromatography (for selectivity $\alpha = 1.01$), while the weakest dispersive intermolecular interactions in nature are around 50 J/mol.

That said, HPLC and multi-dimensional HPLC are not a panacea for sample characterization. Rather, they will continue to play a vital role by complementing and being hyphenated with other analytical techniques. In a world where both the amount and complexity of chemical systems to be analyzed are constantly increasing, HPLC will remain an essential tool for the success of analytical scientists.

Catani: Yes, certainly. I believe HPLC will still be considered the gold standard separation method. And given the continuous development in terms of instrumentation and column formats, I could envisage an advancement in the design of portable and miniaturized instruments for in-field analysis. This could also significantly reduce challenges in sample preparation and storage.

SPECTROSCOPY

A Day in the Life of a Nuclear Forensic Scientist

Dealing with highly radioactive black powder, revealing how nuclear materials were produced, and catching uranium shoe smugglers…

By Greg Klunder, Analytical Chemist and Staff Scientist at Lawrence Livermore National Laboratory, USA

Nuclear forensics – the field in which I work at the Lawrence Livermore National Laboratory, USA – uses a variety of analytical techniques and data analytics to characterize nuclear (radioactive) materials and provide as much conventional forensic information as possible. The goals generally come down to answering four simple questions about the sample: What is it? Where did it come from? How did it get there? And who was involved?

Over the years, the need for nuclear materials has increased and how those materials are produced and used is of great interest. In addition to national security in the areas of non-proliferation and arms control, there is concern about making sure nuclear materials don't end up in the wrong hands through nuclear smuggling. Interception of smuggled nuclear materials is one area of application and requires sophisticated analytical techniques, especially if there are attempts to obfuscate how or when the material was produced. For example, based on isotope ratio measurements, the age of the production of the nuclear material can be determined, but if a smuggler wanted to try to hide the actual production age, they might blend in some of the daughter isotopes. This can typically be detected with high-precision measurements and there will be another decay sequence from the added material that can be identified.

Prior to receiving the sample, we have some information about it from the sponsor, so we bring together the team based on what we know and the sponsor's requests. When we receive the sample, it's logged in and photographed, evaluated for radiation levels, then we start with non-destructive testing. A typical team will include radiochemists, spectroscopists, chromatographers for GC or LC -MS, and microscopists.

I'm not sure there's a "typical" case in nuclear forensics, but here's one example: I was once involved in an attempted smuggling case where the person who was apprehended was supposedly transporting some uranium ores as a sample to a potential buyer. He had hidden the ores under the inserts of his shoes in his suitcase. In this case, we were able to quickly evaluate the materials using spectroscopic analysis and gamma spectroscopy to determine that these weren't, in fact, uranium ores. There are a few other examples in the book "Nuclear Forensics Analysis," by my colleagues Pat Grant, Ian Hutcheon, and Ken Moody.

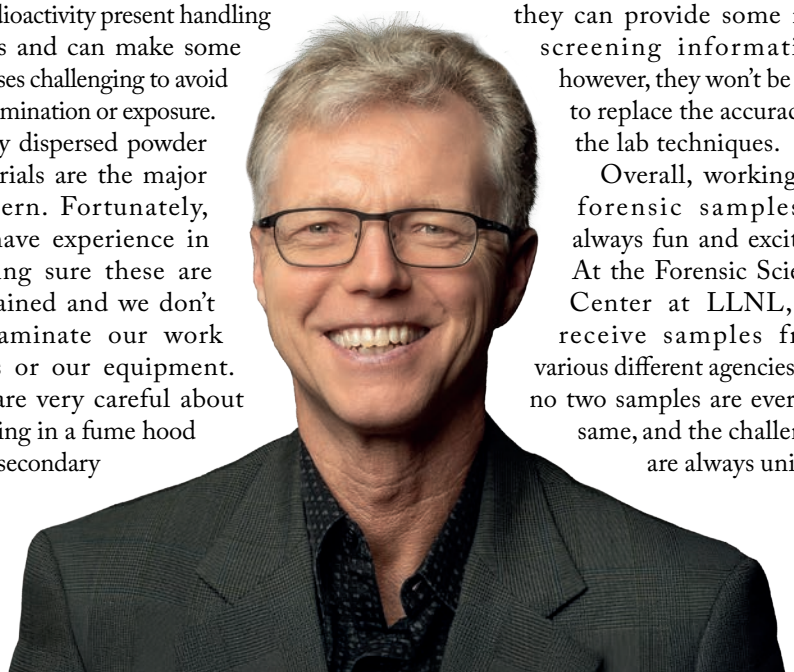
There are some challenges – and risks – when working in this field. In particular, samples with high levels of radioactivity present handling issues and can make some analyses challenging to avoid contamination or exposure. Easily dispersed powder materials are the major concern. Fortunately, we have experience in making sure these are contained and we don't contaminate our work areas or our equipment. We are very careful about working in a fume hood with secondary containment and monitoring our work areas for radiation.

In terms of the techniques used, spectroscopic analysis has several benefits for nuclear forensics. In particular, it can be non-destructive and non-contact, the analysis can be fast, and provides some spatial information. Of course, we use gamma spectroscopy to identify and quantify the radioactive species, although sometimes samples need to counted for extended periods of time. For optical spectroscopy, we rely on NIR diffuse reflectance, FTIR in reflectance or with ATR, and Raman – and these are usually some of the first analyses performed. These can provide some initial information about the sample that we can include in the first 24 hour report.

For example, we once had a sample of highly enriched uranium that was a black powder and had to be handled carefully and in a hood. We were able to measure the NIR diffuse reflectance spectra with a fiber optic probe and, when compared to our database, determined it was a mixture of U_3O_8 and $UO_3 \cdot xH_2O$. Knowing which form of uranium is present provides some insight about how the material was processed.

Of course, we're always looking for new and emerging techniques that can help speed up or improve the analysis. As handheld instruments improve, they can provide some nice screening information, however, they won't be able to replace the accuracy of the lab techniques.

Overall, working on forensic samples is always fun and exciting. At the Forensic Science Center at LLNL, we receive samples from various different agencies and no two samples are ever the same, and the challenges are always unique.



Efficient Separation and Analysis of Antibody Fragments and their Drug Conjugates

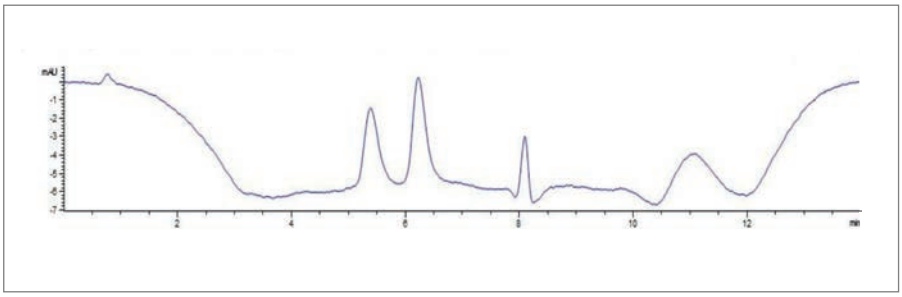


Figure 1: Separation of a single chain variable fragment (scFv, peak II) and its conjugated species (FDC, peak I).

Due to their significantly smaller size, antibody fragments require dedicated analytical methods for precise characterization and quality control.

With this precise SEC-MS method, a single-chain variable fragment (scFv) can be efficiently separated from its conjugated species (FDC). To achieve optimal resolution and peak shapes, a bioinert column hardware is essential. A metal-free PEEK-lined YMC-Pack Diol-120 column was selected for this analysis, ensuring high performance in the characterization of the scFv with a molecular weight of approximately 26 kDa.

Figure 1 illustrates the separation of the scFv and FDC, injected as a mixture, each at a concentration of 0.5 mg/mL. The addition of 4.5% isopropanol to the mobile phase increases the recovery of the hydrophobic FDC. Additionally, isopropanol improves peak symmetry, further enhancing separation performance.

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

**Application data by courtesy of Laura Bouché and Anja Pomowski, ANTIKOR, Stevenage, United Kingdom*


"Science is like a never-ending game where there's always another level to reach. You open one door, discover something, and then realize there are two more doors to open beyond that."

Nanotech Titan

Sitting Down With… Chad Mirkin, Director, International Institute for Nanotechnology & George B. Rathmann Professor of Chemistry, Professor of Chemical and Biological Engineering, Northwestern University, USA

Did you always want to be a scientist?
Actually, I wanted to be an NBA basketball player! When that didn't work out, I even considered becoming a movie critic. I was always good in school, but my drive to succeed was mostly about the competitive aspect of it rather than a particular passion for any one field. It wasn't really until late in college and maybe even early grad school that I realized science was something I truly wanted to do – and do at a high level.

Science is like a never-ending game where there's always another level to reach. You open one door, discover something, and then realize there are two more doors to open beyond that. It's a bit like playing Dungeons and Dragons: you don't know what's in front of you, but you follow your curiosity and find something interesting.

Are you driven more by scientific curiosity or the desire to make an impact on the world?
I'd say it's definitely a combination, but scientific curiosity comes first. That's the main difference between a scientist and an engineer, in my view. An engineer might say, "I want to solve this problem for the world. What existing tools can I combine to create the most efficient solution?" But as scientists, we're more driven by curiosity about new forms of matter. For example, with spherical nucleic acids – globular forms of DNA and RNA we developed by merging ideas from nanotechnology and DNA synthesis – we created a structure with no natural equivalent. It has unique properties and interacts with living systems differently from conventional DNA and RNA – and that took us about a decade to understand fully. Our curiosity led us to many discoveries and, ultimately, to ways of engineering these structures for real-world applications, like new diagnostics and therapies.

Do you consider yourself an analytical scientist?
First and foremost, I consider myself a scientist. We work across different fields, so my view is that if you learn to do science well – ask meaningful questions and apply the scientific method – you can use that in many areas. I think my career reflects that. Before coming to Northwestern, we hadn't worked with DNA, and now we're one of the leading labs in DNA synthesis and structural design globally. We also hadn't worked with scanning probe microscopes, but we trained ourselves, invented a technology known as dip-pen nanolithography, and essentially pioneered a technique that's now used all over the world in commercial applications.

Your discovery of spherical nucleic acids and the publication of your landmark paper must have been a big turning point in your career…
The paper you're referring to – the one in Nature in 1996 – was a huge turning point. I believe it is the most cited Nature paper from the 1990s across all fields, which is amazing, right? Even 30 years later, it still garners a couple hundred citations a year and has over 8,500 citations. The reason it was so foundational is that it introduced this entirely new concept of "programmable atoms," which redefined how we think about chemistry. We showed that you could take particles and, by attaching DNA to their surfaces, transform them into building blocks with bonding properties determined by that DNA.

We initially pursued this as a basic scientific question, but it quickly became apparent that this new structure could have practical uses. We weren't developing it with diagnostics or therapeutics in mind, but as we studied how it behaved, new possibilities emerged: the particles would aggregate when binding to complementary DNA, creating distinct colorimetric changes. Suddenly, we could develop colorimetric DNA and RNA sensors. Then, we discovered they could enter cells without needing transfection vehicles, which opened doors to cellular diagnostics and even manipulating cell behavior for therapeutic purposes.

What excites you most in your current scientific research?
I'm really excited about structural nanomedicine. I think it's the future, and I believe it has the potential to be transformative across the scientific community. The challenge is creating complex medicines that are structurally well-defined, where we can use analytical techniques to verify their design and employ AI to help optimize the composition, reducing the massive combination space needed to get to medicines that are not only chemically precise but optimized for efficacy and minimal toxicity. These materials would allow us to target diseases that current small molecules and biologics just can't tackle. Structural nanomedicine is really an exciting frontier.

The second area that's really crucial is using the high-throughput synthesis tools we've developed to create an inflection point in materials discovery. This could revolutionize the way we, as scientists and engineers, find materials that make a difference. We're talking about new catalysts, superconductors, battery materials, display technologies – you name it. Our ages of progress have always been defined by the materials we could access: the Stone Age, Bronze Age, Iron Age, Silicon Age, even today's advanced alloy age. When we discover materials that redefine these standards, we unlock new possibilities for innovation.

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