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CHEMICAL & ENGINEERING NEWS
DECEMBER 4, 2023

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ACS Chemistry for Life®

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Quote of the week

"Most people have one [NMR] console, and when something breaks, there's no backup."

—Sophia Hayes, vice-dean of graduate education and a nuclear magnetic resonance researcher, Washington University in St. Louis

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Illustration by Sam Falconer

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CENEAR 101 (40) 1–40 • ISSN 0009-2347

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Volume 101, Number 40

Guest editorial

Alla fine del cammin

This is a guest editorial by **Rick Mullin**, *a senior editor on C&EN's business team.*

The first time I encountered a painting by the Belarusian artist Chaim Soutine, I was repulsed. I had no point of reference. It was a landscape edging so close to abstraction that it crossed the line in a lot of places. The color, the texture . . . incomprehensible, if weirdly familiar. Plus, I'd never heard of him. Soutine? I ran to the nearest Matisse.

Six years later, my biographical novel *Soutine* (written in the Italian poetic form of terza rima) was published.

This passage of devotion had a lot to do with my being a painter and a poet. It took place midway in my journey at C&EN—*nel mezzo del cammin*, as Dante Alighieri put it in the opening line of his terza rima classic, *Inferno*. That journey, which pushed painting and poetry aside to make adequate room for science, ends in a few weeks with my retirement.

None of this would matter here if not for a more recent encounter with the paintings of Soutine at the Paul Kasmin Gallery in New York City. A catalog essay on the 2014 exhibit written by Eric R. Kandel, a neuropsychiatrist who won a Nobel Prize for his work on memory storage in neurons, explores how our brains respond to pictures.

Poor Soutine, I thought. While Kandel's essay provides historical and cultural background on the painter and his art, its hook is science. I couldn't help thinking that the information on cerebral response might interfere with a gallerygoer's discovery of Soutine, pulling attention away from the pictures and deflecting hard-to-place emotions or explaining them away.

I walked away from the exhibit believing that the science-forward portal to the arts was merely fashionable and temporary. I should have known better. Traffic through that door has only picked up, keeping pace with a popular enthusiasm for the science angle on everything.

Last year, for example, the Barnes Foundation in Philadelphia presented an exhibit of paintings by Soutine's roommate in Paris, Amedeo Modigliani, called *Modigliani Up Close*. Several paintings were presented alongside their X-ray images.

And last month, my Google Alerts for articles on the British painter Leon Kossoff delivered stories on a project at London's Courtauld Gallery that measures the impact of art on the brain using electrocardiograph monitors. Paragraphs about a dark, thickly painted landscape by Kossoff—a painter as obscure and magnificent as Soutine—focused on corkscrew brain waves on a computer screen and measurements of confusion and lack of curiosity among participants. Poor Kossoff.

One hesitates to draw conclusions regarding the evolution of our species toward the mechanical and empirical, away from the sublime. On the other hand, there is evidence of a disturbing evolution on an individual level, dating back to the 19th century.

***View of Cagnes*, by Chaim Soutine**

"My mind seems to have become a kind of machine for grinding general laws out of large collections of facts," Charles Darwin writes in his autobiography. "If I had to live my life again, I would have made a rule to read some poetry and listen to some music at least once every week; for perhaps the parts of my brain now atrophied would thus have been kept active through use. The loss of these tastes is a loss of happiness, and may possibly be injurious to the intellect, and more probably to the moral character, by enfeebling the emotional part of our nature."

What I will remember most fondly about my 21 years at C&EN is the leeway that I was given to rage against the fact-grinding machine, to explore the emotional part of our nature, and to engage on topics such as poetry, drama, theater, and the atrophy of education in the humanities with eminent chemists—most memorably Roald Hoffmann and Carl Djerassi, artists both.

These explorations assured me of our capacity to pursue the empirical discoveries of science along with the immeasurable revelations of art. Domains in natural dialogue.

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

CREDIT: SHUTTERSTOCK

Reactions

Letters to the editor

Thorium for nuclear power

This is a response to the editorial of Sept 18, 2023 (page 2).

I agree 100% with the premise that nuclear power can serve our energy needs for the future. However, the use of thorium is a better choice for the smaller modular reactors. Thorium should be strongly considered for nuclear reactors for the US and world energy needs to significantly reduce carbon dioxide emissions. Thorium is more abundant and more safely mined than uranium. Thorium power cannot develop a runaway, uncontrolled reaction like uranium reactors. Thorium reactors are less costly, and permitting should be considerably less of a challenge. Thorium reactor by-products cannot make nuclear bombs since the wrong isotopes are produced. They produce less radioactive waste, and these by-products are safe after about 100 years, versus 24,000 years for uranium reactors. The safe storage of thorium nuclear waste is much less complex. Thorium alleviates the concerns that people have about nuclear reactor safety.

CANDU (Canada deuterium uranium) thorium reactors have already been built. The US has built 1, 3, and 5 MW prototypes and evaluated them, indicating that development work has been significant. Grid connection is not an issue since the electricity is constant. Many nations could be provided safe and reliable electricity using thorium nuclear power.

Now is the time for thorium to be in the energy discussion. Thorium nuclear energy should be an important component for power generation and is safer than uranium for this use. The US and the world need it.

Lawrence Ingram
Greenville, North Carolina

Correction

▶ **July 24, 2023, page 14:** The business news story about the approval of Beyfortus for protecting children from respiratory syncytial virus incorrectly describes the drug. It is an immunization, not a vaccine.

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Concentrates

Chemistry news from the week

Highlights

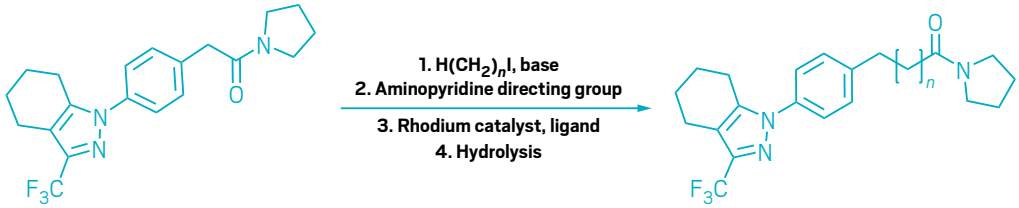
SYNTHESIS

Hook-and-slide extends amides

A new homologation method can expand typically unreactive carbonyl compounds' carbon skeletons by multiple atoms at a time

Extending or trimming the length of a drug molecule's carbon backbone by just a couple of atoms can significantly alter its properties, even if none of the reactive groups in the structure change. So medicinal chemists often want to make several homologs, or versions of a molecule with different numbers of carbons, and compare their activities. Reactions that can change the number of carbons in complex molecules are extremely helpful for making those different versions without requiring too much synthetic backtracking.

Now, researchers at the University of Chicago have devised what they call a hook-and-slide homologation strategy for adding multiple carbons to carbon chains adjacent to amides, all at once. "Ideally, we can homologate as long as we want," says Guangbin Dong, who led the work along with two of his students (*Science* 2023, DOI: 10.1126/science.adk1001).



AMPAR modulator

n **= 1–4**

Amide groups are often used in drug molecules, but it's difficult to make changes to their carbon skeletons because they contain an electron-rich nitrogen that stabilizes the group. That makes it much less reactive than the rest of its relatives in the carbonyl family. Making a homolog of an amide often requires going back to the beginning of the synthesis, Dong says. For more reactive functional groups, typical methods add or remove only one carbon at a time, so generating longer chains means repeating the reaction multiple times. This new method overcomes both those limitations.

To accomplish the transformation, the researchers first "hook" an additional carbon chain to the molecule they're modifying using a base-mediated alkylation reaction at the carbon adjacent to the amide's carbonyl, creating a branch point. They then install a directing group and use it to guide a rhodium metal catalyst to insert into the bond between the carbonyl and the branch point. Once inserted, the metal "slides" to the end of the added chain, taking the amide with it and resulting in a molecule with an extended linear carbon backbone. Finally, the directing group is removed by hydrolysis.

In proof-of-concept experiments, the researchers successfully added extensions of up to 16 carbons to model compounds. No matter how many carbons were added, the catalyst always shuttled the amide straight to the end of the chain without stopping or creating side products. Additional experiments revealed that the kinetics of the reaction discourage it from stopping early, Dong says.

The researchers illustrated the utility of their new method by adding chain extensions to several complex bioactive molecules, including an α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) modulator (shown).

The hook-and-slide strategy can also be used to modify carboxylic acids, though the carboxyl groups have to be temporarily made into amides to make the directing group work. Altering the final hydrolysis step restores the carboxylic acid.

Vittorio Pace of the University of Torino, who published a book about homologation earlier this year, calls the new method "brilliant" and "extremely well conceived." He says it expands not only the scope but also the definition of homologation chemistry beyond single-carbon insertion reactions.

Molecular editing expert Richmond Sarpong at the University of California, Berkeley, says the strategy is "bound to capture the imagination of many scientists that are interested in new ways to modify amides."

The team is working on a number of other improvements to the method, including getting the directing group installation to work under milder conditions. And the technique currently works only if there is an aromatic group on the substrate. "It doesn't bother us too much for now," Dong says. Plenty of drug motifs fit the requirement, but it would be good to eventually find a way around it, he adds.

Dong says he also hopes that multiple-carbon homologation strategies could be developed for other classes of molecules to further build out the list of ways to selectively edit carbon skeletons.—BRIANNA BARBU

GEOCHEMISTRY

Dolomite problem may be solved

Scientists have failed for hundreds of years to show how the abundant crystal grows

Mountains formed of dolomite, a calcium magnesium carbonate crystal, abound. And yet researchers have struggled for hundreds of years to form the mineral in a lab at close to ambient conditions. A new study finds a way to overcome what researchers have dubbed "the dolomite problem" through cycles of undersaturation and supersaturation (*Science* 2023, DOI: 10.1126/science.adi3690).

"They should be really easy to grow," says Wenhao Sun, a materials scientist at the University of Michigan.

Ten years ago, when Sun initially modeled the surface of dolomite, it was "immediately clear" why the crystals wouldn't form, he says. The surface of dolomite had a perfect alternating order of calcium and magnesium atoms. "There's no way that ions can come from solution in perfect alternating order," he says.

A crucial insight came when graduate student and coauthor Joonsoo Kim saw another researcher's video of copper being deposited smoothly under pulses of electricity. This process caused a bit of copper to dissolve before more material was added. The team's simulations suggested that it would take millions of years to grow a dolomite crystal through constant exposure to a supersaturated solution. Sun surmised that fluctuating conditions might help overcome the barriers in growing the crystal's layers.

The team's modeling showed that if a liquid solution was undersaturated—it contained less than the typical maximum amount of calcium and magnesium—this would cause some of the dolomite to dissolve. The surface would reorganize, giving the magnesium and calcium a chance to land in the correct spots. Then, if the surface was exposed to a supersaturated solution, ions could be added. Another cycle of undersaturation could shuttle these ions to the correct spots again.

Next, the researchers placed slivers of dolomite in contact with liquid and used the electron beam from transmission electron microscopy to dissolve the sample. This made a supersaturated solution, from which a bit of dolomite deposited. By repeating the process—which occurred at 80 °C—the team grew hundreds of layers of dolomite within hours. Similar patterns could happen during cycles of rain and drought or in areas that periodically flood.

"They've used some very novel approaches, but they did not form dolomite at Earth's surface conditions," says Cameron Manche, a sedimentologist at Texas A&M University who wasn't part of the work. Manche points out that scientists have known that dolomite grows by dissolution and reprecipitation. But he finds the team's use of state-of-the-art computational approaches, such as density functional theory, and direct observation of the crystal growth, new and impressive. "This is an important stepping stone," he says.

Dolomite forms huge mountains, including a range in northeastern Italy. Yet, researchers have struggled to form the abundant mineral at ambient temperatures.

Using physical and chemical fluctuations could help researchers understand the growth of other minerals, such as magnesite, says Carlos Pimentel, a geochemist at Grenoble Alpes University who wasn't part of the work.

The approach might provide hints about how to grow other tricky crystals, including those used in solar cells or light-emitting diodes, Sun says. Dissolving semiconductor materials a little while they are being grown might help order the materials and improve their performance, he says.—CAROLYN WILKE, special to C&EN

POLYMERS

Tracking polymerization with laser focus

Researchers at Cornell University have devised a new single-molecule microscopy method for studying polymers as they grow (*Nat Chem.* 2023, DOI: 10.1038/s41557-023-01363-2). "We see every monomer," says Peng Chen, who led the work.

Chen and his team accomplish this by tethering every monomer to a masked fluorescent dye that can be unquenched using a laser, then imaged and bleached with a different laser. By timing the laser pulses correctly, the researchers are able to see monomers being added to surface-tethered polymer chains, one by one. They call the method CREATS, for coupled reaction approach toward superresolution imaging.

CREATS can track individual polymers as they grow through hundreds of sequential monomer additions. "In principle, we can follow it for as long as we want," Chen says.

The researchers used their method to study the kinetics of ring-opening metathesis polymerization (ROMP). They found that interactions with the surface slow down the reaction at the beginning of the polymerization.

In a copolymerization with two different monomers, each tagged with a distinct fluorescent label, the team found that the sequence isn't completely random. It's slightly biased toward the next monomer added to the chain being the same as the one before it, leading to repeated segments.

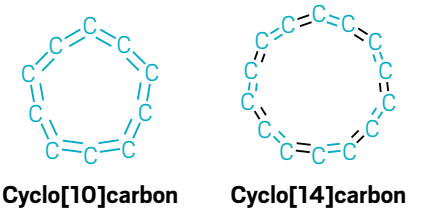
In an email, Hao Shen of Kent State University calls the method "ingenious" and says he expects that many other researchers will want to try CREATS. Chen says that his group has looked only at ROMP processes so far but that the method should work for any chain-growth polymerization mechanism.—BRIANNA BARBU

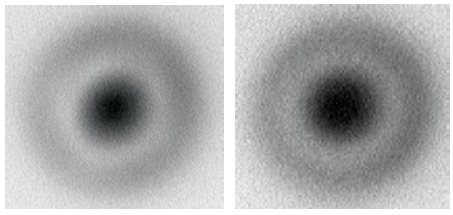
CREDIT: SHUTTERSTOCK

CHEMICAL BONDING

Smaller all-carbon rings

Cyclo[10]carbon's and cyclo[14]carbon's bonds differ from those of larger all-carbon rings





AFM shows that C_{10} has a cumulenic structure, and C_{14} is in between cumulenic and polyynic, as indicated by double bonds of different colors.

Two new carbon allotropes have been zapped into being and imaged using atomic force microscopy (AFM). Researchers at Tongji University led by Wei Xu used on-surface synthesis to make rings composed of 10 and 14 carbon atoms, known as cyclo[10]carbon (C_{10}) and cyclo[14]carbon (C_{14}). Although C_{10} and C_{14} have been studied in the gas phase, this is the first time that chemists have managed to make and characterize them on a surface, an accomplishment that gives deeper insight into their bonding.

To make C_{10} and C_{14}, Xu's team started with fully chlorinated naphthalene ($C_{10}Cl_8$) and anthracene ($C_{14}Cl_{10}$) and used an AFM tip to gradually pluck off chlorines. Removing the chlorines prompted the precursor molecules to undergo ring-opening reactions, which ultimately produced the 10- and 14-carbon rings (*Nature* 2023, DOI: 10.1038/s41586-023-06741-x).

The synthesis differs from that of cyclo[16]carbon (C_{16}) and cyclo[18]carbon (C_{18}), which used more complex precursors. The University of Oxford's Harry L. Anderson, who co-led the syntheses of those larger rings, says in an email that starting with readily available polycyclic aromatic chlorocarbons "will open up the field by making cyclocarbons easier to synthesize."

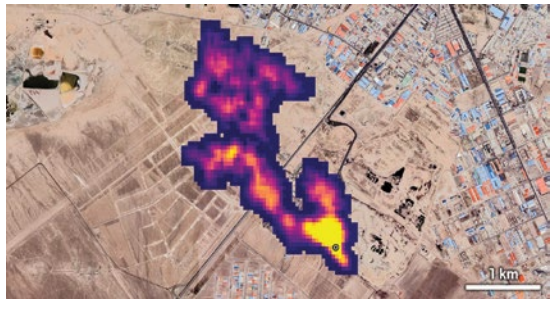
AFM imaging reveals that C_{10}'s and C_{14}'s bonding characters are distinct from their larger all-carbon siblings, C_{16} and C_{18}. Bonds in the larger rings are polyynic, meaning that they alternate between single and triple bonds. C_{10}'s bonds are cumulenic—essentially consecutive double bonds. C_{14} also has only double bonds, but those bonds are not all the same, which indicates that the molecule is somewhere in between cumulenic and polyynic.

IBM Research-Zurich's Leo Gross, who collaborated with Anderson on the syntheses of C_{16} and C_{18}, says it's great to see that C_{10} has the cumulenic structure predicted by theory and that C_{14} is a transition structure between cumulenic and polyynic. "For us experimentalists it is nice that we see cyclocarbons in all these different forms," he says in an email.—BETHANY HALFORD

POLLUTION

Space sensor spots greenhouse gas sources

Instrument for studying desert dust also detects methane and carbon dioxide plumes



An instrument designed to study desert dust detects methane plumes such as this one from a landfill site south of Tehran, Iran.

CREDIT: ADAPTED FROM *NATURE* (CARBON); NASA/JPL-CALTECH (MAP)

In 2022, an imaging spectrometer developed at NASA's Jet Propulsion Laboratory (JPL) was installed on the International Space Station. It was designed to study dust particles from arid areas and understand how their presence in the atmosphere affects Earth's climate. Researchers are now using the instrument to detect greenhouse gas emissions.

In a recent study, they spotted methane and carbon dioxide plumes from oil and gas operations, power plants, landfills, and wastewater treatment facilities in the Middle East and Central Asia (*Sci. Adv.* 2023, DOI: 10.1126/sciadv.adh2391). The strengths of the technology are its fine-scale mapping capabilities and wide geographic coverage, says Andrew Thorpe, a research technologist at JPL and the study's lead author.

The instrument captures images of Earth from space at a resolution of 60 m per pixel, scanning strips of land as the space station orbits the planet and covers an area about the size of South Africa every day. Such high resolution is necessary to detect plumes that are typically less than 1 km long and that contain high concentrations of methane and CO_2. Instruments mounted on aircraft often provide these measurements, but their coverage is limited by how far and how often they can fly. These surveys can miss emissions that tend to be intermittent.

In the first month of the spectrometer's operation, Thorpe and his colleagues could identify CO_2 plumes from two coal-fired power plants in China that lacked continuous emission monitoring and reporting. They were also able to detect methane plumes from oil and gas operations, landfills, wastewater treatment and power plants in several countries.

"It's an impressive system," says Chris McLinden, an atmospheric physicist at Environment and Climate Change Canada who was not involved in the study.

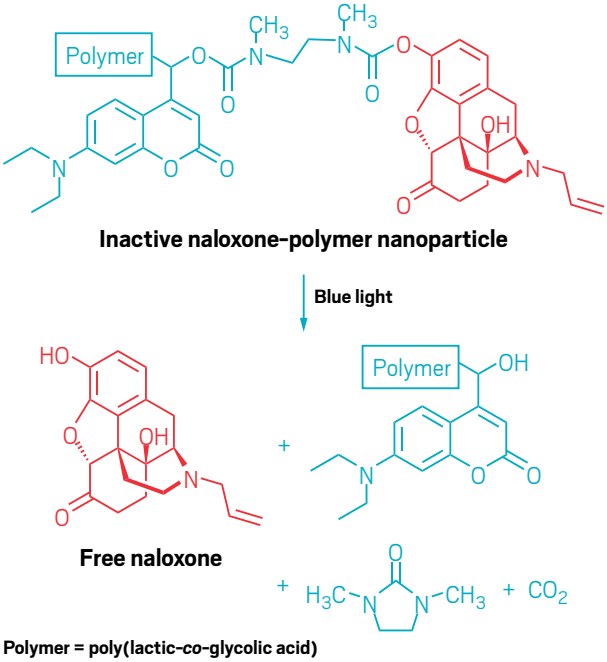
Although JPL's instrument isn't the only space-based sensor detecting point source emissions, "it's one piece of what will hopefully be a much larger constellation of satellites doing more or less the same thing," McLinden says. That will help address key data gaps, he adds.—PRIYANKA RUNWAL

Activating naloxone with light

If it works in people, the new formulation may help those at high risk of overdosing

More than 100,000 people in the US died after overdosing on opioid drugs last year, according to the National Center for Health Statistics. Naloxone, a potent opioid antagonist, swiftly reverses overdoses by binding to the same receptors that opioids bind to, thereby crowding out opioid molecules. Despite naloxone's coming in easy-to-administer nasal sprays, people experiencing an opioid overdose often don't have access to the lifesaving drug at the crucial moment they need it.

Now, researchers have created an inactive version of naloxone that can be administered to someone at high risk of overdosing. When naloxone's effects are needed, the drug can then be activated with a burst of blue light (*ACS Nano*. 2023, DOI: 10.1021/acs.nanolett.3c03426).



Blue light activates the new nanoparticles by releasing naloxone.

Daniel S. Kohane, a biomaterials scientist and anesthesiologist at Harvard Medical School and Boston Children's Hospital who led the work, envisions that people who receive the injection would also carry the light source, perhaps in the form of something like a medical bracelet. "The irradiance that we use is about 100 times ambient light," so the risk of activating the naloxone accidentally is low, Kohane says. He also says the injection site could be covered to prevent that.

The modified naloxone has so far been tested only in mice. But if it works in people, it may be a key addition to existing options, which must be administered after a person has an overdose, Kohane says.

To make the molecule, he and his colleagues started with poly(lactic-*co*-glycolic acid) (PLGA), a biodegradable, biocompatible polymer used for drug delivery. They bound a naloxone molecule to each end of the PLGA with a light-sensitive linker designed to be cleavable with 400 nm (blue) light.

The researchers injected these molecules, formulated as nanoparticles, under the skin of mice that had been given morphine. Shining a blue light on the injection site for 2 min released the naloxone molecules from the linker, allowing the naloxone to reverse the effect of the morphine.

They were able to activate the naloxone to counteract morphine for about a month after the mice received the nanoparticle injection; during that period, they could activate it about three times.

The light activation system is "interesting," but it may not be realistic to expect someone experiencing an overdose to activate it or to tell others to do so, says Thomas Kosten, a psychiatrist and pharmacologist at Baylor College of Medicine. "I do not see a practical clinical application of this technology," he says.

But Sharon Levy, an addiction medicine specialist at Boston Children's Hospital who was not involved with the work, says that although it won't be for everyone, the approach may be important for people at especially high risk of overdosing. "The problem of opioid overdose is so deep that I think we are going to need to combine all kinds of solutions," she says.—ALLA KATSNELSON, special to C&EN

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Golden fleece

This wool glows under ultraviolet light thanks to a natural dye. At the Autonomous University of Coahuila, undergrad Fabiola Ramírez Arismendez and professor Catalina M. Perez Berumen are looking for dyes derived from resources native to northern Mexico. This dye was extracted from the Palo Azul, or kidneywood, tree, whose wood is rich in flavonoids that spontaneously oxidize in air and can fluoresce eerie colors. The project is a collaboration with Escuela del Sarape La Favorita, a technical institution dedicated to handcrafts. The school aims to preserve the local tradition of making woven shawls or blankets known as serapes.—MANNY MORONE

Submitted by Catalina M. Perez Berumen and Fabiola Ramírez Arismendez

DNArt

It might not sound out of the ordinary to say that the colors of this parrot come from DNA, but the DNA in question isn't stored in the parrot's cells. Instead, this image was assembled on a 2D grid with DNA strands tagged with red, green, and blue fluorescent dyes. Chemist Jory Lietard at the University of Vienna and Tadija Kekić, a PhD student in Lietard's lab, created the image by printing a template made from colorless DNA onto this surface, which is about the size of a fingernail. Each of the DNA sequences on the grid have been tailored to bind to the red, green, and blue DNA strands with a particular strength. In this case, the stronger the binding affinity is to each color strand, the stronger the color of each pixel. Lietard and Kekić say that by tweaking the DNA sequences, they can create high-definition images with up to 16 million different colors. The pair demonstrated their technique by reproducing several images, including Polly here.—LAURA HOWES

Credit: Courtesy of Jory Lietard. Read the paper in the "Journal of the American Chemical Society" (2023, DOI: 10.1021/jacs.3c06500).

Silver snake

As part of the lectures he gives to undergraduates at the University of Illinois Springfield, Harshavardhan Bapat likes to trot out this classic demonstration: the displacement of copper metal by silver ions. When Bapat places a coil of copper wire into a solution of silver nitrate, it seems at first like nothing is happening. But after about 10 min, a mane of silver crystals forms as the silver ions in solution and the copper atoms in the wire start switching places. Specifically, silver ions pick up electrons from the copper, and the copper atoms in turn become soluble ions and impart a blue color to the solution. The demo teaches students about the activity series of metals, a ranked order of metals that reflects which ions can displace which metals. But Bapat likes it because it shows students that some chemical reactions don't happen all at once but take time to go to completion.—MANNY MORONE

Submitted by Harshavardhan Bapat

Magic mushroom

Despite appearances, no actual magic or mushrooms are involved in this photo. The vial contains a spiropyran compound dissolved in toluene. The compound starts off colorless, but when hit by ultraviolet light, it isomerizes, forming a merocyanine that is bright blue (visible light or heat can switch the molecule back to its colorless form). When the UV light is shined up from the bottom of the vial for a couple of seconds and then switched off, the merocyanine molecules in solution drift upward and outward in a distinctly mushroomlike plume. The shape probably arises because of local heating and convection within the vial, according to Alexander Shokurov, who captured the image. Shokurov is a postdoctoral researcher in the Biomedical and Mobile Health Technology Lab at the Swiss Federal Institute of Technology (ETH), Zurich. His research focuses on developing materials that change their properties in response to light. The goal is to incorporate these materials into sensors for health applications.—BRIANNA BARBU

Submitted by Alexander Shokurov

CONSUMER PRODUCTS

Symrise loses bid to avoid animal tests

Court judgment renders animal testing ban for cosmetics 'meaningless,' advocacy group says

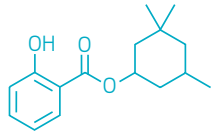
The German specialty chemical firm Symrise will be forced to conduct animal testing on two chemicals used as ultraviolet filters in sunscreens after a European court ruling on Nov. 22.

The chemicals at issue are 2-ethylhexyl salicylate and homosalate, which are both used solely in cosmetic products.

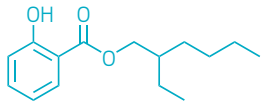
The European Chemicals Agency (ECHA) requested the tests in 2018, but Symrise took the issue to the agency's board of appeal, the first stop for legal disputes with the agency. The appeal was dismissed, and Symrise took its case to the European General Court in 2020.

The long-running dispute highlights the conflict between a European ban on animal testing of cosmetic ingredients and REACH—a database for the registration, evaluation, authorization, and restriction of chemicals—requirements.

The EU's cosmetic product regulation forbids the sale of animal-tested cosmetic products and ingredients. But according to REACH, testing on vertebrate animals must be used if there is no alternative way to demonstrate safe use of chemicals.



Homosalate



2-Ethylhexyl salicylate

Symrise argued that ECHA could not require animal tests for substances used exclusively as cosmetic ingredients because the ban takes precedence over the REACH requirement.

But the court dismissed this argument and ordered Symrise to pay the costs of the case and to conduct the tests requested.

Animal rights groups say the decision opens the door to further animal testing on other cosmetic substances.

Responding to the judgment, Cruelty Free Europe declares the animal testing ban "virtually meaningless."

ECHA says the judgment confirms how it has interpreted the interplay between REACH and the cosmetics regulation.

The agency notes that while the cosmetics regulation aims to protect consumers, it does not address occupational exposure to chemicals.

"To make sure that workers are not at risk, REACH requires safety data on the properties of chemicals they handle, regardless of if substances are used for cosmetics. To protect the health of workers, animal testing may be required under REACH," an ECHA representative says in an email.—VANESSA ZAINZINGER, special to C&EN

Battery companies hit speed bumps

Firms are pausing projects or laying off workers despite the industry's rapid growth

The battery industry is expanding, but a number of companies are pausing projects or laying off staff as they confront the high cost of building big facilities and the difficulty of scaling up new technologies.

Freyr Battery recently announced that it is struggling to scale up a new low-cost battery manufacturing technology licensed from 24M. The company plans to lay off employees and cut spending by 50% while it resolves issues with the process.

Freyr will also minimize spending on its European battery plant and focus on building its facility in Georgia, where generous US government subsidies make the project more attractive. But the company says the US facility will now incorporate conventional technology to start production faster while it tries to master the 24M process.

Similarly, the battery recycling firm Li-Cycle recently laid off workers and paused construction at a facility in Rochester, New York. The company originally expected the facility to cost about $550 million but now says it could cost $1 billion. Li-Cycle says it will likely need additional financing to finish the project and is looking into alternatives. One option is to build the facility in phases.

In Michigan, the battery firm Our Next Energy recently laid off 25% of its workforce. In a statement, the company says the move is a response to market conditions. Our Next Energy's technology combines a cheap lithium iron phosphate battery for everyday use with a powerful lithium metal battery that can occasionally boost range. The firm recently started up pilot production and still intends to scale up.

Michael Sanders, a senior adviser with the battery consulting firm Avicenne Energy, says such speed bumps are normal for a rapidly changing industry in which many players don't have much experience. "There's going to be lots of these value chain stress moments where things didn't quite get put together in the appropriate time frame," Sanders says.

Jill Pestana, who leads the battery practice in North America for the consulting firm Accenture, adds that it's hard for battery companies to navigate the period between receiving a major investment and achieving profitability because it can be long, and many investors are hoping for a quick return. "You really need a solid investor base to carry you through the hard times," she says.—MATT BLOIS

CREDIT: FREYR BATTERY

Freyr Battery is perfecting its manufacturing process at this site in Mo i Rana, Norway.

START-UPS

Flagship launches first UK start-up

Quotient Theraputics will hunt for new drug targets in the genetic diversity of individual cells

A Quotient scientist prepares extracted DNA for sequencing.

CREDIT: QUOTIENT THERAPEUTICS

Quotient Therapeutics emerged from stealth Nov. 21 with $50 million in funding from the life sciences investment firm Flagship Pioneering. Quotient's platform hunts for new drug targets by using sensitive genetic sequencing that explores the genetic variation between individual cells. The firm will have its main base in Cambridge, England, close to three of its scientific cofounders at the Wellcome Sanger Institute.

"There's been a revolution in drug development over the last 20-plus years following the sequencing of the human genome," says Quotient's president, Jake Rubens. But he says that finding new drug targets requires a more fine-grained study of variation on the cellular level.

"Each of us has not one genome, but trillions of genomes inside of each of our bodies," Rubens says. Each cell has an average of 2,000 mutations, he notes. "That means that every single base in our human genome is mutated roughly 30 million times across our body. And there's five times more genetic diversity inside of each of our livers than there is in the germline of the entire world's population."

To seek out these variations, Quotient scientists first identify and isolate individual cells in a tissue that seem to have favorable or deleterious changes. They then sequence the DNA of those cells using technology that can detect low levels of mutation. Computation helps sift out typos that either cause disease or give cells a favorable benefit.

After finding variations that could be drug targets, Quotient starts to look more like any other drug discovery company, Rubens says—though one that is keeping its options open regarding therapeutic areas and drug modalities. So far, he says, the team has found and validated targets in areas including infectious disease, autoimmunity, immuno-oncology, and cardiometabolic disease. The firm is also active in neurodegeneration, rare diseases, and aging, he adds.

Quotient is the first Flagship company with significant research operations outside the US. The Cambridge site currently hosts 20 genomic scientists, who make up the core of Quotient's platform. The translational research group is based in Cambridge, Massachusetts.—LAURA HOWES

ECONOMY

US chemical group expects turbulent 2024

Big consumers of chemicals like automotive and housing will be sluggish

The US chemical industry had a tough 2023, and next year it will have to weather a tougher economic climate, possibly even a downturn.

That was the message delivered by the American Chemistry Council (ACC), a chemical trade group, in its industry forecast on Nov. 28. The ACC estimates that the industry's output, excluding pharmaceuticals, will decline by 1.0% in 2023. The group predicts a modest turnaround to 1.5% growth next year.

"We saw weakness really emerge last year in the third quarter, and it's continued through much of this year," ACC chief economist Martha Gilchrist Moore told reporters on a conference call.

Moore said the weakness was caused by inventory destocking. Consumers worldwide went on a spending spree as countries came out of COVID-19 pandemic restrictions. When demand cooled, retailers and manufacturers realized they had too much inventory and eased their own purchases.

That trend has played out and the industry is recovering, but next year it must contend with an economic slowdown that could morph into a downturn. "There are many reasons to think we're poised for a downturn," Moore said.

For example, she pointed out, people must start paring student loans again, credit card debt defaults are increasing, and consumers have worked through much of the savings they accumulated during the pandemic.

After posting 2.3% growth in gross domestic product in 2023, the US will experience economic growth of only 1.1% in 2024, the ACC predicts.

Some sectors will likely suffer from slow sales due to high interest rates on loans. For example, the auto industry is a major consumer of chemicals such as polymers, with each car consuming, on average, about $4,000 worth of chemical industry products. Carmakers saw a sharp recovery in 2023 and are expected to sell 15.5 million light vehicles in the US, up from 13.8 million in 2022. The ACC forecasts flat sales in 2024.

The trade group anticipates that the housing market will continue to slide. US housing starts dropped from 1.55 million in 2022 to 1.39 million this year, and the ACC expects an even lower figure, 1.35 million, for 2024.

With their subsidies for sustainability and other industrial investments, the US Inflation Reduction Act and CHIPs and Science Act helped boost business investment by 4.1% in 2023. However, higher borrowing costs and slower consumer spending will cool growth in investment to 0.6% in 2024. Further, the ACC expects no growth in the US industrial sector in 2024.

A bright spot for the US chemical industry will continue to be its relatively cheap feedstocks. In the US major petrochemicals are typically made from natural gas; they are derived from oil in other regions like Europe and East Asia.

As natural gas prices in the US have come down over the past decade, chemical companies have built massive petrochemical and polymer projects to exploit that advantage. And polymer exports have indeed been buoyant, increasing 14% through September compared with the same period last year. "This is what everybody was waiting for: competitive US product going out to the world market," Moore said.—ALEX TULLO

–1.0%

The estimated decline in US chemical output in 2023

1.5%

The increase in US chemical output forecast in 2024

Source: American Chemistry Council

LITIGATION

Ohio settles PFAS suit with chemical firms

The state of Ohio has agreed to a settlement with Chemours, DuPont, and Corteva over pollution claims stemming from the manufacture and sale of per- and polyfluoroalkyl substances (PFAS). The chemical firms will pay $88 million for past discharges into the Ohio River watershed from a plant just over the border in West Virginia and $22 million for PFAS claims in other parts of the state. Chemours will pay half while DuPont and Corteva split the other half—an arrangement the firms negotiated in 2021.—CRAIG BETTENHAUSEN

PETROCHEMICALS

Dow green-lights low-carbon cracker

Dow's board has given the go-ahead to a $6.5 billion project that will expand and decarbonize ethylene and polyethylene production at its complex in Fort Saskatchewan, Alberta. Dow will build a new ethylene cracker and downstream polyethylene plants. Linde will construct a plant that will reform off-gases from the cracker to make hydrogen to fire the cracker's furnaces. That plant will capture and store carbon dioxide emissions. Dow also intends to integrate the site's existing cracker into the same carbon capture and storage system. The company plans to start the first phase of the project, centered on the new cracker, in 2027 and complete the second phase in 2029.—ALEX TULLO

ECONOMY

Petroineos to shutter Scotland refinery

Petroineos, a joint venture between Ineos and PetroChina, plans to convert its Grangemouth, Scotland, refinery to a fuel importation terminal. The company says that the refinery will continue running at least until early 2025 and that the facility has been facing market pressures. Petroineos is considering sustainable investments at the site, including building a biorefinery. Due to dwindling supplies of natural gas from the North Sea, Ineos converted the feedstock at its Grangemouth ethylene cracker to ethane imported from the US in the middle of the last decade.—ALEX TULLO

ENERGY

Biobased fuels take flight

The first transatlantic flight to run on 100% sustainable aviation fuel (SAF) landed in New York on Nov. 28. Virgin Atlantic Airways flew a Boeing 787 from London using a jet fuel blend derived by BP and Virent from waste fats and plant sugars. Though the flight was just a demonstration, companies making SAF and renewable diesel are racing to meet a projected boom in biofuel demand. Agriculture giant ADM recently opened a $350 million soybean processing plant in North Dakota as part of a joint venture with Marathon Petroleum that the firms say will make enough vegetable oil for 280 million L of diesel per year. In Kansas, CVR Renewables has selected a Honeywell technology for a plant that will convert more than 3 million L of waste oil per day into SAF. And in California, Chevron has converted a petroleum-fed diesel production line at its El Segundo refinery to yield SAF or diesel from biobased oils. In his remarks commemorating the flight, Virgin CEO Shai Weiss said SAF is too rare and costly today to make 100% SAF flights commonplace. "There is simply not enough SAF, and it's clear that in order to reach production at scale, we need to see significantly more investment."—CRAIG BETTENHAUSEN

RENEWABLES

Maersk to buy green methanol for ships

The shipping giant A.P. Moller-Maersk has signed an agreement to purchase 500,000 metric tons of methanol from the Chinese firm Goldwind to use as fuel for ships. Goldwind is developing a project, to be completed in 2026, in northeast China to make biomethanol and methanol via electrolysis powered by wind. Maersk expects to take delivery of its first methanol-enabled ship early next year.—ALEX TULLO

Maersk is buying methanol for fuel for a new fleet of ships.

CREDIT: A.P. MOLLER-MAERSK

MERGERS & ACQUISITIONS

PCBL to acquire water treatment firm

The Indian carbon black maker PCBL has agreed to acquire Aquapharm Chemicals, a producer of water treatment chemicals, for about $455 million. PCBL says it aims to become a multiplatform global specialty chemical company. Aquapharm makes phosphonates, biodegradable chelating agents, polymers, biocides, and oil field chemicals. It had sales of about $250 million in its most recent fiscal year.—ALEX TULLO

BIOTECHNOLOGY

Boehringer buys Swiss oncology firm

Boehringer Ingelheim has acquired the Swiss biotechnology firm T3 Pharmaceuticals for up to $515 million. T3 has a drug in Phase 1 clinical trials based on technology it developed that uses live bacteria to deliver immune-modulating proteins to cancer cells and tumor microenvironments. Boehringer says it plans to improve long-term remission in people with cancer by combining various immunotherapies, such as the one T3 is developing. Boehringer's venture capital fund was one of the main investors in T3, which will keep its operations in Switzerland.—MICHAEL MCCOY

PHARMACEUTICALS

Novo Nordisk to expand GLP-1 output

Novo Nordisk will invest $2.3 billion to expand manufacturing at its plant in Chartres, France. The project includes finished-drug production for products based on a glucagon-like peptide-1 (GLP-1) agonist, semaglutide, the active ingredient in two of its blockbusters. Last month, the company announced a $6 billion expansion at its plant in Kalundborg, Denmark, which makes GLP-1 products. Novo Nordisk has been straining to keep up with demand for semaglutide. Its Weygovy, a weight loss drug, and Ozempic, for type 2 diabetes, booked sales of $4.5 billion in the third quarter, a 37% increase over the same period last year.—RICK MULLIN

FOOD

Solar Foods gets cash for protein

Solar Foods has raised $8.8 million through a firm, Springvest, which allows individual investors to buy shares of start-ups. Solar Foods makes a protein powder by feeding microbes carbon dioxide, hydrogen produced through water electrolysis, and other nutrients. The company will use the funding to start production in Finland next year; the facility there will house a 20,000 L bioreactor and electrolyzers to produce hydrogen. In May, ADM started collaborating with Air Protein, which has a similar technology.—MATT BLOIS

A Solar Foods bioreactor

PHARMACEUTICALS

Thermo Fisher, Flagship partner on biotech tools

Thermo Fisher Scientific and Flagship Pioneering are forming a partnership to create companies that make biotechnology tools. The partnership will match Flagship's venture formation expertise and Thermo Fisher's background in developing technologies for life sciences research. Launched in 2000, Flagship has spawned 40 companies, including Denali Therapeutics, a drug discovery firm focused on neurodegenerative diseases, and Foghorn Therapeutics, a specialist in medicines targeting genetic mutations in the chromatin regulatory system.—RICK MULLIN

ENERGY

Pilot plant for low-carbon methanol opens

A consortium of German companies and research organizations has opened a pilot plant to produce methanol with low carbon emissions. The system electrolytically converts carbon dioxide into carbon monoxide and water into hydrogen to produce synthesis gas; a catalyst developed by C_1 Green Chemicals is then used to make methanol from the gas. The partners say methanol can be used as a fuel for container ships.—MATT BLOIS

START-UPS

Vivodyne launches for lab-grown organs

Vivodyne has launched with $38 million in seed funding, led by the investment firm Khosla Ventures, to discover and develop drugs by testing them on lab-grown human organs. The Philadelphia-based biotechnology firm was founded by University of Pennsylvania bioengineers Andrei Georgescu and Dan Huh. Vivodyne says it has created more than 20 types of human organs on which it can test drugs, mitigating risk before clinical trials. It uses robotic automation to analyze more than 10,000 human tissues at a time and then trains an artificial intelligence–based model on the resulting data to predict therapeutic efficacy, Vivodyne says.—MICHAEL MCCOY

Business Roundup

Ineos is mothballing a purified terephthalic unit in Geel, Belgium, that has been offline since 2022. The company says that the plant, one of two on the site that makes the polyester raw material, has been increasingly uncompetitive against imports from Asia.

Borealis has agreed to acquire Integra Plastics, a plastics recycler based in Bulgaria. Integra's facility, which mechanically processes polyolefins, was built in 2019.

Sika is increasing capacity in Sealy, Texas, for polymers used in concrete admixtures. The investment is the company's second in Texas in the last 5 years.

BASF will receive a $136 million subsidy from the German government for a water electrolyzer at the its site at Ludwigshafen. The plant will draw 54 MW of power and yield 8,000 metric tons of hydrogen per year when it opens in 2025.

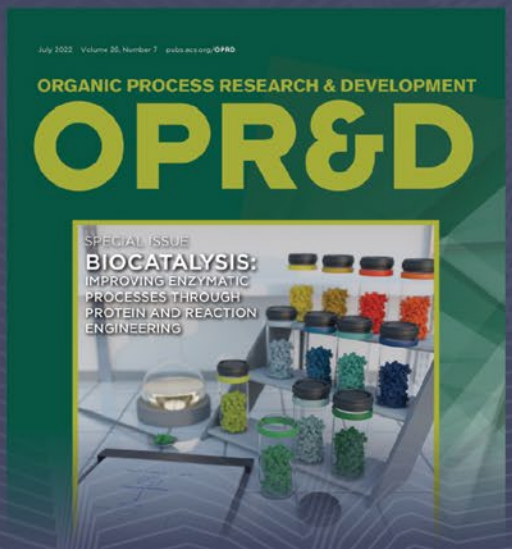
Kemira will add 70,000 metric tons of capacity for ferric sulfate at its site in Goole, England. $Fe_2(SO_4)_3$ and its hydrates are used as coagulants to remove suspended solids in wastewater treatment.

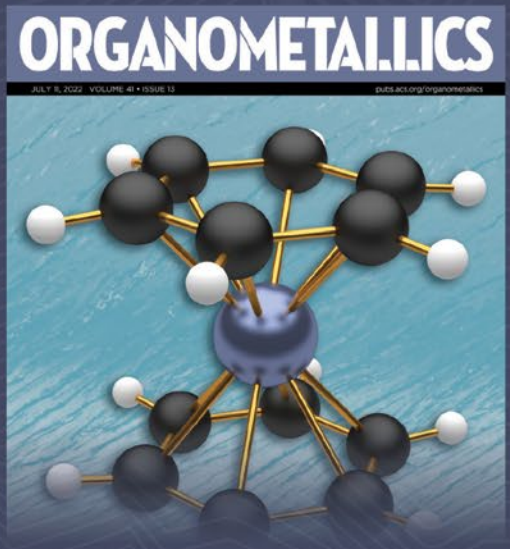
Lhyfe has won the contract for a 210 MW water electrolyzer installation at a port on France's Atlantic coast. The hydrogen project will also include distribution infrastructure.

Ginkgo Bioworks will help ingredient start-up Vivici develop microbial strains that produce dairy proteins. Vivici, which spun out of DSM-Firmenich's venture arm and Fonterra, hopes to start selling a fermentation-derived whey protein next year.

Vink Chemicals has begun construction on a $33 million production facility in Schwerin, Germany. The new plant will provide raw materials for the manufacture of biocides at Vink's headquarters in Kakenstorf, Germany.

CREDIT: SOLAR FOODS





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ETHICS

UAE university breaks ties with nanoscientist

Decision follows article in C&EN describing unethical practices by scientific journal he runs

The University of Sharjah is a private institution in the United Arab Emirates.

The University of Sharjah in the United Arab Emirates has parted ways with nanoscientist Yarub Al-Douri after C&EN published an article revealing that he was running a journal that stole the identities of several prominent scientists, among other infractions.

C&EN reported on Nov. 19 that *Experimental and Theoretical Nanotechnology* (*ET Nano*), a journal that Al-Douri edits, has been publishing studies that are often plagiarized. Many articles list well-known researchers as authors despite their having had nothing to do with the work.

The journal also listed as members of its editorial advisory board people who weren't aware of *ET Nano* when they were notified about the journal. *ET Nano* originally identified Al-Douri as being based at institutions in Turkey, but his listed affiliation changed to the University of Sharjah after he was contacted by scientists whose identities had been stolen.

In a letter to C&EN on Nov. 27, the University of Sharjah's chancellor, Hamid M. K. Al Naimiy, notes that Al-Douri had joined his institution as visiting faculty Sept. 1.

"Upon reading your article, we launched an investigation and found that the evidence provided about Dr. Al-Douri's questioned practices as the journal's editor were substantial," Al Naimiy writes. "As a result, the University of Sharjah has decided to terminate the relationship with Dr. Al-Douri with immediate effect. Meanwhile, we reiterate that the University of Sharjah as an institution has had nothing to do with Dr. Al-Douri's predatory journal."

Al-Douri says he stands by the journal and its content. "This is a respectful journal," he writes in an email.

Michael Fischer, a geoscientist at the University of Bremen who was instrumental in exposing *ET Nano*'s practices, says he is pleased with the outcome. Fischer says the university is "sending the right signal to the scientific community: fraudulent behavior cannot be tolerated and must have consequences."

C&EN emailed Munir Nayfeh, *ET Nano*'s honorary editor and a physicist at the University of Illinois Urbana-Champaign, for a comment but didn't hear back by deadline.—DALMEET SINGH CHAWLA, special to C&EN

SALARIES

Scientists with disabilities paid less than peers

Ableist attitudes in STEM responsible for pay disparities, researcher says

Science, technology, engineering and mathematics (STEM) employers in the US pay doctorate recipients who accquired a disability early in life $10,580 less per year on average than those without disabilities, according to a Johns Hopkins University study (*Nat. Hum. Behav.* 2023, DOI: 10.1038/s41562-023-01745-z). The pay gap is even larger for disabled scientists and engineers within academia, whose average annual salary is $14,360 less than that of their nondisabled peers.

$14,360

The pay gap for scientists and engineers with disabilities within academia

Although many studies have examined the wage gaps for women and people of color in STEM, researchers have mostly overlooked disparities for scientists and engineers with disabilities. Until now, "there's been little understanding and little analyses on gaps that people with disabilities in STEM face," says Bonnielin Swenor, director of the Johns Hopkins University Disability Health Research Center and one of the authors of the study. "It's hard to change what you don't know you need to change."

Many factors could explain the pay disparities the researchers uncovered, but Swenor says most of them arise from the fact that STEM is not designed with disabled people in mind. She explains that inaccessible spaces combined with the ableist belief that disabled people can't succeed in science or academia can limit job opportunities and negatively affect salary negotiations for scientists and engineers with disabilities.

And even after people with disabilities are hired, bias from nondisabled peers and managers can creep in, limiting the chance for career advancement. When Swenor and her colleagues analyzed data from the US National Science Foundation's 2019 Survey of Doctorate Recipients, they found a dearth of disabled STEM professionals among higher-ranking academic roles, such as professors, tenured academics, and university deans and presidents. The researchers believe this fact may account for the larger pay gap in academia.

The study's results are worrying, says Alyssa Paparella, a biology PhD candidate at the Baylor College of Medicine. "As someone who is openly disabled in my early-career stages, I am concerned of how this pay discrepancy will impact my future career," she writes in an email.

Alleviating the pay disparities will require collecting more data, Swenor says. "It's hard to advocate for change when you don't have evidence to substantiate that change."—KRYSTAL VASQUEZ

CREDIT: NOURA BOUSH/WIKIMEDIA COMMONS

This NMR at Washington University in St. Louis was one of the last sold by Agilent Technologies.

CREDIT: MANMILAN SINGH/WASHINGTON UNIVERSITY IN ST. LOUIS

ANALYTICAL CHEMISTRY

The challenges of working with legacy NMRs

Nearly a decade after Agilent stopped making the instruments, researchers work to keep old systems running

CELIA HENRY ARNAUD, SPECIAL TO C&EN

In 2014, Agilent Technologies announced that it would stop selling nuclear magnetic resonance systems. Agilent, which had acquired its NMR rival Varian in 2010, continued to fulfill existing orders, so the last of its systems wasn't installed until 2016. The owners of NMR spectrometers manufactured by either firm now face an uncertain future.

Agilent says it has no plans to stop supporting the instruments, but customers know that they're living on borrowed time: when the company decides to leave the field completely, they will face the choice of maintaining the systems themselves, finding third-party companies to provide service, or upgrading their systems with newer control consoles.

NMR systems are core tools for research chemists. In proton NMR spectroscopy, samples are placed in a spinning probe in a strong magnetic field—typically between 400 and 900 MHz. The nuclei of hydrogen atoms in the sample align with the magnetic field. To detect the atoms, the sample is subjected to electromagnetic pulses. The pulses perturb the alignment, an action that causes emission of electromagnetic waves. These carry information about the chemical environment of each of the hydrogen atoms, which makes it possible to distinguish one bonding arrangement from another and deduce the structure of the sample molecules.

To function properly, the magnet typically must be cooled with liquid helium. Researchers use a console to control the pulses and detect the nuclear responses.

So far, Agilent's NMR service is going strong. David Rice has been director of the NMR facility at the University of California, Merced, since 2016. He was previously an application scientist at Varian and Agilent. "The UC Merced NMR facility has had a service contract with Agilent for my Varian and Agilent instruments since I joined here," he says. "They've given me excellent advice and come through with parts for me when I needed them."

The High-Resolution NMR Facility at Washington University in St. Louis (WUSTL) is home to one of the last NMR systems Agilent sold. In addition to that 600 MHz instrument, the facility runs four other Varian legacy instruments, according to Manmilan Singh, director of the facility.

Singh still calls Agilent when he needs a part to repair a machine. "The newer instruments, if something goes wrong with them, they definitely have the parts for it," he says. "Some of the older ones, they can find the part for you, but it takes a while sometimes. Then you have to start exploring other avenues."

One avenue is do-it-yourself maintenance. The High-Resolution NMR Facility has multiple defunct Varian systems that researchers mine for parts. Singh is "extremely good with hardware," says Sophia Hayes, vice-dean of graduate education and an NMR researcher in WUSTL's chemistry department. "His skills with NMR hardware are extraordinary. Most people have one console, and when something breaks, there's no backup."

Daniel Holmes, who runs the NMR facility at Michigan State University, takes a similar DIY approach. "Mostly I rely on myself and my years of experience with these systems. I've been doing this for 20-some years, so I know what tends to break," he says.

At both WUSTL and Michigan State, the

NMR facilities stockpile old consoles after upgrades to scavenge them for parts. And they don't keep just their own systems. Some universities give away old consoles when they upgrade because they don't have the storage space. "We will snap them up, so I have a lot of spare parts," Holmes says.

For people looking to keep their existing systems running, user groups can provide advice. After Agilent announced that it was leaving the NMR market, Rice helped organize IVAN—which originally stood for International Varian–Agilent NMR—as a place for Varian and Agilent users to ask and answer questions.

IVAN has since expanded into a general NMR discussion forum; the acronym now stands for Inspiring a Versatile and Agile NMR Community. The group sponsors user meetings immediately before the annual Experimental NMR Conference.

Properly maintained magnets can last for decades. But as control technology improves, an older console can become a hindrance. Users with legacy NMR spectrometers have the option of installing either new or refurbished consoles.

"In a 15-year-old NMR spectrometer, the magnet still has many, many years of life to it," says Jon Webb, the founder and CEO of MR Resources, a company that sells late-model, reconditioned spectrometers, consoles, and magnets. Webb is also one of the founders of IVAN. A customer with such a spectrometer "might choose the path of a reconditioned console," he says. "We would sell them a console new to them, which would be 2 or 3 or 4 years old and would have a significantly lower price point than a brand-new console."

Or people can opt for a brand-new console. JEOL, Bruker, and Q One Tech are the remaining suppliers of large NMR instruments. Earlier this year, JEOL launched a re-consoling initiative for legacy NMRs. "Some of those NMR systems are pushing 20 years old, so the electronics in the computers are getting dated, and failure modes are increasing," says Michael Frey, an emeritus NMR product manager at JEOL who was involved in developing the initiative.

"It's very cost effective to just pull out the console, leave the magnet, and put a new console on it," Frey says. "The large investment is the magnet. The console is, depending on the field, anywhere from 50% down to 20% of the value of the system. So that's a big cost savings." Despite being less expensive than an entirely new system, a new console is still in the six-figure range and can be out of reach for smaller institutions.

For re-consoling, the system is stripped of everything but the magnet. That means removing the old console, shim system, and probes and installing new components. The shim system controls the homogeneity of the magnetic field, and the probes hold samples and contain the electronics used for exciting nuclei and detecting NMR signals.

> "Every research-oriented chemistry department needs an NMR—at least one, if not two."
>
> **—Sophia Hayes,** vice-dean of graduate education, Washington University in St. Louis

"It's like a standard NMR system installation after that, although you're not going through the hassle of having to go through a complete magnet installation," Frey says. "It's usually much quicker, typically less than a week, and you're back up and going with a brand-new system with typically better performance than what you had before, as well as greatly increased reliability."

Not every magnet is a good candidate for re-consoling. "We ask the customers to fill out some documentation because we have to know what the magnet is. They are mechanically different," Frey says. "There are a few very strange magnets that only a couple of versions of were sold." In addition, if a magnet has been quenched or shut down, the likelihood is slim of being able to make it work with a new console.

While researchers deal with the practical ramifications of Agilent's exit, WUSTL's Hayes is considering the broader implications. "I think we might see changes, because what this has shown is that it's like a single-point-of-failure model. We are now in a situation where hardware with very high capital equipment costs is purchased, only to learn that the company may choose not to be in this business within a year or two thereafter," she says.

NMR instruments are unique in their longevity, Hayes notes. "In many cases we have been fortunate as a department to keep them for 20 or 30 years. So what do you do in terms of robust decision-making when the landscape for vendors of such equipment is so uncertain?"

Hayes predicts that in the next decade or two there could be a shift toward benchtop instruments for routine analysis in synthesis labs—both to avoid the large purchases and to circumvent difficulties with the helium market. But until then, she adds, "every research-oriented chemistry department needs an NMR—at least one, if not two."

Celia Henry Arnaud is a freelance writer based in College Park, Maryland.

CREDIT: DANIEL HOLMES/MICHIGAN STATE UNIVERSITY

Old NMR consoles, such as these stored at Michigan State University, can be scavenged for parts.

PEOPLE

C&EN talks with John Moon, retired Freedom House paramedic

Long before naloxone was an OTC drug, he was one of the first people to use it in the field

HARINI BHAT, SPECIAL TO C&EN

Moon worked with the Pittsburgh Emergency Medical Services in the 1980s.

In September, some major pharmacies in the US began stocking over-the-counter naloxone, a nasal spray that reverses opioid overdoses sold under several brand names, including Narcan and RiVive. Although naloxone is now more accessible than ever, the story of how it moved from its original use in operating rooms in the 1960s to a spray that can be administered in the home remains largely unknown to the public.

In the '60s, hospital staff members used the newly discovered drug to alleviate side effects of opioid use, and in the '70s they began giving it to patients after surgery to reverse opioid-involved anesthesia. But the drug was never used outside hospitals until the US's first all-Black paramedics team, the Freedom House Ambulance Service in Pittsburgh, developed and published protocols for using naloxone in the field.

Harini Bhat spoke with John Moon, a former Freedom House paramedic who eventually became assistant director of the Pittsburgh Bureau of Emergency Medical Services, about his firsthand experience administering naloxone starting in 1972. Moon told C&EN about the health-care landscape before doctors recognized naloxone's value in the field and about the paramedics who pioneered its use there to save patient lives. This interview was edited for length and clarity.

What did Narcan look like back in the mid '70s when you first administered it on the streets?

Definitely no Narcan nasal spray back then! We titrated naloxone into an IV bag of D5 [5% dextrose solution] and water and administered it that way. It was used for years in the operating room and the emergency room until Peter Safar, the founder of Freedom House Ambulance Service, put naloxone in our ambulance med kits to reverse opioid overdoses on the streets.

The general rule was to get the patient to the emergency room as fast as you possibly could. Basically that determined whether they lived or died. But, by redesigning the ambulances themselves and

Vitals

- **Hometown:** "Pittsburgh. However, I was born in Atlanta."
- **Most recent position:** Retired as the assistant chief of Pittsburgh Emergency Medical Services in 2009.
- **Education:** Paramedic training, Freedom House Ambulance Service, 1971; master of public administration, Point Park University, 2016
- **Professional highlights:** Working at Freedom House. "I owe that organization a very deep debt of gratitude. I consider myself on this mission of spreading the history of Freedom House as a way to try and repay that debt."
- **Toughest problem you had to solve:** Acceptance by the medical community while working at Freedom House. "During my first intubation in a hospital, everything stopped, total silence, with everyone looking at me. And the reason they were looking is because anytime someone who looked like me [a Black man] came through that door, they had a mop or a bucket."
- **Best professional advice you received:** After I was laughed at by an emergency room nurse, Freedom House medical director Nancy Caroline told me, "If you don't learn to speak the language of the emergency room, no one will ever listen to you."
- **Where do you hope the paramedics profession will be in 20 years?** I hope they're still around! Unfortunately there's a shortage of paramedics, and on top of that there is a very serious diversity issue in the emergency medical services community.
- **Hobbies:** I love to garden. But when I can't get outside, I have a very costly hobby, which is collecting DVDs. I have probably about five or six hundred.
- **If your life were a movie, who would you cast to play you?** A combination of Denzel Washington, Morgan Freeman, and Samuel L. Jackson. If you can find somebody to roll all of them into one person.

CREDIT: COURTESY OF JOHN MOON

fully stocking them with medical equipment and medications, we made them hospitals on wheels. So that overall focus to bring naloxone to the patient—as opposed to the patient coming to the drug itself—was an extension of practices we had already been implementing.

I look at what we did back then and try to compare it to today with the OTC nasal spray formulation. We could control the naloxone dose through titration, which kept you in a relaxed state until we got you to a more controlled environment—the emergency room—unlike using a fixed-dose nasal spray, which can result in a more abrupt overdose reversal and withdrawal symptoms. That's why it's always important to call 911 and seek professional medical help after giving someone naloxone nasal spray. The spray is a short-term solution to a problem, and it's greatly needed, but it does not replace in-hospital treatment.

Moon in January signing a book at a showing of the WQED documentary *Freedom House Ambulance: The First Responders*

When did you get a sense that naloxone was a tool that was needed in the field?

When we first began implementing naloxone in the early '70s in the Black communities of Pittsburgh, the rates of overdoses actually decreased there and increased in White neighborhoods. That's when we knew this worked and began rolling it out across the country.

How hard was it for paramedics and regular citizens to get naloxone in the '60s and '70s, and how did that change over time?

We were actually the only ones using it. No one else even conceived to take naloxone from one location to the next. We had to actually prove that the different procedures and techniques that you were using could be administered by a person that's not trained to the level of a physician.

It wasn't until Freedom House began writing the training manual for paramedics that paramedics began using naloxone across the country. [The manual was published in 1977.]

When the training program was implemented nationwide, administering naloxone became a standard practice among paramedics.

How do you feel about the new OTC designation?

I've seen the change primarily as an improvement. I think it's a very good idea to make it readily available to ordinary citizens.

Years ago, I was part of an organization called Prevention Point Pittsburgh that was a needle distribution site. In a perfect world [syringe service programs] would be something you would frown upon, but you have to look at the purpose behind it: to try to combat hepatitis or another AIDS epidemic.

Naloxone basically is the same way. You're trying to combat a problem that is going to occur, regardless of whether naloxone is used or not. There will always be this risk as long as you have illicit drugs. In that regard, it's a very good practice to make naloxone readily available to your ordinary citizen.

Freedom House Ambulance Service group photo; John Moon is in the second row, center, wearing glasses.

CREDIT: BOB BATZ JR./PITTSBURGH UNION PROGRESS (SIGNING); UNIVERSITY OF PITTSBURGH (GROUP)

What final words would you like to leave the readers with?

One of the things that we have to try to impress upon the general public is that a person who has recently received naloxone should still seek medical treatment. Naloxone has a short half-life inside the body, and the individual could unfortunately fall back into the overdose state.

Also, Narcan's availability at the drugstore is a remarkable progression, but I want people to realize that Freedom House used naloxone to treat overdoses back in 1972. We were a group of Black men, part of a revolution to change the outlook on medical care in the community, much of which we take for granted today. It is not about John Moon so much as it is about the individuals that worked there and the organization itself. I'm just a vehicle that's being utilized to get that point out there.

ACS central science

Harini Bhat is a freelance science writer and digital creator based in San Diego who covers topics at the intersection of science and culture.

A version of this story first appeared in *ACS Central Science*: cenm.ag/naloxonehistory.

Recovery from addiction is possible. For help in the US, please call the free and confidential treatment referral hotline (1-800-662-HELP) or visit findtreatment.gov. Visit the National Harm Reduction Coalition website to find naloxone and other harm reduction resources near you. If you are in another country, call your local emergency hotline. You can find a directory of other helplines for addiction at helpguide.org.

CREDIT: SAM FALCONER

C&EN's YEAR IN PHARMA

2023 saw more readjustments from the pandemic

LAURA HOWES, C&EN STAFF

After several years of disruption and hard work, the pharmaceutical industry has dusted itself off and gotten back to business as usual. The number of drugs approved by the US Food and Drug Administration was certainly back up after 2022's lean year, and drug companies with bulging coffers went on some high-profile spending sprees, snapping up biotechs to help their business development strategy as patent expirations loom.

But what is business as usual? Our post-COVID-19 normality has changed our lives. In 2023, the pandemic-fueled pharma funding bubble also well and truly burst. Beyond the failure of Silicon Valley Bank and rising interest rates, investor sentiment seems to have cooled on biotechnology as a brand. Patients and industry executives are also watching to see how government-mandated price controls may begin affecting the pharma business.

Both smaller biotechs and larger firms, such as Pfizer, Bayer, and GSK, have announced restructuring and job losses in their R&D teams. Some of that was to be expected as part of the readjustments after firms went on hiring sprees with cheaper cash and optimistic outlooks. But for those affected, it's a kick in the teeth as we exit the pandemic era.

Yet start-ups still launched, new drugs were approved, and one molecule in particular came out a winner. Messenger RNA (mRNA) leaped into popular consciousness during the pandemic as mRNA vaccines rapidly came to our rescue. In 2023, the achievements of mRNA leaders Katalin Karikó and Drew Weissman were recognized with the Nobel Prize in Physiology or Medicine. Karikó's tale in particular is one of hard work and challenges followed by the ultimate vindication.

Contents

PHARMACEUTICALS

The FDA ramped up approvals and reconsidered some notable existing drugs

2023 was marked by several first-time approvals, while some previously approved drugs came under scrutiny

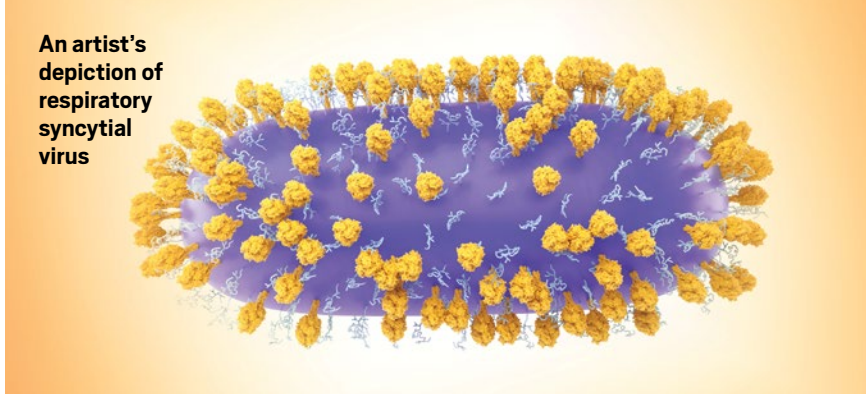
BETHANY HALFORD, C&EN STAFF

If 2022 was a sparse year for US Food and Drug Administration approvals of new molecular entities, 2023 was a return to the pace the agency had achieved from 2017 through 2021. By mid-September, the FDA had already surpassed the 37 approvals it had made in all of 2022 and by mid-November reached 50 approvals.

In addition to approving firsts in prescription drugs and vaccines, the agency approved over-the-counter versions of a birth control pill and naloxone, used for reversing opioid overdoses, for the first time. Also making headlines this year, FDA advisory panels scrutinized an ingredient in popular over-the-counter cold medicines and a trial of a first-in-class cancer drug.

Leqembi was approved to treat Alzheimer's disease

Eisai and Biogen's Leqembi (lecanemab) became the second monoclonal antibody drug to receive accelerated FDA approval to treat Alzheimer's disease on Jan. 6. It then received full approval from the agency—a first for this class of Alzheimer's treatment—on July 6. In 2021, the FDA granted accelerated approval to Biogen and Eisai's monoclonal antibody Aduhelm (aducanumab), but the decision was controversial; many doctors and scientists argued that clinical trials of Aduhelm showed no benefit to patients. Both drugs clear amyloid-β deposits in the brains of people with Alzheimer's disease. But unlike Aduhelm, Leqembi slowed cognitive decline, albeit modestly, in clinical trials of people with early-stage Alzheimer's. The FDA is expected to decide on approval for another monoclonal antibody treatment for Alzheimer's, Eli Lilly and Company's donanemab, by the end of the year.



An artist's depiction of respiratory syncytial virus

CREDIT: NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES/SCIENCE SOURCE

RSV immunizations became available

On May 3, the FDA approved GSK's Arexvy, the first vaccine for respiratory syncytial virus (RSV) for use in people aged 60 and older. Before May was over, the agency also approved Pfizer's Abrysvo, a second RSV vaccine for the same age group. On Aug. 21, Abrysvo also received the FDA's approval for use in pregnant individuals between 32 and 36 weeks' gestation to prevent RSV in babies from birth to 6 months of age. Both vaccines use an RSV surface protein called the fusion glycoprotein to initiate an immune response from the body. The agency green-lit a different type of RSV immunization on July 17 when it approved AstraZeneca and Sanofi's Beyfortus (nirsevimab), a monoclonal antibody that can be given to babies and children up to 24 months in age. Moderna submitted an application to the FDA for its messenger RNA–based RSV vaccine in July. Bavarian Nordic's vaccine, which featured a live virus decorated with RSV proteins, failed to meet all its primary end points, prompting the company to discontinue its RSV program.

Drug store shelves are full of oral cough and cold medicines that contain phenylephrine.

Phenylephrine isn't an effective oral decongestant, according to an FDA panel

In 2022, people in the US spent an estimated $1.8 billion on over-the-counter pills and liquids containing phenylephrine, such as DayQuil and Sudafed PE, according to manufacturer sales data compiled by the FDA. But this September, an FDA advisory panel agreed in a unanimous vote that the ingredient doesn't work as a decongestant when taken orally.

Phenylephrine, which has been used medically since the 1930s, constricts blood vessels. The FDA has deemed it generally recognized as safe and effective, or GRASE in the agency's parlance, for over-the-counter medications since 1976. For decades, though, scientists have argued that the FDA's decision was based on flawed data. They say that when taken orally, phenylephrine is quickly metabolized in the gut to inactive molecules and never makes its way into the bloodstream. Nasal sprays that contain phenylephrine are still considered effective at stopping runny noses.

The drug came into widespread use in oral formulations after the US federal government enacted the Combat Methamphetamine Epidemic Act of 2005. That legislation required pharmacies to keep cold remedies with a different decongestant—pseudoephedrine, which can be easily converted to methamphetamine—behind the counter, and it required consumers to show identification to purchase them. Drugmakers used phenylephrine to fill the public's demand for cold medicines.

The FDA panel reviewed the old data along with the results of more recent clinical trials that showed that oral phenylephrine didn't work, even at doses higher than those recommended on the packaging. The FDA is considering the panel's recommendation and will make the final decision about whether phenylephrine should keep its GRASE designation, but the process could take more than a year.

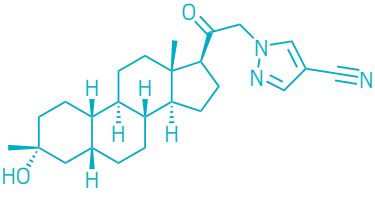
A birth control pill and Narcan became available over the counter

The FDA first approved norgestrel as a prescription oral contraceptive in 1973. Fifty years later, on July 13, the agency approved Perrigo's Opill as a version of this birth control pill that doesn't require a prescription.

In another notable over-the-counter approval, the FDA made Narcan (naloxone), Emergent BioSolutions' nasal spray for reversing opioid overdoses, available to consumers without a prescription on March 29. Previously, advocates had managed to work around the drug's prescription-only status via a patchwork of state laws, standing orders, and collaborative practice agreements among pharmacists.

Zurzuvae got the nod for the treatment of postpartum depression but not major depressive disorder

The FDA granted approval to Sage Therapeutics and Biogen's Zurzuvae (zuranolone) as the first oral treatment for postpartum depression on Aug. 4. Previously approved treatments for postpartum depression have to be injected. Zurzuvae is a neuroactive steroid that modulates γ-aminobutyric acid (GABA) receptors in the central nervous system, thereby calming nerve activity. But the FDA rejected the drug as a treatment for major depressive disorder. That split decision was bad news for both firms, which saw their share prices take a knock. Sage subsequently announced a reorganization that included axing 40% of its workforce.

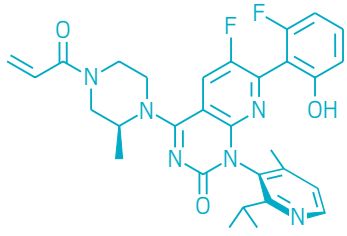


Zurzuvae (zuranolone)

Lumakras study was called into question

A Phase 3 trial that was meant to confirm the data that won Amgen's Lumakras (sotorasib) expedited approval didn't pass muster with a panel of FDA advisers. In October, the panel voted 10–2 that the CodeBreaK 200 trial results could not be reliably interpreted.

In 2021, the FDA granted expedited approval to Lumakras to treat people who have advanced non-small-cell lung cancer driven by the *KRAS* G12C mutation and had previously taken another chemotherapy. Lumakras was



Lumakras (sotorasib)

the first drug to inhibit KRas, a notoriously challenging target.

The FDA required further data to convert its accelerated approval into full drug approval. The study that was intended to provide those data, CodeBreaK 200, showed that progression-free survival was about a month longer for people who took Lumakras compared with people who took docetaxel, a standard second-line treatment for this type of cancer. The study found no difference in overall survival.

But the FDA advisers questioned CodeBreaK 200's results. They cited a high dropout rate among patients in the docetaxel arm of the study, which may have introduced bias. The advisers were also concerned because independent reviews of tumor imaging scans differed significantly from those conducted by the study's investigators.

The advisory panel's conclusion does not mean that Lumakras will be withdrawn from the market, but further studies may be needed. The FDA will make its decision on Lumakras's full approval later this month.

CREDIT: BETHANY HALFORD/C&EN

LEGISLATION

The US got ready for drug price controls

Analysts are split over whether the Inflation Reduction Act will be a boon for patients or a bust for the pharmaceutical industry

BENJAMIN PLACKETT, SPECIAL TO C&EN

David Mitchell has a rare form of blood cancer. In the US, that's not a cheap diagnosis. "My cancer drugs keep me alive, but my disease is incurable because nothing works forever. Currently, my doctors have me on a four-drug combination that carries a list price of more than $960,000 per year," he says. Fortunately, Mitchell benefits from Medicare, a federal health insurance plan available for people 65 and over, so most of that cost is covered by the government. Even so, he still faces an annual bill of about $17,000.

"The Inflation Reduction Act is going to help patients like me," he says. "After 20 years of fighting, the government is finally going to do what the British already do. They're going to negotiate on the prices for the most expensive drugs." Prescription drugs cost roughly 40% more in the US than in Europe, according to analysts at the private bank LGT.

Mitchell is also the president and founder of Patients for Affordable Drugs, an organization that advocates for cheaper prescription drugs and lobbied for the Inflation Reduction Act (IRA) to be passed by Congress, which it was and then subsequently signed into law by the president in August 2022. The implications of the legislation will begin to be felt in the coming years, but some are warning that not all effects will be positive.

The law means that from 2026, Medicare will

CREDIT: SHUTTERSTOCK

haggle directly with drugmakers over the prices of some of its most costly drugs. The US Department of Health and Human Services announced the names of the first 10 drugs earlier this year. The number of drugs covered by the act is expected to reach 60 by 2030. To be eligible for price negotiations, a drug needs to have been approved by the US Food and Drug Administration for at least 9 years if it's a small-molecule drug and at least 13 years if it's a large-molecule drug. The development and rollout of large molecules are more expensive and time consuming than small molecules, which is why they're being granted a longer exemption from price negotiations, but some pharmaceutical industry executives have criticized this distinction and would prefer a longer time for all drugs. The new law will also limit the out-of-pocket expenses for Medicare users to $2,000 per year.

"The Inflation Reduction Act is going to help patients like me."

—David Mitchell, founder and president, Patients for Affordable Drugs

"It's putting price controls on drugs for the first time in the US, and people say, 'That already exists in foreign countries, so what's the big deal?' says John LaMattina, a former president of global research and development at Pfizer. "People don't appreciate the consequences, though. Pharma companies currently invest 25% of their revenues into R&D. That's significant, and that's the industry standard. Companies will have less revenue, and so they'll have less money for R&D."

Less money for R&D will ultimately lead to fewer new drugs in the future, LaMattina says. Using estimates from the Committee for a Responsible Federal Budget—which states that the US government will save $300 billion from the IRA—LaMattina says the legislation would translate to a reduction of $75 billion in R&D spending from the pharmaceutical industry.

The only reason that other markets, such as the UK and the European Union, get away with tighter price controls is because they rely on drug companies' making larger profits from the US to fuel their drug development, LaMattina argues. "Other jurisdictions basically freeload off the US. Should the US go to the UK system, you'd slash R&D by a third or more," he says.

Others share his concerns. "It's going to discourage innovation," says Laura Hobbs, the director of health-care policy at the American Action Forum, a think tank in Washington, DC, that describes itself as center right in its political leaning.

Studies have shown a link between diminished income for drug companies and fewer new molecules coming onto the market. A 2019 report from the Galen Institute estimated that the US

had access to close to 90% of new drugs launched between 2011 and 2018. At the same time, higher-income countries with price-control policies had access to only 47% of the same novel medicines. That doesn't necessarily mean that price control thwarts innovation; it's possible that the authorities in countries with price controls just decided that some new drugs weren't worth paying for.

Mitchell says the new law still provides plenty of opportunity for pharmaceutical companies to make money. First, the legislation covers only Medicare drug purchases, he points out. It has no effect on the price that private insurers pay for medicine. The think tank KFF estimated that Medicare spending accounts for roughly 30% of US prescription drug sales. Second, companies still get to choose the launch price, and, initially at least, only 10 drugs out of thousands are going to be subject to price negotiations.

These arguments irritate LaMattina, however, who says that proponents of the act simultaneously praise how much money will be saved while trying to downplay the impact of lost revenues for pharmaceutical companies. "You can't have it both ways," he says.

> **"Companies will have less revenue, and so they'll have less money for R&D."**
>
> **—John LaMattina,** former president of global research and development, Pfizer

Even putting the question of profits to one side, LaMattina remains unconvinced of the legislation's merits. "In the past, you'd develop a drug for a rare cancer or disease because you get approvals quicker and so you start to generate revenue faster," he says. Once that initial approval is achieved, drugmakers often seek to gain additional clearance to market the same drug for more-profitable diseases. That pattern is less likely to happen under the new system, he argues, because the first approval would start to run down the clock on exclusivity before a drug is potentially eligible for Medicare price negotiations. "This is going to change drug companies' philosophy on clinical trials; they'll wait on results until they can apply for approvals for more-profitable cancers," he says. "That penalizes patients. There are a bunch of unintended consequences."

But for patient advocate Mitchell, price negotiation is just common sense. He believes the warnings from the pharmaceutical industry are exaggerated. "When I hear them say this stuff, it's infuriating to me as a patient," he says. "Medicare already negotiates for everything else it pays for—doctors, hospitals, and tests. All we're going to do is negotiate over 60 drugs at full implementation of the Inflation Reduction Act."

Benjamin Plackett is a freelance writer based in London.

An aerial view shows the damage that a tornado caused to a Pfizer pharmaceutical factory in North Carolina in July.

CREDIT: ASSOCIATED PRESS

PHARMACEUTICAL CHEMICALS

Drug shortages peaked in 2023

Things might be getting better, but the problem is far from over

BENJAMIN PLACKETT, SPECIAL TO C&EN

Ongoing drug shortages in the US reached their highest rates in a decade in 2023, according to the American Society of Health-System Pharmacists. A series of regrettable events conspired to worsen persistent supply chain problems, and survey data show that these shortages are beginning to affect patient care. Chemotherapies and local anesthetics are some of the drugs most commonly in short supply.

"Shortages have definitely felt worse this year," says Erin Fox, an associate chief pharmacy officer at the University of Utah Health who studies drug shortages. Intense pricing competition is partly to blame, she says. "The FDA rates all generic drugs as equal, and that means that they can only compete on price. And many companies will undercut each other."

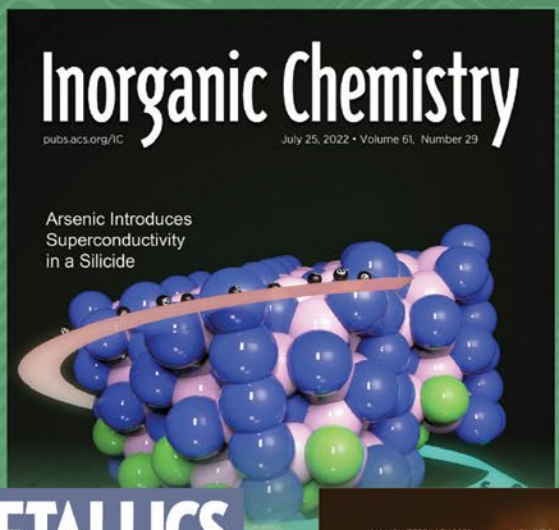
This price competition has two knock-on effects. The first is that the quality of the production line—not the medicine itself—decreases in a bid to save on cost, increasing the risk of a fault and causing delays. According to the US Food and Drug Administration, manufacturing quality issues are the principal cause of recent disruptions. Second, the intense competition to manufacture generics simply drives some firms out of business, further reducing the supply. For example, generics manufacturer Akorn Operating Company filed for bankruptcy in February. "This led to a large number of shortages, as they were the sole supplier of many drugs," Fox says.

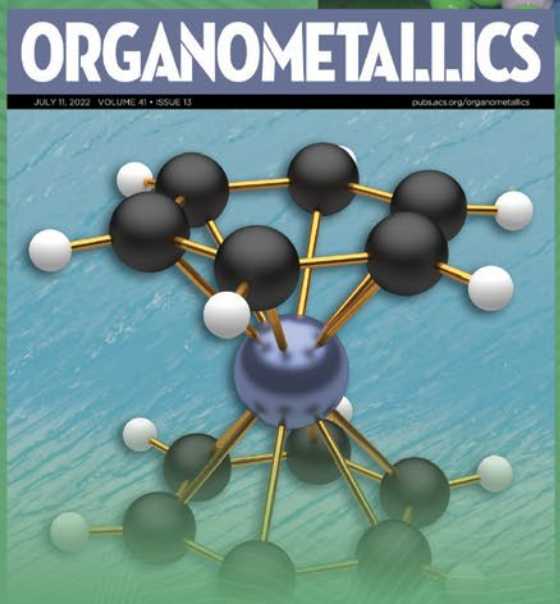
But the economics of the generic-drug market are only part of the picture. In July, Meera Bhavsar, who leads Pfizer's sterile injectables portfolio, had to write to customers to explain how a 130,000 m^2 manufacturing facility in North Carolina had been damaged by a tornado.

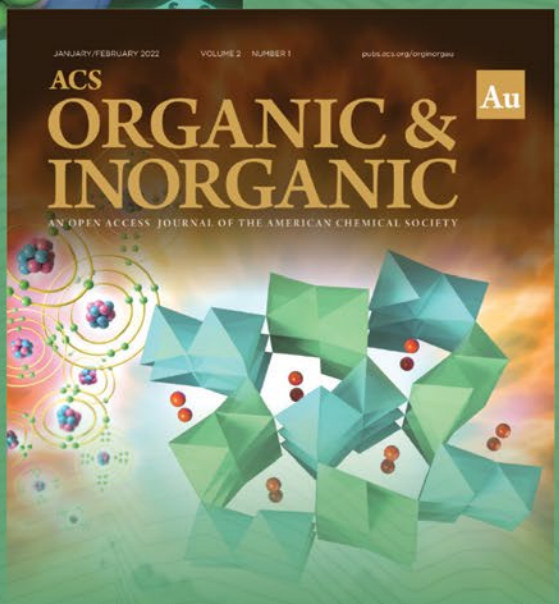
"Luckily the production lines weren't damaged, just the distribution areas and some of the already-prepared products," Fox says. "But this also has stretched some supplies thin."

Shortages are also exacerbated by geopolitical tensions, such as the US-China trade war and Russia's invasion of Ukraine. COVID-19 disruptions also linger. Some of these problems are being resolved, but the underlying issue of manufacturing quality needs to be remedied if shortages are ever going to become a thing of the past, Fox says. "This is a problem that I've been following for over 20 years. While I am always optimistic that progress can be made, I don't think shortages will completely go away in 2024."

Benjamin Plackett is a freelance writer based in London.







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ECONOMY

Biotech woes worsened

Rising interest rates and a dearth of cash slowed the sector's recovery

ALLA KATSNELSON, SPECIAL TO C&EN

If you thought 2022 was bad for biotechnology, this year managed to hit an even lower point.

Capital markets remained largely closed, leaving companies gasping for cash, and steadily rising interest rates have dragged down valuations. The SPDR S&P Biotech ETF (XBI), an index that tracks biotech companies, has fallen 12% since the start of the year. Though XBI's value is a hair's breadth higher than it was at its lowest point in 2022, its performance stands in contrast with the S&P 500 Index, which rose more than 18% during the same period.

As a result, the industry largely hunkered down in survival mode in 2023. Many companies were forced to undertake serious belt-tightening to stay afloat. As of Nov. 28, 173 companies had announced layoffs, compared with 119 in all of 2022, according to Fierce Biotech. Twenty-seven companies have shuttered completely this year, compared with just 7 in 2022.

Tellingly, the successes of GLP-1 agonists—a new class of medicines for diabetes and weight loss—have dominated the pharmaceutical news this year, but these successes have been for Big Pharma, not biotech.

In investor calls in late October and early November, "universally, the sentiment was the absolute worst it's ever been in biotech," says Michael Perrone, a biotech specialist at Baird. "I would say this year there was a little more despair" simply because the slump has dragged on for so long.

Much of the biotech sector's pain reflects the ongoing correction from the wild highs experienced during the pandemic, experts say. "We are still living through the hangover from the free-money party we saw in 2020 and 2021," says Barbara Ryan, senior adviser for life sciences at the professional services firm EY.

That glut of cash drove investors to fund risky research programs that had slim chances of success, Perrone says. Too many companies went public too early with not enough experienced managers to run them. "We needed some of these companies to go away," he says. "It's essentially culling the herd—and the herd getting stronger by losing its weakest members."

The number of initial public offerings (IPOs) of stock this year reflects this trend: 24 US biotech companies have notched IPOs as of Nov. 15, according to the business intelligence firm PitchBook. That's on par with the 25 IPOs in all of 2022 but well off the 109 in 2021.

Poor performance

How key indexes fared between Jan. 3 and Nov. 28

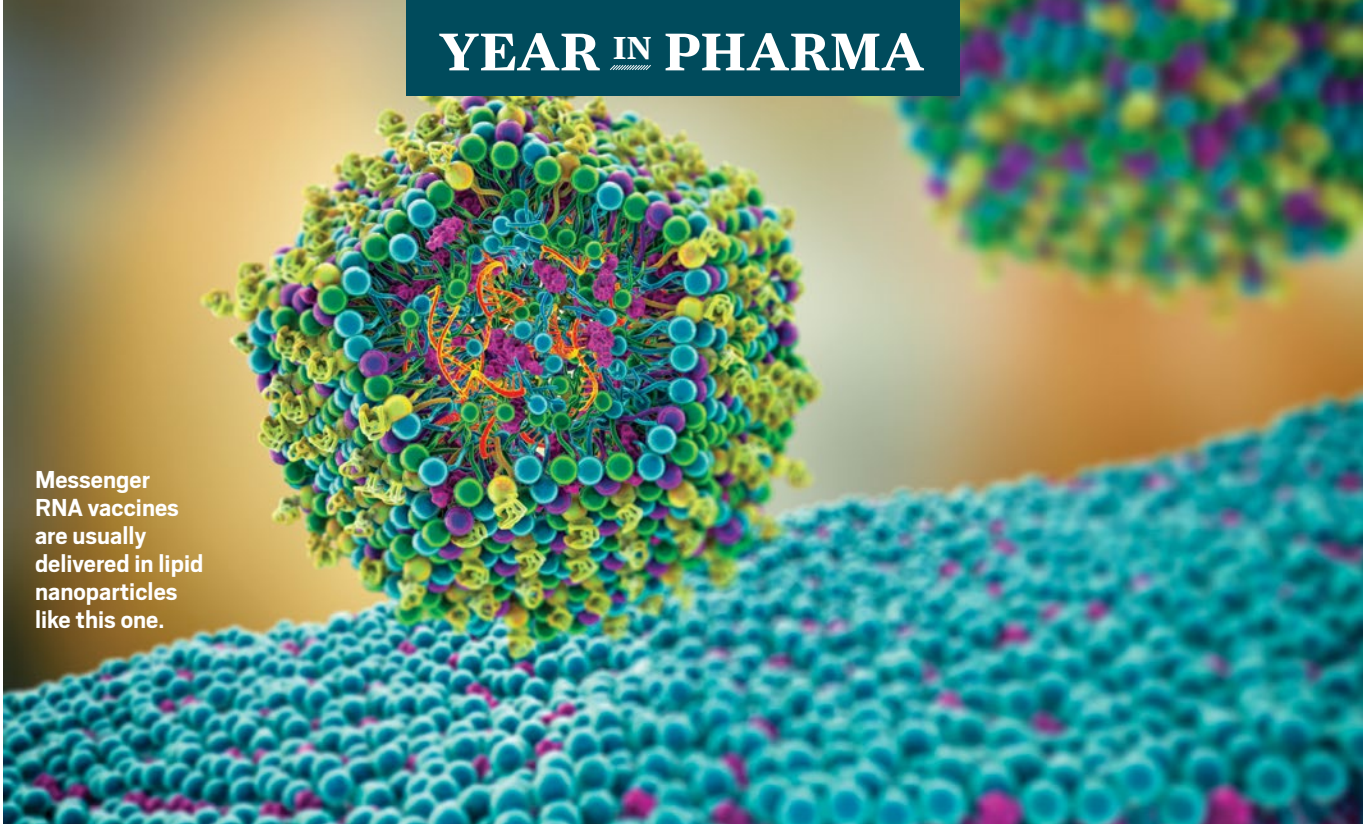
XBI	S&P 500
–12%	+18.6%

Amid the pain, however, there have been some bright spots. Mergers and acquisitions among public companies are strong, numbering 31 deals announced so far in 2023. They have "been a savior for many investors," Ryan says. And in a record high, she adds, 15 of the deals have been worth more than $1 billion—most notably, Pfizer's $43 billion purchase of Seagen, announced in March.

Big companies often buy biotechs to help offset the loss of products that go generic. And considering that a slew of therapies—representing some $200 billion in product sales—will go off patent at the end of the 2020s, the trend is likely to continue, Perrone says. "They really need to start filling that late-stage pipeline."

As the new year approaches, there are strong hints that the Federal Reserve Board will cut interest rates in 2024, Perrone says. "That, I think, will be the single biggest catalyst" for bringing general investors back to biotech and nudging the industry toward regaining its balance.

Alla Katsnelson is a freelance writer based in Southampton, Massachusetts.



Messenger RNA vaccines are usually delivered in lipid nanoparticles like this one.

CREDIT: SCIENCE SOURCE

VACCINES

In a Nobel year, mRNA vaccines progressed toward new targets

Clinical trials in infectious diseases, cancer, and rare diseases pressed onward; investors hung back

LAUREL OLDACH, C&EN STAFF

The impact of messenger RNA (mRNA) as medicine hardly needs to be stated. Billions of people worldwide have received at least one mRNA vaccine for COVID-19. This year, the research that enabled this global immunization was recognized with a Nobel Prize, while the candidate vaccines and therapeutics that companies hope will become the next generation of mRNA medicines advanced through large clinical trials. Despite these successes, research investment has slowed compared with the frenzy of recent years.

In a highly anticipated Nobel nod, Katalin Karikó of the University of Szeged and Drew Weissman of the University of Pennsylvania received the Nobel Prize in Physiology or Medicine in October for discovering a way to slip RNA past a cell's defenses so that it can be translated into protein.

"The whole world has now seen . . . that RNA therapeutics could allow for making fast, potent, flexible vaccines that can generate very strong immune responses," says Vinod Balachandran, a physician-scientist at Memorial Sloan Kettering Cancer Center who is testing mRNA vaccines for pancreatic cancer.

The use of RNA for medicine is not new; a number of therapies use short RNA molecules to block protein production. But for now, COVID-19 vaccines are the only products approved by the US Food and Drug Administration that use mRNA, which encodes proteins, to produce new proteins in cells. Multiple mRNA drug candidates are advancing through clinical trials.

Buoyed by the success of COVID-19 shots, research to develop mRNA vaccines for other infectious diseases is well underway. Companies have completed clinical trials and requested approval for vaccines for influenza and respiratory syncytial virus (RSV), and Moderna is testing a combination shot against COVID-19 and the flu. Cocktail vaccines against multiple antigens are "one of the key advantages of mRNA," says Yusuf Erkul, CEO of Kernal Biologics, a biotechnology company working on mRNA therapeutics.

Another advantage is the speed with which mRNA can be produced and manufactured. These attributes, along with their robust immune activation, make mRNA vaccines attractive to oncologists who hope to train the immune system to recognize cancer cells. Researchers are pursuing mRNA vaccines against markers shared by multiple cancers. They are also working on individualized cancer vaccines; study teams assess a tumor's genome, use an algorithm to predict which mutations will make the best targets, and manufacture patient-specific doses in just weeks. This year, the FDA gave breakthrough therapy designation to a personalized mRNA vaccine for melanoma under joint development by Moderna and Merck & Co. after a promising midstage trial.

But researchers hope that mRNA can deliver much more than immune system training. Some investigators are aiming to treat rare metabolic diseases by using mRNA therapies to replace key enzymes in the body; others want to deliver gene editors via mRNA. One preclinical study in mice used targeted, mRNA-loaded nanoparticles to edit genes only in bone marrow, a potential alternative to stem cell editing in a lab. Improving tissue-specific delivery is also an area of active research.

Despite the Nobel recognition and profusion of research and development, 2023 has been a "reset year" for mRNA commercially, says Fenwick Eckhardt, senior manager of consulting and analytics at Citeline. Revenues for COVID-19 vaccines have dipped, and investors are hanging back, waiting to see whether large trials succeed and position candidate drugs for FDA approval.

Those approvals may come more slowly than investors once expected, Eckhardt says. The next generation of mRNA vaccines and other drugs will follow a more traditional regulatory path than the superfast approvals seen during the pandemic years.

CREDIT: PEGGY PETERSON/PENNTODAY

Winners of the 2023 Nobel Prize in Physiology or Medicine, Katalin Karikó (left) and Drew Weissman

PHARMACEUTICALS

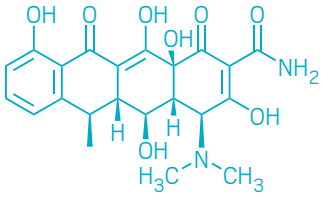
Memorable moments

These are the moments, numbers, and news that the C&EN team found noteworthy this year

LAURA HOWES, C&EN STAFF

Doxycycline helps prevent STIs

In October, the US Centers for Disease Control and Prevention shared draft guidelines recommending that people take the antibiotic doxycycline to prevent sexually transmitted infections (STIs). The strategy is named doxycycline postexposure prophylaxis, or doxy PEP.

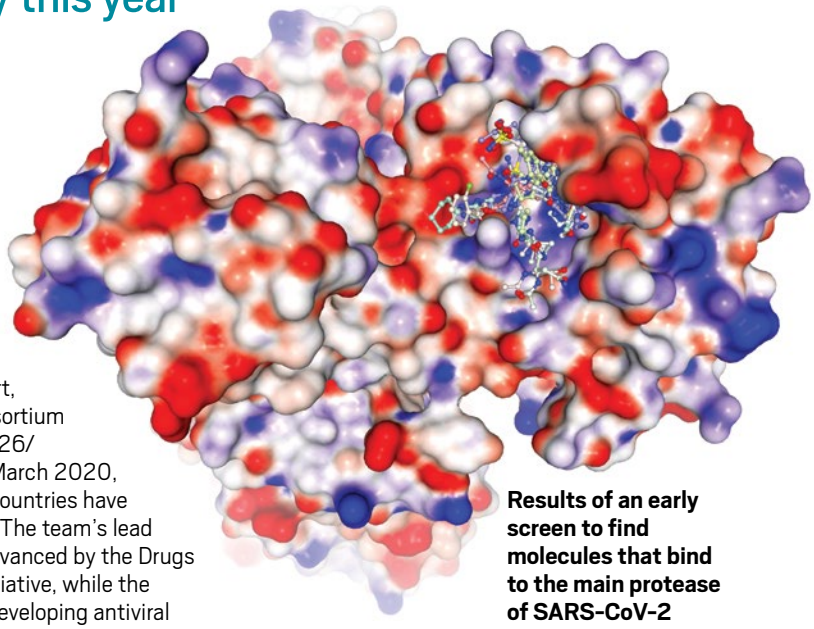


Doxycycline

In trials, researchers found that the drug helped transgender women as well as men who have sex with men, who have increased chances of getting an STI. For participants who took a single dose of the tetracycline-based drug after having sex without a condom, bacterial STIs were reduced by two-thirds. Cities such as San Francisco had already started providing the drug to at-risk communities.

Open-source drug discovery prepared for the next pandemic

New antiviral drug leads were reported by an open-source drug discovery effort, the COVID Moonshot Consortium (*Science* 2023, DOI: 10.1126/science.abo7201). Since March 2020, 212 scientists across 25 countries have contributed to the project. The team's lead compound is now being advanced by the Drugs for Neglected Diseases initiative, while the consortium will continue developing antiviral drugs for viruses of pandemic concern.



Results of an early screen to find molecules that bind to the main protease of SARS-CoV-2

CREDIT: FRANK VON DELFT GROUP/CENTER FOR MEDICINES DISCOVERY, UNIVERSITY OF OXFORD

"As a malaria researcher, I used to dream of the day we would have a safe and effective vaccine against malaria. Now we have two."

—Tedros Adhanom Ghebreyesus, director general, World Health Organization, in a news release

In October, about 2 years after recommending the first malaria vaccine, the World Health Organization endorsed a second one to protect children against the deadly disease. The R21/Matrix-M vaccine was developed by the University of Oxford and is manufactured by the Serum Institute of India.

$452.70 billion

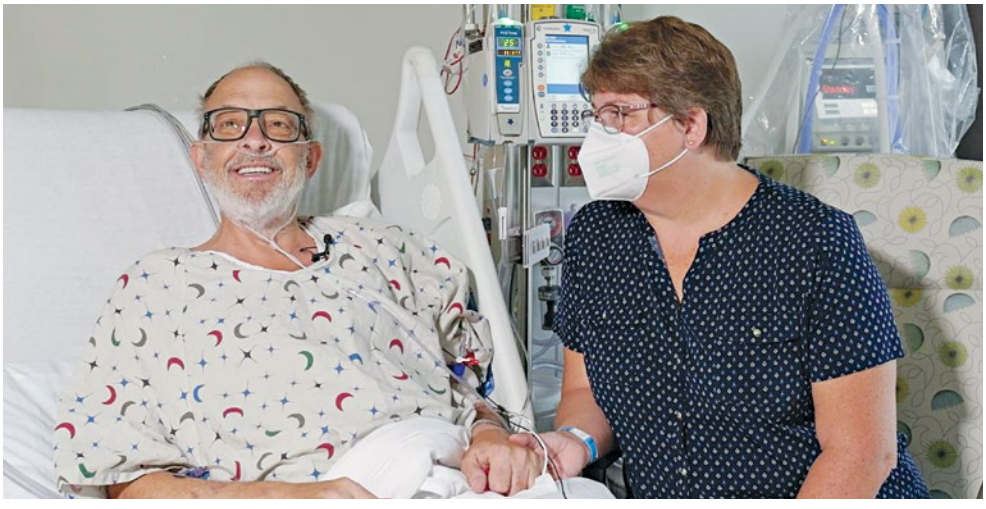
The market capitalization of Novo Nordisk as of Nov. 10. In September, the Danish pharmaceutical firm Novo Nordisk overtook luxury brand LVMH to become the largest European company by market capitalization. The company's success in creating a value larger than the gross domestic product of Denmark has helped stave off recession in the firm's home country and has meant that the national bank has kept interest rates lower than those of other European countries. Novo Nordisk's share price has soared with the commercial success of its GLP-1 agonist semaglutide, sold as Wegovy for weight loss and Ozempic to treat diabetes. Researchers have found that GLP-1 drugs have health benefits.

$3.2 million

The price of Elevidys, Sarepta Therapeutics' onetime gene therapy for Duchenne muscular dystrophy. The US Food and Drug Administration gave conditional approval to the drug in June. While the drug failed to significantly improve functional mobility versus a placebo in a clinical trial later in the year, Sarepta says it is still pursuing full approval. The firm made $69.1 million from the drug in its first quarter of sales, CEO Douglas S. Ingram said on a third-quarter earnings call.

Another xenotransplantation milestone

In September, Lawrence Faucette became the second-ever patient to receive a genetically altered pig's heart. Although Faucette did well after the operation, he later died. "He never imagined he would survive as long as he did, or provide as much data to the xenotransplant program," his wife, Ann Faucette, says in a statement. In the US, 17 people die each day waiting for an organ transplant, according to the Health Resources and Services Administration. To meet that need, various groups of scientists are genetically modifying pigs to make their organs more humanlike, but more data are needed before the US Food and Drug Administration will sign off on human trials.

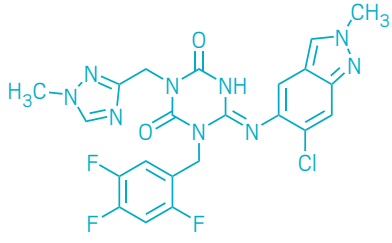


Lawrence (left) and Ann Faucette pre-operation at the University of Maryland Medical Center

CREDIT: UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE

More insight into COVID-19 antivirals

Data presented at the IDWeek conference in Boston in October suggested that an antiviral called ensitrelvir could help with loss of smell and taste in people with mild COVID-19. While Pfizer's drug Paxlovid (nirmatrelvir/ritonavir) and Merck & Co's Lagevrio (molnupiravir) are both used for people at high risk of severe disease, Japanese regulators gave emergency



Xocova (ensitrelvir)

use approval to Shionogi's 3CL protease inhibitor Xocova (ensitrelvir) for people irrespective of risk status or disease severity. The drug is not licensed in the US. Meanwhile, researchers found that molnupiravir can accelerate SARS-CoV-2 mutations (*Nature* 2023, DOI: 10.1038/s41586-023-06649-6).

New hope for mental health

Designing new psychiatric drugs has been a particular challenge for the pharmaceutical industry, but a couple of biotechnology moves this year suggest that the field might be reviving. Neuromedicine-focused Rapport Therapeutics launched in March and raised $250 million total in series A and B funding rounds. And in May, Boehringer Ingelheim signed a $181 million deal with Kinoxis Therapeutics to develop therapies for neuropsychiatric disorders. After positive trial results, Karuna Therapeutics submitted its new schizophrenia medicine to the US Food and Drug Administration for approval in September.

"As NIH director, I look forward to ensuring that NIH continues to be the steward of our nation's medical research while engaging all people and communities in the research effort that includes informing medical practice that drives equitable access to health care for all."

—Monica Bertagnolli, director, National Institutes of Health, in a news release

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ACS Career Tips

Reach out—it's good for you

There are 24 h in a day, and most professionals have very few of those hours to spare. With limited free time, you might find it difficult to justify volunteering some of it to organize or assist with science outreach activities. That said, a paper recently published in the *Journal of Chemical Education*, shows that there are many professional benefits of science, technology, engineering, and mathematics (STEM) outreach—and that it might just be worth your time.

Enhance skills. Outreach events give you opportunities to develop soft skills in areas such as communication, teamwork, organization, and time management. An outreach event might require you to communicate scientific concepts to audiences with little science background or to people of various ages. If you are an organizer, you will have to understand the science at a higher level to explain it clearly to volunteers with different backgrounds. You might also gain experience with logistic arrangements and skills such as leading, managing, and motivating others. The more skills you are able to use and practice, the more you will learn what you are good at, what you enjoy, and what you want to use in your professional life.

Add accomplishments. Sometimes, because of confidentiality agreements, you can't discuss your professional accomplishments outside your own company. But outreach is by its very nature public, and talking about it is often even expected. Sharing how you organized an event for 400 people or met a seemingly impossible deadline can be a great way to show a potential employer what you can do—because you've already done it. Most potential employers are indifferent about whether an experience was paid.

Obtain training. In some cases, volunteers receive training not only in specific outreach activities but also in delivery skills, such as two-way communication and active listening and handling special requests. While that training is perhaps not comprehensive, it is usually free. Volunteering also gives you the opportunity to put your new skills to use right away, which helps solidify the learning process. Some organizations offer advanced training to regular volunteers, enabling you to improve your abilities in leadership, management, or other specialty topics that could be useful in your professional life.

Deepen understanding. The best way to make sure you really understand something is to explain it to someone else. Developing interesting hands-on activities related to your scientific field can force you to think deeply about the basic principles of your work. Questions asked by event participants excited to learn about your science can make you think about the subject in different ways and might even spark an idea for a new direction or work project.

Build your network. Volunteering is a great way to meet local professionals with similar interests. By working closely with other volunteers, you can learn about where they work and what they do. They will also get to know you, observe your strengths, and learn about your professional interests.

Sharing your passion for STEM or any other topic through volunteer work can reinspire your own enthusiasm, and you might even learn something in the process. The fact that you'll be having fun is just a bonus!

Get involved in the discussion. The ACS Career Tips column is published monthly in C&EN. Send your comments and ideas for topics for future columns to careernavigator@acs.org.—Brought to you by ACS Careers

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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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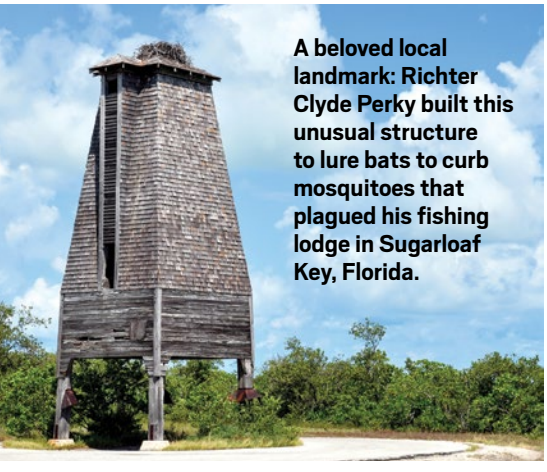
Newscripts

Curating quirky science since 1943

The truth about bat bait

Until 2017, a solitary wooden tower about 9 m tall, pyramid shaped, and supported by sturdy posts stood on a small island in the Florida Keys. A fishing lodge owner named Richter Clyde Perky built this structure in 1929 for an unusual purpose: pest control.

The tower was supposed to serve as a roost for insect-eating bats that might devour mosquitoes thriving in the surrounding mangrove swamps and salt marshes. To attract the chiropterans, he secured a bat bait from Charles Campbell, a bacteriologist who had constructed such towers in and around San Antonio. Although the exact recipe for this foul-smelling lure remains unknown, it possibly contained a mixture of bat poop and the ground-up genitalia of female bats.



A beloved local landmark: Richter Clyde Perky built this unusual structure to lure bats to curb mosquitoes that plagued his fishing lodge in Sugarloaf Key, Florida.

But no bats came, and the experiment failed.

Although bats use odor cues to find their offspring, select mates, or locate food, it's unclear if and to what extent they rely on scents to locate roosts. In a recent study focusing on three group-living bat species in Panama and the US, researchers did not find clear evidence that bat urine and droppings were reliable chemical lures for attracting bats to artificial bat houses (*R. Soc. Open Sci.* 2020, DOI: 10.1098/rsos.201055). Common vampire bats, on the other hand, were immediately enticed when the researchers played recorded calls from the bats' roost mates.

Still, the business of using scents to bait bats persists. Sprays that mimic the smell of bat urine, poop, or pheromones continue to be sold on the market. They claim to attract chiropterans to artificial bat houses. Some concoctions even come with a 60-day money-back guarantee.

"In my experience, those bat attractants don't work," says Mylea Bayless, a mammalogist at the nonprofit organization Bat Conservation International.

But some people turn to them out of curiosity or frustration from bats' not using the artificial houses they put up. The intent isn't always mosquito control but often to attract bats to pollinate the flowers of many plants or devour agricultural pests such as moths and beetles. For others, it's the joy of having bats in their backyard and providing an alternative refuge where natural habitats are shrinking.

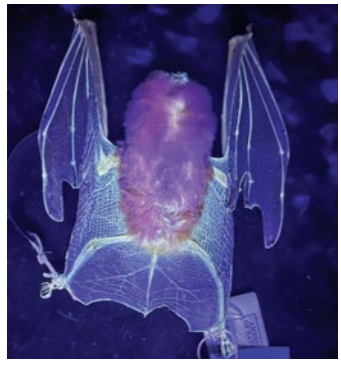
"I would urge them to check and see if the design of the bat house they're using is adequate and then reconsider its placement," Bayless tells Newscripts. Putting bat houses on trees, for example, doesn't work well because that placement is too shaded and accessible to predators, she explains. Mounting them on buildings or poles is a better option.

Although Perky's tower and the bat bait he used failed to lure the winged mammals, the peculiar monument became a local landmark. In 1982, it was added to the US National Register of Historic Places. Hurricane Irma destroyed the structure in 2017.

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

Glowing bats

Reports of birds, reptiles, amphibians, and fish glowing under ultraviolet light have accumulated over the past decade or so. But only recently have researchers in Australia showed that such biofluorescence is also widespread among mammals (*R. Soc. Open Sci.* 2023, DOI: 10.1098/rsos.230325).



Gorgeous glow: This orange leaf-nosed bat is among the 125 mammal species that researchers examined for fluorescence under ultraviolet light.

They shined UV light on 146 specimens, representing 125 mammal species, housed at the Western Australian Museum. Animals as varied as house cats, dogs, flying squirrels, bats, bandicoots, wombats, lions, and polar bears all fluoresced to varying degrees. "It was the light-colored fur—so, whites to light browns or very pale colors," says Kenny Travouillon, lead author of the study and curator of mammalogy at the museum. "But the dark colors weren't fluorescent at all."

In bats, however, it wasn't the fur that glowed, except when the animals sported goldenish hairs on their body. "It's their skin that glowed a lot," Travouillon tells Newscripts. "It's quite beautiful to see."

Such fluorescence can be traced to the presence of unpigmented keratin—a protein found in mammalian hair, nails, and the outer skin layer. For animals such as marsupials exhibiting a reddish glow, it's the porphyrin pigments accumulating in the fur that may be responsible for the creatures' lighting up. But why exactly these mammals evolved to fluoresce is still a mystery.

CREDIT: SHUTTERSTOCK (BAT TOWER); WESTERN AUSTRALIAN MUSEUM (BAT)

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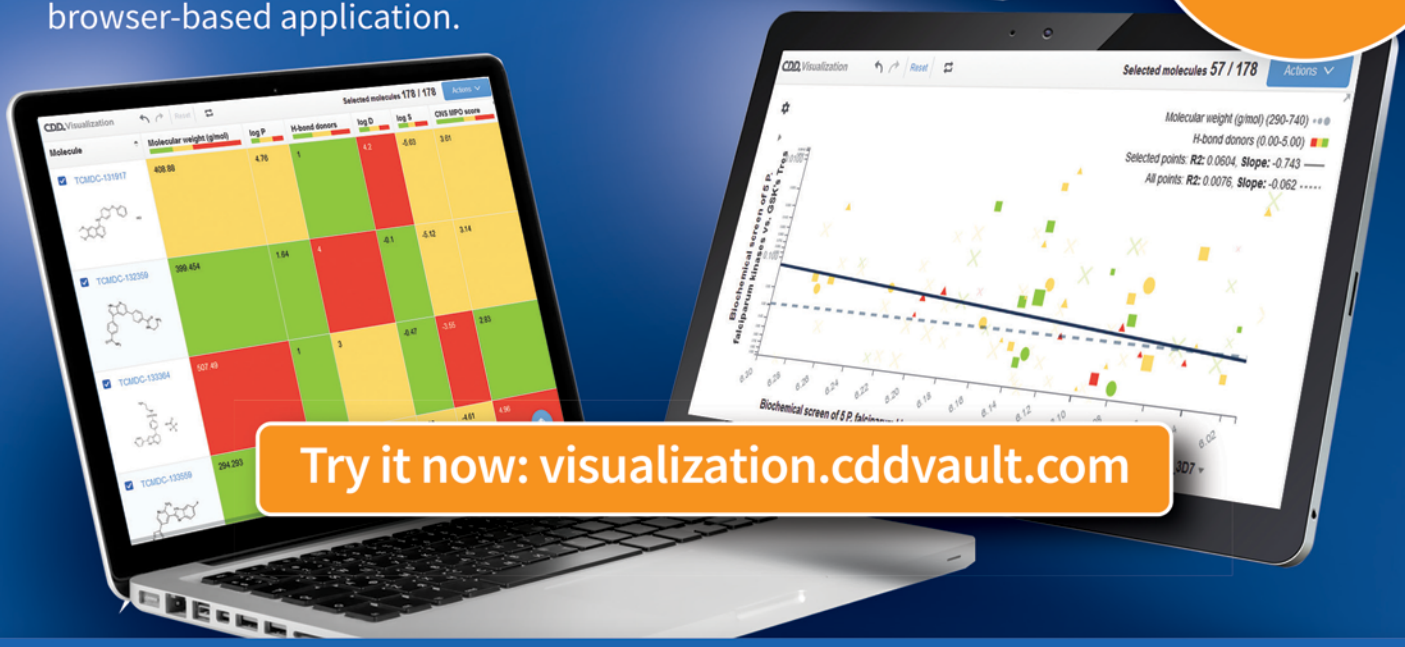

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