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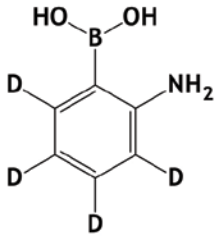
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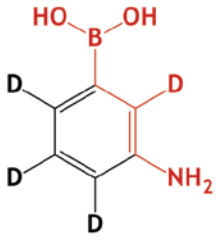
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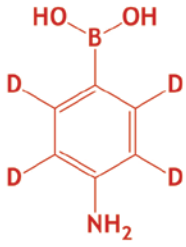
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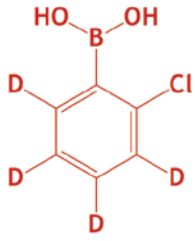
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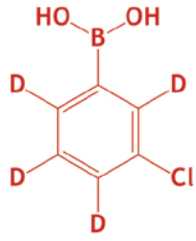
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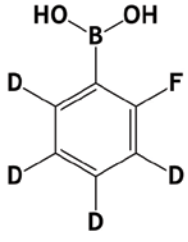
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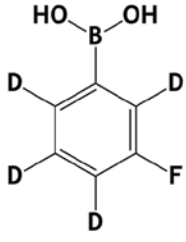
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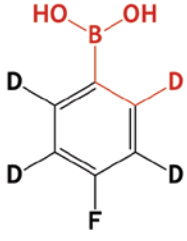
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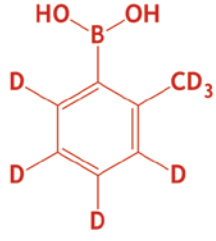
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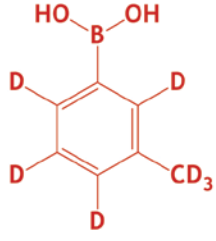
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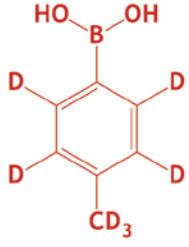
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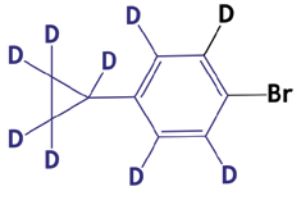
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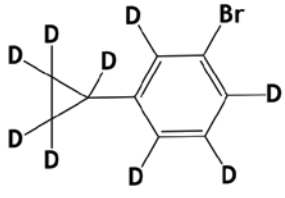
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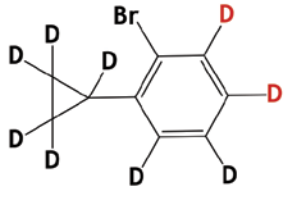
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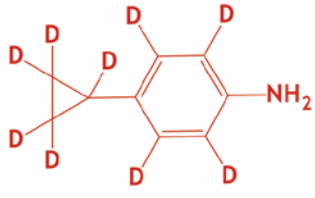
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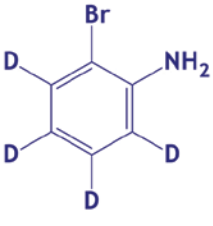
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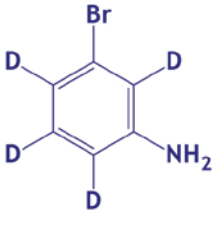
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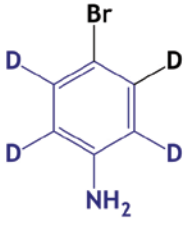
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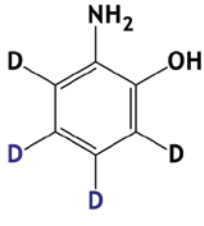
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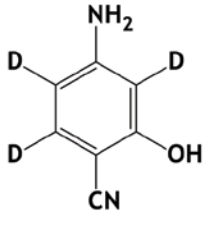
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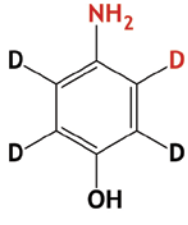
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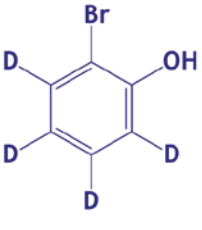
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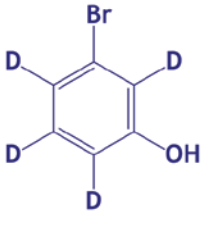
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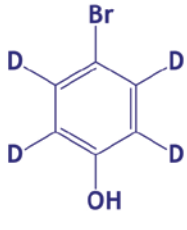
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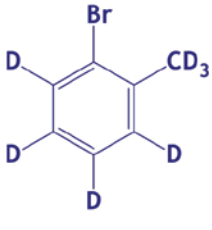
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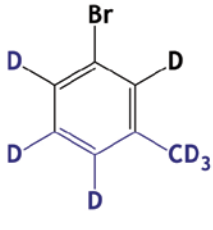
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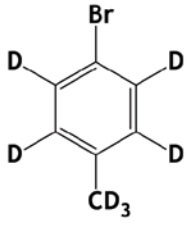
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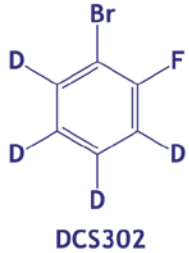
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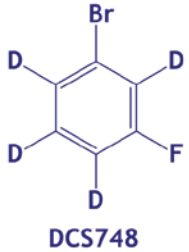
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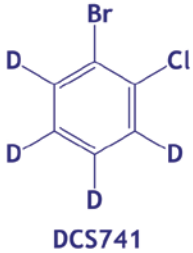
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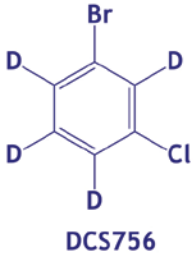
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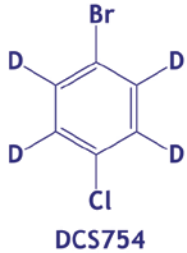
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"Great drugs are developed on the backs of great relationships."

—**Robert Huizinga,** executive vice president of research, Aurinia Pharmaceuticals

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Illustration by Mike Reddy

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ACS News

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ACS Chemistry for Life®

Guest editorial

Science meets policy

This is a guest editorial by **Karen L. Howard**, *a director in the Science, Technology Assessment, and Analytics team at the US Government Accountability Office.*

It was 1921. Biochemist Elmer McCollum identified a component in cod-liver oil that cured rickets, and he called it vitamin D. That same year, President Warren G. Harding signed a law creating what is known today as the US Government Accountability Office (GAO).

Science and the government have come far in the past century. New scientific and technological capabilities have changed the lives of every American. All the while, the GAO has provided Congress with fact-based, nonpartisan information to improve government programs and save taxpayers billions of dollars. In 2020 alone, the GAO had a return on investment of $77.6 billion, saving the federal government $114 for every dollar it invested in the agency.

Over the years, the GAO has worked to make science and technology a priority. Established as a legislative agency aimed at auditing government spending, the GAO broadened its portfolio in the 1960s to include performance audits and, in the 1970s, began recruiting scientists and other experts in fields such as health care, public policy, and computer science. By 2002, Congress asked the GAO to begin producing technology assessments on a pilot basis before making the role permanent in 2008. Today, the Science, Technology Assessment, and Analytics (STAA) team provides Congress with more than audit reports; we analyze scientific and technological developments and present policy makers with clear, concise options to consider in light of these developments—options that can effect change.

In the STAA team's testimony to Congress in July 2019, for instance, we took a closer look at the chemical industry, and drawing on our sustainability chemistry report, we identified options to make sustainable chemical processes and products a priority. Because of this work, Congress enacted legislation directing the Office of Science and Technology Policy to convene an interagency entity responsible for coordinating federal programs and activities in support of sustainable chemistry. In another example, STAA's study of 5G wireless networks revealed that these networks require a greater share of the radio-frequency spectrum—a scarce resource. To address this, we provided options such as promoting research into advanced spectrum-sharing technologies.

Developing policy options like these takes STAA's research one step further: looking not just at the innovations themselves but at their impact on the local, state, and national levels. These two examples only hint at the breadth of STAA's portfolio, which spans topics as varied as vaccine development, artificial intelligence, water quality, and air cargo screening.

In addition, STAA also publishes performance audits, which help Congress better understand the management of science- and technology-focused agencies, programs, or projects. In a recent audit, our team examined how the National Institutes of Health licenses its intellectual property to private companies and the steps it can take to make the process more transparent. The STAA team also developed a two-page report, or Spotlight, to help policy makers keep pace with the rapidly evolving field of science and technology. In a recent Spotlight, we took a closer look at the technologies used to identify chemical warfare agents such as Novichok. With governments suspected of using chemical weapons despite international prohibitions, this work provides timely information that could help nations better defend against future attacks.

Our work is only as useful as the change it generates. And we are working with experts on cutting-edge reports to make that change, for Congress and for the American people. As advances in science and technology continue at a breathtaking pace, nonpartisan scientific analysis and support for Congress will be essential today, tomorrow, and for the century to come.

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

Reactions

Letters to the editor

Mental health

I want to say that I appreciate C&EN's new consistent emphasis on mental health over the last few years. Though I'm no longer in chemistry, it seemed to me that many of the grad students I overlapped with during my undergraduate studies were enduring some sort of mental duress, whether from their research, advisers, or peers, to name just a few sources. While challenges are natural to any course of research, especially a PhD program, it doesn't help to brush those issues under the rug, and the underlying sentiment I always felt was that for some reason it was unprofessional to admit or discuss them. Regarding mental stress caused by advisers or other people (that is, challenges beyond just the science), it seemed all too common, and that mistreatment feeds on secrecy and is only enabled by it.

The bottle-it-up attitude is unhealthy and causes damage to people, if it doesn't go all the way to tragedy. It can also bleed over into other issues, such as harassment. If we're to see positive change, chemistry (and likely all of the sciences) could use more openness and honesty from its community. I applaud C&EN's efforts to foster that.

Andrew D. Royappa
Cantonment, Florida

Greener insulation?

While we applaud the effort of the insulation industry to reduce the use of potent greenhouse gas emissions in their products (C&EN, May 31, 2021, page 24), the article does not mention another class of chemicals that make these products much less green. Virtually all foam plastic building insulation sold in the US—polystyrene (extruded polystyrene, or XPS, and expanded polystyrene, or EPS), polyurethane, and polyisocyanurate—contains flame-retardant chemicals that are necessary to meet building codes. Nearly all the flame retardants used are organohalogens. The long-term health and environmental effects of these chemicals and their eventual breakdown products are not well understood.

One example is PolyFR, the polymeric flame retardant used in most EPS and XPS insulation. A recent Viewpoint article in *Environmental Science and Technology* titled "High Production, Low Information: We Need to Know More about Polymeric Flame Retardants" identifies several points during the life cycle of PolyFR that may expose workers, communities, and ecosystems to this flame retardant and its potentially toxic breakdown products (2021, DOI: 10.1021/acs.est.0c08126).

Furthermore, foam insulation is one of the leading uses of flame retardants, and for most applications, these potentially harmful chemicals do not provide a proven fire safety benefit. Building codes already require that insulation be protected by a thermal barrier, such as gypsum wallboard, capable of withstanding 15 min of flashover fire. Codes in Sweden, Norway, Finland, and Spain allow flame-retardant-free insulation behind such barriers, and in 2019, the California Building Standards Commission voted unanimously to update the state's building codes to allow below-grade use of foam plastic building insulation without flame retardants. These codes demonstrate that the flame retardants used in foam insulation are not necessary. Yet their addition continues to make foam insulation less sustainable—even after replacing hydrofluorocarbon blowing agents.

The health and environmental impacts of the chemicals used in building and consumer products must be considered when deciding how to evaluate how green the materials are. We do indeed need more information about PolyFR and other potentially toxic flame retardants before their continued widespread use in building materials and consumer products.

Donald Lucas (Moraga, California), Vytenis "Vyto" Babrauskas (New York City), Arlene Blum (Berkeley, California), and Lydia Jahl (Berkeley, California)

Corrections

- **March 2/9, 2020, page 26:** The news story on how limiting global warming is getting harder incorrectly states that the Paris Agreement aims to limit global average temperature rise to less than 2 ºC over preindustrial levels by 2030. It aims to do so by 2100.
- **April 19, 2021, page 25:** The Periodic Graphics on flavorings incorrectly describes molecules extracted from plants as artificial flavors. Those molecules can be described as natural flavors under US law.
- **June 14, 2021, page 29:** The "Carbon emissions" graphic in the cover story on green steelmaking incorrectly describes one of the methods. Not all electrolytic reduction processes represented by the "Electrolytic reduction and electric arc furnaces" number involve an electric arc furnace.
- **June 21, 2021, page 11:** The news story on deals in the field of anti-TIGIT antibodies misstates Arcus Biosciences' agreement with Gilead Sciences. Arcus received $375 million, not $175 million, up front from Gilead. Also, Gilead has an option to codevelop and cocommercialize, not a license to, the anti-TIGIT antibody AB154.
- **June 21, 2021, page 26:** The cover story on hyperlocal air quality monitoring incorrectly defines PM_{10} as particles between 2.5 and 10 μm in diameter. PM_{10} refers to all particles 10 μm or smaller.

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Concentrates

Chemistry news from the week

Highlights

AWARDS

Peter B. Dervan named 2022 Priestley Medalist

Caltech researcher honored for pioneering contributions in chemical biology


Peter B. Dervan

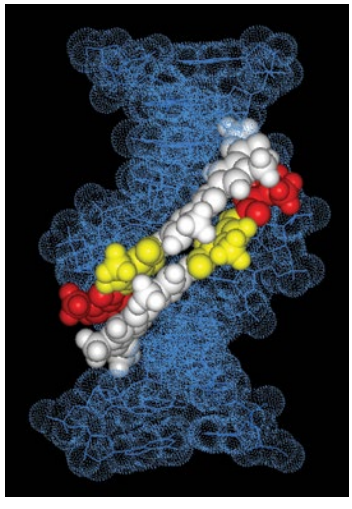
CREDIT: CALIFORNIA INSTITUTE OF TECHNOLOGY (DERVAN); COURTESY OF PETER DERVAN (STRUCTURE)

Peter B. Dervan, the Bren Professor of Chemistry, Emeritus, at the California Institute of Technology, has been named the recipient of the 2022 Priestley Medal, the American Chemical Society's highest honor. He is being recognized for his contributions to the field of chemical biology, especially the development of molecules that bind specific DNA sequences.

Dervan trained as a physical organic chemist, but as a young assistant professor in the 1970s, he realized that he would never be satisfied making incremental advances in the already-mature field.

"I had to look for a new direction," Dervan says. "As a chemist, I wanted to bring the intellectual rigor of my field of physical organic chemistry to biological materials." He decided to study the interactions between small molecules and DNA. At the time, working with DNA was daunting: crystal structures of DNA didn't exist, and sequencers and automated synthesizers had yet to be invented.

"Peter has been a pioneer in bringing the principles of organic chemistry and mechanistic analysis to DNA research," says Eric T. Kool, a nucleic acid chemist at Stanford University who was a postdoctoral researcher in Dervan's group. Dervan developed molecules that could bind and cleave specific DNA sequences. His team showed that these DNA-binding molecules could be used, for example, to inhibit specific binding of transcription factors or to modulate aberrant gene expression in cells and animal models. "He was a world leader in the design and study of triple-helical DNAs and in the design of DNA-minor-groove-binding molecules," Kool says.


Shown here is a crystal structure reported by Peter B. Dervan's lab in 1998 of a programmable synthetic polyamide containing imidazole (red), 3-hydroxypyrrole (yellow), and pyrrole (white) bound as an antiparallel dimer in the minor groove of a targeted DNA sequence.

Dervan made early contributions to the field of chemical biology, though he considers his lab to have been an incubator for students and postdoctoral researchers who went on to invent the field. In the 1980s, "there just weren't that many prominent examples of well-established organic chemists who were working in the biological realm," says Samuel H. Gellman, a chemistry professor at the University of Wisconsin–Madison who was a postdoctoral researcher with Dervan. "Peter's work was so thrilling because he was doing organic chemistry with authentic biopolymers."

Dervan "was a pioneer of this concept of modularity," says Laura L. Kiessling, a chemical biologist at the Massachusetts Institute of Technology who was a postdoctoral researcher in Dervan's lab. "He saw that you could take and mix molecules that on their own had separate functions, and he put them together to create a molecule with a new function." Dervan and his team, for example, designed molecules in which one end could bind DNA and the other end could cleave it.

In addition to his research, Dervan has also served the educational and philanthropic community. He was a member of the Yale Corporation, the university's governing board, from 2008 to 2016. He received his PhD from Yale, where he worked with Jerome Berson. He currently serves as the chair of the scientific advisory board at the Welch Foundation.

"I consider myself deeply fortunate to have been mentored by him across different scales and projects," says Scott A. Strobel, who is the current provost at Yale and was a graduate student in Dervan's lab. "He is both a great scientific partner and an excellent administrative partner. His impact is already legendary and will continue to grow."

With this award, Dervan is now part of a dual–Priestley Medal household. His wife, Jacqueline K. Barton, received the Priestley Medal in 2015.—CELIA ARNAUD

BIOLOGICAL CHEMISTRY

Possible molecular mechanism of Rett syndrome identified

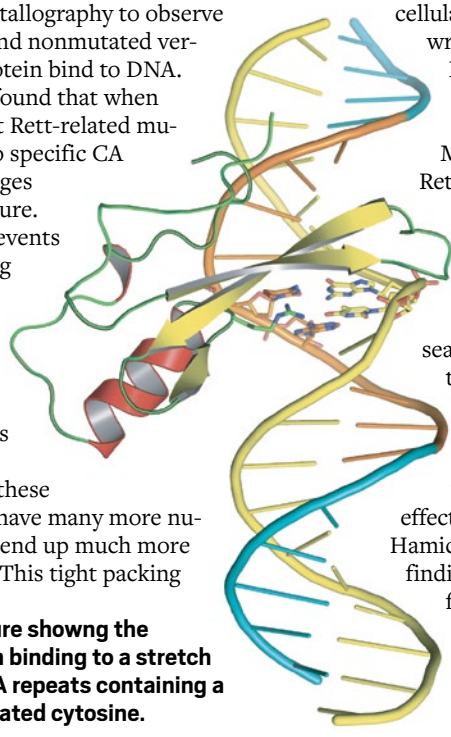
Epigeneticists stumble across link between methylated DNA repeats and protein involved in rare genetic disorder

Researchers have found a new molecular role for MeCP2, the protein that doesn't work correctly in people with Rett syndrome. The findings could suggest new ways to treat the neurodevelopmental condition, the scientists say.

Rett syndrome is a genetic condition that mainly affects girls, and usually becomes apparent in children 6–18 months old. Those children with the syndrome regress developmentally and lose motor control and the ability to speak. In 1999, Huda Zoghbi at the Baylor College of Medicine and colleagues determined that the disorder was caused by mutations in the gene coding for the protein MeCP2.

Ali Hamiche at the Institute of Genetics and of Molecular and Cellular Biology in Strasbourg and his group found the new role for MeCP2 while investigating methylated and hydroxymethylated cytosine and adenosine repeats in DNA (CACACACA, and so on). The group was looking for proteins that bind or interact with these genetic elements to understand how these sequences affect gene regulation. To their surprise, Hamiche says, the researchers found that MeCP2 binds these repeating sequences (*Science* 2021, DOI: 10.1126/science.abd5581).

Hamiche and his colleagues then teamed up with structural biologists and used X-ray crystallography to observe how mutated and nonmutated versions of the protein bind to DNA. The scientists found that when MeCP2 without Rett-related mutations binds to specific CA repeats, it changes the DNA structure. This change prevents DNA from being wrapped up into nucleosomes. In contrast, mutated MeCP2 proteins can't bind the CA repeats, so these repeat regions have many more nucleosomes and end up much more tightly packed. This tight packing could change the regulation of genes along that stretch of DNA.



Crystal structure showng the MeCP2 protein binding to a stretch of DNA with CA repeats containing a hydroxymethylated cytosine.

In a commentary accompanying the new paper, Zoghbi says the findings back up previous evidence that MeCP2 is involved in the organization of chromatin, the cellular material consisting of DNA wrapped up into nucleosomes. But Qiang Chang, who researches MeCP2 at the University of Wisconsin–Madison, says the relevance to Rett syndrome of this newly discovered function for MeCP2 remains to be proved. MeCP2 has functions other than DNA binding, Chang says, and more research is needed to show that this wrapping mechanism happens in the neurons of people with Rett syndrome and to show how it leads to the neurodevelopmental effects of the disease.

Hamiche hopes the team's new findings can help in the search for a treatment. His team continues to work on how exactly MeCP2 affects nucleosome binding.—LAURA HOWES

MICROSCOPY

Microscopy method achieves superresolution without labels

Combining microscopy methods achieves superresolution imaging without fluorescent labels. Lu Wei and coworkers at the California Institute of Technology have combined stimulated Raman scattering (SRS) with expansion microscopy (*Nat. Commun.* 2021, DOI: 10.1038/s41467-021-23951-x). They call the approach vibrational imaging of swelled tissues and analysis (VISTA). It combines the molecular specificity of SRS with the spatial resolution of expansion microscopy.

In VISTA, the researchers embed biological tissue samples in a polymer hydrogel, expand the hydrogel in water, and image the sample using CH_3 vibrations in proteins. When they followed conventional expansion microscopy protocols, which involves chemical cross-linking and protein digestion, a large fraction of the protein in the sample was lost. Instead of digesting the proteins, they denatured them, which preserved the Raman signal. The method achieved spatial resolution of 78 nm.

The researchers used VISTA to image various biological samples, including cells undergoing division, zebrafish embryonic retinas, and a mouse hippocampus. By using machine learning for data analysis, they were able to image multiple components in the mouse hippocampus.

The work is "a creative and effective combination of SRS with expansion microscopy," says Renee F. Frontiera, a Raman microscopy expert at the University of Minnesota Twin Cities. "While SRS microscopy is likely not readily available for labs currently working in expansion microscopy, ideally this work will spur the development of easy-to-use commercial systems."—CELIA ARNAUD

CREDIT: ALI HAMICHE

BIOLOGICAL CHEMISTRY

Looking for birds' magnetic compass

Retina protein forms radical pairs that could guide European robin's migration

A protein in the retina of a migratory bird can respond to weak magnetic fields, researchers have found (*Nature* 2021, DOI: 10.1038/s41586-021-03618-9). The discovery suggests that the protein, cryptochrome 4 (CRY4), may be a biological compass that enables the birds to navigate during long journeys.

"We've known that animals have a magnetic sense for at least 50 years, but how they actually sense the Earth's magnetic field is still a mystery," says Eric J. Warrant, a neurobiologist at Lund University who studies vision and magnetic sensing in animals and was not involved in the research. "I would say it's the last holy grail of sensory physiology, and this paper brings us tantalizingly closer to actually having a solution."

The European robin (*Erithacus rubecula*) contains CRY4 proteins in its retina that could help it navigate by sensing Earth's magnetic field.

CRY4 is found in certain photoreceptor cells in birds. It binds to a light-sensitive molecule called flavin adenine dinucleotide (FAD) and contains four crucial tryptophan residues that form a conduit between FAD and the protein's surface.

Using various spectroscopic techniques to study the version of CRY4 in the European robin (*Erithacus rubecula*), the researchers found that blue light excites an electron in FAD, which enables the molecule to pull another electron from a neighboring tryptophan to become a radical anion ($FAD^{\bullet-}$). More electrons then hop along the chain from one tryptophan to the next in a domino effect, which ultimately leaves the fourth and final tryptophan as a protonated radical cation ($TrpH^{\bullet+}$).

"Well within 1 ns, you get a radical pair," says Peter J. Hore at the University of Oxford, a coleader of the study. In this radical pair ($FAD^{\bullet-}$ and $TrpH^{\bullet+}$), the unpaired electrons' spins can interconvert millions of times per second between two excited states.

These so-called triplet and singlet states can shuffle protons around to form stabler neutral radicals, $Trp^{\bullet}$ and $FADH^{\bullet}$. But only molecules in the singlet state can take a different path, relaxing to their original ground states containing no radicals. The researchers found that a magnetic field of a few millitesla shifts the balance between singlet and triplet states, changing the overall yield of proteins containing the neutral radical products. The scientists think that when the protein sports a $FADH^{\bullet}$, it can trigger a signaling cascade in the robin's sensory system that allows the bird to sense Earth's magnetic field.

The experiments show that CRY4 fulfills some major requirements of a biological compass, Warrant says. Not only is the radical pair sensitive to a magnetic field, but it also produces sufficient amounts of $FADH^{\bullet}$ with long enough lifetimes to potentially generate a sensory signal.

But several key questions remain unanswered. To confirm that CRY4 is a biological compass, researchers will also need to show that its radical pairs are at work in living birds, possibly by studying genetically modified robins that lack parts of CRY4's tryptophan chain.

Finally, it will be important to identify the biochemical processes that carry the information from the radical pair in the retina all the way to a bird's brain. This could provide important clues about how the animal perceives those signals. "It might be possible that birds actually see the Earth's magnetic field," Warrant says.—MARK PEPLOW, special to C&EN

GENOMICS

Coronaviruses caused epidemics for millennia

Inside modern human DNA lie traces of ancient coronavirus infections from many, many years ago (*Curr. Biol.* 2021, DOI: 10.1016/j.cub.2021.05.067). Around 25,000 years ago, in fact.

That's the conclusion of a team of researchers led by David Enard of the University of Arizona. The scientists used a large database of individual human genomes known as 1000 Genomes to compare the genes coding for proteins that interact with coronaviruses, including SARS-CoV-2. They found evidence in the DNA of people whose families came from East Asia that a coronavirus epidemic raged in that region around 25,000 years ago. In addition, the virus had changed the DNA of the survivors and their descendants.

After completing the computational genomic analysis, the researchers synthesized human and coronavirus proteins and confirmed that they interact, as suggested by the team's earlier results. The researchers also identified previously unknown drug targets that they say could be useful for future therapeutic development.

The adaptations detected by the genomic study aren't found in everyone in East Asia today, and the findings don't mean that people with East Asian heritage are better adapted to survive the current COVID-19 pandemic, the researchers say. Instead, these statistical associations demonstrate that coronaviruses have been infecting humans in East Asia for thousands of years. And the impact of these earlier epidemics can be found in genomic databases today. Perhaps searching inside more human genomes might identify other evidence of ancient pandemics and the viruses that caused them.—LAURA HOWES

SYNTHESIS

Taking the steam out of γ-cyclodextrin synthesis

Hydrazone template could make it cheaper to prepare this host molecule

A new template-based method for making γ-cyclodextrin could provide a cheaper and simpler route to this promising yet pricey host molecule.

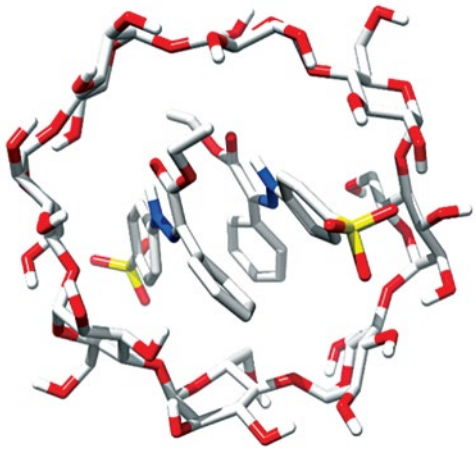
Cyclodextrins—multiple glucose moieties linked together in a ring—have hydrophobic interiors and hydrophilic exteriors. This allows them to protect and solubilize guest molecules, including fragrances and pharmaceuticals. Cyclodextrins release perfumes when warmed by body heat and are used as excipients for many drugs, including the anti-inflammatory agent dexamethasone and the angina treatment nitroglycerin.

Cyclodextrins' properties and prices vary according to their size. Relatively large γ-cyclodextrin, which is made of eight glucose moieties and is highly water soluble, costs almost $800 for just 5 g of material. That solubility makes γ-cyclodextrin attractive as a host molecule but also makes the molecule tough to synthesize and isolate on an industrial scale. Organic templates boost the yield of γ-cyclodextrin in enzymatic syntheses. However, removing these templates requires an energy-intensive steam distillation process, which makes the molecule expensive.

Now, chemists have come up with a template that eliminates the need for steam distillation. Researchers led by Dartmouth College's Ivan Aprahamian and Dale F. Mierke and the Technical University of Denmark's Sophie R. Beeren have developed an enzymatic synthesis of γ-cyclodextrin that uses a photoswitchable hydrazone (shown) as a template (*Chem* 2021, DOI: 10.1016/j.chempr.2021.05.013).

The chemists start with maltohexaose—a linear chain of six glucose units—and add the enzyme cyclodextrin glucanotransferase. This enzyme can shorten, elongate, cyclize, or open sugary molecules to form different structures, including γ-cyclodextrin. These sugary molecules are in equilibrium, Beeren explains, until the chemists add the Z isomer of the hydrazone template. Two of these *Z*-hydrazones bind within γ-cyclodextrin. That binding stabilizes the molecule and pushes the equilibrium to favor γ-cyclodextrin formation. Then the chemists destroy the enzyme and use light to switch to the E isomer of the hydrazone, which no longer fits within γ-cyclodextrin.

"We don't need steam distillation," Aprahamian says. "We just shine light, the hydrazone changes its shape, the binding affinity goes down, and we release the γ-cyclodextrin." Using the hydrazone produces six times as much γ-cyclodextrin as is made without the template molecule.



This computational model shows how two molecules of the *Z*-hydrazone act as a template for γ-cyclodextrin (C = white, O = red, N = blue, and S = yellow).

CREDIT: *CHEM.*

Rosa Iacovino, who studies cyclodextrins at the University of Campania Luigi Vanvitelli, says the work will encourage widespread use of γ-cyclodextrin and will allow chemists to use larger guest molecules within these host molecules.

Christopher Barner-Kowollik, who studies photochemistry in synthesis at Queensland University of Technology, writes in an email that "it will be interesting to follow if the process shows industrial viability."

In terms of scale-up, Aprahamian and Beeren tell C&EN that both the hydrazone and the cyclodextrin glucanotransferase enzyme are inexpensive. Next, they plan to use inexpensive starch as their starting material.—BETHANY HALFORD

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CANCER

X-rays activate cancer drug

Radiation removes molecular mask to free anticancer agent in mice

X-rays can activate an anticancer drug at a tumor site, researchers have found. Experiments in mice showed that this simultaneous chemotherapy and radiotherapy was effective in treating tumors, with minimal side effects (*Nat. Chem.* 2021, DOI: 10.1038/s41557-021-00711-4).

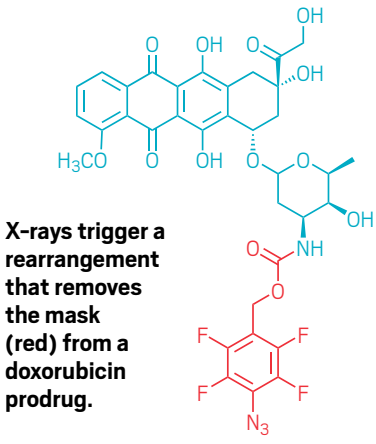
The method relies on a prodrug, a medicinal compound carrying a chemical masking group that renders it inactive and nontoxic. Once the prodrug reaches a treatment site in the body, removing the mask frees the active drug to go only where it is needed, which helps avoid systemic side effects.

The advantage of using X-rays for this purpose is that it can be targeted precisely, says Mark Bradley of the University of Edinburgh, who led the new study. In addition, the X-ray doses that unmask the drug are comparable to those used in cancer radiotherapy, so the treatment acts as combined chemotherapy and radiotherapy, which tends to be more effective than either alone. Although researchers have previously investigated radiation-activated cancer prodrugs, these efforts were ineffective in vivo (*Molecules* 2008, DOI: 10.3390/molecules13102370).

Bradley's team attached a (*p*-azido)-2,3,5,6-tetrafluorobenzyl oxycarbonyl group to the powerful cancer drug doxorubicin and delivered it to tumor tissues. When X-rays hit tissue near the prodrug, they generate hydroxyl radicals that reduce the azide to an amine, triggering a rearrangement that frees doxorubicin. Although naked doxorubicin has toxic side effects, its masked form is nontoxic at clinically relevant concentrations.

When the researchers injected tumor-bearing mice with masked or unmasked doxorubicin and supplied a dose of X-rays, the combination therapy effectively halted tumor growth. "By using radiotherapy to turn on prodrugs, this work opens a new avenue in chemotherapy," says Peng Chen of Peking University, who was not involved in the work, in an email interview.

Bradley hopes that the same mask could be applied to a wide variety of other cancer drugs. "In principle, we can attach this group to any cancer drug that contains a free amine or hydroxyl group," he says. His team is already planning to develop the masked doxorubicin prodrug so that it is ready for clinical testing.—MARK PEPLOW, special to C&EN



X-rays trigger a rearrangement that removes the mask (red) from a doxorubicin prodrug.

Masked doxorubicin prodrug

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ECONOMY

Recovery to come slowly for US chemical industry

Pent-up demand will boost 2021 numbers, but bottlenecks and labor shortages may slow recovery

A worker treats metal parts with a powder coating, an area of strong expected growth for chemicals in 2021.

The US chemical industry is a few months into recovery from the COVID-19 pandemic, but full recuperation won't happen until 2023.

That's the view from the American Chemistry Council (ACC), the US chemical industry's main trade association. US chemical sales should recover this year, the ACC says, with a projected total of $525 billion, not including pharmaceuticals, up from $486 billion in 2020 and $509 billion in 2019. But employment, capital expenditures, and production volumes won't return to prepandemic levels until late 2022 or early 2023, ACC predicts.

The trade group expects strong chemical demand through 2021 from consumer-focused industries such as auto, construction, and durable goods. That notion is supported by projections from the World Bank, which said in June that the overall US gross domestic product (GDP), a measure of economic growth, will be up by 6.8% for the year.

The ACC expects specialty chemicals, notably coatings, to have a better year than basic chemicals. Martha Moore, an ACC economist, says stimulus money from the US and other governments is helping fuel demand for consumer products, and pent-up demand for travel and other outings is bolstering transportation.

Moore's colleague, Kevin Swift, warns that inflation could constrain recovery in the US and worldwide. He says a related concern among his peers at other industry groups is employee and supply shortages. "It's all they talk about. They can't get labor; they can't get materials," Swift says. He cites foams, semiconductors, and lumber as being in especially short supply, with kinked supply chains expected to continue at least into the fall.

Despite those risks, the US chemical industry is in a strong position compared with those in other countries, the ACC's data suggest. Low prices for natural gas favor US petrochemical firms. The group forecasts a US trade surplus of about $34 billion in 2021, rising to almost $40 billion by 2023.—CRAIG BETTENHAUSEN

By the numbers

14,800

Jobs the US chemical industry shed in 2020.

1.4%

Projected US chemical volume growth in 2021.

Source: American Chemistry Council

MERGERS AND ACQUISITIONS

Indorama is in talks to buy Oxiteno

The Thai chemical maker Indorama Ventures has entered exclusive negotiations with the Brazilian conglomerate Ultrapar Participações to buy Oxiteno, Ultrapar's specialty chemical business.

The parties have yet to hammer out a purchase agreement. "Conditions of the transaction, including value, are still under consideration," Ultra says.

Oxiteno is one of the linchpins of Brazil's chemical industry. Its key products include surfactants, solvents, glycols, ethanolamines, fatty alcohols, glycerin, and fatty acids. It earned $70 million in 2020 on $1.0 billion in sales. Its assets are valued at $1.7 billion.

In recent years, the company has been branching out of its home country. Its biggest such move came in 2018, when it started up a $150 million ethoxylation unit in Pasadena, Texas, on the site of a former vitamin E plant. Oxiteno claims to be the world's second-largest producer of ethoxylated chemicals, behind BASF.

Indorama has grown over the past 2 decades into a global giant in polyethylene terephthalate (PET) resins and fibers, with sales last year of about $10 billion. As it built its polyester business, the company also became involved in surfactants, a direction it has embraced as a diversification maneuver.

In 2012, Indorama bought Old World Industries, a producer of ethylene glycol—a PET raw material—in Clear Lake, Texas. That plant also makes ethylene oxide, the raw material needed for ethoxylated surfactants.

Indorama built on this foundation in 2020, when it completed the purchase of Huntsman's chemical intermediates and surfactants unit, a competitor to Oxiteno, for $2.1 billion.—ALEX TULLO

RECYCLING

Mattel has launched a collection of beachy Barbie dolls whose bodies are 90% made from plastic collected near waterways in areas lacking formal waste collection systems. The firm says the launch is in line with its goal of making all the plastics in its products and packaging recycled, recyclable, or biobased by 2030. The new Barbies are not quite there yet. As Mattel says: "Doll head, shoes, tablet and beach lantern accessory excluded."

CREDIT: SHUTTERSTOCK (POWDER COATING); MATTEL (BARBIES)

INFORMATION TECHNOLOGY

AI firm Insilico raises $255 million

The artificial intelligence pioneer has added 50 scientists as it pivots to discovery research

Insilico Medicine, a developer of artificial intelligence technology for drug discovery, has raised $255 million in series C financing. The investment round is the second this year to top $200 million for an AI-based drug discovery firm.

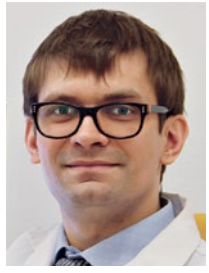
The investment follows Insilico's announcement in February that it used AI to identify a novel target and develop an investigational small-molecule therapy to treat idiopathic pulmonary fibrosis. Claiming a first, Insilico says it identified the target, developed molecules, and completed preclinical trials in 18 months.

Exscientia, an AI competitor, netted $225 million in a financing round announced in April. Three drug candidates designed with Exscientia AI are in clinical trials, including a therapy for obsessive-compulsive disorder developed with Sumitomo Dainippon Pharma.

Insilico's funding was led by Warburg Pincus with participation from 25 other investors, a majority of them based in China. Insilico says it will use the proceeds to progress its pipeline of 16 therapeutic programs and to initiate new programs. It will also continue to invest in AI software and associated robotics, according to CEO Alex Zhavoronkov.

Insilico also announced a partnership with Teva Pharmaceutical. The firm has already collaborated with Pfizer, Astellas, Johnson & Johnson, and Taisho.

From its base in developing AI tools, Zhavoronkov says, Insilico has turned to building a drug discovery research engine this year. Insilico has hired 50 scientists in 2021 to do discovery research at facilities in China, Taiwan, and the US.



Insilico CEO Alex Zhavoronkov says the new proceeds from investors will go to further developing AI and advancing Insilico's drug discovery pipeline.

Insilico announced a $37 million series B investment round last September. While some repeat investors, such as Sinovation Ventures, show an interest in digital healthcare technology, first-time investors in the new funding round frequently invest in pharmaceutical start-ups. Zhavoronkov says the new backers reflect Insilico's effort to grow as a hybrid AI and drug company.

Alán Aspuru-Guzik, a professor of chemistry and computer science at the University of Toronto and cofounder of Kebotix, a materials discovery AI firm, says the spate of investment in AI indicates that the pharmaceutical sector needs new ideas. Aspuru-Guzik, who has advised Insilico, anticipates that AI for materials discovery is next up for major venture capital backing.—RICK MULLIN

BIOLOGICS

Abata launches with $95 million in funding

The company wants to engineer T cells to tackle autoimmune diseases like multiple sclerosis

Abata Therapeutics has launched with $95 million in series A funding to take cell therapy into a new realm: the treatment of multiple sclerosis.

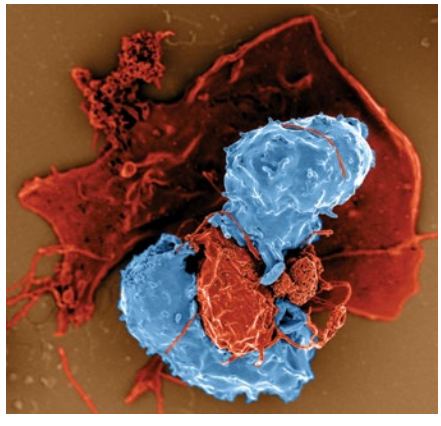
The investment comes primarily from Third Rock Ventures. ElevateBio, which specializes in manufacturing cell therapies, has also invested and is helping Abata develop its production process. The company started quietly 3 years ago and is still in preclinical stages.

Abata's technology involves regulatory T cells (T regs), immune cells that tamp down immune activity. Abata is one of several companies investigating how to manipulate these cells to treat the immune overreaction that characterizes inflammatory and autoimmune diseases.

"They're essentially the ideal therapy for an autoimmune disease," Abata CEO Samantha Singer says about T regs. "They can promote repair as well as stop tissue destruction, and they last a long time."

Abata's primary disease target is multiple sclerosis in people who have nonrelapsing disease. Current MS treatments include antibodies, small-molecule medications, and injectable proteins. Most available treatments work on earlier stages of the disease, says Abata chief medical officer Richard Ransohoff.

Abata scientists plan to take the cells from a person who has MS, engineer them to carry a molecule called a T-cell receptor that is specific to a nerve coating damaged in MS, grow them in large quantities, and then reintroduce them into that person.



Regulatory T cells tamp down the immune system. Abata Therapeutics hopes to use these cells to treat multiple sclerosis.

Singer and Ransohoff think the engineered T regs will travel through the cerebrospinal fluid, get to the sites of inflammation, and dampen the inflammatory response.—MEGHA SATYANARAYANA

CREDIT: INSILICO MEDICINE (ZHAVORONKOV); SCIENCE SOURCE (T CELL)

MERGERS & ACQUISITIONS

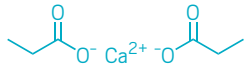
Westlake will buy building product firm

Moving further downstream into polyvinyl chloride (PVC) goods, Westlake Chemical will buy the North American building product business of Australia's Boral for $2.15 billion. The Boral unit has about $1 billion per year in sales of roofing, siding, trim, shutters, windows, and decorative stone. Westlake already makes about $1.4 billion worth of PVC building products annually. That business secures much of its raw material from Westlake's PVC resin business, the second-largest PVC producer in the world, behind Japan's Shin-Etsu Chemical.—ALEX TULLO

FOOD INGREDIENTS

Kerry is buying preservative maker Niacet for $1 billion

Kerry Group, an Irish food ingredients firm, has agreed to acquire the food preservative maker Niacet for about $1 billion from the private equity firm SK Capital Partners. Based in Niagara Falls, New York, Niacet calls itself North America's largest producer of organic acid salts, including sodium acetate and calcium propionate, used in preservation and other food applications. It expects to have about $220 million in sales this year. SK acquired Niacet from the Brannen family in 2017. In a presentation for investors, Kerry executives say the global food preservation market is about $1.8 billion per year, split roughly evenly between "clean label" and conventional products. Kerry already offers clean label preservatives that are based on vinegar, fermentation, and plant extracts. Niacet's calcium propionate, used in baked goods, and acetates, used in processed meats, are considered conventional preservatives, though the firm also offers vinegar-based products.—MICHAEL MCCOY



Calcium propionate

FOOD INGREDIENTS

Oterra eyes another food-coloring deal

The natural food-coloring company Oterra is in talks to purchase the natural pigments business of Diana Food, a subsidiary of the flavor and fragrance firm Symrise. Diana Food extracts colorful compounds from plant sources such as beets, carrots, and spirulina using a water-based process. Oterra, which was the natural colors division of the food science company Chr. Hansen until it was spun off by the private equity firm EQT in March, aspires to be a dominant force in naturally derived pigments. In May, Oterra bought the Spanish pigment maker Secna Natural Ingredients.—CRAIG BETTENHAUSEN

Plant-derived pigments, such as purple made from purple carrots, are displacing synthetic dyes in many major-brand foods.

RECYCLING

South Korea's SK to buy stake in Loop

South Korea's SK Global Chemical will invest $56.5 million in Loop Industries, giving it 10% of the Canadian firm. Loop is developing a technology to break down polyethylene terephthalate (PET) into its raw materials, dimethyl terephthalate and ethylene glycol. Loop says it will use the proceeds to build a plant in Bécancour, Quebec. The companies also intend to build a plant in South Korea in 2022 and a total of four facilities in Asia by 2030. In May, SK bought a 10% stake in the Chinese PET depolymerization firm Shuye Environmental Technology.—ALEX TULLO

ENERGY STORAGE

Oxis Energy files for bankruptcy

Oxis Energy, a British developer of a battery featuring a sulfur-based cathode and lithium metal anode, has filed for bankruptcy. Lithium-sulfur batteries have a theoretical energy density of 2,700 Wh/kg—far higher than that of lithium-ion batteries—but their energy density fades after fewer charge-discharge cycles than do lithium-ion batteries. Oxis shareholders include Samsung and the chemical makers Sasol and Umicore.—ALEX SCOTT

AGRICULTURE

Enko signs pesticide deal with Syngenta

The agricultural product firm Syngenta has signed a deal to develop crop protection chemicals with Enko Chem, a start-up that adapts drug discovery methods to agricultural applications. The firms say that by screening massive molecule libraries for activity against specific enzymes in target pests, they will be able to cut the time it takes to bring a new pesticide to market—currently about a decade—in half.—CRAIG BETTENHAUSEN

GENE THERAPY

Danaher to acquire Aldevron for $9.6 billion

Danaher, a supplier of health-care and process industry products, has agreed to acquire Aldevron, a supplier of plasmid DNA, messenger RNA, and recombinant proteins used in the manufacture of vaccines and cell and gene therapies, for $9.6 billion. Headquartered in Fargo, North Dakota, Aldevron employs about 600 people. The company plans to more than triple capacity this year by adding an 18,000 m^2 facility to its 6,500 m^2 operation in Fargo. The seller, the private equity firm EQT, bought a majority interest in Aldevron in 2019.—RICK MULLIN

CREDIT: SHUTTERSTOCK

DRUG DISCOVERY

Orum eyes protein-degrader antibodies

Orum Therapeutics has raised $84 million in series B financing to develop antibody-drug conjugates that deliver small-molecule protein degraders to cancer cells. When the antibodies bind a target on the surface of a cancer cell, they are engulfed and digested, then release a degrader. The degrader then binds to an intracellular protein and tags it for degradation. The start-up, based in Cambridge, Massachusetts, and Daejeon, South Korea, will use the money to advance programs for undisclosed targets in solid tumors and blood cancers.—RYAN CROSS

ONCOLOGY

BMS will acquire Eisai ADC for cancer

Bristol Myers Squibb will pay Eisai $650 million to jointly develop the Tokyo-based firm's first antibody-drug conjugate (ADC) for cancer. Eisai also could earn up to $2.45 billion in milestone payments. The antibody targets cancers expressing folate receptor α. It then delivers a small-molecule payload called eribulin, Eisai's simplified and synthetic version of halichondrin B, a toxic microtubule dynamics inhibitor derived from sea sponges. The therapy is in Phase 1 studies as a possible treatment for endometrial, ovarian, lung, and breast cancers.—RYAN CROSS

NATURAL PRODUCTS

Enveda raises funds for drugs from plants

Enveda Biosciences has raised $51 million in series A funding to develop small-molecule therapies from plants. The funding round was led by Lux Capital. Enveda is creating what it calls the first high-resolution chemical map of the natural world, and applying machine learning and metabolomics to predict novel chemistry. The company hopes to identify candidate molecules to treat diseases such as nonalcoholic steatohepatitis and Parkinson's disease.—MEGHA SATYANARAYANA

PROCESS CHEMISTRY

Corning debuts flow chemistry center

Corning has opened a training center for flow-chemistry technology in Changzhou, China. The academy is part of the new headquarters of Corning's advanced flow reactor business in Changzhou Science and Education Town. The training center will take up three floors with demonstration rooms, an R&D lab, lecture classrooms, and 3D simulation technology intended to demonstrate the benefits of flow chemistry over batch chemistry.—RICK MULLIN

Corning hopes its new academy will spread knowledge about flow chemistry.

BIOLOGICS

Cellex and Intellia start CAR-T company

Blackstone Life Sciences has pledged $250 million to form a company with Cellex Cell Professionals and Intellia Therapeutics to develop universal chimeric antigen receptor T-cell (CAR-T) therapies that can use donor cells instead of cells from a person with the disease being treated. The new firm will acquire the immunotherapy and cell therapy company GEMoaB from Cellex. GEMoaB is developing switchable CAR-T therapies intended to have increased safety and efficacy across several types of cancer. Intellia is a gene-editing company that uses CRISPR-Cas9 to develop therapies.—MEGHA SATYANARAYANA

Business Roundup

Dow and Shell will receive $4.2 million in funding from the Dutch government toward their work in electrically heated ethylene steam-cracking furnaces. The companies say they are evaluating the construction of a pilot plant by 2025, "subject to investment support."

Tosoh will spend $90 million to renovate and expand its Tokyo Research Center in Ayase, Japan. The firm says the project, set for completion in 2026, will include a building for advanced organic materials research.

Johnson Matthey, Thomas Swan, and the UK technology agency CPI are investigating ways to increase the performance of Johnson Matthey's lithium-ion battery materials using carbon nanotubes and graphene nanoplatelets. The project will receive funding from the UK government's Faraday Battery Challenge.

Invista plans to build a nylon 6,6 technology application center in Shanghai at a cost of $15 million. The center will undertake analytical and mechanical testing of engineering polymers for markets including automotive and electronics.

Yara International and other are investing $4 million in Boomitra, a Silicon Valley start-up with a method for monitoring carbon levels in the soil without the need for physical soil samples. The technique is meant to help small-scale farmers access carbon-credit markets.

Lonza will help Selectimmune Pharma develop a process for manufacturing its immunotherapy protein NlpD. Lonza has also agreed to make ValenzaBio's anti-insulin-like growth factor-1 receptor antibody to treat thyroid eye disease and other inflammatory disorders.

Viiv Healthcare is paying $40 million to Halozyme Therapeutics for exclusive use of Halozyme drug delivery technology based on human hyaluronidase PH20 enzyme. The goal is injectable HIV treatments that last longer than 3 months.

Veralox Therapeutics has raised $16.6 million in series A financing to develop small-molecule inhibitors of the enzyme 12-lipoxygenase. The start-up plans to test the compounds on a blood clot disorder called heparin-induced thrombocytopenia.

CREDIT: CORNING

POLLUTION

EPA to reexamine ethylene oxide risks

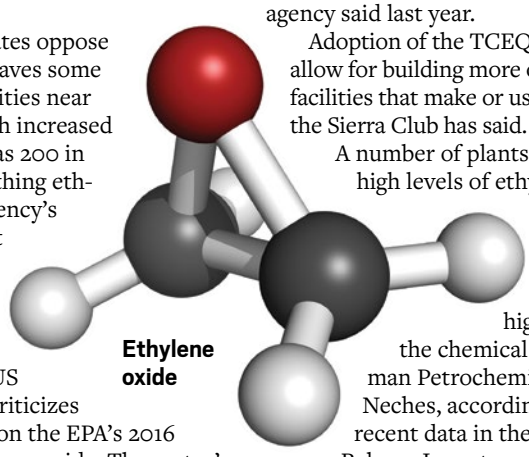
Move could impact crackdown on chemical plant emissions

In an action sought by both the chemical industry and environmental advocates, the US Environmental Protection Agency will reexamine its 2020 regulation of ethylene oxide.

The EPA will ask the public for more input on the potency of the carcinogenic gas, the agency told C&EN in a June 22 email. This toxicity value guides the EPA in deciding whether to continue, relax, or strengthen regulation of ethylene oxide leaks from chemical plant equipment, vents, and storage tanks to protect the health of nearby communities.

Made from natural gas or petroleum, ethylene oxide is a basic starting material for manufacturing a variety of products, including plastics and medicines. The gas is also used to sterilize medical equipment.

In a 2020 Clean Air Act rule, the EPA under the Trump administration required manufacturers of organic chemicals to curb their ethylene oxide emissions collectively by 0.69 metric tons per year. Environmental advocates oppose the rule, saying it leaves some fence-line communities near chemical plants with increased cancer risk as high as 200 in 1 million from breathing ethylene oxide. The agency's rules generally limit increased cancer risk from exposure to pollutants to 100 in 1 million.



Ethylene oxide

Meanwhile, the US chemical industry criticizes the rule for relying on the EPA's 2016 assessment of ethylene oxide. The sector's main lobbying arm, the American Chemistry Council (ACC), calls that assessment flawed.

The ACC also faults the agency for failing to consider an analysis by the Texas Commission on Environmental Quality (TCEQ), which concluded last year that ethylene oxide is far less hazardous than the EPA has determined. The TCEQ's assessment was not peer-reviewed in time for the EPA to consider it for the rule, the agency said last year.

Adoption of the TCEQ approach could allow for building more or expanding facilities that make or use ethylene oxide, the Sierra Club has said.

A number of plants in Texas have high levels of ethylene oxide emissions. They include the US facility that reported the highest releases of the chemical in 2019, Huntsman Petrochemical of Port Neches, according to the most recent data in the EPA's Toxics Release Inventory.

Huntsman Petrochemical, the ACC, the TCEQ, the Sierra Club, and other advocacy groups petitioned the EPA to reconsider the rule.

"We appreciate the EPA's willingness to consider the latest science on this issue," the ACC says in a statement

"EPA must substantially strengthen these chemical plant rules by following the science to protect public health from cancer and other illnesses," says Emma Cheuse, attorney for Earthjustice, the law firm representing the environmental groups seeking reconsideration of the rule.—CHERYL HOGUE

"EPA must substantially strengthen these chemical plant rules by following the science."

— Emma Cheuse, attorney, Earthjustice

CREDIT: SHUTTERSTOCK

AGRICULTURE

Climate-friendly agriculture falls short, EU audit finds

Greenhouse gas emissions from farming in the European Union have not decreased since 2010, despite the government spending over €100 billion ($119 billion) to combat climate change from agriculture between 2014 and 2020, a report by the European Court of Auditors concludes. The report finds that greenhouse gas emissions from the use of chemical fertilizers and manure in the EU rose from 2010 to 2018. Such emissions account for nearly a third of the EU's agricultural greenhouse gas emissions, according to the report. The auditors claim that practices supported by agricultural funding that are intended to reduce fertilizer use, such as organic farming and growing legumes, have an unknown impact on greenhouse gas emissions. But other practices that have been demonstrated to reduce those emissions, such as precision agriculture methods that apply fertilizer only where it's needed, have received little EU funding. Livestock emissions, which represent about half of agricultural greenhouse gas emissions, have remained steady in the EU since 2010, the report finds.—BRITT ERICKSON

Precision farming methods, which allow farmers to apply fertilizers only where crops need it, have received insufficient funding in the EU, auditors say.

CREDIT: ANDY MANIS/ZUMAPRESS/NEWSCOM (FIRE); SHUTTERSTOCK (FIELD)

ENVIRONMENT

US EPA selects air pollution advisers

After purging its members in late March, US Environmental Protection Agency administrator Michael Regan has reconstituted the Clean Air Scientific Advisory Committee (CASAC). Four of the seven members, whom Regan selected from a pool of 100 candidates, have previously served on the panel. They include two scientists who were on the committee when Regan removed all its members and directed the EPA staff to assemble a better blend of expertise than the panel had during the previous administration. The committee now consists of six academics and a state air pollution regulator. This mix reflects the composition of CASAC for decades before the EPA under the Trump administration banned academics as advisers if they received agency grants. A federal court struck down the ban last year. In addition, Regan is resurrecting a group of scientific advisers that the Trump administration eliminated. That group has expertise in science around particulate matter, a major type of air pollution.—CHERYL HOGUE

INDUSTRIAL SAFETY

CSB sends 2 staff to Chemtool after fire

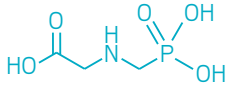
The US Chemical Safety and Hazard Investigation Board (CSB) has sent two senior staff members to Rockton, Illinois, after a June 14 fire destroyed a Chemtool manufacturing plant. No workers were injured in the incident. Chemtool, a subsidiary of Lubrizol, makes greases and industrial fluids such as cleaners and lubricants. CSB acting managing director David LaCerte and Stephen Klejst, executive director for investigations and recommendations, traveled to "engage with Federal, State and local emergency responders, the Environmental Protection Agency (EPA) and others" and "gather information from the incident site and make a recommendation on how best to proceed," the CSB says in a statement. Neither official has chemical manufacturing experience: LaCerte is an attorney who worked with the US Office of Personnel Management and Louisiana Department of Veterans Affairs, and Klejst is a safety professional who came to the CSB from the US National Transportation Safety Board and the railroad industry. Investigators from other federal agencies have determined that the incident was not caused by suspicious or criminal activity, the CSB statement says.—JYLLIAN KEMSLEY

All 70 workers that were in the Chemtool plant in Rockton, Illinois, evacuated safely after it caught fire June 14.

PESTICIDES

Glyphosate is not carcinogenic, EU report confirms

Glyphosate, the active ingredient in the herbicide Roundup and many generic formulations, is not carcinogenic or toxic to reproduction, an assessment conducted by authorities from four European Union countries concludes. The assessment is part of the process to renew the authorization of glyphosate for use in the EU. The current authorization expires Dec. 15, 2022. The assessment is a starting point for further discussion among EU members and a peer-review process managed by the European Food Safety Authority (EFSA) and the European Chemicals Agency (ECHA). EFSA and ECHA plan to organize parallel public meetings in September to discuss the assessment. After ECHA publishes its opinion, EFSA will finalize and publish its assessment, which is expected in late 2022. The European Commission will then determine whether to renew glyphosate's authorization. The commission granted a 5-year renewal for glyphosate in 2017, amid debate over a 2015 report from the World Health Organization's cancer agency that deemed the chemical a probable carcinogen.—BRITT ERICKSON



Glyphosate

UNDERGRADUATE EDUCATION

Teaching chemistry labs from a distance

The pandemic forced chemistry instructors to rethink their undergraduate chemistry lab courses

EVA AMSEN, SPECIAL TO C&EN

The Pontifical Catholic University of Chile mailed students a lab box filled with equipment to learn biochemistry techniques from home during the COVID-19 pandemic.

CREDIT: JOSEFINA JARA

When the Pontifical Catholic University of Chile sent students home during the COVID-19 pandemic, Fernán Federici needed to find a new way to teach his biochemistry lab course. Using open-source equipment, which anyone can reproduce and use, he created a lab box filled with tools to allow students to do experiments at home. Distributing the lab supplies didn't all go smoothly. Mailing the box along the length of Chile caused some delays, and students had to be guided remotely through video calls to make sure everyone was able to use the equipment and understand the experiments. But Federici was surprised at how well the remote course worked.

This past year has been challenging for instructors of undergraduate chemistry courses. It's hard enough to convert in-person lectures to engaging online content, but remotely teaching a lab course requires a whole new level of creativity. Some departments postponed courses; others relied on online videos or emphasized data analysis.

Teaching groups of students as they stand side by side at lab benches has been the gold standard of chemistry education since the 19th century. It's how generations of chemists have learned how to follow a protocol and how to do basic lab techniques. But those standard experiments aren't always representative of current research techniques and don't reflect how researchers work. Some instructors and universities saw the lockdown as an opportunity to completely rethink the way they teach their science students.

Finding the right tools

One of the challenges for instructors who want to move away from lab courses is finding tools that still teach their students the skills that they would have learned from hands-on experimentation.

Eamonn F. Healy was in the middle of teaching his organic chemistry course at St. Edward's University when the COVID-19 outbreak forced students off campus in March 2020. Healy had planned to teach a retrosynthesis module with a lab component after spring break, but like many other chemistry instructors, he was forced to quickly find a way to teach the same concepts online. "I put videos and animations up on the web, but they were going to have to step through mechanisms without my daily guidance in the classroom," he says.

Like Federici, Healy found a creative solution. He had been following the latest online chemistry tools and had found IBM's artificial intelligence–driven tool RXN for Chemistry, which helps chemists predict reactions and design retrosynthesis pathways. Healy quickly created a new set of activities for his students, tailored to learning at home. The adapted course content asked students to design a retrosynthesis using RXN rather than follow or memorize a given reaction (*J. Chem. Educ.* 2020, DOI: 10.1021/acs.jchemed.0c00473).

At IBM Research in Zurich, Teodoro Laino noticed an increase in the total number of reaction mechanisms requested on the RXN platform after many scientists around the world left their labs in April 2020. While much of the activity was the result of chemists planning reactions from home, Laino wasn't surprised to learn that part of the increase in use was due to students using the tool in their courses. "People will always find dozens of ways to apply the technology," Laino says.

Adapting the course using RXN worked for Healy. He noticed that his students—despite not having the in-person support they would have had in the lab—were getting a more realistic experience because they had to plan their own reactions rather than follow step-by-step guidance. "The fact that it is a true functioning expert sys-

> "We took a step back and thought: What kind of DNA detection can everyone do in their own kitchen?"
>
> **—Ariel Lindner,** cofounder and research director, CRI

tem was a huge advantage," he says.

Finding new ways to use existing technologies was the fastest way for educators like Healy, Federici, and many others to quickly adapt lab classes to distance learning. The different open-source kits that Federici combined to create his lab box were not necessarily created to be part of an undergraduate class. These kits included a small polymerase chain reaction machine to amplify DNA, a fluorescence detector, and reagents to carry out experiments.

One of the people Federici collaborated with to create the lab box was Guy Aidelberg, a PhD student working with Ariel Lindner at CRI, an interdisciplinary research center at the University of Paris. A few years ago, Aidelberg and Lindner developed an easy-to-use genetic testing kit to help fight the Zika outbreak in Brazil. The kit included reagents and materials that allowed anyone to detect the Zika virus, even without access to a lab. This inspired them to think about ways to get more people to learn basic genetics experiments. After the Zika kit, Lindner says, "we took a step back and thought: What kind of DNA detection can everyone do in their own kitchen?"

This led Aidelberg to develop GMO Detective, an open-source set of protocols and instructions for finding reagents and basic equipment for running an experiment on food to see if it contains certain DNA sequences indicating genetic modification. It's one of the kits that Federici included in the lab box for his students. The materials were created for citizen scientists and high school students, so Federici's biochemistry undergraduates found them easy to use. Aidelberg thinks that the best way to learn is to have students explore on their own—and make mistakes along the way. "You learn way more than when it all works exactly like it's supposed to," he says.

Rethinking teaching

Federici and Healy each took a very different approach to adapting their courses to distance learning, but both of them noticed that their students were obtaining skills that would have been hard to teach in traditional lab classes, where students often follow the same protocols at the same time to come to a predefined goal. In the updated courses, students were working more independently, which gave them the confidence and ability to learn from their mistakes or to follow a protocol on their own.

What started as emergency solutions in response to the pandemic got the professors thinking about the way they taught. "What I want to do with my students as much as I can is show them what real chemistry is like," says Healy, who plans to keep using tools to let students explore chemical reactions on their own. Federici, meanwhile, wants to incorporate open-source kits in his future lab courses, even when classes are back on campus, to allow students to work together in small groups rather than all crowd around the same machines.

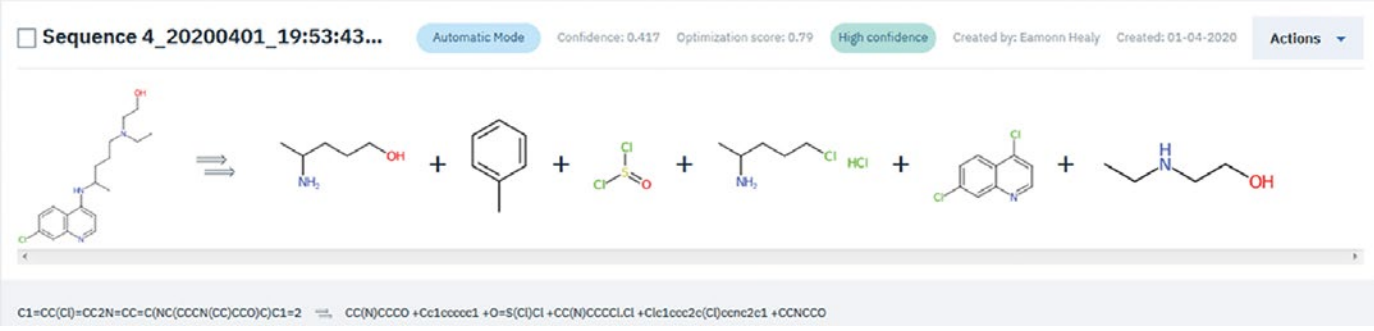
Chemistry instructors who want guidance on how to adapt their courses to distance learning can look to institutions that have designed their entire science curricula with minimal in-person contact hours. Abha Ahuja, formerly a lecturer and curriculum fellow at Harvard Medical School, is an associate professor of natural sciences at Minerva Schools at KGI, a university where students learn online while spending each semester in a different city around the world. When Minerva was launched less than a decade ago, Ahuja and other faculty were able to reflect on the skills they wanted their science graduates to have. "And when we looked at that list, we realized that you don't need a high-tech laboratory and a white coat," Ahuja says. In designing the curriculum, "we had the privilege of starting from scratch."

Minerva doesn't have labs. It doesn't even have its own campus. Instead, students learn through a proprietary online teaching platform and acquire practical experience through internships. For students interested in a lab-based career, their entire practical training comes from internships in research labs.

Xiaotian Liao, who was part of Minerva's first graduating class in 2019, works as a research assistant in Vijay Sankaran's lab at Boston Children's Hospital and Broad Institute of MIT and Harvard, where she researches the genetics of blood-cell-production disorders. She did an internship in the same lab as a student, despite not having taken any undergraduate lab courses. "I didn't even know how to pipette," Liao says.

For a group to take on a student without basic lab experience might seem like a risk, but Ahuja has been pleasantly surprised at how research groups like Sankaran's have responded to Minerva students. "Any lab that has accepted a student from us in the past has welcomed another one."

Another remote university, the Open University (OU) in the UK, has decades of experience in distance learning. "When the university started in the 1970s, they used to send out home experiment kits," says



As part of a revamped organic chemistry course, students at St. Edward's University used IBM's RXN for Chemistry platform to design a retrosynthesis for the antimalarial drug hydroxychloroquine.

CREDIT: *J. CHEM. EDUC.*/IBM

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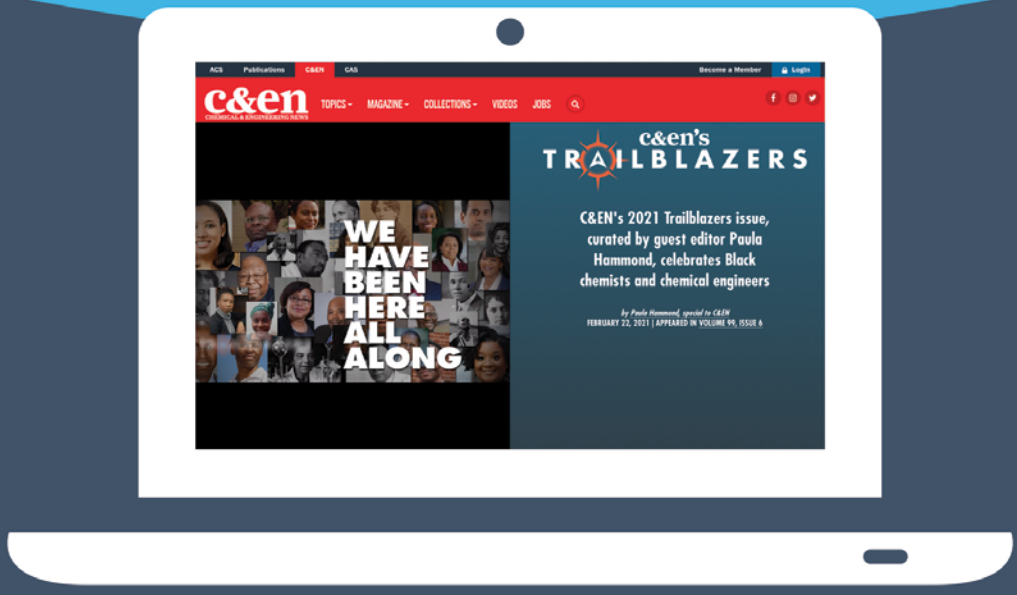

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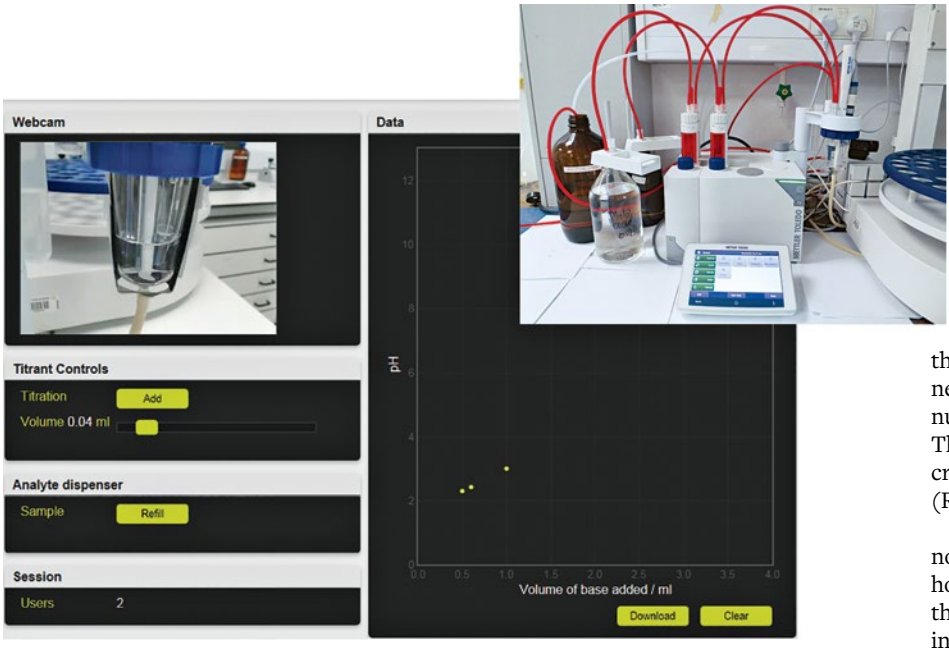


An automated titrator (top right) at the Open University lets students control experiments remotely via a computer interface.

CREDIT: THE OPEN UNIVERSITY

Eleanor Crabb, director of teaching for the OU's School of Life, Health, and Chemical Sciences. Since then, the school has found other ways to engage students from a distance. For example, students can book time on an automated titrator set up in an OU lab in Milton Keynes, England, and control it from anywhere in the world. Or they can watch a live "labcast" and interact with one of the university's staff members as the person does experiments in the lab.

Crucially, some in-person contact is still required for the OU's chemistry students. "We cannot entirely replace the hands-on experience of the lab," says Maria Velasco-Garcia, a senior lecturer in analytical sciences who leads curriculum design for chemistry at the OU. To learn practical skills that can be acquired only in person, such as carrying out an organic synthesis, students meet for a short summer course. But by using remote teaching to cover the preparation and analysis aspects of the course, the school has minimized contact hours.

Challenges ahead

Although Minerva and the OU have found ways to teach chemistry lab skills remotely, they had to carefully consider all the challenges that came with remote teaching and find ways to adapt. But their experience could provide helpful advice for any chemistry departments considering a departure from traditional lab courses.

One challenge for remote chemistry education is providing a safe environment, particularly if students are doing experiments at home. The OU no longer mails kits, because of safety concerns, and when Federici designed his traveling lab experiments, he had to make sure to use reagents that could be sent by post and used safely at home. Some of Minerva's students who do experiments at home use regular kitchen equipment as part of a biochemistry module on food fermentation.

If students later work in a research lab, they will need to learn safety procedures, but many research institutes regularly train all incoming staff. For example, Liao says that her lab has a manual ready for any new group members. Basic skills like pipetting, pouring liquids, or reading specialized equipment can also be learned very quickly in a research lab—as long as labs are willing to train incoming interns.

Without a centralized teaching lab, however, evaluating student performance can be more complex. "One thing I did have to adapt for the course is the grading," Healy says. "I'm never looking for a correct answer. I'm looking for reasonable analysis." Similarly, Ahuja evaluates students' general understanding and communication of their work, even if they all worked on individual projects. "We might assess them on their data visualization, for example, or how they applied statistical tests."

> "What I want to do with my students as much as I can is show them what real chemistry is like."
>
> **—Eamonn F. Healy,** chemistry professor, St. Edward's University

Finally, one downside of fewer lab-based contact hours for science courses uniquely affects chemistry degrees. For a degree to be approved by the American Chemical Society, students need to be in an in-person lab for a certain number of hours. (ACS publishes C&EN.) The same is true for chemistry degrees accredited by the Royal Society of Chemistry (RSC) in the UK.

Unsurprisingly, many universities did not reach the minimum number of contact hours this past year, which has prompted the ACS Committee on Professional Training to propose adjusting the guidelines for the period when regular lab courses were disrupted and the RSC to allow some practical hours to be replaced with virtual labs. But if course instructors continue to teach with fewer contact hours in the lab, accrediting bodies may need to consider permanently changing requirements for chemistry degrees.

Still, lab courses are unlikely to completely disappear, as students who are planning a future career in research will need some lab training eventually, whether that's in a traditional lab course or, as Ahuja suggests, in an internship in a research lab. She explains that a research lab might be a better option because "we want our students who want to learn a particular technique to do it in the authentic setting."

Even IBM's Laino, whose work touches on what the chemistry lab of the future might look like, sees the benefit of lab-based training. He is working on RoboRXN, which links RXN with automated, remotely controlled lab equipment. "However, there will always be the case where something will not work," he says, so eventually, someone is going to have to step into the lab and handle the equipment.

That's why Laino thinks that, despite all the technological advancements, we shouldn't forget traditional lab training entirely: "Not because that's the way we want to continue to do chemistry, but because we want to build a better way of doing chemistry in the future."

ACS central science

Eva Amsen is a freelance writer based in London. A version of this story first appeared in *ACS Central Science*: **cenm.ag/lab-courses**.

Italmatch Chemicals has steadily increased its manufacturing capacity and product portfolio through acquisitions, including the purchase of this multifunctional plant in Arese, Italy.

CREDIT: ITALMATCH CHEMICAL

SPECIALTY CHEMICALS

Italmatch: Making an Italian giant

A once-tiny producer of phosphorus for matches may soon have $1 billion in sales

ALEX SCOTT, C&EN STAFF

Italy's entrepreneurial culture has led to an abundance of small chemical companies across the country. None has grown to become a major multinational corporation with billions in sales, but this could be about to change. Specialty chemical producer Italmatch Chemicals—driven by Sergio Iorio, its charismatic CEO of 20 years—is threatening to break the mold.

An expected uptick in sales of Italmatch's materials for sustainable technologies combined with the company's plan for one or two substantial acquisitions in the next couple of years could see Italmatch's annual sales grow to $1 billion from about $600 million today.

If so, the growth would continue a trend that began in 1997, when Iorio bought into Italmatch as a minority shareholder. At that point, the company was a stand-alone factory supplying phosphorus solely for making the striking surface on matchbooks. Annual sales were less than $18 million.

While Italmatch's growth has been remarkable, 2020 marked a sobering pause. Plummeting business at the start of the pandemic conspired to cause a 13% drop in Italmatch's sales in 2020 compared with the year earlier. According to financial analysts, Italmatch's debt now looks heavy. Any designs the firm has for hitting $1 billion in sales may need to be reconsidered.

As CEO, Iorio knows the pandemic's impact on the financial ledger, but he prefers to focus on how the firm's employees got Italmatch through the pandemic and how that bodes well for the future.

"We didn't know the extent of the crisis. In March and April 2020 everything was absolutely dark," Iorio recalls. Among the market shifts that occurred at the start of the pandemic, a rapid drop in demand for energy hit the firm's water treatment chemicals and detergents for the oil and gas sector.

At that point, Iorio was forced to apply cost-cutting measures across the company. Rather than cut jobs, though, his executive team cut their own salaries by 30% and looked for other ways to trim costs. Many employees contributed to a solidarity fund. In the end, not one of Italmatch's 955 employees lost their job in 2020, Iorio says.

The outcome is a nod to the values of profit sharing and partnership with employees that Iorio says he brought to Italmatch in 1997. These values continue to play an important role in the way the company is managed today, Iorio says.

Back in 1997, Italmatch had just 20 workers, and one product—phosphorus—that it made only for manufacturers of matches. Initially, Iorio was chief financial officer, chief marketing officer, and head of recruitment. "In the first month I had to do everything—issuing invoices to customers, paying suppliers, and writing the checks to the workers," Iorio says.

Iorio quickly recruited a cadre of managers, some of whom are still employed by Italmatch. "They are the backbone of the company today," he says.

The investment firm Bain Capital now owns the majority of Italmatch. But in 1997, the firm's backer was 21 Invest, an Italian venture capital firm. "21 Invest told me to pull out my entrepreneurial spirit," Iorio says. He did that by targeting new applications and customers outside the match business. One of Italmatch's first successful new businesses was using phosphorus as a raw material for flame retardants for plastics.

"Our second big success was phosphorus-based antiwear additives for automotive lubricants," Iorio says. This business emerged after Italmatch secured a low-cost supply of elemental phosphorus by forming a joint venture in China. The venture ensured the company had a steady supply at a time of global phosphorus scarcity and made it a highly attractive partner.

Auto industry suppliers soon began to call on Italmatch for products—including lubricant and fuel additives—that the Ital-

ian firm had never made before. Breaking into such new fields enabled Italmatch to increase sales over a decade to about $120 million.

"But by 2008 more or less we had exploited all the opportunities that we had for organic growth," Iorio says. And so Italmatch began an acquisition spree. Its first, and arguably its most important, acquisition was AkzoNobel's Italian lubricant and specialties business, which had a plant in Arese near Milan.

The AkzoNobel purchase enabled Italmatch to make phosphates, esters, and polymers. "This acquisition opened up a completely new world of organo-specialties to Italmatch," Iorio says. By introducing new chemistry and making the most of the plant with its many batch reactors, Italmatch increased the pretax profit generated by the former AkzoNobel plant from $2.4 million annually to more than $14 million.

More than 10 acquisitions around the world came next, the most recent coming in January. Iorio says each of the early acquisitions added value across the company's four product divisions of water treatment, lubricants, performance products, and flame retardants.

And yet, Italmatch's aggressive acquisition strategy has raised eyebrows among some financial analysts because of the debt it has created—$829 million at the end of 2020. The firm's debt-to-profit ratio of over seven "is high," says Sebastian Bray, an analyst at the investment bank Berenberg. And Italmatch's recent dip in financial performance hasn't helped.

Iorio declines to say whether he is concerned about the company's debt. According to Italmatch's financial report for 2020, debt "remains under strict control."

And in keeping with his optimistic nature, Iorio still plans to make one or two substantial acquisitions that could push the firm's sales closer to $1 billion. "We would consider mid to large acquisitions to speed up the process," Iorio says. But he also expects Italmatch to experience strong organic growth, especially in materials for sustainable technologies, such as those used in electric vehicles.

In a boost for its sustainable-product strategy, Italmatch was recently chosen to participate in three projects partly funded by the European Commission to develop advanced materials for lithium-ion batteries.

Italmatch's involvement includes a precursor for the battery electrolyte $LiPF_6$; a process for extracting metals such as cobalt, nickel, and lithium out of old lithium-ion batteries using chelating agents; and specialty greases that work with brakes for electric vehicles. Lubricants for the brakes of combustion engine vehicles are exposed to high temperatures, while lubricants for electric vehicles must be effective at ambient temperature, Iorio says.

Italmatch's participation in the European electrolyte project builds on an R&D effort the firm began 3 years ago to create safer and more durable electrolytes for lithium-ion batteries. The company currently produces about 1 metric ton of liquid electrolyte precursor each month. "The product works," Iorio says. In the coming years Italmatch hopes to also produce precursors for solid electrolytes.

Italmatch's latest acquisition, in January, was its purchase from Israel Chemicals of intellectual property for RecoPhos, a process for recovering elemental phosphorus from waste. The Italian firm has since been awarded European Commission funding to further develop the technology to recover phosphorus from the ash generated by industrial incinerators.

"Phosphorus is very difficult to extract, so we are trying to introduce the concept of urban mining," Iorio says.

Italmatch's future will involve electric vehicles, circular production, waste recovery, and desalination technologies, Iorio says. "We are starting the process for moving into sustainable products now. The aim is to have more than 50% of sales from sustainable products in the next 5 years," he says.

Italmatch continues to recover from the economic effects of the pandemic and aims to maintain a tight grip on its debt. But rather than dwell on such issues, Iorio is preparing for another wave of substantial growth. If his record is anything to go by, expect Italmatch to break the $1 billion sales mark within the next few years. ■

Italmatch at a glance

- **Headquarters:** Genoa, Italy
- **Key products:** Water treatment chemicals (52% of sales), lubricants (26%), performance chemicals such as personal care ingredients (12%), and flame retardants (10%)
- **2020 sales:** $616 million
- **2020 pretax profits:** $114 million
- **Debt:** $829 million
- **Employees:** 955
- **Manufacturing plants:** 18

Source: Company.

INDUSTRIAL SAFETY

C&EN talks with David Michaels, former OSHA head

US worker safety agency's longest-serving director calls for regulatory transformation

JEFF JOHNSON, SPECIAL TO C&EN

Fifty years ago, the US Occupational Safety and Health Administration—the first federal agency created solely to protect America's workers—opened its doors. Part of the Department of Labor, OSHA changed the landscape of worker health and safety in the US. It is credited with cutting on-the-job deaths per day from 38 in 1970 to 14 today, despite today's much larger workforce.

OSHA's charge is vast: to protect millions of people laboring in factories and fields, meat processing and agriculture, construction, and every type of commerce—all of them essential to the US economy. In addition to workers who go to a job one day and never return home, 3 million are injured annually, according to industry-reported data. These numbers include only those workers known to have died or been injured as a direct result of their jobs, not those who might be harmed—for example, by exposure to a chemical with unknown or undisclosed toxicity.

The agency is chronically underfunded and understaffed, however. It's also criticized by fans and foes alike. Supporters, mostly labor union leaders and worker rights and safety advocates, say it should be more aggressive in promoting worker safety. Opponents tend to be industry leaders and conservative politicians who are generally against regulation and see OSHA as needlessly interfering in the production of valuable goods and services. And, the critics say, if the government would only step out of the way, industry would limit accidents on its own, if only to maintain production and profits.

Under President Donald J. Trump and a Republican-controlled Senate, the deregulators won out. Although Trump nominated a director, he was never confirmed by the Senate, and open inspector slots remained vacant.

The new climate under President Joe Biden "presents the perfect opportunity to build [OSHA] back much better," says former agency director David Michaels.

Michaels knows OSHA's strength and weakness well. He ran the agency from 2009 to 2017, which makes him the longest-serving assistant secretary of labor for occupational safety and health.

An epidemiologist by training, Michaels is now a professor at the George Washington University's Milken Institute School of Public Health. For decades, he has applied epidemiological methods to the health and safety needs of diverse communities, including people incarcerated at New York's Rikers Island, children orphaned by the AIDS epidemic, and workers. His career has alternated be-

CREDIT: COURTESY OF DAVID MICHAELS

US Occupational Safety and Health Administration at a glance

- **Established by:** Occupational Safety and Health Act of 1970
- **Mission:** To ensure safe and healthful working conditions for workers by setting and enforcing standards and by providing training, outreach, education, and assistance
- **2021 budget:** $592 million
- **Parent agency:** Department of Labor
- **Number of workplace inspections by federal inspectors in 2019:** 33,393
- **Number of workers who died on the job in 2019:** 5,333
- **Three most frequently cited violations of standards in 2020:** Fall protection, construction; hazard communication, general industry; respiratory protection, general industry

Source: US Occupational Safety and Health Administration.

tween academia and government. During a stint at the US Department of Energy, Michaels led a reform effort within its huge and troubled nuclear weapons manufacturing and cleanup program. He has a keen sense of what workers face and of both the power and shortfalls of government agencies.

Michaels points out that when OSHA was created, the initial buzz brought a national focus on industrial safety, and fatalities and injuries declined. Death and injury rates have flatlined in recent years, however.

"Pouring more money into rebuilding the current system would be a mistake," he says. "It is time to reimagine the US industrial safety and health system."

Biden should support this, Michaels says, since he issued an executive order on his inauguration day that called for modernizing federal regulations. So too should Biden's labor secretary, Marty Walsh, who began his career in the unionized building trades. "As a construction worker, I think I would want, first of all, safety on the job site," Walsh told NPR in an interview in April. "When I was a young construction worker, OSHA had more of a presence on job sites—not after an accident happened, but before an accident, to make sure these job sites were safe. That was number 1." (Biden has nominated Doug Parker, the current head of the California Division of Occupational Safety and Health, to lead OSHA, but as of C&EN's deadline he had not been confirmed by the Senate.)

"Before OSHA, there was no government agency to call and no clear legal responsibility for employers to supply a safe workplace," Michaels notes. "There were laws in some states, but with much less power than OSHA. There were no limits on workplace exposure to hazardous chemicals and no mechanism to bring this about and to reduce exposure."

As a start to limiting chemical exposure, OSHA in its first couple of years turned to so-called industry consensus standards developed and used by companies. They were adopted without modification in hopes of improving them later. That proved to be nearly impossible because of OSHA's restrictive regulatory maze coupled with opposition from industry and many members of Congress.

On average, it takes OSHA over 10 years to issue a new chemical standard, and it has issued only 32 new standards in 50 years, Michaels says. One of those was an exposure limit for silica dust, which can cause serious lung disease. OSHA began the update process in 1997 and faced significant industry opposition. When the agency issued the final standard in 2016, it dropped the limit from 250 to 50 µm per cubic meter of air over an 8 h period. "Nineteen years to get through the law's hurdles and to update a pathetically weak standard," Michaels says.

Michaels estimates that 90% of OSHA's permissible exposure limits date to industry consensus standards of the 1960s. The agency itself says that it "recognizes that many of its permissible exposure limits (PELs) are outdated and inadequate for ensuring protection of worker health."

"If you look at the large, global chemical manufacturers, none of them use OSHA standards, because they know the standards are not safe," Michaels says. But even when manufacturers follow stricter standards to protect their workers, the weaker OSHA standards put companies at legal risk. For instance, if a company sells a chemical to another that follows the agency's standards and a worker gets sick, the worker and the buyer may sue the supplier, Michaels says. "It is in the long-term interest of large chemical companies to improve OSHA standards, and some have quietly told us so."

"If you look at the large, global chemical manufacturers, none of them use OSHA standards, because they know the standards are not safe."

Industry support is what it finally took for OSHA to update its standard for beryllium, which can also cause serious lung disease. The DOE uses beryllium in nuclear weapons and developed a strong standard for exposure during Michaels's time there. Decades slipped by and finally, with support from industry and unions, OSHA adopted the DOE standard for all US workplaces that use beryllium. That standard was one of Michaels's final acts at the agency.

Meanwhile, whether standards are strong or weak, penalties for breaching them are minimal. OSHA's maximum penalty for a serious violation is merely $13,653. And OSHA inspectors—or even those at the 22 state agencies that operate under its umbrella—are unlikely to find violations on their own. In total, the US has only about 5.6 workplace safety inspectors for every million workers. Forty years ago, there were about 17 per million workers.

"I have been told by chemical manufacturers that they see OSHA fines and penalties as inexpensive industrial hygiene consultations" rather than as a deterrent to allowing unsafe workplaces, Michaels says. "Meaning they have to pay more for an outside consultation than they have to pay for an OSHA fine," he adds. "It is a means for a company to get a good and cheap assessment by a regulatory agency with little risk or cost."

These failings, combined with a growing number of companies that claim not to be responsible for the safety of contract, temporary, or gig workers, demand a rethinking of US industrial safety law, Michaels says.

He wants to initiate a national conversation about worker safety regulations in the US and hopes that Biden's executive order will lay the groundwork for that examination and necessary changes.

Michaels suggests that a regulatory approach similar to that of Australia, New Zealand, and a few other countries could serve as a model to address the changing workforce. Those countries have a "duty of care" mandate: companies must ensure and demonstrate their production processes and products are not harmful to their workers, their customers, or the public. The definition is broader than the traditional employer-employee relationship that currently serves as the basis for US safety laws, Michaels notes.

It would require a significantly different approach to safety regulation. Other fundamental problems of OSHA's 50-year-old regulatory system, such as low penalties and many opportunities for opponents to stall or block stronger regulations, must also be addressed to enhance safety, Michaels says.

"It is time for a bold new approach to workplace safety and an overhaul of the system."

ACS CHEMICAL HEALTH & SAFETY

Jeff Johnson is a freelance writer based in the US. A version of this story first appeared in *ACS Chemical Health & Safety*: **cenm.ag/overhaulosha**.

CREDIT: MIKE REDDY

On the shoulders of giants

When biotechs need a molecule for drug trials or the market, they often turn to big pharmaceutical services firms

The drug industry's biggest players are massive. Pfizer's sales last year were almost $42 billion. Johnson & Johnson's were $83 billion. These companies have deep internal resources, and they closely direct any tasks they farm out to smaller firms.

But these days, many new drugs come from much smaller biotechnology firms that don't have nearly the same resources. So when it's time to manufacture the molecules at the heart of their drugs, biotechs often turn to outsourcing companies for help.

Increasingly, these outsourcing companies are big—much bigger than the biotech firms they are aiding. But that difference doesn't bother many biotech executives, who appreciate the helping hand of a large, experienced partner. Read on for three stories of small biotechs that turned to large outsourcing partners to manufacture their small-molecule drugs.

Inside

Synthesizing a natural product

Mithra chooses Seqens to scale up manufacturing of an estrogen found in nature

MICHAEL MCCOY, C&EN STAFF

Seqens's facility in Villeneuve-la-Garenne, France, was established almost 130 years ago to extract the malaria treatment quinine from the bark of the cinchona tree. It is considered one of the oldest pharmaceutical chemical sites in the world.

Today, Villeneuve is making the main ingredient in one of the world's newest drugs: Mithra Pharmaceuticals' oral contraceptive, Estelle, approved by the US Food and Drug Administration on April 15 and now marketed by Mayne Pharma. The ingredient is estetrol, a natural estrogen touted as having a better side-effect profile than the estrogen in most contraceptives. Synthesizing it for use in a drug, though, is no easy task.

Like the site where estetrol is being made, the story behind the new drug is many years old. Estetrol was first identified in 1965 by Egon Diczfalusy, a reproductive endocrinologist at the Karolinska Institute. But Diczfalusy didn't pursue its potential as a contraceptive, says Jean-Manuel Fontaine, Mithra's vice president of external and scientific affairs. "It was kind of shelved for 40 years," Fontaine says.

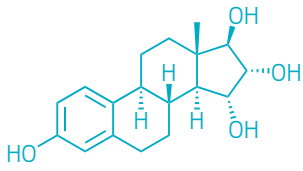
Estetrol, also known as E4, was revived around the year 2000 by Herjan Coelingh Bennink, an executive at the contraceptive maker Organon. "He was convinced that E4 would be a fantastic estrogen to explore as a therapeutic agent," Fontaine says.

Bennink was struck by the high concentration of E4 in fetal blood at 9 weeks of pregnancy. "If at the ninth week of gestation you have such high concentrations at such a delicate moment of life, it's got to be safe" was Bennink's reasoning, Fontaine says.

The leading oral contraceptives today are based on ethinyl estradiol, a synthetic derivative of another estrogen, estradiol. Like Estelle, many also include the progestin drospirenone. Current products are effective at preventing pregnancy, but they carry the risk of liver damage and blood clots and are associated with an increased risk of breast cancer. Moreover, ethinyl estradiol is considered an endocrine-disrupting chemical that, after people excrete it, can build up in creatures living in rivers and oceans. Mithra says estetrol doesn't accumulate in living organisms.

Estelle at a glance

- **Active ingredient:** Estetrol



- **Discovered:** 1965 by Egon Diczfalusy; conceived as a therapeutic around 2000 by Herjan Coelingh Bennink
- **Indication:** Pregnancy prevention
- **Innovation:** An estrogen with fewer side effects than current products
- **Status:** US Food and Drug Administration approval in April 2021

Seqens's 128-year-old site in Villeneuve-la-Garenne, France, continues to get new investment.

CREDIT: SEQENS

Bennink left Organon soon thereafter to form his own company, Pantarhei Bioscience, which launched studies on estetrol in women's health and oncology applications. In 2009 the company formed a contraceptive-focused joint venture with Mithra; by 2015, Mithra had acquired full rights to estetrol for contraceptive and menopausal uses. Pantarhei continues to develop the molecule for oncology and veterinary use.

Mithra had picked Cambridge Major Laboratories' ChemShop unit in Weert, the Netherlands, to manufacture estetrol in the early days of development. Output was enough for preclinical studies and Phase 1 clinical trials, but yields were low. "There was a need to find a different provider to get a better yield," Fontaine says. Mithra focused its hunt for another supplier on western Europe to ensure intellectual property protection and rapid response.

Meanwhile, executives at Seqens had their eyes on estetrol. A drug services and specialty ingredient firm based in France, Seqens operates 24 plants and seven R&D centers across Europe, North America, and Asia. Its pharmaceutical synthesis business includes facilities acquired from several long-standing players in the business, including PCAS and Uetikon in Europe and PCI Synthesis in the US.

Philippe Clavel, Seqens's vice president for pharmaceuticals, says his team saw estetrol as a good fit. The company had experience making another hormone at its site in Aramon, France, and the Villeneuve facility likewise had the equipment and health safeguards needed to produce a compound considered highly potent. Mithra apparently agreed. It chose Seqens out of the 10 contract manufacturers it was considering, and in 2012 the two firms signed an agreement covering production of estetrol for clinical trials.

Estetrol is not an easy molecule to manufacture, according to Fontaine and Clavel. Development of the industrial-scale process now being carried out in Villeneuve took about

4 years, mostly at Seqens's R&D center in Porcheville, France, Clavel says.

A production campaign, which takes several months, starts with a phytosterol extracted from soybeans. Getting to estetrol requires eight synthetic steps plus associated purifications. Multiple protection and deprotection steps are needed, Clavel says, as are tricky oxygenation reactions. All the while, both the stereochemistry and the molecule's four hydroxyl groups must be maintained.

Seqens first established production at an existing unit in Villeneuve that it modified for the purpose. But as the contraceptive cleared hurdles in clinical trials and regulatory approval looked more and more likely, Clavel and his team took stock. Estelle could eventually require multiple metric tons per year of estetrol, more than the modified facility could make. They realized they would have to step up to keep Mithra as a customer.

So Seqens decided to spend roughly $35 million on a brand-new facility in Villeneuve dedicated to estetrol production. The firm began construction in the second half of 2018 and completed it in mid-2020. Last August, the president of France, Emmanuel Macron, visited Villeneuve for the new facility's inauguration. Seqens is validating the facility now, Clavel says, in anticipation of beginning commercial production later this year.

Clavel says Macron's visit demonstrates the French government's understanding that more and more pharmaceuticals are considered highly potent and that the ability to make them is key to keeping drug production alive in the country. "France has very few manufacturing facilities of this type," Clavel says. "What is at stake is France's and Europe's sovereignty in manufacturing highly active APIs."

Both Clavel and Fontaine say the new facility in Villeneuve may not be enough if Estelle and estetrol live up to their potential. In addition to the US, Estelle has been approved in the European Union and Canada. KBC Securities, an investment firm that covers Mithra, says Estelle could bring in nearly $1.2 billion in sales by 2031, capturing 8% of the global oral contraceptive market.

And Mithra sees potential for estetrol in other applications as well. "Next is menopause, where a safer estrogen is even more important," Fontaine says. The company is conducting clinical trials of an estetrol-based product for relieving menopause symptoms and plans a product for perimenopause, also known as menopause transition.

Beyond reproductive health, Mithra is researching the use of estetrol in wound healing and reducing neonatal encephalopathy. And it is even conducting clinical trials of estetrol to help hospitalized patients with COVID-19 recover.

Anticipating continued growth in demand for estetrol, Mithra is studying the best way to make it. "We have a whole department dedicated to the synthesis of E4," Fontaine says. Among the scientists' goals are production routes with fewer steps and syntheses that incorporate both chemical and biotechnological transformations.

Fontaine also wants to diversify Mithra's supply of estetrol beyond the Villeneuve complex. Seqens and Mithra are already discussing the idea of establishing Seqens's Aramon site as a backup, Clavel says, and Seqens is prepared to build another dedicated facility that would be ready by 2027 or 2028.

Fontaine says Mithra is looking at a range of companies for its future manufacturing needs, but he says he's committed to his relationship with Seqens. "It's an important contract for them and for us," Fontaine says. "We're going to be working together for many years."

A long collaboration arrives at production

Aurinia will use a dedicated Lonza plant to produce its new lupus nephritis drug

VANESSA ZAINZINGER, SPECIAL TO C&EN

On Friday, Jan. 22, at around 3:00 p.m. on the US West Coast, Robert Huizinga celebrated a milestone. He received word that the US Food and Drug Administration had approved voclosporin, a drug developed by Aurinia Pharmaceuticals for the treatment of adults with lupus nephritis. To Huizinga, Aurinia's executive vice president of research, the FDA approval was the culmination of more than 15 years of work.

"It was immensely gratifying," he recalls. "I will remember that day for the rest of my life."

Voclosporin was discovered in the mid-1990s at Isotechnika Pharma, which merged with the Canadian biotech firm Aurinia in 2013 and took the firm's name. Huizinga led the clinical development program for voclosporin before and after the acquisition—including a shift in the synthesis from one that yielded racemates to one that yields a single trans isomer. The result was the first FDA-approved oral therapy for lupus nephritis.

Now Aurinia is gearing up to take the drug to market under the trade name Lupkynis. In December, the company entered an agreement with the giant contract manufacturer Lonza, which will build a dedicated plant for voclosporin in its small-molecule active pharmaceutical ingredient (API) facility in Visp, Switzerland.

Lupus is a chronic autoimmune disease that, if poorly controlled, can lead to lupus nephritis, a dangerous kidney condition. Lupus disproportionately affects women and people of African or Asian background. In the US, 1 out of every 250 African American women will develop lupus, according to a 2015 paper in the journal *BMJ Clinical Evidence*.

Lupus nephritis has historically been treated with high doses of steroids and calcineurin inhibitors such as cyclosporine. But calcineurin inhibitors cause side effects that can limit their long-term use. High doses of cyclosporine can lead to arterial hypertension or hyperlipidemia, both of which are risk factors for cardiovascular disease—the primary cause of death for people with lupus nephritis.

"There's been a long history of drugs failing on lupus nephritis," Huizinga says. But over time, "we discovered these really interesting aspects of voclosporin that differentiate it from the legacy drugs that have been used in this disease."

Voclosporin is an analog of the immunosuppressive drug cyclosporine in which a single amino acid has been modified. Voclosporin binds more effectively to calcineurin than cyclosporine does, making it effective at much lower doses. In Phase 2 and 3 clinical studies, voclosporin, given in combination with mycophenolate mofetil and steroids, was twice as effective as the current standard of care at achieving complete renal response—a measure of protein levels in the kidneys that is a key marker of recovery from lupus nephritis.

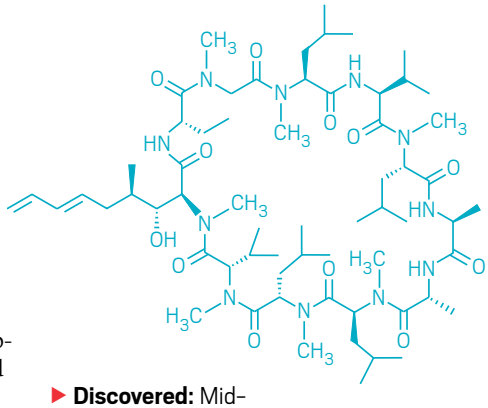
In addition, the tweak to the amino acid changes the way the drug is metabolized. It has fewer metabolites and so has fewer adverse effects and a more predictable pharmacokinetic profile across ethnicities, ages, sex, and clinical profiles, according to Aurinia. The compound seems to have no effect on lipid concentrations, thereby reducing the risk of hyperlipidemia.

More than 2,600 patients used voclosporin during its years in development, a number Huizinga is proud of. "Without their participation, and without organizations like the Lupus Foundation of America and the National Kidney Foundation, we would not have been able to do this," he says. "Drugs are developed on the backs of relationships, and great drugs are developed on the backs of great relationships."

Huizinga considers Aurinia's cooperation with Lonza one of those great relationships. It goes back to 2004, when Lonza began to offer development services to Isotechnika and provided materials for clinical trials. Christian Dowdeswell, Lonza's vice president of commercial development for

Lupkynis at a glance

- **Active ingredient:** Voclosporin



- **Discovered:** Mid-1990s by Isotechnika Pharma scientists
- **Indication:** Lupus nephritis
- **Innovation:** An analog of cyclosporine in which a single amino acid has been modified
- **Status:** US Food and Drug Administration approval in January 2021

Having its own facility at Lonza's Visp, Switzerland, site means Aurinia Pharmaceuticals won't have to wait for space at Lonza's multipurpose complex, a part of which is shown here.

CREDIT: LONZA

small molecules, says the company is keen to support customers from an early stage through launch and commercialization of a product. “Taking the final step to enter into a commercial supply agreement was a natural progression of the way that we worked with Aurinia,” he says.

Isotechnika developed the single-enantiomer synthesis of voclosporin during a period of collaboration with Roche. Over the years, Lonza and the biotech firm were able to further refine the manufacturing process, making it as efficient and sustainable as possible, Dowdeswell says.

That included optimizing solvents and reagents for low toxicity profiles. Lonza developed a crystallization technique for voclosporin, a peptide, allowing the firm to move away from chromatography and the large amounts of associated solvent waste. The key was gaining a deep understanding of the impurity profile, Dowdeswell says, and the mechanics around controlling the crystallization procedure.

“There was a good deal of work in getting to a very scalable and controllable crystallization procedure, which, for a peptide, is no small feat,” Dowdeswell says. “But it’s our bread and butter to solve complex technical problems to make an API scalable.”

Voclosporin will be made in Visp at a dedicated plant that Lonza calls a monoplant. The Swiss firm opened its first monoplant, for Clovis Oncology’s cancer drug rucaparib, in 2018. Aurinia’s monoplant is scheduled to open in 2023; until then, demand will be met from inventory.

For Aurinia, a monoplant eliminates the inevitable wait for a manufacturing slot in a multipurpose plant. And Lonza can respond to changes in demand in weeks rather than months, Dowdeswell says. Max Donley, Aurinia’s executive vice president for operations and strategy, adds that monoplants allow manufacturing to be nimble, which is valuable for a new product that might encounter peaks and troughs in demand.

The privilege of a monoplant comes at a price, but neither Lonza nor Aurinia see this as significant in the grand scheme of things. “It’s a multivariable equation, for sure,” Donley says. “But, you know, as you think about the ability to move in a scalable way, without having to put the capital investment in place to build your own plant, it makes a lot of sense for a company in our position.”

Aurinia isn’t revealing its manufacturing targets for voclosporin, but it looks set to scale up. The company plans to file a marketing authorization application with the European Medicines Agency this year and has signed a licensing agreement with Japan’s Otsuka Pharmaceutical for the commercialization of voclosporin in Europe and beyond.

Huizinga says the drug will likely find applications beyond lupus nephritis. Already, a small study in Europe is exploring its effects on SARS-CoV-2-positive renal transplant patients. Meanwhile, Aurinia is working on treating kidney and autoimmune diseases with new compounds that could one day join the manufacturing line at the Visp monoplant.

Aurinia’s promising future is beginning to draw speculation over its continuing independence. In May, the UK newspaper the *Times* reported on “whispers” that AstraZeneca and GlaxoSmithKline are interested in a potential takeover. Donley says an acquisition is “not our strategy” but that an offer for the company would get “due consideration.” Come what may, the company’s priority, he says, is the patients whom voclosporin can help.

Vanessa Zainzinger is a freelance writer who covers the chemical industry.

A small firm checks in at a big partner's complex

Cassava picks Evonik to make the experimental Alzheimer's treatment simufilam for Phase 3 trials

RICK MULLIN, C&EN STAFF

The controversial approval of Biogen's Aduhelm earlier this month spotlights the challenges for big companies developing antibody treatments for Alzheimer's disease. The US Food and Drug Administration signed off on the drug, but many neurologists were unimpressed, if not frustrated, with the approval, viewing the antibody's impact as marginal at best and the FDA's vetting as substandard.

Recent results from a Phase 2 clinical trial of a small-molecule Alzheimer's disease treatment developed by the tiny biotech firm Cassava Sciences, however, suggest a new approach to halting the progress of the seemingly intractable neurodegenerative disease.

"Clinical data around our compound is very promising," says Remi Barbier, CEO of Austin, Texas–based Cassava, which Barbier founded as Pain Therapeutics in 1998. "If the data continues to replicate, then we are looking at a monster, monster commercial manufacturing opportunity."

Something of a David among pharma Goliaths, Cassava has signed with a giant among contract development and manufacturing organizations (CDMOs)—Evonik Industries—for Phase 3 and potentially commercial manufacturing of simufilam, the active pharmaceutical ingredient (API) in its drug candidate. Still in its early stages, the project may seem lost on Evonik's sprawling Tippecanoe campus in Lafayette, Indiana, a former Eli Lilly and Company factory. But it could take up sizable real estate at Tippecanoe if Phase 2 results carry over to Phase 3 and the drug is approved.

And Barbier is optimistic that simufilam will score that breakthrough.

Most drugs being developed for Alzheimer's disease are large molecules that target the buildup of amyloid-β plaque or tau fibrils in the brain. While these drugs reduce plaque buildup, there is no conclusive evidence of improved cognition as a result. Simufilam, on the other hand, aims to neutralize the ill effects of neuroinflammation and neurodegeneration attributed to plaque buildup.

"It works by binding with superhigh affinity—with femtomolar affinity—to target a protein called altered filamin A," Barbier says. "It's a scaffolding protein, one of several scaffolding proteins that physically hold you up."

People with Alzheimer's disease have an altered shape of filamin A. Simufilam binds to receptors on the protein, restoring its shape and function. "And when you restore the shape and function of filamin A," Barbier says, "you stop many of the downstream pathologies associated with Alzheimer's disease." Cassava holds seven patents covering a range of filamin-binding molecules. It hasn't disclosed which one it is developing as simufilam.

The compound demonstrated positive cognitive effects with no safety issues in Phase 2b studies that were completed last year. In a 6-month interim analysis of a separate, ongoing study, simufilam improved cognition in people with Alzheimer's disease, the firm says.

Looking for a contract manufacturer to produce simufilam for Phase 3 trials, Cassava came across Evonik serendipitously, according to Barbier. "One of our guys here worked with Evonik previously. He had a good experience, so we put them on the short list," he says. The German firm came out "head and shoulders" above the rest on that list in subsequent due diligence, Barbier says.

Barbier says he had learned to approach large contract manufacturers with caution. "If you get people from a big company that are rigid and tell you, 'This is how we have always done things,' you should pretty much run away." Evonik, he says, listened to Cassava's requirements and reviewed earlier simufilam development work so it could understand unique aspects of the chemistry without imposing a template approach.

"We found a team that rolls up its sleeves," Barbier says. "They don't start with 'The problem is . . .' and then launch into 30 different problems. We know what the problems are. What we're looking for are solutions."

Cassava liked Evonik well enough not to pursue a single-source deal with another service firm that offered to provide both API and finished-dose drug production. Cassava, according to Michael Zamloot, senior vice president of technical operations, decided to choose the best fit at each stage rather than opt for the theoretical efficiency of working with a single service company.

"We have a selection process that is

Simufilam at a glance

- **Discovered:** 2010 by Cassava Sciences scientists
- **Intended indication:** Alzheimer's disease
- **Mechanism:** Restores normal shape and function of altered filamin A, a scaffolding protein
- **Status:** Phase 3 clinical trial planned for second half of 2021

Evonik Industries acquired its Tippecanoe site in Lafayette, Indiana, from Eli Lilly and Company in 2009.

CREDIT: EVONIK INDUSTRIES

multivariable," he says. "We consider the facilities, the scientific staff, the track record of the company, their experience with regulators." A good working relationship with Evonik emerged, Zamloot says.

Working with a small company is not a new experience for Evonik, says Eric Neuffer, the firm's senior director of CDMO sales. "We actually enjoy working with smaller companies because they are quick to make decisions," he says. And the Cassava project has proceeded without the typical holdups.

Those holdups can include issues with the handling, isolation, and stability of APIs or unusual solvent requirements, Neuffer says. But Cassava presented a "very well-developed package."

Neuffer says capacity considerations were essential to striking a deal. "Part of the reason they came to us is that they saw we had the right-size equipment," he says. "They were in clinical Phase 2 heading into Phase 3. They needed batches less than 100 kilos to supply their clinicals, with the capability to get into metric tons. So we are operating this process with anything from 500 gallons to up to 4,000 gallons."

Cassava has had only a virtual look at the vessels at its disposal because all meetings between the companies have been via phone and videoconference since they started working together early last year. "Just recently," Neuffer says, "we gave them a video introducing them to the people involved with the project. It then went into each of the facilities and showed what was going on in the reactor."

> "If the data continues to replicate, then we are looking at a monster, monster commercial manufacturing opportunity."
>
> **—Remi Barbier,** CEO, Cassava Sciences

All contracts present challenges, says Paul Nichols, director of research, development, and innovation for Evonik's healthcare division. But not every project brings the same level of excitement. "When you talk about the possibility of being involved in bringing an Alzheimer's drug forward, this is something that motivates people at our site," Nichols says.

Bernard Munos, a senior fellow at FasterCures, a center at the Milken Institute, sees some justification for excitement about Cassava. "They offer what patients, clinicians, and investors have been clamoring for in the Alzheimer's space but have never received," he says in an email, commending Cassava on a comprehensive hypothesis that integrates suspected disease triggers from prior research including amyloid-β toxicity.

"This is far more elaborate than the rationales that support the β-amyloid or tau hypotheses," Munos says. Cassava needs to do more to develop a companion diagnostic, says Munos. But he is impressed with the trial data to date. "No retrospective analyses; no anecdotal evidence; no trial protocol modification in midcourse; no 'novel' composite end points; none of the tricks that companies resort to when they cannot support their hypothesis with well-run, controlled trials."

Simufilam enters Phase 3 with some momentum, though Phase 3 has been unkind to other potential Alzheimer's therapies. In any case, Evonik says it is ready to scale up. And the partners are looking toward an important near-term milestone—meeting in person at the Tippecanoe site as COVID-19 restrictions are lifted. "Hopefully we can have them out to our site this summer," Neuffer says. ■

COMMENT

Highlighting the chemical technical professional

JENNIFER MCCULLEY, CHAIR, ACS COMMITTEE ON TECHNICIAN AFFAIRS

As we reflect upon the past year, the American Chemical Society Committee on Technician Affairs (CTA) recognizes the immense value that chemical technical professionals (CTPs) have brought to the chemistry enterprise. The fact is, today, CTPs make up the majority of people working on-site in laboratories. Their work can include collecting, preparing, and analyzing samples on instruments; performing noninstrument sample analysis; and conducting experiments. Chemical technicians are the quintessential linchpin of the lab.

The committee had the pleasure of hearing several CTPs share their successes and challenges in research and development, quality control, and other vital technical roles. During the ACS Spring 2021 virtual meeting, at a symposium titled "Quantity and Quality: Insights and Research from Chemical Technical Professionals," which was sponsored by the Division of Analytical Chemistry, several CTPs presented their contributions, successes, and challenges in the analytical chemistry field. The speakers appreciated the opportunity to present, and for a few it was their first time presenting at a conference. During the ACS Fall 2020 virtual meeting, CTA sponsored a panel session in which members shared insights on their jobs. Early- and midcareer analytical chemists learned about new ideas for their career development, and individuals interested in chemical industrial careers got a glimpse into the field. There were four networking sessions with special topics each day of the conference. Topics included career advice, a day in the life of a CTP, and navigating COVID-19 guidelines in the lab. The sessions received positive feedback, and one participant stated that as a result, they gained confidence during a career transition.

Over the years, the committee has recognized many CTPs with the National Chemical Technician Award (NCTA). The award honors excellence and professionalism among technicians, operators, analysts, and other applied chemical technology professionals. The committee evaluated nominations primarily on technical achievement, leadership, mentoring, communications and publications, awards, community activities, and contributions to quality, safety, and other initiatives. Nita Xu of Dow was selected by CTA as the 2021 award winner. As the committee read Xu's nomination, it was clear that she's highly committed and dedicated to her work. Xu's patents and products, her dedication to safety, and her willingness to mentor others made her a standout choice for the national award.

ACS membership offers chemical technical professionals many opportunities to connect, engage, and grow.

In addition to the NCTA, CTA and the Younger Chemists Committee partnered to grant younger chemists with travel awards to attend the ACS Leadership Institute. The institute supports and enhances the creation of leaders at ACS. Recipients of the grant are given the chance to highlight the role of CTPs and serve as strong leaders for future roles in industry, academia, and ACS.

The committee serves to help with professional development activities for CTPs. Local section leaders and CTPs interested in organizing activities are invited to find inspiration in several CTA activities. A few to consider are networking sessions, career panels, benefits-of-membership messaging, and speaker invitations. Activities can be nominated for the 2022 ChemLuminary Award for Best Event or Activity Organized by, or Benefiting, the Applied Chemical Technology Professional Community. The ChemLuminary Awards are an esteemed program that recognizes ACS local sections, regional meetings, divisions, and international chapters for their extraordinary work in promoting chemistry and the chemical sciences.

ACS membership offers CTPs many opportunities to connect, engage, and grow. The salary calculator, résumé-writing resources, interview strategies, and career consultants are all valuable resources to CTPs. One CTA committee member stated, "Membership in a professional organization such as ACS is essential for a chemical industrial technician or professional who wants to maximize his or her career potential."

ACS membership also provides opportunities for CTPs to gain and enhance their leadership skills by taking leadership courses or accepting a leadership position through local section committees (such as Technicians Group, Industry, or Career) or national committees such as CTA, the Local Section Activities Committee, or the Membership Affairs Committee.

CTA uses social media channels like Twitter and LinkedIn to communicate resources that would benefit CTPs. Topics include project management, communication, and presentation skills. In today's world of being overwhelmed with information, our constituents can look to these channels for information filtered for their needs.

The committee is looking for consultants and volunteers who can guide CTA toward its vision and mission to support and advance the chemical technical professional through career development. For information on CTA, please visit our website at www.acs.org/cta. Feel free to contact the committee at cta@acs.org.

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

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Diversity, equity, inclusion, and respect: It must be different this time

PAUL W. JAGODZINSKI, CHAIR, ACS BOARD OF DIRECTORS

Three years ago, Teri Quinn Gray (ACS director, District III) told me that, as a White male leader with a commitment to diversity, equity, inclusion, and respect (DEIR), I have a responsibility to be proactive in promoting and making change. Her comments provide a clear message: it's not about intent; it's about impact. It is important that all privileged individuals recognize their privilege and that all privileged leaders embrace their responsibility to act for social justice.

The American Chemical Society strives to be a welcoming, inclusive, and supportive professional society. Have we achieved our goal? No. Unfortunately, at present, everyone does not feel included and respected in ACS. Do we engage in many activities that move us in the right direction? Yes. For more than 90 years, ACS has had committees that advocate for marginalized members of the chemistry enterprise. Moving forward, how can ACS do better? What are we doing for lasting change? How do we make it different this time?

The ACS Board of Directors added goal 5 to the ACS Strategic Plan, "Embrace and advance inclusion in chemistry," which is elaborated as "**Promote** diversity, equity, inclusion, and respect; **identify** and dismantle barriers to success; and **create** a welcoming and supportive environment so that all ACS members, employees, and volunteers can thrive" (emphasis added). Promote. Identify. Create. These are actions that must result in impact. We don't need another study or task force . . . we need action.

▶ We now have a newly formed Office of Diversity, Equity, Inclusion, and Respect, which is run by a new vice president for DEIR, who reports directly to the CEO. We now have a mandatory 4-hour training session for staff. Additionally, during May and June we held three 4-hour workshops to hear from a variety of ACS members and staff about what actions need to be taken to change ACS culture to ensure that everyone feels included and respected in ACS.

▶ We now have a voluntary session for ACS volunteer leaders titled "Leading Inclusively: Beyond Lip Service," which started in March and is offered throughout 2021. The course will help guide participants to use a common language for DEIR discussions with the goal of embedding inclusive behaviors in everyday culture. I encourage all journal editors, officers of local sections and divisions, officers of international chemical sciences chapters, faculty advisers to student chapters, career consultants and course facilitators, and members of the ACS Board of Directors who haven't participated to register.

▶ During the past 9 months, four members of the board of directors have published Comments in C&EN detailing their commitment to and perspectives on DEIR. Comments from Christina Bodurow of District II, Gray of District III, Lisa Houston of District IV, and ACS director-at-large Ingrid Montes described activities that ACS is currently engaging in, and they suggested activities that individuals and entities can initiate to make our society more welcoming and inclusive. We all have a responsibility to ensure that everyone is valued for what they bring to our society and to the chemistry enterprise.

▶ The board now holds a "diversity moment" at the beginning of each board executive session to reinforce our individual and collective commitments to DEIR. During this moment, a board member describes something in their experience that has had an impact on them and may offer a suggestion for how the board might change to increase its positive impact on DEIR in the society. Some committees and groups within ACS have been doing this for a while, and the board is following their lead.

We need everyone in the chemistry enterprise to make a difference.

We will continue to grow Project SEED (a summer program for economically disadvantaged high school students) and the ACS Scholars Program (scholarships for undergraduate students from racial and ethnic groups historically underrepresented in the chemical sciences), but we will not use these established programs as our reaction to the question "What is ACS doing about DEIR?" We must do more.

We need everyone in the chemistry enterprise to make a difference. When you are speaking with 1 person or in front of 1,000 people, let them know your personal commitment to goal 5 and DEIR. We must leave ACS stronger than when we inherited it from our dedicated predecessors. Creating an ACS that is truly welcoming and inclusive is the challenge of our time as ACS members, volunteers, and leaders. We need action! We cannot afford to fail.

I encourage members and volunteers to reach out to me with their thoughts on inclusion and equity in ACS (p.jagodzinski@acs.org).

I am personally and professionally committed to goal 5. Are you?

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

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ACADEMIC POSITIONS

Senior and Junior Faculty Positions in Imaging Sciences, Georgia State University, Atlanta, GA, USA

Georgia State University

Georgia State University (GSU) invites applications to fill the first of two senior-level tenured faculty positions in imaging sciences at the Associate or Full Professor level along with a tenure-track position at the Assistant Professor level. GSU has a broad range of expertise in imaging science that extends from the nano and microscopic to the astronomical scale, and the University supports several imaging-related centers and institutes, including the Center for Translational Research in Neuroimaging and Data Science (TReNDS), the Center for High-Angular Resolution Astronomy (CHARA), the Center for Advanced Brain Imaging (CABI), the Creative Media Industries Institute (CMII), and the Institute of Biomedical Sciences.

As a part of its Next Generation Initiative, GSU is bringing together its imaging expertise into a cross-discipline Imaging Hub. Several faculty hires are supporting this effort. In this initial round of hiring, we are recruiting the first of two senior-level faculty members who can work across at least two of the constituent disciplines in the hub and expand the hub's scope and capabilities. The Departments involved in this initiative are Physics and Astronomy (**https://www.phy-astr.gsu.edu**), Computer Science (**https://www.cs.gsu.edu**), Mathematics and Statistics (**https://www.mathstat.gsu.edu**), Chemistry (**https://chemistry.gsu.edu**), Psychology (**https://psychology.gsu.edu**), and Neuroscience (**https://neuroscience. gsu.edu**). We are also recruiting for a junior level position to work across two of the constituent disciplines in the hub with preference being given to candidates with experience in the development of optical microscopy imaging and its applications in chemical sciences and materials engineering.

GSU, the largest University in Georgia, is an enterprising urban research university located in downtown Atlanta and home to one of the most diverse student bodies in the country. The University is committed to diversifying its faculty and generating innovative research. We strongly encourage applications from members of underrepresented groups in the physical sciences.

Required qualifications: Applicants should have a Ph.D. in any of the disciplines represented in the hub or a field closely related to one of the disciplines. They should have a strong desire to work in a cross-disciplinary, collaborative environment. New hires will be expected to develop and lead innovative, externally funded research programs in areas that complement the Imaging Hub's current strengths. They will also be expected to demonstrate a commitment to excellence in the teaching and mentoring of undergraduate and graduate students and take an active role in GSU's service activities and the wider profession.

Preferred qualifications: we are particularly interested in candidates with experience in one or more of the following areas – the design and fabrication of novel imaging systems, imaging-based research related to space situational awareness, brain/body imaging, astronomical imaging methods, image reconstruction, and processing, imaging approaches to link across scales (spatial, temporal, molecular, environmental), medical imaging, or microscopic and nanoscopic imaging and analysis, computer vision, object/pattern recognition, content-based image retrieval, and deep neural networks. We are also looking for candidates who have demonstrated experience working in a collaborative environment across different research fields.

A complete application will include: 1) a curriculum vitae with a publication list, 2) a statement of research interests describing how the proposed research will be synergistic with and complement existing research at GSU, 3) a statement of teaching and mentoring philosophy and experience, 4) a statement on diversity, and 5) contact information for at least three professional references. All materials should be submitted in a single PDF file via email to **ImagingHubsearch@astro.gsu.edu**. Questions may be addressed to the search committee chairs, Dr. Stuart Jefferies, at **sjefferies@gsu.edu**, Dr. Fabien Baron at **baron@astro.gsu.edu**, and Dr. Vince Calhoun at **vcalhoun@gsu.edu**.

Applications will be reviewed starting in July 2021 and will continue until the positions have been filled. The successful candidates will ideally begin in the Spring Semester 2022, although earlier and later start dates are possible.

An offer of employment will be conditional on background verification. Georgia State University is an Equal Opportunity Employer and does not discriminate against applicants due to race, ethnicity, gender, veteran status, or on the basis of disability or any other federal, state, or local protected class.

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Newscripts

Curating quirky science since 1943

Snarfing down carbs is ancient

Modern humans gobble up doughnuts, potato chips, yuca fries, rice, and other starchy victuals with great gusto. Despite what advocates of certain low-carb diets may say about our ancestors eating more meat and less grain, noshing on foods dense in carbohydrates is a behavior we share with our long-ago relatives, according to an international team of researchers.

Pass the chips: Neanderthals crunched starchy carbs, as did ancient humans.

Neanderthals and ancient humans weren't just meat eaters. They also chowed down on starchy grub like roots and tubers as far back as 600,000 years ago, the researchers found. This is much earlier than previously thought and long before humans developed agriculture and domesticated grains like rice.

The researchers made the conclusions after analyzing the multispecies bacterial communities called biofilms that formed tartar on the teeth of ancient humans and Neanderthals. The team extracted DNA from the biofilms and determined the types of bacteria that constituted the films. The scientists then compared the results with those taken from contemporary primates.

They found that the species of bacteria that Neanderthal and modern human teeth harbored were highly similar. But they differed from those on the teeth of modern chimpanzees, humans' closest living relative.

Humans and Neanderthals shared types of *Streptococcus* bacteria that can bind to amylase, helping form biofilms. Amylase, an enzyme found in human saliva, begins the digestion process of breaking down complex carbohydrates into simple sugars. Chimpanzees have different species of oral *Streptococcus*.

The shared bacteria suggest that microbes adapted as Neanderthals' and ancient humans' diets changed to include starches, the researchers say. (*Proc. Natl. Acad. Sci. U.S.A.* 2021, DOI: 10.1073/pnas.2021655118).

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

Our ancestors grazed on starchy comestibles before the Neanderthal and modern human lineages split, the researchers conclude. This diet change could have allowed the development of the larger, more complex cortices of today's humans' brains.

Consuming energy-dense, starchy foods gives the brain rapid access to energy, explains lead author James A. Fellows Yates, a PhD student in archaeogenetics at the Max Planck Institute for the Science of Human History. In contrast, the body takes longer to break down fat and protein, meaning those foods don't fuel the brain as quickly.

So the next time cookies show up in the break room, your brain can rationalize nibbling a couple because carb snacking is a longtime human behavior.

Headset sniffs blood alcohol level

Headsets aren't just for listening to music anymore. Researchers in Japan have modified a headset so that it can determine the wearer's blood alcohol levels.

Our external ears turn out to be a decent spot to measure ethanol—and possibly other volatile organic compounds (VOCs)—off-gassed through the skin, researchers in Japan report (*Sci. Rep.* 2021, DOI: 10.1038/s41598-021-90146-1).

Other scientists have investigated other parts of the body, such as the palm of the hand, as possible sites for transcutaneous blood alcohol measurements. But they found that perspiration interferes with the measurements.

Sweaty ears, unlike damp palms, aren't common. That's because the skin on the ears has a relatively low density of sweat glands. So researchers from Tokyo Medical and Dental University and Kansai University decided to try ears for their measurements.

Beer ears: Researchers converted a headset to capture ethanol off-gassed from a person's ears.

The researchers faced a challenge because skin off-gasses ethanol at a lower concentration than found in the breath, which is the target of widely available Breathalyzers. So they converted commercial headphones into an "over-ear gas collection cell" and attached a biosniffer—a fluorescence-based biochemical gas sensor that detects the presence of an ethanol metabolite. The researchers then compared blood alcohol measurements from the breath and ears of research subjects and found them to be similar.

The device might eventually prove useful for noninvasive metabolism assessments and for disease screenings that measure VOCs, the researchers say.

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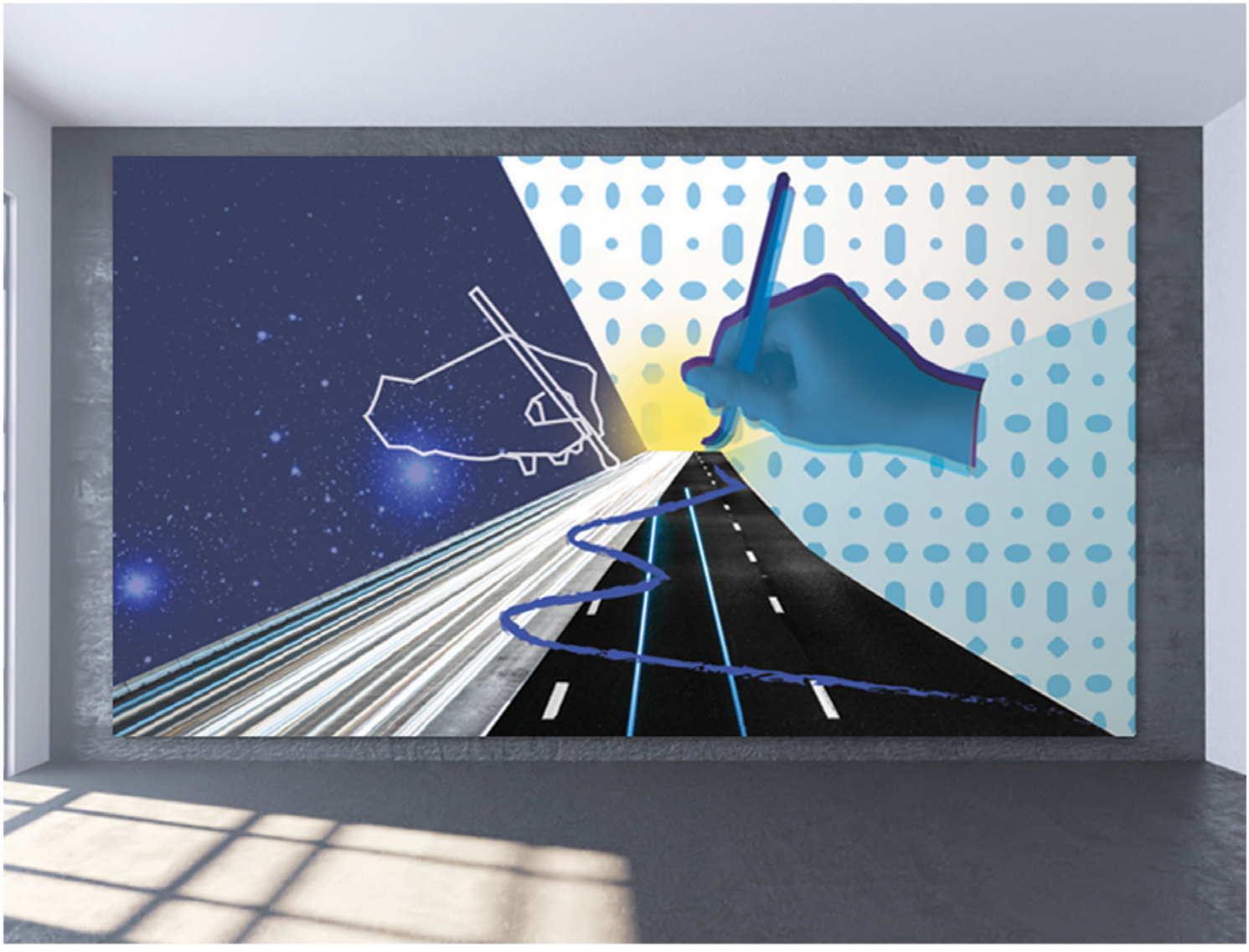

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