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CHEMICAL & ENGINEERING NEWS
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Innovative tools and techniques mean it's an exciting time for medicinal chemists
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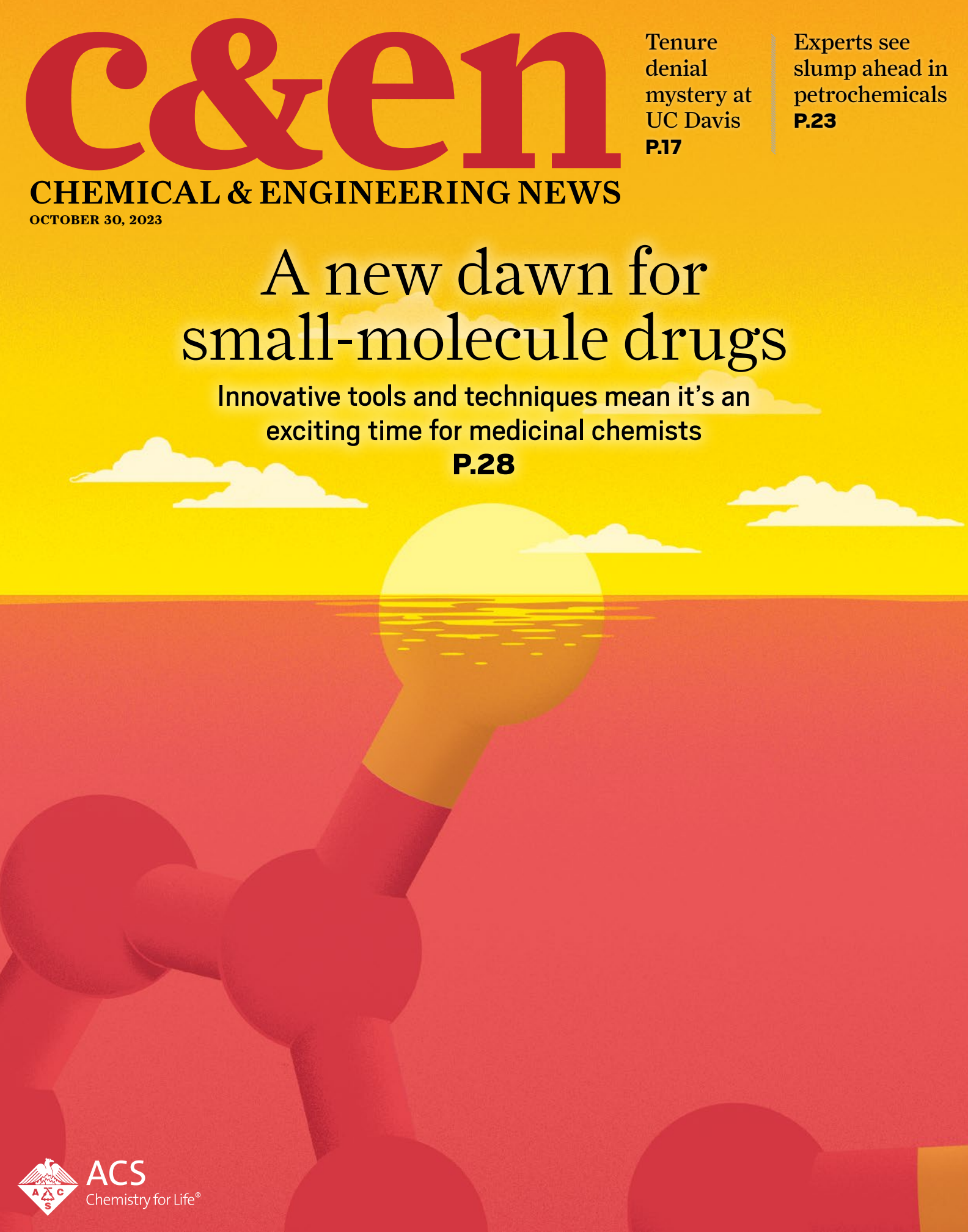

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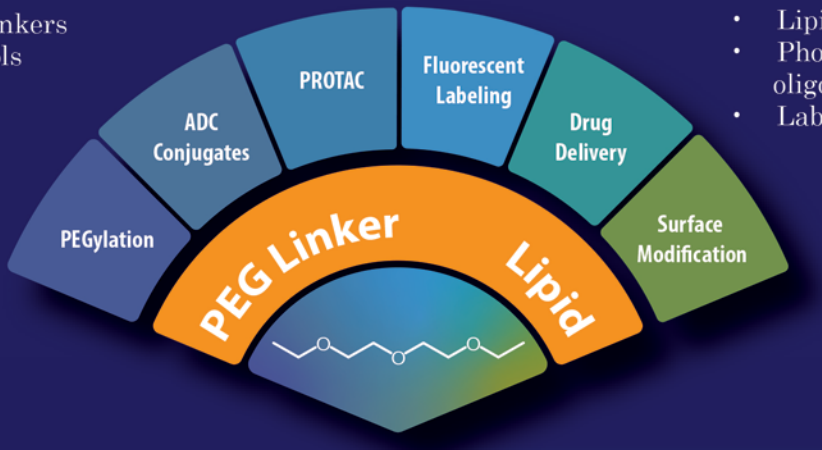

- Lipids in drug delivery
- Phosphoramidite in oligonucleotide synthesis
- Labeling reagents

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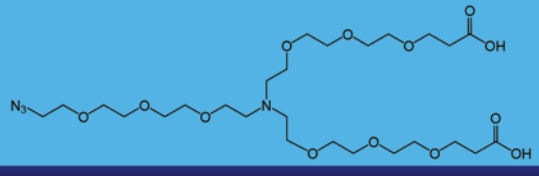
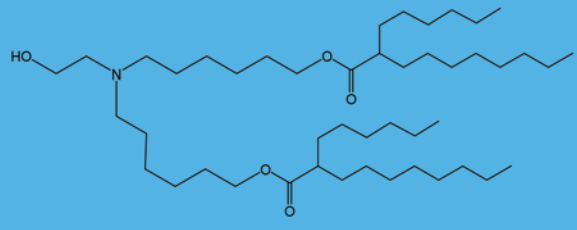


Lipids in Drug Delivery



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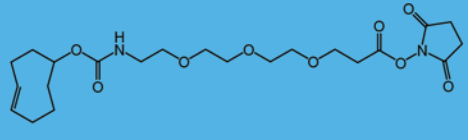
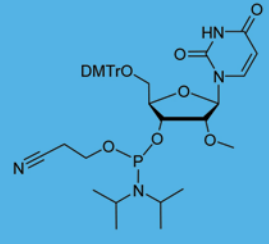


Nucleoside & Nucleotide



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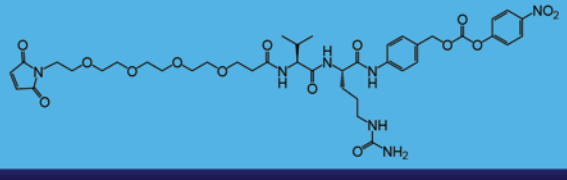

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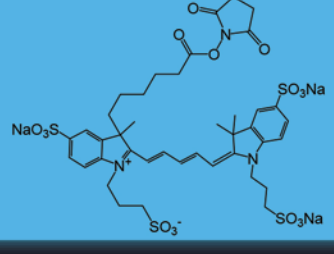

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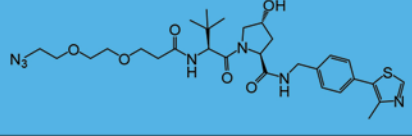

Look for C&EN's next issue Nov. 13

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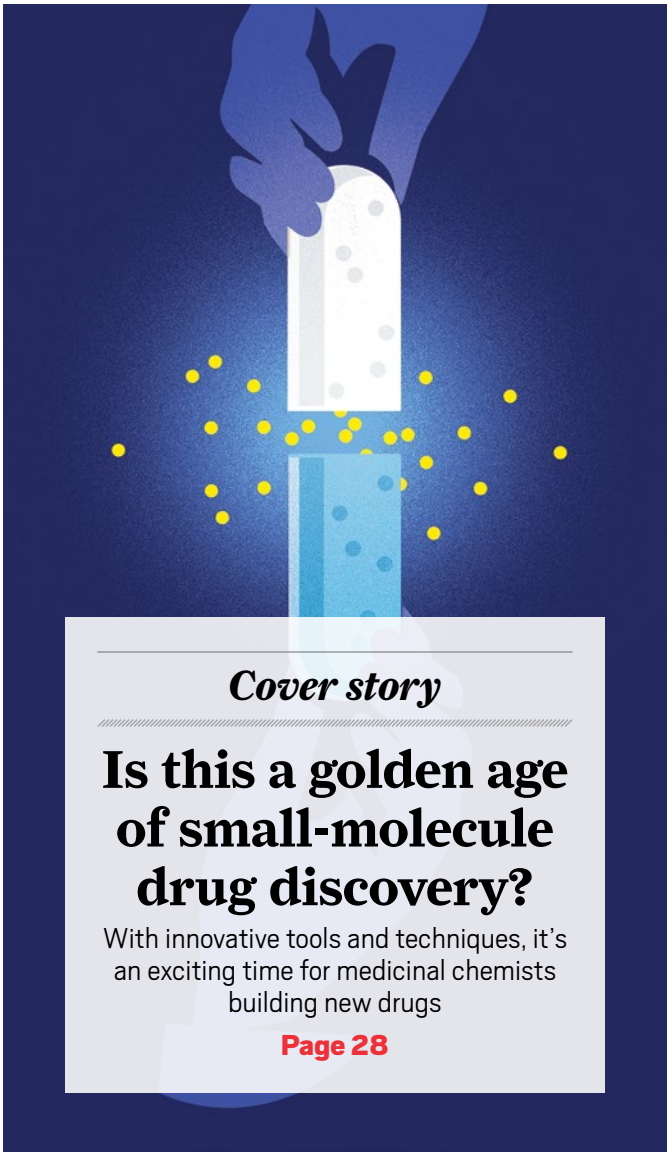

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Is this a golden age of small-molecule drug discovery?

With innovative tools and techniques, it's an exciting time for medicinal chemists building new drugs

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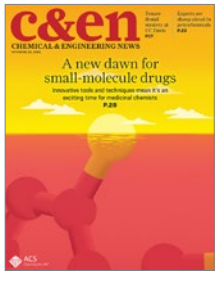

Illustration by Chris Gash

Quote of the week

"If you would have told medicinal chemists 15, 20 years ago that we'd be doing chemistry in cells, we would just laugh at that, but that's what we're doing. I mean, we are basically taking control of the natural regulatory mechanisms."

—Joel Barrish, partner, RA Capital Ventures

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Published by the **AMERICAN CHEMICAL SOCIETY**
Albert G. Horvath, CEO
Sharon Jane Chua, Publisher, C&EN

Canadian GST Reg. No. R127571347
Volume 101, Number 36

Editorial

It's training season at big organizations

Summer is well past, and fall is here in the US. For employees of large organizations, that means training season. Our companies rightfully want us to grow in our jobs and become better managers or scientists or salespeople, so they arrange training opportunities for us.

I'm trying to be positive about this fall's training, I really am, but it can be hard.

Maybe I have a chip on my shoulder because I am not a trained journalist. C&EN has great reporters and editors who went to journalism school and great reporters and editors who didn't. Yes, the learning curve was steep at first, but I became a journalist on the job. Likewise, I can't help thinking I can be a leader and manager by figuring it out as I go.

In recent weeks, I participated in training on three organizational levels at the American Chemical Society: training for ACS leaders, training for managers in the society's Publications Division, and training for the staff of C&EN. C&EN is published by ACS.

The ACS-level training took place in a nice hotel in Tysons Corner, Virginia. The keynote address was by Hamza Khan, an author and speaker who wrote a book called *Leadership, Reinvented*. And that's what he spoke about—reinventing leadership and leading people rather than managing them.

The talk was pretty inspiring at the time, but to be honest, the takeaways are a little hazy now. ACS is helpfully sending a copy of the book to those of us who requested it; I hope it reinspires when it's on my nightstand.

Next up was a series of Zoom meetings for Publications Division managers that focused on emphasizing our strengths rather than our weaknesses. Before the sessions, we all took the CliftonStrengths assessment, which fired a barrage of questions and then delivered our 34 strengths, in order. My top 5 are harmony, context, consistency, restorative, and adaptability.

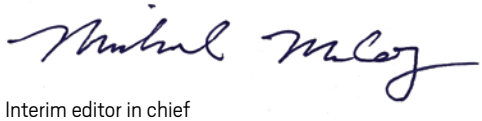
It was cool to see how the seemingly random questions yielded these terms, which actually describe me pretty well. The assessment also used my particular results to put me in one of four broader domains of strength. Mine is executing; the other domains are strategic thinking, influencing, and relationship building. The challenge for me now, 2 weeks and many distractions later, is to put this self-knowledge into practice. I'm working on it.

I'm writing this editorial on Oct. 20 on the Amtrak ride home after the third of my training events, C&EN's annual staff meeting in Washington, DC. It was my favorite of the three, both because it focused on journalism and because it was an opportunity to break bread with C&EN staffers from across the country and Europe. We've had a tough year. It was cathartic to come together.

I said goodbye to my colleagues only hours ago, and the takeaways are still fresh. The first day's main event was a brainstorming session with Butch Ward, a former newspaper reporter and editor. Over 4 h, Ward led us through an exercise that reminded us of our strengths and why we are proud to work at C&EN. We then worked in groups to identify ways that we, as individuals, could help fix the very real problems in our newsroom.

The next day we heard from a project manager at JournalismAI, a Google-backed organization that trains newsrooms to use artificial intelligence as a tool for news gathering, production, and distribution. And a social media expert talked to us about the best channels to use now that X, formerly known as Twitter, is in such flux. (Answer: There's no good answer!)

It all seems clear now. But I'm flying to Las Vegas for a wedding tomorrow, and then I will be catching up feverishly when I return to the office on Wednesday. I hope this latest round of training still resonates then.



Interim editor in chief

Views expressed on this page are those of the author and not necessarily those of ACS.

Concentrates

Chemistry news from the week

Highlights

ENVIRONMENT

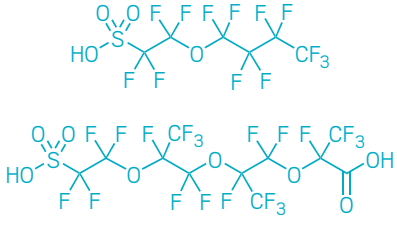
New method spots unreported forever chemicals

A new PFAS-detecting approach finds 11 previously undetected compounds in Cape Fear River

Per- and polyfluoroalkyl substances (PFAS) are ubiquitous synthetic chemicals found in the air, water, and soil. They have contaminated drinking water, accumulated to levels of concern in some fish, and entered the bloodstreams of animals and humans, raising serious health concerns.

While some PFAS are being phased out, they're often replaced with new ones that may also be toxic. Finding and keeping track of these emerging PFAS is challenging. New research has found a way to detect them.

Most commercial laboratories target about 40 PFAS, "but we know many, many more exist," says Erin Baker, an analytical chemist at the University of North Carolina at Chapel Hill. The US Environmental Protection Agency, for example, maintains a list of more than 14,000 PFAS that may be used in making products resistant to oil, water, and heat. The problem is that "there's only a few hundred chemical standards available to validate that you're actually seeing these chemicals," Baker says, "so we're missing over 13,000."



Newly identified PFAS

Along with her colleagues, Baker developed a new approach to detect PFAS that conventional methods may miss. It harnesses previously used techniques, such as liquid chromatography and high-resolution mass spectrometry, to identify different molecules in a mixture according to their mass, solubility, and polarity.

In a novel addition, the research team used ion mobility spectrometry to distinguish these molecules on the basis of their size and shape. "They're putting together a bunch of techniques that not everybody does," says EPA research scientist Mark Strynar, who was not involved in the research. "It is cutting edge; it is different and unique."

This multidimensional approach helped Baker and her team detect 36 known and 11 previously unreported PFAS in North Carolina's Cape Fear River. Eight of them weren't on EPA's list (*Sci. Adv.* 2023, DOI: 10.1126/sciadv.adj7048). "I was really shocked that we found these novel chemicals," Baker says. "It shows that there's a lot more out there that we're missing and why such nontargeted analyses are so important."

The work involved deploying passive samplers—embroidery hoops with two pieces of mesh and resin beads that bind PFAS—upstream and downstream of the Chemours chemical plant in 2016 for 2 weeks. Chemours, along with former company owner DuPont, has attracted lawsuits and millions of dollars in fines for decades of dumping PFAS into the Cape Fear River.

"Most PFAS we found are most likely coming from the company based on what we know they're making and their patent literature," says coauthor and environmental chemist Kaylie Kirkwood-Donelson, formerly a PhD student at North Carolina State University. While researchers are yet to understand if the new PFAS pose health risks, known examples, such as GenX, a member of the PFAS family that they detected, have been linked to issues with the liver, the kidneys, the immune system, and potential cancer risks on the basis of animal studies. Baker and Kirkwood-Donelson hope their method can help pinpoint novel chemicals lurking in the environment whose toxicity can later be tested in the laboratory.

Researchers have identified new PFAS downstream of Chemours's fluoropolymer plant in North Carolina.

CREDIT: ASSOCIATED PRESS

But their approach can't quantify the amounts of such PFAS in the water. Also, ion mobility spectrometry is extremely expensive and not easily accessible. But "a decade ago, high-resolution mass spectrometry was not the norm," Strynar says. "A decade from now, maybe ion mobility spectrometry is something more people will have access to," he adds. That could help more PFAS be detected more frequently.—PRIYANKA RUNWAL

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Are chemistry graduates equipped to solve global sustainability challenges?

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THURSDAY, DEC. 7

SESSION 1: **9:00 am – 9:40 am ET**
Reimagining Chemistry Education

SESSION 2: **10:25 am – 11:45 am ET**
Enabling Tomorrow's Workforce

SESSION 3: **1:30 pm – 2:40 pm ET**
Systems Thinking & Toxicology Modules

SESSION 4: **2:55 pm – 3:55 pm ET**
Challenges of Developing Chemistry Modules

SESSION 5: **3:55 pm – 4:55 pm ET**
Environmental Justice

FRIDAY, DEC. 8

SESSION 6: **9:00 am – 9:15 am (Introduction)**
9:15 am – 10:25 am ET
Technical Training in Sustainable Chemistry

SESSION 7: **10:40 am – 11:55 am ET**
11:55 am - 12:05 pm ET (Summary)
Global Sustainable Chemistry Education

SESSION 10: **11:55 am - 12:05 pm ET**
Summary and Next Steps

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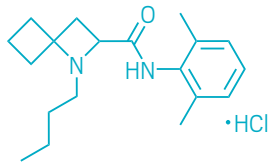
SYNTHESIS

A piperidine proxy

1-azaspiro[3.3]heptanes subs in for the popular functional group



Bupivacaine analog

The molecular motif 1-azaspiro[3.3] heptane may look peculiar, with its two four-membered rings that share a single carbon. But the structure can behave like a mimic of piperidine, a popular heterocycle in many drugs. Until now, however, this molecular motif has been tough to make.

Chemists led by Pavel K. Mykhailiuk at the Kyiv, Ukraine–based pharmaceutical chemical firm Enamine report a synthesis of monosubstituted 1-azaspiro[3.3] heptanes. The route expands the molecular toolbox for medicinal chemists looking to add diverse motifs to their molecules.

2-Azaspiro[3.3]heptanes have been popular piperidine mimics, or bioisosteres, since they were first proposed for this purpose in 2010. The motif has appeared in at least 100 research manuscripts, 500 patents, and 7,000 new compounds. But the isomeric 1-azaspiro[3.3]heptane has been rare because there was no modular route to make this motif with just one substituent.

Mykhailiuk and colleagues decided to take up this challenge because of perceived demand from medicinal chemists. "When you know trends well, when you know literature well, when you know what people want, then one of the most interesting parts is to design molecules," he says.

To make monosubstituted 1-azaspiro[3.3]heptanes, the chemists start by doing a thermal [2+2] cycloaddition between an endocyclic alkene and chlorosulfonyl isocyanate to make a spirocyclic β-lactam. Subsequent reduction of the spirocyclic β-lactam with alane-produced a 1-azaspiro[3.3]heptane. The researchers used their synthesis to make an analog of the painkiller bupivacaine (shown), which still retains some of its anesthetic properties in tests with mice (*Angew. Chem., Int. Ed.* 2023, DOI: 10.1002/anie.202311583).

"Medicinal chemists are always looking for unique bioisosteres to incorporate into their lead molecules, but the great ideas are often met with the sad reality of challenges of incorporating it into a complex scaffold," Donna Huryn, an expert in medicinal chemistry at the University of Pennsylvania, says in an email. "While azaspiro[3.3]heptanes have been described (albeit sparingly) before, this work demonstrates their efficient synthesis and protocols for further functionalization so that embedding it into a complex molecule isn't the hurdle that it sometimes is."

Mykhailiuk tells C&EN that he's had some interest from medicinal chemists since Enamine started advertising 1-azaspiro[3.3]heptane intermediates for sale a few months ago. "I'll give it a couple of years before they become common," he says.—BETHANY HALFORD

STRUCTURAL BIOLOGY

A new tool for protein designers

RoseTTAFold All-Atom incorporates small molecules in protein structure prediction and design

Proteins are important molecules—but they aren't the only molecules in a cell, and they don't operate alone. In a new preprint, the team behind the protein structure prediction software RoseTTAFold has announced a tool that expands the types of chemistry that protein designers using deep learning will be able to incorporate, to reflect proteins' environment better (bioRxiv 2023, DOI: 10.1101/2023.10.09.561603).

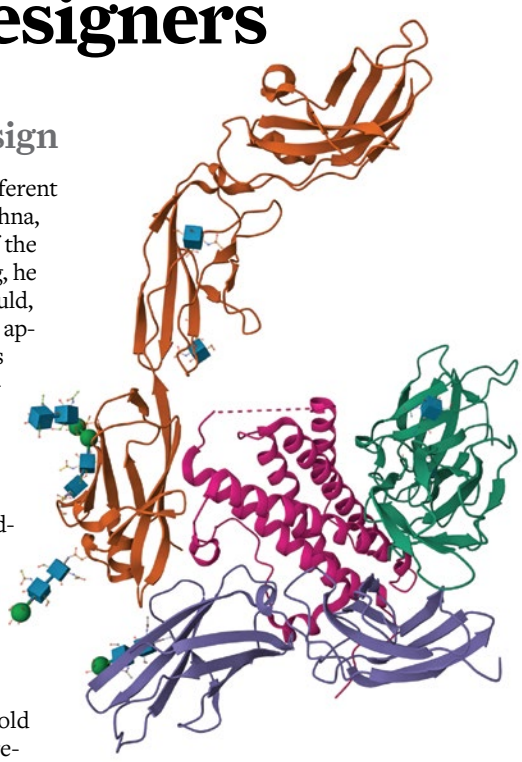
Protein structure prediction algorithms, such as AlphaFold and RoseTTAFold, have swept through the field of structural biology in recent years. These machine learning tools, trained on protein structures that have been solved experimentally, predict new 3D structures based only on proteins' amino acid sequences. Biochemists use those predictions to develop hypotheses about how proteins work and how they fit together, and they have also used the tools to design new proteins with desired functions.

The trouble is, these models overlook many types of chemistry that can influence a protein's structure. "A lot of biology involves, for example, proteins interacting with small molecules," says senior author David Baker, a University of Washington professor whose lab developed RoseTTAFold. The latest update to the model, RoseTTAFold All-Atom, can handle the more diverse chemistry that occurs when proteins bind small molecules or undergo covalent modifications that can dramatically influence their structure and function.

"It's kind of a hypothesis that we wanted to test: Is it possible, even, to train a model that can represent all these different types of molecules?" says Rohith Krishna, a graduate student and first author of the paper. After about 2 years of tinkering, he and his colleagues found that they could, by combining two different modeling approaches for molecules. Like previous RoseTTAFold iterations, the new network represents polymer subunits, like amino acids or nucleobases, as single units, but it also represents every atom as a unit in each covalent modification and small-molecule binding partner. It's hard to say exactly how it works—machine learning models are notoriously opaque—but the researchers think that it arranges all the units present until it reaches a plausible structure.

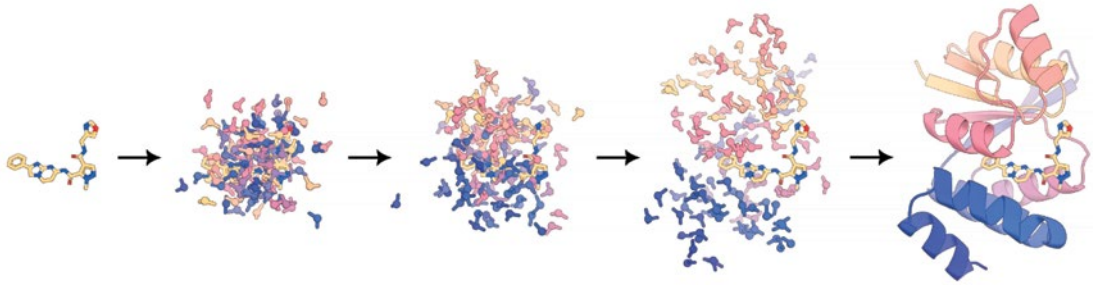
While prior updates to RoseTTAFold focused on specific problems, like predicting how proteins and nucleic acids interact, the team trained this one more broadly. "In principle, a network that's been trained on more diverse sets of data should be able to generalize better," Baker says, adding that the researchers plan for this network to supersede task-specific versions of RoseTTAFold.

The team used RoseTTAFold All-Atom to generate more-accurate predictions of proteins, such as enzymes bound to both their substrates and cofactors, and proteins with numerous covalent modifications. They also designed from scratch several proteins that bind to small molecules, using only the small molecules as inputs. Though he hasn't tried more complex arrangements yet, Krishna predicts that the model may be able to help design proteins that undergo complicated interactions—for example with both a nucleic acid and a small molecule cofactor.



A previously published experimental structure of a protein complex with several glycans represented as blocks. RosetTTAFold All-Atom accurately predicts how the glycans and protein fit together.

A time series from the preprint shows steps that a version of RoseTTAFold All-Atom uses to generate a new protein, given only the small molecule it should bind as an input.



According to Lauren Porter, a computational biologist at the National Library of Medicine, the network is promising, but it will take time to see just how dramatic an advance it represents and where it might fall short. AI models in general, she says, are "only as good as their training set." And they can stumble in areas where limited training data are available, such as when a single protein adopts two substantially different shapes depending on its context. Biochemists themselves aren't aware of many of those cases, so it takes time for these discrepancies to be uncovered. Still, Porter says, "it's a step in the right direction, for sure, and maybe a big one—time will tell."—LAUREL OLDACH

CREDIT: PROTEIN DATA BANK (7U7N); KRISHNA ET AL./BIORXIV (SCHEME)

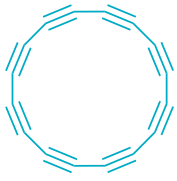
CHEMICAL BONDING

16-carbon ring is doubly antiaromatic

Highly reactive cyclo[16]carbon could be a precursor to other exotic carbon compounds

By manipulating atoms with a high-powered microscope, chemists have coaxed into being a doubly antiaromatic carbon allotrope. Although the molecule, known as cyclo[16]carbon or C_{16}, may exist in interstellar space, its existence on Earth is fleeting. That's because its antiaromatic nature makes it highly reactive—a property that could make it useful for creating other novel carbon compounds.

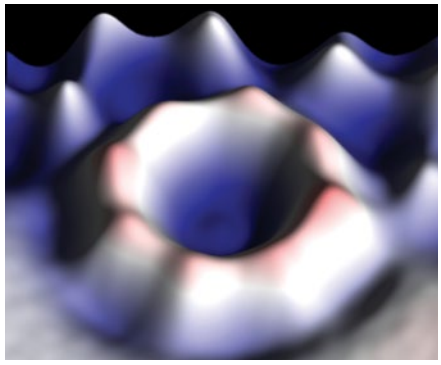
Cyclo[*n*]carbons have haunted University of Oxford chemistry professor Harry L. Anderson for about 30 years. His first project as a postdoctoral researcher, which he abandoned after deeming it too difficult, was to make C_{18}—a ring composed of 18 carbon atoms joined by alternating single and triple bonds. In 2019, Anderson and IBM Research-Zurich's Leo Gross led a team that made the 18-carbon allotrope.



Cyclo[16]carbon

C_{18} proved to be exceptionally stable for its size because it is doubly aromatic, with 18 π electrons running parallel and 18 π electrons running perpendicular to the ring. Aromatic compounds, which possess $4n + 2$ π electrons, have enhanced stability thanks to electron delocalization.

Antiaromatic compounds, which have $4n$ π electrons, aren't delocalized and tend to be unstable. "The difficulties in synthesizing antiaromatic cyclocarbons are mainly due to their reduced stability compared to aromatic ones," Wei Xu, who studies cyclo[*n*]carbons at Tongji University and was not involved in the work, says in an email.



This rendered atomic force microscopy image shows C_{16}'s circular shape.

CREDIT: LEO GROSS/IBM RESEARCH-ZURICH

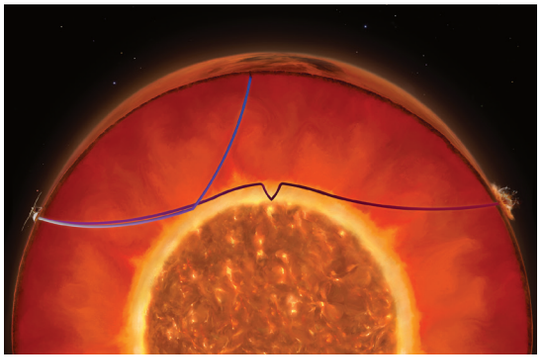
That's true of C_{16}—the newest carbon allotrope from Anderson and Gross's team—which is doubly antiaromatic. The researchers used an atomic force microscopy (AFM) and scanning tunneling microscopy (STM) tip to generate C_{16}, which appears circular, as well as negatively charged C_{16}^-, which adopts an oval shape (*Nature* 2023, DOI: 10.1038/s41586-023-06566-8).

AFM and STM studies revealed that C_{16}'s bond lengths differ significantly. This difference in bond length confirms that there is no delocalization and the compound is antiaromatic. Next, Anderson and Gross say, they want to create other elusive, carbon-rich antiaromatic molecules.—BETHANY HALFORD

ASTROCHEMISTRY

Cracking the chemical mystery of Mars's core

2 analyses of seismic data conclude that the planet's core is surrounded by a molten layer of silicate



Seismic information collected by NASA InSight suggests Mars's iron core is surrounded by a layer of molten silicate.

Scientists need to redraw their diagrams of Mars's interior structure, according to two studies published this week. Based on analysis of seismic data from NASA's InSight lander, both teams conclude that Mars's liquid iron core is smaller than previously thought and is enveloped by a 150-kilometer-thick layer of molten silicate that scientists had not previously observed (*Nature* 2023, DOI: 10.1038/s41586-023-06586-4 and DOI: 10.1038/s41586-023-06601-8).

Research published in *Science* in 2021 provided the first sweeping seismic analysis of Mars, using data from InSight. That work overestimated the size of the planet's core by about 30%, says Henri Samuel, a scientist at the French National Center for Scientific Research who was involved in the 2021 research and its recent revision. "This proves that we need to change our minds sometimes," he says.

Seismologists can infer the structure of a planet based on how pressure and shear waves move through it. Pressure waves can propagate through both solids and liquids, while shear waves can't travel through liquid—they get reflected. In the 2021 research, scientists believed they saw a shear wave that bounced off a liquid surface in the middle of the planet. They assumed this indicated the boundary between the liquid iron core and the solid silicate mantle. They concluded the core was larger and less dense than others had previously estimated.

A core with those properties would have to contain a relatively high proportion of lighter elements like hydrogen, sulfur, oxygen, and carbon along with iron and nickel. But that recipe seemed unlikely, given the volatility of those light elements and prevailing conditions when Mars formed. "Cosmochemists were saying, 'that can't be,'" says Suzan van der Lee, a seismologist at Northwestern University who was not involved with the research.

For the current studies, researchers analyzed tens of additional seismic events caused by meteor impacts and quakes, including a key event where a pressure wave slowed down in a way that suggested it was passing through molten rather than solid silicate. Working independently, both research teams concluded that the core is a relatively dense ball of liquid iron enveloped in a layer of molten silicate—eliminating the light-element problem.

To interpret the waves and what they mean about the layers of Mars, Samuel's team used experimental data about materials such as iron alloys at extreme conditions; another team of planetary scientists at the Swiss Federal Institute of Technology (ETH), Zurich, relied on simulations of these material properties. The two teams' predictions about the light element composition of Mars's core vary a bit. ETH Zurich planetary scientist Paolo Sossi says more data about material properties at high temperatures and pressures should help resolve this. Overall, Sossi says, the teams reached very similar conclusions, which suggests "how robust this discovery is."

Van der Lee says not to expect new data about Mars quakes anytime soon. InSight officially powered down in December 2022. But she expects other teams will continue to mine data from the lander, verifying and expanding on these results.—KATHERINE BOURZAC, special to C&EN

ATMOSPHERIC CHEMISTRY

Metals from space debris found in stratosphere

When space debris reenters the atmosphere, the heat generated from friction causes most of it to vaporize. Scientists have recently found that the vaporized metals condense as they descend, ending up in aerosol particles in the stratosphere (*Proc. Natl. Acad. Sci. U.S.A.* 2023, DOI: 10.1073/pnas.2313374120).

This discovery is part of the Stratospheric Aerosol processes, Budget, and Radiative Effects (SABRE) mission. During a series of flights in February and March, the researchers sampled the stratosphere at altitudes up to 19 km. The researchers detected almost two dozen elements that come from meteors, volcanoes, and vaporized spacecraft.

Meteors are considered the main sources of sodium, magnesium, chromium, iron, and nickel, but the researchers also found aluminum, copper, lead, and lithium that could not be accounted for by natural causes. "What we measured is consistent with what we know about what spacecraft are made of," says Daniel Murphy, an aerosols researcher at the National Oceanic and Atmospheric Administration and one of the authors of the study.

As space debris enters Earth's atmosphere, metals that are virtually absent from meteors such as the Perseids, shown here in August 2016, vaporize and become part of aerosols.

With space launches set to skyrocket, debris has the potential to change the chemistry going on within the stratosphere, Murphy says. "We don't really know what the effects are going to be. For me, that's uncomfortable."

The researchers would like to gather data above other parts of Earth for a broader understanding of stratospheric chemistry.—PAYAL DHAR, special to C&EN

CREDIT: COPYRIGHT IPGP-CNES (CORE); SHUTTERSTOCK (METEOR)

BUSINESS

Beam Therapeutics lays off staff, adjusts research focus

The company hopes its base-editing technology will compete as a sickle cell disease therapy

David R. Liu

CREDIT: CASEY ATKINS/HARVARD

The gene-editing company Beam Therapeutics on Oct. 19 became the latest biotech firm to announce staff layoffs. It plans to cut 100 employees, or 20% of its workforce. The Cambridge, Massachusetts–based firm also says it will pare back its pipeline. The cost savings from these changes will keep the company going into 2026, according to Beam.

Chemist David R. Liu of the Broad Institute of MIT and Harvard launched Beam in May 2018—2 years after his lab developed base editors, the firm's key technology. Base editors deliver a twist on traditional CRISPR-Cas gene editing to make single nucleotide base changes in DNA. In theory, this technology enables the treatment of genetic diseases with more precision and with fewer off-target effects.

But despite base editing's potential, it's taking time for the technology to yield a clinical product. Beam's restructuring will pause the development of an in vivo treatment for the hepatitis B virus. The company will also seek partners for its chimeric antigen receptor T-cell immunotherapy for T-cell leukemia and T-cell lymphoblastic lymphoma.

Instead, Beam will focus on its leading therapeutic candidate, a base editor for sickle cell disease, and a second therapy that delivers hematopoietic stem cells to treat the disease. Investors have largely focused on the former, for which early clinical data should emerge early next year, Sami Corwin, a stock analyst at William Blair, says in a note to investors. Beam will also continue to pursue a base editor therapy for a metabolic disease called α-1 antitrypsin deficiency, for which it aims to submit regulatory applications in the first quarter of 2024.

> "We need to make the difficult decision to focus our resources on those clinical programs and research areas we believe have the highest potential."
>
> **—John Evans,** CEO, Beam Therapeutics

A handful of other companies are developing gene therapies for sickle cell disease, and two firms have already gone to the US Food and Drug Administration for approval of their products. That could limit the market for Beam's alternative, and the base-editing platform will be critical to Beam differentiating itself, Corwin says.

It has been a tough year for layoffs in the biotech industry; 119 biopharma firms had cut staff by Aug. 18 this year, matching the number for the whole of 2022, according to analysis by Fierce Biotech.

In a statement accompanying the announcement, Beam CEO John Evans says, "In this challenging market environment, however, we need to make the difficult decision to focus our resources on those clinical programs and research areas we believe have the highest potential for near-term value creation, while continuing to build a strong company for the future."—ALLA KATSNELSON, special to C&EN

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TRADE

China restricts battery graphite exports

Move reinforces the case for more production outside the country

China's commerce ministry has put the world's battery industry on notice by restricting the export of some graphite materials that are used to make anodes for lithium-ion batteries. The move is calling attention to China's dominance of the market and providing a push to establish graphite processing outside the country.

Graphite anodes can be produced from synthetic graphite—made by heating petroleum coke—or from mined graphite flakes. Graphite flakes must be milled into spherical particles and then coated with carbon. Both forms are mixed with binders to create a battery anode.

Syrah Resources is nearly finished building a facility in Louisiana that will produce graphite anode materials.

CREDIT: SYRAH RESOURCES

Starting in December, companies in China will have to get permission to export some forms of natural and synthetic graphite materials that are used to make anodes.

Over 60% of the world's mined graphite and nearly half of synthetic graphite is produced in China, according to the US Geological Survey. The country also dominates processing steps further down the supply chain. The research firm Benchmark Mineral Intelligence estimates that Chinese firms produce 99% of spherical graphite and 93% of all graphite anode materials.

James Willoughby, a graphite analyst with the consulting firm Wood Mackenzie, says the restriction demonstrates China's control of the graphite market but may not significantly slow battery makers outside China.

Over the summer, the country placed similar restrictions on the export of gallium and germanium. While that caused a slowdown in trade for several months, exports have started again, Willoughby says. "It doesn't seem like they've turned off the tap," he says. "They just wanted to sort of show that they have control." He says the graphite market might follow a similar path.

Even before the export restrictions, several companies had announced intentions to establish graphite mining and processing or anode material production outside China.

Anovion and Novonix, for example, are planning synthetic graphite anode material plants in the US.

Westwater Resources is planning a graphite mine and processing facility in Alabama. With financial support from the US government, Syrah Resources is nearing completion of a plant in Louisiana that will produce anode material from natural graphite. The company says it already has customers. Both firms expect Chinese export restrictions to boost their business.

Graphex Technologies is building facilities in Michigan that will produce spherical and carbon-coated natural graphite. CEO John DeMaio says the Chinese restrictions only emphasize the need for what the company already has planned. "We saw the size of the opportunity here in North America," he says. "We knew there was going to be a need for a localized supply chain."

But it won't be easy for battery makers to transition to a battery anode supply chain that avoids China, according to Daisy Jennings-Gray, an analyst with Benchmark. She says it will take a long time to build anode production capacity and get the material qualified by battery makers.

"This announcement has certainly put graphite, and anodes, on the radar in the West," she says. "There won't be a quick pivot away from the reliance on graphite and anodes from China."—MATT BLOIS

FINANCE

Dow earnings drop on economic woes

Slow economic activity around the world stymied third-quarter performance at Dow, the largest US chemical maker and the first major firm to report results.

Dow's sales were down 24% in the third quarter versus the year-earlier period, while net income fell 57%.

Selling volumes declined by 6%, but a bigger factor in the results were prices for Dow products, which declined 18% from a year earlier—primarily the result of lower energy costs.

Sales in the company's largest business, packaging and specialty plastics, were down 26%. Demand for the segment's key product, polyethylene, was strong, but volumes for merchant sales of chemicals were weak. Moreover, the unit saw a 20% decline in prices.

The main reasons for the sluggish economic performance: Europe, which continues to show tepid growth, and China, which is experiencing a slow recovery from its COVID-19 lockdowns.

24%
Dow's sales decline from the year-earlier quarter

57%
Dow's earnings decline from the year-earlier quarter

Source: C&EN tabulations based on company earnings report.

But the results weren't all negative. "Automotive, I would say, is a bright spot globally," Dow CEO Jim Fitterling told analysts in a conference call. "Even Europe, in spite of a slow GDP, has seen pretty strong automotive builds through the year."

Fitterling noted that activity in the sector should be even stronger once strikes at US assembly plants end.

"We expect the challenging macroeconomic dynamics to continue through the fourth quarter, including sluggish industrial activity," said Howard Ungerleider, Dow's president and chief financial officer.—ALEX TULLO

LITIGATION

Shell seeks damages in ethylene cartel case

Shell Chemicals Europe has filed a claim for about $1 billion in damages in the District Court of Amsterdam against four companies that the European Commission in 2020 found to be operating a buyer's cartel for ethylene. One of the companies, Clariant, issued a statement rejecting Shell's allegations, saying that Shell was not one of its ethylene suppliers.

The EC had found that Clariant, Celanese, Orbia, and Westlake Chemical fixed the price they paid for ethylene in Belgium, France, Germany, and the Netherlands between December 2011 and March 2017. Clariant was fined $175 million, Celanese $93 million, and Orbia $25 million.

Westlake would also have been fined for price-fixing had it not alerted the commission to the cartel activities.

"As a supplier of ethylene to the European market, we have a significant claim against the companies that were found by the European Commission to be operating a buyer's cartel," Shell says in a statement on its filing. "We have started litigation proceedings against them to recover these substantial damages from the impact their price manipulation has had on our business."

In a statement responding to Shell's Oct. 18 filing, Clariant says it "rejects the allegation and will adamantly defend its position in the proceedings." The company adds that it possesses "substantiated economic evidence that the conduct of the parties did not produce any effect on the market."

Celanese, Orbia, and Westlake did not immediately respond to requests for comment.—RICK MULLIN

PETROCHEMICALS

Braskem teams up with Northwestern

The Brazilian petrochemical maker Braskem has formed a partnership with Northwestern University to develop a platform, based on coelectrolysis, to make chemicals from carbon dioxide emissions. The project will be led by Northwestern chemistry professor Ted Sargent and research assistant professor Ke Xie. Sargent's group previously worked out a route to acetic acid that began with the electrolysis of CO_2 and water into carbon monoxide. Braskem has a similar agreement with the University of Illinois. It is also partnering with the start-up New Iridium on an approach to making chemicals from CO_2 using photocatalysis.—ALEX TULLO

RECYCLING

Ascend and Koura to recycle battery graphite

The battery recycler Ascend Elements will work with the fluorine chemical firm Koura—whose parent company, Orbia, has invested in Ascend—to commercialize technology for recycling graphite anode material in batteries. Some battery recycling processes can recover graphite, but Ascend claims that the product isn't usually pure enough for batteries. Graphite has received less attention from recyclers because it's less valuable than cathode metals like cobalt, lithium, and nickel. Orbia is also working with Ascend to recycle fluorine chemicals in batteries.—MATT BLOIS

PETROCHEMICALS

Sumitomo plans propylene from ethanol

Sumitomo Chemical has begun building a pilot plant in Chiba, Japan, that will produce propylene directly from ethanol via a new process. Existing approaches involve multiple intermediates, the firm says. Most propylene is now made from fossil resources, whereas ethanol can be produced from biomass such as sugarcane. Methods of making ethanol from waste plastics or carbon dioxide are being developed, Sumitomo says. The company already makes ethylene from ethanol in a pilot plant in Chiba.—MICHAEL MCCOY

MERGERS & ACQUISITIONS

Lithium M&A activity continues

Merger and acquisition activity in the lithium industry is moving at a brisk pace. Azure Minerals, which is developing a lithium mine in Australia, has accepted a takeover bid from Chile's SQM that values Azure at more than $1 billion. The deal requires 75% shareholder approval. In July, Azure rejected a $585 million bid from SQM, which is the company's largest shareholder with a roughly 20% stake. SQM has also made smaller investments in early-stage lithium miners. It recently agreed to buy a minority stake in Pirra Lithium and is financing exploration activities for Dart Mining in return for equity interest. In addition, Chile's state-owned mining company, Codelco, will acquire Lithium Power International in a deal worth $244 million. Lithium Power is developing a lithium mine in Chile's Maricunga salt flat. These acquisition moves follow the recent collapse of Albemarle's offer to acquire Liontown Resources in a $4.3 billion deal. Other recent deals include Mineral Resources' acquisition of the Bald Hill mine in Australia and Develop Global's plan to buy the lithium miner Essential Metals.—MATT BLOIS

INVESTMENT

Li-Cycle reconsiders recycling plant

Li-Cycle has paused construction on its large-scale lithium-ion battery recycling facility in Rochester, New York, while it reviews options for moving forward. The company has completed engineering and procured materials for the facility, but construction costs were higher than expected. In February, the US Department of Energy made a conditional commitment to loan Li-Cycle $375 million for the project. The facility was expected to come on line at the end of 2023 and process 35,000 metric tons of material per year.—MATT BLOIS

POLYMERS

Vinyl records could be things of the past

South Korea's SK Chemicals and Sonopress, the manufacturing subsidiary of the German media company Bertelsmann, have developed a material for making records that might replace the polyvinyl chloride used for decades. The new records are made from recycled polyethylene terephthalate, which SK processes chemically at a plant in China. Sonopress has been trying to find an alternative to vinyl for 2 years; for the new record, it developed an injection molding machine that exerts a pressure of 300 metric tons.—ALEX TULLO

Records made from recycled polyethylene terephthalate

PHARMACEUTICALS

Daiichi Sankyo and Merck sign ADC deal

Daiichi Sankyo and Merck & Co. have signed a commercialization agreement for three of Daiichi Sankyo's antibody-drug conjugate (ADC) candidates. The three ADCs—patritumab deruxtecan, ifinatamab deruxtecan, and raludotatug deruxtecan—are in various stages of clinical development for the treatment of multiple solid tumors as monotherapies or in combination with other treatments. The partners would jointly commercialize resulting therapies worldwide, except in Japan, where Daiichi Sankyo would be solely responsible for manufacture and supply. Merck will pay

CREDIT: SK CHEMICALS

Daiichi $4 billion up front under terms of the agreement.—RICK MULLIN

BIOBASED CHEMICALS

NatureWorks' Thai plant progresses

NatureWorks says it has made significant progress on a polylactic acid complex it is building in Nakhon Sawan Province,

NatureWorks says its new plant in Thailand is well underway.

Thailand. The facility will have lactic acid fermentation, lactide monomer production, and 75,000 metric tons per year of polymerization capacity when it starts up in 2025. Its feedstock will be locally sourced sugarcane.—ALEX TULLO

RENEWABLES

Borealis signs wind energy pact

Borealis has signed an agreement with the Swiss energy services firm Alpiq to buy renewable electricity from the Finnish wind

Borealis will buy power from this wind farm in Finland.

farm Merkkikallio. Starting next year, Borealis will get 90 GW h per year for use at its chemical complex in Porvoo, Finland. The deal will reduce its greenhouse gas emissions footprint by 45,600 metric tons per year.—ALEX TULLO

ONCOLOGY

Firms launch an actinium-225 venture

Isotope Technologies Munich (ITM), a German radiopharmaceutical firm, and Canadian Nuclear Laboratories (CNL) are forming a joint venture for the industrial-scale production of actinium-225 (^{225}Ac). The rare, α-emitting medical radioisotope is of interest as a precision oncology therapy. The venture, Actineer, plans to build a dedicated actinium production facility in an unspecified location. It will begin supplying ^{225}Ac in the interim; CNL will provide starting material for irradiation at its laboratory in Chalk River, Ontario, and ITM will process the resulting ^{225}Ac to pharmaceutical-grade material. CNL operates a national laboratory at Chalk River on behalf of Atomic Energy of Canada.—RICK MULLIN

MERGERS & ACQUISITIONS

Roche buys Telavant for $7.1 billion

The French pharma giant Roche will buy Telavant Holdings from Roivant Sciences and Pfizer for $7.1 billion. The target of the acquisition is RVT-3101, an anti-TL1A antibody therapy for treating irritable bowl disease. Roivant bought RVT-3101 from Pfizer late last year, before Phase 2 results were published. When the deal closes, Pfizer will retain commercialization rights in most of the world; Roche will gain rights for the US and Japan.—LAURA HOWES

PHARMACEUTICALS

EU fines drug companies for price fixing

In the first time the regulator has acted against an active pharmaceutical ingredient cartel, the European Commission has fined five companies for price-fixing for the antispasmodic butylscopolamine. Alkaloids of Australia, Alkaloids Corporation, Boehringer Ingelheim, Linnea, and Transo-Pharm will have to pay a total of $14.2 million. A sixth firm, C^2 Pharma, was not fined because it revealed the price-fixing to the commission. All six admitted their involvement and agreed to settle the case. A seventh firm, Alchem, did not settle; the investigation in that case is ongoing.—LAURA HOWES

Business Roundup

Evonik Industries will make proprietary fixed-bed catalysts for mobile applications of Hydrogenious LOHC Technologies' organic hydrogen carrier technology. The system uses benzyl toluene, which binds to hydrogen for safe transport.

W. R. Grace has unveiled a new catalyst system for fluidized catalytic crackers at refineries. The new catalyst uses a vanadium trap in a high matrix surface area catalyst, which the company says makes upgrading long-chain hydrocarbons into fuels more sustainable.

Yara, the Norway-based nitrogen producer, says that European nitrogen fertilizer demand is off to a slower start than usual this buying season. If the situation continues, new production curtailments might be needed.

Air Liquide plans to spend nearly $150 million to build a low-carbon industrial gases plant in Bécancour, Quebec. A new air separation facility will use hydroelectric power to make oxygen, nitrogen, and argon.

Versalis has completed purchasing the 64% of the biobased chemical firm Novamont that it didn't already own. Versalis is the chemical arm of the Italian oil company Eni.

Danimer Scientific, which makes the biodegradable polymer polyhydroxyalkanoate, has developed a compostable retail package with packaging maker Biolo and carrot producer Bolthouse Farms. The carrot bags will be available at 240 Meijer stores in the Midwest US.

Nucleus RadioPharma, a supplier of radiopharmaceuticals, has received $56 million in an oversubscribed series A funding round led by Eclipse Ventures and GE HealthCare. The firm plans to develop technology and establish manufacturing sites, including one in Rochester, Minnesota.

CREDIT: NATUREWORKS (PLANT); 3D WIND SERVICE (WINDMILLS)

CHEMICAL REGULATION

EPA seeks to ban trichloroethylene

US agency proposes to end most uses of the carcinogenic solvent within 1 year

After years of evaluating the risks of the solvent trichloroethylene (TCE), the US Environmental Protection Agency has concluded that the carcinogenic chemical has no safe uses.

Under a proposed rule released Oct. 23, the agency plans to ban TCE in most industrial and consumer products within 1 year. A few limited uses of TCE, including the manufacture of separators used in electric vehicle batteries and of rocket booster nozzles, would be exempt from the ban for 10 years with strict worker protection requirements.

TCE was once widely found in metal degreasers and in cleaning and automotive care products. Safer alternatives to TCE are now available for these products, according to the EPA. Although most consumer uses of TCE have been eliminated, a few products containing the toxic substance can still be purchased from online retailers, the agency says.

TCE is also used as an intermediate in the production of certain hydrofluorocarbons (HFCs) that are used as refrigerants. These refrigerants are being phased out because HFCs are potent greenhouse gases.

Exposure to even very low levels of TCE is associated with cancer and adverse neurological, developmental, and immunologic effects, and the risks are irreversible, the EPA says in an evaluation published in January 2023. The assessment builds on assessments published by the agency in 2014 and 2020.

TCE is a contaminant in soil and groundwater at many hazardous waste sites and surrounding areas as a result of decades of widespread use and improper disposal. "For far too long, TCE has left a toxic legacy in communities across America," Michal Freedhoff, assistant administrator for the EPA's Office of Chemical Safety and Pollution Prevention, says in a statement.

The American Chemistry Council, which represents chemical manufacturers, says the EPA is overestimating exposure to TCE. "Where uses of chemistries have decreased over time, this must be reflected in EPA's underlying risk assessment, because decreased use reduces potential exposure," the ACC says in a statement. "Here, for example, in the underlying risk assessment, EPA's exposure assessments were not realistic or reflective of current industrial hygiene practices."

Environmental groups welcome the EPA's proposal—the fifth rule aimed at controlling a high-priority chemical since the Toxic Substances Control Act was amended in 2016. The four other rules target asbestos, carbon tetrachloride, methylene chloride, and perchloroethylene. The EPA plans to propose restrictions on five additional high-priority chemicals in the coming months.

The use of trichloroethylene to produce lithium-ion battery separators for electric vehicles would be allowed for 10 years under a proposed rule.

"The Biden EPA is once again putting the health of workers and consumers first," Scott Faber, senior vice president of government affairs at the Environmental Working Group, says in a press release. "EWG applauds this move to ban most uses of TCE."

The EPA will accept comments on the proposed rule for 45 days after it is published in the *Federal Register*.—BRITT ERICKSON

RESEARCH FUNDING

NIH revamps grant review process to reduce bias

As part of a decade-long effort to level the playing field for investigators seeking money to pursue biomedical research, the US National Institutes of Health is simplifying its grant review process. Expertise and resources—two factors that can lead to potential reputation bias—will be evaluated for sufficiency but will no longer get a numerical score, the agency announced Oct. 19.

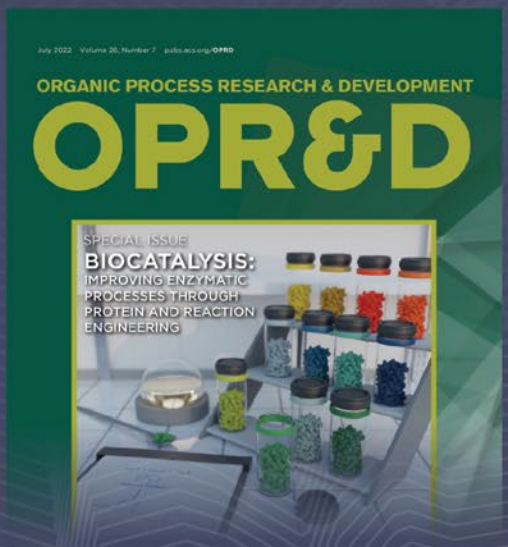
The new framework, which goes into effect for grant applications received on or after Jan. 25, 2025, is designed to give more weight to the importance, rigor, and feasibility of a proposed research project. Such factors will continue to be scored numerically.

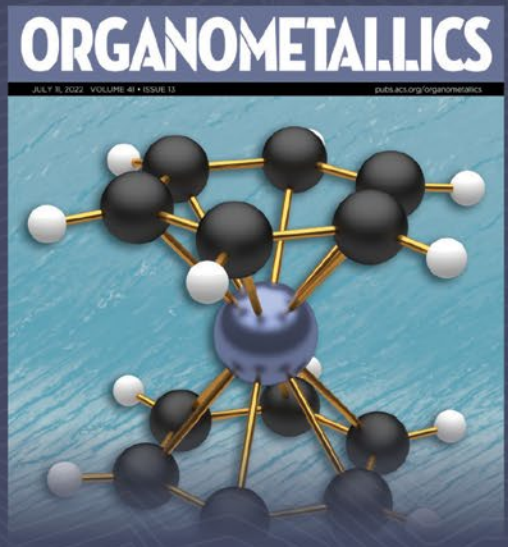
"Studies have shown that consideration of reputation of the institution or investigator in the grant review process could affect assessment of scientific merit, potentially giving reputation greater weight than other factors," Lawrence Tabak, acting director of the NIH, says in a statement. "Ultimately, the potential impact of ideas on advancing science should outweigh the reputation of who is applying and where they work."

The NIH has been struggling for years to make its grant review process fair and to ensure that peer review panels choose the best research proposals. The new framework also shifts some of the administrative burden from peer reviewers to NIH staff to allow reviewers to focus more on the science.

The NIH says it will consider feedback from the biomedical research community on the new framework. It will also collect data to evaluate the impact of the changes over time so that it can improve the process as needed.—BRITT ERICKSON

CREDIT: SHUTTERSTOCK





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The chemistry annex building at the University of California, Davis

EDUCATION

Why hasn't Kristie Koski made tenure?

The University of California, Davis, accused the chemistry professor of violating its faculty code of conduct. A judge and the faculty senate disagreed. Years later, she is still in tenure limbo

SAMUEL LEMONICK, special to C&EN

Kristie Koski is waiting to make tenure. Like many academic chemists, she submitted her tenure package in her sixth year as a professor. That's when professors "are expected to be ready for promotion," according to the personnel manual at the University of California, Davis, where Koski is a physical chemist. The traditional expectation in academia is that a professor makes—or is denied—tenure in their seventh year.

Koski submitted in 2019. It wasn't COVID-19 that disrupted her progression, as it has for others. The university denied Koski tenure for alleged violations of the faculty code of conduct related to two of her trainees. Koski denies she did anything wrong. A faculty senate committee and a California state court both found that the university had not proved some of its charges. But UC Davis didn't restart her tenure process until this past summer.

Four years on, Koski is in a kind of limbo. Her career advancement at UC Davis is stalled. The absence on her résumé of promotion to tenured professor is more prominent with each passing year. It would presumably complicate any attempt to find a new job. Some of Koski's colleagues say that, regardless of the eventual outcome, she has already paid dearly, both emotionally and in her professional reputation.

A full explanation of why this happened to Koski remains out of reach. She and several other UC Davis employees declined C&EN's requests for interviews, through a lawyer and a university spokesperson, respectively. Citing confidentiality rules, the university also refused to release records relating to Koski's tenure application and its investigations of her alleged wrongdoing.

Through interviews and public documents, C&EN has pieced together a partial picture of what happened, although many details cannot be verified independently. What does seem clear is that Koski got stuck in a web of bureaucracy, power dynamics, and personal relationships. It's a tangle that seems easy to avoid for some but impossible to escape for others.

A promising start

Koski arrived at UC Davis in 2016, lured away from a tenure-track position at Brown University that she took in 2013. She had already won a prestigious National Science Foundation (NSF) grant from the Faculty Early Career Development Program for her work on how sound moves through 2D materials. One UC Davis chemistry professor recalls that everyone in the department appeared impressed by Koski after she interviewed for the job; that person has asked to remain anonymous because they are an active member of the faculty.

Koski seemed to find her feet in the department quickly. She continued earning grants from the NSF, National Institutes of Health, and other funders. She won a patent and applied for another.

The *Journal of Physics* included her in a list of 50 rising female stars in physics.

But while she gained the respect and admiration of some of her colleagues, she clashed with Jared Shaw, an organic chemist who has been a UC Davis professor since 2007.

He would go on to be department chair from July 2018 until June 2022.

In November 2017, Shaw sent an email to five department members, including Koski, who had joined within the past 2 years. "You, collectively, as the young, kid-free crowd should make every effort to attend the dinners with the visiting candidates later this quarter. . . . It helps with something that others can't do as easily," it read in part.

Kristie J. Koski

Shaw wrote that when he was a young professor he had worried about going to a lot of candidate dinners, as it might look as if he were just trying to eat well on his department's dime. On the contrary, he wrote, "We will all thank you!!!"

Koski bristled at Shaw's request and saw it as discriminatory toward department members who were single or didn't have children, according to a lawsuit she filed in a California state court in September 2022 against Shaw, the Regents of the University of California, and others. That case has not yet gone to trial. She mentioned the email to an associate dean the following summer, when Shaw was being considered for department chair.

There were also other incidents. In 2018, Koski went to Shaw, who by then was the department chair, about fume hoods in her lab that had been broken for several months. According to the UC Davis professor who requested anonymity, Koski threatened to leave when Shaw told her the department couldn't fix them. Shaw later summoned Koski's senior faculty mentors about her behavior; the "kid-free" email came up again in that meeting.

> "There seems to be a really deliberate effort not to resolve her tenure decision and her appeals"
>
> **—Grant O'Rielly,** physicist, University of Massachusetts Dartmouth

A year later, Koski was trying to decide whether to report possible sexual harassment by a graduate student. Her lawsuit describes several incidents. At a lunch with Koski's lab group in June 2019, the student joked about what an undergraduate could fit into her mouth. In July, she found a graphic cartoon of a penis, apparently drawn by the same graduate student, in a notebook in the lab.

She also discovered that he had watched what the lawsuit describes as "sexually suggestive anime" with two other female undergraduates; Koski later found those three in a darkened laser lab that the undergrads weren't trained to work in. She warned the graduate student that his behavior could be considered sexual harassment and that she was required to report such harassment.

She shared her uncertainty about whether the student's behavior constituted sexual harassment with chemist David Manke, and his colleague, physicist Grant O'Rielly, during the last week of July, when she visited Manke at the University of Massachusetts Dartmouth.

O'Rielly, who was chair of his department at the time, recalls telling her: "You have to report this." Koski would have violated university policy if she hadn't taken her concerns to the appropriate authorities, he adds.

A decision to report

Koski did go to Shaw, the chemistry department chair, on Aug. 1, 2019, about what she had witnessed. He told her to report the incidents to the UC Davis Harassment and Discrimination Assistance and Prevention Program (HDAPP), but Koski did not do so. The University of California system-wide sexual harassment and sexual violence policy includes "department chairs" in the list of people employees can report incidents to. Koski believed that telling Shaw satisfied the university's reporting requirement.

Jared Shaw

She didn't know that the graduate student had gone to Shaw and another professor while she was in Massachusetts and described their conversation about his behavior. According to her suit, Shaw advised him to report Koski to Daniel Gray, the director of academic employment and labor relations in the academic affairs office. Gray has since retired. The student did so July 31, the day before Koski's own discussion with Shaw. The graduate student transferred to another professor's group Aug. 2, with Koski's blessing.

Koski's lawsuit notes that Shaw reminded her twice in the subsequent days to file a sexual harassment report, which she did not do. Instead, on Aug. 6, Shaw reported to HDAPP Koski's concerns about the graduate student's behavior as well as the student's allegations, which the suit describes as "bullying and intimidation by Dr. Koski." Koski's suit claims that Gray contacted HDAPP "and told them to expect a false report" from her.

The second of Koski's alleged violations of the faculty code of conduct happened later that summer. A former graduate student who was still working in Koski's lab went to a new job in June 2019 but did not clean up his lab space or return his keys before he left.

After her email reminders went unheeded, Koski called the former student's new boss to ask her to get a message to him. "He needs to come in during normal working hours, turn in his keys, and deal with this checkout issues," Koski said, according to a transcript of a voicemail she included in a rebuttal to the university's misconduct findings.

The former student didn't make any report about Koski's call. But Gray heard the story from one of the undergrads he interviewed as he investigated the first graduate student's allegation that Koski's report of potential sexual harassment constituted bullying. Philip Kass, the UC Davis vice provost for academic affairs, had directed Gray to look into those allegations, according to Koski's lawsuit.

This was in August 2019. While Gray investigated Koski, HDAPP was investigating the first graduate student's possible sexual harassment, as reported by Koski to Shaw. That process included interviewing Koski about her observations.

More than a year later, when a committee of the UC Davis Academic Senate considered the allegations against Koski, it decided that only the call about the lab checkout was inappropriate; her report about the first student's possible sexual harassment was not.

Koski did not learn about Gray's inquiry until mid-September 2019. Meanwhile, she had filed her application for tenure Aug. 7. Her lawsuit alleges that two other chemists had their tenure hearings heard in October and November 2019, while hers was delayed without an explanation.

Koski's suit also describes emails and meetings between Shaw, Gray, Kass, and UC Davis lawyer Sheila O'Rourke in which they planned how to present the findings

CREDIT: UNIVERSITY OF CALIFORNIA, DAVIS (BOTH)

from Gray's investigation at Koski's faculty tenure hearing, where members of her department would vote on whether to recommend that she get tenure. Shaw even delayed that hearing until Gray's report was ready, the lawsuit alleges.

A favorable review

On Jan. 15, 2020, the full chemistry department faculty gathered to vote on Koski's application for tenure. A committee of three professors had reviewed her application and presented their recommendation to the faculty. The committee's recommendation was a strong endorsement for Koski's promotion, according to people who were in the room.

After the review committee's presentation, Shaw distributed a two-page letter written by James DiCaprio, the school's associate director of academic employment and labor relations at the time. It described details of the allegations against Koski and asserted that, based on Gray's investigation, she had violated the university's faculty code of conduct. A judge would later rule that decisions about faculty code of conduct violations should be made by the academic senate. Koski's lawsuit asserts that Kass and O'Rourke encouraged Shaw to share the letter.

As is customary, Koski was not allowed at the hearing to rebut or explain the charges against her. According to the chemist who requested anonymity, Shaw told the faculty that its discussion was confidential and could not be shared. Shaw collected the copies of DiCaprio's letter before the meeting ended. Despite the accusations, the department voted in favor of granting Koski tenure. Her lawsuit states that the vote was 21–7.

The results of the vote, along with DiCaprio's letter, went to the dean's office. Koski was able to see the letter in a meeting with Shaw after the faculty hearing. She wrote a defense against the charges and sent it to Kass, but it was not added to her tenure package, according to her lawsuit. Citing DiCaprio's letter, Associate Dean Thomas Lee recommended that Koski be denied tenure.

The faculty senate Committee on Academic Personnel also recommended denial but cited an "unbalanced" academic record rather than the code of conduct charges against Koski, according to her lawsuit. On July 2, 2020, Koski was officially denied tenure.

"This was the most incomprehensible thing that ever happened in my academic career," says the anonymous professor, adding that the senate usually votes the same way as the department, yielding to its expertise.

A flurry of complaints

After the January 2020 faculty meeting, Koski filed a discrimination, harassment, and retaliation complaint with the university, as well as a whistleblower complaint. The university closed its investigations of both complaints that July without taking any action. HDAPP had closed its inquiry into the graduate student's possible sexual harassment in October 2019 with the determination that his behavior did not violate university policy.

> "This was the most incomprehensible thing that ever happened in my academic career"
>
> **—Anonymous professor,** University of California, Davis

C&EN filed a public records request for DiCaprio's letter and the reports from UC Davis's investigations into actions by Koski and the first graduate student. The university denied those requests, citing the confidentiality of personnel records.

Koski appealed her tenure denial in August 2020 through procedures outlined in the personnel manual. The university appears so far to have failed to act on her appeal, and Koski accuses Kass of stopping the process.

Kass had formally notified Koski of Gray's investigation results in February 2020, after her department tenure vote, and proposed a 3-month pay cut and a letter of censure in her personnel file. Later that year, the academic senate committee recommended a letter of censure but no pay cut.

Separately, the same committee determined that DiCaprio's letter should not have been in Koski's tenure package and that Shaw and others may have violated university procedures by including it.

In May 2021, against the senate committee's recommendation, UC Davis chancellor Gary May approved a 10% pay cut for 3 months and placing the censure letter in Koski's file. In a different lawsuit that Koski filed in 2021 against the Regents of the University of California, the judge ruled that May had exceeded his authority in "an abuse of discretion." The judge also affirmed the faculty senate committee's decision that only Koski's phone call violated the code of conduct.

The court ordered UC Davis to pay Koski what had been cut from her salary, as well as her legal fees. Her lawyer in that case says it has so far failed to do the latter; earlier this month, his firm began a collection action against the university for those fees.

Koski's unresolved lawsuit, filed in 2022 against Shaw and others, alleges discrimination and retaliation. It asks for damages and legal fees, as well as an injunction against the UC Regents to prevent the alleged policy violations from happening to another professor. It is set to go to trial in January 2024.

Lost years

Meanwhile, Koski is waiting. "There seems to be a really deliberate effort not to resolve her tenure decision and her appeals," says O'Rielly of the University of Massachusetts Dartmouth.

"It's hard on her," her department colleague says. "She's trying her best. I can tell she's stressed." Koski's lawyer says the last 4 years have taken a heavy toll on her mental health.

William Casey, a UC Davis geochemist, is similarly perplexed. "The administration wrecked the career of one of the most talented young physical chemists in the nation" by tainting the evaluation of her academic performance with its allegations of misconduct, he says. Casey adds that he has seen other, less egregious examples of administrators interfering with promotions or raises, which he sees as evaluations of academic performance. He thinks administrative reforms are needed to keep scholarly appraisals and investigations of misconduct separate.

"UC Davis is committed to maintaining an inclusive, respectful, and productive learning, teaching, and working environment for all members of our community," a spokesman tells C&EN.

Koski claims that the university has not addressed her tenure appeal. But it is re-running her application for tenure, which now includes the official letter of censure.

In May 2023, the chemistry department again voted in Koski's favor. Since the first go-round, there is a new chemistry department chair, a new dean, and new faculty senate committees. But 5 months after the second vote, there is no certainty that Koski will make tenure.

Samuel Lemonick is a freelance reporter living in Maine. ■

Recognizing diversity in gender and sexuality and body size

Use inclusive language to resist binary labels and avoid excluding people

SABRINA J. ASHWELL, C&EN STAFF

"Every scientist knows to keep their laboratory tidy." That sentence uses the singular "they" for an unspecified person. People have used the singular "they" in this way for centuries, and major style guides accept its use. That seemingly small grammatical choice—to use the gender-neutral "they" instead of the gendered "he or she"—can have big consequences: it can make people of all genders feel recognized and accepted.

Choices in language, big and small, can affect how welcoming a message is, and that's where the ACS Inclusivity Style Guide comes in. The guide, by the American Chemical Society, aims to help people make communication decisions that draw people in instead of pushing them away or making them feel invisible. Today we're sharing some of the guide's top tips on language around gender and sexuality and body size.

Language on gender and sexuality

The singular "they" rejects the gender binary—the idea that only two genders exist. For many, falling into binary thinking is easy; it's simpler to fit people into one of only two categories than imagine the multitude of identities that people may hold. And the English language often encodes and reinforces binary thinking: "ladies and gentlemen," "boys and girls," "husbands and wives." But that simplicity denies the complexity of people's identities and excludes people.

Many groups—including Native American communities; Indigenous communities in Oaxaca, Mexico; the people of Samoa; and Hindu societies—have recognized this complexity for generations by naming more than two genders. The ACS Inclusivity Style Guide recommends encompassing all gender identities in language by using gender-neutral terms and avoiding the assumption that gender is binary. For example, we can say "everyone," "children," and "spouses" or "partners." These choices will make your content more welcoming to a wider audience.

Language on body size

Another way that language can recognize the full complexity of people's identities is by accepting body size as a dimension of human diversity. People are not in binaries of "good" or "bad" because they have a certain weight. So we should avoid wording that treats weight loss as a universal positive. For example, instead of complimenting someone on losing weight, we can focus on how nice it is to see them.

Similarly, categorizing people into the binaries "healthy weight" and "unhealthy weight" is unhelpful and inaccurate, as people can be "healthy"—an amorphous term—at many weights. And language should respect everyone, regardless of their health status. We can separate health from weight by using straightforward, neutral descriptions of size, like "lower weight," "moderate weight," and "higher weight."

The top advice on language around gender and sexuality and body size is collected in two tip sheets reproduced here. This is the last set of tip sheets of a six-part series in C&EN. To see all the tip sheets and the full ACS Inclusivity Style Guide, visit www.acs.org/inclusivityguide. Email any feedback about the guide or tip sheets to ISG@acs.org.

More online

Like what you've read? See the full guide from the American Chemical Society at www.acs.org/inclusivityguide.

CREDIT: ACS

Gender and sexuality

For more context, review the "Gender and sexuality" section of the Inclusivity Style Guide. Use this tip sheet in combination with the "General guidelines" tip sheet.

Use gender-neutral language

Opt for gender-neutral terms rather than gendered equivalents. Using words that refer to men as a default can reinforce the idea that men are or should be dominant.

Example
✓ **Use:** humankind
⊗ **Avoid:** mankind

Gender is not binary

Not everyone has a gender identity that is completely female or completely male. Some people are a third gender, a mix of female and male, or no gender, for example.

Example
✓ **Use:** Welcome, everyone.
⊗ **Avoid:** Welcome, ladies and gentlemen.

Use the singular "they"

Use the singular "they" for all people who use that pronoun and when referring to an unidentified person. It is a neutral pronoun that can replace gendered language.

Example
✓ **Use:** their memory
⊗ **Avoid:** his or her memory

Know the language

LGBTQ+: Lesbian, gay, bisexual, transgender, queer or questioning, and additional marginalized gender or sexual identities
Nonbinary: An adjective to describe people whose gender identity is not completely male or completely female
Pronouns: The most common are "he/him," "she/her," and "they/them." But many more exist. Ask "What pronouns do you use?" or "What are your pronouns?"
Transgender: Having a gender identity that does not perfectly match the sex assigned at birth. It is typically not a gender. Some consider being transgender as part of their identity, and some do not.
Key reminder: Use "is" instead of "identifies as" for gender and sexuality, and avoid "prefers" in reference to pronouns.

Body size

For more context, review the "Body size" section of the Inclusivity Style Guide. Use this tip sheet in combination with the "General guidelines" tip sheet.

Avoid stigmatizing terms

Use comparative terms such as "higher weight" rather than the medical terms "obese" and "overweight."

Example
✓ **Use:** larger-bodied people
⊗ **Avoid:** people with obesity

Don't conflate weight and health, but also avoid healthism

Don't assume that higher weight causes poor health. Also recognize that higher-weight people deserve equitable treatment regardless of what their health is.

Avoid problematic frames

Avoid framing higher-weight people as an epidemic, a source of blame, or a burden. Avoid describing weight loss, thinness, or dieting as universally good goals that are easy to attain.

Provide context

When making statements about weight, ensure they are backed by strong science. Provide context about the limitations of studies, the harms of intentional weight loss, the myriad factors that contribute to links between weight and health outcomes, and researchers' conflicts of interest.

Example
✓ **Use:** Participants were drawn from [criteria for participating in the study]. [Number of participants] lost on average [overall number and percentage of starting weight] after [amount of time]. This change remained after controlling for [factors controlled for]. [Number of people] dropped out of the study because of [reasons].
⊗ **Avoid:** The drug successfully led to long-term weight loss in a large sample.

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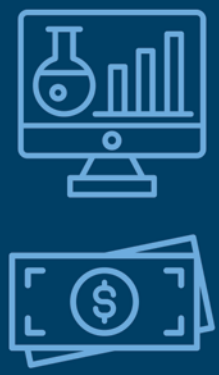

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CREDIT: CHEMICAL MARKET ANALYTICS BY OPIS

Dewey Johnson of Chemical Market Analytics chats with, from left, Emma Lewis, senior vice president of chemicals and products for the US Gulf Coast at Shell; Tom Asselman, senior vice president of strategy and chief strategy officer at OMV; and Bob Maughon, executive vice president of sustainability, technology, and innovation and chief technology and sustainability officer at Sabic.

PETROCHEMICALS

Fallow days loom for petrochemical firms

Years of healthy growth are yielding to slowing demand and a capacity overhang

ALEX TULLO, C&EN STAFF

The petrochemical industry is entering a rough period. A building boom of massive new complexes over the past decade—particularly in the US and China—has left the sector with the greatest overabundance of production capacity in decades. Struggling to find a market for the surplus, chemical producers will see lower prices and profits. Some, particularly in Europe and East Asia, where operating costs are high, will likely rack up losses.

Compounding the overcapacity problem will be a slowdown that may be an enduring fixture in the world economy as China cools from the robust growth of the past 2 decades. In addition, the industry must grapple with increased, and often costly, sustainability demands with no guarantee that its green investments will pay off.

Those were takeaways from the inaugural World Chemical Forum, held last month in downtown Houston. The conference was organized by Chemical Market Analytics by OPIS, a chemical consulting firm that split off from IHS Markit last year and is now owned by Dow Jones. The event drew more than 600 attendees.

The turbulent economic times were at the top of the agenda. "We expect to see a continuing downtrend in economic growth globally in the coming decades," Adrian Cooper, CEO of Oxford Economics, told the audience.

Cooper laid out a case that the world is in for a long period of weak economic growth. Interest rates all over the globe will remain higher than they were before 2020, increasing the cost of investment. Moreover, governments racked up debt during the pandemic, which may discourage stimulus spending—such as investing in infrastructure during recessions.

Access to labor will be another big problem for the world economy, Cooper said. Because of demographic trends such as an aging population, labor supply growth relative to economic output over the next decade will be half what it was over the past 20 years. Increased productivity is unlikely to make up for the shortfall because capital investment will also slow.

And finally, the Chinese economy, which was driven by high levels of private and government investment—45% of its gross domestic product—will also slow, to 4% annual growth by the end of this decade, Cooper said. According to the World Bank, the Chinese economy has averaged over 9% growth since 1978, when it began to adopt free-market reforms.

The slow global growth is bad news for petrochemical makers who bet billions of dollars on expectations of more buoyant markets when they built new facilities. Every major commodity chemical market, with a few exceptions, like chlorine, is now entering a period of severe overcapacity that will make it difficult to eke out profits.

"The overbuild is finally rearing its head," Steve Lewandowski, vice president of global olefins and derivatives at Chemical Market Analytics, said in a talk about ethylene. "We just had too much supply capability chasing too little demand growth."

Similarly, Nick Vafiadis, the consulting firm's vice president of global plastics and polymers, delivered a bleak outlook for polyethylene, which is made from ethylene. "These days of milk and honey for the industry are behind us, at least for now," he told the audience.

Half the problem with polyethylene is demand, largely because of a faltering China, Vafiadis explained. He expects 3.5% annual global growth from 2023 to 2028, down from 4.5% in the 5 years before the COVID-19 pandemic. In a market that's more than 100 million metric tons (t) per year, that annual 1 percentage point

differential is about the same as two polyethylene plants' worth of demand.

"China has been an engine for global demand growth," Vafiadis noted. "I won't say that the engine has stalled, but it is certainly running at a much lower rpm [revolutions per minute] than we have seen in the past."

Chinese polyethylene demand growth in recent years has been over 10% annually, representing about 70% of global growth for the polymer. But as the Chinese economy slows, so too will its consumption of polyethylene, sending its growth down to 4.1% annually over the next several years, according to Vafiadis.

"We expect to see a continuing downtrend in economic growth globally in the coming decades."

—Adrian Cooper, CEO, Oxford Economics

At the same time, China has been adding a "phenomenal" amount of capacity, Vafiadis said: it added about 3 million t last year and is expected to add nearly 9 million t between 2023 and 2025. In just 4 years, the country will have expanded polyethylene capacity by 48%.

North America, which still enjoys some of the lowest ethylene and polyethylene costs in the world because of abundant natural gas resources, has also been adding capacity: some 4 million t per year since 2021.

It will take 2–3 years for demand to expand enough to absorb all this extra polyethylene output. Until it does, Vafiadis expects global operating rates to drop to 80%, the lowest levels in almost 4 decades. "The bottom line is that we expect to see pressure on prices and margins for the next several years," he said.

Polypropylene, the other major polyolefin, is in even worse shape. In a presentation, Joel Morales, vice president of global plastics and polymers at Chemical Market Analytics, said that overbuilding has created a capacity excess in the global market of greater than 14 million t.

Operating rates for polypropylene plants will be around 78% through the end of the decade. "Is there light at the end of the tunnel? It's a long tunnel," he said.

"We're definitely in a down cycle, and it's a pretty ugly down cycle," Emma Lewis, Shell's senior vice president of chemicals and products for the US Gulf Coast, told the audience in a group discussion. "Demand is not great right now. The reality is that we're seeing a bit of a double slump where demand is kind of off, and there's oversupply as well."

And while the industry contends with a downturn, it must also manage customer demands for sustainability. Chemical companies have been increasingly engaging in projects to reduce carbon emissions and recycle plastics. But after a few years of plunging into such initiatives, they are starting to take a sober look at the costs and potential returns.

"Ultimately, decarbonization, sustainability has to be profitable for all of us. We have shareholders, and we have to deliver returns," Lewis said.

She wondered if the market for sustainable products isn't as vibrant as it once seemed. Shell has been running sustainable feedstocks, such as fats and pyrolysis oil made from plastics, at its petrochemical complex in Norco, Louisiana, for 2 years.

"A lot of the consumer goods companies, if you go back a couple of years, were very aggressive about the targets for green products," Lewis said. "And when you are actually able to make them and you tell them what the price is that is associated with those products, they are kind of less than enthusiastic."

Lewis did praise the US government's incentive program for sustainable materials, such as the Inflation Reduction Act, which established tax breaks for carbon capture and storage. "They are allowing us to do some larger-scale things, which as an industry we probably would be more hesitant to do without those financial incentives," she said.

But those incentives have their skeptics. One is Jim Teague, co-CEO of Enterprise Products Partners. His company operates 50,000 mi (80,000 km) of pipelines and exports 2 million barrels per day of products including ethylene and crude oil.

"At Enterprise, we're not going to build a business on government subsidies," Teague told the gathering. The company is working with Occidental Petroleum on carbon dioxide transport, but it isn't looking for the tax breaks. He said, "All we want is a fee," just like it gets from transporting any other product.

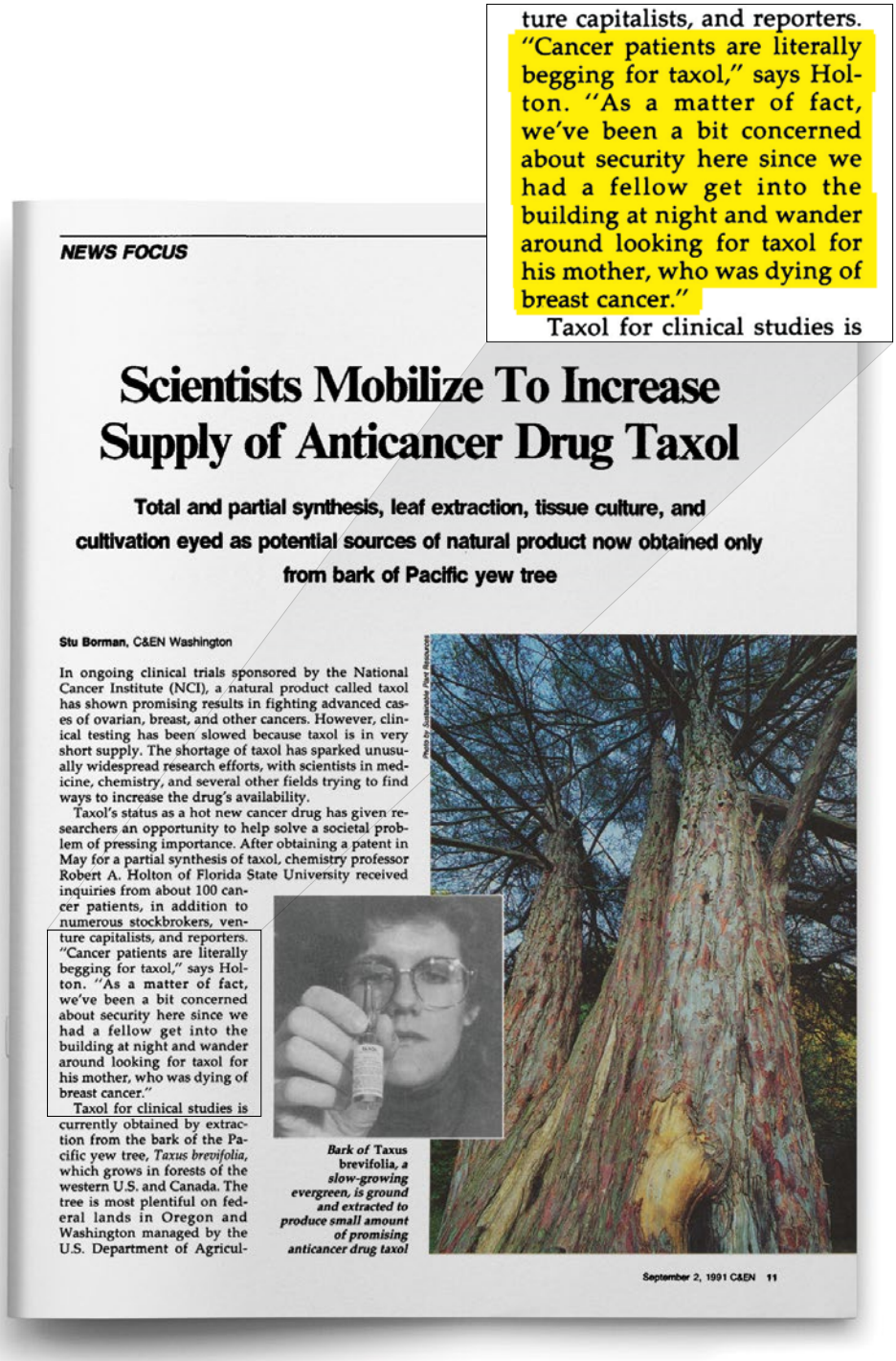
The economics for schemes like carbon capture and storage work only because of government subsidies, Teague said. "You got people coming out of the woodwork trying to get government money," he said.

Teague's remarks prompted seemingly sympathetic chuckles from the audience. An issue that the chemical sector will likely address over the coming years is whether, as times become lean, it will pursue sustainability with the same alacrity that it did when it made hefty profits. ■

From the archives:

The 1990s

A look back at how C&EN covered noteworthy events in chemistry over the past 100 years



ture capitalists, and reporters. "Cancer patients are literally begging for taxol," says Holton. "As a matter of fact, we've been a bit concerned about security here since we had a fellow get into the building at night and wander around looking for taxol for his mother, who was dying of breast cancer."

Taxol for clinical studies is

NEWS FOCUS

Scientists Mobilize To Increase Supply of Anticancer Drug Taxol

Total and partial synthesis, leaf extraction, tissue culture, and cultivation eyed as potential sources of natural product now obtained only from bark of Pacific yew tree

Stu Borman, C&EN Washington

In ongoing clinical trials sponsored by the National Cancer Institute (NCI), a natural product called taxol has shown promising results in fighting advanced cases of ovarian, breast, and other cancers. However, clinical testing has been slowed because taxol is in very short supply. The shortage of taxol has sparked unusually widespread research efforts, with scientists in medicine, chemistry, and several other fields trying to find ways to increase the drug's availability.

Taxol's status as a hot new cancer drug has given researchers an opportunity to help solve a societal problem of pressing importance. After obtaining a patent in May for a partial synthesis of taxol, chemistry professor Robert A. Holton of Florida State University received inquiries from about 100 cancer patients, in addition to numerous stockbrokers, venture capitalists, and reporters. "Cancer patients are literally begging for taxol," says Holton. "As a matter of fact, we've been a bit concerned about security here since we had a fellow get into the building at night and wander around looking for taxol for his mother, who was dying of breast cancer."

Taxol for clinical studies is currently obtained by extraction from the bark of the Pacific yew tree, *Taxus brevifolia*, which grows in forests of the western U.S. and Canada. The tree is most plentiful on federal lands in Oregon and Washington managed by the U.S. Department of Agricul-

Photo by Sustainable Plant Resources

Bark of Taxus brevifolia, *a slow-growing evergreen, is ground and extracted to produce small amount of promising anticancer drug taxol*

September 2, 1991 C&EN 11

Perhaps the biggest challenge of organic synthesis in the 1990s was finding a route to produce significant quantities of paclitaxel, also known by the trade name Taxol. The compound, extracted from the bark of the Pacific yew tree, showed promise back in the early 1960s as an anticancer compound. And in the 1970s, chemists worked out the structure of the drug and a possible mechanism that allowed it to slow cancer cell growth. But by the 1990s, the exotic origin of paclitaxel proved to be a serious impediment to clinical trials and subsequent commercialization. C&EN reporter Stu Borman, in a 1991 cover story, explains the dilemma: "Based on current bark-extraction procedures, NCI [the US National Cancer Institute] estimates that it takes about three trees to provide enough drug to treat one cancer patient. In addition, the trees must be killed to harvest the bark." Producing paclitaxel from the yew trees would be a considerable environmental burden. Moreover, the complicated structure of the molecule didn't yield to organic synthesis easily. Scientists investigated analogs of the molecule that might work about as well, alternative sources of paclitaxel, paclitaxel production via a biological route, and partial synthesis based on more plentiful biological precursors, and they even attempted full synthesis. All these routes met with some success, but a partial synthesis based on a molecule extracted from the needles of the more common and fast-growing English yew shrub won out for Bristol Myers Squibb's early commercialization of Taxol, which became a blockbuster drug. In the aughts, this route was supplanted by a plant cell fermentation process.—ALEX TULLO

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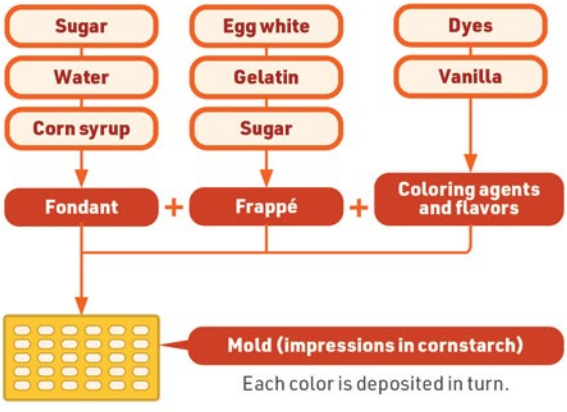
The chemistry of candy corn

PERIODIC GRAPHICS

Confectioners produce around 9 billion pieces of candy corn every year, according to the US National Confectioners Association. Here we look at what candy corn is made of and the chemistry behind its vibrant colors.

How is candy corn made?

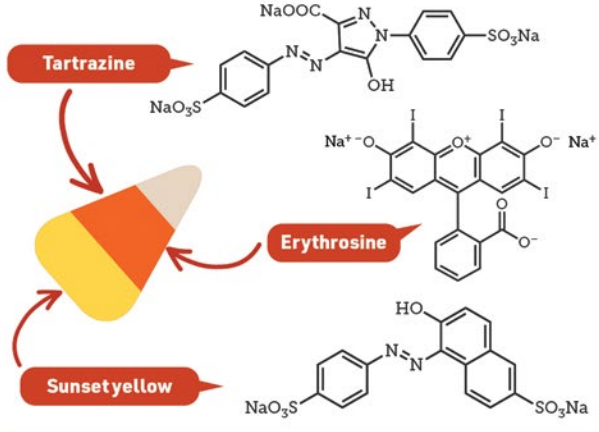
Candy corn is a type of candy called a mallow cream. Manufacturers make candy corn by combining fondant with frappé (a marshmallow-like ingredient), coloring agents, and flavors.



Cornstarch removes moisture from the candies as they dry. Manufacturers then put the dried candy corn into a metal tumbling pan and coat it in shellac wax for a shiny appearance.

The colors of candy corn

Candy corn's colors come from food dyes. These include the azo dyes tartrazine (yellow no. 5) and sunset yellow (yellow no. 6).



Erythrosine (red no. 3) is another dye that candy corn confectioners often use. Manufacturers have also created alternative candy corn, which is colored with turmeric and β-carotene instead of synthetic dyes.

Is this a golden age of small-molecule drug discovery?

With innovative tools and techniques, it's an exciting time for medicinal chemists building new drugs

LAURA HOWES, C&EN STAFF

Last year, sales of the 10 top-selling drugs were split 40:60 between small molecules and larger, more complicated biologics, according to Drug Discovery and Development. But those numbers are skewed by the huge cost of some biologic blockbusters. On a global scale, around 90% of all drugs sold are small molecules, according to a *Medicine in Drug Discovery* paper (2021, DOI: 10.1016/j.medidd.2020.100075).

Not too long ago, these small-molecule drugs looked as if they were going out of fashion. Advances in biotechnology enabled pharmaceutical companies to cost-effectively generate a range of biologics, such as large peptides, recombinant proteins, monoclonal antibodies, antibody-drug conjugates, fusion proteins, and vaccines.

But organic compounds with low molecular weight—molecules that can be administered orally and can pass through cell membranes to reach intracellular targets—have been a mainstay of the pharmaceutical industry for over 100 years. Rather than fade away, they continue to be an important part of the industry's therapeutic arsenal. In the past 10 years or so, advances in technology, synthetic methodology, and biopharmaceutical research have opened up more opportunities for innovative and creative small-molecule drugs.

In brief

At one stage, small-molecule drugs seemed at risk of going out of fashion, as industry began to favor biotherapeutics. But over the past 10 years, small molecules have made it clear that they aren't going away. New classes of molecules, such as proteolysis–targeting chimeras (PROTACs) and molecular glues, have people excited. So do technologies, such as machine learning and generative artificial intelligence, that are helping drive drug discovery. Today, drug hunters have more ambition to go after difficult targets and to use novel chemistry. And that makes it an exciting time for chemists.

CREDIT: CHRIS GASH

Data from the US Food and Drug Administration show that small molecules continue to play a vital role in the pharmacopoeia. Of the 293 new chemical entities that the FDA approved in 2017–22, 182 were small-molecule drugs.

And drug developers are learning new ways to use small molecules to target disease. The traditional approach to drugging many diseases was to find a molecular key that could fit inside a protein, blocking off part of its 3D shape and inhibiting its activity. Increasingly, researchers are instead using small molecules to covalently bind to proteins or to bring proteins near one another so they can work together.

Rather than losing their attractiveness in the modern world of biological advances, small molecules are having something of a renaissance. There's a buzz and a feeling that medicinal chemists can design solutions for diseases they once would have considered impossible to confront.

New modes of action

Many chemists would agree that there is a renewed enthusiasm for what medicinal chemists can do, even if they wouldn't call it a golden age. Keith Hornberger, who leads a team of medicinal chemists at the biotechnology firm Arvinas, says *golden age* is not the right moniker. "I'd say it's the new age," he says. New uses for small molecules are ones that were never considered 20 years ago and have redefined what chemists think of as druggable.

The biggest change, experts say, is the possibilities opened up by covalent inhibitors and induced-proximity molecules, molecules that go beyond the lock-and-key approach to targeting unwanted proteins.

Covalent drugs can grab hold of reactive amino acids on proteins, even when a suitable pocket, or keyhole, does not exist. One high-profile example is the work of Kevan Shokat of the University of California, San Francisco, and his team. In 2013, Shokat's group found a way for a drug to covalently bind to a cysteine in a cancer-causing mutant of KRas and inhibit the protein. Today, it's not just cysteines that can be targeted but many other reactive amino acid side chains as well.

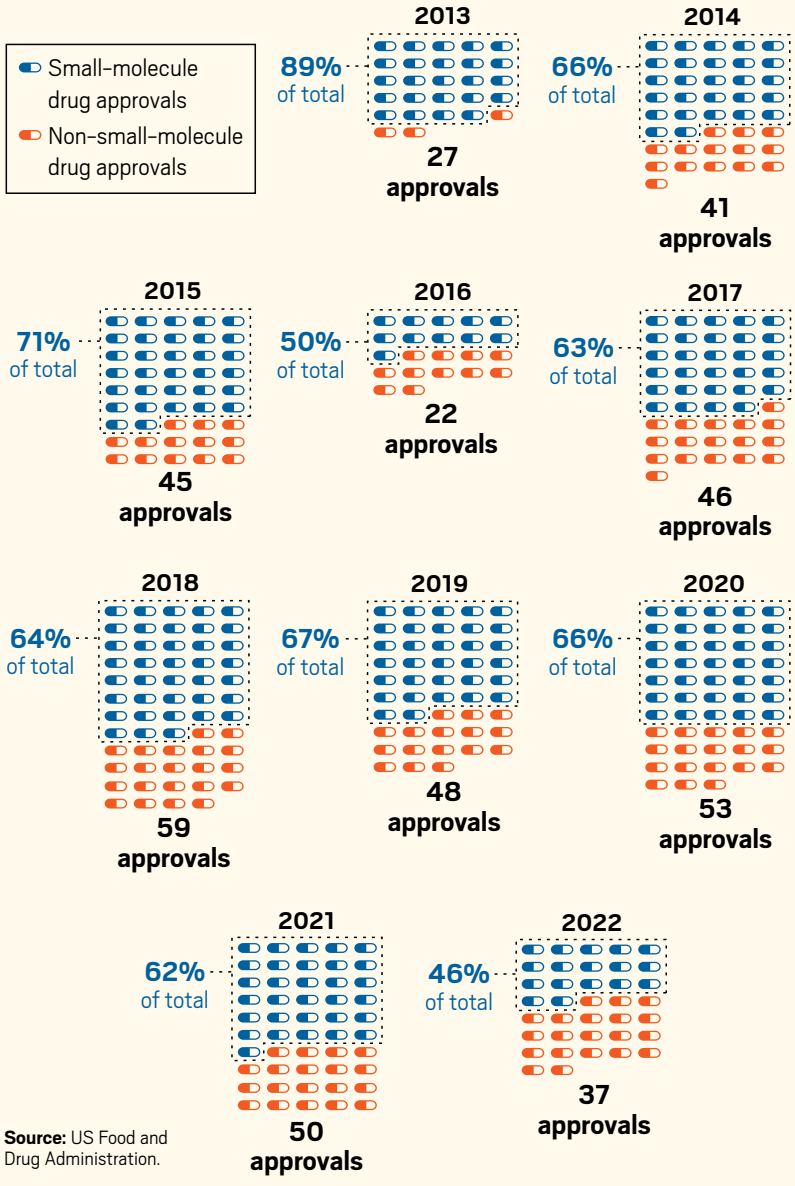
And the most well-known examples of induced-proximity targeting are the proteolysis-targeting chimeras, or PROTACs, first developed by Craig Crews's laboratory at Yale University. These floppy molecules with binders at both ends can draw together two proteins in a cell and add ubiquitin tags to flag the protein of interest for degradation.

Chemists have also since extended the approach to create a host of variants. These include regulated induced proximity targeting chimeras (RIPTACs), which hold on to, stabilize, and inhibit problem proteins, and lysosome-targeting chimeras (LYTACs), which specifically mark extracellular proteins for destruction. These molecules draw together proteins involved in cancer to cause cell death or pull extracellular proteins into the cell for destruction. Chemists can also now create molecules that try different posttranslational modifications, such as deubiquitination, phosphorylation, and acetylation.

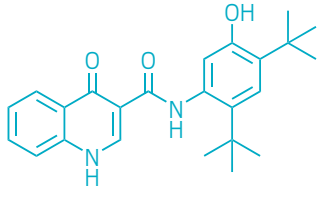
These long molecules might not look like the small-molecule drugs of the past, and they don't have the characteristics that traditionally make a good small-molecule drug. But clinical trials have shown that the molecules can get into cells and effectively treat different cancers.

In the mix

Over the past 10 years, small molecules accounted for almost two thirds of new drug approvals by the US Food and Drug Administration.



Source: US Food and Drug Administration.



Kalydeco (ivacaftor)

Ivacaftor helps keep an ion channel open in people with cystic fibrosis.

No PROTACs have yet jumped over the final regulatory hurdles and won approval. But experts say the induced-proximity concept has proved its naysayers wrong and that it's just a matter of time before such a drug makes it to market.

Meanwhile, molecular glues are smaller ways to induce degradation using ubiquitination. They work by glomming on to one protein to change its affinity for another protein in the cell.

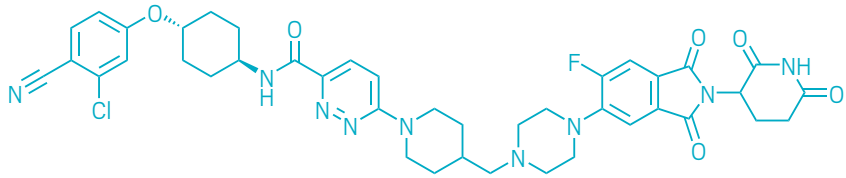
Molecular-glue firms are now signing deals with Big Pharma. For example, Proxygen has inked deals with both Merck KGaA and Merck & Co. to develop molecular glues as degraders in the last year. And Monte Rosa Therapeutics' latest collaboration is with pharma firm Roche to develop glues against cancer and neurological disease targets previously thought undruggable.

Looking back, Hornberger says, these developments came from the careful structural work of chemical biologists like Shokat. This work helped medicinal chemists move away from the lock-and-key paradigm of protein inhibition. Today, many medicinal chemists are looking for different toeholds and ways to alter protein behavior.

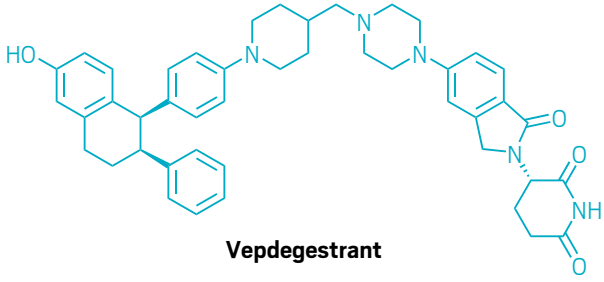
"If you would have told medicinal chemists 15, 20 years ago that we'd be doing chemistry in cells, we would just laugh at that, but that's what we're doing," says Joel Barrish, an industry veteran now at RA Capital Ventures. "I mean, we are basically taking control of the natural regulatory mechanisms."

And it's not just proteins that can be targeted. A key area of small-molecule research is the identification and development of molecular entities capable of targeting RNA. For a long time, human RNA was thought to be undruggable, but researchers now know that RNA assumes 3D structures, creating binding sites for small molecules to interact with.

"My personal opinion is that the next big thing is nucleic acids," says Zoë Waller, an associate professor in drug discovery at University College London. "Targeting nucleic acids was a specialist area, but it is really becoming more mainstream now."



Bavdegalutamide



Vepdegestrant

PROTACs like these from Arvinas contain two binding motifs joined by a linker.

One company working on RNA binding is Arrakis Therapeutics, cofounded by chemist Jennifer Petter. She says the firm is working on multiple approaches for silencing RNA, including binding a regulatory section to modify biology directly, inducing RNA degradation, and even covalently binding the polynucleotide. "Within our walls, we actually have a multimodality small-molecule shop," she says.

How small is small?

But not all those molecules are so small.

Twenty-five years ago, Christopher A. Lipinski created a set of rules, or guidelines, to describe the characteristics of successful small molecules that could be taken orally. Dubbed the rule of 5, they were based on observations that successful drug candidates were often smaller than 500 g/mol in mass and lipophilic. But not all the drugs being developed by medicinal chemists fit those criteria, nor have they ever.

Today, medicinal chemists are making larger and larger molecules. Called beyond-rule-of-5 molecules, these can include bifunctional drugs like PROTACs as well as much larger molecules, such as cyclic peptides. "So what is small anymore?" Barrish asks.

Matthew Disney is a chemist at Scripps Research in Florida who founded Expansion Therapeutics to develop small molecules to bind to RNA structures. He has also noticed the trend toward larger molecules. "FDA-approved drugs are getting larger in size," Disney says. "Industry putting things out in the literature to sort of show that these bigger molecules can be orally bioavailable—I think it just makes the science better for everybody."

Developing those larger molecules requires medicinal chemistry. "I don't think you can make medicine without organic chemists. Both academic and industry," Disney says. "You need the academics to make new methods and industry to deploy them. You need synthetic people in addition to chemical biologists, bioinformatics, and biologists."

And the chemists involved need new synthetic methods to add to their tool kits, according to Matthew Todd, who builds open-source medicinal chemistry projects in his academic lab at University College London. One such development is the skeletal editing techniques that can swap atoms in and out of molecular structures. A recent example can swap a carbon out for a nitrogen in an aromatic ring.

These new synthetic tools give medicinal chemists more options and can help them build on molecules that are shown to bind to a target but perhaps not so well. "Combining these with the prevalence of covalent molecules and the prevalence of degraders opens up things that you can do with molecules," Todd says.

Petter agrees. "If you're willing to take on the larger molecules, this opens up the possibility for some really remarkable, innovative molecular designs," she says.

> "If you would have told medicinal chemists 15, 20 years ago that we'd be doing chemistry in cells, we would just laugh at that, but that's what we're doing."
>
> **—Joel Barrish,** partner, RA Capital Ventures

Technological developments

Industry insiders point out that chemists would not be making these strides without advances in biology and instrumentation. "It's advancements of science, overall," RA Capital Ventures' Barrish says. "It's advancements in chemistry and technologies that really are allowing us to begin to access [targets and biology] that we hadn't been able to do before."

Those technological leaps began in the 1980s with improvements in structural biology, including the development of cryo-electron microscopy and high-resolution X-ray crystallography techniques that allow scientists to visualize biology in atomic detail. But they also involve the bioinformatic screens and assays that can test for places where a protein can interact with another protein.

Genetic screening also helped medicinal chemists' efforts by finding new links between genes and diseases so that drug hunters could identify new drug targets. And perhaps unsurprisingly, Petter says that improvements in genetic sequencing have hugely helped her work developing RNA-targeting molecules.

Another change has been the externalization of services, such as compound library design. The proliferation of contract research organizations and other service firms means that biotechs can buy the chemical expertise they need rather than have to develop it themselves. And those firms can also drive technological innovation—for example, by building DNA-encoded libraries or on-demand compounds.

The services from these molecule-on-demand firms have "really altered things," Todd says. "We've been looking at all the molecules that you can buy, and we're trying to think of ways of expanding that by synthesizing new core building blocks, which you can then decorate with other things that you can buy."

These modular building blocks, and the ways they have been described computationally, also primed researchers to experiment with how to use artificial intelligence and machine learning to help design new drugs. Historically, computational methods helped drug hunters and builders model new small-molecule therapeutics without actually having to synthesize them. That trend has continued with AI-driven start-ups, which are either solely or partially focused on small-molecule drug discovery.

According to a report by BiopharmaTrend, about 45% of all drug discovery start-ups that use or develop specialized AI tools are focused on small molecules, while only about 24% are working to develop biologic drugs. The figures are similar for the cash being invested in these firms by venture capitalists.

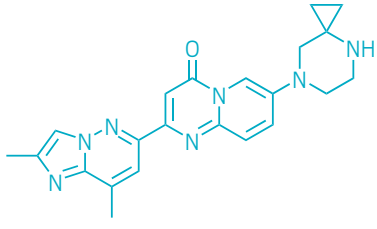
> "I envision there will be types of drugs that will look weird to us because they don't look like what we're expecting."
>
> **—Zoë Waller,** associate professor in drug discovery, University College London

No one expects computers to replace medicinal chemists, but many scientists think AI can help them. Several drug discovery companies with AI-powered platforms have recently progressed molecules to the clinic, sometimes faster and cheaper than might be expected with other techniques.

"That's where the golden opportunity arises: that we can have a renaissance with better small molecules with AI coming in," UCL professor Waller says.

But is it a golden age?

Today, small molecules can do many of the same things that biologic drugs can do and find financial success doing so. For example, among the drugs that treat spinal muscular atrophy are Zolgensma, a one-time gene therapy injection; Spinraza, an antisense oligonucleotide given as an injection into the spine every few months; and, since 2020, a daily small-molecule treatment Evrysdi (risdiplam) given as an oral solution. Evrysdi racked up over $1 billion in sales in 2022, and its sales in the first half of this year grew by 48% from the same period in 2022, while sales of Zolgensma and Spinraza fell.



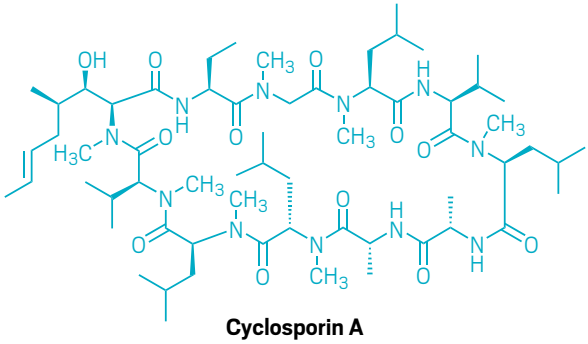
Evrysdi (risdiplam)

Small molecules are often effective and cheap, especially once they come off patent. And they can be easier than biologics to store and take as a patient. As researchers understand more about how diseases and drugs work at a molecular level, older molecules whose mechanisms were perhaps not understood when they were first developed can become useful once more.

The pharmaceutical industry is over 100 years old, and for many, the true golden age of drug discovery ran from the 1940s to the 1970s. Small-molecule drugs from this era, such as antidepressants, antipsychotics, and oral contraceptives, were truly revolutionary. Instead of calling today the golden age, chemists are using different terms: a new golden age, a new age, a renaissance, or a renewal.

Biotech entrepreneur Ethan Perlstein, who is trying to repurpose existing small molecules to treat metabolic disorders, contends that the golden age never ended—people just got distracted by other therapeutic modalities. There is an element of fashion to research, and "*small molecules* is a terrible term for marketing," he says.

As drug hunters gaze into their crystal balls, small molecules are still a key part of the medicinal arsenal. But perhaps more and more, what those molecules look like will change. "I envision there will be types of drugs that will look weird to us because they don't look like what we're expecting," Waller says. "And that's what we need. . . . There's so much potential there." ■



Cyclosporin A

The immunosuppressant cyclosporin A was approved in 1983, before Lipinski published his rule of 5.

Making chemistry accessible to all

MICHELLE CUMMINGS, CHAIR, ACS COMMITTEE ON CHEMISTS WITH DISABILITIES

Recently, I had the privilege of visiting the Renwick Gallery of the Smithsonian American Art Museum in Washington, DC. In the gallery, there are several pieces by modern artists that illustrate loss, grief, and hardship in recent US history, including the impact of racial conflicts and COVID-19. Through their art, each artist conveyed to me their sadness, frustration, and anger about their personal experiences. I found myself thinking about how that relates to people with disabilities and their feelings about lack of accessibility to so many things in society. Their emotions about their need to fight to unlock tools that help bring equity parallel the struggles expressed by the artists in the Renwick Gallery. But it doesn't need to be like this; society can choose a different path to make the world more accessible.

CREDIT: COURTESY OF MICHELLE CUMMINGS

Members of CWD are passionate about chemistry and excited to use our unique skill sets to drive inclusivity throughout ACS membership and beyond.

The tools for an inclusive future

The vision of the American Chemical Society Committee on Chemists with Disabilities (CWD) is "making chemistry accessible to all." Technology has played and will continue to play a significant role as we move toward all people with disabilities being able to participate fully in the chemistry enterprise. Many institutions and companies have not implemented or embraced technologies that can improve equity within their workforce. A key purpose of CWD is to communicate with scientific practitioners about the most effective accessibility technologies and resources for chemistry and chemists.

CWD recently released the fifth edition of the e-book *Teaching Chemistry to Students with Disabilities*, which is downloadable in PDF format from www.acs.org/cwd and is searchable. The resource is much more than just a list of accessibility technologies—it is a 225-page comprehensive manual intended to help start a conversation between a person with a disability and their instructor or employer. The e-book presents some universal design principles that organizations can implement to start moving in the right direction—but the key message is that accommodation conversations must remain specific and intentional for every individual. Each chapter of the e-book includes contact information for its authors, whom readers can contact for consultation.

Improving access to ACS resources

A current goal of CWD is to make ACS journals accessible to all. In the online versions of articles in C&EN and many other magazines, images typically have alternative text (alt text) that describes what is shown. Screen readers read this text aloud. This valuable technology is used by blind and low-vision readers. But did you know that alt text is not the norm for scientific journal articles? Consequently, many journal articles contain visual representations of data and structures that blind or low-vision colleagues cannot access. CWD is working with ACS to rectify this issue and is reaching out to other scientific journals to have them do the same.

CWD also collaborates closely with ACS governance to make other ACS resources more accessible for people with disabilities. Efforts include an accessible presentation guide with information on how to hold inclusive meetings, such as always using microphones, arranging sign-language interpreters, and enabling captions for virtual meetings. Presentation templates will include information about the best font type, font size, and color of slides to use, as well as instructions on adding alt text and other similar information to provide a baseline of universal accessibility.

Showing respect through awards

CWD continues to recognize the need for chemistry professionals with disabilities to have role models and build a community that understands their life celebrations and challenges. The Chemists with Disabilities Travel Award aims to encourage and support undergraduates, graduate students, and postdoctoral scholars with disabilities in presenting talks or posters at an ACS spring or fall meeting. CWD also offers a matching-funds grant of up to $1,000 for accommodation at regional and local ACS events. To apply for the grant, contact cwd@acs.org.

Additionally, CWD is involved in reviewing nominations for the Women Chemists Committee Overcoming Challenges Award. The committee continues to recognize excellence within ACS through its Chemists with Disabilities Inclusion Award, one of the ChemLuminary Awards. This award acknowledges the outstanding efforts of a local section or division that supports the mission of CWD: "accessibility, inclusion, and respect for persons with disabilities in the chemistry enterprise."

Members of CWD are passionate about chemistry and excited to use our unique skill sets to drive inclusivity throughout ACS membership and beyond. We invite all individuals with disabilities working or aspiring to study or work in the chemical sciences to contact us and share their experiences and ask about our activities. Educators, employers, and colleagues may seek support from us or share their own best practices. To contact us, please call the Office of Society Services at 800-227-5558 or email cwd@acs.org.

Views expressed are those of the author and not necessarily those of C&EN or ACS.

ACS celebrates its 2023 Heroes of Chemistry

Industrial chemical scientists are honored for contributions to treating hepatitis C, HIV, and rare blood cancers; creating greenhouse gas alternatives; correcting abnormalities that cause cystic fibrosis; and reducing the side effects of anesthesia

SARA COTTLE, C&EN STAFF

Teams of chemical scientists from AbbVie and Enanta Pharmaceuticals, Honeywell, Incyte, Merck & Co., Vertex Pharmaceuticals, and ViiV Healthcare received 2023 Heroes of Chemistry Awards at a banquet in Alexandria, Virginia, on Oct. 12. The researchers were recognized for advancements in a number of areas: treating chronic hepatitis C, creating non-ozone-depleting greenhouse gas alternatives, developing a versatile treatment for rare blood cancers and graft-versus-host disease, designing a general anesthesia drug with reduced side effects, coming up with drugs that target and correct genetic abnormalities that cause cystic fibrosis, and improving HIV treatment.

Now in its 27th year, the Heroes of Chemistry Awards recognizes scientists whose use of chemistry acts as a service to society. The award is based on three criteria: technical merit, commercial impact, and benefit to humankind. It is the American Chemical Society's most prestigious distinction for industrial chemists and is supported by ACS's Board Committee on Corporation Associates.

"All of us who work in industrial science, and especially you who are being honored, provide new products and innovations, and you've improved all of our lives," ACS president Judith C. Giordan, who has been an industrial scientist her entire career, said at the event. "And that's what really matters."

This year's company teams and their commercialized products are:

▶ ABBVIE AND ENANTA PHARMACEUTICALS: MAVYRET

Hepatitis C is an infectious liver disease that affects approximately 58 million people worldwide.

Teams from AbbVie and Enanta Pharmaceuticals discovered and developed two antiviral agents used in Mavyret, a drug that treats chronic hepatitis C in adults and children. The disease occurs after infection with the hepatitis C virus (HCV); depending on the genetic variation, it can cause short- or long-term effects that can vary in prevalence and aggressiveness.

Steve Elmore, vice president of drug discovery science and technology at AbbVie, described the discovery process of Mavyret as long and difficult. "It was only made possible through the combination of strong collaboration, remarkable persistence, and the courage to push the boundaries of both medicinal chemistry and synthetic chemistry."

The collaboration between the discovery teams at AbbVie and Enanta started in 2006. AbbVie, with a long history in virology, developed and commercialized the drug. The teams had to overcome a number of synthetic challenges before they could achieve a scalable, economical, and robust syntheses of the two active ingredients.

"This was at least a decades-long scientific journey that led to the discovery and enhancement of six distinct molecular entities across two companies with the approval of three HCV treatment regimes—culminating in Mavyret," Elmore said.

Mavyret can be considered the second generation of HCV treatment; it follows Viekira Pak and Technivie, which could treat only patients with certain mutations.

The World Health Organization is focused on eliminating hepatitis globally by 2030, and Mavyret meets the requirements of a treatment to be used on a large scale to eradicate HCV.

"We and others are committed to the eradication of HCV with a goal in the near future," Elmore said. In November 2018, AbbVie and the Medicines Patent Pool, a United Nations–backed public health organization, entered into a royalty-free licensing agreement to accelerate access to the drug in 99 low- and middle-income countries and territories.

"As a result of this and others' work,

ACS president Judith C. Giordan (far left) with the teams from AbbVie and Enanta Pharmaceuticals on stage at the Heroes of Chemistry 2023 awards event

CREDIT: EPNAC.COM (ALL)

ACS president Judith C. Giordan (far left) with the team from Honeywell on stage at the Heroes of Chemistry 2023 awards event

once considered a difficult-to-treat illness, HCV infection is one of the few diseases today that is effectively curable," Elmore said. "In 2021, we reached the remarkable milestone with the cure of 1 million HCV patients by treatment with Viekira Pak and Mavyret."

HONEYWELL: SOLSTICE LBA

In 2007, the Montreal Protocol on Substances that Deplete the Ozone Layer agreed to regulate the consumption and production of close to 100 synthetic chemicals that are ozone-depleting substances. This included an amendment to accelerate the phaseout of hydrochlorofluorocarbons and, later, hydrofluorocarbons (HFCs). To answer this global imperative, a challenge was issued to industry.

"Without the perseverance and tenacity of this team, we wouldn't be here today," said Laura Reinhard, vice president and general manager at Honeywell Advanced Materials.

The Honeywell team developed Solstice Liquid Blowing Agent (LBA)—hydrochlorofluoroolefin-1233zd(E)—a next-generation LBA that replaces HFCs, a group of greenhouse gases, in applications such as refrigeration and insulating foam. Soltice LBA serves as a sustainable replacement for specific compounds with high global warming potential (GWP) with a range of 794–3,220. It achieves high performance and safety with a reduced environmental impact.

Previous alternatives did not thermally insulate effectively and were not energy efficient. Solstice LBA has a GWP of 1. It is nonflammable, non-ozone-depleting, highly insulating, thermally stable, and compatible with existing components; it also has low toxicity.

"Sustainability was not something that the world was talking about yet," Reinhard said. "This innovation was so well ahead of its time, so we needed to get early adopters to come together to allow us to be able to scale up and get leadership buy-in that this was the 'big bet' that they should be investing in. The one big concern that we had was, Is the world ready to pay to reduce climate change?"

Honeywell mobilized a cross-functional team to educate customers, regulators, and industries on the benefits of Solstice LBA.

Solstice LBA received final approval from the US Environmental Protection Agency in 2012. Demand has since grown rapidly—most likely as a result of a variety of rules (e.g., the Kyoto Protocol) implemented worldwide to help curb climate change. In turn, Honeywell has invested over $1 billion in research, development, and new capacity.

As of July 2022, the new Solstice technology discovered and developed in the commercial production process has helped avoid the potential release of the equivalent of more than 295 million metric tons of carbon dioxide into the atmosphere—the equivalent of eliminating the use of 688 million barrels of oil.

When people ask Reinhard why the team was so successful, she responds, "We were shaping the future. We knew this innovation was ahead of its time. . . .We assembled a team that would not accept defeat."

INCYTE: JAKAFI

The team from Incyte led the discovery and development of Jakafi, a versatile drug that can treat certain bone marrow and blood cancers in people who don't respond favorably to other chemotherapy treatments. It also can inhibit janus kinase (JAK), which are proteins involved in vital cell functions such as signaling, growth, and survival. Additionally, the US Food and Drug Administration granted it breakthrough therapy and orphan drug designation for treating graft-versus-host disease (GvHD), which occurs when donated or transplanted tissues attack the recipient's body cells.

"Every single step of this process was a team effort and would not be possible without the dedication and collaboration of our entire organization," said Xiaozhao Wang, head of medicinal chemistry at Incyte.

In 2002, the then-small team at Incyte began investigating JAK inhibitors—work that would continue into the 2010s. The active ingredient in Jakafi was synthesized in 2005 as part of the research and discovery.

The team had set out to develop a drug for patients with life-altering and life-threatening illnesses like myelofibrosis.

ACS president Judith C. Giordan (far left) with the team from Incyte on stage at the Heroes of Chemistry 2023 awards event

Ruxolitinib quickly advanced to Phase I clinical trials. The trials were successful, and the need to scale up ruxolitinib production was recognized. With the team's diligence, Jakafi was approved by the FDA in 2011.

"This was of course an enormous milestone for the company, but also I think I can say this for all the folks out there in the field of drug discovery—that when you see your hard work and your creative ideas finally reach patients and make a difference in their lives, that's one of the proudest moments you can have as a scientist," Wang said.

ACS president Judith C. Giordan (left) with the team from Merck on stage at the Heroes of Chemistry 2023 awards event

MERCK & CO.: BRIDION

The Merck team pursued and proved a novel concept leading to the development of Bridion, a reversal agent, used during general anesthesia, for skeletal muscle relaxants that has reduced side effects.

Skeletal muscle relaxants help facilitate surgical procedures by blocking the physiological effects of neurotransmitters on striated muscle cells. The neuromuscular blockade is reversed to aid in a safe postoperative recovery of the patient. The most widely used reversal agent is an inhibitor that can lead to side effects such as lower heart rate, irregular heartbeat, and narrowed airways to the lungs.

"It makes me very proud to be recognized for the pivotal role of aspiration and creativity in chemistry," said Jonathan Bennett, Merck's vice president of discovery chemistry. "We recognize that it is absolutely essential to the delivery of these goals.

The Merck team came up with the novel idea that chemical encapsulation by an external host molecule of skeletal muscle relaxants helps it dissociate and reverses the neuromuscular blockade. Because this is an indirect action of the neurotransmitters usually inhibited by relaxants, it bypasses the less desirable side effects.

"There was a substantial amount of innovation required in discovery and development to be able to bring that to fruition," Bennett said.

Creating Bridion required chemically modifying sugar molecules known as cyclodextrins. In turn, that required a multidisciplinary chemistry team who could optimize synthetic, purification, and analytical techniques.

The US Food and Drug Administration approved Bridion in 2015, and patient demand for the drug spiked. After a 40% batch failure rate with the first generation synthesis of the chemical, a second generation was developed that focused on stabilizing the supply chain. That action contributed to the broader scientific community. These efforts have resulted in a 100% success rate on a development and commercial scale.

Bridion has been approved in over 95 countries for reversal of the effects of certain neuromuscular blocking agents in adults undergoing surgery and over 106 million vials have been distributed.

James Caldwell, a professor of anesthesia and perioperative care at the University of California, San Francisco, stated that "cyclodextrin-mediated reversal of neuromuscular block is potentially the

Those honored include:

ABBVIE
- Alessandra Mattei
- Brian Kotecki
- Clifford Mitchell
- Daniel Mack
- David Hill
- Jean-Christophe Califano
- Jeffrey Kallemeyn
- John Randolph
- Jordan Stobaugh
- Keith McDaniel
- Kirill Lukin
- Laurie Mlinar
- Mark Matulenko
- Mathew Mulhern
- Matthew Pelc
- Michael Abrahamson
- Moiz Diwan
- Kenneth Engstrom
- Nandkishor Nere
- Pamela Donner
- Rolf Wagner
- Russell Cink
- Seble Wagaw
- Shashank Shekhar
- Shuang Chen
- Timothy Towne
- Warren Kati
- Westin Morrill

ENANTA (In collaboration with AbbVie)
- Guoqiang Wang
- Jun Ma
- Yat Sun Or

HONEYWELL
- Daniel Merkel
- David Williams
- Haiyou (Hugh) Wang
- Hang Pham
- Jim Ling
- Joshua Close
- Mary Bogdan
- Michael Van Der Puy
- Rajiv Singh
- Ryan Hulse

INCYTE
- Bhavnish Parikh
- Dave Meloni
- Greg Hollis
- Haisheng (Jason) Wang
- Jack Shi
- James Rodgers
- Jiacheng Zhou
- Kris Vaddi
- Laurine Galya
- Lixin Shao
- Maryanne Covington
- Mei Li
- Nikoo Falahatpisheh
- Peggy Scherle
- Pingli Liu
- Ryan McGee
- Stacey Shepard
- Swamy Yeleswaram
- Thomas Maduskuie
- Trupti Sheth
- Yanlong Li
- Yong Ni
- Yongchun Pan
- Yvonne Lo

MERCK & CO.
- David Rees
- Jamie McCabe Dunn
- Jonathan Bennett
- Michael Ward
- Ming-Qiang Zhang
- Ronnie Palin
- Yu He

VERTEX PHARMACEUTICALS
- Alexander Abela
- Bérénice Lewandowski
- Billie Kline
- David Siesel
- Fabrice Pierre
- Hari Khatuya
- Jason McCartney
- Jeremy Clemens
- Jinglan Zhou
- Johnny Uy
- Mark Miller
- Sabine Hadida
- Thomas Cleveland
- Vito Melillo
- Yanwei Zhang

VIIV HEALTHCARE
- Chungping Herman Chen
- David Conlon
- John Kadow
- Jonathan Brown
- Martin Eastgate
- Nicholas Meanwell
- Peter Timmins
- Pin-Fang Lin
- Richard Colonno
- Tao Wang
- Timothy Connolly
- Yasutsugu Ueda

CREDIT: EPNAC.COM (ALL)

ACS president Judith C. Giordan (far left) with the team from Vertex on stage at the Heroes of Chemistry 2023 awards event

greatest advance in neuromuscular pharmacology in the last 20 years."

VERTEX: TRIKAFTA

Cystic fibrosis (CF) affects more than 80,000 people around the globe. It is one of the most common severe single-gene disorders, and in 2017 it was reported that the estimated median age of people who died from CF in the US and Europe ranged from 29 to 32 years old.

The team from Vertex developed Trikafta, a combination of three therapies that target and correct the genetic abnormalities that cause CF in 93% of people with the disease.

About 90% of all CF patients in the US have the F508del mutation. In the drug discovery, the team faced an unprecedented challenge in developing a treatment that targeted F508del: inventing small molecules that promote the maturation to the cell surface of a misfolded protein.

The researchers had learned during previous CF drug development that they should find molecules that are both chemically and mechanistically distinct and that, in combination with other Vertex-developed drugs, they could be effective.

"It took 48,000 compounds to discover Trikafta, over 20 years of research," said Mark Bunnage, Vertex's global head of research.

The US Food and Drug Administration approved Trikafta in 94 days, one of the fastest regulatory approvals in history. The team took prior learnings and leveraged synthetic tools to create a product synthesis that has delivered dozens of batches of the drug and only one failed batch. The FDA has described the achievement of this Vertex team as "unique" and "groundbreaking."

About 16,000 patients have been treated with Trikafta. They have seen an 87% reduction in the risk of lung transplant, a 77% reduction in pulmonary exacerbations, and a 74% reduction in the risk of death.

"There are many of hundreds of colleagues who played a key role in getting this medicine all the way through discovery to commercialization, and it really is a true team sport," Bunnage said. "I would also like to thank the true heroes of our CF journey, and that is the patients and the families who have been with this team all the way."

VIIV HEALTHCARE: RUKOBIA

Approximately 1.2 million people in the US have HIV, the virus that, if untreated, can lead to AIDS. In 2022 alone, it is estimated that 630,000 people worldwide died of HIV-related illnesses.

"ViiV Healthcare's commitment is, quite simply, to leave no person with HIV behind, and it's a mission that we've been on for almost 15 years," said Eric Gillis, senior director, head of chemistry at ViiV Healthcare.

The ViiV team discovered and developed Rukobia, a first-in-class attachment inhibitor that prevents HIV-1 from interacting with immune cells. The drug was developed for people who have run out of other HIV treatment options.

The discovery of Rukobia was complex and challenging. It required systematic mapping, the development of new synthetic methodologies, and innovation. A series of more than 15 new synthetic methodologies were developed in this process.

To address certain limitations, ViiV decided upon an oral delivery approach to control the concentration of the parent drug when measured in plasma. The success of Rukobia also required the development of an innovative slow-release formulation.

"People living with HIV have benefited from innovative medicines that have transformed diagnosis of this serious disease from a death sentence to one in which millions can live their lives today on their own terms," Gillis said.

HIV is constantly evolving, meaning that it has the potential of becoming resistant to certain classes of medicine after years of use.

"To stay ahead of this, we need new medicines that can attack the virus in novel ways," Gillis said. "From 2007 until 2020 there were no new drug approvals for oral HIV medicines that could do this, and it would have been longer if it had not been for the incredible team of scientists that we're honoring."

The US Food and Drug Administration approved Rukobia in July 2020. This came after the FDA designated Rukobia a breakthrough therapy and granted it fast-track and priority review status. The drug is now approved in the US and Europe. ■

ACS president Judith C. Giordan (far left) with the team from ViiV Healthcare on stage at the Heroes of Chemistry 2023 awards event

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Chemical & Engineering News (ISSN 0009-2347) is published weekly except for the last week in December by the American Chemical Society at 1155 16th St. NW, Washington, DC 20036. Periodicals postage is paid at Washington, DC, and additional mailing offices.**POSTMASTER:** Send address changes to: Chemical & Engineering News, Member & Subscriber Services, P.O. Box 3337, Columbus, OH 43210.

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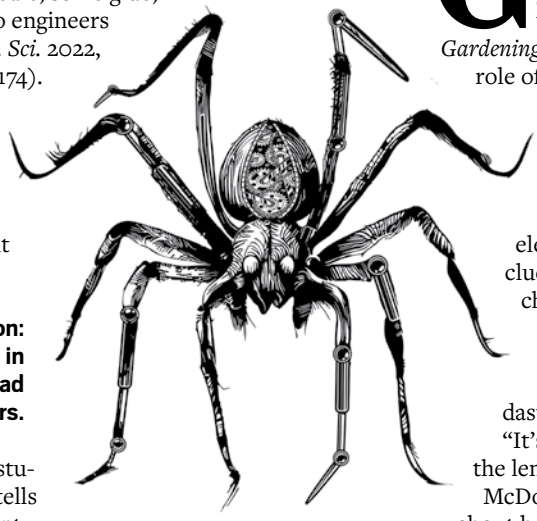
Newscripts

Curating quirky science since 1943

New life for dead spiders

If you've ever wanted to have your own personal army of miniature zombie robots, this story is for you. It turns out that all it takes to reanimate a dead spider is a needle, some glue, and a syringe, according to engineers from Rice University (*Adv. Sci.* 2022, DOI: 10.1002/advs.202201174).

Daniel Preston's lab works on soft robotics that use nontraditional materials—usually that means stuff like rubbers and gels. But in this case, it means spiders.



Reanimation innovation: The next big thing in robotics could be undead spiders.

Faye Yap, the graduate student who led the project, tells Newscripts that the concept originated when she found a dead spider in a forgotten corner of the lab and was curious about why it had curled up. She learned that spider limbs operate hydraulically. From there, it was only a short inductive leap to realizing that it is not only possible, but incredibly easy to turn dead spiders into tiny hydraulic actuators.

Yap and her fellow reanimation researchers euthanized wolf spiders and inserted needles into their backs—secured and sealed with a drop of superglue. That enabled them to open and close the spiders' legs using a syringe to control the pressure. The result was an unconventional yet highly effective mechanical gripper for small, delicate objects, including other spiders.

Spiders are "basically the robotic component that nature has built for us," Preston tells Newscripts. He says that the so-called necrobots his lab makes aren't really so different from mechanical devices made from leather or wood or any other material sourced from formerly living things. Plus, unlike conventional robot parts, spiders are biodegradable.

This research was honored with a 2023 Ig Nobel Prize in mechanical engineering and garnered a mention on *The Late Show with Stephen Colbert*.

Yap and Preston say this is just the beginning of their necrobotic explorations. They're working on a number of improvements to the spider bots, including moving each leg separately and adding wireless controls. And they envision that their reanimation techniques could be easily extended to other crawly critters, such as scorpions.

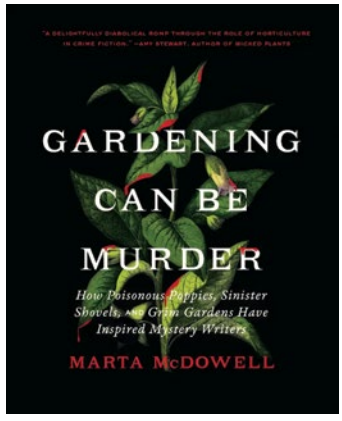
Brianna Barbu wrote this week's column. Please send comments and suggestions to newscripts@acs.org.

Where the bodies are buried

Gardens and the many things inside them are a timeworn trope in whodunits, as avid gardener, mystery reader, and nonfiction writer Marta McDowell explains. Her book *Gardening Can Be Murder* systematically reviews the role of horticulture in whodunits from the 19th century to the present day.

McDowell structured her previous books as biographies of writers and their gardens, but she organizes *Gardening Can Be Murder* around the common elements of the mystery genre. The book includes chapters discussing gardens as settings, characters and authors with a fondness for flora, and of course the myriad ways that garden tools and plants (and the chemical substances within) can be used to commit dastardly deeds.

"It's really a survey of detective fiction through the lens of the botanical and horticultural world," McDowell tells Newscripts. "There are facts about botany and facts about chemistry and facts about the authors."



Garden plots: Marta McDowell combined her lifelong interests in murder mysteries and gardening in her latest book.

Though McDowell is not a scientist by profession—she spent 20 years in the corporate world before devoting herself to horticulture and nonfiction writing—she says she appreciates how the scientific method connects gardening and mystery solving.

McDowell says she delighted in learning and sharing how scientific facts found their way into detective fiction. She gives Agatha Christie as the classic example of a mystery writer who used real chemistry and toxicology—picked up during Christie's work in a pharmacy during World War I—to devious effect in her novels.

Asked what her perfect horticultural crime would be, McDowell says she'd procure spider venom from her neuropharmacologist cousin and paint it on rosebushes for a rival gardener to discover on pruning day.

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