MAY 4, 2015

C&EN

CHEMICAL & ENGINEERING NEWS

HEPATITIS B
At new company, a chemist seeks a cure **P.18**

A SMELLY DEBATE
Scientists tussle over how olfaction works **P.29**

Industry Rises In India

Chemical makers see bright future under new government **P.10**

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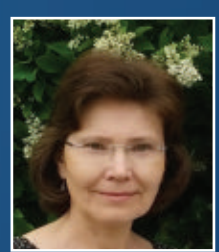

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CHEMICAL & ENGINEERING NEWS

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COVER STORY

INDIA ON THE RISE

Approaching a year in office, the Indian prime minister promises less regulation of the country's chemical makers. PAGE 10

QUOTE OF THE WEEK

"If you are following science, it is like following your favorite TV drama because there is always a new development."

MICHAEL E. ROGERS; RECENTLY RETIRED DIRECTOR OF THE DIVISION OF PHARMACOLOGY, PHYSIOLOGY & BIOLOGICAL CHEMISTRY; NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES PAGE 25

NEWS OF THE WEEK

BUSINESS

GOVERNMENT & POLICY

SCIENCE & TECHNOLOGY

THE DEPARTMENTS

COVER: *A BASF chemical plant in Mangalore, India. BASF*

CENEAR 93 (18) 1–40 • ISSN 0009-2347

IT'S OFFICIAL: CANNABIS CHEMISTRY COMMITTEE

AN EFFORT TO ESTABLISH a cannabis chemistry division at the American Chemical Society has been under way since September 2014 (C&EN, Nov. 10, 2014, page 4). Great strides were made at the ACS national meeting in Denver. The Cannabis Chemistry Committee was established as an official committee of the Small Chemical Businesses Division (SCHB). I was elected chair; additional members will be found among many of the individuals who expressed strong interest in active membership.

The greatest student interest (undergraduate and graduate) comes from schools in the Northwest and Southeast. These will likely be the first locations for networking events that will bring students face-to-face with industry leaders, academic researchers, and like-minded peers.

The petition for division formation received more than 300 signatures—50 signatures are needed.

The committee will plan programming at upcoming meetings and will hold networking events. At the 2016 spring ACS national meeting in San Diego, a full-day symposium cohosted by SCHB and the Agricultural & Food Chemistry Division will be organized. The first networking events will take place in June.

For those who were not able to meet us in Denver but would like to participate, please contact us at acscannabischemistry@gmail.com. Member activities could include mentoring, participating in regional events, or contributing to educational programs. If you would like to see the petition and support us with a signature, please go to tinyurl.com/naonap7.

Ezra M. Pryor
Chair, Cannabis Chemistry Committee
Ontario, Calif.

CASTING DOUBT ON SYRIA'S GUILT

"WHEN CHEMICALS Became Weapons of War" claims that "hundreds of Syrian civilians [were] killed by their military's use of sarin" (C&EN, Feb. 23, page 21). Not to put too fine a point on it, but the attribution of responsibility for this atrocity has been far from unanimous. The French government, former colonial ruler of Syria, led the charge in accusing the Syrian government of having launched the attack.

An article on the website truth-out.org, on April 29, 2014, summarizes evidence that casts doubt on this rush to judgment. The author writes that "the debate over the Aug. 21 attacks has focused primarily on a series of assertions about 'smoking guns' that allegedly proved Syrian government guilt." The article proceeds to quote evidence that the areas within a radius of 2 km from the impact sites were controlled by rebels.

Credible alternatives to C&EN's version of events in Syria do exist.

Karl H. Hiller
Spring Valley, N.Y.

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‘Nothing Goes On Forever’

THAT’S THE FIRST SENTENCE of a great *Angewandte Chemie* article by George M. Whitesides in which he looks at the evolution of chemistry from World War II until now (2015, DOI: 10.1002/anie.201410884).

The postwar years were very kind to chemistry. Efforts to analyze and understand complexity gave birth to academic chemistry, while society’s need for essential chemicals such as high-octane fuels or synthetic rubber created a vibrant chemical industry. But of course, “nothing goes on forever,” and by the time we get to the 1980s, Whitesides deems this prolific era “over.” He argues that the public perception of chemistry today remains “unarguably essential, but not exciting.” But he also points to opportunities. In fact, he goes on to describe many of these as “urgent necessities,” including rational design of drugs, determining how the brain works, and more. Whitesides offers chemistry as “the most plausible expertise” to resolve these challenges.

But if there is little appreciation of a field, there is little public support for it and ultimately little money. I agree this is a serious and real risk: Little support will influence the decisions made by governments, whose preference in terms of areas to invest in may fluctuate with public opinion, which will of course directly affect the monies that go to funding bodies.

Interestingly, Whitesides notes that other scientific fields “manage to be exciting.” I spoke about this during the American Chemical Society Board of Directors open meeting at the recent ACS national meeting in Denver. I argued that other sciences are perceived as “sexier.” Physicists talk about the stars, the origin of life, black holes, and the Big Bang Theory; biologists talk about Earth, oceans, and all living things including cute furry animals that make people go “ooooh.” But chemists talk about chemicals and man-made stuff, terms that often carry negative connotations. So I’d agree that chemistry has a serious image problem and advocate that individual chemists and organizations and societies like ACS need to work together to turn that around.

150 YEARS OF BENZENE

Besides BASF’s 150th anniversary (see page 9), 2015 marks another 150-year milestone: that of August Kekulé’s cyclohexatriene representation of the structure of benzene. Kekulé was a chemistry professor at Belgium’s University of Ghent when at the beginning of 1865 he revealed his molecular vision of benzene in a short article presented at a meeting of the Société Chimique de Paris (*Bull. Soc. Chim. de Paris* **1865,** *3,* 98) .

The empirical formula for benzene had been known for some time, but its highly unsaturated structure was challenging to determine. In the preceding years, other scientists had suggested structures containing multiple rings or double bonds, but the evidence at the time was insufficient to pinpoint the correct structure. So chemists of Kekulé’s day had to rely on evidence from chemical reactions (wet chemistry) rather than using instrumental methods.

Kekulé suggested that benzene contained a six-membered ring of carbon atoms with alternating single and double bonds. But it wasn’t until 1929 that the cyclic structure of benzene was finally confirmed by crystallographic analysis.

In any case, Kekulé’s idea of assigning certain atoms to certain positions within the molecule and connecting them using what we now call bonds makes him the founder of the theory of chemical structure. He was hailed as one of the most prominent chemists in Europe at the time.

The new understanding of benzene, and hence of aromaticity, was very important for both pure and applied chemistry. To this day, aromaticity is a matter of discussion for the chemical science community as evidenced by the arguments expressed in “Aromaticity for All,” a recent article by C&EN Senior Correspondent Stephen Ritter about how the concept should be invoked. You can follow and contribute to the debate at http://cenm.ag/aromaticity.

Editor-in-chief

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

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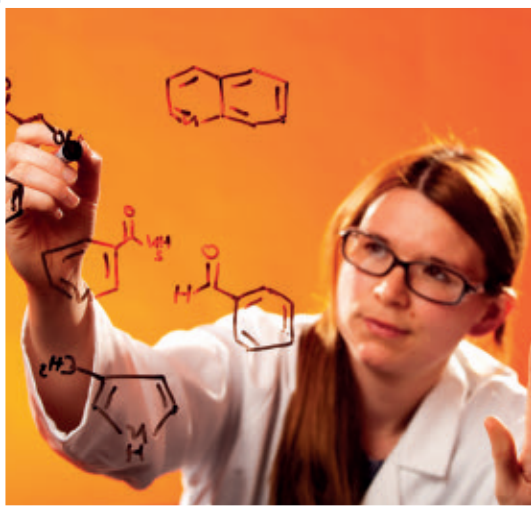

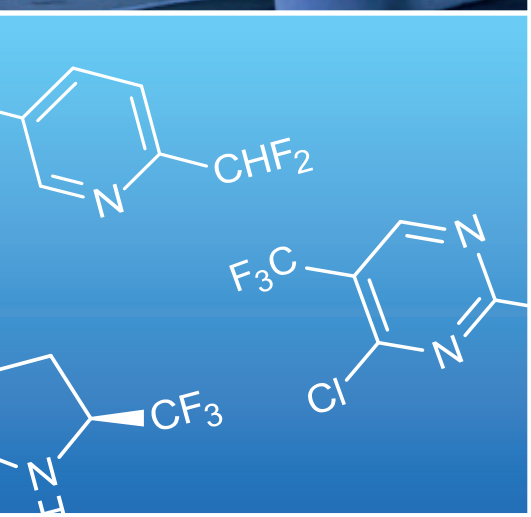

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C&EN news of the week

MAY 4, 2015 EDITED BY WILLIAM G. SCHULZ & SOPHIA L. CAI

DNA CONJUGATES DART INTO CELLS

DRUG DISCOVERY: New method delivers therapeutic transcription factors to cells

TRANSCRIPTION FACTORS control how cells work because they activate specific genes to produce proteins. If used as drugs, the factors could be equally powerful by boosting underperforming cellular activities or turning on genes to treat medical conditions or diseases.

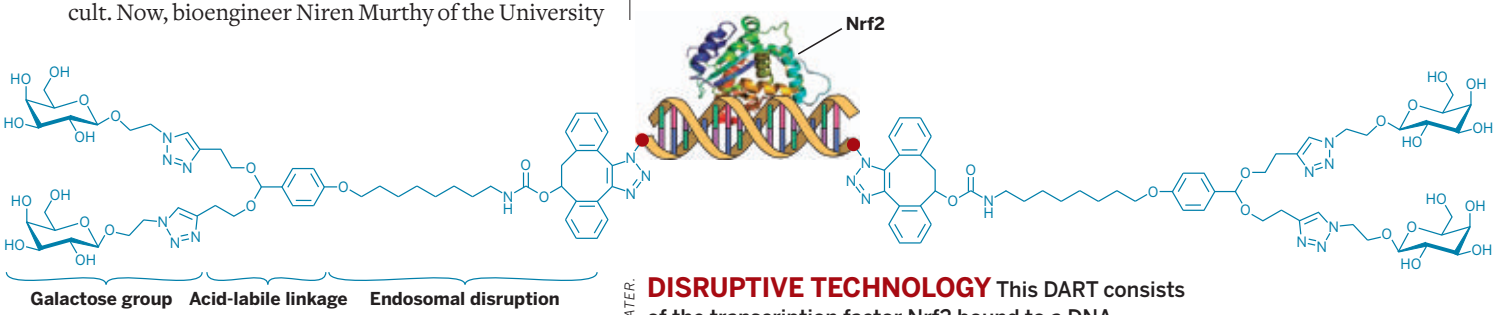
But delivering transcription factors to specific cells or tissues without toxic side effects has proven difficult. Now, bioengineer Niren Murthy of the University of California, Berkeley, and coworkers demonstrate how to safely smuggle transcription factors into liver cells using a method that could also work for a wide range of other cell types.

The Murthy group's concept involved targeting transcription factors to specific cell-surface receptors on liver cells that would shepherd the cargo into cell compartments called endosomes. The factors would then break out of the endosomes so they could enter the cytoplasm and then the nucleus, where they could perform their gene-activation magic.

To make the magic happen, the researchers designed and synthesized DNA-assembled recombinant transcription factors, or DARTs (*Nat. Mater.* 2015, DOI: 10.1038/nmat4269). A DART has a set of three major components that can bind the transcription factor of choice, deliver it to endosomes in a specific cell type, and then break apart endosomes to give the factor access to the nucleus.

The researchers tested the technique by injecting DARTs into mice that had been given a dose of acetaminophen sufficient to cause liver damage. The DARTs delivered a transcription factor called nuclear erythroid 2-related factor (Nrf2) directly to the liver cells, where it turned on protective genes that prevented liver injury.

These DARTs contained a short DNA sequence that binds Nrf2. To this DNA strand, the researchers attached hydrophobic alkyl chains that are protected by acid-sensitive linkers and galactose end-caps. Masking the hydrophobic alkyl chains prevents them from disrupting membranes in nontarget cells, which could cause side effects. The galactoses also allow the DARTs to bind to receptors on liver cells and then scoot into liver-cell endosomes. Once inside, the acidic environment breaks the acid-labile linkers. This unmasks the hydrophobic alkyl chains, allowing them to disrupt endosome membranes by a surfactant-like process. Endosome disruption releases DARTs into the cytoplasm and then the nucleus, where they activate antioxidant and anti-inflammatory genes that protect against liver damage.



ADAPTED FROM *NAT. MATER.*

DISRUPTIVE TECHNOLOGY This DART consists of the transcription factor Nrf2 bound to a DNA strand, a hydrophobic group that disrupts endosome membranes, an acid-labile linkage, and a galactose group to target the assembly to liver cells.

José Manautou of the University of Connecticut, an expert on liver toxicity who has studied Nrf2 activation, comments that the technique seems powerful for deterring liver toxicity following acetaminophen administration. But he points out that the mice were treated with DARTs only an hour after administration of acetaminophen—sooner than would be practical for addressing most cases of acetaminophen poisoning in people. It remains to be determined, he says, if DARTs will work as well if administered later, when they might need to reverse liver damage, not just prevent it. Nevertheless, it's "a novel and promising technology that warrants further evaluation," he says.

The modular structure of DARTs makes it possible to customize them to carry other transcription factors besides Nrf2 and target other types of cells besides liver cells by changing the DNA strand and end-caps, respectively. Murthy says his team is improving DARTs' efficacy and testing them in mice with chronic liver disease in hopes of moving them to clinical trials.—STU BORMAN

CHEMICAL REFORM BILL ADVANCES

CONGRESS: Senate panel clears compromise that would update law on commercial substances

U.S. CONGRESS (BOTH)

Vitter

Udall

LAWMAKERS ON Capitol Hill have taken a major step toward overhauling the nation's outdated law governing commercial chemicals. A Senate committee on April 28 approved a bipartisan bill to reform the 1976 Toxic Substances Control Act (TSCA).

Because a handful of Democrats support the measure, the legislation, S. 697, stands a solid chance of passage by the Republican-controlled Senate.

Both the chemical industry and advocacy groups for years have pressed Congress to modernize TSCA, though they don't see eye to eye on S. 697.

Environmental and health activists say the measure, which the Senate Environment & Public Works Committee approved 15-5, is an improvement over previous TSCA reform bills. But they say it still falls short in some provisions. For instance, Andy Igrejas, director of Safer Chemicals, Healthy Families, an environmental and public health coalition, says S. 697 would "roll back EPA's authority to restrict significant new uses of a chemical."

The chemical sector, on the other hand, is applauding lawmakers for hammering out a bipartisan deal. Calvin M. Dooley, president and CEO of the American Chemistry Council, an industry group, says the compromise bill "reflects a carefully balanced approach that incorporates interests of several Democratic senators and maintains important priorities for manufacturers."

"Updating the outdated, inefficient TSCA will better protect the safety of our families and also advance innovation in our economy," says Sen. David B. Vitter (R-La.), who introduced S. 697 with Sen. Tom S. Udall (D-N.M.) in March.

Initially, the bill didn't sit well with other Democrats. But Sens. Jeff A. Merkley (D-Ore.), Sheldon Whitehouse (D-R.I.), and Cory A. Booker (D-N.J.) negotiated a compromise with Republicans that addresses a number of concerns activists and some state officials raised about state laws on chemicals. In particular, the newly approved bill would allow states, in certain circumstances, to regulate chemicals while EPA is evaluating the safety of those substances.

"This bipartisan agreement greatly strengthens the ability of states to protect citizens from toxic chemicals when the federal government has failed to do so," Merkley says.

Senate leaders have yet to decide when to bring the bill to the chamber's floor for a vote.—BRITT ERICKSON

ADVISORY SERVICES BACK DUPONT FOE

STRATEGY: Two of three advisers say Trian Fund Management should get seats on DuPont's board

JASON COHN/REUTERS/NEWSCOM

Peltz

ACTIVIST INVESTOR GROUP Trian Fund Management has won the partial backing of two voting advisory services in its contest to win seats on DuPont's board of directors at the company's May 13 annual meeting. However, a third service rejected all four Trian candidates.

DuPont is downplaying the value of the support for Trian's directors and says shareholders will make up their own minds when they vote.

The most influential of the three advisory services, Institutional Shareholder Services (ISS), recommends that shareholders elect two of Trian's four board nominees, including Trian CEO Nelson Peltz. Advisory service Glass, Lewis & Co. recommends a vote for Peltz but none of the other Trian nominees, while the third service, Proxy Mosaic, rejects all four Trian nominees.

In its assessment of DuPont, ISS notes that "this is not a broken company," as Peltz has suggested, but contends "there is compelling evidence that the dissidents are onto something in their critique." Trian aggressively promotes change at companies in which it takes a stake. Its targets have included PepsiCo, industrial conglomerate Ingersoll Rand, and food maker Danone.

In a letter to DuPont shareholders, Trian hails ISS's voting recommendations, saying it is pleased that the advisory service agrees that "change is needed on the DuPont board." But Trian added that all four of its nominees "are needed in the DuPont boardroom."

Peltz and Trian have argued that DuPont's overhead costs are too high and that the firm ought to be broken up. ISS gives some credence to that take: "Operating efficiency is not what it should be, yet instead of addressing the core issues, the [DuPont] board and management, at least in their communications with shareholders, are more inclined to obfuscation than accountability."

DuPont disagrees. "We strongly believe ISS reached the wrong conclusion," the company says. The company also says Glass, Lewis erred "in failing to recommend a vote for all 12 DuPont nominees."

In attempting to unseat four DuPont directors, Trian "would deprive DuPont's board of critical skills that are central to DuPont's purpose and value proposition," the company claims.

DuPont also points out that institutional shareholders, who control about 70% of its stock, don't always accept advisory service recommendations. "We are confident that shareholders will do their own analysis," the firm says.—MARC REISCH

BEETLE'S EXPLOSIVE SPRAY REVEALED

BIOWEAPON: Pulsed mechanism driven by chemical reaction

TO FEND OFF PREDATORS, bombardier beetles spray a hot, irritating liquid from a gland that behaves like a microscopic chemical reactor. Researchers have now used synchrotron X-ray imaging to reveal details about how the beetles control their built-in weapon (*Science* 2015, DOI: 10.1126/science/1261166).

The beetles' pygidial glands have multiple parts, including a reservoir chamber, a reaction chamber, and an exit channel. The reservoir chamber contains an aqueous solution of 25% hydrogen peroxide, 10% *p*-hydroquinones, and 10% alkanes. The reaction chamber contains peroxidase and catalase enzymes.

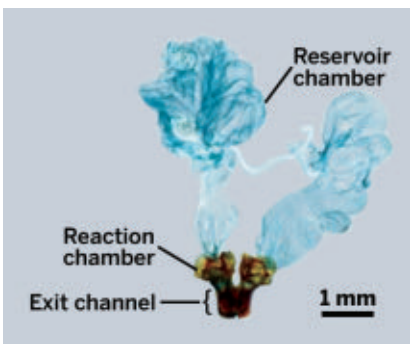
When a beetle goes into defensive mode, it transfers the reservoir fluid into its reaction chamber, where enzymatic reactions produce *p*-benzoquinones—the irritating component of its spray—along with oxygen and heat. Water vaporizes, pressure builds up, and the spray explodes from the exit channel. For one particular group of bombardier beetles, spray explosions come out at about 100 °C, with a velocity of 10 meters per second and a range of several centimeters. They also pulse as quickly as 700 Hz.

But how the beetles control their complex machinery has been a mystery. The new work "is the first internal experimental analysis of the intricate mechanism used by the beetle," says Andrew McIntosh, a thermodynamics professor at England's University of Leeds. McIntosh has studied bombardier beetles but was not involved in the current work. He notes that the study confirms earlier research that suggested valves play a role in the beetle spray explosions.

The experiments were carried out by Massachusetts Institute of Technology graduate student Eric M. Arndt and professor of materials science and engineering Christine Ortiz, University of Arizona entomology professor Wendy Moore, and Brookhaven National Laboratory scientist Wah-Keat Lee.

The method they developed was to anesthetize a beetle by cooling it down, then use modeling clay to hold it on a mount. "When the beetle warms up, it realizes that it's fixed in place, so it gets scared" and releases its explosive spray, Ortiz says. The researchers were able to obtain X-ray images of the spray explosions at 30 to 2,000 frames per second.

Muscles within the reservoir chamber contract to push fluid into the reaction chamber. But only a little fluid goes in at a time, in the form of 5-nL droplets, the team found. As soon as fluid enters the reaction chamber, the enzymes within immediately go to work, and the rising pressure serves both to close a valve between the reservoir and reaction chambers and to blast the spray out the exit. Then the reduced pressure allows the valve to reopen for another cycle. "It's a very efficient way of controlling the pulse explosion," Ortiz says.—JYLLIAN KEMSLEY



Bombardier beetles (top) produce a hot, irritating spray of benzoquinones from their pygidial glands, shown stained in a micrograph (bottom).

SCIENCE (BOTH)

& VIDEO ONLINE

View X-ray video of a beetle ejecting its defensive spray at cenm.ag/beetle.

EXPORTS Trade fight looms as key bills head for House and Senate votes

Congressional committees recently agreed to give President Barack Obama the authority he needs to wrap up the Trans-Pacific Partnership (TPP), the proposed free-trade pact between the U.S., Japan, and 10 other countries mostly in the Asia-Pacific region.

But the real fight over the legislation (S. 995 and H.R. 1890) will occur in the coming weeks when the controversial measure comes up for final votes in the Senate and the House of Representatives. The trade promotion bill would allow President Obama to submit the completed TPP deal to Congress for an up-or-down vote, rather than allowing lawmakers to amend it.

Without this fast-track procedure, analysts say that no trade partner will make concessions to U.S. negotiators because Congress could pick the deal apart.

The chemical industry, one of the nation's top exporting sectors, supports both the legislation and the TPP.

"For U.S. chemical manufacturers to succeed in today's global economy, we must be able to compete effectively in international markets," says Michael P. Walls, vice president of regulatory and technical affairs at the American Chemistry Council, an industry trade association.

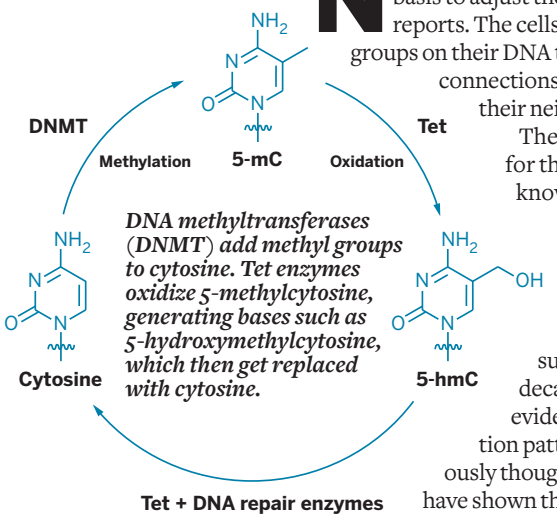
The fast-track mechanism will "help open markets and ensure the U.S. chemical industry can capitalize on its massive export potential," Walls adds.

But the legislation faces strong opposition from the labor movement and its Democratic allies, who argue that trade agreements have caused an outflow of manufacturing jobs from the U.S. to other nations.—GLENN HESS

NEURONS TWEAK DNA CONSTANTLY

EPIGENETICS: Demethylation enzyme helps regulate neuronal communication

NEURONS MAY MODIFY their DNA on a regular basis to adjust their level of activity, a new study reports. The cells change the pattern of methyl groups on their DNA to strengthen and weaken the connections—or synapses—they make with their neighbors.



The findings provide more support for the idea that DNA modifications, known as epigenetics, may play a fundamental role in learning and memory.

For a long time, biologists thought DNA methylation was static in fully developed cells such as neurons. But in the past decade, researchers have found evidence that these DNA methylation patterns are more fluid than previously thought. In particular, some studies have shown that enzymes called Tet proteins, which help remove methyl groups from cytosine bases in DNA, are involved in memory formation.

In the new study, Hongjun Song of Johns Hopkins University School of Medicine and colleagues found that one of these enzymes, Tet3, helps tune how neurons respond to signals from their neighbors (*Nat. Neurosci.* 2015, DOI: 10.1038/nn.4008). When the researchers reduced the amount of Tet3 expressed in cultured neurons, the cells' responses to incoming signals got larger. Overexpressing the enzyme had the opposite effect.

Through further experiments, the team found that Tet3 influences neuronal responses by somehow controlling the number of glutamate receptors at a nerve cell's synapses. For example, adding receptors strengthens synapses and allows cells to amplify their responses.

Changing the strength of synapses, neuroscientists think, is a key step in learning and memory. And Tet3 appears to tune synapses as part of a process to ensure neuronal activity doesn't get too high or too low. If neurons become excessively active or inactive, they are less able to respond to signals from their neighbors.

Neurons are taking some big risks using demethylation to control their activity, says Li-Huei Tsai, a neuroscientist at Massachusetts Institute of Technology. Demethylation requires oxidizing methylated DNA, so there are plenty of opportunities for the cellular machinery to accidentally damage DNA and create mutations.

"I wonder if by engaging in this risky business, neurons set themselves up for degeneration over time," Tsai says.—MICHAEL TORRICE

ROADBLOCK FOR POLLUTION RULES

CONGRESS: Senate panel advances bill requiring EPA to use only publicly available and reproducible data

Critics say a bill would hamper EPA's ability to regulate air and other pollution.

SHUTTERSTOCK

LEGISLATION THAT WOULD undercut EPA's ability to regulate pollution in air, water, and soil got approval from a Senate panel last week. The bill would force EPA to rely only on health research that is publicly available and reproducible.

The bill seemingly would impose uncontroversial data-sharing requirements on EPA. But the legislation would force the agency to ignore credible health data because of the need to protect patient confidentiality, critics charge. "It's a catch-22 to say you may not release health data and therefore you may not regulate based on that information," says Andrew Rosenberg at the Union of Concerned Scientists, an advocacy group.

The Senate Environment & Public Works Committee's 11-9 party-line vote on S. 544, the so-called Secret Science Reform Act, echoes a companion bill, H.R. 1030, which the House of Representatives passed 241-175. The White House has threatened to veto the legislation.

Sen. John Barrasso (R-Wyo.), sponsor of S. 544, says the measure "will give Americans more confidence that EPA's policies will deliver the environmental and public health benefits the agency has promised."

Republicans are pushing the bill in large part because EPA failed to provide congressionally requested raw health data from studies the agency used to review the risks of particulate matter air pollution. The agency says information about individual participants remains under the control of the institutions that did the research.

"It would be good to see thoughtful legislation that advances data access while addressing the complexity and costs of doing so," says Dan Greenbaum, president of the nonprofit Health Effects Institute, which is jointly funded by EPA and the automotive industry. The Congressional Budget Office says S. 544 would cost EPA $250 million a year to implement, but the bill only provides $1 million in funding, Democrats say.

Researchers are concerned that new mandates on EPA to release confidential health data would also constrain recruitment for clinical health studies. Institutional review boards that examine plans for studies involving human subjects "would take this very seriously and tell researchers, 'You can't guarantee subjects' confidentiality if Congress wants to access your health information,'" Rosenberg says.—STEVEN GIBB

GRAPHENE THAT'S FIT TO PRINT

MATERIALS: New inks create promising structures for energy storage and tissue regeneration

RESEARCHERS HAVE PRINTED inks containing nanoscopic graphene flakes to build macroscopic, three-dimensional objects that they say could benefit numerous fields, including energy storage and bioengineering.

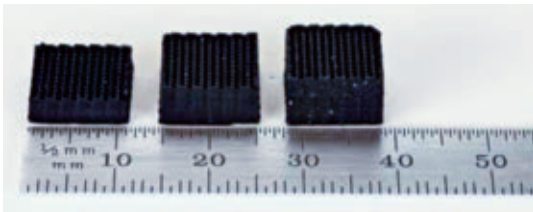
A team at Lawrence Livermore National Laboratory has 3-D printed porous, highly compressible aerogels using a graphene oxide ink (*Nat. Commun.* 2015, DOI: 10.1038/ncomms7962). And researchers at Northwestern University designed tissue scaffolds with ink that contains graphene flakes within a flexible, biocompatible polymer (*ACS Nano* 2015, DOI: 10.1021/acsnano.5b01179).

These are not the first examples of graphene inks. However, scientists are still searching for formulations that fully capitalize on the atomically thin material's remarkable properties. For example, some existing inks sacrifice mechanical properties for high electrical conductivity.

"We were really trying to avoid making compromises," says Marcus A. Worsley, who led the Livermore researchers along with his colleague Cheng Zhu. Their goal was to devise a 3-D printing process that allowed conductive flakes to controllably coalesce and ultimately form aerogels: spongelike materials that are about as light as air yet mechanically robust.

Their ink contained water, graphene oxide flakes, silica filler particles, and a gelation agent, such as ammonium carbonate. By printing the ink in a bath of isooctane, the team prevented the ink from drying and gave the gelation agents time to fix the flakes into a porous framework.

Once the printer finished, the team replaced the isooctane with air, etched away the silica, and was left with supercompressible aerogels with large surface areas and good conductivities, Worsley says. These properties make the aerogels attractive for batteries, capacitors, and hydrogen fuel cells.



Livermore researchers 3-D printed graphene aerogels of different shapes and sizes.

NAT. COMMUN.

Instead of printing into a solvent bath, the Northwestern team, led by Ramille N. Shah, used several solvents in its graphene ink, along with a biocompatible elastomer.

One of the ink's solvents, dichloromethane, evaporated quickly to fix a printed layer in place. But the remaining solvents, 2-butoxyethanol and dibutyl phthalate, evaporated at a slower rate and kept that layer wet enough to adhere to the next layer printed on top of it.

After the ink dried, two components remained: graphene flakes and a polymer called polylactide-*co*-glycolide. This allowed the team to print flexible scaffolds that could be cut to size and sutured into living tissue to support cell growth and tissue regeneration without eliciting any severe immune response, Shah says. The conductivity of the scaffolds also appears to facilitate cell signaling and differentiation, she adds, but the long-term health effects of such implants still needs to be evaluated.

Developing 3-D printable graphene inks is an important undertaking, clearly evidenced by the attention it's now receiving, says Esther García-Tuñon Blanca, a materials researcher at Imperial College London who was not involved in either study. "The more research groups working with it, the sooner we all find out the actual potential graphene has in everyday life."—MATT DAVENPORT

Scientists at Northwestern University can print their graphene-based ink into complex shapes, such as this 1-inch-diameter skull.

ADAM JAKUS/SHAH LAB/NORTHWESTERN UNIVERSITY

INDUSTRY BASF 150th anniversary event punctuated by sharp words from Angela Merkel

In an event that at times felt more like a wedding than the anniversary of the founding of a major chemical company, leaders of German industry and politics gathered in Ludwigshafen to toast the success that is BASF, the world's largest chemical company.

The celebration took place on April 23, almost 150 years to the day after the firm was founded. Guests included German Chancellor Angela Merkel—who also holds a doctorate in physical chemistry—and Bayer Chairman Marijn Dekkers.

In her speech, Merkel silenced the audience of about 1,000 people by ripping into the company for inventing chemical weapons used in the First World War and for making the gas used to murder Jews in the Second World War. "In the history of BASF, we see reflections of our country, including its darker moments," she said.

In the end, Merkel managed to receive a standing ovation from the largely German audience by also stressing how important BASF is as a force for innovation in a world faced with limited resources and a growing population.

Merkel's exit was followed by the first public performance of "Water Dances," a symphony written for BASF's anniversary by British composer Michael Nyman. It was played by London's Royal Philharmonic Orchestra. The performance was prefaced by a musical montage, recorded by Nyman, comprising some of the actual sounds of BASF—everything from machines whirring to water flowing.

If there is such a thing as the sound of chemistry, then perhaps this was it. If there was a defining event for celebrating the chemistry enterprise, then perhaps this was it as well.—ALEX SCOTT

INDIA: UNDER NEW MANAGEMENT

In power for a year, the administration of Prime Minister Modi is promising to **DELIVER CHANGE TO INDIA**

JEAN-FRANÇOIS TREMBLAY, C&EN HONG KONG

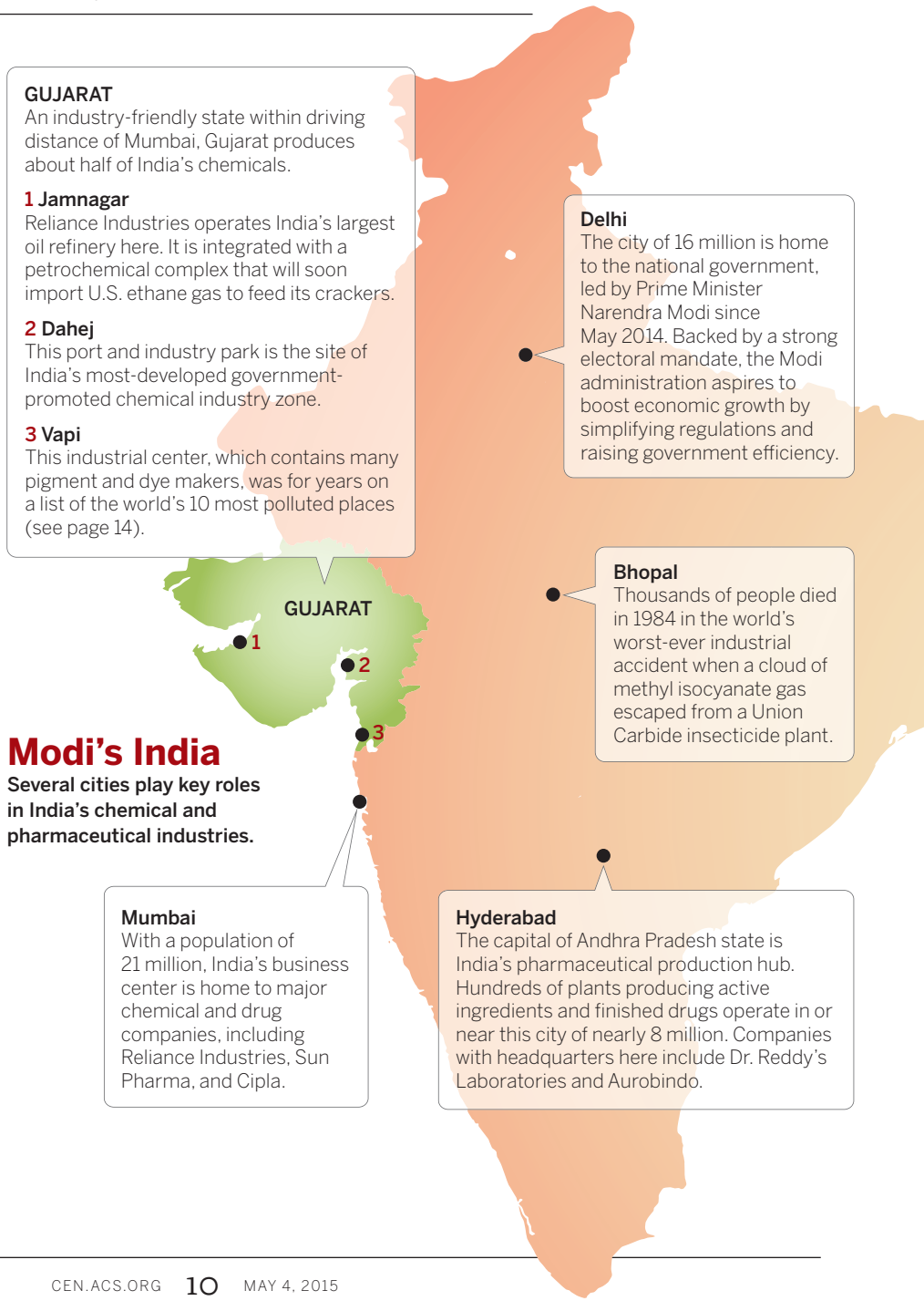
SWORN IN NEARLY a year ago, Prime Minister Narendra Modi has raised expectations in India after years of economic and social stagnation under ineffective coalition leadership.

Modi's ambitious new government hopes to raise living standards for the poor, modernize cities, improve public health and sanitation, improve education, and deliver steady and strong economic growth without harming the environment. Over the past year, Modi has toured the world in his quest for foreign friends and investors who can help him achieve his dream for India.

Of course all new administrations have lofty goals. But according to those who have met Modi or members of his team, the new government seems to have the discipline and work ethic to pull them off. Modi is said to hold regular meetings lasting several days at which he grills senior public servants on what they are doing to promote growth in India. Under pressure to deliver, officials are seeking input from industry executives on how to remove impediments to growth. Usually ignored, leaders of the Indian chemical industry are delighted to be included in the consultation process.

Modi has taken charge at an auspicious time for the chemical industry in India. Integrated industry zones that have long been discussed are finally coming together. Demand is strong for everything from plastics to crop protection chemicals. And new petrochemical complexes are opening across the country, improving local availability of needed raw materials.

The first of the two stories in the pages to follow offers the chemical industry's take on where India is going and what it needs to do to succeed. The second is a look at how the Modi administration intends to balance environmentalism and economic growth in an Indian city where, in years past, industry ran amok.



Indian Chemicals At A Glance

- **Sixth-largest** producer of chemicals in the world, third-largest in Asia after China and Japan
- **$144 billion** total chemical market size, according to the Indian government
- **Number one** in FDA-approved drug manufacturing plants outside the U.S.
- **9%** chemical industry average growth rate over the past five years

Haldia
This small city near Calcutta is home to a medium-sized petrochemical maker, Haldia Petrochemical (now part of Gail), as well as MCC PTA India, a producer of purified terephthalic acid majority-owned by Mitsubishi Chemical.

Growth Drivers

Infrastructure: The quality of infrastructure has long hindered industry growth. The government is promoting chemical industry zones, as well as an improved road and rail network.

Government: The new Modi government has boosted business confidence by listening to industry leaders. It is promising to spur growth through administrative reforms, accelerated investment in infrastructure, and increased power generation.

Urbanization: Farmers are moving into cities, raising demand for transportation, construction materials, and treated water. The Modi government has called for the creation of 100 "smart cities" that are expected to feature modern urban transit systems and advanced energy and water management.

Oil Industry: Indian oil companies are adding petrochemical complexes to their refineries to maximize value.

Technology: Farmers, who represent 60% of India's population, have been investing in crop protection to boost yields. The Indian government is expected to invest in water quality, boosting demand for necessary treatment chemicals and polymers.

SHUTTERSTOCK/C&EN

INDUSTRY TURNS OPTIMISTIC

Even if it has done little so far, **INDIA'S NEW GOVERNMENT** has improved the outlook for chemicals

IT'S CLEAR UPON LANDING on a flight to Mumbai that things are changing in India. The city, India's largest, recently completed the construction of an immense and modern international terminal. Long lines for passport inspections and security checks are, to the relief of many, a thing of the past.

Leaving the airport reveals what is still the same. Like most Indian cities, Mumbai lacks an efficient mass transit system, so only in the dead of night are streets uncongested. Distances and travel times need to be carefully considered in order to arrive on time at appointments in the vast city.

Indeed, many of the old stumbling blocks to doing business in India are still there. But for the country's chemical sector, the outlook has shifted under the administration of Prime Minister Narendra Modi, who took office a year ago. Whereas in years past Indian chemical company executives tended to see an array of hurdles to economic success, the mood today in Mumbai, also the nation's business capital, is definitely upbeat.

Even before Modi's election, growth in the Indian chemical industry had accelerated to an uncharacteristically strong 9% per year, compared with the 2005–10 period when chemical production barely expanded. Now, with a government that appears to be serious about removing perennial obstacles to business, executives are beginning to shed their doubts.

"Now is the best of times for the Indian chemical industry," said Sudhir Shenoy, head of Dow Chemical's operations in India, speaking at a conference organized by India's *Chemical Weekly* magazine last month. "The new government has improved the outlook, so the industry could grow at 10, 15, or even 20% in coming years."

It will be growth from a small base. Although India is home to one-sixth of the world's population and is Asia's third-largest economy after China and Japan, the country has a tiny chemical industry that accounts for only about 3% of world chemical output, according to Tata Strategic Management Group, an Indian consulting firm.

Dow and other companies seeking to increase that figure will be buoyed by initiatives championed by the new government, Shenoy said. For instance, the chemical industry can only benefit from the Modi administration's goal to build 100 "smart cities"—places where such things as traffic flow, trash collection, and transit system operation are centrally monitored and controlled through

BUSTLING India's traffic, shown here in Mumbai, is a sign of both vibrancy and chaos.

JEAN-FRANCOIS TREMBLAY/C&EN

comprehensive information technology.

Although other executives at the conference shared some of Shenoy's enthusiasm, many are skeptical that unbridled optimism is warranted at this early stage of the Modi administration. The critical problem of India's poor infrastructure will take a long time to solve, they pointed out.

Stephan Pilz, vice president of business development in India for Germany's Evonik Industries, noted that the World Bank presently ranks the country 134, out of 183, in ease of doing business. The chemical industry in India is challenged by impediments such as an inverted import duty structure that discourages manufacturing.

"Custom duties are currently 8% on spinal implants made with PEEK"—polyether ether ketone, an engineering plastic—"and 30% on PEEK resin," Pilz noted. "So who will import PEEK to make implants in India?" He also observed that India compares unfavorably as an investment destination with Singapore, even though the city-state has a small market for chemicals and no indigenous source of natural gas or crude oil.

Industrial growth is hampered by myriad regulations, such as those that prevent foreign ships from ferrying cargo from one Indian port to another, added Matthew George, head of petrochemical exports at Indian Oil Corp., a large state-controlled refiner. Using the Indian companies that control coastal shipping is slow and expensive, he added, and partly explains India's overreliance on trucks. It's a dynamic that won't be easy to change, George said. "India has many lobbies. The local shipping industry opposes opening the market."

The simple act of sending chemicals from one plant to another is a challenge for foreign companies, concurred Steve Stilliard, managing director for India at the U.S. chemical maker Huntsman Corp. "Headquarters will never approve an investment plan that involves hazardous materials traveling 200 miles in small-capacity trucks on bad roads. We need pipelines," he said.

But on the whole, Stilliard has a positive outlook for the chemical industry in India under the Modi administration. "The interest of the Indian government in the chemical industry is almost unprecedented anywhere in the world," said Stilliard, a British-born chemical industry veteran who has been at Huntsman for 15 years.

THE PHARMACEUTICAL chemicals sector could also shine if certain reforms are implemented, said Dinesh Dua, chief executive officer of Nectar Lifesciences, an antibiotics manufacturer. Indian companies have a better understanding than their Chinese counterparts of regulations in developed countries and how to make complex active pharmaceutical ingredients (APIs), according to Dua. But in recent years, generic drug makers in India have become increasingly reliant on China.

BASF IN INDIA

Local Manager Of World's Largest Chemical Firm Is Encouraged So Far By The Modi Administration

The views of Raman Ramachandran, managing director of BASF India, have weight given his company's size—it's the world's largest chemical maker—and its already substantial presence in the country. Ramachandran says he sees a lot to like about the new central government in India.


BASF

Ramachandran

"For the past year, there has been a sense of optimism in India about the whole economy," he says. "For the first time, the government has come out with a much more comprehensive approach on a number of social and economic aspects of the country and is really trying to make it happen."

To start with, he says, the government looks different. Ministries in the capital, New Delhi, are now far more disciplined, with emphasis on stricter deadlines and being approachable. Among its first moves, Prime Minister Narendra Modi's administration combined 17 related ministries into seven groups. And bureaucrats are now empowered to make more decisions, which he expects to speed up the implementation of long-planned investment and infrastructure projects.

The new administration has come up with a number of initiatives that add up to an integrated approach to economic and social development, even if most policy details are for the moment missing. For instance, a Clean India campaign aims to improve public health by providing every Indian access to a toilet within a few years.

The Make in India campaign aims to stimulate manufacturing and industrial growth. But it's also a social campaign, given that manufacturing could provide much-needed employment to young adults. Every year, Ramachandran notes, 10 million to 20 million youths enter the job market.

And through his much-publicized trips to foreign countries, Modi does more than promote investment and meet Indians living overseas. For instance, during his recent visit to Germany, he both met with industry captains and explored the possibility of working with Germany on skills development, an area in which the country excels.

In India, BASF employs close to 2,200 people and operates nine production facilities across the country. Since the Modi administration took office, BASF has started construction near Mumbai of an R&D facility that will accommodate as many as 300 scientists when ready in 2017. "As the economy expands in India, BASF will invest to capture the big growth opportunity that the country will offer," Ramachandran says.

Still, BASF is not planning one of its major integrated *Verbund* complexes in India to produce upstream petrochemicals and basic chemicals. He says the main hurdle is not infrastructure, the top challenge cited by most chemical company managers in India. It's mostly that the size of the Indian market does not yet warrant such a commitment from BASF, Ramachandran says. And when the time comes, "the issues pertaining to feedstock and raw material availability will also have to be addressed," he notes.

But in view of the high growth rates India is expected to experience in the coming years, BASF may well decide to tackle those practical challenges sooner rather than later.

LEADER Modi, here on a recent trip to Germany, has won the confidence of India's chemical industry.

REYNALDO PAGANELLI/SIPA/NEWSCOM

"I used to make my own intermediates, but Chinese costs are 50% lower," Dua said. Producers in China have access to the well-developed infrastructure of industrial parks as well as cheap and reliable electricity, he noted.

If for one reason or another—a crackdown on pollution, for example—Chinese producers of pharmaceutical ingredients stopped shipping to India, the country's generic drug industry would be wiped out, Dua warned. But he's heartened that the new government seems to share the drug industry's concerns about relying on China. The Modi administration has promised to improve infrastructure—including effluent treatment—at seven industrial clusters and to provide financial incentives to the industry, Dua said.

"If all this is done by this absolutely business-friendly government, we will not only be self-sustaining in APIs, we will also push China 10 to 15 years behind us," he said.

Experts at prominent consulting firms agree that the Indian chemical industry is positioned for spectacular growth in the near future. Alok Verma, director of strategy at PricewaterhouseCoopers, said the overall Indian economy could grow sustainably at 9% per year if certain reforms are made. In its latest predictions, the International Monetary Fund said the Indian economy will expand by 7.5% in 2015, surpassing China's growth.

And if the overall economy expands by 9% annually, the chemical industry should grow at close to 15%, Verma pointed out. The government will do what is required to facilitate growth, he predicted, partly because India's high birthrate requires it. "If we don't create 240 million new jobs in the coming 20 years, we will face a demographic nightmare," he warned.

In the near term, Manish Panchal, practice head for chemicals and energy at Tata, cautioned that business confidence is likely to drop in the coming months because the Modi government has created sky-high expectations while so far delivering little except promises. Among its few concrete changes is a controversial move to allow companies to expand in highly polluted areas (see page 14).

But the government will deliver, Panchal predicted. "I've never seen the Indian government working so hard," he said. When it comes to the economy, the government's immediate focus is to make it easier to do business in India. At this juncture, foreign chemical companies that don't have a presence in India should consider an acquisi-

JEAN-FRANÇOIS TREMBLAY/C&EN

ON THE MOVE Industry and citizenry coexist uneasily in the polluted city of Vapi.

tion, he advised. And those that are already present should get ready to produce chemicals for export.

The Indian chemical industry is buoyant for reasons beyond the feel-good influence of the new Modi administration, said Gaurav Moda, a partner at consulting firm KPMG India. For instance, the general move of India's rural population to cities is resulting in demand for transportation, clean water, and construction materials.

Another source of industry growth is a trend by Indian oil companies to build petrochemical complexes alongside their refineries to increase the value they get out of crude oil. Between 2013 and 2018, he expects, India's petrochemical sector will expand by 13% annually.

Among the companies building new projects are Oil & Natural Gas Corp., Gail India, and Hindustan Petroleum Corp. Some of these companies are newcomers to the petrochemical industry, and their entry means more options for buyers of basic chemicals. With greater choice, bargaining power will shift to buyers, Moda expects, and lower prices will stimulate industrial growth.

Whether created by the new government or not, tremendous opportunities are emerging in India's chemical industry, Moda contends, and the question becomes whether companies are ready to take advantage of them. For example, because the chemical industry in India is highly fragmented, companies hoping to gain market share will have to establish a sophisticated marketing and distribution infrastructure.

It's by no means assured that chemical companies will rise to the occasion and take advantage of new opportunities in India. But the government, Moda said, is intent on "extending the red carpet to chemical companies, rather than the red tape."

NEW APPROACH IN VAPI

To promote growth in one of its most polluted cities, India tries lifting a BAN ON INDUSTRIAL EXPANSION

COMPARED WITH WHAT it was 15 years ago, Vapi seems to have cleaned up its act. Streams no longer change color depending on the time of the day. The city's chemical industry, which includes several dye and pigment makers, has improved effluent collection so that most wastewater is sent in for treatment instead of being discharged into the closest stream.

But the city, north of Mumbai in India's Gujarat state, remains one of the most polluted in India. As a result, a decision last summer by the new administration of Prime Minister Narendra Modi to lift a moratorium on industrial expansion has drawn much attention. Even if it's a clumsy and unfair way to control pollution, the blanket ban on industrial expansion had proven effective, environmentalists claim. Lifting it will only raise pollution in a city already saturated with it.

Vapi (pronounced Wappy) illustrates in vivid ways the challenge the new Modi government faces in using deregulation as a means to promote industrial growth. Growth in industrial clusters such as Vapi has been frustrated by the moratorium. But lifting it could backfire unless the government remains vigilant. In already-polluted Vapi, allowing expansion again could easily result in worsening environmental quality.

"In every part of India where a moratorium was put in place, pollution went down," says Sanjeev K. Kanchan, a researcher at the Centre for Science & Environment (CSE), a nongovernmental organization in New Delhi. Kanchan conducted field research in Vapi in 2010 to measure pollution there. "Government officials had tried to implement other action plans before that," he says, "but they weren't effective."

One of India's oldest chemical industry clusters, Vapi is home to hundreds of plants. Besides dyes and pigments, it's known for materials including agrochemicals and pharmaceutical ingredients. A few big producers such as United Phosphorous and Aarti Industries operate there, but the majority of companies are small to medium-sized firms.

Vapi has long ranked as one of India's most polluted cities. During a visit in 2000, C&EN was easily able to find a stream that changed color from red to green at different times of day and another stream that was deeply red (C&EN, May 15, 2000, page 27). In 2013, India's Central Pollution Control Board ranked Vapi and another Gujarat city, Vatva, as having the worst surface water quality in India.

Between 2010 and 2014, companies operating in Vapi and other Indian cities deemed "critically polluted areas" were slapped, on and off, with blanket bans on industrial expansion. Last June, less than a month after the Modi administration took office, the Ministry of Environment, Forest & Climate Change lifted the ban in Vapi and seven other badly polluted areas.

The ministry said it lifted the expansion

bans because the Central Pollution Control Board in Delhi didn't follow through on a promise to review the methods used for measuring pollution in the eight locations. Rohit Prajapati, an environmental activist based in Vadodara, Gujarat, claims that the decision to lift the bans in fact happened after intense lobbying by industry.

Although the ban has been lifted, companies hoping to expand in the polluted areas still have to apply for environmental clearance from the ministry.

LIFTING THE MORATORIUM means that the environment in Vapi will not improve, CSE's Kanchan laments. "You have to hurt producers in their pockets, and then they will do something," he says. It's not the first time that the moratorium on industrial expansion in Vapi was lifted, he recalls. When it happened a few years ago, pollution in the city quickly worsened.

Even during the moratorium, enforcement of regulations was lax, adds M. S. H. Sheikh, an environmental activist based in the Gujarat city of Surat. Officers of the local environmental protection bureau rarely inspect production facilities unless the public complains, he says. After delinquent facilities are ordered closed, Sheikh claims, they usually can resume production a few weeks later after a paying a small fine but without doing anything to reduce emissions.

But Gaurav Moda, a partner at the consulting firm KPMG who works in the company's Global Chemicals Institute, sees some wisdom in lifting the moratorium. The city may be polluted, he says, but it has improved compared with a few years ago. And the environmental group Blacksmith Institute (now called Pure Earth) removed Vapi in 2009 from a list of the world's 10 most polluted places.

The moratorium served its purpose, Moda adds. Prevented from expanding in Vapi, many companies added facilities in other cities where they were required to use cleaner production processes. Companies can now take these better processes to Vapi and expand without significant environmental impact, he reckons.

And since the lifting of the moratorium, officials in charge of environmental protection have proven to be strict against companies that violate regulations. Last month, Gujarat authorities ordered a two-month closure of 42 plants producing paper, pharmaceuticals, agrochemicals, and dyes for not complying with environmental norms and for failing to install monitoring equipment.

Perhaps of most spectacular note, the Vapi water treatment plant, which is owned by Vapi Industries Association, was hit with a temporary suspension order last December after the Gujarat Pollution Control Board found that posttreatment water did not come close to meeting standards for biological and chemical oxygen demand, two key environmental metrics.

Among its many pledges and slogans, the Modi administration has advocated "zero defect, zero effect," meaning that India should aim to produce high-quality products without environmental impact. Although environmentalists are skeptical, it could be that, given time, a less environmentally harmful chemical industry will take shape in Vapi. ■

CRODA TO PRODUCE BIO-ETHYLENE OXIDE

Croda International will spend $170 million at its New Castle, Del., site to build what will be the only commercial U.S. facility to dehydrate ethanol into ethylene and then oxidize it to ethylene oxide. After the plant opens in 2017, the company plans to use the ethylene oxide to make nonionic surfactants entirely from sustainable feedstocks. Today, Croda produces surfactants at the site by reacting tropical oil derivatives with synthetic ethylene oxide. The firm will use technology from Scientific Design. "This investment represents a tidal shift, especially for consumer goods manufacturers who are striving for sustainability and performance," says Croda CEO Steve Foots.—MM

HONEYWELL AND CEPSA OPEN PLANTS IN CHINA

Honeywell has started up a plant in Zhangjiagang, China, that will produce catalysts used to convert propane to propylene. In the past four years, the company says, it has licensed its Oleflex process for propane conversion to 30 companies worldwide, 25 of them in China. Propylene production in ethylene crackers is on the decline, Honeywell explains, as petrochemical makers switch to natural gas as a raw material. Separately, the Spanish petrochemical producer Cepsa has started up a 250,000-metric-ton-per-year phenol plant in Shanghai. The facility can also produce up to 150,000 metric tons of acetone per year.—JFT

CEPSA

This phenol and acetone plant is Cepsa's first outside Spain.

LSB INDUSTRIES BOWS TO ACTIVIST INVESTOR

LSB Industries, a maker of agricultural and mining chemicals, has named five new members to its board to avoid a proxy fight with activist investor Starboard Value. Two existing directors stepped aside to make way for Starboard-backed directors including Louis Massimo, a former Arch Chemicals executive. LSB says it now plans to separate its chemical business from its climate control products business and set up a master limited partnership for the chemical operations. In response to the news, credit rating agency Moody's revised its outlook on the firm's debt to negative from stable. Some of the director changes are positive, Moody's says, but many directors on the 13-member board "do not have plant-level manufacturing experience."—MSR

ARSENAL CAPITAL SELLS OFF ADHESIVES

Arsenal Capital Partners has agreed to sell Royal Adhesives & Sealants to another private equity firm, American Securities, for an undisclosed sum. Arsenal acquired Royal in 2010. After internal investment and eight acquisitions, the South Bend, Ind., firm now has annual adhesives and sealants sales in excess of $600 million. Arsenal has a long history of buying, building, and then selling chemical businesses. Among them are plasticizer maker Genovique Specialties, sold to Eastman Chemical in 2010, and battery electrolyte maker Novolyte Technologies, sold to BASF in 2012.—MSR

TAKEOVER TRIANGLE AT IMPASSE

Generic drug firms Teva Pharmaceutical and Mylan keep upping the ante in a clash of hostile takeover bids but have gotten no closer to ending their impasse. Last week, Mylan rejected Teva's $40 billion offer as too low and too risky because of stock value and antitrust issues. A merger "would expose Mylan to a problematic culture and leadership with a poor record of delivering shareholder value," Mylan's board maintains. Combining the number-one- and -four-ranked generic drug suppliers would also result in "massive consolidation of supply and manufacturing, creating implications for pricing power and shortages," it added. Meanwhile, Mylan has made three offers to buy Perrigo, the most recent at nearly $36 billion. Perrigo has rejected all of them as undervaluing the company. With Mylan making aggressive moves on Perrigo, Teva will likely have to increase its offer price to win over Mylan. Teva faces a "long, drawn-out battle" that could last several months, says Evercore ISI stock analyst Umer Raffat, who doesn't expect Teva to go much more than 10% higher.—AMT

MEXICAN AND SPANISH FIRMS BOOST VENTURE

Mexico's Grupo Kuo and Spain's Repsol are expanding their Dynasol synthetic elastomers joint venture. Dynasol, which the companies have run since 1999, makes styrene-butadiene rubber and block copolymers in Mexico, Spain, and, soon, China. To that, Kuo will add its Mexican nitrile and emulsion rubber business and a nitrile rubber plant that is set to start up later this year in Nanjing, China. Repsol will contribute its Spanish vulcanization accelerators business. With the new assets, Dynasol will have about $750 million in annual sales.—AHT

AIR PRODUCTS WORKING WITH SUNY

Air Products & Chemicals will work with SUNY Polytechnic Institute's Colleges of Nanoscale Science & Engineering and the nonprofit Sematech to develop chemical mechanical planarization (CMP) slurries in Albany, N.Y. The CMP Center is expected to attract $5 million in investment over three years and support 50 jobs, according to SUNY. At the center, Air Products will work on CMP materials for sub-10-nm integrated circuit fabrication. Two Japanese companies, Mitsubishi Chemical and Hitachi Chemical, also recently agreed to work at the CMP Center.—AHT

EVONIK INVESTS IN POLYMER TESTING

Evonik Industries has opened an application technology center for superabsorbent polymers at its Krefeld, Germany, site. Built at a cost of about $1 million, the center will permit efficient testing of the highly absorbent polymers in both baby diaper and adult incontinence applications, the firm says. A highlight of the lab is a new mannequin test for incontinence products.—MM

EVONIK

Evonik's new lab includes mannequins for absorbent polymer testing.

KOLON ADMITS THEFT OF DUPONT SECRETS

South Korea's Kolon Industries pleaded guilty in federal court in Alexandria, Va., last week to stealing trade secrets regarding DuPont's Kevlar aramid technology. The company was sentenced to pay $85 million to the U.S. and $275 million in restitution to DuPont. The U.S. Justice Department had previously sought a $225 million fine, and an earlier court decision found Kolon liable to pay DuPont $920 million. DuPont filed suit against Kolon in 2009.—MM

DOW FINDS BUYER FOR AGROFRESH BUSINESS

Dow Chemical will sell its AgroFresh business to Boulevard Acquisition, a publicly traded investment company set up by the private equity firm Avenue Capital Group. AgroFresh sells a system that uses 1-methylcyclopropene to keep fruit from spoiling. The $860 million price is nine times AgroFresh's pretax earnings. When the deal is completed, AgroFresh will become a public company traded on the NASDAQ exchange, and Dow will initially retain a 40% stake. The sale is part of a Dow plan to divest up to $8.5 billion in businesses by mid-2016.—AHT

CELGENE ACQUIRES GENOMICS SPECIALIST ...

Celgene will acquire Quanticel Pharmaceuticals, a privately held specialist in cancer drug discovery. The deal will give Celgene access to Quanticel's platform for the single-cell genomic analysis of human cancer as well as Quanticel's lead programs targeting specific epigenetic modifiers. The deal caps a 2011 collaboration between the companies, during which time Quanticel generated several drug candidates expected to begin clinical trials next year. Celgene will pay $100 million for Quanticel plus milestone payments of up to $385 million.—RM

... AND INVESTS IN CANCER THERAPIES

Celgene will pay AstraZeneca $450 million to participate in development of MEDI4736, an anti-PD-L1 inhibitor for hematologic malignancies. The pact will focus on combining the AstraZeneca antibody with products in Celgene's pipeline. Separately, Celgene has paid Northern Biologics, a biotech firm backed by Versant Ventures, $30 million for rights to license oncology antibodies in Northern's pipeline and to acquire Northern. And Celgene has paid Agios Pharmaceuticals $10 million to expand an earlier pact to develop AG-881, a small molecule in development to treat brain cancer.—MM

WUXI CEO SEEKS TO TAKE FIRM PRIVATE

WuXi Pharmatech, a Chinese provider of drug R&D and manufacturing services, has received a takeover offer worth more than $3 billion from founder and CEO Ge Li and Ally Bridge Group Capital Partners. WuXi will form a committee to consider it. Li founded WuXi in 2000, expanding it into a research outsourcing behemoth with more than 8,000 employees and sales last year of $674 million. Last week the firm announced that it is building the world's largest disposable-bioreactor-based mammalian cell culture facility in the city of Wuxi, China.—MM

BUSINESS ROUNDUP

EUROCHEM has selected a site in St. John the Baptist Parish, La., for an up-to-$1.5 billion nitrogen fertilizer plant it announced in 2013. The Russian company is now looking for a buyer for land in Iberville Parish that it had purchased as a possible site.

FERRO CORP. will acquire Nubiola Pigmentos, a Spanish provider of pigments for plastics and construction uses, for about $162 million. Nubiola makes specialty inorganic pigments and is the world's largest producer of ultramarine blue, Ferro says.

AKZONOBEL and ICL are joining to produce 1.5 million metric tons per year of high-purity vacuum salt at ICL's mining facility in Catalonia, Spain. The project will also yield a smaller amount of white potash.

CARGILL has acquired OPX Biotechnologies' fermentation-based processes and systems. Cargill says it will use the technology to expand in fermentation products outside of food and feed. OPX will wind down after the transition is complete in six to nine months.

CHINA STEEL of Taiwan has agreed to put $46 million into the construction of a 50,000-metric-ton-per-year ethanol plant that will use as feedstock off-gases from a steel mill in Kaohsiung, Taiwan. The plant will use technology from Skokie, Ill.-based LanzaTech.

BAYER MaterialScience has picked BioAmber to supply biobased succinic acid for a new line of biobased polyurethanes intended for textile applications. Bayer says the Impranil waterborne polyurethanes have renewable content as high as 65%.

ROCHE AND 4D Molecular Therapeutics will jointly discover and develop adeno-associated virus (AAV) vectors to treat underserved medical conditions using 4D's AAV vector discovery platform. The partnership was facilitated by QB3, a University of California biotech accelerator where 4D is based.

CALICO, the Google-founded company focused on therapeutics for aging, will support research at the Buck Institute for Research on Aging. Calico has the option to obtain rights to discoveries made under research it supports.

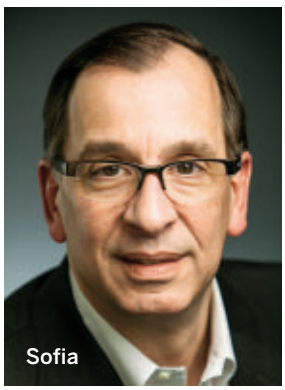
STRIKING GOLD TWICE

After discovering a game-changing pill for hepatitis C, **MICHAEL SOFIA** has turned his attention to hepatitis B

LISA M. JARVIS, C&EN CHICAGO

THE CHANCES of any one chemist discovering a drug that works—a molecule that is safe and improves people's lives in a meaningful way—are small. The chances of discovering an actual cure? Minuscule.

Medicinal chemist Michael Sofia has managed to beat the odds. He invented what is now one of the most successful drugs in the pharmacopoeia: sofosbuvir, better known as Gilead Sciences' blockbuster hepatitis C virus treatment Sovaldi. For many people with HCV, the pill sliced the treatment time for the virus from a year to just 12 weeks while eliminating the harsh side effects of older, less effective therapies.


Sofia

TEKMIRA

That quick cure made Sovaldi the biggest drug launch in history. Approved late in 2013, Sovaldi brought in more than $10 billion for Gilead last year.

Now, Sofia has set his sights on the hepatitis B virus, another serious liver infection. He's spent the past three years thinking about what a cure for HBV might look like and, through a biotech firm he cofounded called OnCore Biopharma, acquiring promising molecules.

In January, OnCore was acquired by Canada's Tekmira Pharmaceuticals, which has its own HBV activities. Now at the helm of Tekmira's R&D operation and in charge of a broad new drug pipeline, Sofia faces the challenge of repeating the success of Sovaldi. No pressure.

Despite an available vaccine, the hepatitis B virus chronically infects some 240 million people around the world, almost twice the number who have HCV, according to the World Health Organization. Although a handful of antivirals are approved to treat HBV, they don't work for most people; those who do respond aren't actually cured and have to take the pills for the rest of their lives.

Sofia first started contemplating how to cure hepatitis B while at Pharmasset, the Princeton, N.J.-based biotech where he discovered sofosbuvir.

Then, in 2011, Gilead put down $11 billion to acquire Pharmasset. Although Sofia was offered a job at Gilead, he had learned during earlier stints at big pharma firms that he prefers a more entrepreneurial environment. He stayed on as an adviser to Gilead during a transitional period but was already starting to think about a hepatitis B-focused start-up.

In mid-2012, Sofia, along with three other Pharmasset veterans, launched OnCore in Doylestown, Pa. The idea was to build on their collective experience in HCV to tackle HBV.

They knew that a cure for HBV would likely require a combination of drugs, just as the HCV cure did. And as for HCV, an effective HBV treatment would need to cripple the virus's ability to replicate.

But HBV has two more survival tricks that make it more complicated to fight than HCV: The virus can evade detection by modulating the host immune system, and in its most clever ploy, it leaves a reservoir of viral DNA in the liver of its host. As Sofia explains, even if replication is shut down, the reservoir allows the virus to bounce back with new viral proteins, genomic material, and, ultimately, new viral particles.

Sofia and his OnCore partners were convinced that eliminating the virus would require a drug cocktail that addresses each of those survival mechanisms—viral replication, immune system control, and the liver viral reservoir. With that goal in mind, they set out to assemble a portfolio.

THE TINY COMPANY was self-funded until mid-2014, when one of the original investors in Pharmasset provided its first round of external funding, allowing Sofia and his team to quickly acquire a collection of assets.

One of their first purchases was OCB-030, a sangamide-based cyclophilin inhibitor from Stockholm's NeuroVive Pharmaceutical. Cyclophilin inhibitors were also explored in HCV, but Sofia points out that OCB-030 is structurally very different than the molecules tested in HCV. Moreover, it has proven more potent in preclinical studies, he says.

Other acquisitions include Enantigen Therapeutics, another Doylestown-based start-up. It brought surface antigen secretion inhibitors, meant to tackle viral immune control, and capsid assembly inhibitors, which target the viral reservoir.

OnCore also licensed several projects from the Blumberg Institute, a nonprofit research institute associated with the Hepatitis B Foundation that is also located in Doylestown. Two of those projects focus on other ways to attack the viral reservoir, which is composed of covalently closed circular DNA.

"We believe strongly that cccDNA is going to be the solution to the cure, ultimately, and we've put a lot of effort into this area," Sofia says.

Armed with a portfolio of molecules spanning

TACKLING HEPATITIS B

The combined pipeline of Tekmira and OnCore addresses the multiple ways the hepatitis B virus survives in its host

	VIRUS SURVIVAL TARGET			
CANDIDATE	VIRAL REPLICATION	IMMUNE CONTROL	VIRAL RESERVOIR	DEVELOPMENT STAGE
TKM-HBV	x	x		Phase I
OCB-030	x	x		IND-enabling studies
CYT003		x		IND-enabling studies
Capsid assembly inhibitors	x			Lead optimization
Surface antigen secretion inhibitor		x		Lead optimization
cccDNA formation inhibitor			x	Lead optimization
STING agonist		x		Research
cccDNA epigenetic modifier			x	Research

IND = investigational new drug. **cccDNA=** covalently closed circular DNA. **SOURCE:** Tekmira

multiple mechanisms of action, OnCore's managers intended to take the company public. They had gone so far as to compile the lengthy document required by the Securities & Exchange Commission, known as the S-1, before selling stock to the public and were in the midst of a road show to potential investors. Then Tekmira came calling.

Tekmira was one of several companies that OnCore had been chatting with as it explored the potential for treating HBV with small interfering RNA. "It became clear when we talked to the people at Tekmira that they had a very similar vision," Sofia says. And because there was minimal overlap between Tekmira's siRNA capabilities and compounds and OnCore's small-molecule ones, "it became a natural fit."

IN JANUARY, Tekmira and OnCore agreed to merge in a deal that gave OnCore shareholders 50% of Tekmira's stock. At the time, the combined company was valued at $750 million.

For Tekmira, the deal was transformative. Although several other companies—including Gilead, Alnylam, and Arrowhead Research—are working on HBV treatments, industry watchers were happy to see a broad collection of assets under one roof. News of the merger sent Tekmira's stock price up roughly 50%.

When the transaction closed in March, Sofia became the chief scientific officer of Tekmira. He is now part of a team of roughly 120 people—about twice the size of Pharmasset during most of its existence, although still a far cry from a big pharma firm.

Meanwhile, Tekmira's siRNA-based HBV treatment, TKM-HBV, is already in a Phase I trial, and a Phase I trial of OCB-030 is planned for the second half of this year. If all goes well, analysts expect the company to start its first study combining TKM-HBV and OCB-030 next year.

As trials begin to roll out, Sofia expects to see a transformation in how HBV is treated. "HBV is where HCV was about 12 years ago," he says. "You can imagine a stepwise scenario like you saw in HCV where new therapies improve cure rates, then reduce duration of therapy, and ultimately get to the point where we all want to be—an all-oral, combination therapy with a high cure rate."

Sofia would like to be a part of finding that cure. Still, he knows he's the rare medicinal chemist to have even one cure under his belt. "Sofosbuvir is a hard act to follow," he says. ■

CHASING CHEAP SILICON

WACKER CHEMIE hopes a novel production technology it is developing can make it more competitive

IF YOU HAVE LUNCH with Rudolf Staudigl, the measured chief executive of Wacker Chemie, the Bavarian chemical producer, don't expect him to be a barrel of laughs.

It's been a tough time for Wacker's polysilicon business, as well as Siltronic, the firm's silicon wafer subsidiary. Already faced with high capital and energy costs, Wacker and its competitors have had to swallow a huge dip in selling prices for polysilicon and silicon wafers after the market became swamped with supply.

Ask Staudigl to name his favorite in-house R&D project, though, and he will crack a smile. That's because it is a novel approach for making certain semiconductor wafers that could lead to significant cost savings. Staudigl is optimistic. "It's a very exciting project," he tells C&EN.

The standard approach to manufacturing high-purity polycrystalline silicon is the Siemens process. Developed by the German firm Siemens in the 1950s, it involves heating thin silicon rods in large vacuum chambers in the presence of hydrogen and trichlorosilane at 1,100 °C for several days.

When the reaction is complete, the bell-shaped chamber lid is lifted to reveal several tons of high-purity silicon coating the silicon rods. After being smashed into chunks, this polysilicon is then melted and grown into large monocrystalline ingots using a method named after its inventor, the Polish scientist Jan Czochralski. The ingots are sliced to form the silicon wafers used in semiconductors and solar panels.

"Wacker's biggest problem is not being Chinese."

In recent years, Wacker and some of its competitors have independently developed fluidized-bed deposition techniques as a potentially lower-cost alternative to the Siemens process. Instead of polysilicon chunks, it creates polysilicon granules.

Now Wacker is seeking to use granular polysilicon in a novel approach to make so-called float-zone silicon wafers, which are used to make high-end electronic switches rather than solar panels and semiconductors. The market is growing rapidly and represents a major opportunity, Wacker says. The firm has named its technology the granular float-zone process, or GFZ.

In the standard float-zone process, Siemens polysilicon is melted with an induction coil and grown into a monocrystalline ingot. The crystal is highly pure because surface tension allows it to "float" around a support rod without the need for a containing vessel that might cause contamination. A drawback is the high cost of running the Siemens process. GFZ avoids this by using lower-cost polysilicon granules, according to Hans-Peter Bortner, director of silanes production for Wacker.

Yet several technical challenges must be overcome for the GFZ technology to meet its targets for quality and cost-effectiveness, Wacker says. Although the fluidized-bed approach is economical, the polysilicon granules it yields have higher levels of impurities than do the chunks from the Siemens process. A focus of Wacker's development of GFZ is reducing these impurities in the final product.

Wacker has begun operating a development reactor at its biggest polysilicon plant, in Burghausen, Germany, dedicated to testing the manufacture of float-zone ingots from granular polysilicon. "We are working on getting the costs down and on reaching the needed product quality," Bortner says.

Although Wacker says it expects GFZ to become a commercial success, the firm has to date been reluctant to manufacture granular polysilicon at large scale.

POLYSILICON GRANULES may yield not only a cheaper route for GFZ but also cheaper commercial production of solar panels. But recent claims by other leading polysilicon producers—including REC Silicon, SunEdison, and GCL-Poly—that they are on track to scale up granular polysilicon production have been met with skepticism by industry analysts.

"While fluidized-bed reactor systems are a proven technology, at this point, polysilicon manufacturers have not proven that it leads to sustainable success in the market," says Mark Barineau, a solar analyst with Lux Research, a market research firm.

Industry experts estimate that the granular process could reduce the cost of making polysilicon to $10 to $15 per kg compared with $12 to $20 per kg for the latest iterations of the Siemens process. Although granular processes may be the future, right now the Siemens process "is much more reliable and bankable than fluidized-bed reactors," says Richard M. Winegarner, president of Sage Concepts, a consulting firm with expertise in the polysilicon sector.

WACKER

LOW-COST OPPORTUNITY A silicon ingot produced by Wacker with the process known as GFZ.

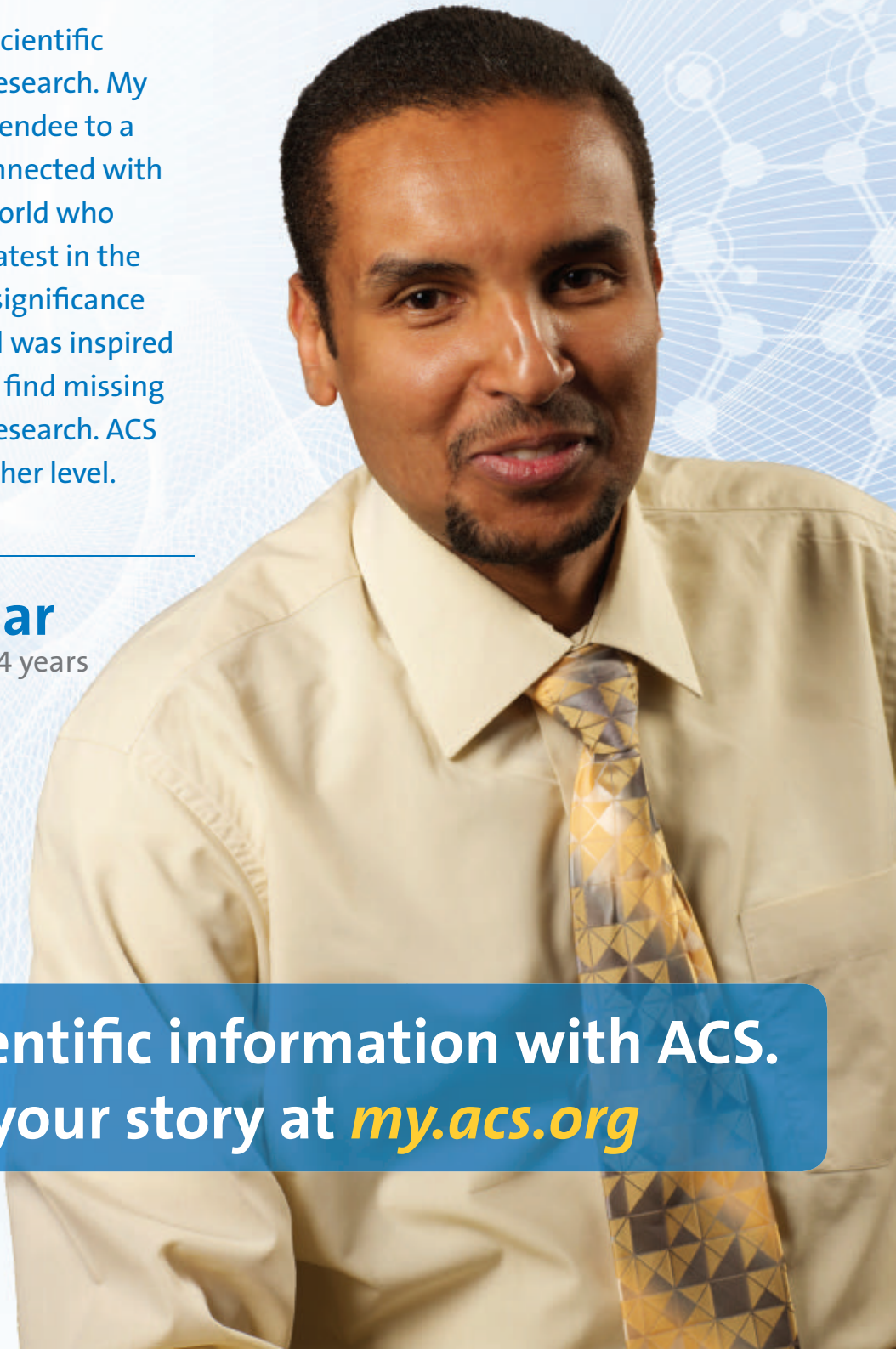
A more immediate concern for Wacker, Winegarner points out, is the domination of the silicon sector by Chinese firms potentially propped up and protected by their government. "Wacker's biggest problem is not being Chinese," he says. Even if Wacker were to step up its activities relating to granular polysilicon, "I don't think Siltronic is ever going to be a huge moneymaker," Winegarner says.

Indeed, the silicon wafer market is such a tough place to do business that Staudigl recently initiated a review to determine whether Wacker should sell Siltronic.

Although GFZ may yet prove to be the exciting commercial technology Staudigl hopes it will be, for Wacker it may be one technology that delivers too little, too late.—ALEX SCOTT

DISCOVER

My ACS helped me discover scientific information needed for my research. My membership began as an attendee to a national meeting where I connected with scientists from all over the world who all attended to discover the latest in the field. I instantly realized the significance of being an ACS member and was inspired to start using ACS content to find missing information needed for my research. ACS has helped guide me to a higher level.



Mohamed Baqar
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BILL WOULD LET STATES OPT OUT OF CO_2 CUTS

States could duck upcoming EPA regulation of carbon dioxide emissions from power plants under a bill the House Energy & Commerce Committee adopted last week. The measure, H.R. 2042, would put EPA's rule for curbing CO_2 from existing power plants on hold until federal courts have finished a review of EPA's authority to address climate change under the Clean Air Act. "We're not repealing the regulation," says Rep. Ed Whitfield (R-Ky.), the bill's sponsor. "Let's let the courts render a decision." The legislation would allow governors to opt out of the EPA rule, expected to be out in July, if they determine the regulation would threaten electricity reliability or have "adverse effects" on ratepayers. Governors would be required to consult with state regulators, environmental agencies, and others in making the determination. Democrats are strongly opposed to the bill. "This is a thinly veiled excuse to do nothing about climate change," says Rep. Bobby L. Rush (D-Ill.). The committee passed the measure 28–23, clearing the way for the full House to vote on, and likely pass, the bill.—SG

FLUORIDE LEVELS IN WATER LOWERED

For the first time in more than 50 years, the Department of Health & Human Services has changed the recommended concentration of fluoride in drinking water. New guidance from the U.S. Public Health Service recommends 0.7 mg/L rather than the previous range of 0.7 mg/L to 1.2 mg/L. The change affects more than 12,000 communities that add fluoride to their drinking water supply to prevent dental cavities. The recommendation updates and replaces the agency's 1962 Drinking Water Standards for community water fluoridation. The change comes as data suggest that fluoride is now available to Americans from several sources, including toothpastes, mouth rinses, and dietary supplements, the agency says. The American Academy of Pediatrics and the American Dental Association issued statements in support of the updated guidelines. Excess fluoride in drinking water can cause dental fluorosis, a condition that can cause noticeable white stains or pits on the teeth.—JM

SHUTTERSTOCK

The federal government has tightened the levels of fluoride in drinking water for the first time since 1962.

INDUSTRY ASKS FDA TO DITCH CHANGES TO DRUG-LABEL RULES

Trade groups representing the branded and generic pharmaceutical industries are urging the Food & Drug Administration to scrap its proposal to change the way generic drug labels are updated to reflect safety risks. FDA has proposed to allow generic drug manufacturers to independently modify labels if they become aware of new safety issues that might pose a risk for consumers. Currently, generic drug makers must wait until either FDA requires an update to the drug's labeling or the original manufacturer decides to change its label. At that point, the generic drug must bear the same label as the reference drug. But the proposed rule creates a scenario "where potentially conflicting information from multiple manufacturers for single medicines could be widespread," causing confusion and putting patient safety at risk, says the Generic Pharmaceutical Association (GPhA). Instead, GPhA and the branded drug lobby, the Pharmaceutical Research & Manufacturers of America, say FDA should determine whether new warnings on drug labels are needed and, if so, require all manufacturers to make the changes.—GH

ENERGY INFRASTRUCTURE NEEDS UPGRADES

Obsolescence of the electric grid and natural gas and oil infrastructure warrants new investment to ensure resilience and reliability, the Energy Department says in its "Quadrennial Energy Review." According to the report, released last week, about 50% of natural gas pipelines were built between 1950 and 1970, and surges in gas volume necessitate between $2.6 billion and $3.5 billion in new investment by 2030. The report focuses on the role of transport, storage, and distribution infrastructure in a rapidly changing energy landscape. Although much of this infrastructure is privately held, the federal government owns significant portions, including transmission lines and storage facilities, and has a role in regulating what it does not own. Climate-related changes such as sea-level rise, thawing permafrost, and extreme weather are already affecting this infrastructure in many regions, the report adds. In addition, domestic petroleum consumption is flat, coal use is declining, and natural gas and renewables are surging. The U.S. is emerging as the world's leading producer of oil and natural gas combined, according to the report.—SG

MEASURE TAKES AIM AT 'PATENT TROLLS'

Reviving a push for reform that stalled last year, members of the Senate Judiciary Committee introduced bipartisan legislation last week that would crack down on "patent trolls." The bill is aimed at combating what some businesses say is growing abuse of litigation by companies that buy patent portfolios for the sole purpose of trying to extract fees and financial settlements from alleged infringers. Sen. Chuck Grassley (R-Iowa), committee chairman and one of the bill's cosponsors, says the panel will vote on the measure by late May. The legislation was quickly praised by pro-reform groups, including the recently formed United for Patent Reform, whose members include Google, Facebook, telecom giants, and retail lobbying groups. The Biotechnology Industry Organization, a trade association, says the bill includes "noticeable improvements" over an anti-patent-troll measure (H.R. 9) pending in the House of Representatives. But the group says the Senate proposal still needs to better protect the ability of biotech companies to assert their intellectual property rights.—GH

JIM URQUHART/REUTERS

COAL POWER PacifiCorp's Jim Bridger Plant in Wyoming burns 8 million to 9 million tons of coal annually.

HIGH COURT WEIGHS EPA MERCURY RULE

Justices will determine whether agency must consider both costs and public health in deciding whether to regulate **AIR POLLUTION**

GLENN HESS, C&EN WASHINGTON

THE ENVIRONMENTAL Protection Agency's first-ever regulation limiting releases of mercury and other toxic air pollution from power plants is facing its final legal hurdle. The Supreme Court is considering whether EPA went too far when it finalized a rule to protect public health that the agency estimates will cost electric utilities and their customers almost $10 billion per year.

Mercury is a potent neurotoxin; tiny doses can harm children's development and pose risks for fetuses of pregnant women. Coal-burning power plants, which are the largest source of mercury in the U.S., are facing a series of EPA regulations that require owners to invest in pollution controls or shut down aging facilities.

The justices are evaluating industry and state arguments that EPA violated the Clean Air Act by failing to consider the potential financial burden before it decided to issue those emission limits. "Congress did not intend for EPA to act with deliberate indifference to cost when answering the basic regulatory question of whether it is appropriate to regulate," the plaintiffs' brief asserts.

EPA's Mercury & Air Toxics Standards, which began to take effect in April, require power plants to reduce their emissions of mercury by 90%. The pollution control technology needed to strip mercury out of the plants' releases to the air will also reduce emissions of acid gases such as hydrogen chloride by 88% and particulate-forming sulfur dioxide by 41%—providing what the agency calls "cobenefits." EPA believes that the regulation will produce between $37 billion and $90 billion in public health cost savings per year.

That means lower health care costs for downwind residents, fewer lost workdays, and a reduction in early deaths. Up to 11,000 people die prematurely as a result of power plant pollution each year, according to the agency.

The high court is expected to issue a ruling in the case, *Michigan v. EPA*, by the end of June. The decision could set an important precedent on whether the agency needs to consider the potential costs before it decides whether regulation is warranted under the Clean Air Act.

When Congress amended that federal law in 1990, it directed EPA to aggressively control emissions of mercury and more than 180 other hazardous air pollutants. The statute says the agency "shall regulate" the major sources of these pollutants where it is "appropriate and necessary."

EPA concluded that it was both appropriate and necessary to regulate mercury from power plants based in part on studies of Americans who rely on fish for a substantial part of their diet. Mercury pollution from these facilities may be making fish unsafe for human consumption in 65% of the U.S. waters that receive atmospheric fallout of the metal, according to the agency.

EPA also says the acid gases and microscopic particles emitted by electric utilities can cause asthma, lung problems, and heart disease.

In December 2011, the agency finalized new standards requiring about 1,400 generating units at 600 power plants, most of which burn coal and are in the South and upper Midwest, to install high-tech scrubbers and other devices to remove the pollutants. At the time, the Energy Information Administration reported that 64% of the facilities had already installed pollution control equipment to comply with the new standards.

"By affirming these vital emission standards, the Supreme Court would also help level the playing field for the two-thirds of coal-fired plants that have already upgraded their plants," says Graham McCahan, a staff attorney at the Environmental Defense Fund, an advocacy organization.

BUT INDUSTRY GROUPS such as the National Mining Association and nearly

"EPA has expressly refused to consider the cost of its regulation, which will result in rate increases."

two dozen states assert that EPA's regulation amounts to a prohibitively expensive "overreach" by the Obama Administration.

They argue that the benefits of controlling the utility emissions of mercury amount to only $4 million to $6 million annually and that the rest of the benefits come from the reduction of particulate pollution, which is regulated by other EPA programs.

A three-judge panel of the U.S. Court of Appeals for the District of Columbia Circuit upheld the new standards last year. But 21 states, the mining association, and the Utility Air Regulatory Group, a utility lobbying group, petitioned the Supreme Court to hear the case. They contend that the Clean Air Act required EPA to take into account compliance costs when it was deciding whether to regulate toxic air emissions from power plants.

"EPA has expressly refused to consider the cost of its regulation, which will result in rate increases for citizens across the country, and threatens the reliability of the electricity grid by forcing the closure of many power plants," says Michigan Attorney General William D. Schuette.

Supporters of the rule hope the justices will lean toward giving EPA deference to interpret the Clean Air Act as it did when it decided to consider only public health risks in determining that the rule was necessary. EPA has said it took the cost of technology into account at a later stage in the regulatory process when it crafted the specific emission standards.

DURING ARGUMENTS before the high court last month, U.S. Solicitor General Donald B. Verrilli Jr. defended the agency. He called it "certainly appropriate for EPA to list power plants for regulation based solely on health and environmental hazards." The relevant section of the Clean Air Act, Verrilli pointed out, does not mention costs anywhere in its text.

The Court's four-member liberal wing largely voiced support for EPA's approach. For instance, Justice Elena Kagan said the argument that the agency must consider costs despite the law's silence on the issue is at odds with a 2001 Supreme Court decision.

In that case, *Whitman v. American Trucking Associations,* the justices unanimously agreed that EPA is prohibited from considering cost when setting national ambient air quality standards for ground-level ozone and other common air pollutants.

Congress has often explicitly required EPA to consider the cost of its regulations but said nothing to that effect in the Clean Air Act's provision on power plant emissions, Kagan said. "Congress knows how to require consideration of costs," she remarked. "To get from silence to this notion of a requirement seems to be a pretty big jump."

Justices Ruth Bader Ginsburg and Sonia M. Sotomayor both signaled that the Court should defer to an agency's interpretation of an ambiguous statute as long as the agency's reading is reasonable.

Ginsburg said Congress often directs an "expert agency," such as EPA, to use its judgment to determine whether regulation is appropriate. "Is there any case in all of our decisions where we have said even though there was no instruction to consider costs, EPA is required to consider costs?" she asked.

Sotomayor added that all the Supreme Court has to do is find that EPA made a "plausible reading" of the Clean Air Act to rule in the agency's favor.

But several members of the Court's conservative majority criticized EPA's position. Justice Antonin Scalia, who authored the 2001 decision on costs under the Clean Air Act, called the mercury regulation "outrageously expensive." He said the decision not to conduct a cost-benefit analysis early in the rule-making process was "a silly way" to interpret the statutory language.

Chief Justice John G. Roberts Jr. said the rule's estimated $9.6 billion annual price tag "raises the red flag" because only a "tiny proportion" of the calculated benefits are attributable to a reduction in mercury emissions.

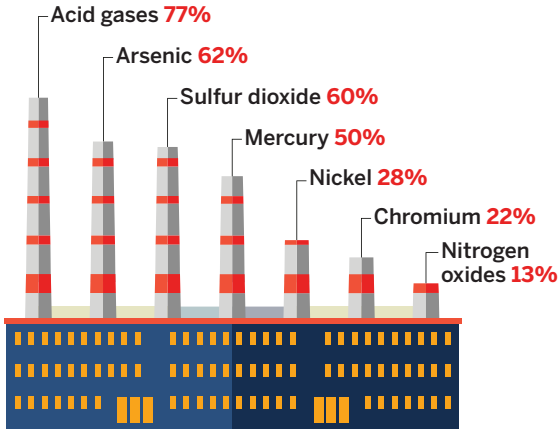
"I'm just questioning the legitimacy" of counting cobenefits from reductions of particulates that are regulated under other sections of the Clean Air Act, Roberts said. He described that approach as an "end run" around the statutory language.

ON THE OTHER HAND, Justice Anthony M. Kennedy, who has often been the swing vote on the nine-justice Court, expressed sympathy for both sides of the issue. He said the word "appropriate" is ambiguous, which suggests Congress gave EPA some leeway.

But Kennedy also seemed skeptical of the agency's decision to wait and consider cost later in the regulatory process, when it set the exact emission standards. Once EPA decided that power plants should be regulated, "at that point, the game is over," he said.

Although the justices were clearly divided over the mercury rule, the Court has sided with EPA in recent decisions. Last year, the justices upheld a rule that curbs air pollution that drifts across state lines, deferring to EPA's reading of the clean air law. The Court also largely validated the agency's plan to regulate major sources of greenhouse gas emissions. ■

EMISSIONS A large portion of U.S. air pollution comes from power plants.



SOURCE: EPA

Up to 11,000 people die prematurely as a result of power plant pollution each year, according to EPA.

MICHAEL E. ROGERS

Medicinal chemist has overseen much of **NIH'S CHEMISTRY RESEARCH** since 1993

ANDREA WIDENER, C&EN WASHINGTON

FOR MICHAEL E. ROGERS, working at the National Institutes of Health is the chemist's equivalent to being a kid with a job in a candy store.

"If you have interests in biomedical science, I can't think of any better place to be," he says.

That is what kept Rogers, 69, at NIH for almost 35 years. Through the decades, his career has spanned from peer review to legislative affairs to creating chemistry research programs.

For the past 20 years, Rogers oversaw the majority of chemistry research funded through NIH as director of the Division of Pharmacology, Physiology & Biological Chemistry in the National Institute of General Medical Sciences (NIGMS). "My whole professional life has been combining chemistry and biology," explains Rogers, who retired on May 1.

ANDREA WIDENER/C&EN

Chemist Mike Rogers is retired from NIH.

Growing up in rural Georgia, Rogers didn't expect to become a chemist. His parents didn't finish grammar school, and he was the first person in his family to graduate from high school. But an aunt encouraged him to attend community college. There, he gravitated toward chemistry, inspired by his experience in a high school chemistry class.

Rogers went on to earn a bachelor's degree in chemistry from Berry College in Georgia. As he neared graduation, he heard a talk given by some pharmaceutical chemists from the University of Mississippi. "I liked chemistry, but the idea of being able to use that knowledge to make drugs? I was totally snowed," he remembers.

So off he went to graduate school at the University of Mississippi in the department of medicinal chemistry, which he followed with a postdoc at NIH in 1972. After that, Rogers took a faculty position at Virginia Commonwealth University. When it became clear he wasn't going to get tenure, he returned in 1980 to NIH, where he remained until last week.

Rogers started out overseeing grant review in what was then called the Division of Research Grants. He founded the bioorganic and natural products chemistry study section and chose its first members. "I always considered it one of the great wonders of the world that they let me do that," he says.

A few years later, Rogers took a six-month assignment working on the Senate's Labor & Human Resources Committee, which was then led by Sen. Edward Kennedy (D-Mass.). "That was a blast," he says, pointing out a picture of himself and Kennedy hanging in his office. "I didn't have any power. But just because I was there, people thought I did."

While on detail in Congress, he became more interested in the research programs at NIH, so when he came back to the agency he joined NIGMS. He became acting director in 1993 of what became the Division of Pharmacology, Physiology & Biological Chemistry, which funds approximately 60% of NIH chemistry research, he says.

That has put Rogers in a position to make vital investments at the intersection of biology and chemistry. One of the most important may have been creating grants to train chemists in biological concepts, he says.

In the early 1990s, "if you were a chemist and you wanted to get some training in biology, it wasn't necessarily that well accepted," Rogers remembers. The program, he says, "provided validation for a lot of people who wanted to work at the chemistry-biology interface," an area that is booming now.

Looking back, one the most exciting times to work at NIH was in the late 1990s, when the agency's budget doubled. "We were able to start some programs that we wouldn't have been able to do otherwise," he says. One example is the agency's so-called glue grants, which fund large-scale team research projects in many fields, including chemistry.

The financial situation now is significantly different. "You have more people competing for the same money, and the money doesn't goes as far," he says.

"If you have interests in biomedical science, I can't think of any better place to be."

One of Rogers's biggest concerns is the pressure this puts on young scientists, who feel like they have to make a major breakthrough to get a job and research funding. "The thrill of discovery itself gets lost," he says.

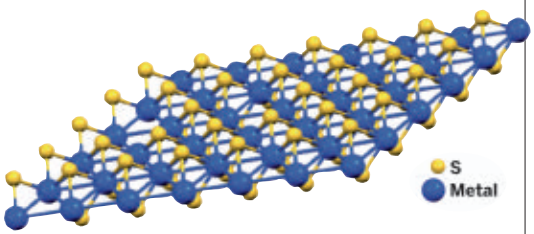
That thrill is what has kept Rogers engaged through the years. He sees the human microbiome as an up-and-coming research area for chemists. "We know relatively little about the chemical communication that goes on between gut bacteria and the body," he says. "That offers a lot of opportunities for chemists."

He has also been leading a push into quantitative and systems pharmacology research, which looks at the body as a system and how a drug interacts broadly within it. "That is the one area I really hate to give up," he says.

Rogers says what he'll miss the most, besides the people at NIH, is that amazing sense of discovery. "If you are following science, it is like following your favorite TV drama because there is always a new development." ■

GROWING THE THINNEST OF SEMICONDUCTORS

For supermodels and semiconductors, it seems that thin is always in. As electronics makers continue to squeeze more components into increasingly smaller spaces, they're on the lookout for materials that can achieve the ultimate in small—atomic-scale electronic devices. Now, Jiwoong Park and colleagues at Cornell University report an advance toward realizing such materials. They've grown sheets of the transition-metal dichalcogenides MoS_2 and WS_2 that are only three atoms thick, but stretch over an area of about 10 sq in (*Nature* 2015, DOI: 10.1038/nature14417). Park's team made the monolayer sheets via a new metal-organic chemical vapor deposition process, using $Mo(CO)_6$ or $W(CO)_6$ as the transition-metal source and diethylsulfide as the sulfur source. They



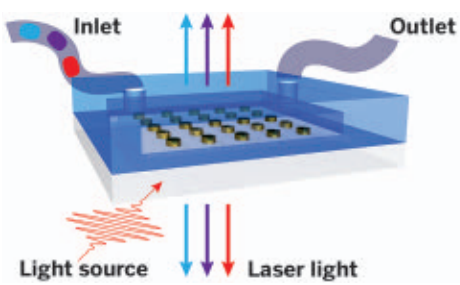
NATURE

MoS_2 and WS_2 can now be grown as atomically thin films with a measured area of 10 sq in.

added hydrogen gas to remove any built-up carbonaceous deposits. The resulting films were of sufficient quality to make field-effect transistors. The method does have some limitations: It takes about 26 hours and requires temperatures of 550 °C. Even so, Park and coworkers note that the technique is "a step toward the realization of atomically thin integrated circuitry" and could find use in the fabrication of flexible electronics, photovoltaics, and displays.—BH

SWITCHING SOLVENTS TUNES NANOLASERS

Nanolasers, which could be used to supply light to lab-on-a-chip devices, have been made with solid lasing, or "gain," materials. But the output of these light sources couldn't be tuned after fabrication. Teri W. Odom of Northwestern University and coworkers have now made plasmonic nanolasers that are tunable from 858 to 913 nm in real time (*Nat. Commun.* 2015, DOI: 10.1038/ncomms7939). The researchers made the nanolasers from a gold nanoparticle array surrounded by a liquid gain material composed of dye molecules dissolved in organic solvent. The nanolaser is activated by pumping it optically with an external light source. The resulting emission wavelength is dictated by the refractive indexes of the solvent and the substrate. Thus, for a given substrate and nanoparticle array, changing the solvent changes the emission wavelength. By integrating the nanoparticle array in a microfluidic device, the researchers were able to change the solvent and the lasing wavelength in real time. For example, a nanolaser made from the dye IR-140 in dimethyl sulfoxide and a nanoparticle array on fused silica emitted light at 862 nm. By switching to benzyl alcohol, the same device lased at 891 nm.—CHA



NAT. COMMUN.

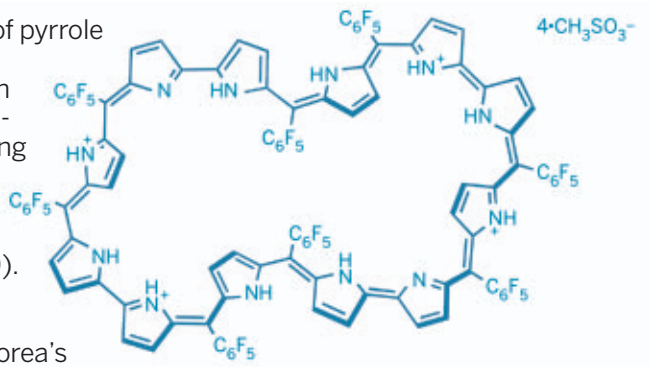
By varying the composition of a liquid medium (colored plugs at inlet) flowing over a gold nanoparticle array, the laser light emitted by this tiny device can be quickly tuned over a range of wavelengths.

METHYLATED ADENINE FUNCTION DETERMINED

The methylated genomic base N^6-methyladenine (6mA) has been found in the genomes of bacteria and small eukaryotic organisms such as ciliates and algae but not in higher organisms, and its function in eukaryotes has been unknown. Now, researchers have found it in two higher organisms and have determined a functional

GIANT PORPHYRIN GOES BIG ON AROMATICITY

By increasing the number of pyrrole groups in a porphyrin ring from the usual four to 12, an international team of chemists has succeeded in making the largest aromatic molecule known to date (*Chem. Eur. J.* 2015, DOI: 10.1002/chem.201500650). Expanding the realm of aromaticity is nothing new for Dongho Kim of South Korea's Yonsei University and Atsuhiro Osuka of Japan's Kyoto University. Their groups have been collaborating for a few years to make big aromatic porphyrins in the quest to study anion and metal binding and electrochromic effects. In their latest effort, the researchers used a tripyrrole building block to construct a [52π]dodecaphyrin, a porphyrin ring consisting of a dozen connected pyrrole groups and adorned with pentafluorophenyl groups. This conjugated molecule has 52 π electrons and is nonaromatic—it doesn't obey Hückel's rule of possessing $4n + 2$ π electrons. To meet the criterion, the team oxidized the molecule with a benzoquinone to form a [50π]dodecaphyrin, which bests the former aromaticity record holder, a [46π]decaphyrin the groups made last year. Subsequently protonating the [50π]dodecaphyrin using methanesulfonic acid helped flatten the molecule and improve its electron delocalization, thereby enhancing its aromaticity further.—SR



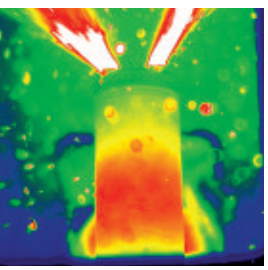
This tetraprotonated dodecaphyrin, with 50 π electrons, has set a new record for aromaticity.

CHEM. EUR. J.

role in algae. Eric Lieberman Greer and Yang Shi of Harvard Medical School and coworkers found 6mA in worms; Hailin Wang and Dahua Chen of the Chinese Academy of Sciences, Beijing, and colleagues discovered it in fruit flies; and a group led by Chuan He of the University of Chicago studied its role in algae (*Cell* 2015, DOIs: 10.1016/j.cell.2015.04.005, 10.1016/j.cell.2015.04.018, and 10.1016/j.cell.2015.04.010). He and coworkers found that 6mA is widely distributed between DNA-packaging units in the algal genome, suggesting that it regulates gene expression. Epigenetics expert Thomas Carell of Ludwig Maximilian University of Munich comments that the findings emphasize that modified bases have important regulatory functions and are more widespread than was previously thought.—SB

PEERING INSIDE AN EXPLODING BATTERY

By coupling high-speed X-ray tomography and thermal imaging methods, researchers have demonstrated that events occurring



NAT. COMMUN.

A new imaging method reveals in real time events inside a commercial Li-ion battery (roughly 18 mm in diameter) that cause it to explode and eject molten material.

inside a lithium-ion battery as it heats up and explodes can be imaged in high resolution and real time (*Nat. Commun.* 2015, DOI: 10.1038/ncomms7924). The three-dimensional imaging method provides a novel way to investigate heat-induced damage to internal structures of Li-ion batteries, which could lead to improved battery safety. Standard analytical methods are limited to scrutinizing the internal components of failed batteries only after the events that caused the failure have run their course. So a team led by Paul R. Shearing of University College London devised the tomography method and used it to study two standard types of commercial Li-ion batteries as they heated the battery shells to roughly 250 °C. One battery, strengthened with an internal support, remained largely intact until chemical reactions triggered thermal runaway. The internal temperature then spiked above 1,000 °C, melting copper structures inside the battery. The other battery simply exploded, blowing off the battery cap and ejecting molten material.—MJ

SULFIDE MINERAL REDUCES CO_2

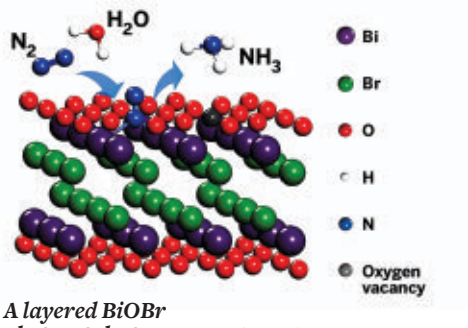
An iron sulfide mineral that forms in deep sea hydrothermal vents can convert CO_2 and hydrogen to small bioorganic molecule precursors such as methanol and formic, acetic, and pyruvic acid (*Chem. Commun.* 2015, DOI: 10.1039/c5cc02078f). The discovery, by Nora H. de Leeuw of University College London and colleagues, provides a potential lead for developing environmentally friendly catalytic syntheses of plastics and fuels. It also lends credence to the theory that prebiotic chemistry flourished in the mineral- and carbon-rich alkaline environment that typifies some hydrothermal vents. Scientists have known that this mineral, greigite (Fe_3S_4), resembles the ferredoxin center of the CO dehydrogenase enzyme. In previous studies, researchers showed that greigite can convert CO_2 to gaseous CH_4 and CO. However, to serve as prebiotic precursors, small organics must be in solution. So the team performed experiments at various pH values and found that an alkaline environment was key to producing methanol and the other small organics that are solution-based at atmospheric pressure and room temperature. And by using computational methods, the group explained the dependence of the methanol and formic acid formation mechanisms on alkaline conditions.—EKW

'ZOMBIE BACTERIA' KILL USING SILVER BULLETS

In a newly discovered mechanism, after an antimicrobial silver agent kills bacteria, the agent is then capable of moving on to kill still more bacteria (*Sci. Rep.* 2015, DOI: 10.1038/srep09555). Dubbed the "zombies effect" by David Avnir of Hebrew University of Jerusalem and colleagues, the extended toxicity of silver nitrate stems both from the ability of the silver to form nanoparticles and remain active after it kills and from its subsequent release from the corpses of bacteria. The group first used silver nitrate to kill *Pseudomonas aeruginosa*. They then separated and cleaned the dead bacteria and added them to a live culture of the same bacteria, killing more than 99.99% of them. Although the authors say it's too early to make definitive predictions, they see this finding as being useful for wound-healing applications. Though the team studied only one death cycle, "one of our aims is to test how many generations of zombies can be extracted from a single dose," Avnir says. "In principle, if the silver is not washed away, then many generations are expected."—EKW

NANOSHEETS CATALYZE NITROGEN FIXATION

A research team in China has invented a light-harvesting layered semiconductor nanosheet that could one day significantly



J. AM. CHEM. SOC.

A layered BiOBr photocatalyst binds N_2 in oxygen vacancy sites as part of a low-energy nitrogen-fixing process.

reduce the energy required for chemically reducing nitrogen to ammonia. Converting N_2 to NH_3 via the iron-catalyzed Haber-Bosch process is one of the most important industrial chemical reactions. But splitting N_2 and preparing hydrogen via steam reforming of methane at high temperature and pressure make it one of the most energy-intensive processes. Lizhi Zhang of Central China Normal University and coworkers designed a layered BiOBr catalyst with oxygen vacancies that is ideal for binding N_2 molecules. When the researchers shine visible light on the nanosheet surface the semiconductor generates electrons to reduce adsorbed N_2 while at the same time it oxidizes water solvent molecules to generate H^+ and O_2. Overall, the process couples nitrogen and hydrogen to make NH_3 at room temperature and atmospheric pressure with better efficiency than previously reported semiconductor systems (*J. Am. Chem. Soc.* 2015, DOI: 10.1021/jacs.5b03105). "Although photocatalytic reduction is unlikely to replace the Haber-Bosch process at present," the researchers write, "this study might open up a new vista."—SR

from the SCENEs

A selection of stories from C&EN's six online **TOPICAL NEWS CHANNELS**

FROM THE **NANO SCENE**

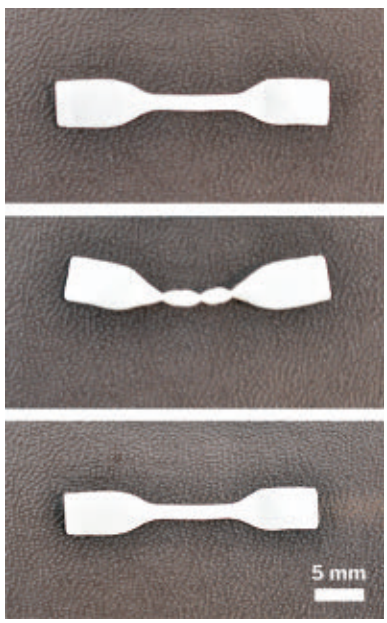
CARBON NANOTUBES MAKE GOOD BRAIN ELECTRODES

Electrodes made from carbon nanotube fibers can both stimulate and receive signals from the brain without causing inflammation (*ACS Nano* 2015, DOI: 10.1021/acsnano.5b01060). Compared with conventional metal electrodes, the nanotube fibers make better electrical connections with brain tissue in rats, which may improve prosthetic devices and deep-brain stimulation (DBS) therapies for disorders such as Parkinson's disease. Chemist Matteo Pasquali and neural engineer Caleb Kemere of Rice University implanted 12-μm-diameter nanotube fibers in rats with Parkinson's-like symptoms and compared them with platinum electrodes coated with iridium. The nanotube electrodes—which are much smaller and thus capable of targeting brain regions more precisely—delivered current for DBS as effectively as the metal electrodes. The flexibility of the nanotube electrodes offered another benefit: After six weeks of implantation, nanotube fibers did not trigger inflammation in the brain tissue, unlike the more rigid metal electrodes. The team is now designing arrays of the electrodes to interact simultaneously with multiple brain areas.

FROM THE **MATERIALS SCENE**

SHAPE-SHIFTING SUBSTANCE STAYS SOFT

Shape-memory polymers can be bent or twisted into a new configuration, which they'll hold until some stimulus—such as heat—reverts them to their original shape. But the same material properties that help fix these polymers into a new shape also tend to make them inflexible, limiting their use in biomedical applications. Now, using a simple technique, researchers have made a soft, rubbery shape-memory elastomer by combining two different polymers (*ACS Macro Lett.* 2015, DOI: 10.1021/acsmacrolett.5b00106). Patrick T. Mather of Syracuse University and his group chose a commercially available thermoplastic polyurethane that stays soft at room temperature and poly(ε-caprolactone), which remains crystalline until heated above 56 °C. The second polymer helps the material "remember" its shape at room temperature. The researchers electrospun separate solutions of the two polymers onto a metal cylinder, forming a composite fiber mat. They then compressed and heated the mat into the final product, a dense film. By heating, twisting, and cooling the film, the researchers could reshape the material.



ACS MACRO LETT.

Researchers made an object out of a shape-memory elastomer composite (top) then heated and fixed it into a twisted shape (center). When they heated it again, it untwisted itself into its original shape (bottom).

FROM THE **ENVIRONMENTAL SCENE**

PLASTIC BAGS CUT DOWN ON MARSH WILDLIFE

Plastic bags do not simply harm individual birds and mammals when the animals get tangled in the trash, the bags also can affect entire communities of wildlife, according to a new study (*Environ. Sci. Technol.* 2015, DOI: 10.1021/acs.est.5b00277). Marine ecologist Dannielle Senga Green of Trinity College, in Ireland, and colleagues examined plastic litter's effects on a marsh near Dublin, in which sediments serve as home to algae and a variety of invertebrates such as worms, crabs, and snails. The team pinned down conventional high-density polyethylene plastic bags and biodegradable bags made from cornstarch in sediment plots in the marsh. After nine weeks, the researchers found that oxygen levels in sediments under both types of bags were far lower than in bagless plots. The mud beneath bags had one-sixth as many animals. And algae may have suffered because chlorophyll concentrations were half as high. Green says the results indicate that plastic bags, even biodegradable ones, could harm marsh ecosystems, but she warns it's unclear how they might affect other types of habitats.

DANNIELLE SENGA GREEN

A plastic bag litters a marsh near Dublin.

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THE HEADY MUSK OF SCIENTIFIC DEBATE

New data rebut **VIBRATIONAL THEORY** of olfaction

SARAH EVERTS, C&EN BERLIN

HOW EXACTLY OUR sense of smell works is one of the most important, unanswered questions in sensory science. It's also a question that has resulted in an acrimonious, nearly two-decade-long controversy.

On one side of the battle are a majority of sensory scientists who argue that our odorant receptors detect specific scent molecules on the basis of their shapes and chemical properties. On the other side are a handful of scientists who posit that an odorant receptor detects an odor molecule's vibrational frequencies.

A new study, led by Eric Block, chemistry professor at the University at Albany, SUNY, takes aim at the vibrational theory of olfaction and finds no evidence that olfactory receptors distinguish vibrational states of molecules.

The vibrational theory was first proposed about a century ago, but its modern-day proponent is biophysicist Luca Turin, a visiting professor at Ulm University, in Germany. Block's new study challenges a 2013 paper by Turin and his colleagues that had given the vibrational field a boost (*PLOS One,* DOI: 10.1371/journal.pone.0055780). Turin's 2013 paper reported that human subjects could identify a difference in odor between deuterated and nondeuterated musk molecules, such as normuscone. Human subjects thought the deuterated versions smelled burnt or roasted.

These experiments supported the vibrational model of olfaction because deuteration doesn't significantly alter the chemical structure of a molecule, yet it does alter its vibrational frequencies. The take-home message of Turin's 2013 paper was this: If humans are able to smell the difference between deuterated and nondeuterated forms of the same odorant, then vibration could have a role in olfaction.

SHUTTERSTOCK

AIR OF MYSTERY
The precise mechanism of how we smell remains a mystery.

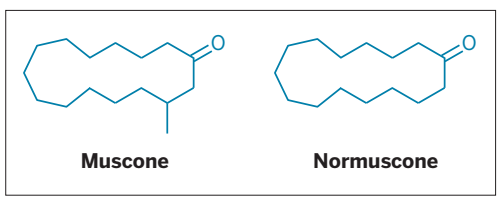
In the new study, Block and his colleagues prepared deuterated versions of normuscone and other musk molecules. Then they expressed a human musk receptor called OR5AN1 in human embryonic kidney cells, a common cellular system that has been used to study the mechanisms for sight and taste, and evaluated the response of the musk receptor to their array of musk odorants.

The researchers found that the musk receptor did not respond any differently when presented with deuterated and nondeuterated versions of normuscone, muscone, and other musk odorants (*Proc. Natl. Acad. Sci. USA* 2015, DOI: 10.1073/pnas.1503054112).

"Even though I like underdog hypotheses, this is by far the strongest evidence refuting the vibrational hypothesis to date," says blogger and drug discovery chemist Derek Lowe, who has long followed the olfaction debate on his blog, In the Pipeline. "They ran a lot of good experiments with a lot of care. The vibrational hypothesis had a lot of chances to rear its head, and it didn't."

"It's frankly a sledgehammer to Turin's vibrational hypothesis," says Kenneth S. Suslick, a sensory scientist at the University of Illinois, Urbana-Champaign, who has argued for some time against the vibrational olfaction model.

IN RESPONSE, Turin calls the new study "very interesting," but he does not think it makes a successful case against vibrational theory. In particular, Turin believes that the musk receptor studied by Block and colleagues may not correspond to the one he studied in the noses of human test subjects who differentiated deuterated and nondeuterated versions of normuscone.



"Their entire paper rests on the fact that the musk receptor that they are studying is the same one that the humans were using to perceive the musk in the *PLOS* paper. Humans have multiple

musk receptors," Turin says. "We just don't know if it was the right receptor."

Block says if Turin can point him to another human musk receptor—one that is involved in vibrational olfaction—he'd be happy to study it. Block adds that his team screened a full panel of all the human odor receptors, and of these, only OR5AN1 "robustly responded to musk."

ANOTHER OF TURIN'S objections is that Block and colleagues did their experiments with cells in a dish rather than within whole organisms. He argues that expressing an olfactory receptor in human embryonic kidney cells doesn't adequately reconstitute the complex nature of olfaction and is not biologically significant.

Leslie B. Vosshall, a sensory scientist at Rockefeller University, doesn't accept that argument because scientists have successfully used human embryonic kidney cells to study rhodopsin and adrenaline receptors, which are related to olfactory receptors. "Embryonic kidney cells are not identical to the cells in the nose," she says. "But if you are looking at receptors, it's the best system in the world."

Turin thinks that neither side of the debate has totally satisfactory data. On the one hand, "what we have are behavioral tests on flies and on humans," he says. And on the other hand, there are receptors expressed in cells.

One way to move the field forward would be to solve the crystal structure of an olfactory receptor. Scientists have yet to do so because the receptors are membrane proteins that can't be expressed in large amounts, Suslick says.

"Smell is a fascinating, beguiling sense, the more so because we don't really understand how it works," notes Tim Jacob, emeritus professor in sensory science at Cardiff University, in Wales. "It is a shame that the quest to find a solution to the puzzle of smell, has been distracted by the attempt just to refute the opposing theory."

"These scientists have paid Luca Turin the compliment of taking the theory seriously," Lowe says. "When his hypothesis came out a lot of people just brushed it aside as a stupid, annoying idea. And that's not appropriate." However, he says, Turin "is the one proposing the more unusual hypothesis, so he's the one who has to bring the extraordinary evidence to support it." ■

BIRTHDAY SHOT NASA unveiled this Hubble image of a giant cluster of hot, new stars for the telescope's 25th anniversary.

A. NOTA/NASA/ESA/HUBBLE HERITAGE TEAM (STSCI/AURA)/ESA/STSCI/WESTERLUND 2 SCIENCE TEAM

HUBBLE'S 25TH BIRTHDAY BASH

World celebrates the spacecraft that's revealed details about the structure and **CHEMISTRY OF THE UNIVERSE**

ELIZABETH K. WILSON, C&EN WEST COAST NEWS BUREAU

IT WAS 1992, and the Hubble Space Telescope had been in orbit around Earth just two years.

A group of astronomers trained Hubble's high-resolution spectrograph on an ancient star 100 light-years away and found something never before seen in a star: boron.

This element's emissions lie in the ultraviolet part of the electromagnetic spectrum—in a range only observable from outside Earth's atmosphere and only detectable by Hubble at the time.

The star, estimated to be about 15 billion years old, was expected to contain only the elements believed to have formed during the Big Bang: primarily hydrogen, helium, and lithium. But this discovery got astronomers wondering whether boron, a heavier element, could have been formed during the Big Bang as well. It's a question that still hasn't been answered.

That early, startling, and chemical-based finding is just one in a lengthy parade of cosmological game-changing discoveries that have cemented Hubble's place as one of the technological marvels of the modern space age.

Hubble was launched 25 years ago on April 24, 1990. No spacecraft's birthday has been so elaborately feted: In recent weeks, more than 100 events have been held in the U.S. alone, including the unveiling of an official Hubble 25th anniversary image at the Newseum in Washington, D.C.

Hubble team members and officials celebrated Friday, April 24, at a private party at the Smithsonian Institution's National Air & Space Museum; the next day, the museum threw another Hubble party for the public. From April 20–26, Times Square in New York City was alive with celestial Hubble images, broadcast from the area's iconic Toshiba Vision dual LED screens.

"Hubble has changed the way scientists view the universe, and it's captured the imagination of the public," Amber Straughn,

& MORE ONLINE To see more of Hubble's chemical hits, go to http://cenm.ag/hubble25yr.

NASA

LOOKING OUTWARD The Hubble telescope orbits Earth.

an astrophysicist at the National Aeronautics & Space Administration, said during a panel discussion on Hubble's 25 years at the Space Telescope Science Institute (STScI) in Baltimore.

"It's been a great 25 years," Ken Sembach, interim director at STScI, said at the conference. "Hubble is doing science now that was never before envisioned."

HUBBLE'S VISUAL STUNNERS have included images of events close to home—the impact of comet Shoemaker-Levy 9 on Jupiter in 1994—as well as those of objects at the edges of the universe, including galaxies that formed only 400 million years after the Big Bang. Hubble found proof of the exotic phenomenon of gravitational lensing, in which dense objects can bend light from an object behind it. Hubble also provided evidence for the acceleration of the expansion of the universe.

Many of the breathtaking images of quasars, interstellar dust formations, and colliding galaxies have become so iconic that it might seem that Hubble's primary function has been to explore the macrostructure and grand cosmology of the universe.

But Hubble is also, at its heart, a chemist. A full 50% of Hubble's observations have been made with its spectrometers, which lead to chemical discoveries, says Douglas Duncan, one of the astronomers who made the boron discovery. "Few people know that." Duncan is now in the department of astrophysical and planetary sciences at the University of Colorado, Boulder, and is also director of Fiske Planetarium.

Although they don't always lend themselves to spectacular images, Hubble's chemical discoveries have been some of the most intriguing: the discoveries of sodium, methane, and water in the atmospheres of exoplanets, water in the remnants of a dead star, and a complex organic soup in a solar-system-forming protoplanetary disk.

Hubble's technological history will also be remembered. The most famous event, perhaps, was the discovery soon after the spacecraft's launch of an optical flaw in its Wide Field & Planetary Camera. In 1993, astronauts were able to fit the mirror with corrective optics, and soon Hubble was sending back vivid, crisp images.

The telescope has undergone four servicing missions, including the 1993 repair. Traveling via space shuttle, astronauts have journeyed to the spacecraft to replace old cameras and gyroscopes with new ones. The final repair mission was in 2009.

Hubble will keep taking images and data until its instruments give out, NASA says. Scientists are hoping it will last until at least 2020.

In October 2018, NASA is set to launch the first of a next generation of space telescopes, the James Webb Space Telescope. Much more powerful than Hubble, Webb will focus on studying infrared wavelengths, which easily penetrate dust and gas that mask objects in space. The telescope will also be able to more completely study the chemical composition of atmospheres on planets outside the solar system. Many organic compounds have characteristic infrared spectra.

"The exoplanet community is very excited about the Webb telescope," said Jacob L. Bean, an astronomy and astrophysics professor at the University of Chicago. With Webb's improved precision and infrared focus, astronomers hope to be able to find exoplanets that are truly analogous to Earth.

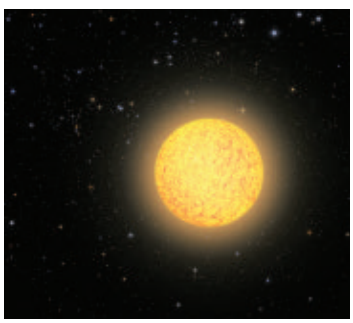
Hubble may still have a chance to break new ground during its final years, especially if it overlaps with the first years of the Webb telescope: Because Hubble's instruments observe primarily visible and ultraviolet wavelengths, it could complement Webb's infrared observations.

According to STScI's Sembach, "The combination of these two observatories will be very powerful, scientifically." ■

HUBBLE'S GREATEST CHEMICAL HITS

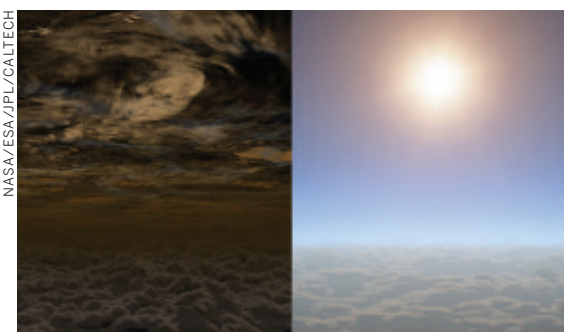
Although the spacecraft is best known for its spectacular galactic images, many of its discoveries have been chemical in nature. Here, we highlight a few of those, accompanied by artists' renderings.

F. SUMMERS/A. FIELD/NASA/ESA



◀ **1992** Hubble detects the element boron in an ancient star, causing astronomers to wonder whether boron formed during the Big Bang. In 2013, Hubble confirmed that this star is the oldest yet detected.

NASA/ESA/JPL/CALTECH



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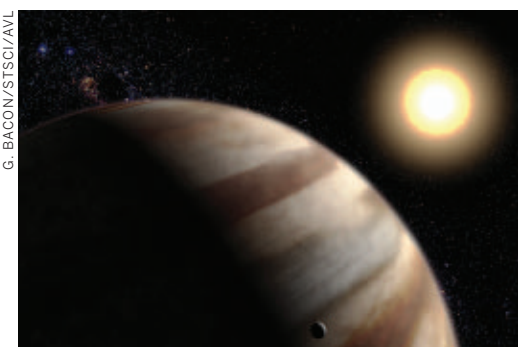

▲ **2014** Hubble detects water in the atmosphere of an exoplanet. Most exoplanets discovered so far have been large, often many times larger than Jupiter. This exoplanet is the smallest on which a molecule has ever been detected.

◀ **2001** Hubble makes the first discovery of an atmosphere—composed of sodium—on an exoplanet outside the solar system.

VISIT ÅLAND

SHIPWRECKED FIZZ In 2010, divers found this cache of 170-year-old champagne in the Baltic Sea.

170-YEAR-OLD CHAMPAGNE ANALYZED

Chemical analysis of **SHIPWRECKED BUBBLY** reveals secrets of 19th-century French winemaking

A 170-YEAR-OLD STASH of perfectly preserved champagne taken from a shipwreck off the coast of Finland has brought to light an array of curious facts about past winemaking practices. Chemical analysis of the vintage sparkling wine revealed particularly high levels of sugar and salt compared with modern-day champagne, as well as the presence of unexpected metals, likely introduced by 19th-century wine preservation and storage methods (*Proc. Natl. Acad. Sci. USA* 2015, DOI: 10.1073/pnas.1500783112).

The champagne also tasted "fabulous, with hints of tobacco," says Philippe Jeandet, a champagne chemistry expert at the University of Reims Champagne-Ardenne, in France, who led the team of researchers, and who sampled 100 µL of the golden liquid. That drop of vintage champagne "was probably one of the best wines I've tasted in my life," he says.

Jeandet isn't the only person to have sampled the shipwrecked bubbly. In 2010, divers who discovered the 168 bottles in the cool, dark—and preservative—waters of the Baltic Sea popped a cork when they hit dry land and realized they were most likely drinking century-old champagne, Jeandet notes. Although the bottles no longer had labels, the corks were engraved with the name of a French champagne house, Veuve Clicquot Ponsardin.

Because Veuve Clicquot Ponsardin has been in operation since 1772, the researchers were able to compare the 170-year-old champagne with modern incarnations from the champagne maker. The discovery, and consequent chemical analysis on three of the shipwrecked bottles, was an "unequaled opportunity in ferreting out aspects of the evolution of sparkling wine production that's been unavailable in the written record," says Ronald S. Jackson, a wine science scholar at Brock University, in Ontario.

One of the most interesting aspects of the recovered champagne is that the sugar levels are "spectacularly high—higher than most dessert wines produced today," let alone champagne, comments Andrew L. Waterhouse, a wine scientist at the University of California, Davis. Current champagne comes in two main styles: "very dry," which contains little residual sugar, and an even drier "brut." Both contain two orders of magnitude less sugar then than the shipwrecked champagne. "The idea of making champagne with so much sugar" today, Waterhouse says—"a winemaker would just laugh at you."

In fact, the levels of sugar measured in the ancient champagne were higher than those found naturally in grape juice. This finding suggests that winemakers in the 19th century probably boosted levels artificially. Jeandet and his team believe that these winemakers did so with concentrated grape juice sugar instead of cane sugar, which was also available then. The researchers came to this conclusion because they detected furfural derivatives in the ancient champagne, which are produced during the Maillard reaction as grape juice is slowly heated.

Initially, the team of scientists thought that the ship ferrying the champagne must have been en route to Russia, where there was a predilection for sweet wine. But according to historical documents, the nearly 150 g/L of sugar in the shipwrecked champagne corresponds to German and French sweetness preferences of that era. Russians of the 19th century wanted even sweeter wine: vino that contained 30% sugar, a whopping 300 g/L, Waterhouse says.

JEANDET AND HIS GROUP also discovered three orders of magnitude more salt in the preserved bottles than in modern vintages. At first the team suspected that there must be some seawater contamination, Jeandet says. But the researchers ruled out this possibility by comparing the ratio of bromine and chloride ions in the bubbly with ratios of those ions found in the Baltic Sea.

Instead, the salt was probably added by the champagne producer, albeit not intentionally. Champagne makers used to add gelatin to keep wine from going cloudy, Jeandet says, and salt was added to the gelatin to keep it stable. Today, gelatin is used as a clarifying agent, but the substance is now much purer and, thus, less salty, Waterhouse says.

The shipwrecked champagne also contained unusually high levels of iron, lead, copper, and arsenic compared with modern vintages. Arsenic and copper sulfate found in the century-old fizz likely originated from antiquated pesticides used to kill fungus. Meanwhile the iron and lead probably came from storage containers.

If the idea of aging wine underwater sounds like the basis for a new industry, regulators in the U.S. don't agree. In March, the Alcohol & Tobacco Tax & Trade Bureau issued a warning about the niche industry of ocean-aging, called "aquaoir." The regulatory body worries that the industry's wares may be adulterated or contaminated by seawater pollutants, such as gasoline, heavy metals, drug residues, pesticides, and effluent from sewage treatment plants. Aquaoir enthusiasts will certainly point to this champagne's successful 170-year storage in rebuttal.—SARAH EVERTS

Speaking For More Than 158,000 Members

JOHN ADAMS, DISTRICT V DIRECTOR AND CHAIR, COMMITTEE ON PUBLIC AFFAIRS & PUBLIC RELATIONS

AS A MEMBER OF the American Chemical Society Board of Directors, I am often asked why our society is not doing anything about (take your pick here) research funding, science education, climate, or any of a dozen other issues. Once I explain what we in fact are doing on the issue, the member often follows with a question about how these things get decided.

ACS is a large, multifaceted organization. Most of our members are very familiar with those specific programs that provide them with direct professional benefit, but few are experts on all ACS offerings. One important activity that is noticed by few members is fulfillment of our national charter responsibility to provide science and engineering advice to the government and to advocate the advancement of chemistry.

The members of the ACS Board, and particularly the members of the Board Committee on Public Affairs & Public Relations (PA&PR), spend substantial time in this arena because we are charged by the ACS constitution with approving "any statement purporting to express the position of the Society on any public matter." As you might imagine, speaking for an organization of more than 158,000 members with varied interests is no small task. Fortunately, we have considerable help in fulfilling these responsibilities.

So how do we determine what ACS will say on the broad array of issues covered by U.S. science-related policy at the national and state levels?

First and foremost, we work with a wide range of members, committees, and divisions to follow the issues and get advice on what our positions might be. Every other year, we include 15 ACS committees in the development of a one-page document that lays out an overview of the society's public policy priorities.

Our positions fall into four broad categories: fostering innovation through research and technology, strengthening science education and the scientific workforce, advancing science through openness, and promoting science and sustainability in public policy.

PETER CUTTS PHOTOGRAPHY

ACS is an active leader in the Washington, D.C. science and technology policy community.

For many issues, more detail is required to make us effective advocates for chemistry and its practitioners. That detail is provided in ACS policy statements. There are currently 24 such statements that can be found at www.acs.org/policy. Several ACS committees routinely work with the board to draft these positions, and PA&PR gives final approval (C&EN, March 2, page 36).

Last year, PA&PR, acting on the recommendations of seven ACS committees and one technical division, adopted 11 policy statements. The committee process allowed hundreds of ACS members to contribute to ACS position development. Through coverage in C&EN and on the Web, all ACS members were invited to offer input to the process.

WITH SO MANY POSITIONS on such a wide range of matters (most of which are important to some sector of ACS or the practice of our science), priorities need to be set to keep the focus on those issues where advocacy effort from members and staff will yield maximum benefit. These priorities are set by the board, working with staff to evaluate the likelihood of legislative or other policy action and to assess the society's ability to have an impact on the outcomes.

This process allows us to put the lion's share of our resources on the highest priorities in a top tier while differentiating three other tiers of investment, the lowest level consisting of issues that are monitored for targets of opportunity. Furthermore, ACS is an active leader in the Washington, D.C., science and technology policy community, working across sectors in coalition with the science and engineering, education, and business communities on a wide range of topics.

Now, how do we actually advance these positions? That effort is a shared responsibility among members, governance, and professional staff in Washington, D.C.

Our staff, housed in the ACS Office of Public Affairs (OPA), provides us a wide range of services. In consultation with PA&PR, staff translate policy positions into letters to Congress, into talking points for ACS members to use when visiting elected officials, and sometimes into legislative language that works its way into congressional bills. They also provide nonpartisan briefings on the application of science and technology to public policy issues through the ACS Science & the Congress Project. The sum of all of these efforts is a bipartisan policy agenda that allows us to work effectively with both political parties no matter who is in charge of Congress, the Administration, or statehouses.

To the surprise of some of our members, our staff also includes registered lobbyists who work directly with Congress to advance our positions. Like most U.S. not-for-profit organizations, we are allowed to spend a small fraction of our annual budget to advance policy positions through professional lobbying, and OPA provides that service as part of a comprehensive ACS advocacy program.

Here, though, is the most important part of my message to members. All this ACS policy infrastructure is pointless unless our members are involved. Therefore, let me end by sharing this advice: In order for our common interests to gain currency and the power to influence, your elected officials need to hear from you. Yes, I mean YOU!

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

AIC GOLD MEDAL TO JACQUELINE BARTON

Jacqueline Barton, Arthur & Marian Hanisch Memorial Professor of Chemistry and chair of the division of chemistry and chemical engineering at California Institute of Technology, is the recipient of the 2015 AIC Gold Medal, presented by the Chemical Heritage Foundation (CHF) and the American Institute of Chemists.

The medal recognizes service to the science of chemistry and to the profession of chemist or chemical engineer in the U.S. It will be presented on May 15 during CHF's Heritage Day festivities.

Barton pioneered the application of transition-metal complexes to probe recognition and reactions of double-helical DNA. She has designed chiral metal complexes that recognize nucleic acid sites with specificities rivaling DNA-binding proteins. These synthetic transition-metal complexes have been useful in elucidating fundamental chemical principles that govern the recognition of nucleic acids, in developing luminescent and photochemical reagents as new diagnostic tools, and in laying a foundation for the design of novel chemotherapeutics.

She has received numerous awards, including the 2015 ACS Priestley Medal and 2010 National Medal of Science.

2015 REMSEN AWARD TO JOANNE STUBBE

JoAnne Stubbe, Novartis Professor of Chemistry and professor of biology at Massachusetts Institute of Technology, is the recipient of the 2015 Remsen Award, presented by ACS's Maryland Section. It is named after Ira Remsen, Johns Hopkins University's first chemistry professor and second president.

Stubbe's research group has helped reveal the mechanisms of some of nature's most complex and important enzymes. Some of her group's most noted work defines how nature harnesses the reactivity of free radicals to carry out difficult chemistry with great specificity.

Stubbe will present a lecture on Sept. 24 at Johns Hopkins.

JAMES COWAN RECEIVES 2015 MORLEY MEDAL

The ACS Cleveland Section has named **James A. Cowan** as the winner of its 2015 Edward W. Morley Medal. Cowan, who is the Melvin S. Newman Professor of Chemistry & Biochemistry at Ohio State University, will receive the prize during a conference and dinner hosted by the Cleveland Section at John Carroll University in University Heights, Ohio, on May 20.

The Morley Medal recognizes significant contributions to chemistry through achievements in research, teaching, engineering, research administration, and public service, as well as outstanding service to humanity or to industrial progress in the Cleveland region.

Cowan's research focuses on catalytic and physicochemical properties of iron cofactors and their biosynthesis, cellular trafficking, and regulation of metal cofactors; the development of catalytic metallodrugs; and the biological chemistry underlying the role of metals in disease.

PORTOGHESE LECTURESHIP TO NICHOLAS MEANWELL

Nicholas Meanwell, executive director of discovery chemistry at Bristol-Myers Squibb, is the recipient of the Philip S. Portoghese Medicinal Chemistry Lectureship. The lectureship is named in honor of the former editor-in-chief of the *Journal of Medicinal Chemistry* and is administered by Portoghese and the ACS Division of Medicinal Chemistry.

The lectureship honors the contributions of an individual who has had a major impact on medicinal chemistry research. It consists of a $3,000 honorarium, a plaque, and $1,500 to cover travel expenses to the fall ACS national meeting in Boston to present the lecture.

Meanwell has led drug discovery programs in the cardiovascular, neuroscience, and virology therapeutic areas. This work has resulted in the advancement of more than 25 clinical candidates for the prevention of thrombosis, the treatment of stroke, and therapy for viral infections such as HIV.

INORGANIC NANOSCIENCE AWARD TO STANISLAUS WONG

Stanislaus S. Wong, a professor of chemistry at Stony Brook University, SUNY, who holds a joint appointment at Brookhaven National Laboratory, is the winner of the 2015 Inorganic Nanoscience Award, presented by the ACS Division of Inorganic Chemistry to honor excellence in research. The award is sponsored by the University of South Carolina's NanoCenter.

Wong's research focuses on inorganic nanomaterials. His efforts include probing the covalent surface chemistry of carbon nanotubes as well as studying the synthesis, characterization, and energy-related applications of novel noncarbonaceous, metal-based nanostructures.

Wong will receive a plaque and $3,000 at the fall ACS national meeting in Boston.

PUBLICATION WINS INAUGURAL *ENERGY & FUELS* AWARD

The publication "Hydrothermal Liquefaction and Gasification of *Nannochloropsis* sp." (2010, DOI: 10.1021/ef100203u), by **Phillip Savage** of Pennsylvania State University, is the inaugural winner of the *Energy & Fuels* Joint Award for Excellence in Publication.

The award is presented by the journal *Energy & Fuels* and the ACS Division of Energy & Fuels to honor an outstanding article published in the journal. Savage will give a talk at the ACS national meeting in Boston in August.

COMP ANNOUNCES 2015 AWARDS

The ACS Division of Computers in Chemistry presented several awards during the spring 2015 ACS national meeting in Denver.

The OpenEye Outstanding Junior Faculty Award in Computational Chemistry helps new faculty members gain visibility within the COMP community. The winners are **Arindam Chakraborty,** Syracuse University; **Rhiju Das,** Stanford University; **Konrad Patkowski,** Auburn University; and **Jordan Schmidt,** University of Wis-

consin, Madison. Each winner received a $1,000 prize.

The Chemical Computing Group Excellence Award for Graduate Students, cosponsored by CCG and COMP, recognizes outstanding research performance by a graduate student in computational chemistry. The recipients are **Vivek Bharadwaj,** Colorado School of Mines; **Feizhi Ding,** University of Washington; **Nan Li,** North Carolina State University; **Greg Medders,** University of California, San Diego; and **Heather Wiebe,** Simon Fraser University. The winners each received $1,150 and a copy of CCG's MOE (Molecular Operating Environment) software with a one-year license.

CARB PRESENTS DIVISION AWARDS

The ACS Division of Carbohydrate Chemistry presented its 2015 division awards during the 2015 spring ACS national meeting in Denver.

Arland Hotchkiss, lead scientist at the U.S. Department of Agriculture's Agricultural Research Service, is the winner of the Melville L. Wolfrom Award, which acknowledges outstanding service to the division and to the field of carbohydrate chemistry.

Matthew Pratt, assistant professor of chemistry and of molecular and computational biology at the University of Southern California, is the winner of the David Y. Gin New Investigator Award, which acknowledges and encourages outstanding contributions to research in carbohydrate chemistry by scientists in the first seven years of their independent career.

Katsunori Tanaka, associate chief scientist at Japan's RIKEN, is the winner of the Horace S. Isbell Award, which acknowledges excellence in and promise of continued quality of contribution to research in carbohydrate chemistry.

PETROLEUM RESEARCH FUND ANNOUNCES GRANT RECIPIENTS

The ACS Petroleum Research Fund has announced the recipients of research grants in 2014. The ACS Board of Directors approved 192 grants with a total value of $19 million for advanced scientific education and fundamental research related to petroleum and other fossil fuels. The list of grantees is available online at acsprf.org by clicking on "About ACS PRF." Additional information on grant programs and upcoming proposal submission dates is also available on the site.

CALL FOR BUCK-WHITNEY AWARD NOMINATIONS

The ACS Eastern New York Section is soliciting nominations for the Buck-Whitney Award. The award, named after late section members Johannes S. Buck and Willis R. Whitney, recognizes original work in either experimental or theoretical aspects of pure or applied chemistry.

Nominees must have made outstanding contributions to chemistry and be residents of North America. Chemists whose work has not yet received a significant national or international award, and whose careers would be advanced by such recognition, are especially encouraged to apply. The award includes a medal and citation, a $1,000 honorarium, and travel expenses to deliver an award address to the section.

Nominations should include the nominee's name, affiliation, and accomplishments in chemistry. Mail nominations by June 1 to Michael Hagerman, Buck-Whitney Award Committee Chair, Department of Chemistry, Union College, Schenectady, NY 12308, or e-mail to hagerman@union.edu.

LINDA WANG *compiles this section. Announcements of awards may be sent to l_wang@acs.org.*

MEETINGS

Joint Southeastern/Southwest Regional Meeting Call For Papers

The call for papers for the 2015 Joint Southeastern/Southwest Regional Meeting has been issued. The meeting will take place on Nov. 4–7 at the Memphis Cook Convention Center and the Sheraton Memphis Downtown Hotel, in Tennessee.

Details, including names and contact information for program and session chairs, can be found on the meeting website at 2015sermacs-swrm.com. The final program summary will be published in C&EN in the fall; the online program will be available on Sept. 28.

Special events at the meeting will include a barbecue dinner, regional awards luncheon, exposition and graduate school fair, and a program for high school chemistry teachers. The undergraduate program will include a luncheon, demonstration session, green chemistry workshop, and a quiz bowl competition involving SMACS (Student Members of ACS) clubs from the two regions.

Symposia for the meeting include "Biomedical Materials," "Biomolecular Crystallography," "Biomolecular NMR," "Biorelated Polymers: Synthesis & Applications," "Chemical Genetics," "Computational Studies of Protein Function," "DNA-Modifying Enzymes," "Drug Discovery Technologies," "Entrepreneur's Tool Kit: Resources & True Stories," "Environmental Analysis," "Frontiers in Nucleic Acids Chemistry," "Gold Nanoparticles in Nanomedicine," "Intrinsically Disordered Proteins: From Physical Chemistry to Biology," "Ion-Conducting Polymers," "Mass Spectrometry," "Materials for Alternative Energy Applications," "Mobile Analysis," "Multiscale Modeling of Macromolecular Systems," "Nanomaterials: Synthesis, Characterization & Applications," "Recent Advances in Chemical Physics," "Student-Centered Learning in the Chemistry Classroom & Laboratory," "The Chemical Industry in the South: Future Careers, Directions & Challenges," "The Interface of Ab Initio Computational & Bioorganic Chemistry," "The Interface of Chemistry with Art & Archaeometry," and "Tomorrow's Therapeutics: Natural Products."

General technical sessions will cover analytical, biological, computational, inorganic, organic, and physical chemistry. In addition, the meeting will include a plenary lecture, five undergraduate symposia, and 13 poster sessions.

ACS's Meeting Abstracts Programming System (MAPS) opened on April 27 for submission of abstracts. Please visit either the symposium website or MAPS at maps.acs.org to submit an abstract. Abstracts are due by 11:59 PM EDT on Aug. 10.

Learning To Lead

NO MATTER HOW PRODUCTIVE you are, some things you simply cannot do alone. For bigger accomplishments, you must become more than an individual contributor, more than a team player—you must become a leader. Leadership is not about telling people what to do, it's about getting them excited about your vision and engaged in making it a reality. To be a truly effective leader, you must go beyond just assigning duties.

BE EXCELLENT. People only follow those they trust. For others to believe in you and your ideas, you must have impeccable moral character, integrity, and ethical standards. You must really believe in and care about what you are asking them to do, without a hidden or ulterior motive. A sterling reputation is not something that appears overnight but something you must build over time and maintain throughout your career.

GUIDE, DON'T DICTATE. Most people don't like being told what to do. They prefer to be involved in the decision-making process, providing input that is listened to and valued. Instead of dictating orders, offer gentle suggestions to guide others—and maybe they'll arrive at even better solutions than you were planning. Leading questions such as "Have you thought about ...?" or "What would happen if ...?" will help them think through the possibilities and come to their own conclusions. Being involved in the planning will allow them to take ownership and become more invested in the project's success. And asking "How can I help?" is a great way to get them thinking about what else needs to be done.

NEGOTIATE. If you are working with only one person or a small number of other people, you may be able to negotiate. Determine what you need them to do for you, as well as what you can do for them, and propose a trade. The best deals come about when each person thinks the other is doing more of the work or when each person is doing something the other person is not good at, or does not enjoy.

BALANCE TASKS AND RELATIONSHIPS. If you'll be working with the same group over the long term, you'll want to factor in tasks as well as relationship status. To maintain a good, long-term working relationship, you may need to compromise on some tasks. If that's the case, make sure that the compromises do not affect the quality of your final deliverable—or that they take the form of an acceptable trade-off.

SHUTTERSTOCK

CREATE BETTER CONSEQUENCES. Before approaching others with your project, spend some time considering the consequences. What will be the consequences for the other people if your project succeeds, and what will happen to them if it fails? Can you make modifications so there are more desirable consequences for getting it done and fewer reasons for not doing it? With these facts firmly in mind, you will be able to present a strong case that helping you is going to help them and not helping you would be an opportunity missed.

If you want to make a larger impact on the world, you need to engage others in bringing your vision to life. You need to learn how to lead.

Get Involved In The Discussion. The ACS Career Tips column is published the first week of every month in C&EN. Post your comments, follow the discussion, and suggest topics for future columns in the Career Development section of the ACS Network (www.acs.org/network-careers).—*Brought to you by ACS Careers*

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CHEMICAL ARTISTRY, MICROWAVE OVEN ASTRONOMY, SCIENTIFIC MUSICALITY

Veronica Berns faced a common graduate student challenge: how to explain what you're doing to a nonchemist family member or friend.

Her solution? **A COMIC BOOK.** "I tried to come up with something that would convey the ideas and purpose and motivation without using technical jargon," says Berns, who got her Ph.D. from the University of Wisconsin, Madison, last year and now works as a research scientist for chemical company UOP.

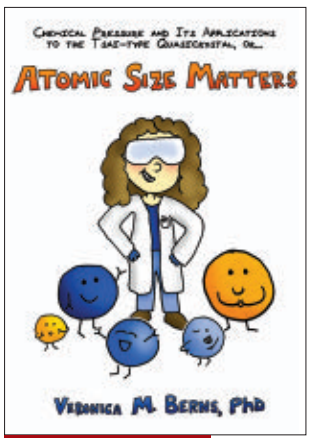
Berns's artistry describes her research in Daniel C. Fredrickson's lab to understand the three-dimensional structures that form when metals are mixed together.

"In crystals, atoms pack orderly and tightly, like oranges in a grocery store display," Berns writes in the comic. "Crystals are organized and repeat themselves. In every direction. Predictably. This allows us to summarize a whole big crystal in one tiny box: the unit cell."

She told her lab group about the project when it was about halfway done. Fredrickson became a big proponent and convinced her to include it as the final chapter in her thesis, she tells Newscripts.

In January, she launched a Kickstarter campaign to print the comic book on its own. She hoped to raise $5,965 and did that within a week; as of C&EN press time, she was up to $14,400. She's received messages from people saying things like, "My daughter's interested in chemistry and I don't know anything about it, maybe we can read this together," she says. "Those have been the most rewarding e-mails to get," Berns notes. "I'm happy to be able to be the instigator for that conversation that they wanted to have."

VERONICA BERNS



Communicator: Berns on her book cover.

While Berns worked to explain her science in common language, astronomers were working to discover a common source for perytons. Perytons are transient, 250-millisecond bursts of radio signals detected at observatories in Australia and Switzerland. Because perytons typically occurred on weekdays during office hours, the scientists were pretty sure they were of human origin. But what precisely was the **PERYTONS' PROVENANCE?**

SHUTTERSTOCK

Astronomer confounder: Microwave ovens opened midcycle produce perytons.

The key lay in linking the perytons with other signals around 2.3 to 2.5 gigahertz, a frequency at which microwave ovens are known to emit. That led to a set of tests spearheaded by Emily Petroff of Swinburne University of Technology, in Australia, that involved heating mugs of water in microwaves at that country's CSIRO Parkes Observatory.

But perytons didn't appear when scientists just ran the ovens. It wasn't until someone opened a microwave door before the timer ran out that the source of perytons was conclusively identified (arXiv:1504.02165 [astro-ph.IM]).

Last year, Newscripts featured the "Song of the Chemist," a chemically themed ditty by 19th-century composer George F. Root (C&EN, May 5, 2014, page 40). Lew Naylor of Apple Environmental Services and Indiana's Goshen College requested the words and music, then worked with students—a male quartet and videographer—to create a **DELIGHTFUL MUSIC VIDEO.** To view it, go to cenm.ag/chemistsong.

JYLLIAN KEMSLEY *wrote this week's column. Please send comments and suggestions to newscripts@acs.org.*

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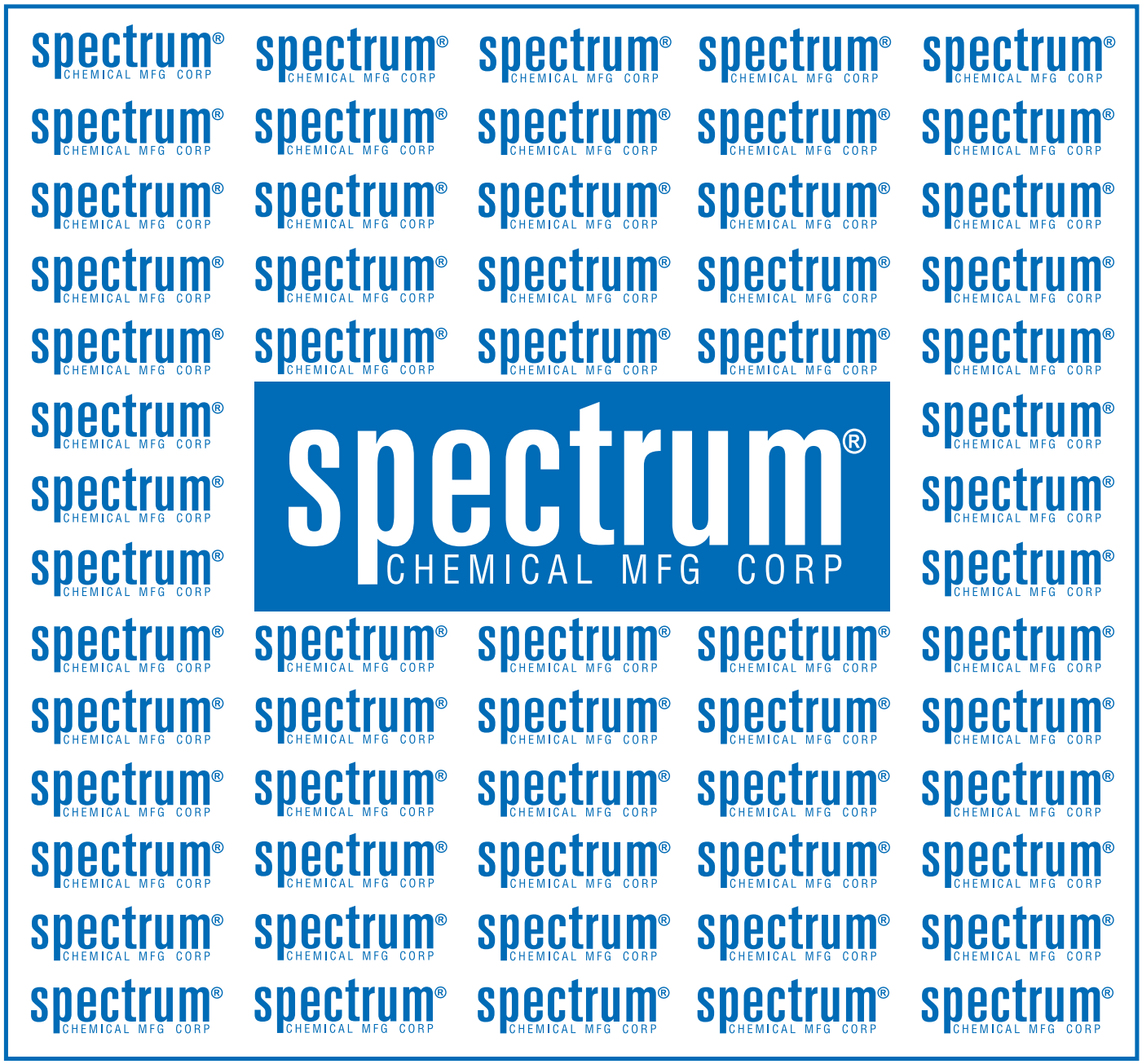

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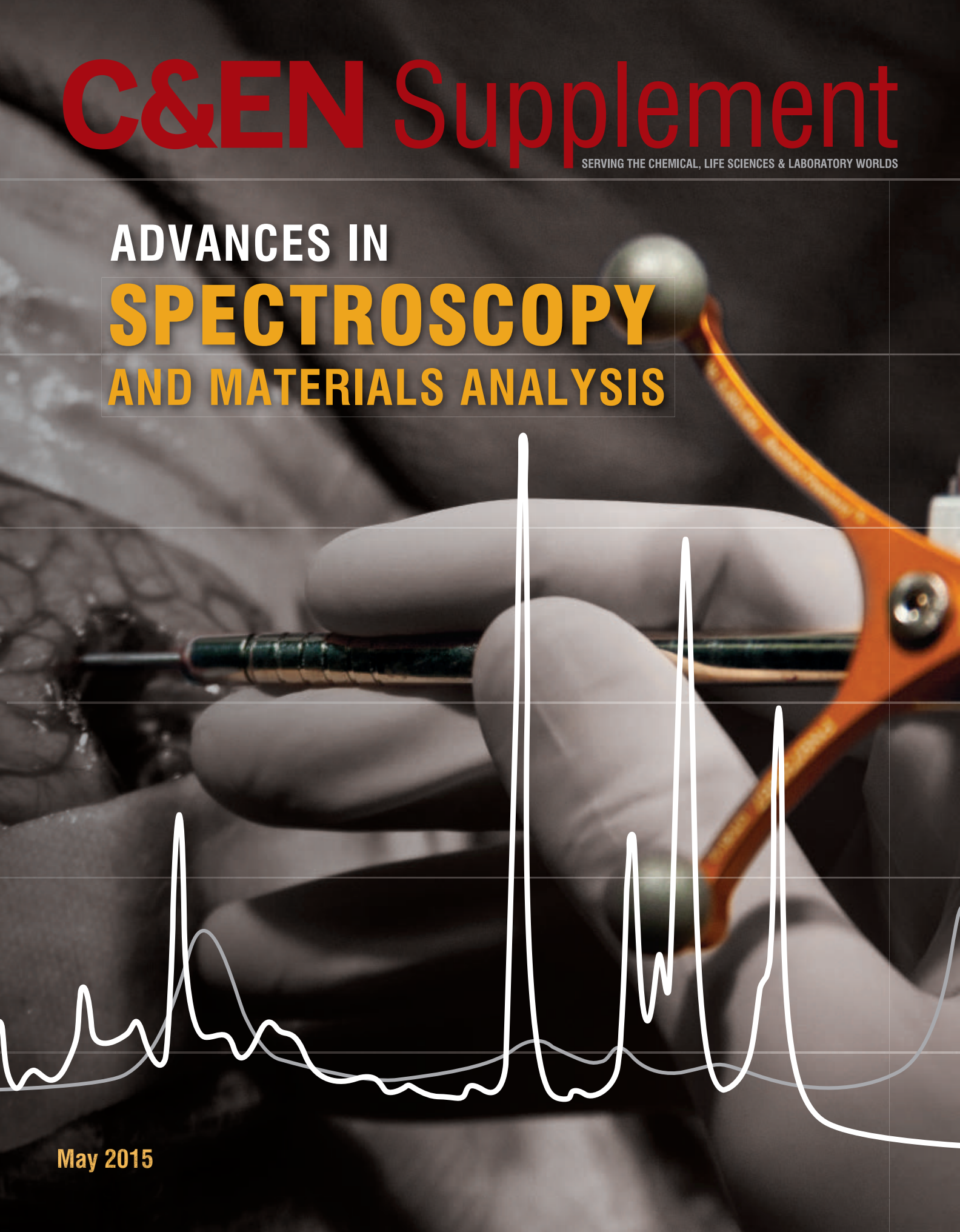
ADVANCES IN SPECTROSCOPY AND MATERIALS ANALYSIS



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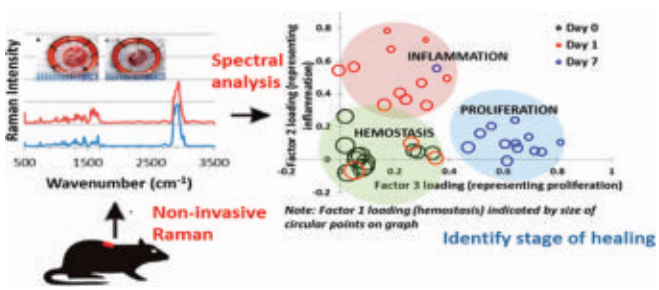

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C&EN
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PUBLISHER'S NOTE

Materials World

WELCOME TO THE second C&EN Supplement for 2015. This supplement is devoted to "Advances in Spectroscopy and Materials Analysis," and features a selection of application notes from leading instrumentation companies that are pushing the boundaries of spectroscopy analysis. Many of these tools were on display at recent conferences including Pittcon in New Orleans and the ACS National Meeting in Denver.

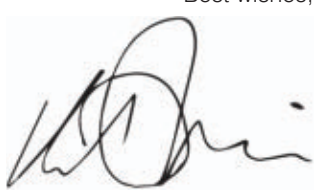
These vendor contributions are complemented by an editorial selection of abstracts from ten of the most impactful research articles relevant to this field, as seen over the past 12 months in the peer-reviewed journal *Analytical Chemistry,* published by the American Chemical Society.

Thanks to our contributing editor, Victoria Mountain, who shepherded this supplement to fruition with the help of C&EN's digital production manager Renee Zerby and her staff. Our thanks also to *Analytical Chemistry* managing editor Antonella Mazur for gathering the Top Ten list and to the companies that contributed to this C&EN Supplement.

We have an exciting series of supplements in store for the rest of this year, including a special edition on technology in BRICS countries and an in-depth issue looking at the Top 20 Drugs in the Pipeline later this summer.

If you are interested in participating in future C&EN supplements or any of our print, digital or lead-generation media offerings, please visit the C&EN media site—http://acsmediakit.org/—and don't hesitate to contact me.

Best wishes,



Kevin Davies, PhD
Publisher, C&EN
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For the record: The editorial content in this supplement was created without direct involvement of C&EN reporters or editors.

LIGHT ON MY MIND

Vicki Mountain, Ph.D.

GREETINGS, AND welcome to this latest special supplement to *Chemical & Engineering News* magazine. The prominent theme of this issue is spectroscopy, a technique founded on the study of visible light, although it has since expanded to encompass other forms of radiative energy. The connection to light is fortuitous, especially for those of us in the Northeast who endured a long, arduous winter and are now delighting in the arrival of spring, and the increasing hours of daylight this season brings.

This year more than others, throughout the world, light has been at the forefront of popular science news, grabbing the attention of the general public. In March 2015, a solar eclipse, where the moon passes between the Earth and the Sun, was observed throughout Europe, as well as in parts of Northern and Eastern Asia, and Northern and Western Africa. In some places a total solar eclipse could be seen, turning day into night by blocking all direct sunlight for a time.

The greatest celebration of light this year, however, is taking place across the globe: 2015 has been designated the International Year of Light by the United Nations Educational, Scientific, and Cultural Organization, UNESCO. A series of events is planned throughout the year with the intention of raising public awareness and understanding of the importance of light and optical technologies to people throughout the world. More information on the International Year of Light can be found at http://www.light2015.org.

Within the American Chemical Society, Harry A. Atwater, Editor in Chief of the journal ACS Photonics, noted in his editorial from January 20151, "As proud sponsors of the International Year of Light, in this issue, and during this year, we will join together with other professional societies around the world to celebrate the role of light in science and technology."

In February this year, C&EN Senior Editor Celia Arnaud highlighted a brilliant example of researchers using light for the direct benefit of human health[2], specifically a tool that enables neurosurgeons to differentiate between healthy and cancerous cells during surgery to remove brain cell tumors.[3] As Arnaud explains in her story, this is a breakthrough for neurosurgeons who currently face the dual challenges of first finding the cancer cells—an especially difficult task for invasive cancers—and second, making sure they have removed all the cancerous tissue knowing that if they leave these cells behind, tumors may regrow and impact the patients life. The tool, developed by a team of Canadian researchers from Montréal Polytechnique and McGill University, is a handheld contact Raman spectroscopy probe that detects cancer cells locally in live human brains, during surgery. In the C&EN report, Petrecca, one of the team leaders, notes that the next step is to run clinical trials to demonstrate that the Raman technique can improve surgery outcomes, and that such a trial will begin soon. We will be certain to revisit this story as the results of the clinical trial are revealed.

Not surprisingly, Raman spectroscopy is used in several of the articles featured in our latest selection of Top 10 papers from Analytical Chemistry. Innovations in a range of other spectroscopic techniques are reported in our contributed Applications notes. We hope that you enjoy this selection, and as always welcome your comments.

References

1. http://pubs.acs.org/doi/pdf/10.1021/acsphotonics.5b00001
2. http://cen.acs.org/articles/93/i7/Raman-Technique-Helps-Surgeons-Excise.html
3. *Sci. Transl. Med.* 2015, DOI: 10.1126/scitranslmed.aaa2384

Vicki Mountain, Ph.D. is a contributing editor on this C&EN Supplement and is a freelance science editor and writer based in Medford, MA.

TOP TEN SPECTROSCOPY, AND MATERIALS ANALYSIS PAPERS

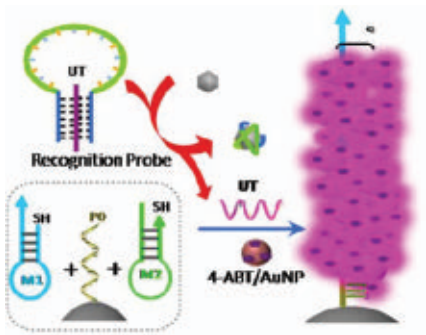
***Analytical Chemistry's* Most Popular Papers of 2014**

HOW HAVE the fields of spectroscopy and materials analysis changed it was last the focus of our special supplement to C&EN in June 2014? With their unique perspective on chemical research, the Editors of *Analytical Chemistry* have answered this question by selecting from their archives, reports that they consider representative of the 10 most significant advances in these areas from this last year. To whet your appetites, we have reproduced the abstracts of these noteworthy papers below, along with links to the articles to fill up on later. Keep current with the latest developments in this field throughout 2015 by reading the most recent publications at http://pubs.acs.org/journal/ancham

Universal Surface-Enhanced Raman Scattering Amplification Detector for Ultrasensitive Detection of Multiple Target Analytes

Jing Zheng, Yaping Hu, Junhui Bai, Cheng Ma, Jishan Li, Yinhui Li, Muling Shi, Weihong Tan, and Ronghua Yang
State Key Laboratory of Chemo/Biosensing and Chemometrics, College of Chemistry and Chemical Engineering, College of Biology, and Collaborative Innovation Center for Chemistry and Molecular Medicine, Hunan University, Changsha, Hunan 410082, China
Anal. Chem., **2014,** *86* (4), 2205–2212
DOI: 10.1021/ac404004m

Here, we describe a novel "switch-on" biosensor based on quinonyl glycosides functionalized quantum dots (QDs) for the specific targeting and imaging of transmembrane glycoprotein receptors on the surface of cancer cells. The design of the quinonyl glycosides lies in that the quinone moiety serves as a quencher of QDs and the glycoside moiety as a biospecific



ligand for targeting a receptor. We observed that the quenched photoluminescence of the quinone glycosides functionalized QDs could be significantly recovered by a specific lectin that selectively binds to the glycosides clustering the QDs but was not affected by a panel of nonspecific lectins. Moreover, we determined that quinonyl galactoside functionalized QDs could optically image the asialoglycoprotein receptors of a hepatoma cell line in a target-specific manner. This system might provide new insights into the fabrication of photoluminogenic biosensors for the analysis of the universal ligand–receptor recognitions in nature. ■

Target-Specific Imaging of Transmembrane Receptors Using Quinonyl Glycosides Functionalized Quantum Dots

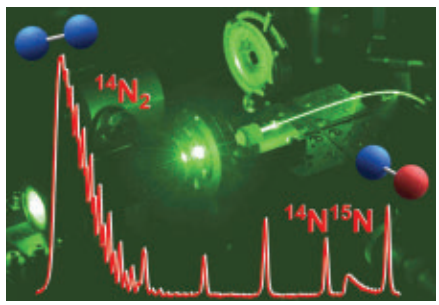
Wei Ma †, Hui-Ting Liu †, Xiao-Peng He †, Yi Zang ‡, Jia Li *‡, Guo-Rong Chen †, He Tian †, and Yi-Tao Long †
† Key Laboratory for Advanced Materials & Institute of Fine Chemicals, East China University of Science and Technology, Shanghai, P. R. China
‡ National Center for Drug Screening, State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Shanghai Institutes of Biological Sciences, Chinese Academy of Sciences, Shanghai, P. R. China
Anal. Chem., **2014,** *86* (11), 5502–5507
DOI: 10.1021/ac501463u

Here, we describe a novel "switch-on" biosensor based on quinonyl glycosides functionalized quantum dots (QDs) for the specific targeting and imaging of transmembrane glycoprotein receptors on the surface of cancer cells. The design of the quinonyl glycosides lies in that the quinone moiety serves as a quencher of QDs and the glycoside moiety as a biospecific ligand for targeting a receptor. We observed that the quenched photoluminescence of the quinone glycosides functionalized QDs could be significantly recovered by a specific lectin that selectively binds to the glycosides clustering the QDs but was not affected by a panel of nonspecific lectins. Moreover, we determined that quinonyl galactoside functionalized QDs could optically image the asialoglycoprotein receptors of a hepatoma cell line in a target-specific manner. This system might provide new insights into the fabrication of photoluminogenic biosensors for the analysis of the universal ligand–receptor recognitions in nature. ■

Fiber-Enhanced Raman Multigas Spectroscopy: A Versatile Tool for Environmental Gas Sensing and Breath Analysis

Stefan Hanf †, Robert Keiner †, Di Yan †, Jürgen Popp †‡§, and Torsten Frosch ††‡
† Leibniz Institute of Photonic Technology, Jena, Germany
‡ Institute for Physical Chemistry, Friedrich-Schiller University, Jena, Germany
§ Abbe School of Photonics, Friedrich-Schiller University, Jena, Germany
Anal. Chem., **2014,** *86* (11), 5278–5285
DOI: 10.1021/ac501463u

Versatile multigas analysis bears high potential for environmental sensing of climate relevant gases and noninvasive early stage diagnosis of disease states in human breath. In this contribution, a fiber-enhanced Raman spectroscopic (FERS) analysis of a suite of climate relevant atmospheric gases is presented, which allowed for reliable quantification of CH_4, CO_2, and N_2O alongside N_2 and O_2 with just one single measurement. A highly improved analytical sensitivity was achieved, down to a sub-parts per million limit of detection with a high dynamic range of 6 orders



of magnitude and within a second measurement time. The high potential of FERS for the detection of disease markers was demonstrated with the analysis of 27 nL of exhaled human breath. The natural isotopes $^{13}CO_2$ and $^{14}N^{15}N$ were quantified at low levels, simultaneously with the major breath components N_2, O_2, and $^{12}CO_2$. The natural abundances of $^{13}CO_2$ and $^{14}N^{15}N$ were experimentally quantified in very good agreement to theoretical values. A fiber adapter assembly and gas filling setup was designed for rapid and automated analysis of multigas compositions and their fluctuations within seconds and without the need for optical readjustment of the sensor arrangement. On the basis of the abilities of such miniaturized FERS system, we expect high potential for the diagnosis of clinically administered ^{13}C-labeled CO_2 in human breath and also foresee high impact for disease detection via biologically vital nitrogen compounds. ■

Fabrication of Gold Nanoparticle-Embedded Metal–Organic Framework for Highly Sensitive Surface-Enhanced Raman Scattering Detection

Yuling Hu *, Jia Liao, Dongmei Wang, and Gongke Li
School of Chemistry and Chemical Engineering, Sun Yat-sen University, Guangzhou, Guangdong 510275, China
Anal. Chem., **2014,** *86* (8), 3955–3963
DOI: 10.1021/ac5002355

Surface-enhanced Raman scattering (SERS) signals strongly rely on the interactions and distance between analyte molecules and metallic nanostructures. In this work, the use of a gold nanoparticle (AuNP)-embedded metal–organic framework was introduced for the highly sensitive SERS detection. The AuNPs were in situ grown and encapsulated within the host matrix of MIL-101 by a solution impregnation strategy. The as-synthesized AuNPs/MIL-101 nanocomposites combined the localized surface plasmon resonance properties of the gold nanoparticles and the high adsorption capability of metal–organic framework, making them highly sensitive SERS substrates by effectively preconcentrating analytes in close proximity to the electromagnetic fields at the SERS-active metal surface. We discussed the fabrication, physical characterization, and SERS activity of our novel substrates by measuring the Raman signals of a variety of model analytes. The SERS substrate was found to be highly sensitive, robust, and amiable to several different target analytes. A SERS detection limit of 41.75 and 0.54 fmol for Rhodamine 6G and benzadine, respectively, was demonstrated. The substrate also showed high stability and reproducibility, as well as molecular sieving effect thanks to the protective shell of the metal–organic framework. Subsequently, the potential practical application of the novel SERS substrate was evaluated by quantitative analysis of organic pollutant *p*-phenylenediamine in environmental water

and tumor marker alpha-fetoprotein in human serum. The method showed good linearity between 1.0 and 100.0 ng/mL for *p*-phenylenediamine and 1.0–130.0 ng/mL for alpha-fetoprotein with the correlation coefficients of 0.9950 and −0.9938, respectively. The recoveries ranged from 80.5% to 114.7% for *p*-phenylenediamine in environmental water and 79.3% to 107.3% for alpha-fetoprotein in human serum. These results foresee promising application of the novel metal–organic framework based composites as sensitive SERS-active substrates in both environmental and clinical samples. ■

Raman Spectroscopy Enables Noninvasive Biochemical Characterization and Identification of the Stage of Healing of a Wound

Rishabh Jain †, Diego Calderon ‡, Patricia R. Kierski ‡, Michael J. Schurr §, Charles J. Czuprynski ƒ, Christopher J. Murphy ⊥¶, Jonathan F. McAnulty ‡, and Nicholas L. Abbott †

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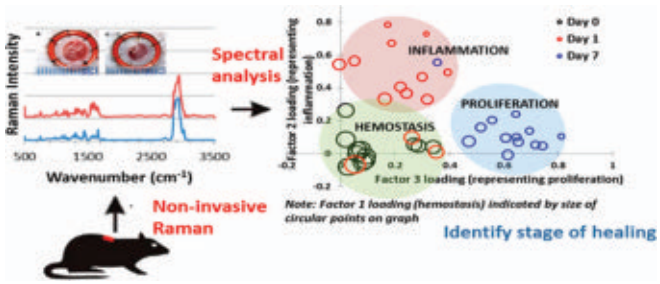
Anal. Chem., **2014,** *86* (8), 3764–3772

DOI: 10.1021/ac500513t

Accurate and rapid assessment of the healing status of a wound in a simple and noninvasive manner would enable clinicians to diagnose wounds in real time and promptly adjust treatments to hasten the resolution of nonhealing wounds. Histologic and biochemical characterization of biopsied wound tissue, which is currently the only reliable method for wound assessment, is invasive, complex to interpret, and slow. Here we demonstrate the use of Raman microspectroscopy coupled with multivariate spectral analysis as a simple, noninvasive method to biochemically characterize healing wounds in mice and to accurately identify different phases of healing of wounds at different time-points. Raman spectra were collected from "splinted" full thickness dermal wounds in mice at 4 time-points (0, 1, 5, and 7 days) corresponding to different phases of wound healing, as



verified by histopathology. Spectra were deconvolved using multivariate factor analysis (MFA) into 3 "factor score spectra" (that act as spectral signatures for different stages of healing) that were successfully correlated with spectra of prominent pure wound bed constituents (i.e., collagen, lipids, fibrin, fibronectin, etc.) using non-negative least squares (NNLS) fitting. We show that the factor loadings (weights) of spectra that belonged to wounds at different time-points provide a quantitative measure of wound healing progress in terms of key parameters such as inflammation and granulation. Wounds at similar stages of healing were characterized by clusters of loading values and slowly healing wounds among them were successfully identified as "outliers". Overall, our results demonstrate that Raman spectroscopy can be used as a noninvasive technique to provide insight into the status of normally healing and slow-to-heal wounds and that it may find use as a complementary tool for real-time, in situ biochemical characterization in wound healing studies and clinical diagnosis. ■

Toward Biocompatible Nuclear Hyperpolarization Using Signal Amplification by Reversible Exchange: Quantitative in Situ Spectroscopy and High-Field Imaging

Jan-Bernd Hövener ††§, Niels Schwaderlapp ‡, Robert Borowiak ††§, Thomas Lickert ‡, Simon B. Duckett ||, Ryan E. Mewis ||, Ralph W. Adams ||, Michael J. Burns ||, Louise A. R. Highton ||, Gary G. R. Green ||, Alexandra Olaru ||, Jürgen Hennig ‡, and Dominik von Elverfeldt ‡

† German Consortium for Cancer Research (DKTK), Heidelberg, Germany

‡ Medical Physics, Department of Radiology, University Medical Center Freiburg, 79098 Freiburg, Germany

§ German Cancer Research Center (DKFZ), Heidelberg, Germany

‖ Centre for Hyperpolarisation in Magnetic Resonance, University of York, York, YO10 5DD, U.K.
Anal. Chem., **2014,** *86* (3), 1767–1774
DOI: 10.1021/ac403653q

Signal amplification by reversible exchange (SABRE) of a substrate and *parahydrogen* at a catalytic center promises to overcome the inherent insensitivity of magnetic resonance. In order to apply the new approach to biomedical applications, there is a need to develop experimental equipment, *in situ* quantification methods, and a biocompatible solvent. We present results detailing a low-field SABRE polarizer which provides well-controlled experimental conditions, defined spins manipulations, and which allows *in situ* detection of thermally polarized and hyperpolarized samples. We introduce a method for absolute quantification of hyperpolarization yield in situ by means of a thermally polarized reference. A maximum signal-to-noise ratio of ~10^3 for 148 μmol of substance, a signal enhancement of 10^6 with respect to polarization transfer field of SABRE, or an absolute ^{1}H-polarization level of ≈10^{-2} is achieved. In an important step toward biomedical application, we demonstrate ^{1}H *in situ* NMR as well as ^{1}H and ^{13}C high-field MRI using hyperpolarized pyridine (d_3) and ^{13}C nicotinamide in pure and 11% ethanol in aqueous solution. Further increase of hyperpolarization yield, implications of *in situ* detection, and *in vivo* application are discussed. ■

Structural and Optical Nanoengineering of Nanoporous Anodic Alumina Rugate Filters for Real-Time and Label-Free Biosensing Applications

Tushar Kumeria †, Mohammad Mahbubur Rahman †‡, Abel Santos †, Josep Ferré-Borrull ‡, Lluís F. Marsal ‡, and Dusan Losic †
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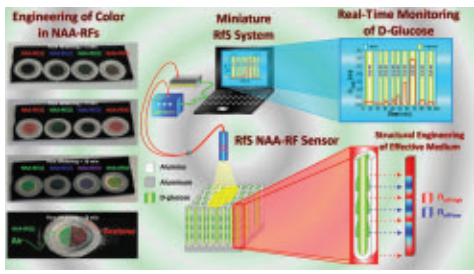
Anal. Chem., **2014,** *86* (3), 1837–1844
DOI: 10.1021/ac500069f
In this study, we report about the structural engineering and optical optimization of nanoporous anodic alumina rugate filters (NAA-RFs) for real-time and label-free biosensing applications. Structurally engineered NAA-RFs are combined with reflection spectroscopy (RfS) in order to develop a biosensing system based on the position shift of the characteristic peak in the reflection spectrum of NAA-RFs (Δλpeak). This system is optimized and assessed by measuring shifts in the characteristic peak position produced by small changes in the effective medium (i.e., refractive index). To this end, NAA-RFs are filled with different solutions of D-glucose, and the Δλpeak is measured in real time by RfS. These results are validated by a theoretical model (i.e., the Looyenga–Landau–Lifshitz model), demonstrating that the control over the nanoporous structure makes it possible to optimize optical signals in RfS for sensing purposes. The linear range of these optical sensors ranges from 0.01 to 1.00 M, with a low detection limit of 0.01 M of D-glucose (i.e., 1.80 ppm), a sensitivity of 4.93 nm M^{-1} (i.e., 164 nm per refractive index units), and a linearity of 0.998. This proof-of-concept study demonstrates that the proposed system combining NAA-RFs with RfS has outstanding capabilities to develop ultrasensitive, portable, and cost-competitive optical sensors. ■



In Vivo Proton–Electron Double-Resonance Imaging of Extracellular Tumor pH Using an Advanced Nitroxide Probe

Alexandre Samouilov †§, Olga V. Efimova †, Andrey A. Bobko †‡, Ziqi Sun †, Sergey Petryakov †, Timothy D. Eubank †‡, Dmitrii G. Trofimov ‖, Igor A. Kirilyuk ‖, Igor A. Grigor'ev ‖, Wataru Takahashi †⊗, Jay L. Zweier †§, and Valery V. Khramtsov †‡
†The Dorothy M. Davis Heart and Lung Research Institute: ‡Division of Pulmonary, Allergy, Critical Care, and Sleep Medicine, and §Division of Cardiovascular Medicine, Department of Internal Medicine, The Ohio State University, Columbus, Ohio 43210, United States
‖ **Vorozhtsov Institute of Organic Chemistry, Novosibirsk 630090, Russia**
⊗ Hokkaido University, Sapporo, Hokkaido 060-0814, Japan
Anal. Chem., **2014,** *86* (2), 1045–1052
DOI: 10.1021/ac402230h

A variable radio frequency proton–electron double-resonance imaging (VRF PEDRI) approach for pH mapping of aqueous samples has been recently developed (Efimova et al. *J. Magn. Reson.* **2011,** *209,* 227−232). A pH map is extracted from two PEDRI acquisitions performed at electron paramagnetic resonance (EPR) frequencies of protonated and unprotonated

forms of a pH-sensitive probe. To translate VRF PEDRI to an *in vivo* setting, an advanced pH probe was synthesized. Probe deuteration resulted in a narrow spectral line of 1.2 G compared to a nondeuterated analogue line width of 2.1 G allowing for an increase of Overhauser enhancements and reduction in rf power deposition. Binding of the probe to the cell-impermeable tripeptide, glutathione (GSH), allows for targeting to extracellular tissue space for monitoring extracellular tumor acidosis, a prognostic factor in tumor pathophysiology. The probe demonstrated pH sensitivity in the 5.8–7.8 range, optimum for measurement of acidic extracellular tumor pH (pHe). *In vivo* VRF PEDRI was performed on Met-1 tumor-bearing mice. Compared to normal mammary glands with a neutral mean pHe (7.1 ± 0.1), we observed broader pH distribution with acidic mean pHe (6.8 ± 0.1) in tumor tissue. In summary, VRF PEDRI in combination with a newly developed pH probe provides an analytical approach for spatially resolved noninvasive pHe monitoring, *in vivo*. ■

Direct Detection and Speciation of Trace Explosives Using a Nanoporous Multifunctional Microcantilever

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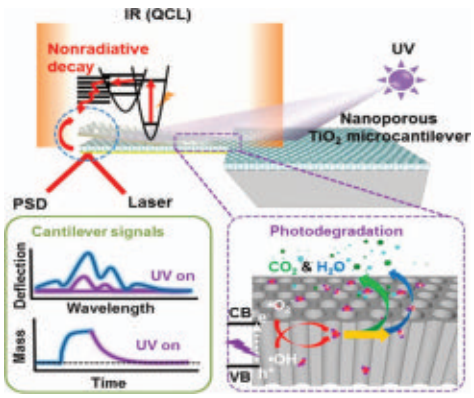

A variable radio frequency proton–electron double-resonance imaging (VRF PEDRI) approach for pH mapping of aqueous samples has been recently developed (Efimova et al. J. Magn. Reson. 2011, 209, 227−232). A pH map is extracted from two PEDRI acquisitions performed at electron paramagnetic resonance (EPR) frequencies of protonated and unprotonated forms of a pH-sensitive probe. To translate VRF PEDRI to an *in vivo* setting, an advanced pH probe was synthesized. Probe deuteration resulted in a narrow spectral line of 1.2 G compared to a nondeuterated analogue line width of 2.1 G allowing for an increase of Overhauser enhancements and reduction in rf power deposition. Binding of the probe to the cell-impermeable tripeptide, glutathione (GSH), allows for targeting to extracellular tissue space for monitoring extracellular tumor acidosis, a prognostic factor in tumor pathophysiology. The probe demonstrated pH sensitivity in the 5.8–7.8 range, optimum for measurement of acidic extracellular tumor pH (pH_e). *In vivo* VRF PEDRI was performed on Met-1 tumor-bearing mice. Compared to normal mammary glands with a neutral mean pH_e (7.1 ± 0.1), we observed broader pH distribution with acidic mean pH_e (6.8 ± 0.1) in tumor tissue. In summary, VRF PEDRI in combination with a newly developed pH probe provides an analytical approach for spatially resolved noninvasive pH_e monitoring, *in vivo*. ■

Detection and Quantification of Early-Stage Malaria Parasites in Laboratory Infected Erythrocytes by Attenuated Total Reflectance Infrared Spectroscopy and Multivariate Analysis

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New diagnostic modalities for malaria must have high sensitivity and be affordable to the developing world. We report on a method to rapidly detect and quantify different stages of malaria parasites, including ring and gametocyte forms, using attenuated total reflectance Fourier transform infrared spectroscopy (ATR-FT-IR) and partial least-squares regression (PLS). The absolute detection limit was found to be 0.00001% parasitemia (<1 parasite/μL of blood; $p < 0.008$) for cultured early ring stage parasites in a suspension of normal erythrocytes. Future development of universal and robust calibration models can significantly improve malaria diagnoses, leading to earlier detection and treatment of this devastating disease. ■

DETECTION OF METHYLMALONIC ACID (MMA) IN PLASMA USING HYDROPHILIC INTERACTION LIQUID CHROMATOGRAPHY (HILIC) COUPLED WITH MASS SPECTROMETRY (MS) OR TANDEM MASS SPECTROMETRY (MS/MS)

Maricar Dube and Patrik Appelblad EMD Millipore

Abstract

Methylmalonic acid (MMA) is a biomarker for vitamin B12 deficiency. This application note describes a fast, simple, and sensitive method to detect MMA in plasma that uses a zwitterionic hydrophilic interaction chromatography (ZIC®-HILIC) column with LC-MS or LC-MS/MS.

Introduction

Methylmalonic acid (MMA) levels in serum, plasma and urine are used to monitor cobalamin (vitamin B12) deficiency[1] and methylmalonic acidemia. Different methods have been developed to quantify MMA in biological samples, including GC-MS, LC-MS/MS, HPLC, and capillary electrophoresis (CE). The main challenges that must be overcome for accurate measurement are the low physiological concentrations of MMA in human serum (100-500 nM), and the fact that MMA is a hydrophilic non-volatile compound. Retention and separation of MMA on reversed phase liquid chromatographic columns is difficult since MMA is poorly retained, and the structural isomer, succinic acid (SA), causes ion suppression because the concentration SA in serum is usually considerably higher than MMA.

Many laboratories have adopted protocols that require extraction of MMA plus steps to yield MMA-derivatives that are compatible with GC-MS or LC-MS/MS techniques using reversed phase columns[2]. This way, derivatives of MMA and SA may be differentiated due to their different fragmentation patterns. As a consequence however, the cost per MMA-test is usually considerably higher than standard immunological assays for B12.

HILIC columns efficiently separate polar hydrophilic compounds, which are not retained on reversed phase columns. The base material of HILIC columns can be either silica or polymer, and may be modified with different types of polar functionalities such as zwitterionic sulfoalkylbetaine (ZIC®-HILIC column). Because of its highly polar nature, MMA is retained on a ZIC®-HILIC column without the need to generate MMA-derivatives, making the workflow simpler, easier and faster[3]. This report describes a sensitive LC-MS/MS method to measure MMA using a ZIC®-HILIC column.

Experimental Conditions

Chromatography Conditions

Table 1

Column	SeQuant® ZIC®-HILIC (3μm, 100Å) PEEK 100× 2.1 mm
Injection	7 μL
Mobile phase	80:20 Acetonitrile/ 100 mM ammonium acetate pH 4.5*
Flow rate	400 μL/min
Temperature	40ºC
Detection	(a) ESI-MS (b) MS/MS, ESI(-), MRM (m/z 117.1→73.0, 55.1)

*** There is a gradient wash process between injections**

Sample Preparation

800 μL acidified acetonitrile containing 170 nM of internal standard (D3-MMA) was used to precipitate proteins in 200 μL serum/plasma samples. Supernatant was directly injected into the column after centrifugation[3].

Results and Discussion

Isocratic separation of MMA in plasma on a ZIC®-HILIC column was achieved in less than 3 minutes. The void volume was 0.5 min, while the retention times for MMA and D3-MMA were 2.14 min and 2.13 min, respectively.

For the single stage MS detection, the limit of detection (3 x SD) and limit of quantitation (10 x SD) were 30 nM and 90 nM MMA, respectively, in plasma/serum. The method is linear up to 200 μM. Day-to-day and intra-day CVs are lower than 5%. The recovery is between 90% and 93%.

For the MS/MS detection, the limit of detection (3 × SD) was 5 nM and the limit of quantification (10 × SD) for MMA was 15 nM. Figure 1 (on next page) shows the MS/MS chromatogram of MMA in a plasma sample.

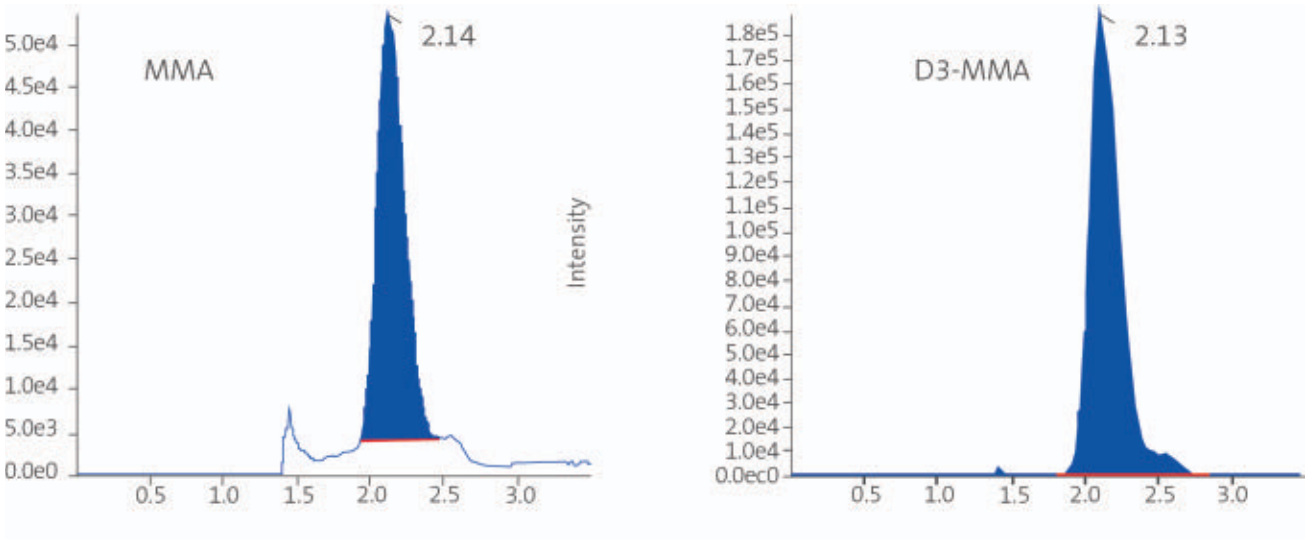

Figure 1.
ZIC®-HILIC-MS/MS chromatogram of MMA (m/z 117.1 73.0) and D3-MMA (m/z 119.9 75.9) in a plasma sample

Conclusion

A fast, simple, and sensitive means to determine MMA levels in serum/plasma was developed that combined ZIC®-HILIC separation with single stage negative ESI-MS or tandem MS. As neither MMA sample extraction nor derivatization were required, the ZIC®-HILIC-MS/MS method reported here may be an attractive alternative to existing means for measuring MMA in clinical laboratories where the existing GC-MS or reversed phase LC-MS/MS methods are tedious and laborious.

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DUAL-FLOW REFRACTIVE INDEX DETECTOR FOR DETERMINATION OF MOLAR MASS AVERAGES IN GEL PERMEATION CHROMATOGRAPHY

Amandaa K. Brewer, Ph.D. Tosoh Bioscience LLC

Introduction

Gel permeation chromatography (GPC) is the most widely accepted and used analytical method for obtaining molar mass averages and distributions of both synthetic and biological polymers. Traditionally, molar mass averages and distributions are obtained via a peak position calibration using a series of standards of known molar mass and chemistry, analyzed by GPC coupled to a differential refractive index (RI) detector. In the context of GPC, GPC/RI continues to be heavily employed as it provides excellent day-to-day reproducibility, and is ideal for quality control procedures.

One caveat to single detector GPC performance is the baseline stability of the RI detector. A conventional RI detector is constructed in such a way that there are two sides: (1) the reference side that contains stagnant pure solvent; and (2) the sample side, which has a flowing stream of analyte in the same solvent as in the reference side. Over time, the stagnant pure solvent in the reference side slowly changes, resulting in baseline drift. For peak position calibration, a drift in the RI baseline has been shown to drastically affect the accuracy and precision of measurements of molar mass averages and distributions with an increase in the error rate of 25%.

Here, we have studied the repeatability, reproducibility, and baseline stability of a dual-flow RI detector in the EcoSEC® GPC System for the determination of molar mass averages via peak position calibration. The unique dual flow design of the RI detector is constructed in such a way that the reference side of the RI flow cell contains a flowing stream of pure solvent. The dual flow design is shown to compensate for the changes in the refractive index of the solvent over time by continuously flowing pure solvent through the reference side of the flow cell.

Experimental Methods and Conditions

GPC analysis was performed on a system consisting of either an all-in-one EcoSEC GPC System equipped with a dual-flow refractive index detector or a modular HPLC system with an external conventional refractive index detector. Separation of polystyrene standards (PS) occurred over a column blank consisting of TSKgel® SuperMultiporeHZ-M columns, with THF as the mobile phase.

Results and Discussion

To demonstrate the repeatability, reproducibility, and baseline stability of a dual-flow RI detector compared to a conventional RI detector a series of identical experiments was performed on the EcoSEC GPC System (Figure 1) and two conventional

Figure 1
EcoSEC GPC System

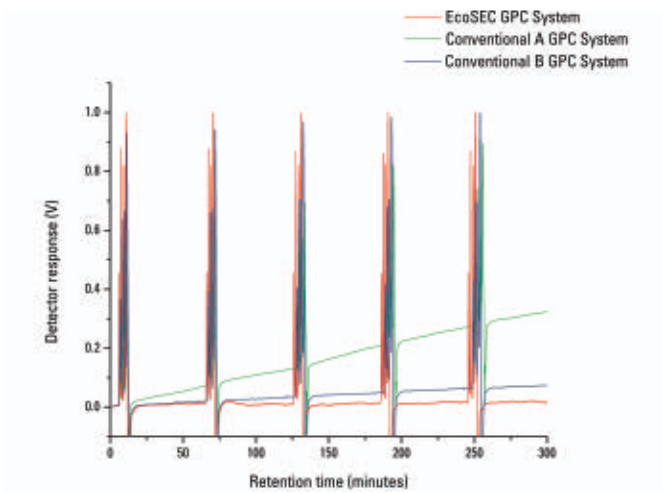


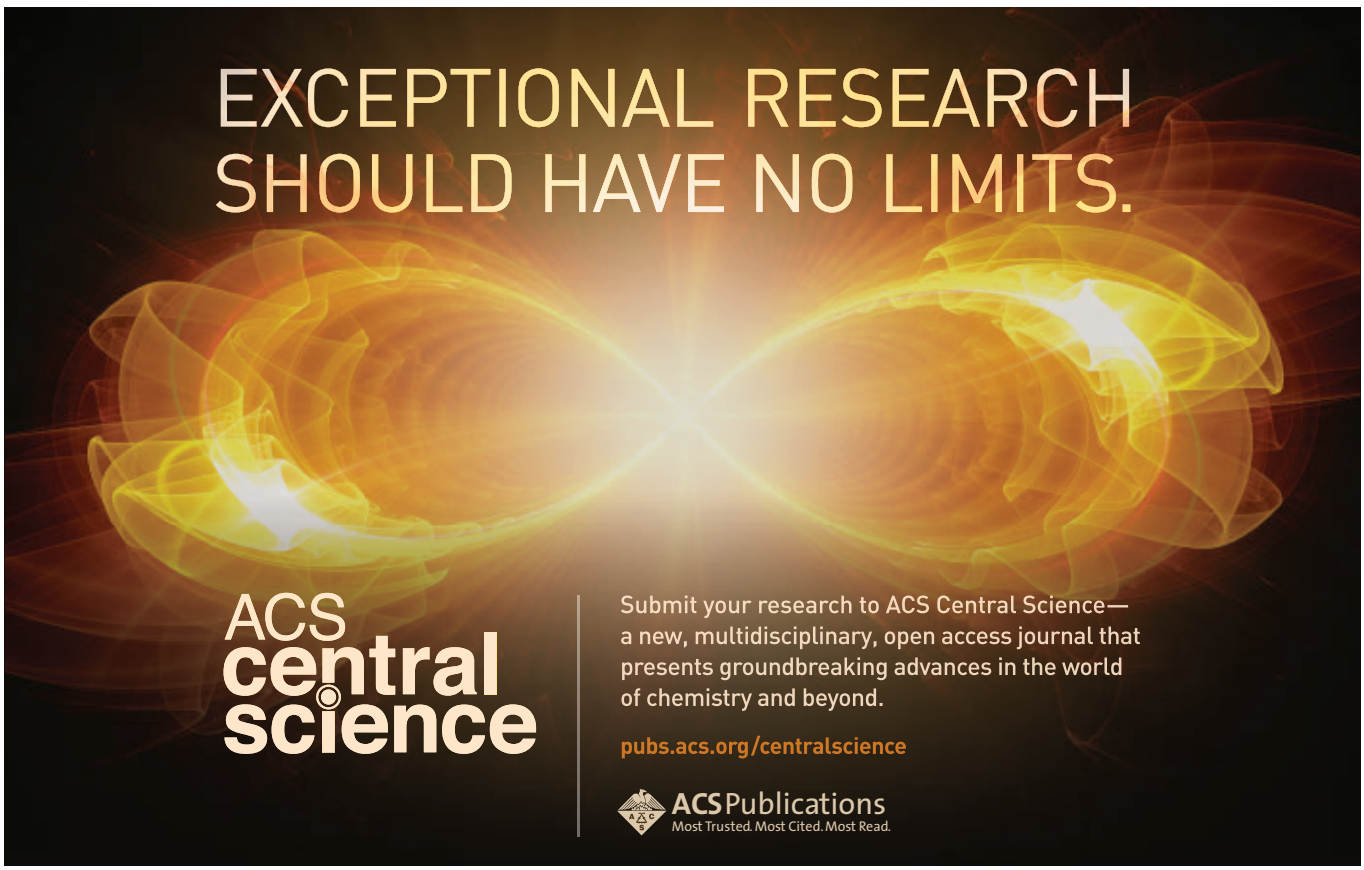
Figure 2
Baseline drift comparison between a dual-flow refractive index detector and conventional systems

HPLC systems. As shown in Figure 2, five consecutive injections of PS with run times of one hour without auto zeroing the detector between injections for a total of five hours, resulted in an extremely stable baseline with low baseline drift for the dual-flow RI detector and a significantly drifting baseline on the two conventional RI detectors.

The repeatability and reproducibility of the molar mass averages as obtained via the dual-flow and conventional RI detectors were also compared. The reproducibility of the weight-average molar mass, M_w, of the dual-flow RI detector was determined to be superior by a factor of 3 to that of a conventional RI detector. Additionally the day-to-day reproducibility and repeatability for the determination of molar mass averages was shown to vary less than 0.5% for the dual-flow RI detector, while the conventional RI detector produced day-to-day variations in molar mass averages between 1% and 3%.

Conclusion

A stable RI detector baseline is required for successful experiments, and repeatable and reproducible molar mass averages. Extreme care must be taken when molar mass averages and distributions are determined via peak position calibration as uncertainties and instabilities in the RI baseline can result in relatively large errors, inconsistencies, and deviations in molar mass averages. The repeatability and reproducibility of the molar mass averages were shown to increase greatly when a conventional RI detector was replaced with a dual-flow RI detector.



MODULAR SPECTROSCOPY TOOLS FOR MEASURING INTRINSIC PROTEIN FLUORESCENCE

Yvette Mattley, Ph.D. Ocean Optics

Abstract

In this application note, a UV LED and a high performance modular spectrometer were used together to measure the intrinsic fluorescence of the protein lysozyme in different conformational states. The objective was to demonstrate the power of modular spectroscopy for measuring inherent protein fluorescence as a means to monitor changes in the folded state of proteins.

Introduction

Proteins contain aromatic amino acids that fluoresce when excited with UV light. This intrinsic protein fluorescence depends on the amino acid composition and conformational state of the protein. As the protein goes from a native (folded) to a denatured (unfolded) state, the local environment surrounding the aromatic amino acids changes, affecting the fluorescence properties of the amino acids.

Proteins containing tryptophan and tyrosine (280 nm and 274 nm excitation, respectively) are best suited for conformation monitoring by UV-excited fluorescence emissions due to the relatively high quantum yield and similar excitation wavelengths of these amino acids. Phenylalanine is used less frequently as an indicator of protein conformation because it has a much lower quantum yield with a lower excitation wavelength (~257 nm excitation).

The native state of a protein can be altered in different ways including elevating temperature, adding chaotropic or other chemical agents such as guanidine hydrochloride or urea, and changing pH. As the protein unfolds, amino acids previously buried in the hydrophobic core of the protein are exposed to the solvent. Solvent exposure quenches the fluorescence of the amino acids and decreases the intensity of the intrinsic protein spectrum.

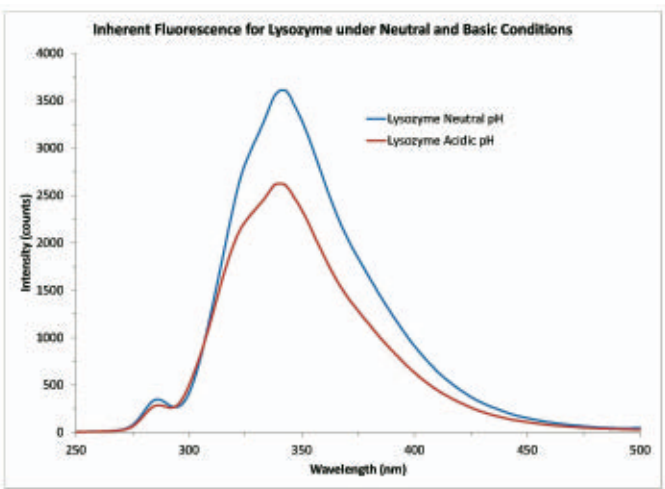


Figure 1
Changes in the fluorescence spectra of lysozyme with exposure to a low-pH

Experimental Conditions

A 280 nm UV LED in combination with a high-sensitivity QE *Pro* spectrometer was used to measure fluorescence from samples of lysozyme diluted in neutral and acidic solutions. We prepared 3 mg/mL lysozyme (L6876 Sigma) in phosphate buffered saline (1X PBS pH 7.4), and 0.1 M HCl/KCl (pH 1) solution. Lysozyme suspended in 1X PBS was in its native (folded) state, while lysozyme suspended in the acidic 0.1 M HCl/KCl solution began to denature and expose amino acids previously contained within the core of the protein to the solvent environment.

Results and Discussion

The intrinsic protein fluorescence spectra for lysozyme diluted in 1X PBS (neutral pH) and 0.1 M HCl/KCl (acidic pH) are shown in Figure 1. When lysozyme was exposed to low pH, the protein conformation changed exposing the tryptophan and tyrosine amino acids to a different environment. As a result, the fluorescence spectrum decreased in intensity as the protein changed from a folded conformation to an unfolded state.

Conclusion

Intrinsic fluorescence is a powerful indicator of protein structure and function. Inherent protein fluorescence can give researchers insight into the protein's conformational state, and corresponding biological activity under different conditions, including changes in temperature, pH and ion concentration. These changes in intrinsic protein fluorescence can be used to monitor protein unfolding for medical diagnostics applications where researchers are investigating neurodegenerative and other diseases associated with improper protein unfolding.

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ON-LINE QUALITY CONTROL MEASUREMENTS IN VARYING CONDITIONS

Yvette Mattley, Ph.D. Ocean Optics

Abstract

With the use of a new generation of robust, repeatable and stable instrumentation, manufacturers can more easily assess sample quality under rigorous conditions. In this application note, we investigate the thermal stability of a spectrometer system for process line transmission measurements at different temperatures.

Introduction

Even as advances in engineering technologies and manufacturing processes have lowered the cost of making and distributing products, the demand for continued improvement is as strong as ever. In an environment where small improvements in characterization of raw materials or subtle changes in process parameters can result in significant production savings, the ability to design faster, smarter and more robust instrumentation is paramount.

When the emergence of miniature spectrometers coincided with development of modular fiber optics, spectroscopy was no longer limited to the lab. Now you can bring the instrument to the sample, which allows industrial users to integrate the measurement into the process. Small-footprint modular systems can be rapidly configured for a variety of absorbance, reflectance and emission measurements, with a number of potential applications.

The Flame spectrometer addresses some of the limitations associated with miniature spectroscopy systems in dynamic process environments.

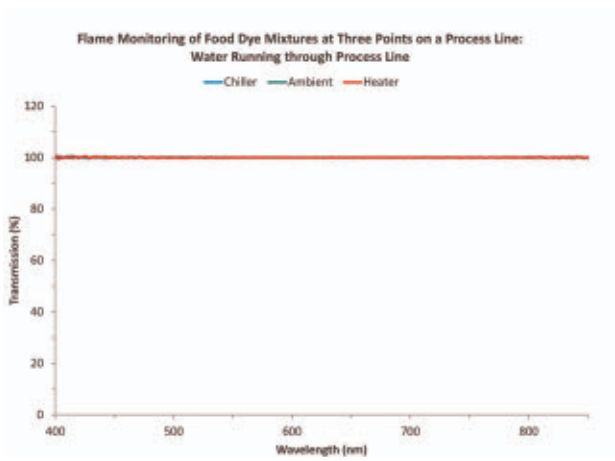

Figure 1

Water was tested as the reference for each condition – chilled (24 °C), ambient (27 °C) and heated (30 °C).

Experimental Conditions

To evaluate the effectiveness of the Flame spectrometer at different temperatures, we measured transmission of several

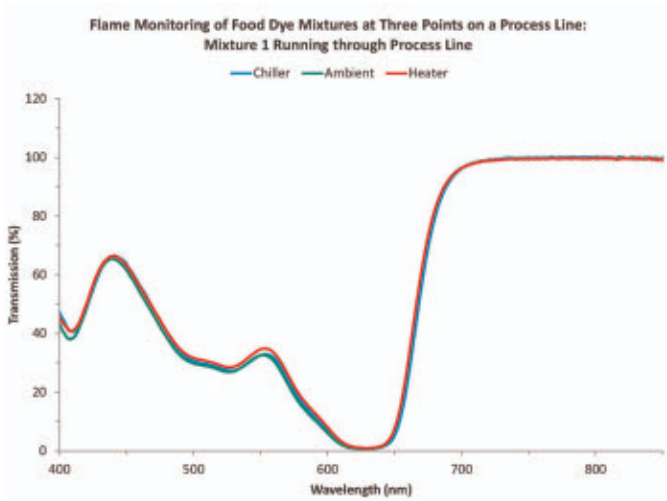

Figure 2

Mixture 1: spectra measured across each temperature condition – chilled (24 °C), ambient (27 °C) and heated (30 °C) – were consistent.

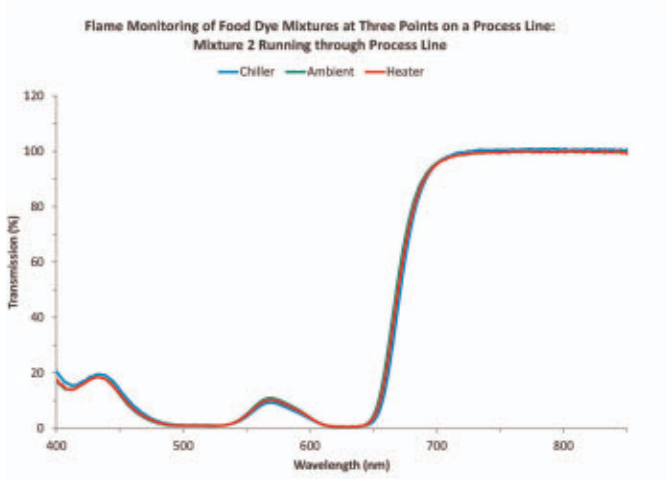

Figure 3

The Flame spectrometer produced consistent results across different temperature conditions, as these transmission spectra reveal.

concentration levels of food dye mixtures on a simulated process line with typical conditions encountered in a process environment. Then we isolated each Flame spectrometer in a different temperature environment – cool (using a chiller), ambient and hot (using a lab heater). Several sample mixtures were prepared for testing, using the Z-type flow cell to move each sample through the system. Water moving through the flow cell was measured as a reference (Figure 1).

Results and Discussion

Although the Flame spectrometers measured the transmission of the mixtures flowing through the system at different temperature conditions, the resulting spectra—and sample composition information derived from the spectra—were nearly identical (Figure 2 and Figure 3). This result is significant for process line applications, where temperatures can vary from zone to zone within the stream. For quality control professionals, getting the correct answers under all sorts of conditions—including temperature extremes—is critical.

Conclusion

Process environments can be harsh, with extremes in temperature and humidity, and the harmful effects of dust and vibration. That's why process-ready spectroscopic instrumentation such as Flame has been designed with few moving parts, has a high degree of thermal stability, and is easily adapted for different setups. The availability of such robust, repeatable, thermally stable instrumentation allows manufacturers to assess sample quality online at multiple points in processes, helping to improve yields, eliminate waste and reduce costs.

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THERMOPLASTIC ELASTOMER FLOW PROPERTY DETERMINATION BY DYNAMIC RHEOLOGY

TA Instruments

Abstract

Rate-dependent viscosity data of thermoplastic elastomers is important for effective material property prediction and manufacturing process design. Rheological data also reveals compositional differences and the presence of a percolation threshold of the dispersed phase.

Introduction

Thermoplastic elastomers have gained considerable interest for their appealing combination of rubber-like final properties and convenient thermoplastic processing. Thermoplastic vulcanizates (TPV) are among the most prevalent thermoplastic elastomers for the replacement of cured rubber parts. TPV can be processed like thermoplastics, however characterization of their flow behavior is critical to effective manufacturing design. Many TPV producers offer material grades based on both variable hardness and tailor-made processing types such as injection molding, blow molding or extrusion.

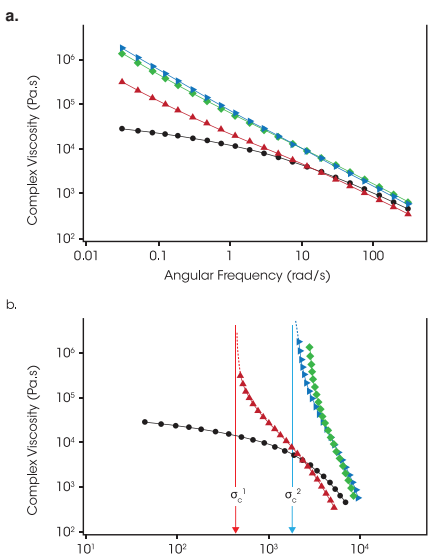

Figure 1

(a) Frequency dependent complex viscosity of four TPV materials of varying composition. (b) Rubber content of samples and corresponding yield stress

Experimental Conditions

Samples of TPV of varying composition were tested with the RPA elite oscillatory shear rheometer (TA Instruments, New Castle, DE USA). The RPA elite is a closed-cavity dynamic shear rheometer with grooved biconical dies designed for rubber and elastomer characterization. Pre-molded sample discs were used to improve homogeneity. Samples were loaded at 180°C and conditioned with a low strain and frequency (0.5%, 10 rad/s) for 10 minutes prior to data collection. Frequency sweep experiments were performed at 1% strain.

Results

Four samples were tested, each with a different TPV content, to demonstrate shear-thinning behavior, which is common for polymers. At moderate to high frequencies (shear rates), the complex viscosity values are similar for each specimen (Figure 1a). Larger differences become evident at low frequencies, which correlate with low shear rate behavior. The fourth sample (Figure 1, black curve) exhibits a Newtonian viscosity plateau at low frequencies.

Discussion

TPV are multiphase materials with a discontinuous cured rubber phase dispersed in a continuous polyolefin phase. The ratio of cured rubber to polyolefin is used to adjust the final hardness value; greater polyolefin content leads to higher hardness values. In Figure 1, the specimen indicated by the black curve has a hardness value of 50 Shore D, indicative of a polyolefin-rich material. All other materials (red, blue, and green curves) have hardness values from 50 to 75 Shore A, and are rubber-rich materials.

The viscous behavior of the low-hardness materials (high rubber-phase content) can be appropriately described by the Herschel-Bulkley model: $\sigma = \sigma_c + K(\dot{\gamma})^n$

This model is specifically used for compounded materials such as rubbers and plastics with filler content above the percolation threshold. This model highlights a critical stress (σc) at which the viscosity is infinite and under which the material does not flow, information that is particularly important for injection mold and extruder die design. The critical stress for rubber-rich TPV is clearly illustrated in Figure 1b. This representation of the data also reinforces the earlier conclusion that the polyolefin-rich material (black curve) does not exhibit a critical stress.

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