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C&EN

CHEMICAL & ENGINEERING NEWS

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CHEMICAL & ENGINEERING NEWS

Serving the chemical, life sciences, and laboratory worlds



SPECIAL REPORT

HELP FOR PATIENTS WITH ORPHAN DISEASES

New pharma business model, genetic advances, and savvy parent-advocates end years of neglect. PAGE 10

QUOTE OF THE WEEK

"Science opens doors for foreign policy objectives that aren't necessarily shut, but you would have to use a crowbar to get them open."

JONATHAN MARGOLIS, ACTING DEPUTY ASSISTANT SECRETARY, U.S. STATE DEPARTMENT BUREAU OF OCEANS & INTERNATIONAL ENVIRONMENTAL & SCIENTIFIC AFFAIRS PAGE 34

NEWS OF THE WEEK

BUSINESS

GOVERNMENT & POLICY

SCIENCE & TECHNOLOGY

EDUCATION

THE DEPARTMENTS

COVER: *Melissa Hogan's son Case, who has Hunter syndrome, is in an enzyme replacement clinical study. His missing enzyme is delivered directly into his cerebrospinal fluid. Lisa Jarvis/C&EN*

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& THIS WEEK ONLINE

Orphan Drug Renaissance

Children with rare diseases have received scant help from drug companies that could not profit from small patient populations. Now changes in business models, science, and Food & Drug Administration regulations have sparked new treatments (see page 10). Online, hear parent advocates describe children's therapies, watch a slide show of young patients, and read about a pharma scientist trying to kick-start new research efforts.
http://cenm.ag/rare

Analyzing Fingerprints With A Dash Of Turmeric

SHUTTERSTOCK

Turmeric has a long history as a kitchen spice, dye, and traditional medicine. Now researchers have cooked up a new use for the gold-colored powder: Its main ingredient, curcumin, could help forensic scientists analyze the molecular constituents of fingerprints using mass spectrometry.
http://cenm.ag/anl91

Chemical Safety Roundup

C&EN Senior Editor Jyllian Kemsley recaps the latest news about chemical health and safety, including updates on the investigation of the April 17 explosion at a fertilizer facility in West, Texas. The National Council for Occupational Safety & Health released a report on preventing workplace fatalities. And in Florida, a high school student was expelled for combining aluminum foil and toilet bowl cleaner in a water bottle, causing it to explode.
http://cenm.ag/blg139

Bionic Ear Listens To Beethoven

Using a three-dimensional printer, researchers fabricated a bionic ear that can detect sounds outside the normal range of human hearing (see page 5). In a video, C&EN Senior Editor Celia Arnaud explains how researchers integrated tissue engineering with electronics to make the device and demonstrates the ear's response to the musical strains of Beethoven's "Für Elise" broadcast through radio frequencies.
http://cenm.ag/ear

ATTRIBUTING UNDUE SIGNIFICANCE

HAVING RECENTLY BECOME a 50-year member of the American Chemical Society, I am embarrassed to see that C&EN has become a propaganda machine attempting to brainwash ACS members. Strong claim, you say?

The cover of the March 25 issue points to the article about ocean acidification with the words: "Shellfish die-off threatens Pacific Northwest" (C&EN, March 25, page 36). The article says: "Over the past 250 years, the average upper-ocean pH has decreased by about 0.1 units, from about 8.2 to 8.1." This is the only quantitative data, relative to ocean acidification, in this two-page article.

But 250 years ago an acid was a substance that tasted sour, and a base was a substance that tasted bitter. Fritz Haber and Zygmunt Klemensiewicz constructed the first glass pH electrode in 1906. So the pH scale did not exist before 1909. In 1934 Arnold Beckman began marketing his commercial pH meter, the first manufactured in the U.S.

The convention taught in chemistry was that the right-most digit of a quantitative measurement was uncertain; it could be at least one or two units greater or lesser. Therefore, the data cited in the article should not be interpreted as if any change has occurred.

Relative to a shellfish die-off threatening the Pacific Northwest, near the end of the article it says: "In recent years, the tribe's natural resources have been threatened by oil spills, overharvesting, and illegal poachers supplying the Asian seafood market." Maybe it is these three factors, instead of ocean acidification, that threaten Pacific Northwest shellfish.

Jerry L. Krause
Salem, Ore.

THOUGHTS ON DE-EXTINCTION

"REVIVING THE DEAD" brings up some fascinating possibilities (C&EN, April 8, page 34). For the moment, let's avoid any "Jurassic Park"-type scenarios and confine ourselves to plant and animal species that have gone extinct during the past few centuries.

It would certainly be nice to bring back the great auk and the Caribbean monk seal. Going a little further back, it would be nice to revive the mammoths, which seem to have been hunted to extinction. (The last known mammoth died in South America around A.D. 600.) Revival of the two extinct species of dodo and the Rodrigues solitaire would be desirable, although they would probably have to be kept in zoos; their native habitat is now teeming with too many predators for them to survive in the wild. Other species would be nice to revive, although we might not notice the difference. Audubon's bighorn sheep were not that different from their Rocky Mountain cousins.

However, there are some species we would not want to see revived, such as the passenger pigeon. If we brought it back, we would probably lose all cereal grain farming east of the Mississippi to vast flocks of feathered locusts. Another example is the Antillean giant rice rat, whose name speaks for itself. Let sleeping pests lie.

James M. Castro
Helena, Mont.

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Work-Life Balance

This guest editorial is by **Geraldine L. Richmond** *and* **Celeste M. Rohlfing.** *Richmond is the Richard M. & Patricia H. Noyes Professor of Chemistry at the University of Oregon and the director of COACh, a grassroots organization working to increase the number and career success of women scientists and engineers. Rohlfing is the deputy assistant director of the Mathematical & Physical Sciences Directorate at the National Science Foundation.*

EQUILIBRIUM IS DEFINED as a state in which opposing forces or influences are balanced. Although the academic scientific enterprise prides itself on understanding these forces in laboratory systems, it has fallen short in recognizing and remedying the imbalance between the demands of career and those of personal life. This imbalance contributes to extreme professional sacrifices and lowered retention of many talented individuals striving for successful careers in science.

The National Science Foundation's Career-Life Balance Initiative, launched in September 2011 at the White House with the first lady, Michelle Obama, is a notable federal agency step toward rectifying this imbalance. NSF policy currently permits no-cost extension of award duration for principal investigators (PIs) who take an extended leave of absence for dependent care responsibilities, as well as the use of award funds to temporarily replace project personnel who take a leave of absence because of dependent care responsibilities. NSF also offers flexibility in the start dates of its awards. And NSF CAREER PIs can now submit supplemental funding requests to support additional personnel (for example, research technicians or equivalent) for up to three months, for a maximum of $12,000 in salary compensation, for the purpose of sustaining research when the PI is on family leave.

The commitment to work-life balance in academia has recently been reinforced by another organization in the federal government: the Office of Management & Budget. OMB has released for public comment a new circular on improved administration of federal grants and cooperative agreements. If implemented, it will allow inclusion of temporary dependent care costs directly resulting from travel to scientific meetings as an allowable travel cost, family-related leave as an allowable fringe benefit, and identification of locally available dependent care as an allowable meeting cost.

Academic institutions must also develop and implement clear, concise family-friendly policies that will assist graduate students, postdoctoral associates, technicians, and faculty in staying on their career track when faced with dependent care responsibilities. Last year, the grassroots organization COACh conducted a Web-based survey to learn how these groups combine family responsibilities and academic careers. Although sampling was not scientific because respondents were self-selected, the 300 responses provide a useful snapshot of views and concerns on these topics.

Some respondents stated that their institutions had developed family-friendly plans, but when asked about a series of specific policies, roughly half did not know whether their campuses or their departments had such policies. These numbers were highest for graduate students and postdoctoral associates. When policies are not written, documented, and readily accessible, inconsistencies in their implementation can occur. In fact, more than 70% of the survey respondents said that they find variability in family-friendly policies or procedures from one department chair to another. Respondents recommended that their institutions promote clear and consistent policies that are widely disseminated, more flexibility in scheduling, stable and well-supported leave policies, and accessible and affordable child care.

If federal agencies can make policy that helps support talented scientists to pursue their career dreams and have a family, so too can academic institutions. When it comes to work-life balance, particularly for graduate students and postdoctoral associates who are in their prime childbearing age, avoiding an open discussion and disregarding these very real challenges are out-of-date approaches. The time for action is now, and there is no better place to lead than from the chemistry community.

Geraldine L. Richmond
Celeste M. Rohlfing

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

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C&EN
news of the week

MAY 13, 2013 EDITED BY WILLIAM G. SCHULZ & NADER HEIDARI

HEAR, HEAR FOR THE BIONIC EAR

TISSUE ENGINEERING: 3-D-printed devices detect frequencies beyond human perception

ONE GOAL of tissue engineering is to create devices that give humans abilities that they don't naturally possess. For example, imagine being able to detect sounds outside the normal range of human hearing. Human ears can typically pick up sounds within the frequency range of 20 Hz to 20 kHz. At the low end are the rumblings of engines; at the high end are the shrill screeches of high-pitched whistles.

A new bionic ear, developed by a team of engineering researchers at Princeton University, can detect not just those frequencies but others in the megahertz to gigahertz range—the range of radio waves. The bionic ear "hears" by detecting electromagnetic waves instead of sound waves, although the signals it detects can be converted into sounds audible to humans.

To develop the device, researchers had to integrate sophisticated electronics—capable of transmitting signals to the auditory nerve—into engineered tissue that looks and functions like an ear. The team, led by Michael C. McAlpine, an assistant professor of mechanical and aerospace engineering, used three-dimensional printing to pattern the tissue (*Nano Lett.* 2013, DOI: 10.1021/nl4007744). Other researchers have previously made molds for ears using 3-D printing, or they have placed flexible electronics on top of bioengineered tissue. But McAlpine's team is the first to have inserted electronics directly into growing tissue layers during the printing process.

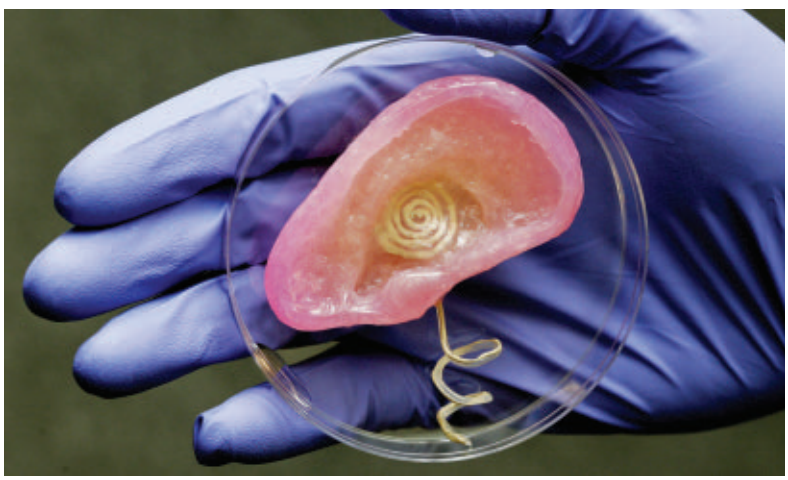
"This research team is the first to combine these individually demonstrated components into an integrated bionic construct," says Jennifer A. Lewis, an engineering professor at Harvard University who was not involved in the work.

"The ear is one of the simpler organs to make, in the sense that the cartilage has no vasculature," McAlpine says. But at the same time, the outer ear's complex geometry is difficult to mimic with conventional tissue engineering methods. So he and his coworkers adopt a new approach.

In typical tissue engineering methods, cells are seeded on a scaffold. The cells excrete their own scaffold as the tissue grows, and the original scaffold dissolves. McAlpine's team instead uses computer-aided design to make a 3-D model of an ear, which they print using a combination of biological, electronic, and structural "inks." The biological ink is a hydrogel matrix containing cartilage-forming cells, the electronic ink is silver nanoparticles, and the structural ink is silicone.

The 3-D printer builds the structure layer by layer in a few hours. "If it took longer, the cells would die," McAlpine says. Then they put the ear in a cell culture medium to grow the tissue. "The tissue we have at the end completely surrounds the electronics, such that the electronics are interwoven with the biology," he says.

The engineered ear consists of cartilaginous tissue with an electronic receiver coil near the surface. The coil penetrates the ear and connects to a cochlea-shaped helical structure with nanoparticle electrodes. The cochlea is a spiral-shaped cavity containing hair cells that convert acoustic vibrations to nerve impulses that are then interpreted as sounds by the brain.



FRANK WOJCIECHOWSKI

The bionic ear integrates cartilage with an electronic receiver coil.

McAlpine and coworkers exposed the 3-D printed ears to left and right channels of stereo music. They connected the cochlear electrodes to a digital oscilloscope, which allowed them to visualize the sounds. They also attached the cochlear electrodes to speakers, which allowed them to play back the output. After going through the entire system, the music was recognizable as Beethoven's "Für Elise."

The ears detect radio waves and other electromagnetic radiation, but McAlpine envisions 3-D-printing other structures that detect acoustic signals directly.

The ears are a long way from being used in a person, but "this work represents a first step," Harvard's Lewis says. "An important next step is to extend this work by printing more complex 3-D tissue with embedded vascular and conductive networks."—CELIA ARNAUD

& VIDEO ONLINE To see bionic ears "listening" to Beethoven, go to http://cenm.ag/ear.

‘BREAKTHROUGH’ DRUGS RISING

PHARMACEUTICALS: New FDA program could cut time for approvals in half, but details are vague

AN INVESTIGATIONAL hepatitis C treatment from AbbVie, the pharmaceutical spin-off of Abbott Laboratories, was granted “breakthrough therapy” status by FDA this week. AbbVie’s combination therapy joins a fast-growing list of drugs in early-stage development to be labeled as such since April 1, although FDA has yet to clarify what the status entails beyond a suggestion that the agency will collaborate with drug sponsors to expedite clinical trials and application review.

The breakthrough therapy designation is part of last year’s FDA Safety & Innovation Act. In a recent speech before the Massachusetts Biotechnology Council, FDA Commissioner Margaret A. Hamburg characterized the new program as a way to boost an existing priority review process called fast track.

The criteria for awarding breakthrough therapy designation are fluid, according to Michael Kleinrock, director of research development at IMS Institute for Healthcare Informatics, who notes that the initial awards seem to have been made on a case-by-case basis. Nevertheless, he is enthusiastic about the potential. “It’s a real change in the speed with which drugs will make it from discovery to market,” he says.

Whereas the fast-track designation might shave a year off the roughly 10-year drug development cycle, Kleinrock says, candidates awarded breakthrough status could move from the start of trials in humans to the market in as little as three to five years.—RICK MULLIN

LABELED FOR ACTION

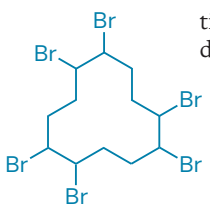
Drugs recently granted FDA’s breakthrough designation

COMPANY	DRUG	INDICATION
AbbVie	ABT-450/r, -267 & -333 with ribavirin	Hepatitis C
Bristol-Myers Squibb	Daclatasvir, asunaprevir & BMS-791325	Hepatitis C
Johnson & Johnson	Daratumumab	Myeloma
Johnson & Johnson/Pharmacyclics	Ibrutinib	Blood cancer
Merck & Co.	Lambrolizumab	Melanoma
Novartis	LDK378	ALK & non-small-cell lung cancers
Pfizer	Palbociclib	Breast cancer
Scioderm	SD-101	Inherited epidermolysis bullosa
Vertex Pharmaceuticals	Kalydeco with VX-809	Cystic fibrosis

GLOBAL BAN FOR FLAME RETARDANT

UNITED NATIONS: Countries agree to end production and use of hexabromocyclododecane

CHEMICAL MAKERS and environmental advocates are praising a move last week by governments from around the world to end production and use of the flame retardant hexabromocyclododecane (HBCD). Published studies show that HBCD, which has been widely used in polystyrene foam insulation for buildings, is toxic to aquatic organisms, can disrupt thyroid hormone in laboratory animals, and persists in the environment.



Hexabromocyclododecane (HBCD)

The Bromine Science & Environmental Forum, a group of four chemical firms that make bromine-containing flame retardants, says it welcomes the HBCD phaseout, which governments adopted at a United Nations meeting in Geneva. The forum says its members—Albemarle, ICL Industrial Products, Chemtura, and Tosoh—“are committed to substituting HBCD with sustainable alternatives.” Chemical firms have been developing and commercializing new flame retardants as alternatives to HBCD for polystyrene foam insulation for some time (C&EN, Oct. 29, 2012, page 39).

The International POPs Elimination Network, a coalition of advocacy groups seeking eradication of persistent organic pollutants (POPs), also praised the move to ban HBCD, saying it will protect people from harmful health effects.

At the Geneva meeting, which ended on May 10, government negotiators added HBCD to a list of 22 other substances targeted for global elimination under the Stockholm Convention on Persistent Organic Pollutants. Other chemicals controlled by this treaty include polychlorinated biphenyls and a number of pesticides.

Parties to the treaty gave HBCD a reprieve before the global ban takes effect. Under the agreement, HBCD can continue to be used in expanded or extruded polystyrene insulation for buildings until 2019, a UN spokesman tells C&EN. The industry forum says this exemption “will provide downstream users with the time that they need to ensure a smooth transition to alternatives.”

Treaty members also created labeling requirements for new building insulation products that contain HBCD, says Joseph DiGangi, senior science adviser for the network of advocacy groups. Labels will provide information to purchasers of insulation products and will also help ensure proper disposal of HBCD-containing materials when buildings are renovated or torn down, he says.—CHERYL HOGUE

DRUG DELIVERY WITH A BANG

NANOSCIENCE: Chain-shattering polymeric therapeutics could release medicines on demand

POLYMER AND NANOPARTICLE conjugates have been widely studied for their potential to deliver drugs selectively to specific tissues and organs, but many such conjugates are structurally diverse, and the amount of drug they deliver can be hard to control—characteristics that are not conducive to drug approval.

A new class of conjugates called chain-shattering polymers, which have highly controlled structures and release predictable drug amounts, could help resolve such problems (*Angew. Chem. Int. Ed.* 2013, DOI: 10.1002/anie.201300497). The polymers, developed by Jianjun Cheng and coworkers at the University of Illinois, Urbana-Champaign, could be useful for treating skin lesions, tumors, and other conditions at localized sites and tissues.

Conjugates have often been structurally variable because drugs attach to different numbers of polymer or nanoparticle sites. Chain-shattering polymers, which are made of alternating units of drug and "suicidal" chemical residues, have more highly controlled structure and composition because the drug is an integral part of the polymer backbone. In the presence of an ultraviolet or peroxide trigger, a protecting agent is removed from each suicidal group, causing polymer chain shattering and near-complete drug release, making the amount of drug supplied more predictable.

"This is the only polymeric nanomedicine I know that has nearly perfect control over composition, structure, and release profile," Cheng says. "We are interested in commercializing the technology."

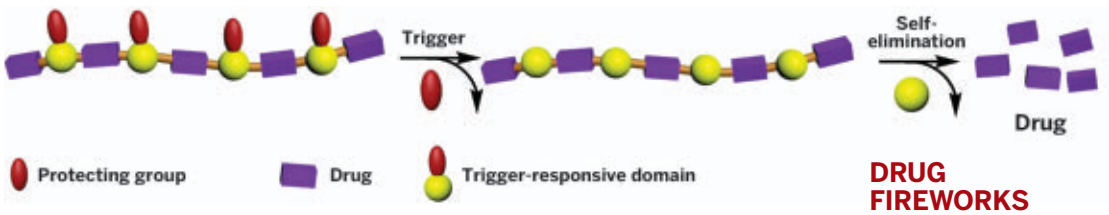
Drug delivery specialist Kathryn Uhrich at Rutgers University and coworkers previously designed Poly-Aspirin, in which the aspirin is also incorporated directly into the polymer backbone. Cheng's group combined that concept with chain shattering to release drug molecules on demand. They demonstrated 80% release of camptothecin, an anticancer agent, in about 10 minutes.

Uhrich says "the chemistry is clever—relatively simple and broadly applicable to various functionalities" but notes that in vivo delivery, formulation stability, possible side effects from polymer degradation, and other factors still need to be demonstrated or evaluated.

Chun Li, a drug delivery expert at the University of Texas M. D. Anderson Cancer Center, says chain shattering "can deliver high drug payloads, the release is sharp, and it can be done in a highly controlled fashion." Capabilities for intravenous administration and targeting of specific tissues and organs are important areas for future evaluation, he notes.

UV radiation doesn't penetrate tissue easily but has potential for treating skin lesions, whereas peroxide can be generated internally and therefore has potential for internal treatments. Cheng's group is also trying to develop triggers based on near-infrared radiation, which penetrates tissue more deeply than UV does.

If the polymers can be harnessed effectively in vivo, they could have "a lot of potential benefits therapeutically," says Todd Emrick, a specialist in polymer therapeutics at the University of Massachusetts, Amherst.—STU BORMAN



DRUG FIREWORKS
Chain-shattering polymer releases drug on demand in response to a UV or peroxide trigger.

ADAPTED FROM *ANGEW. CHEM. INT. ED.*

REGULATION EPA sued for undercounting toxic emissions at refineries, chemical plants

Several community organizations have filed a lawsuit to force the Environmental Protection Agency to review the way it measures toxic air pollution from oil refineries and petrochemical plants along the Texas-Louisiana Gulf Coast.

In a complaint filed in early May in the U.S. District Court for the District of Columbia, Air Alliance Houston and three other activist groups charge that EPA's formulas for estimating emissions of benzene, butadiene, and other pollutants are "outdated and inaccurate."

Recent independent studies at Marathon Oil, Shell, and BP refineries measured actual emissions at levels 10 to 100 times higher than estimates based on the methods facilities currently use to report their releases, the suit says.

"We have filed this complaint as a last resort, and only because EPA has ignored repeated requests to address the problem," says Adrian D. Shelley III, executive director of Air Alliance Houston. "We must know what is in our air if we are going to clean it up and protect public health. Basically, it's an 'enough is enough' situation."

EPA has not reviewed its methodology for calculating air emissions from wastewater treatment systems since 1998, and air emission equations for liquid storage tanks have not been examined since 2006, according to the complaint. The Clean Air Act requires the agency to review and, if necessary, modify the formulas at least once every three years.

An EPA official says the agency is reviewing the suit.—GLENN HESS

LANGER RECEIVES WOLF PRIZE

HONORS: MIT chemical engineer recognized for work in drug delivery and tissue engineering

Langer (left) receives the Wolf Prize from Peres (center).

ODED ANTMANN

ROBERT S. LANGER, a chemical engineer and the David H. Koch Institute Professor at Massachusetts Institute of Technology, received the 2013 Wolf Prize in Chemistry on May 5 in a ceremony at the Knesset in Jerusalem. The award was presented by Israeli President Shimon Peres.

The Wolf Prizes, which are sometimes called the Israeli Nobels, are given by the Wolf Foundation, a nonprofit organization in Israel that honors scientists and artists for achievements that benefit humanity. Langer received the $100,000 prize in recognition of his work on polymer systems for drug delivery and tissue engineering.

Notably, he invented polyanhydride polymers with tunable degradation properties to controllably release macromolecular drugs over sustained periods of time. These polymers steadily erode in water, releasing macromolecules embedded in them. The erosion rate can be tuned by changing the chemical properties of the polymers.

Langer's first therapeutic success in this area was with Gliadel wafers, which he developed in collaboration with Henry Brem, a neurosurgeon at Johns Hopkins University. The wafers are surgically implanted to deliver a drug that treats brain cancer. Langer went on to develop many other polymer systems that release drugs in response to magnetic, ultrasonic, or biological stimuli.

In addition to his drug delivery work, Langer "has been the leader in designing bioabsorbable polymers to serve as scaffolds for holding mammalian cells in place during tissue reconstruction," according to the Wolf Prize committee. Langer's work in this area in collaboration with Joseph P. Vacanti of Harvard Medical School led to the first approved artificial skin based on synthetic polymers for burn patients.

Langer's work has resulted in more than 800 patents. He has founded or cofounded at least 25 companies to commercialize his research.

Langer has received numerous other awards, including the 2006 National Medal of Science. He received the Priestley Medal, the highest honor bestowed by the American Chemical Society, in 2012.

The Wolf Prizes, which were established by German-born inventor and philanthropist Ricardo Wolf, have been awarded since 1978. In addition to chemistry, prizes are given in agriculture, mathematics, medicine, physics, and the arts.—CELIA ARNAUD

A MAJOR AWARD FOR MASS SPEC

HONORS: Dreyfus Prize given to R. Graham Cooks, who shrank MS devices and expanded the technique

PURDUE U

Cooks

GOOD THINGS sometimes come in small packages. The Camille & Henry Dreyfus Foundation took that maxim to heart when bestowing its 2013 Dreyfus Prize in the Chemical Sciences on R. Graham Cooks, a pioneer in mass spectrometry, including miniaturized MS instrumentation.

The inexpensive miniaturized mass spectrometers devised by Cooks and coworkers at Purdue University, where he is the Henry Bohn Hass Distinguished Professor of Chemistry, are portable handheld devices useful for many applications. But that is just one among several notable developments in MS for which he is honored.

Cooks "has enriched analytical chemistry in unparalleled ways," the foundation notes. "Virtually every pharmaceutical and biotechnology company relies on mass spectrometry at a level that has become possible, in part, through Cooks's innovations."

Cooks's group developed and commercialized handheld MS instruments by shrinking individual components of conventional instruments. The team's other achievements include important contributions to the development of tandem MS and ambient ionization MS techniques.

Tandem MS improves on the structural information available from conventional single-stage MS by fragmenting ions in two stages separated in space or time. The technique is a particularly powerful approach for the study of complex mixtures.

Cooks and coworkers also pioneered ambient ionization MS techniques such as desorption electrospray ionization and desorption atmospheric pressure ionization, in which molecular sampling and ionization are concerted, making it possible to analyze samples rapidly in air at room temperature with no sample preparation.

Cooks "has invented technology for quick chemical analysis that has applications ranging from medicine to food safety to national security," says Purdue President Mitchell E. Daniels Jr. "Advances made in his laboratory have not only shaped his field of science but also created tools to keep us safer and to make medical tests easier and treatments more precise."

The biennial Dreyfus Prize consists of $250,000, a citation, and a medal. Cooks will receive the award at a fall ceremony at Purdue.—STU BORMAN

EUROPEAN VINYLS GIANT EMERGES

PLASTICS: Solvay, Ineos say joining together will help them tough out a rough marketplace

IN A FURTHER CONSOLIDATION of the troubled European polyvinyl chloride industry, Belgium-based Solvay and Switzerland-based Ineos have agreed to pool their chlorine and PVC-related assets in a new joint venture.

The venture will be the second-largest PVC maker in the world, behind Shin-Etsu Chemical and just ahead of Formosa Plastics. The partnership will have $5.6 billion in annual sales and about $340 million in before-tax profits. It will operate 17 plants, all in Europe, and employ 5,650 people. The plants make PVC as well as raw materials such as chlorine, ethylene dichloride, and vinyl chloride.

The aim of the joint venture "is to improve its competitiveness in an environment which is, once again, a challenging one," Solvay CEO Jean-Pierre Clamadieu told stock analysts last week. Europe has been a tough region for PVC makers in recent years. According to Solvay figures, European demand for the plastic, used in construction materials such as pipe, has declined 30% since 2007. Another European PVC producer, Kem One, recently declared bankruptcy.

PVC demand is being hit on all fronts by the weak European economy, according to Janet Wright, chlor-alkali and vinyls business manager at the consulting firm Tecnon OrbiChem. "This has impacted industries such as construction and automobile production, which consume vast quantities of PVC," she says. "Governments have very little money to spend on infrastructure projects. Consumers are reluctant to spend on high-value goods such as cars and housing."

Ineos CEO James A. Ratcliffe hopes consolidation of the two units will help. "The newly combined business, which will be of world scale, will be able to better respond to rapidly changing European markets and to match increasing competition from global producers," he said.

Ineos, which is composed largely of the cast-off assets of large chemical companies, has been a consolidator in the European PVC industry. In 2011, it bought Tessenderlo's PVC operations. Earlier this year, it announced the closure of smaller PVC-related operations at various European plants.

The partners, however, don't plan to shutter manufacturing capacity, Clamadieu said. Instead, they will seek to reduce costs through greater purchasing power for raw materials and electricity.

For Solvay, the deal is a stepping-stone to an exit from the PVC business. In four to six years after the joint venture is formed, Ineos will have an option to buy out Solvay's share for 5.5 times earnings plus $325 million in cash. In February, Solvay revealed its intention to sell off its Latin American PVC affiliate, Indupa.

Solvay's interest in RusVinyl, a PVC joint venture with Russian partner Sibur, and its business in the packaging resin polyvinylidene chloride will not be included in the deal.

Neither of the parties is contributing any cash to the venture, though both are contributing liabilities such as debt and pensions.—ALEX TULLO

SOLVAY

Solvay's PVC plant in Jemeppe-sur-Sambre, Belgium.

BRITISH BIOSCIENCE AstraZeneca's Alderley Park site remade as multicompany biotech campus

Three U.K. biotech firms are moving to BioHub, a new bioscience center at AstraZeneca's Alderley Park research campus near Manchester, England. The influx comes less than two months after AstraZeneca disclosed that it is ending research at Alderley Park and moving the site's 1,600 scientists to other locations.

Redx Pharma, a Liverpool, England-based drug discovery and development firm, is creating a subsidiary, Redx Anti-Infectives, that will locate in BioHub. The new business will establish a $16 million R&D center where a team of 119 scientists will develop drugs for combating antibiotic resistance and new medicines for viral infections. Redx has secured a $7 million grant from the U.K. government's Regional Growth Fund. AstraZeneca "made a compelling commercial case to attract us to Alderley Park," says Redx CEO Neil Murray.

Imagen Biotech, a drug discovery firm and provider of screening technologies for the pharmaceutical industry, and Blueberry Therapeutics, a drug discovery firm targeting medicines for unmet medical needs, have already moved to Alderley Park. With assistance from a government task force, AstraZeneca plans to attract more science companies to the site.

Plans to repurpose Alderley Park as a biotech hub are similar to those that followed Pfizer's 2011 closure of an R&D campus in Sandwich, England, a move that eliminated about 1,500 science jobs. More than a dozen biotech firms have since moved to the Sandwich site, where benefits include company tax relief.—ALEX SCOTT

ORPHANS FIND A HOME

After years of neglect by pharma companies, **RARE DISEASE TREATMENT** is coming into the limelight

LISA M. JARVIS, C&EN NORTHEAST NEWS BUREAU

ONE AFTERNOON A WEEK, usually on a Tuesday, a nurse arrives at the Elmwood Park, N.J., home of Jeff and Deena Leider to give their sons, Justin and Jason, their "muscle juice." On each visit, she carefully inspects a handful of vials, empties them into an intravenous bag, and calibrates a pump that will slowly dole out the bag's contents. Justin, who at four is the younger of the boys, is the first to be hoisted onto the kitchen counter. After taking off his shirt, he sits, swinging his legs and patiently waiting for his superpowers to be activated.

The nurse, whom the boys clearly adore, gently removes a bandage on Justin's chest, revealing a small bump that allows her to home in on his implanted IV port. After she inserts an IV line, Justin pulls his shirt back on and shrugs on a Batman backpack holding the IV bag and the pump. Fully suited up, he reaches for a reward of a sour gummy worm and hops down. Minutes later, Jason takes his place on the counter, and the nurse repeats the process with him.

For the next four hours, while Justin and Jason go about their evening routine with their matching backpacks in tow, their muscle juice—known to technical-minded grown-ups as Shire's drug Elaprase—slowly infuses into their bloodstream. The superpowers it imparts make it easier for them to run, jump, and climb like other kids their age.

The boys have Hunter syndrome, a rare and fatal genetic disease caused by a deficiency in an enzyme that breaks down sugar molecules. The missing enzyme is just one of more than 100 housed in the lysosome, the cell's waste bin. Today, some 50 different inherited diseases—known broadly as lysosomal storage diseases—are caused by genetic mutations that disable one of those enzymes.

In Hunter syndrome, which affects only boys, the buildup of sugar molecules over time causes symptoms such as stiff joints, enlarged spleens, and difficulty breathing. For children like Justin and Jason, who have a form of the disease that affects the brain, the accumulation also causes a rapid decline in mental function. And it's rare—just one in 155,000 boys are born with the disease.

Elaprase replaces the missing enzyme, iduronate-2-sulfatase, buying the boys valuable time by shrinking their spleens and helping their heart and lungs function. Yet it won't save their lives. Elaprase can't get past the blood-brain barrier, the cellular security gate that protects our most complex organ, so it can't stop the mental deterioration that will cause the boys to lose their ability to walk and talk. Most boys with Hunter syndrome die by age 15.

Elaprase is also breathtakingly expensive. As his sons run in circles through

LISA JARVIS/C&EN

ROUTINE A nurse gives Jason Leider his weekly dose of the treatment Elaprase, while his brother, Justin, watches. They are two of only a few hundred boys in the U.S. with Hunter syndrome. The boys carry backpacks containing an IV bag with the drug, which takes four hours to infuse into their bloodstream.

the kitchen and living room, Jeff Leider holds up a small glass vial filled with clear liquid. "That's, like, $10,000 right there," he says, eying the bottle with a mix of awe and disbelief. Having two kids with Hunter syndrome who need several vials per treatment, the Leiders' annual bill approaches $1 million. Deena's insurance covers the bulk of the cost, and Shire, the drug's manufacturer, takes care of the rest through a patient assistance program.

Two-and-a-half years after Justin and Jason's diagnosis of Hunter syndrome, the high price of treatment and its limited effectiveness have led the Leiders to start a nonprofit and to lobby Congress to make it easier for children to get diagnosed and for drugs to be developed.

That has put the Leiders in the middle of a movement that is creating new treatments for even the rarest of diseases. Because they afflict so few people, thousands of diseases have been ignored for decades. Now, a shift in big pharmaceutical companies' business models away from multi-billion-dollar blockbuster drugs is coinciding with a deeper understanding of the genetic underpinnings of rare diseases. And government policies introduced just last year have created new incentives to serve small patient populations.

The collision of factors has made rare disease drugs one of the fastest-growing areas of drug development. Orphan drugs will account for 15.9% of all branded-drug sales by 2018, up from just 5.1% in 1998, according to the health care consultancy EvaluatePharma. In five years' time, orphan drugs will be a $127 billion-per-year business, the firm says.

The surge in interest is made possible by the inverse relationship between patient population size and drug price. The high price for a treatment like Elaprase, which runs well into six figures, annually, per person, might raise eyebrows for those not immersed in the rare disease world. Because Hunter syndrome affects such a tiny group, Shire charges a high premium for Elaprase to offset the risk and cost of developing it.

The pricing paradigm has put rare diseases on drug companies' radars. Even with few patients, there is money to be made. As big pharma tries to reinvent itself in an era of few blockbuster drugs, that's an attractive proposition.

When the Orphan Drug Act was introduced 30 years ago to create incentives to develop treatments for diseases with patient populations of less than 200,000, the drug pipeline for the estimated 7,000 rare diseases was barren. Even as recently as a decade ago, the number of major companies committed to developing drugs for rare diseases could be counted on one hand.

But as Christopher P. Austin, director of

the National Institutes of Health's National Center for Advancing Translational Sciences (NCATS), declared at an event in February marking World Rare Disease Day, such illnesses are no longer in the wilderness.

NIH and the Food & Drug Administration are trying hard to foster innovation and clear the drug development path for often-overlooked patient populations. Last year, FDA was granted a new set of tools that stakeholders describe as the most important advancement in promoting rare disease development since the Orphan Drug Act.

Patient advocates are the common denominator pulling together the rare disease movement. Their role in raising awareness and encouraging drug development has been critical to piquing the interest of both academia and industry.

Sometimes, patient advocates simply try to raise awareness so that others can be diagnosed and treated earlier. According to a recent study conducted by Shire, a specialty pharmaceutical firm with a large presence in rare diseases, it takes on average 7.6 years and eight physicians for people with a rare disease to be diagnosed. Often, they get two or three misdiagnoses before someone can tell them what's really going on.

The Leiders' foundation, Let Them Be Little x2, puts a spotlight on Hunter syndrome, with the hopes that awareness will prompt more research and, eventually, a cure. "I had a choice to make," Jeff Leider says. "I could go in a closet and hide from this evil world, or I could scream and yell as loud as I possibly can so that somebody will hear me."

Others are going further by directly funding research, setting up patient registries that can be useful for clinical trial recruitment, and even starting companies. They've pushed the government to adjust its policies to fit the current state of drug development for rare diseases, pointing to the estimated 10% of the population suffering from a rare disease as evidence for the common good the changes would bring.

They connect previously disparate research, invent new models for collaboration, and use social media to make their voices heard. They tick off acronyms for government programs like true Washington, D.C., bureaucrats, and they speak about research for their disease like Ph.D. scientists. Without their efforts and collaboration, company executives say, drug development would be difficult, if not impossible.

For these patient crusaders, the motivation is clear: They are in a race for their loved ones' lives. Jeff and Deena wince each time they see a Facebook photo of a friend's child with the caption, "Time Flies." That casual two-word refrain from fellow parents is another reminder that time is running out for their boys.

LISA JARVIS/C&EN

STICKER SHOCK Elaprase, Shire's enzyme replacement treatment for Hunter syndrome, is one of the most expensive drugs in the world.

THE BUSINESS OF RARITY

The current groundswell of interest in rare diseases can be traced to Genzyme, the first firm to show that drugs for small patient populations could be profitable

ANYONE PUZZLING over the business case for developing drugs for tiny patient populations need look no further than Genzyme. Founded in Boston in 1981, the biotechnology firm pioneered the model for rare disease drug development that is followed today: make an impact on a previously untreated rare disease, charge high prices, and be rewarded with significant revenues and a long reign in the marketplace.

Genzyme made its mark by introducing the first treatment for Gaucher's disease, a lysosomal storage disease caused by a deficiency in the lipid-busting enzyme glucocerebrosidase. Similar to Hunter syndrome, Gaucher's occurs when the absence of that key enzyme causes a buildup of molecules in the lysosome and results in a variety of problems. Complications from Gaucher's include enlarged organs, bone pain, and anemia.

When Genzyme embarked on developing an enzyme replacement therapy for type 1 Gaucher's, which does not affect the central nervous system, the disease was thought to affect just 1,500 people worldwide. Conventional wisdom at the time was that a company could not turn a profit on a drug for such a minuscule patient population.

But the naysayers were proven wrong. The Food & Drug Administration approved the drug in 1994, and Genzyme charged an unprecedented $200,000 per year. Although insurance companies balked at the cost, they eventually agreed to cover it. Companies like Genzyme ensured patient access by introducing assistance programs that helped families with potentially high copays.

With a treatment on hand, the diagnosed patient population more than tripled, reaching roughly 5,000 people, industry watchers say. Moreover, Genzyme had a captive audience: The first competition for its drug, Cerezyme, didn't arrive until 2010, when Shire won approval to sell a rival, Vpriv. At their peak in 2008, annual sales of Cerezyme reached $1.2 billion.

The success of that model—a small, genetically defined patient population and a high-priced drug—spawned two other companies that continue to be mainstays in the rare disease arena: Transkaryotic Therapies, founded in Cambridge, Mass., in 1988 and acquired by Shire for $1.6 billion in 2005, and BioMarin Pharmaceutical, started in 1997 in Novato, Calif. Together, Genzyme, Shire, and BioMarin have gone on to develop some of the most expensive drugs—all enzyme replacements.

Those three firms laid the foundation for the current corporate interest in rare diseases. Alumni from Genzyme now populate the executive suites of many of the companies focused on rare diseases. Notably, the chief executive officers of Aegerion Pharmaceuticals, Amicus Therapeutics, Prosensa, and Synageva BioPharma all had stopovers at Genzyme.

But all this activity isn't just about high premiums, says Austin of NCATS. "I think people have really internalized the concept that rare diseases are a window into common diseases," Austin says. Rare genetic disorders occur when a gene is completely turned off; more common diseases often happen when that same gene's function is simply turned down.

He points out that the first scientific clue in the development of cholesterol-lowering drugs like Pfizer's Lipitor—for years the world's best-selling drug—was the discovery of a cluster of families with a rare, genetic mutation that causes very high levels of "bad" cholesterol.

Rare disease advocates have taken that concept to heart. Hunter syndrome belongs to a collection of more than a dozen diseases, each caused by a deficiency in a different sugar-busting enzyme. Many of these so-called mucopolysaccharidosis (MPS) diseases primarily affect the brain, and patient groups trying to win funding for MPS research often point to the connection between MPS diseases and common neurological disorders.

In 2009, for example, University of California, Los Angeles, scientists discovered that children with a type of MPS disease called Sanfilippo syndrome produce high levels of tau, one of the two telltale proteins found in the brains of people with Alzheimer's disease.

The link means that better understanding the mechanism of Sanfilippo could lead to treatments for Alzheimer's. At a recent lobbying day for rare disease advocates, Jill Wood, a mom from Brooklyn whose son has Sanfilippo type C, also known as MPS IIIC, tried to impress upon her local congressmen that although Sanfilippo research might directly affect only a few dozen children in the U.S., the greater good for society makes it a worthwhile investment.

Congressional staffers' eyes clouded when Wood uttered words like mucopolysaccharidosis. They sat up and listened when she said Alzheimer's.

Although rare diseases could open the door to treatments for common ailments, the flip side is that common diseases are starting to be segmented into smaller subpopulations on the basis of genetics. "The paradigm for orphan drug development today may become the paradigm of more common drug development tomorrow," says Philip J. Vickers, global head of R&D for Shire's rare disease unit.

Industry experts like to hold up lung cancer as an example of this shift. As scientists pick apart the different biological drivers of lung cancer, they can provide more personalized treatments for the nearly 230,000 people diagnosed with the disease each year.

Pfizer's Xalkori, a drug designed to treat roughly 7% of lung cancer patients whose disease is caused by a mutation in the ALK gene, illustrates how segmenting can be profitable. Because the drug makes such a dramatic impact on patients' survival, Xalkori reached the market just four years after the discovery of the ALK mutation. Clear efficacy data and a small patient population enabled Pfizer to slap a $9,600 monthly price tag on the treatment. Consultancy firm EvaluatePharma expects that Xalkori will bring in more than $900 million in annual sales by 2018.

"Rare diseases in some ways set a template for the future," says Kevin Lee, chief scientific officer of Pfizer's rare disease group. "We believe we're going to learn far more about some of these basic diseases, which will allow us to segregate them much more specifically by molecular mechanism. Ultimately, these large diseases will become constellations of many small diseases, all of which have the same symptoms."

Meanwhile, scientific understanding of rare diseases has grown by leaps and bounds. Although the Human Genome Project failed to deliver on the promise of clear drug targets for common diseases, the rapid gene-sequencing and publicly available data it spawned have enabled scientists to swiftly figure out the underlying cause of many rare diseases, NCAT's Austin says. Two decades ago, scientists had teased out the molecular basis for fewer than 50 rare diseases, Austin says; today, they know the genetic underpinnings for roughly 4,500.

"That is a complete sea change," Austin says. "Thirty years ago, when I was in training, I saw patients with these rare syndromes that were characterized in really arcane, clinical ways. We had no idea what the molecular basis was."

That jackpot of genetic information has drawn new players to the rare disease space. Agios Pharmaceuticals, for example, saw exploring genetically defined rare metabolic diseases as a natural progression for its drug discovery platform, which was built to tackle cancer cell metabolism. At the same time, small patient populations mean Agios can develop its own pipeline of drugs without the infrastructure needed to commercialize treatments for more common diseases.

Investors like the strategy. In late 2011, Agios was able to raise $78 million to support its foray into rare diseases.

& MORE ONLINE See images of the patients and hear scientists and parents talk about their challenges at http://cenm.ag/rare.

RARE DISEASES BY THE NUMBERS

A disease is defined as orphan in the U.S. when it affects fewer than **200,000 people**

There are approximately **7,000 types** of rare diseases and disorders

95% of rare diseases have no FDA-approved drug treatment

80% of rare diseases are genetic in origin

Approximately **50%** of those affected by rare diseases are children

30% of children with a rare disease will not live to see their fifth birthday

8: Average number of physicians visits before diagnosis

3: Average number of misdiagnoses

7+ years: Average time until diagnosis

SOURCES: National Organization for Rare Diseases, Global Genes Project

Big pharma's interest in rare diseases took longer to foment. When Summit Corp. was spun off from England's Oxford University in 2003 to develop drugs for Duchenne muscular dystrophy, a fast-moving muscle-wasting disease, it was clear that "big pharma just wouldn't look at a disease like DMD," says Andrew Mulvaney, a Summit cofounder and its director of business development. At the time, the biotech firms working on rare diseases were largely focused on lysosomal storage diseases, where the orphan drug model had been proven.

Today, a race for FDA approval between two firms—Prosensa and Sarepta Therapeutics—with drug candidates that treat a small slice of the DMD population is one of the closest-watched competitions in the biotech industry. And Summit, which has a drug with the potential to treat all children with DMD, suddenly finds itself being courted by big pharmaceutical companies, Mulvaney says.

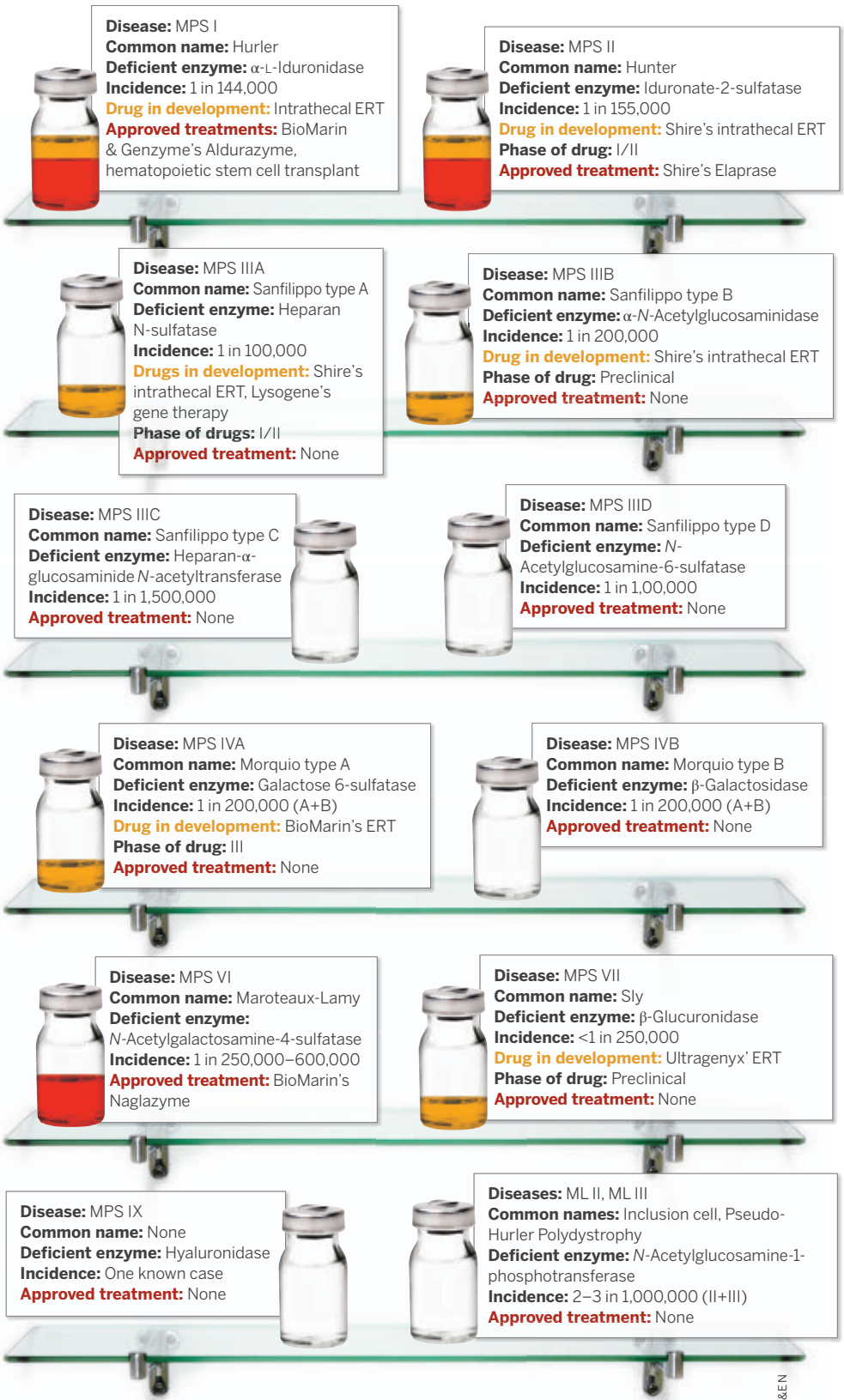
The shifting interest comes as big pharma struggles to get new drugs across the finish line to offset revenue losses as, one after another, its blockbuster products lose patent protection. Suddenly, orphan products, including those for the rarest of the rare diseases, carry appeal.

In 2010, GlaxoSmithKline and Pfizer became the most visible new players when they formed dedicated rare disease units. Others, such as Roche, have made a series of deals that collectively amount to a sizable rare disease portfolio.

But it was Sanofi's purchase of Genzyme for $20 billion in 2011 that really put the spotlight on rare disease assets, according to Ritu Baral, a stock analyst at the investment firm Canaccord Genuity.

Venture capital firms have become equally enchanted with the rare disease space. Not only is significantly more venture capital being devoted to rare disease drugs today than in the past, "but I think there's more venture capital money for orphan drugs than for any other type of drug, save oncology," Baral says.

Some firms have even started funds specifically targeting rare diseases. Among the biggest moves was a partnership between Atlas Venture and Shire to make early-stage investments in rare disease opportunities. And just last month, New Enterprise Associates and Pfizer Venture Investments committed $16 million to Cydan, which will pluck rare disease projects from academia and start companies around the most promising ideas.



SHUTTERSTOCK/C&EN

TREATMENTS These 13 mucopolysaccharidosis diseases are caused by a deficiency in an enzyme that breaks down sugar molecules. Expensive enzyme replacement therapies are approved for three MPS diseases. But none of the marketed drugs address the neurological effects of MPS.

ERT = enzyme replacement therapy. **SOURCES:** Companies, *J. Am. Med. Assoc.*, MPS Society, NIH

Figures for how much money has been poured into drugs for rare diseases are hard to come by. Many drug development pacts have been inked, but even venture capital firms working in the space can't quantify the overall investment, a kind of hand waving that contributes to worries that interest in rare diseases is a fad.

One statistic everyone touts is growth in R&D projects. According to a recent report by the Analysis Group and Pharmaceutical Research & Manufacturers of America, a drug industry trade association, 1,795 projects in the clinical pipeline as of October 2011 had orphan designation. And between 2001 and 2010, the number of products with orphan designation grew 10% annually, despite a decline in the total number of drug candidates during that period.

PATIENTS IN THE DRIVER'S SEAT

Although companies ultimately bring treatments to market, it's patient groups that are creating the awareness needed to start the drug discovery process

MOST PEOPLE think of a patient advocate as someone who is raising money for a charity. Many e-mail in-boxes and Facebook pages contain pleas for donations to the latest walk for breast cancer awareness or bike ride for AIDS research. But in the rare disease space, patient advocates aren't just walking in the 5K, they're organizing it and immediately sending the proceeds to a researcher. They tweet, they blog, and they create apps to update patients on research or keep tabs on clinical trials.

Jill Wood's son, Jonah, was diagnosed in May 2010 with Sanfilippo syndrome type C, one of four subtypes of mucopolysaccharidosis (MPS) III, each of which is caused by the lack of an enzyme needed to break down heparan sulfate. No treatments exist for Sanfilippo, and although the subtypes progress at different rates, each type leads to dementia and loss of motor function. Ultimately, patients succumb to the disease in adolescence or early adulthood.

"He's in the prime of his life at four-and-a-half years old," Wood explained to congressional staffers at a lobbying event in Washington, D.C., during a week of activities in February marking World Rare Disease Day. "This disease will progress substantially over the next few years. He'll most likely be confined to a wheelchair, feeding tube, and won't really know who I am by the time he's 15 years old."

Whether it's to a congressman or a reporter, Wood speaks about Jonah's disease with urgency, rattling off scientific facts at a speed that can be disorienting for rare disease newbies. After she walks away from a group, there's often a moment of stunned silence while people digest what they've heard, followed by a quiet comment: "Wow. She is amazing."

She's also quick to laugh and has a warmth that inspires people to join her fight for Jonah. Indeed, in the three years since Jonah's diagnosis, Wood has amassed a network of collaborators whom she groups into three categories: "my scientists," "my moms," "my mentors." With their help, she started a nonprofit that has raised substantial money for Sanfilippo type C research. More recently, she founded a virtual biotech company to develop any drug candidates that might arise from their work.

DODI HOLM/RUSTIC PEAR PHOTOGRAPHY

SUPPORT Jonah's mom, Jill Wood, is fighting for her son's life. Her foundation, Jonah's Just Begun, supports academic drug discovery efforts for Sanfilippo type C.

Wood is part of a legion of advocates taking on more active roles in the drug development process. Patient advocates "really are at the core" of the recent progress in rare disease R&D, according to Stephen C. Groft, director of the National Institutes of Health's Office of Rare Diseases. Because of their hard work and determination, he says, "all of a sudden, there are a lot of pieces of the puzzle coming together."

Their motivation springs from necessity. Not all 7,000 rare diseases attract the same level of attention or offer the same commercial potential.

Under the Orphan Drug Act, a drug developed for any disease that affects fewer than 200,000 people is eligible for orphan designation. When created 30 years ago, the legislation was intended to draw orphan diseases out of the wilderness by creating incentives to develop drugs for small patient populations. A drugmaker that wins approval for an orphan drug enjoys seven years of marketing exclusivity regardless of its patent status, gets a waiver for the fee the Food & Drug Administration charges when a New Drug Application is filed, and is granted tax credits for half the cost of the drug's development.

The incentives have worked: Whereas just 10 treatments for orphan indications were approved in the decade before the act was introduced, more than 400 have come to market in the subsequent 30 years.

But there's the legal definition of an orphan disease, and then there's the reality that not all diseases have the same commercial potential. In the post-blockbuster-drug era, it's a no-brainer to take on a disease with a patient population nearing 200,000, no existing treatments, and reasonable science behind it. Convincing companies to invest in a disease affecting only 200 people is a much harder sell.

The 7,000 rare diseases include a long tail of disorders that affect anywhere from

a few dozen to a few thousand people. The tiniest patient populations struggle to get NIH funding for the kind of research that can spark interest from industry. Even if academic research efforts are under way, advocates think the regulatory incentives aren't enough to catch the eye of industry. "The Orphan Drug Act is great, but it doesn't meet our needs yet," Wood told her state's representatives at the lobbying day.

Some advocates for diseases with tiny patient populations have started to identify themselves as part of the "ultrarare" community. The term carries no legal significance, Groft warns, but patient advocates say it helps them unify the thousands of disparate patient groups. Alone, they are the orphans of the orphans. Collectively, their voice has heft.

The divide between the rare and the ultrarare became crystal clear for Wood in May 2010. When Jonah was diagnosed with Sanfilippo type C, which affects just a few dozen kids in the U.S., she was heartbroken to learn that not only were there no treatments, but scant research was under way to find them.

Her response was to take action. Just months after Jonah's diagnosis, Wood's mom and her best friend organized a wine-tasting fund-raiser in Oregon. With their help, by August 2010 Wood had pulled together $20,000, started a nonprofit called Jonah's Just Begun, and wrote her first check to a scientist.

The money went to University of Montreal biochemist Alexey Pshezhetsky, one of two researchers who popped up on Wood's Internet search about the disease. In 2006, Pshezhetsky and his team discovered the genetic mutations that cause Sanfilippo type C, in which an enzyme called heparan-α-glucosaminide *N*-acetyltransferase (HGSNAT) is lacking.

Pshezhetsky was able to turn Wood's $20,000 gamble into a five-year grant from the Canadian Institutes of Health Research. The $130,000 in annual funding from the government agency helped the scientist better understand the pathology of the disease and create a mouse model for Sanfilippo type C, a critical tool if a drug is going to be developed.

Researchers have shown that sugar molecules don't aggregate in the cells of Sanfilippo type C mice that make as little as 10% of the normal amount of HGSNAT. With this in mind, Pshezhetsky is looking for drugs that can assist the faulty enzyme produced by Sanfilippo patients. This "chaperone therapy" approach is being pursued for several lysosomal storage diseases and is the basis of Amicus Therapeutics' drugs in development for Fabry and Gaucher's diseases.

"How long can you keep going to your tight-knit supporters of family and friends and ask for compassion for your story?"

Meanwhile, Wood teamed up with three other families with Sanfilippo type C foundations—based in Massachusetts, France, and Spain—to jointly fund drug discovery and development efforts in labs across the globe. They brought researchers together for the first time with patients and physicians and in the past three years have supported many approaches to tackling the disease. In addition to Pshezhetsky's chaperone therapy, they have high hopes for a gene therapy project by stem cell specialist Brian Bigger at the University of Manchester, in England, and separate efforts by two scientists at the Telethon Foundation, in Italy.

Together, the four family-run organizations have sunk roughly $500,000 into Sanfilippo type C research over the past two-and-a-half years. Wood has even started a company, prompted by a chance encounter at a conference with former pharma researcher Sean Ekins.

They launched Phoenix Nest last year. For now it's inactive while the families wait for their investments in academic science to pay off. If one of the projects is promising and an industry partner doesn't step in to support it, the idea is to develop it through Phoenix Nest.

The bootstrapping done by Wood and her partners reflects an increasingly common approach to early drug development. They are walking in the footsteps of venture philanthropy pioneers like the Cystic Fibrosis Foundation and nonprofits supporting Duchenne muscular dystrophy (DMD).

CF Foundation, which began investing in drug discovery efforts in 1998, reached the ultimate goal last year when FDA approved Vertex Pharmaceuticals' Kalydeco, the first drug to correct the underlying genetic defect in a subset of CF patients. Similarly, the DMD foundations are supporting several disease-modifying drugs, two of which are currently racing toward approval.

Small, family-run nonprofits look to larger organizations with both awe and envy. The hundreds of millions of dollars raised to support CF research seems out of reach for nonprofits supporting diseases with names that are hard to pronounce and that personally touch so few. Although rare disease groups have gotten creative to pull in funds, they see the limits to that approach.

"How long can you keep going to your tight-knit supporters of family and friends and ask for compassion for your story?" asks Lori Sames, who has raised millions of dollars to support Hannah's Hope Fund, a nonprofit focused on an ultrarare disease called giant axonal neuropathy. "That well can only get drained so many times."

Even as Wood and her collaborators move as fast as they can to develop potential drugs, they are keenly aware of the unlikelihood that any firm—be it biotech, venture capitalist, or big pharma—will be willing to risk trying to commercialize their product.

Dozens of patients may seem like an impossibly small market, but drug executives say the bar for corporate investment is dropping. At the time the Orphan Drug Act was passed, no one was interested in investing in diseases affecting fewer than 100,000 people, says John F. Crowley, chief executive officer of Amicus. Crowley, whose two kids have Pompe disease, was instrumental in bringing the first treatment for that lysosomal storage disease to market.

"Now, if you find something that's 1,000, it's a home run," Crowley says. "Really, the break point in the last couple of years has been 500 to 1,000—and now we're measuring sub-500."

Many in the rare disease field hold up Ultragenyx Pharmaceutical's ability to raise $75 million in venture funding in late 2012 as a sign that investors see opportunity in the ultrarare space. The company is pursuing a treatment for MPS VII, which affects just 200 patients in the developed world.

But Ultragenyx' CEO, Emil D. Kakkis, cautions against making sweeping assessments based on that product. "I'd say we're an outlier," he says. MPS VII affects tissues—the liver, spleen, and joints—that are accessible with an enzyme replacement therapy. "When you start talking about the bone and the brain, it becomes ever more difficult. Clinical trials are challeng-

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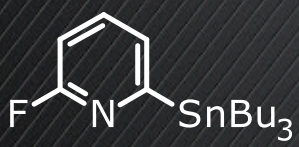

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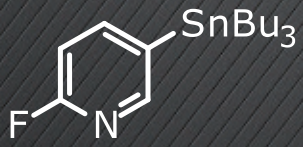

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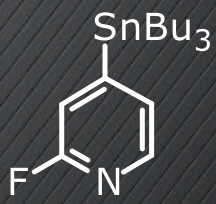

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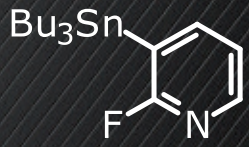

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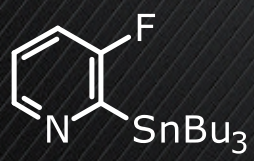

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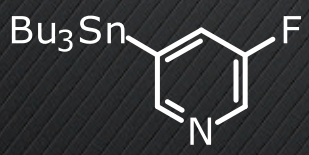

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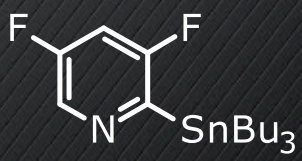

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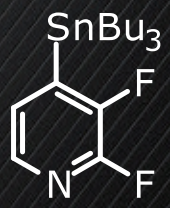

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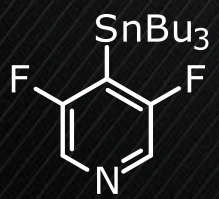

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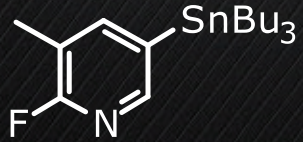

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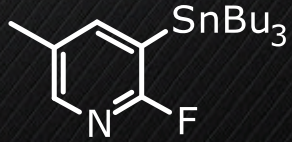

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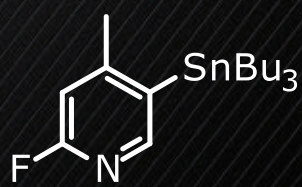

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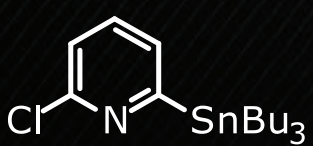

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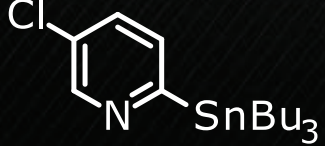

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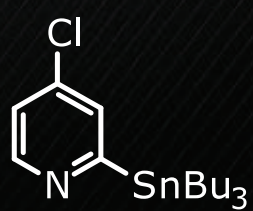

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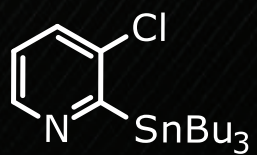

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ing, and the cost of doing them is high."

Kakkis, who earlier in his career developed Aldurazyme, a BioMarin Pharmaceutical product that was the first drug for an MPS disease, thinks the bar is higher. "You probably will have trouble getting financial support to do development for a disease with less than 500 patients in the developed world," he says.

And some observers are doubtful that big pharma firms will ever cross into the realm of the ultrarare. "It's not hard for me to imagine a big biotech company looking at a disease that affects 1,000 people in the Western world," says Philip R. Reilly, a partner at the investment firm Third Rock Ventures. "It's still hard for me to believe that big pharma would fit that into its portfolio."

Alvin Shih, chief operating officer of Pfizer's rare disease unit, says the firm doesn't have hard-and-fast rules to decide whether a project is commercially viable but rather asks a few key questions: Are there clear endpoints for a clinical trial? Are there enough patients for a trial? And are there advocacy groups that can help the company navigate the space? "When you're under 1,000 patients, it's tough to have all that," Shih says. A disease with several thousand patients is "more of our comfort zone."

One way to get around the commercial limitations of the ultrarare world is to find treatments or technology that can benefit more than one disease. Back when Wood first heard a doctor utter the words Sanfilippo type C, just one company was working on a treatment that might help her son.

Zacharon Pharmaceuticals, with financial backing from the nonprofit Team Sanfilippo Foundation, was trying to prevent the cellular buildup by developing small molecules that block the synthesis of heparan sulfate. An effective drug could treat all four subtypes of Sanfilippo, bringing it into the realm of commercial viability.

Developing technologies that could yield multiple drugs or address multiple patient populations underpins GlaxoSmithKline's efforts in rare diseases. The big pharma firm's establishment of a dedicated unit for rare disease research was a tacit acknowledgment that things must be done differently for this market.

With more traditional products, the commercialization plan is well defined, explains Mike Diem, head of business development for GSK's rare disease unit. "Take diabetes," he says. "GSK has been developing drugs here for many years, and we have a very simplified path we go down when we know a space well." With small patient populations and no existing treatments, companies are walking into the unknown. "You're defin-

GROWING INTEREST

Deals To Develop Rare Disease Therapies Have Proliferated In The Past Three Years

October 2009: In a pact worth up to $680 million, GlaxoSmithKline and Prosensa team to develop RNA-modulating therapies for Duchenne muscular dystrophy.

December 2009: Pfizer agrees to pay Protalix Biotherapeutics up to $115 million for worldwide rights to taliglucerase alfa, to treat Gaucher's disease.

February 2010: GSK launches a unit dedicated to developing treatments for rare diseases.

March 2010: GSK and Isis Pharmaceuticals establish a pact to develop antisense therapies for rare diseases.

June 2010: Pfizer establishes a dedicated rare disease unit.

September 2010: Pfizer acquires FoldRx Pharmaceuticals, which brings a portfolio of compounds to treat diseases caused by protein misfolding.

October 2010: GSK, the Telethon Foundation, and the San Raffaele del Monte Tabor Foundation join to develop gene therapies for rare genetic disorders.

October 2010: GSK partners with Amicus Therapeutics to develop Amigal, a small molecule to be used with enzyme replacement therapy for Fabry disease.

February 2011: Sanofi agrees to acquire Genzyme for $20.1 billion.

April 2011: The International Rare Diseases Research Consortium is established to help coordinate global efforts in rare disease research.

November 2011: Agios Pharmaceuticals raises $78 million to support a research effort around inborn errors of metabolism.

November 2011: Roche pays $30 million for worldwide rights to PTC Therapeutics' spinal muscular atrophy program.

December 2011: Shire and Atlas Venture team to identify and invest in early-stage rare disease therapeutics.

February 2012: GSK pays Angiochem $31.5 million as part of a deal to develop compounds that can cross the blood-brain barrier and treat lysosomal storage diseases.

June 2012: Roche and Seaside Therapeutics agree to jointly develop mGluR5 antagonists for the treatment of fragile X and autism spectrum disorders.

July 2012: Sanofi and Spain's Centre for Genomic Regulation sign a three-year research collaboration that emphasizes genetic and rare diseases.

November 2012: Shire and Boston Children's Hospital sign a three-year research pact to develop treatments for rare pediatric diseases.

November 2012: Pfizer and the Cystic Fibrosis Foundation establish a six-year preclinical research program to find drugs for people whose CF is caused by the ΔF508 mutation.

January 2013: Shire buys Cambridge, Mass.-based Lotus Tissue Repair, gaining a protein replacement therapy for the treatment of dystrophic epidermolysis bullosa.

January 2013: BioMarin Pharmaceutical acquires Zacharon Pharmaceuticals, gaining small molecules to block heparan sulfate synthesis for mucopolysaccharidosis disorders and ganglioside synthesis inhibitors for Tay-Sachs disease.

February 2013: Roche pays Chiasma $65 million up front for the rights to Octreolin, a peptide in a Phase III trial for acromegaly, a rare hormonal disorder.

February 2013: The European Commission sets aside $187 million in funding for 26 rare disease projects.

March 2013: Shire acquires Premacure, gaining a protein replacement therapy for a rare eye disease that primarily affects premature infants.

April 2013: Roche pays Isis $30 million as part of deal to develop antisense drugs to treat Huntington's disease.

April 2013: New Enterprise Associates and Pfizer Venture Investments lead a $16 million round of financing to launch Cydan, an orphan drug accelerator.

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ing the path as you go along," Diem adds.

To mitigate that risk and create a sustainable model for rare disease drug development, GSK has moved beyond the one-drug approach. Diem points to the company's collaboration with the Dutch biotech firm Prosensa as an example of how a technology-based approach can generate a whole pipeline of products. The companies are developing antisense therapies for DMD, a disease that is primarily caused by deletions of one or more exons in the DMD gene.

Much attention is focused on GSK2402968, the partners' lead candidate, which is in Phase III studies and addresses the roughly 13% of patients who have a deletion at exon 13 in the DMD gene. But behind that program are five or six additional therapies addressing other exon deletions. The regulatory path for the first drug will be rocky, but GSK is betting that it can "learn from the first one to develop the second, third, fourth, and others in a more efficient manner," Diem says.

GSK is replicating the approach in other collaborations. A partnership with Angiochem around peptide-drug conjugates that can cross the blood-brain barrier is focused on treating the neurological impact of lysosomal storage diseases. "If you're leveraging what you're learning along the way, something 'ultra orphan' theoretically could be viable in the scheme of building a platform around five or six products instead of one," Diem says.

Wood is well aware that attracting the attention of venture capitalists or biotech firms will require coming up with a drug or drug delivery method that could affect a larger patient group than the few dozen kids with Sanfilippo type C. She has one project up her sleeve that she thinks has a chance.

Montreal's Pshezhetsky recently found something unexpected in the brains of mice with the Sanfilippo type C mutation. As the central nervous system of the mice is progressively debilitated by the buildup of sugar molecules, the mice become hyperactive, fearless, and lose their ability to learn. But Pshezhetsky made a curious observation: The symptoms aren't caused by dying neurons.

That finding runs counter to common wisdom that the brain cells of Sanfilippo kids become clogged and die. The scientist hypothesizes that the buildup is instead causing defective synaptic transmission, or a disruption in the cross talk between brain cells, and he is searching for molecules that could protect or restore that neurological function.

Synaptic markers in the brain appear to be reduced in all four types of Sanfilippo. Moreover, Pshezhetsky thinks the effect could exist in the broader MPS population; academic studies are ongoing to confirm the hypothesis. He is also testing existing neuroprotective drugs to see whether any show signs of efficacy.

Wood, meanwhile, is still waiting for more news of Zacharon's heparan sulfate inhibitors. In 2011, Pfizer partnered with the biotech firm to develop rare disease drugs. The partnership gave Wood and other Sanfilippo families hope that big pharma was swooping in to speed the molecules through development. But that deal ran into trouble, and in the end, investors sold Zacharon to BioMarin.

Despite the new owner's long-standing commitment to rare diseases, Wood is worried that research momentum has slowed. The relationship she had developed with Zacharon's research chief, Brett Crawford, has changed. Now, when Wood runs into Crawford at conferences, she dissects his every sentence and parses his every gesture, trying to get a sense of what's going on with the program. "You just try to analyze everything," she says. "Nobody can tell us what's happened, so there are lots of rumors going around."

BioMarin says heparan sulfate inhibitors are an active project but that it is still in the process of optimizing the molecules. "It is too early to predict when, or even if, we will be successful at making a compound suitable to move into clinical development," the firm says.

THE REGULATORY FRONT

Patient advocates and companies are encouraged by the recent introduction of new regulatory tools to speed the development of drugs for rare diseases but worry they may not go far enough for the smallest patient groups

EVEN AS JILL WOOD breathes a little easier knowing several drug discovery programs to treat her son's rare disease, Sanfilippo syndrome type C, are under way, she's also aware that the hardest part is yet to come. Testing a drug in kids for rare diseases and gathering enough evidence to convince the Food & Drug Administration it is safe and effective is no cakewalk.

Trying to win approval by showing that disease progression has slowed or stopped is one of the bigger challenges in the rare disease space. Patient populations are often heterogeneous, meaning everyone declines at different rates and with different symptoms. With so few patients and so much variation, it's difficult to choose endpoints for a clinical trial that can show a drug is, statistically speaking, making a difference.

Few clinicians know the challenges better than Joseph Muenzer, a pediatrics professor at the University of North Carolina, Chapel Hill. Muenzer has run clinical trials for several mucopolysaccharidosis (MPS) enzyme replacement therapies, including Aldurazyme, for MPS I, and Elaprase, for MPS II, or Hunter syndrome.

Muenzer's experience with treating certain MPS diseases is so vast that his office is often the first stop for families with a recently diagnosed child. As Jeff Leider, whose two sons recently enrolled in a UNC study of the cognitive progression of boys with Hunter syndrome, puts it, "He's the guru."

Now Muenzer is contributing to the development of Shire's HGT-2310, an enzyme replacement therapy for Hunter syndrome that is delivered directly into the spinal canal. Known among Hunter families as the IT trial because it is administered intrathecally, the study is intended to address the neurological effects of the disease.

Last month, on a sunny day in Chapel Hill, Muenzer was sequestered inside UNC's North Carolina Children's Hospital to give two boys in the study their monthly dose of HGT-2310. One of the boys was Case Hogan, a deliciously rambunctious six-year-old who, that morning, was darting around the hospital in red cowboy boots and a hat.

After about an hour of shuttling between rooms to check Case's vitals and go over a long list of questions from Case's mom, Melissa Hogan, Muenzer was ready to get the show on the road. A crew of nurses trailed the lanky physician into yet another room, where he hopped up on an examining table and lifted Case up next to him.

Hogan hovered over Case, who clutched his DVD player, not wanting to shift his focus from "The Princess Bride." A mask delivering anesthesia was placed over Case's mouth, and as he squirmed in protest, Hogan and the nurses broke into song to soothe him. After three short rounds of "You Are My Sunshine," Case was out.

LISA JARVIS/C&EN

BRAVE COWBOY Case Hogan, who loves his red cowboy boots, rests after his dose in a clinical trial to treat the neurological effects of Hunter syndrome.

The nurses quickly slipped off his cowboy boots—purchased days earlier in Gatlinburg, Tenn., during the family's trip from their home in Nashville to the hospital—and Hogan left the room to let Muenzer work his magic.

More than two years into Case's participation in the IT study, the team has this routine down pat.

Between April 2010, when the family first suspected he might have Hunter syndrome, and early 2011, when he entered the clinical trial, Case's mental decline was precipitous. He began to stutter and lose words, going from nine-word sentences to two- or three-word phrases. Hogan looks back at photos from a family vacation about a week before they realized Case might have an MPS disorder and sees a boy who looks vacant.

But by winning a spot in the clinical trial, the Hogans now have reason for hope. On each visit, Muenzer draws out a bit of spinal fluid—or, as he calls it, liquid gold—that he sends to Shire for analysis. Muenzer then injects a dose of the enzyme that Case's body is unable to produce.

The entire process takes minutes, but for Hogan it's nothing short of a miracle. As she broadcasts on her blog, Saving Case, the changes in her son's behavior and cognitive ability were almost immediate after the first injection.

Two-and-a-half years into the study, Case can do simple puzzles, count to 20, and stay nimble on his feet. His behavior and ability to focus have improved as well. When he first arrived at UNC to be evaluated, Case was in a stroller with a six-point harness because he was too unfocused and hyperactive.

On their long drive to Chapel Hill last month, Hogan had a moment of panic when she thought she had forgotten something; then she took a breath and realized they were simply traveling like a "normal" family—no wheelchair stroller, no special equipment or food. Indeed, the boy sitting in the recovery room after the procedure eating pudding, flirting with the nurses, and generally charming anyone in his vicinity was far from vacant.

In March, Muenzer and colleagues presented early data from the IT enzyme trial at the American College of Medical Genetics & Genomics' annual meeting in Phoenix. They reported a drop in the level of the built-up sugars, glycosaminoglycans, in the cerebrospinal fluid of patients receiving two high doses of the enzyme, compared with high levels of glycosaminoglycans in four untreated patients.

Muenzer detailed signs of improvements in cognitive measures. Case is one of four boys in the small study who have shown stable or improved cognitive measurements. One child, who has been in the IT trial the longest, is now able to attend a regular kindergarten class, Muenzer notes.

Hogan is over the moon about Case's progress, which also has raised hopes in the Leider household that Justin and Jason, their sons with Hunter syndrome, might benefit from the approach. But Muenzer is cautious about the next steps for the drug. The looming question is what kind of data FDA will want to approve the treatment. The challenge will be to come up with appropriate endpoints, or measurements to prove a drug's efficacy, for an upcoming late-phase clinical trial, which Shire expects to begin by the end of this year.

As Shire considers the design of the trial, industry observers say the company's experience mirrors what other firms face when trying to develop drugs for rare diseases. Those with a history in rare diseases argue that the challenge of pulling together the right patients and designing the right trials to get drugs approved goes underappreciated.

Newcomers look at the relatively small trials and see an easy path to approval. According to a recent study by EvaluatePharma, a Phase III study for an orphan drug enrolls on average 528 patients; the average Phase III trial for a nonorphan drug enrolls 2,234 patients. And several drugs have been approved on the basis of studies with just a few dozen patients. Moreover, FDA offers a slew of incentives designed to trim the timeline and cost for getting a rare disease drug to market.

Rare disease veterans suggest tempering those rosy assessments. "It's a bit of a fal-

lacy that it's easier, or that the bar is lower," says Genzyme's Chief Executive Officer David Meeker.

The flip side of having so few patients is having only one chance to get things right. In April, Muenzer flew to Washington, D.C., to join Shire executives in a meeting with FDA to discuss the data needed to approve the drug. Earlier that day, Hogan quizzed him on what FDA wants. Muenzer, whose relationship with Hogan feels more like teacher and student than physician and parent, walked her through the complexities and realities of drug development for ultrarare diseases.

As he explained, all the kids in the study appear to have stabilized. They aren't all necessarily seeing the same cognitive improvements that Case is, but they also aren't declining. Yet that kind of soft measurement is unlikely to be enough to convince FDA that the IT delivery is working.

"I can't tell FDA at what rate they decline because we didn't ever have that quantitative data to say, 'Here's what we anticipate for this population,'" Muenzer says.

For more common diseases, information about patients is compared with a large pool of historical data culled from others with the disease. But another major challenge for rare disease drug development is the lack of understanding of the natural history of a rare disease—that is, how it progresses in the absence of medical intervention.

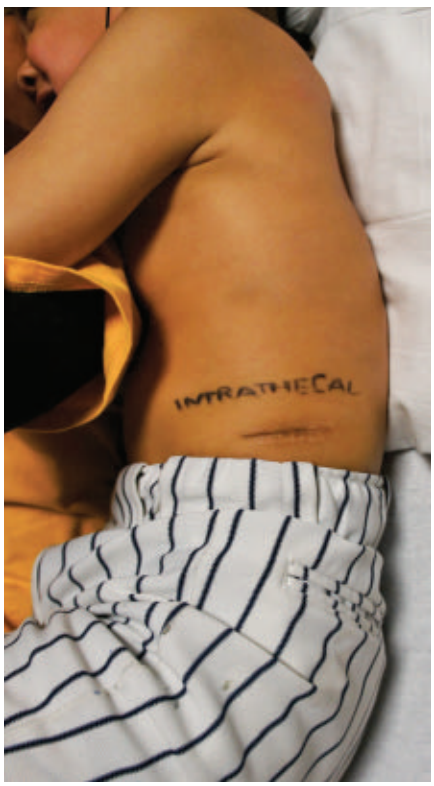
Companies usually have to conduct their own natural history study, an expensive and lengthy process in which a group of untreated patients is watched over time to determine what biomarkers could be useful in a clinical trial and to define endpoints that can show a potential drug is effective.

A natural history study is at the top of the mental checklist Wood keeps of things needed to get a treatment for Sanfilippo type C into the clinic. The consortium of families she works with is funding a natural history study of the disease, slated to start in the next month, that will collect the data they think will be essential if a drug candidate makes it into the testing clinic.

Wood is aware that a misstep in how resources are spent could cost both her son and other kids with Sanfilippo type C who haven't been diagnosed yet. "I'm the kind of person that jumps in headfirst, but I've found really fast that this is going to affect generations to come," she says. "I can't make rash decisions." She feels an immense pressure to get the design of the natural history study right.

"We'll never be able to do it again," Wood says. "We don't have the patient population to do it again."

Patient advocates are hopeful that FDA is becoming more willing to accept surrogate endpoints, or measurements such as biomarkers that suggest a drug is working, rather than data that directly prove that a potential treatment helps people live longer or feel better. They are encouraged by a series of incentives and changes introduced with the passage last year of the FDA Safety & Innovation Act, or FDASIA, which reauthorized FDA's ability to collect fees from industry.



LISA JARVIS/C&EN

MARKED Case Hogan has a medical tattoo to distinguish his two ports; one is for intravenous delivery of Elaprase, and the other is for intrathecal delivery of an enzyme.

Advocates are most excited about a measure that expands to rare diseases the accelerated approval path, which allows early approval of a drug on the basis of surrogate markers, and a measure creating "breakthrough status," an incentive to speed development of innovative drugs that show promise in early human studies. The legislation also calls for patients to have more of a voice in the review process.

The National Organization for Rare Disorders (NORD) calls FDASIA the most important piece of legislation for the rare disease community since the Orphan Drug Act. John F. Crowley, CEO of Amicus Therapeutics, puts it succinctly, "We've just turbocharged regulatory science."

FDA appears to be taking the leeway offered by the new law seriously. Between July 2012, when FDASIA was signed into law, and April 25, FDA received 39 requests for breakthrough therapy designation. All of the requests were reviewed within 60 days of receipt, and 11 treatments received the designation.

Still, FDASIA alone isn't enough to bring more rare disease drugs to market, says Anne Pariser, associate director for rare diseases at FDA's Center for Drug Evaluation & Research (CDER). "If you look at drug development and disease research along a continuum, a lot of the work goes on pre-FDA," she notes. New ways to involve the National Institutes of Health, academia, and other stakeholders will be equally important to finding treatments.

And rare disease veterans point out that the new incentives and tools introduced with the passage of FDASIA are, for now, largely theoretical. The policy "creates a framework which has a high potential to have a positive impact," says Philip J. Vickers, global head of R&D for Shire's rare disease unit. "But it's really a framework at the moment, and the details need to be worked out."

The devil is indeed in the details. Although the agency has been quick to hand out the breakthrough designation, no one is sure what the status means in practice. FDA also has agreed to include patient voices, but it has yet to define a role for advocacy groups. The question of the role of surrogate endpoints, like the ones that the Hogans and other Hunter families hope will be useful in a trial of Shire's drug, also remains.

Still, some executives are confident common ground is forming between companies and regulators about clinical trial design. Genzyme's Meeker sees FDA moving toward an era where data suggesting a positive effect, combined with changes in biomarkers, could be enough for approval. "I think increasingly there will be a willingness to allow these products to be approved," Meeker says, provided that companies commit to monitoring patients over time.

While families and companies worry about what regulators want, FDA officials

"More access to accelerated approval could reduce the cost of development by almost two-thirds."

point out that the agency has a long history of being flexible when reviewing New Drug Applications for rare disease treatments.

It's "a pretty common misconception" that FDA has the same expectations for rare disease drug applications as it does for ones for more common diseases, says Gayatri R. Rao, director of the Office of Orphan Products Development at CDER. "I think folks believe that two randomized, well-controlled trials will always be required, even for small patient populations."

That's true in cases where there are enough patients, Rao says. But more often than not, FDA is willing to work with companies to support a clinical program that makes sense for the disease. At the same time, patients and drug developers need to remember the efficacy bar is not lower just because patients lack treatment options, Pariser says.

She stresses that FDA has "a long and established record of flexibility" when it comes to small patient populations. Pariser points to a 2011 study by NORD as proof of FDA's willingness to adjust its standard mode of operation when it comes to rare diseases. NORD waded through the 135 noncancer orphan drugs approved between 1983 and June 2010 and found that the agency exercised a degree of flexibility in two-thirds of the cases.

Marc Beer, CEO of Aegerion Pharmaceuticals, is confident that the agency is evolving. Over the past two decades, he has participated in four review panels for orphan products, and in each case, "the FDA got it right," Beer recounted earlier this year at a conference in New York City. The agency took the time to understand the intricacies of each disease and understand the drug at a deep level, he noted.

The difference between the FDA of the early 1990s and the FDA that reviewed Aegerion's Juxtapid, approved last year for a rare form of high cholesterol, was the level of communication between the company and the agency. "It wasn't a 'pass it over the transom' type relationship," Beer said. "It wasn't just 'give us the data.'"

With more companies dipping their toes into the rare disease market, many question the ability for the inverse relationship between patient group size and drug cost to hold up. Already, some governments are toughening their stance on big-ticket drugs. The U.K., for example, agreed to cover the cystic fibrosis drug Kalydeco, which costs nearly $400,000 per year, only after a highly publicized campaign by patients. And although high prices are generally accepted in the U.S., more than 100 oncologists recently lodged a public protest over the cost of cancer drugs.

If scientists are to develop treatments for the 10% of the population that has a rare disease, the price of health care under the current model will skyrocket, warns Emil D. Kakkis, Ultragenyx Pharmaceutical's CEO. "More access to accelerated approval could reduce the cost of development by almost two-thirds," he says, citing a study he authored in *Orphanet Journal of Rare Diseases.* Instead of developing six or seven drugs with $1 billion in investment, 36 drugs could be developed, he adds.

"We need to find that place where there's comfort with the amount of data you really need and number of patients needed," Kakkis says, "and accept the fact that we can't spend hundreds of millions of dollars for every single rare disease and expect the system to work."

THE KIDS ARE WAITING

Progress can't happen fast enough for patient advocates, who worry that time is slipping away for their children

IF SHIRE DOES SUCCEED in getting the Hunter syndrome treatment HGT-2310 over the finish line, the door is opened for other lysosomal storage diseases where the brain is affected. The company is already testing an intrathecally (IT) delivered enzyme for Sanfilippo syndrome type A and has started a natural history study for Sanfilippo type B that could lay the groundwork for a clinical development program. "We're very actively considering other programs," says Philip J. Vickers, global head of R&D for Shire's rare disease unit.

Even the mention of other lysosomal storage diseases that affect the brain brings hope to a legion of parents. But hope is a tricky word. It leads to a roller coaster of emotions with guaranteed highs and impossible lows.

For Melissa Hogan, Shire's IT trial has fundamentally changed her outlook for her son Case. "When we started the trial, my whole goal was just to save his life. All I wanted was life," she says. Now, with the dramatic improvement she sees in Case, she's gone from no expectations to finding herself imagining her son as a grown man.

Around Christmas, someone sent the family a gift made by adults with special needs. Hogan was hit with the realization that Case could live and even have a job. And yet, she's afraid to hope and has a hard time not analyzing the tiniest details about her son's behavior and wondering whether the drug has stopped working.

Hogan's progress reports about Case have kept hope alive for Jeff and Deena Leider. But they are in a torturous holding pattern while Shire settles the details of the next IT trial. They worry that by the time it is under way, their sons' IQs won't be in the right range or that they will miss other criteria to be included. They worry that each day they have to wait, Jason, who is older and whose disease is more advanced, will not benefit from treatment.

With no treatments available for her son Jonah, Jill Wood is careful about the word hope. She prefers to talk about action. As she says, "I busy myself controlling the controllable."

Wood does believe that 2013 will be a big year for Sanfilippo research. Jonny Lee Miller, the star of "Elementary," a television show that Wood's husband, Jeremy, works on, agreed to fund-raise on behalf of Jonah's Just Begun in conjunction with an ultramarathon he ran earlier this month. Thanks to corporate sponsorships, Miller's tweets, and television appearances to promote the event, the nonprofit collected more than $130,000. Wood already has plans for every last dime and is plotting where the next influx of cash might come from.

But amid that momentum came a reminder of the urgency of her efforts. While in Oregon in March, Wood got word that another child with Sanfilippo type C died in her sleep. Mia Pruett, who was 19, had been high functioning and hadn't even been sick prior to her death. "I'm just heartbroken," Wood says. ■

ACRYLONITRILE FUMES KILL ONE IN BELGIUM

A 64-year-old man died and 116 other nearby residents were taken to the hospital as a result of exposure to fumes from burning acrylonitrile after a train carrying the chemical derailed and caught fire near Wetteren, Belgium. Hydrogen cyanide is generated when acrylonitrile burns. The incident happened in the early hours of Saturday, May 4, as the train was traveling from the Netherlands to the port of Ghent in Belgium. The acrylonitrile was made by DSM and was being transported in tank cars leased by the firm. "We deeply regret the incident," DSM says. Authorities are still investigating the cause.—AS

The derailed train carried acrylonitrile and butadiene.

BENOIT DOPPAGNE/AFP/GETTY IMAGES/NEWSCOM

KUWAITI COMPANY SETTLES UP WITH DOW

Dow Chemical has been paid $2.2 billion by Petrochemical Industries Co. of Kuwait over the failure of their planned K-Dow joint venture in late 2008. Dow expected to reap $7 billion from forming the joint venture, which would have been made up of the bulk of Dow's petrochemical operations. The Kuwaiti government scuttled the deal, and Dow turned to the International Chamber of Commerce to arbitrate the dispute. Dow has other ties with PIC, including Equate, a Kuwaiti joint venture that makes ethylene glycol and polyethylene.—AHT

CHEMIST NOT GUILTY OF SECRETS THEFT

An organic chemist charged with stealing trade secrets from his employer, Frontier Scientific, has been found not guilty. A judge for the U.S. District Court for the Northern District of Utah ruled that information for the manufacture of 2,2-dipyrromethane and other Frontier compounds that Prabhu Mohapatra e-mailed to a would-be competitor did not meet requirements to be considered proprietary information. Mohapatra pled guilty a year ago to unlawful access to a protected computer, and the Utah judge ordered him to pay compensation of $3,435 to his former employer.—MSR

LG READIES BATTERY PLANT

LG Chem Michigan says it will begin long-delayed production in July at its automotive lithium-ion battery cell plant in Holland, Mich. The business, a U.S. arm of South Korea's LG Chem, will supply batteries for General Motors' Volt, a plug-in electric hybrid. In 2010 the Michigan plant was awarded more than $150 million in funding from the Department of Energy and tax relief from state and local governments worth up to $175 million. Battery cell assembly was supposed to begin in 2012, and the plant was expected to employ 440 workers. But demand for the batteries was slow, and LG instead supplied GM from its factory in South Korea. In January, LG paid back $842,000 of the DOE grant after a government audit found that it had used the money to pay workers who "had little work to do and were spending time volunteering at local nonprofit organizations, playing games, and watching movies." LG Chem says it has set up three of five planned production lines at the site and is planning to attract more electric-vehicle business in the U.S. In 2012, GM sold 23,461 Volts, up from 7,671 in 2011.—MMB

BAYER WILL EXIT CARBON NANOTUBES

Bayer MaterialScience is winding down its carbon nanotubes business, saying it wants to focus on activities more closely linked to its core polymer operations. Bayer's nanotube assets include a $30 million plant it built in Leverkusen, Germany, in 2009. The company once had high hopes for nanotubes, but CEO Patrick Thomas now says the potential markets are either very fragmented or have little overlap with its core business. Bayer says it's in contact with parties interested in the know-how it has generated.—MM

FERRO, DISSIDENTS REACH AN AGREEMENT

Ferro and dissident shareholders Quinpario Partners and FrontFour Capital Group have buried the hatchet and now jointly support a revised slate of directors for election at the company's May 15 annual meeting. Ferro will now support the election of Quinpario's Jeffry N. Quinn and FrontFour's David A. Lorber. A third dissident representative, Nadim Qureshi of Quinpario, will not stand for election and instead a current Ferro board member will be the third candidate. After the election, Quinn, Lorber, and three yet-to-be-determined Ferro directors will form a committee to look at ways to enhance shareholder value. Sure to be considered is an unsolicited takeover bid made in March by the plastics company A. Schulman.—MSR

CHINESE PROTEST AROMATICS AGAIN

Residents of Kunming, in southwestern China, gathered on May 4 to protest the construction of a *p*-xylene plant by the state-owned conglomerate PetroChina. According to China's Xinhua news agency, 200 people took part in the protest while about 1,000 watched. Another report, on the website of the *People's Daily*, claimed that the Kunming government has not yet approved the project. In recent years, residents of several Chinese cities have protested in large numbers against *p*-xylene plants. The chemical is mostly used to make polyester fiber and plastics.—JFT

SHOKUBAI RESTARTS MORE PLANTS IN JAPAN

Japanese authorities have authorized Nippon Shokubai to reopen its methacrylic acid and methyl methacrylate facilities in Hime-

ji, Japan. The company had to shut down most of its Himeji operations after a deadly fire and explosion in an acrylic acid tank at the site in September 2012. At the time, the site accounted for about 20% of the world's supply of superabsorbent acrylic polymer (SAP), a material used in disposable diapers. The SAP facilities have yet to restart.—JFT

ICIG GETS ANOTHER TESSENDERLO BUSINESS

Belgian chemical maker Tessenderlo has sold its Tessenderlo Italia industrial chemical subsidiary to International Chemical Investors Group for an undisclosed sum. The business, which had sales last year of around $40 million, produces chlorinated aromatics and operates two hydroelectric power plants. Tessenderlo sold its pharmaceutical chemicals business to ICIG last year. ICIG, which already owns four sites in Italy, calls itself a significant customer of Tessenderlo Italia's and thus a natural owner.—MM

AESICA TAPS ACADEMIA FOR AMIDE SYNTHESIS

Aesica, a British contract manufacturer for drug firms, has formed a research partnership with England's University of Nottingham to develop commercial methods for amide bond synthesis. It is the firm's fourth collaboration with an academic institute in less than six months. The partners plan to introduce amide bond formation techniques that offer high chemical yields at lower cost and with less environmentally harmful reagents compared with existing processes. The new technology is based on a coupling agent developed by the university in 2005.—MM

AESICA

A researcher at Aesica's Cramlington, England, site.

TAKEDA CONTINUES PUSH INTO VACCINES

Japan's Takeda Pharmaceutical has agreed to acquire Inviragen, a Fort Collins, Colo.-based vaccine developer, for $35 million plus future payments of up to $215 million. Inviragen's lead candidate, now in Phase II clinical trials, is a four-strain recombinant viral vaccine for the prevention of dengue fever, a mosquito-borne illness. Building on a Japanese vaccine business, Takeda launched a global vaccine division in January 2012. Later that year it acquired LigoCyte Pharmaceuticals and its norovirus vaccine candidate.—MM

AMBRX AND BMS JOIN FOR DRUG CONJUGATES

Ambrx and Bristol-Myers Squibb have agreed to discover and develop antibody-drug conjugates using Ambrx' protein medicinal chemistry technology. In exchange for commercial rights, BMS will supply Ambrx $15 million up front, R&D funding, and up to $97 million per product upon reaching certain milestones. The two companies have worked together since September 2011 on the discovery of biologic drugs. As a result of that work, BMS is currently developing a potential diabetes drug and a heart failure treatment.—AMT

ASTELLAS SIGNS NOVEL DEVELOPMENT PACT

Astellas and Drais Pharmaceuticals will collaborate on the development of an Astellas compound that treats nocturia, a sleep disorder. Under the agreement, Astellas will license ASP7035, currently in Phase II clinical trials, to Tacurion Pharma, a virtual company operated by Drais. The deal is similar to two others Astellas entered with other Drais-run virtual companies, Telsar Pharma and Seldar Pharma, to develop drugs for ulcerative colitis and inflammatory bowel disease. Astellas and two venture capital firms, InterWest Partners and Sutter Hill Ventures, will invest a total of $15 million in Tacurion.—RM

BUSINESS ROUNDUP

OMV, an Austrian refiner, is investing $300 million to expand butadiene production at two of its refineries. It will build a new butadiene plant in Burghausen, Germany, and expand an existing plant in Schwechat, Austria. The company expects strong growth for the synthetic rubber raw material.

INTERNATIONAL Flavors & Fragrances will close its fragrance ingredients manufacturing facility in Augusta, Ga., by July 2014 and consolidate production in existing plants. The firm did not say how many jobs will be affected.

EXXONMOBIL has signed formal agreements regarding the sale of its biaxially oriented polypropylene film business to the Indian firm Jindal Poly Films for $235 million. BOPP films are used in packaging such as potato chip bags and cigarette boxes.

SOLAZYME, a developer of algae-derived oils, has formed a partnership with AkzoNobel to develop renewable oils for surfactants and coatings, two of Akzo's main businesses. Solazyme expects oils to be available from its Brazilian joint venture next year.

PIXELLIGENT Technologies, a maker of nanocrystal dispersions for electronic display, semiconductor, and industrial markets, has raised $5.1 million in a round of equity funding led by current investor Abell Foundation. The Baltimore-based company began commercial shipments earlier this year.

DSM has acquired a 19% stake in Yantai Andre Pectin, a Chinese producer of pectin, which is a texturizing agent derived from apple and citrus peels. DSM has the option to increase its stake to a majority at a later stage. Andre Pectin posts annual sales of about $40 million.

NIMBUS DISCOVERY and Shire are teaming up to develop small-molecule treatments for rare genetic diseases known as lysosomal storage disorders. The partners say they will use Nimbus computational chemistry to develop drugs that can penetrate inaccessible tissues.

CELGENE is collaborating with Concert Pharmaceuticals on designing deuterium-modified compounds to target cancer and inflammation. Celgene will pay an up-front fee to Concert and possibly more than $300 million in milestones for each candidate it pursues.

ABIDE THERAPEUTICS and Merck & Co. will develop small-molecule therapies to treat metabolic disease with a focus on type 2 diabetes. Abide, a specialist in hydrolase-targeting drug development, will receive an up-front payment and as much as $430 million in milestone payments for three products.

TOP 50 U.S. CHEMICAL PRODUCERS

Financial results reflect the economic challenges of 2012, but stock values point to OPTIMISM

ALEXANDER H. TULLO, C&EN NORTHEAST NEWS BUREAU

C&EN'S LATEST SURVEY of the Top 50 U.S. chemical companies reveals a chemical industry that, although healthy, is in no better condition than it was a year ago. Both sales and profits for the largest chemical makers were down slightly in 2012, the period of record for the survey.

However, chemical company stock prices rose strongly over the course of the year. Investors are apparently sending a signal: The sluggishness experienced by the global economy in 2012 was only temporary, and many of the problems that worried investors early in the year—including a European recession and softness in China—will be overcome.

In his letter to shareholders, Andrew N. Liveris, chief executive officer of Dow Chemical, noted the challenges he faced navigating his firm, again number one in C&EN's ranking, through a difficult year. "The world continued its rocky recovery in 2012, with volatility and uncertainty proving to be the new normal," he wrote. "Persistent weakness in Europe was a continued drag on global [economic] growth, while dramatic declines in China, Brazil, and other emerging geographies introduced new risks to a sustained recovery."

U.S. chemical companies were pulled down by these factors, but not sharply. Combined sales for the Top 50 were $318.7 billion, a 3.1% decline from 2011. Twenty-six of the companies—and seven of the top 10—posted sales declines. Although the sales figure can be considered a disappointment, it should be noted that the 2011 total was a record.

Profits also fell. The 42 chemical firms in the ranking that report operating profits together posted a 3.2% decrease to $38.9 billion. As was the case for sales, the comparison year of 2011 was a record for chemical company profitability.

Only one firm, Ferro Corp., reported a loss. Ferro is a company in turmoil. Its CEO resigned last year. Activist shareholders are trying to get new directors elected to its board. And it is fending off a hostile takeover attempt by plastics compounding firm A. Schulman.

Mergers and acquisitions had a big impact on the Top 50 ranking this year. Four firms that previously appeared didn't make the list this year because of acquisitions.

TPC Group, number 30 in 2012, was acquired by the private equity firms SK Capital Partners and First Reserve and no longer reports its results. Solutia, number 34 last year, was purchased by tenth-ranked Eastman Chemical. Titanium dioxide maker Tronox, number 37 in last year's survey, merged with the mineral sands business of Exxaro Resources and now has its headquarters in Australia. Sunoco, number 45 last year, exited chemicals through deals such as the sale of its polypropylene business to Brazil's Braskem.

OTHER TRANSACTIONS made chemical firms move up and down the ranking. Ashland jumped to 14, from 20 the year before, thanks to a full year of regular operations after its 2011 purchase of International Specialty Products. Cytec Industries dropped to 35, from 26, largely because of the divestiture of its coatings resins business to the private equity firm Advent International.

Mergers and acquisitions activity also influenced C&EN's

MARKET CAPITALIZATION

DuPont slipped but held on to the lead for the third consecutive year

RANK 2012	RANK 2011	COMPANY	MARKET CAP ($ MILLIONS) 2012	CHANGE FROM 2011
1	1	DuPont	$41,966	-1.0%
2	2	Dow Chemical	38,903	14.2
3	3	Praxair	32,419	1.6
4	4	Mosaic	24,107	12.4
5	6	PPG Industries	20,790	63.9
6	5	Air Products	17,443	-2.8
7	7	CF Industries	12,799	35.0
8	11	Eastman Chemical	10,473	95.9
9	8	Sigma-Aldrich	8,830	16.8
10	10	FMC Corp.	8,058	34.2
11	9	Celanese	7,107	2.6
12	13	Ashland	6,352	41.9
13	12	Albemarle	5,522	20.7
14	16	Westlake Chemical	5,305	98.3
15	14	W.R. Grace	5,083	49.8
16	15	Rockwood Specialties	3,883	28.2
17	18	Huntsman Corp.	3,789	60.8
18	17	NewMarket Corp.	3,513	32.4
19	21	Cytec Industries	3,090	52.1
20	22	Cabot Corp.	2,547	25.8
21	20	Kronos Worldwide	2,260	8.1
22	25	Chemtura	2,083	90.8
23	24	H.B. Fuller	1,738	51.9
24	23	Olin	1,732	10.0
25	30	Axiall	1,424	113.7
26	27	Stepan	1,222	49.4
27	26	Innophos	1,014	-3.4
28	32	Innospec	804	24.5
29	29	Koppers	786	11.0
30	31	Kraton Polymers	776	19.1
31	28	OM Group	708	-0.8
32	25	Ferro Corp.	390	-14.5
33	35	Omnova	329	56.1

NOTE: Based on share prices on Dec. 31, 2012 and Dec. 30, 2011. These 33 companies are firms on the Top 50 list that generate more than half of their revenues through chemical manufacturing.

Investors are apparently sending a signal: The sluggishness experienced by the global economy in 2012 was only temporary.

TOP 50 U.S. CHEMICAL FIRMS

Revenues declined at most large companies because of economic woes in 2012

RANK 2012	RANK 2011	COMPANY	CHEMICAL SALES ($ MILLIONS) 2012	CHANGE FROM 2011	CHEMICAL SALES AS % OF TOTAL SALES	HEADQUARTERS	CHEMICAL OPERATING PROFITS[a] ($ MILLIONS)	CHANGE FROM 2011	CHEMICAL OPERATING PROFITS AS % OF TOTAL OPERATING PROFITS	OPERATING PROFIT MARGIN[b]	IDENTIFIABLE CHEMICAL ASSETS ($ MILLIONS)	CHEMICAL ASSETS AS % OF TOTAL ASSETS	OPERATING RETURN ON CHEMICAL ASSETS[c]
1	1	Dow Chemical	$56,786	-5.3%	100.0%	Midland, Mich.	$4,425	-2.1%	100.0%	7.8%	$69,605	100.0%	6.4%
2	2	ExxonMobil	38,726	-7.7	8.5	Irving, Texas	4,885	-16.9	6.4	12.6	26,124	7.8	18.7
3	3	DuPont[d]	30,216	-13.1	86.8	Wilmington, Del.	4,688	-15.5	97.0	15.5	16,243	64.0	28.9
4	5	PPG Industries	14,168	2.5	93.2	Pittsburgh	2,199	13.9	97.2	15.5	10,990	69.2	20.0
5	4	Chevron Phillips	13,307	-4.5	100.0	The Woodlands, Texas	na	na	na	na	9,409	100.0	na
6	6	Praxair[d]	11,224	-0.2	100.0	Danbury, Conn.	3,460	-0.1	100.0	30.8	18,090	100.0	19.1
7	7	Huntsman Corp.	11,187	-0.3	100.0	Salt Lake City	931	23.6	100.0	8.3	8,884	100.0	10.5
8	8	Mosaic[e]	11,108	11.8	100.0	Plymouth, Minn.	2,675	-2.7	100.0	24.1	16,690	100.0	16.0
9	9	Air Products[f]	9,192	-5.1	95.6	Allentown, Pa.	1,582	-2.6	97.3	17.2	15,574	91.9	10.2
10	11	Eastman Chemical	8,102	12.9	100.0	Kingsport, Tenn.	920	-9.2	100.0	11.4	11,619	100.0	7.9
11	10	Momentive	7,113	-9.3	100.0	Columbus, Ohio	465	-39.7	100.0	6.5	6,229	100.0	7.5
12	12	Celanese	6,418	-5.1	100.0	Dallas	583	-27.3	100.0	9.1	9,000	100.0	6.5
13	17	Honeywell[d]	6,184	9.3	16.4	Morristown, N.J.	1,154	10.7	19.6	18.7	6,396	15.3	18.0
14	20	Ashland[f]	6,172	36.2	75.2	Covington, Ky.	628	108.6	72.7	10.2	9,665	90.5	6.5
15	13	Dow Corning	6,119	-4.8	100.0	Midland, Mich.	na	na	na	na	13,301	100.0	na
16	15	CF Industries	6,104	0.1	100.0	Long Grove, Ill.	2,962	7.1	100.0	48.5	10,167	100.0	29.1
17	14	Lubrizol	6,100	0.0	100.0	Wickliffe, Ohio	na	na	na	na	na	na	na
18	16	Styron	5,500	-8.3	100.0	Berwyn, Pa.	na	na	na	na	na	na	na
19	19	Ecolab	5,161	11.0	43.6	St. Paul	682	27.2	53.1	13.2	11,215	63.8	6.1
20	18	Occidental Petroleum	4,580	-4.9	18.9	Los Angeles	720	-16.4	9.3	15.7	3,854	6.0	18.7
21	22	FMC Corp.	3,748	11.0	100.0	Philadelphia	696	12.4	100.0	18.6	4,374	100.0	15.9
22	23	Monsanto[g]	3,715	14.7	27.5	St. Louis	477	69.8	15.7	12.8	4,280	21.2	11.1
23	21	Westlake Chemical	3,571	-1.3	100.0	Houston	615	37.7	100.0	17.2	3,412	100.0	18.0
24	25	Cabot Corp.[f]	3,300	6.4	100.0	Boston	290	19.3	100.0	8.8	4,399	100.0	6.6
25	24	W.R. Grace	3,156	-1.8	100.0	Columbia, Md.	564	7.5	100.0	17.9	5,090	100.0	11.1
26	27	Rockwood Specialties	2,819	-7.7	80.4	Princeton, N.J.	363	-26.3	75.1	12.9	4,070	68.1	8.9
27	29	Albemarle	2,745	-4.3	100.0	Richmond, Va.	518	-11.9	100.0	18.9	3,437	100.0	15.1
28	31	Axiall	2,685	4.3	80.7	Atlanta	302	96.4	94.3	11.2	1,147	63.6	26.3
29	28	Chemtura	2,629	-13.1	100.0	Philadelphia	348	0.3	100.0	13.2	3,030	100.0	11.5
30	33	NewMarket Corp.	2,212	3.5	100.0	Richmond, Va.	366	21.1	100.0	16.5	1,258	100.0	29.1
31	35	Kronos Worldwide	1,976	1.7	100.0	Dallas	377	-31.9	100.0	19.1	2,027	100.0	18.6
32	39	H.B. Fuller[h]	1,886	21.1	100.0	St. Paul	163	26.0	100.0	8.6	1,786	100.0	9.1
33	36	Stepan	1,804	-2.1	100.0	Northfield, Ill.	129	8.6	100.0	7.1	986	100.0	13.1
34	32	Ferro Corp.[d]	1,769	-18.0	100.0	Mayfield Heights, Ohio	-5	def	def	def	1,079	100.0	def
35	26	Cytec Industries	1,708	-44.4	100.0	Woodland Park, N.J.	326	5.8	100.0	19.1	3,922	100.0	8.3
36	40	Sigma-Aldrich	1,574	4.7	60.0	St. Louis	na	na	na	na	na	na	na
37	41	Kraton Polymers	1,423	-1.0	100.0	Houston	102	-45.4	100.0	7.2	1,229	100.0	8.3
38	42	Olin	1,411	1.6	64.6	Clayton, Mo.	263	7.4	81.5	18.7	1,782	64.1	14.8
39	39	Goodyear	1,260	-20.9	6.0	Akron, Ohio	na	na	na	na	na	na	na
40	43	Reichhold	1,162	-1.8	100.0	Research Triangle Park, N.C.	na	na	na	na	na	na	na
41	—	Taminco	1,116	-0.6	100.0	Allentown, Pa.	120	-23.1	100.0	10.8	1,847	100.0	6.5
42	46	Koppers	1,106	8.9	71.1	Pittsburgh	83	-6.7	65.6	7.5	516	66.2	16.1
43	48	MeadWestvaco	939	15.8	17.2	Richmond, Va.	224	10.3	32.1	23.9	506	9.1	44.3
44	47	Omnova[i]	865	-9.2	76.8	Fairlawn, Ohio	90	3.6	95.9	10.4	543	62.1	16.5
45	44	OM Group	864	-22.2	52.8	Cleveland, Ohio	44	-69.0	nm	5.1	1,092	43.7	4.1
46	48	Innophos	862	6.4	100.0	Cranbury, N.J.	110	-19.7	100.0	12.8	739	100.0	14.9
47	50	Innospec	776	0.3	100.0	Littleton, Colo.	100	91.0	100.0	12.8	579	100.0	17.2
48	—	Petrologistics	751	22.1	100.0	Houston	144	221.9	100.0	19.2	798	100.0	18.1
49	—	PolyOne[d]	704	29.2	23.5	Avon Lake, Ohio	67	53.9	40.0	9.5	888	41.7	7.5
50	—	Emerald Performance Materials	700	5.3	100.0	Cuyahoga Falls, Ohio	na	na	na	na	na	na	na

a Operating profit is sales less administrative expenses and cost of sales. **b** Operating profit as a percentage of sales. **c** Chemical operating profit as a percentage of identifiable assets. **d** Sales include a significant amount of nonchemical products. **e** Fiscal year ended May 31. **f** Fiscal year ended Sept. 30. **g** Fiscal year ended Aug. 31. **h** Fiscal year ended Dec. 3. **i** Fiscal year ended Nov. 30. **na** = not available. **nm** = not meaningful. **def** = deficit.

ranking of the Top 25 foreign firms by U.S. chemical sales. For example, Solvay climbed to number eight because of its 2011 acquisition of French chemical maker Rhodia. AkzoNobel fell four spots to number nine after selling its U.S. architectural paints business to PPG Industries.

Christopher D. Cerimele, director of the chemical practice at the investment banking firm Houlihan Lokey, has seen a pickup in deal-making over the past year. Companies that are selling are trying to get rid of divisions that are no longer a good fit, he says, and those that are acquiring want operations that line up closely with what they already have.

A DECADE AGO, in contrast, companies often ventured into unfamiliar territory for greater size and diversification. "Companies in this market are not making big stretches to grow revenues," Cerimele says. "Now there is a strong strategic rationale."

Private equity firms are also eyeing the chemical industry, Cerimele says. Financing, which took a hiatus during the housing meltdown, has come back strong, largely because of central bank policies around the world aimed at stimulating economies with low interest rates. "The financing markets are as good as they have ever been," he says.

AIR PRODUCTS

ALL CLEAR Workers in the control room at Air Products & Chemicals' Pasadena, Texas, customer service center.

Private equity firms also have a positive impression of the chemical sector, according to Cerimele. "They see it as an attractive sector within industrials right now," he says. Because chemical companies supply every sector of the economy, a chemical investment is a way for a private equity firm to position itself for a strong recovery ahead.

Stock buyers seem to agree. C&EN's ranking of firms by market capitalization shows that 2012 was a good year for chemical stock prices. The combined market capitalization for the 33 publicly traded chemical firms in the Top 50 was $277.2 billion at the end of 2012, an 18.1% increase from 2011. In contrast, the Standard & Poor's 500 stock index rose 13.4% during the year.

DuPont held on to the top spot in this ranking, despite a 1.0% decline in its market cap. Its margin over number two Dow shrank to $3.1 billion from $8.3 billion the year before.

There were a few impressive gainers in the capitalization ranking. Axiall, the polyvinyl chloride and chlor-alkali firm formerly known as Georgia Gulf, enjoyed a 113.7% increase in market cap to $1.4 billion. Axiall is merging with PPG's commodity chemicals business. Three other firms—Eastman, Westlake Chemical, and Chemtura—each posted gains of more than 90%.

If the instincts of stock investors and private equity firms turn out to be correct, C&EN's 2014 U.S. Top 50 will reflect strong improvement in the chemical sector. Perhaps the industry will even return to hitting records for sales and profits. ■

STRONG YEAR

Foreign-owned chemical firms mostly saw strong increases

RANK 2012	RANK 2011	COMPANY	U.S. CHEMICAL SALES ($ MILLIONS) 2012	CHANGE FROM 2011	U.S. CHEMICAL SALES AS % OF TOTAL U.S. SALES	COUNTRY
1	1	BASF	$18,772	-0.9%	100.0%	Germany
2	2	LyondellBasell Industries	12,934	-13.1	100.0	Netherlands
3	3	Agrium[a]	10,776	12.8	100.0	Canada
4	4	Bayer	5,908	20.5	48.0	Germany
5	6	Air Liquide	3,996	8.7	100.0	France
6	7	Evonik Industries	3,116	-12.4	100.0	Germany
7	15	Linde	3,095	44.6	91.9	Germany
8	22	Solvay	3,002	100.6	100.0	Belgium
9	5	AkzoNobel	2,950	-30.8	100.0	Netherlands
10	10	Alfa Group	2,935	15.7	64.0	Mexico
11	8	Braskem	2,889	12.1	100.0	Brazil
12	12	Arkema	2,819	12.6	100.0	France
13	17	Indorama	2,719	36.5	100.0	Thailand
14	9	Potash Corp.	2,648	2.8	100.0	Canada
15	14	Syngenta	2,577	19.4	65.6	Switzerland
16	11	Nova Chemicals	2,309	-8.7	100.0	Canada
17	16	Yara	2,253	10.7	100.0	Norway
18	18	DSM	2,093	8.2	100.0	Netherlands
19	20	Lanxess	2,071	10.5	100.0	Germany
20	21	Sasol[b]	2,031	26.2	100.0	South Africa
21	19	Shin-Etsu Chemical[c]	2,000	4.3	100.0	Japan
22	23	Lonza	1,803	48.2	100.0	Switzerland
23	13	Total	1,759	-28.3	7.8	France
24	25	Israel Chemical	1,115	8.1	100.0	Israel
25	—	Wacker Chemie	1,051	4.4	100.0	Germany

NOTE: Figures from companies that report in native currencies were converted to dollars at average annual exchange rates from the Federal Reserve. **a** Sales include a significant amount of nonchemical products. **b** Fiscal year ended June 30. **c** Fiscal year ended March 31.

DOW CHEMICAL

HAIR FIX Dow scientists examine hair treated for curl retention.

HAIR CARE INGREDIENT MAKERS GET CREATIVE

Chemists meet demand for **NOVEL INGREDIENTS** that repair, add shine, and protect color

MARC S. REISCH, C&EN NORTHEAST NEWS BUREAU

CONSUMERS DEMAND A LOT from hair care products beyond keeping hair clean. They want shampoos and conditioners that make hair shiny, manageable, and soft. They want to repair hair damaged and weakened in the dyeing process, and they want to protect newly colored hair from fading in the sun or with repeated washing. They also want a tonic, if they can get it, to make hair grow.

Chemists who formulate hair care products and those who develop new ingredients bring a veritable arsenal of raw materials to hair treatment. Some of them work for major consumer product brand owners such as L'Oréal and Henkel; others work for chemical companies that supply ingredients to the personal care industry.

Ingredients for hair care include the well established: silicones for shine, quaternary ammonium compounds for easier combing, proteins for thickening, and polyvinylpyrrolidone for shaping and styling. But the hair care sector is being enlivened by entirely new ingredients as well as proprietary packages that combine the old standbys in novel ways.

These days, shampoos and conditioners are meant to do more than cleanse and ease combing, says Ameann DeJohn, a product development consultant for small to medium-sized consumer product formulators. These products are being called on to strengthen the hair so it doesn't break, repair frizzy hair, and give hair the radiant shine of youth.

"In many ways, hair care formulators are treating hair like skin, with antiaging ingredients," DeJohn says. Just as skin care companies incorporate sunscreens in their products to protect the skin from the damaging effects of the sun's ultraviolet rays, hair care firms are developing ingredients that protect hair from the bleaching and fading effects of the sun.

The major consumer brand owners often set the pace for ingredient invention. Paris-based L'Oréal, for instance, has developed a number of novel ingredients for hair. The firm describes Intra-Cyclane, introduced in 2010, as a molecule capable of penetrating to the core of hair fibers to create "a flexible and resistant molecular network that fills out and strengthens the fiber." Intra-Cyclane can be found in the filler serum Fiberceutic by L'Oréal Professional.

Germany's Henkel is also on the hunt for novel hair care ingredients. "Innovation in hair repair is a key element in Henkel's hair care strategy," Erik Schulze zur Wiesche, head of hair care basic development, tells C&EN. "A deep understanding of hair composition and the mechanisms of aging are the basis of new hair repair innovations."

Among those innovations is a combination of nine amino acids with structural proteins known as keratins that Henkel developed and patented for its BC Bonacure Hairtherapy line. The active ingredients add "strength and elasticity for outstanding shine," according to Henkel.

COMPANIES SEEK OUT novel ingredients to gain a competitive advantage in the global hair care products business, which attracts more than $60 billion in annual consumer spending, according to industry consultants Kline & Co. About 21% of the $300 billion spent globally last year on personal care products was devoted to cleaning, conditioning, dyeing, and arranging human tresses. Only skin care gets a bigger share of consumers' wallets.

Overall, the retail hair care market is growing by 4.5% per year, according to Nikola Matic, chemical and materials industry manager at Kline. Growth rates are faster, Matic says, in emerging markets—they are as high as 8.0% in China, Southeast Asia, and India. A growing middle class in these regions is demanding products that have long been available in Europe and the U.S., he notes.

Chemical companies, which supply the cosmetics industry with $14 billion to $18 billion per year of ingredients, should also see sales grow quickly in emerging markets, Matic says. Specialty ingredients for hair care products is a lucrative $2.5 billion subset of their business, he points out.

Out to garner a piece of the hair care ingredients market is Symrise, an established supplier of fragrances and sunscreens that is becoming increasingly interested in hair care. At the In-Cosmetics ingredient sup-

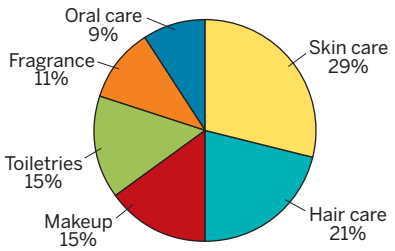
"People are damaging their hair more and more with what they do to stay beautiful."

pliers' show in Paris last month, Symrise debuted SymHair Force 1631, an algae-derived compound intended to prevent hair loss and encourage hair growth.

INGREDIENT SUPPLIERS have long had an interest in hair growth, especially since minoxidil, a blood pressure medication, was found years ago to prevent hair loss and induce new hair growth. L'Oréal, for instance, developed stemoxydine, an ingredient that it claims revitalizes hair follicles that have become dormant while increasing the volume and density of hair. European consumers can find the ingredient in L'Oréal's Neogenic by Vichy hair treatment.

Makers of similar active ingredients generally try to avoid claiming that those ingredients actually grow new hair. Companies that make the claim in the U.S. take the risk of running afoul of Food & Drug Administration regulations that prohibit cosmetic makers from making druglike claims for their products. Since 2002, FDA has sent warning letters to six cosmetics makers that claim their products grow hair or prevent male pattern baldness. Minoxidil is the only FDA-approved hair growth ingredient in the U.S.

PERSONAL CARE Hair and skin care products dominate the consumer market.



2012 worldwide retail sales = $300 billion

SOURCE: Kline & Co.

Symrise's target market for SymHair—at least in the U.S.—is formulators of minoxidil-free products that profess to prevent hair loss. The development of SymHair was a joint effort with the Italian microalgae producer Archimede Richerche, explains Véronique Maurin, global product director for Symrise. Opportunity knocked, Maurin says, when Cutech Biotechnology, an Italian skin and hair testing laboratory with which Symrise has a long relationship, paired Symrise with Archimede.

Of the thousands of microalgae species known, only a few are commercially available, Maurin explains. One of those screened by Symrise and Cutech seemed promising: *Isochrysis*, a species of microalgae that comes from Mataiva Atoll, in French Polynesia.

Easily cultivated in photobioreactors, the microalgae are currently used as a fish food because they are loaded with unsaturated fatty acids and micronutrients. Symrise found in laboratory tests that an extract from the algae prevented hair loss and improved volume. "We don't know what the active component is that makes SymHair effective," Maurin acknowledges.

Minoxidil aside, hair care companies can't necessarily make hair grow, but they can bring an arsenal of ingredients to the task of protecting its color. Given the multitude of people who color their hair, products that protect color between dye treatments have become something of an indus-

try obsession. Examples on store shelves include Avon's Advance Techniques Color Protection shampoo, Nivea Color Protect conditioner, and Dove Hair Therapy Conditioner Color Repair.

SILICONES TEND TO BE the workhorse of hair conditioners and shampoos. They are widely used to make hair shiny and easy to comb, but more recently silicones have been developed that coat the hair, protecting it from breakage and helping to preserve color. "A major trend is the Swiss-Army-knife approach to hair care ingredients," says David Cohon, personal care global marketing director for Momentive, a silicones supplier.

With silicones such as its Silsoft AX-emulsion formulation, Momentive can provide consumer product formulators with multiple benefit claims. Those claims, Cohon says, include color protection, hair repair, shine, and protection from damage caused by blow-dryers and curling irons.

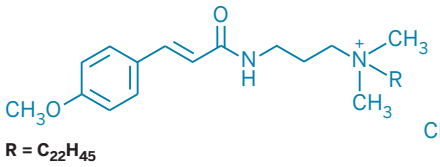
Silicones are often seen as the chemistry to beat in the hair conditioning arena. Under attack a few years ago because of suspicion that they harm the environment, silicones have been seen more favorably since the Canadian government agency Environment Canada gave silicones used in hair care a clean bill of health in 2012.

In addition, silicones are often attacked because they are not considered natural ingredients, acknowledges Stewart Long, global market manager for Dow Corning, another major silicone supplier. "The reason silicone chemistry was invented was to get properties not already in nature," he says. The trick is to use the right technology in the right place, he adds.

Very small amounts of silicones can often allow formulators to provide more desirable consumer products, Long says. For instance, formulating shampoos and conditioners with just 2% of Dow Corning's CE-8411 nonionic silicone emulsion provides color protection benefits, enhances hair shine, and helps prevent hair breakage, Long says.

One challenger to silicones is the combination of a quaternary ammonium compound and an ultraviolet light absorber. Hair care product makers have recently launched a number of shampoos and sprays intended to protect dyed hair from color washout and ultraviolet light damage, notes Nirmal Koshti, innovation process head at India's Galaxy Surfactants. Often the products incorporate this ingredient pairing.

But such water-soluble formulations tend to rinse off in the shower, leaving little to protect the hair, Koshti says. Galaxy's new GalHueShield Hair Color Seal combines in a single molecule "the best" quaternary ammonium compound, behenyl trimethyl ammonium chloride, with "the best" UV absorber, octyl methoxy cinnamate, he claims. The molecule's active cationic center gives it a high affinity for hair, leaving more of the active ingredient behind after rinsing to condition dyed hair and protect its color.



R = $C_{22}H_{45}$

GalHueShield HCS

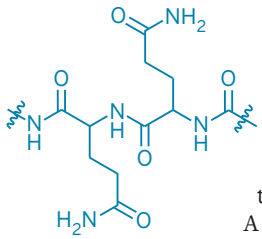
Other chemistry systems also compete in the color protection space. Some are based on acrylic technology, such as a new

line of ingredients from Ashland, which bought International Specialty Products and its personal care ingredients business in 2011. "People are damaging their hair more and more with what they do to stay beautiful," says Dianne Leipold, Ashland's care specialties marketing director.

Ashland's Conditioneze 22, an aqueous copolymer of dimethyl ammonium chloride and acrylic acid, for instance, can be incorporated into a hair coloring system as well as into shampoos and conditioners for damaged and treated hair, Leipold says. Using acrylics makes it possible to offer formulators a high-performance system "at price points amenable to mass markets," she adds.

Another silicone challenger using acrylic chemistry is Dow Chemical's EcoSmooth Silk. Its acrylic-based polymer helps disperse an anionic polyolefin that binds to the hair surface, offering protective benefits, Dow says. Greater use of heat to dry and style hair means a need for conditioning agents that protect hair from damage, says Lucréce Foufopoulos, a Dow general manager for Europe, Middle East, and Asia.

Dow touts EcoSmooth's low toxicity to aquatic organisms. Other firms, meanwhile, are emphasizing hair treatment agents based on nature-derived ingredients.



Dragoderm

Tri-K Industries, a U.S.-based cosmetic ingredients supplier owned by India's Galaxy, used a protein from grain, in this case quinoa, to design a conditioner to help dyed hair retain its color after repeated washing. "Consumers are looking for conditioners that help with color retention in addition to strengthening and repairing hair weakened in the dyeing process," says Elzbieta Kasprzyk, innovation and application director at Tri-K.

ON THE BASIS OF the amino acid profile of Quinoa Pro Ex, the Tri-K protein, company scientists theorized that it could be especially color protective, Kasprzyk says. Pro Ex forms a "protective scaffold" around hair to lock in and protect the color, she says. It brings other benefits as well, she adds, such as making hair easier to comb and giving it a youthful sheen.

Symrise also has a plant-derived hair care ingredient, Dragoderm 118726, intended to make hair softer and shinier. A hydrophobic solution of wheat proteins, the product coats the hair shaft and helps keep colored hair from fading, Symrise says.

A new ingredient from BASF, called Plantaquat NC, calls on plant-derived lecithin to give conditioning properties. Ulrich Issberner, head of hair care marketing for BASF, says the lecithin-based ingredient "gives performance that couldn't be achieved with an all-natural conditioner before." Blending in an anionic surfactant forms an emulsion allowing the lecithin to more effectively deposit on the hair, reducing hair breakage and adding volume to thin hair, Issberner says.

Given the large number of consumers who color their hair, Matic, the Kline consultant, predicts that conditioning polymers will be the fastest-growing specialty ingredient category. And with consumers obsessed with colorful, glowing, shiny hair, chemical companies should have a ready market for ingredients of all types for years to come. ■

CO_2 CAPTURE EFFORT PROGRESSES

The Department of Energy will support the FutureGen carbon capture and storage facility in Meredosia, Ill. In a draft environmental impact statement, DOE recommends spending $1 billion in cost-shared funding to modify a 168-MW coal-fired electric generation plant to use advanced combustion technology to capture CO_2. If completed, the modified facility will capture, compress, and transport some 90%, or 1 million metric tons, of the plant's yearly CO_2 emissions. CO_2 would be injected at a geological storage site 30 miles away. First announced in 2003, this project has had difficulty finding investors willing to match DOE's funding. Although FutureGen would be the world's largest carbon capture facility, it would only incrementally reduce U.S. CO_2 emissions. For comparison, coal-fired plants in 2012 released some 1.6 billion metric tons of CO_2.—JJ

BOARD REJECTS BID TO SHIFT HAZMAT LIABILITY

The Surface Transportation Board (STB) has rejected a petition filed by Union Pacific that would have allowed the freight railroad to require shippers of highly toxic chemicals to assume most of the financial risk of transporting these commodities. The board, which is part of the Department of Transportation, concluded that Union Pacific failed to adequately show that shifting liability from the rail carrier to the shipper is reasonable. Under the proposal, chemical shippers would have been required to indemnify Union Pacific for "any and all liabilities," except those caused by the negligence or fault of the rail company. But STB ruled that the plan was "overly broad" because it would have required shippers to shield Union Pacific from liability even in situations where the railroad "can already protect itself through insurance."—GH

SHUTTERSTOCK

GOVERNOR SEEKS CHANGES TO PROPOSITION 65

California Gov. Edmund G. (Jerry) Brown Jr. (D) is proposing changes to the state's Proposition 65. That 1986 law lists chemicals known to cause cancer, birth defects, or reproductive harm; requires warning labels on products that contain those substances; and prohibits their discharge into drinking water sources. One reform Brown proposed last week would affect warning labels for products containing chemicals causing reproductive toxicity. Prop 65 now exempts businesses from labeling such chemicals if they are present in a product at a concentration no greater than 0.001 of the level at which there are no observed effects in humans for that substance. Citing advances in risk assessment since 1986, Brown is seeking to loosen this limit to 0.01 of the no-observed-effects level. The proposal also would toughen legal requirements for those suing businesses for allegedly violating Prop 65.—CH

CANADA REVAMPS RESEARCH COUNCIL

Canada's ruling conservative government announced last week that it will refocus the country's National Research Council (NRC) on industry-related research. The organization, which includes 4,000 workers in 50 research facilities nationwide, had primarily supported basic science since its founding in 1916. NRC will now focus on "large-scale research projects that are directed by and for Canadian businesses," according to a statement announcing the change. The goal is to help companies bridge technology gaps. "The refocused NRC will provide Canadian industries with access to strategic research and development; technical services; and specialized scientific infrastructure, technical expertise, and people," says Gary T. Goodyear, minister of state for science and technology.—AW

GOVERNMENT ROUNDUP

MILK'S legal definition, along with those of 17 other dairy products, would change under a proposal from dairy industry groups. It would allow producers to include artificial sweeteners without using a prominent label. Current rules require a label descriptor such as "reduced calorie." FDA is accepting comments on the plan through May 21.

THREE NEW manufacturing research institutes will be launched in 2013, the White House says. The centers will focus on integrating digital design and robotics with manufacturing, designing advanced materials, and creating the next generation of electronics. They will be chosen through competitive grants at the Departments of Defense and of Energy.

ENERGY BILLS were approved by the Senate Energy & Natural Resources Committee last week. The measures would encourage energy efficiency in buildings for both the public and private sectors (S. 761) and support development of small hydropower electricity generation units of less than 5 MW (S. 306, S. 545, H.R. 628, and H.R. 267).

LIBYA has completed the destruction of sulfur mustard agent that was stored in bulk in transportation containers, says the Organisation for the Prohibition of Chemical Weapons. That brings the total amount of chemical weapons destroyed by Libya to 22.3 metric tons, or nearly 85% of its declared stocks.

NANOPARTICLES of germanium dioxide are now covered by a new regulation in Canada. Manufacturers must notify the government if they make more than 100 kg per year of GeO_2 nanoparticles. Canadian regulators are concerned about the potential toxicity of this nanomaterial.

DEPARTMENT OF STATE

CONNECTIONS Gast (right)has tea in Uzbekistan with local residents (center) during her trip to Central Asia as a science envoy.

STATE OF SCIENCE DIPLOMACY

Science is becoming increasingly important in **DIPLOMATIC EFFORTS** at the State Department

ANDREA WIDENER, C&EN WASHINGTON

ALICE P. GAST isn't a diplomat. But when the Department of State asked the president of Lehigh University to serve as a science envoy to Central Asia, she was eager to help.

Gast, a chemical engineer, traveled with State Department representatives across the part of the former Soviet Union that bridges the Middle East and Asia. She talked with all types of people, from presidents to business leaders to student scientists.

Her work as a science envoy was "an opportunity to bring a private citizen—not a member of the diplomatic corps—in to talk to fellow scientific and government leaders in ways that were really beneficial," says Gast, who has international interests and research connections dating back to when she was a postdoc in Paris in 1984 and 1985.

Science envoys are high-profile scientists chosen by the State Department to make connections and identify opportunities for engagement in different regions. "I would hope that my report on the situation there will help point out how to build more U.S. bridges in that region," Gast says.

The four-year-old science envoy program is just part of the increasing recognition at the State Department that science can play a valuable role in diplomacy.

Since a National Research Council (NRC) report 14 years ago criticized the department for its lack of science expertise, State has increased its efforts to understand and incorporate science into its diplomatic work. Further spurring this change was demand from countries that State works with as well as recognition by those inside the department of the scientific challenges that all nations face, from disease pandemics to water shortages.

"We are trying to use science as a tool to advance a more prosperous, secure, peaceful world," says E. William Colglazier, science adviser to the secretary of state. "I'm really optimistic" that science can help.

Both supporters and critics say State could do better, but acknowledge that in the past decade the department's scientific expertise has improved. However, State is fighting an uphill battle against those—including several prominent members of Congress—who would prefer that research done in the U.S. stay at home.

"Science is central to some of the major foreign policy challenges today, and the really remarkable thing has been the State Department's recognition of that," says Vaughan Turekian, chief international officer with the American Association for the Advancement of Science (AAAS).

The new secretary of state, John F. Kerry, recognizes the international importance of science and its value in addressing some of the world's most entrenched challenges such as climate change.

THAT WASN'T THE CASE in 1999, when NRC released its report criticizing State's knowledge of and expertise in science. In the wake of the Cold War, much of the science knowledge that State had built up—primarily surrounding nuclear weapons issues—began fading. The report called for the agency to make major changes to ensure that it was not isolated from important science developments affecting the world.

"An appreciation of how [science, technology, and health] factors are inextricably embedded in international relations is essential if the department is to effectively avail itself of the expertise of the U.S. [research] communities," the report states. "More importantly, the department must be equipped to reach its own conclusions, particularly when conflicting technical views are expressed by vested interests outside the department."

State did not implement all of the changes suggested in the report, but it has made major efforts to bring more science knowledge into the department. The highest-profile change was creating the position of science adviser to the secretary of state, whose office serves as the go-to location for those interested in science diplomacy, both inside and outside the department.

"I think the issues are still real, but a lot has changed," says Norman P. Neureiter, a chemist who served as the first science adviser from 2000 to 2003 under both Madeleine Albright and Colin Powell.

"The hallmarks of good science ... just happen to reinforce good government concepts and democratic procedures."

In the everyday affairs of your average embassy or consulate, "science is usually not the dominant issue," Neureiter says, and foreign service officers on the ground often lack scientific expertise. This becomes a problem when they need to make a policy recommendation on an issue but might not recognize that science could help them in the first place.

"A policy decision usually starts down low and has to come up through the chain," Neureiter says. "It is too late if you are waiting to whisper in the secretary's ear."

Some offices within the State Department, like the Bureau of Oceans & Environmental Scientific Affairs (OES), had that expertise internally, but science wasn't part of the larger foreign service culture. "The challenge was, how do we bring the scientific advice necessary for the conduct of foreign policy not just to oceans and environment issues but to the broad sweep of issues we have to deal with as a department?" explains Jonathan Margolis, acting deputy assistant secretary for OES.

IN RESPONSE, State has been increasing the number of scientists who come into the department on a temporary basis through fellowship programs and work at different parts of the agency. Science and technology policy fellows from AAAS form the largest block at State, but other fellowships also bring scientists into the department, including State's own Jefferson Science Fellowships for midcareer scientists.

Shara Williams' experience as a fellow gave her insight into how complicated international relations can be. "You get an understanding of all of the different issues that need to be weighed and the amount of effort that goes into a policy statement," says Williams, who was an American Chemical Society policy fellow at State in 2004 and stayed on at State in 2005.

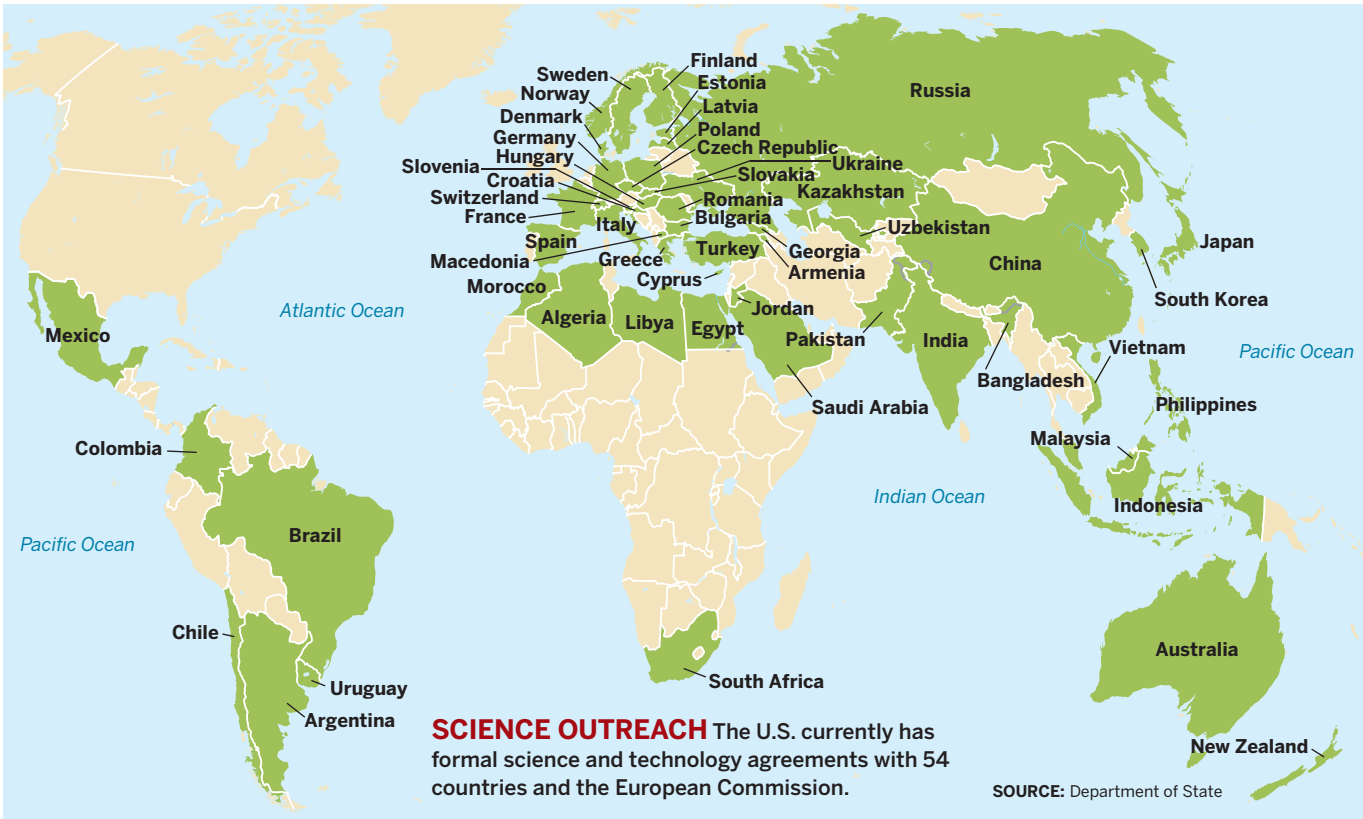
Even if a fellow's training is in, say, chemistry or physics, "it could be surprising to find out that you really are the closest thing to a marine fisheries expert that is available," says Williams, who is now at RAND Corporation, a nonprofit research organization. "What that background does is equip you to have a conversation with someone who knows the science."

The transition from scientist to policy expert, even temporarily, isn't always easy. Mark E. Eberhart, who came to State as a midcareer Jefferson Science Fellow in 2011–12 from the Colorado School of Mines, says he felt underutilized writing speeches and going to meetings.

"Meeting and talking with people is the number one priority" at State, he says. "The value system is quite different" from his research mentality as an academic chemist.

Eberhart is concerned that science advice isn't reaching the highest levels—for example, the science adviser to the secretary of state actually reports to the undersecretary for economic growth, energy, and the environment. He thinks the State Department needs more of a scientific culture of research and analysis.

Although Ph.D. scientists are still in the vast minority at State, their numbers are increasing, Colglazier says. Many fel-



SCIENCE OUTREACH The U.S. currently has formal science and technology agreements with 54 countries and the European Commission.

SOURCE: Department of State

lows end up staying on as staff in various offices. And now someone with a science background is part of each of the regional bureaus, he points out.

In addition, all foreign service members who serve as the environment, science, technology, and health officers for embassies get two weeks of training about science and how it fits into foreign policy issues. Perhaps most important, the training tells them whom to ask for help when faced with a science question.

Those changes are, at least in part, driven by demand from the countries State works with. More and more countries see science and innovation as a way to lift their developing economies and view access to the U.S. R&D infrastructure as a way to do that.

"In most countries in the world right now, the lightbulb has gone on: If they are going to advance, they are going to have to up their game in science and technology," Colglazier explains. "The U.S. is still the leader, so they want to engage with us."

That is shown by the increasing number of formal science and technology agreements between the U.S. and its partner nations, now up to 55. These agreements, overseen by the department's Office of Science & Technology Cooperation, provide a formal connection between the countries on issues ranging from research projects of mutual interest to economic development opportunities.

IN GENERAL, much of State's science work, including the formal agreements and informal relationships, is with countries that are at a level of development to benefit from science exchanges, which Margolis estimates at 140–150 countries worldwide. Countries that are in crisis—where their people are struggling with war, food shortages, or other imminent disaster—often work through the U.S. Agency for International Development, which has also greatly expanded its science programs recently.

State has developed a number of programs to work with those 140–150 countries on ways to raise their level of scientific capability and scientific expertise. In recent years, several department programs have focused on science as a tool for economic development, like the Building Opportunity Out of Science & Technology program (see page 38).

These programs also give U.S. diplomats the chance to talk about issues that might be taboo otherwise. "If you look at the hallmarks of good science—peer review, meritocracy, transparency of operations, access to information, accountability—those just happen to reinforce good government concepts and democratic procedures," Margolis says. "We can talk about scientific goals in a whole range of countries where there would be reticence to talk about democracy goals."

For example, U.S. diplomats can talk about equal opportunities for women in science in countries where women haven't traditionally been seen as equal, and the discussion can include the challenges female scientists in the U.S. continue to face. Or they can discuss how the U.S. government goes to its own scientists to get independent advice on the problems it faces.

"My view is it is in the U.S. interest to have all countries be more scientific in the way they think about things, which will hopefully lead to more rational policies," Colglazier says.

State has also increasingly recognized that science can be a good tool to make connections with countries that it couldn't have made otherwise, Margolis says.

During the Cold War, connections among U.S. and Russian scientists were one of the only ways that the countries

interacted. And even now, scientists in the U.S. are connected to researchers in Iran, where the U.S. doesn't have diplomatic relations.

"Science opens doors for foreign policy objectives that aren't necessarily shut, but you would have to use a crowbar to get them open," Margolis says. "When you think about our relationship with Russia or China, where there are clearly many areas of friction, it is often in the science area where we can build bridges."

But State should be doing more to reach out through science, says Nina Fedoroff, who served as science adviser to then-secretary of state Condoleezza Rice from 2007 to 2010.

"SCIENCE DIPLOMACY is best is when it goes both ways. It builds bonds that connect people across the vast chasms of religion and ethnic identity," Fedoroff says. But State isn't a part of that vigorous international science conversation, which is happening mostly through nonprofits and universities.

Being part of that conversation "is a powerful tool that [the nation has] yet to seize upon," Fedoroff says.

Finding the right balance is a difficult challenge. Because it doesn't fund research, State is never going to be a "science agency." In fact, State doesn't have a formal budget for science and doesn't know how much it spends on science programs because they are integrated with other activities, officials acknowledge. They do say the funds spent on science represent only a small portion of the department's $47.8 billion budget.

The department's major role in science is as a convener, Margolis says. State officials identify major international issues and bring in researchers from inside and outside government to figure out the best way to tackle those problems

A few countries—Egypt, India, Israel, and Mexico, for example—have specific funds set up by Congress to promote cooperative science projects with the U.S. Officials at State point out that it would be useful to have money in its budget to support projects like this in other countries.

"The question is, how do you make the case to the American public, and specifically to Congress, that the reasons we need to engage in international science activities are not only foreign policy driven?" Margolis asks. Being intimately involved in science is important to the U.S. economy, too, he says.

Gast is continuing her work with Kazakhstan, but not with the support of State, which funded her for just one year. She has kept in touch with the ambassador to Kazakhstan, and she's going back soon for a biking vacation around the country.

"I feel strongly that while I'm not an official science envoy anymore, to them I am their only science envoy," she says.

Carrying the message of the increasing internationalization of science—and State's need to play a role in it—is part of the challenge for the agency moving forward, Margolis says.

"The only way that the U.S. is going to stay in the forefront in science and technology is to work with the best, wherever they are in the world," Colglazier says. "To do that you have to engage with them." ■

EMERGING ECONOMIES GET CAREER HELP

State Department program brings ACS career development training to MALAYSIA AND INDONESIA

SOPHIE L. ROVNER, C&EN WASHINGTON, AND
JEAN-FRANÇOIS TREMBLAY, C&EN HONG KONG

IT'S DEPRESSINGLY COMMON that when a speaker makes a presentation at a conference, several attendees chitchat or fiddle with their smartphones. But when an American Chemical Society team presented a career development workshop at the University of Malaya, in Kuala Lumpur, in late February, they faced a dream crowd: a roomful of attentive participants who asked thoughtful questions at the end of every panel.

ACS was in town thanks to a $198,000 grant from the U.S. State Department's Building Opportunity Out of Science & Technology program. The department has funded four other BOOST projects that are being spearheaded by U.S. universities. All of the projects are based in Indonesia, Malaysia, Morocco, Tunisia, or Turkey.

BOOST "fits into the broader State Department mission to use science as one of our tools for diplomacy," according to Samuel B. Howerton, a chemist and the deputy director of the department's Office of Science & Technology Cooperation (see page 34). The idea is to provide skills and training to young men and women who are interested in science and technology and who are likely to contribute to their nations' economic growth. "That serves the U.S. interest as well, because economic growth leads to economic stability, which leads to regional stability," Howerton explained to C&EN, which is published by ACS. "People who have jobs are less likely to want to use their skills and intellect for nefarious purposes."

By the time the ACS team of trainers reached the University of Malaya, they had already been on the road for 18 days, presenting their one-day program at universities throughout Indonesia and Malaysia. ACS worked closely with the Indonesian and Malaysian chemical societies and their regional branches to design the program, which was presented at eight events across the two countries. The two Southeast Asian societies also provided local organization such as finding facilities, arranging catering, and helping promote the program.

In each of eight cities selected with the help of the Southeast Asian societies as well as U.S. embassy and consular staff, ACS International Activities Committee Chair H. N. Cheng and ACS staff members gave workshops on four topics: publishing research, communicating science to the general public, mapping out career pathways, and developing research proposals. At the end of the day in each city, the attendees gathered for a session on mentoring the next generation.

The timing of the event at the University of Malaya was fortuitous. The Malaysian government has increased funding for scientific research at the university, but graduate students and lecturers there are not familiar with international journals or with communicating their work to the public. Moreover, the University of Malaya hasn't yet developed many exchange programs with schools abroad, but the researchers there are already eager to interact with foreign scientists.

"ACS is a good partner for us because they have quite a few high-impact journals," said Sithi V. Muniandy, deputy dean of the faculty of science. "This program helps us to improve our outreach, to help us start to collaborate on research projects with scientists abroad."

THE ACS SEMINAR addressed issues that are relevant to young faculty in Malaysia, said Ramili Ismail, a lecturer at the University of Technology, Malaysia, who attended a talk on how to submit papers to international journals. The talk, given by Steven Meyers, ACS manager for international activities, included tips on how to write an abstract and a discussion of the inner workings of the journal peer review process.

"People are really keen to publish in high-impact journals because it's an important part of our assessment and salary level," Ismail told C&EN. "This seminar helps me to understand how a reviewer thinks."

Bradley Miller, head of international activities at ACS, supported the ACS team in Malaysia by presenting a panel on how to communicate with the public about science. The seminars have been helpful within the country as well as beyond its borders, he noted.

"We're helping Malaysian scholars to be more effective scientists, which is good not only for them but also for global science," Miller said. In fact, one goal of the training is to help the attendees build networks so they can collaborate with each other on future projects.

Cheng, who spent eight years as a youth in Malaysia and Brunei, also presented some of the workshops on communicating science to the public. The Department of Agriculture chemist urged the participants to use informal encounters—at a barbeque or a barbershop, for instance—to briefly and simply explain to the public what they do for a living. In that

JODI WESEMANN/ACS

ENTHUSIASTIC TRAINEES BOOST attendees register at a hotel in Balikpapan, an Indonesian city on Borneo's coast.

kind of setting, a researcher could say, "I'm a chemist, and I'm trying to develop a drug to cure a disease." Alternatively, a chemist could write a letter for a newspaper's op-ed page about a topic such as climate change or clean water.

The attendees hadn't previously given much thought to this type of outreach, Cheng noted, but they responded enthusiastically. "Scientists don't make the most money in the world. Many of us become scientists because we enjoy science, we believe it is important for society, and we would like other people to respect us," he said. "But if we don't say good things about science, who is going to do that for us? If all of us can do this, and do it effectively, we can change the general public's image of scientists."

All together, the eight events drew some 750 attendees from more than 100 universities, companies, and other places of employment. About half were students; the rest were faculty members or government or company employees. More than half were women. Two-thirds were chemists or chemical engineers. And some attendees traveled significant distances to participate in the events.

JODI WESEMANN/ACS

WARM WELCOME Local volunteers prepare for a BOOST event at the University of Indonesia, in Depok.

ACS was careful to design a program that would be relevant, Meyers noted. For instance, the career path workshops included appearances by local experts who have jobs in government, industry, academe, or entrepreneurial endeavors. And before heading to the region, ACS hosted focus groups with international students in the U.S. to test out some of the workshop material. It also consulted with the chemical societies in Indonesia and Malaysia "to make sure the materials we were bringing were general enough and weren't focused on a U.S. audience," Meyers said.

The ACS team and the State Department hope that now that the attendees have returned home, they will spread the word about the concepts they learned.

To encourage that diffusion, the State Department grant includes funds for ACS to host a "train the trainer" session in August. Attendees from the first batch of workshops will compete for a chance to go to Thailand and learn additional leadership skills, including how to present the program themselves. ACS will work with them to tailor the materials for their local markets, including the use of translation services, if desired.

"I've been an ACS member for a long time—31 years—and there are only a few programs where I can see the immediate impact of what we do," Cheng said. "But this is definitely a case where you get an instant reaction, and the reaction is overwhelmingly positive." ■

AIRBORNE MINERAL DUST IS KEY TO CIRRUS CLOUD CREATION ...

Clouds play a key role in climate by reflecting solar radiation and by trapping heat from Earth. Understanding how clouds form is critical to modeling climate effects. Studies reveal that airborne mineral dust and metal particles are essential for forming cirrus clouds, which are wispy and found in high altitudes (*Science* 2013, DOI: 10.1126/science.1234145). A group led by Daniel J. Cziczo of Massachusetts Institute of Technology studied cirrus ice crystals during four aircraft measurement campaigns from 2002 to 2011. The researchers found that most of the particles in the air near clouds are made of sulfate and organic carbon. They also found that in the cloud formation process, ice preferentially condenses on aluminosilicate dust or metal particles. The results point to a heterogeneous ice nucleation mechanism in clouds, akin to getting a compound to crystallize from solution by scratching the beaker, rather than a homogeneous mechanism in which ice nucleates without a substrate.—JK

BILL STAFFORD/NASA

A crew prepares the NASA WB-57 high-altitude plane to study cirrus cloud formation.

... AND TO ADDING SULFATE TO PARTICLES WITHIN CLOUDS

Aerosol particles in the air undergo chemical reactions that change their size and hygroscopicity. Those properties in turn influence how airborne aerosols affect climate by scattering radiation and modifying the brightness and lifetime of clouds. Adding sulfate to those particles is a particularly important process. A research group led by Peter Hoppe, Eliza Harris, and Bärbel Sinha of the Max Planck Institute for Chemistry, in Germany, now pinpoints transition-metal ions as key oxidants that turn SO_2 into SO_4^{2-} on airborne mineral dust within clouds (*Science* 2013, DOI: 10.1126/science.1230911). The team studied so-called orographic clouds at Mount Schmücke, in Germany, where clouds form as air rises to go over the mountain. The researchers compared sulfur isotope ratios upwind and downwind of the clouds to determine whether SO_2 was oxidized by H_2O_2, O_3, or transition metals. They estimate that transition metals may account for about 1% of SO_4^{2-} production in urban locations but as much as 58% in rural areas. If incorporated into climate models, the results would decrease the amount and change the geographic distribution of aerosol-driven climate cooling.—JK

ALLOY MAKES IRON ON THE CHEAP

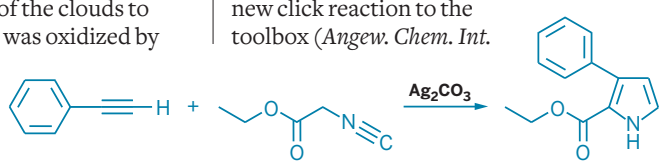
Electrodes made of a chromium-iron alloy may reduce the energy consumption and carbon footprint of iron production. Conventional smelters use carbon (coke) to chemically reduce ores composed of iron oxides. The process releases that carbon in the form of CO_2, emitting a massive quantity of the greenhouse gas into the atmosphere. Now, Donald R. Sadoway, Lan Yin, and Antoine Allanore of Massachusetts Institute of Technology have directly separated the iron and oxygen in iron ore in a bench-scale electrolysis experiment by using an anode made of a cheap alloy of the Earth-abundant metals chromium and iron (*Nature* 2013, DOI: 10.1038/nature12134). Other groups have demonstrated similar metal oxide electrolysis with iridium electrodes, but that rare element is too expensive for wide use. The MIT team's alloy anode produces higher purity iron than that made by conventional smelting methods and liberates molecular oxygen as a secondary product. The iron-smelting industry, which has a capacity of billions of metric tons per year, could reap efficiency gains from processes based on the alloy, says University of Cambridge materials chemistry professor Derek Fray in a commentary about the work. The process could also provide breathable oxygen to astronauts in space, he adds.—CB

SHUTTERSTOCK

An electrolytic iron-making method could reduce energy input and CO_2 output compared with conventional smelting (shown).

CLICKING PYRROLES INTO PLACE

The synthetic tools known as click reactions, which assemble molecules with high efficiency, selectivity, and yield, help chemists construct compounds. In addition to their application in organic synthesis, they've been used for medicinal chemistry, surface science, polymer chemistry, and bioconjugation applications. Now, chemists in China are introducing a new click reaction to the toolbox (*Angew. Chem. Int. Ed.* 2013, DOI: 10.1002/anie.201302604). A team led by Aiwen Lei of Wuhan University found that Ag_2CO_3 can catalyze cycloaddition of terminal alkynes and isocyanides to generate pyrroles (shown). Pyrroles are



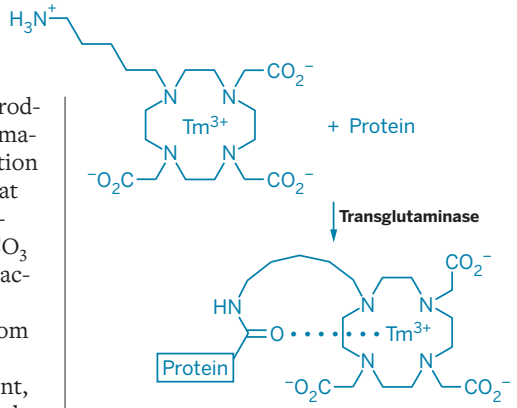
common structural motifs in natural products, biologically active alkaloids, pharmaceuticals, and agrochemicals. The reaction works best in *N*-methyl-2-pyrrolidone at 80 °C and can generate a variety of substituted structures. Interestingly, Ag_2CO_3 proved to be a key component to the reaction, whereas other silver salts, such as Ag_2O and $AgNO_3$, were ineffective. "From a synthetic point of view, this protocol represents an extremely simple, efficient, and atom-economic way to construct substituted pyrroles in good yields with high selectivity," the researchers note.—BH

YOUNG BLOOD HEALS AGING HEARTS

In news that may hearten vampires worldwide, medical researchers have discovered that a dose of youthful blood can rejuvenate an aging heart—at least in mice. Specifically, a protein called growth differentiation factor 11 (GDF11) found in the blood of young mice can reverse a common heart condition in the elderly called cardiac hypertrophy, which often leads to heart failure. To investigate the antiaging compound, a team of researchers led by Amy J. Wagers and Richard T. Lee at the Harvard Stem Cell Institute connected the circulatory systems of old and young mice so that they shared the same blood. After four weeks of sharing the same circulatory system, the cardiac hypertrophy in the old mice "dramatically regressed," they report in *Cell* (2013, DOI: 10.1016/j.cell.2013.04.015). The team used proteomics methods to identify the rejuvenating protein in young mouse blood that is lost with age. Finally, to confirm that GDF11 was the youthful elixir and to rule out other sources of age reversal, the researchers injected the protein directly into old mice and saw the same rejuvenating effects. If the protein works the same way in humans as it does in mice, the discovery may eventually lead to new heart therapies.—SE

MRI SPOTS ENZYME CROSS-LINKER

Magnetic resonance imaging is a powerful tool for locating tumors. It may soon also help clinicians choose a course of treatment. Mark D. Pagel and colleagues at the University of Arizona have developed a new contrast agent to detect the activity of



CEST-active agent

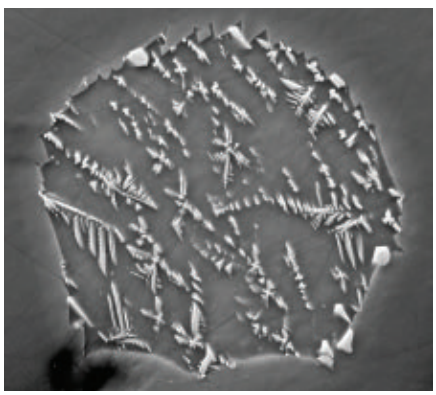
an enzyme, transglutaminase, which is associated with tumor growth and drug resistance (*J. Am. Chem. Soc.* 2013, DOI: 10.1021/ja400254e). Prior attempts to detect transglutaminase in tissue by MRI sometimes yielded false positives on normal tissue surrounding tumors. So Pagel's team developed an agent with an easy-to-follow change in MRI signal. The group's contrast agent features an amine side chain that transglutaminase recognizes. The enzyme cross-links the contrast agent to proteins on a tumor, forming an amide bond that generates a signal in an MRI technique called chemical exchange saturation transfer (CEST). Some of the contrast agent may remain in tissues without being cross-linked, but it generates a different CEST signal so it can be disregarded. The agent has not yet been tested in live animals or people. But if it can detect transglutaminase activity in a tumor, it could indicate drug resistance, which would dictate treatment decisions.—CD

EXHAUST CATALYST TRAPS AND SCRUBS NO_X

Automobile engines designed to combust fuel in a large excess of oxygen can achieve higher fuel efficiency than other common engines. But standard catalytic cleanup technology cannot readily scrub (chemically reduce) the nitrogen oxides (NO and NO_2, or NO_x) in the exhaust of these so-called lean-burn engines because of the overwhelming excess of O_2. A research team led by Hui Xian of Tianjin University, in China, has demonstrated that NO_x can be scrubbed effectively by using a palladium-doped $LaSrCoO_3$ material to trap and treat the pollutants (*ACS Catal.* 2013, DOI: 10.1021/cs400136t). The method works by oxidizing NO_x compounds in excess O_2 and trapping them as nitrates. The nitrates are periodically purged and reduced by hydrocarbons, which are deliberately generated by briefly switching the engine from a fuel-lean to a fuel-rich mode. In contrast to previously studied lean NO_x trap materials, the new compound resists sulfur poisoning and does not depend on costly platinum. In addition, lean NO_x trap technology could be simpler and smaller than an alternative NO_x treatment method that requires carrying an onboard tank of a reductant such as urea.—MJ

EARTH AND MOON SHARE WATER SOURCE

Two years ago, scientists discovered that bubbles of preserved magma in ancient rocks on Earth's moon contained large amounts of water, a finding that contradicted the notion that the moon has always been bone-dry. Now, the same group, headed by Alberto E. Saal of Brown University, finds that this lunar water has the same isotopic composition as water on Earth, implying that Earth and its moon have a common water source (*Science* 2013, DOI: 10.1126/science.1235142). The group examined samples of moon rocks returned to Earth from the Apollo 15 and 17 missions. Earth's water is believed to have been seeded by carbonaceous chondrites, which are common meteorites hailing from an asteroid belt near Jupiter. Because the moon was likely formed from debris flung from the impact of a Mars-sized asteroid on the nascent Earth, the new finding suggests that Earth was already wet at the time of impact. Researchers have also assumed that the moon's lighter elements, such as hydrogen, would have boiled off into space after the impact, but this idea may need to be rethought, the authors say.—EKW



JOHN ARMSTRONG/GEOPHYSICAL LABORATORY/ CARNEGIE INSTITUTION OF WASHINGTON

A 30-μm-diameter lunar melt inclusion from an Apollo 17 mission sample contains water resembling that found on Earth.

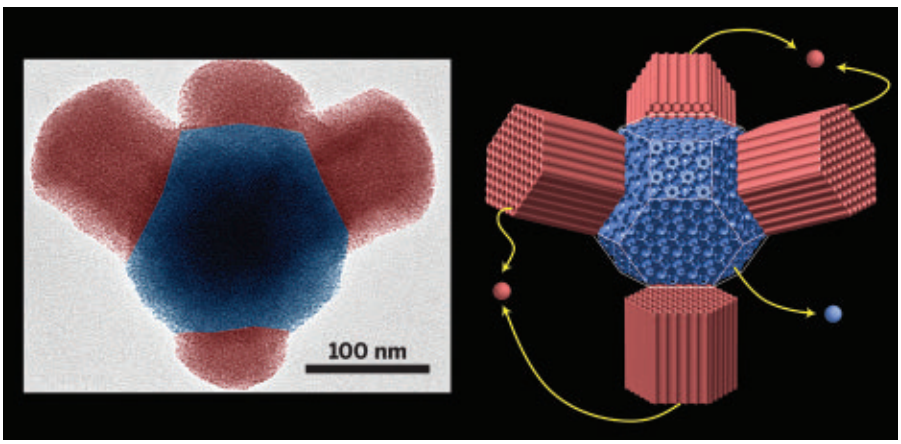
TAILORED GEOMETRY FOR NANOSTRUCTURES

Unique properties could improve CATALYSIS, BATTERIES

MITCH JACOBY, C&EN CHICAGO

LIKE JACKS OF ALL TRADES working in construction, materials chemists serve as civil engineers and architects, designing materials from the ground up and considering the form and function of internal and external structures. They also serve as carpenters, masons, and roofers, setting every building block precisely in its place.

Some of the structures have dimensions measuring mere nanometers from end to end, which can make the assembly job highly demanding. Today, though, researchers are using a variety of synthesis techniques that empower them with extreme dexterity and the ability to tailor molecule-sized structures to suit their needs. As a handful of just-published studies show, that level of adroitness enables scientists to custom-design materials with unique properties that lead to improved performance in catalysts, batteries, drug delivery applications, and other areas.



COURTESY OF ULI WIESNER/CORNELL U

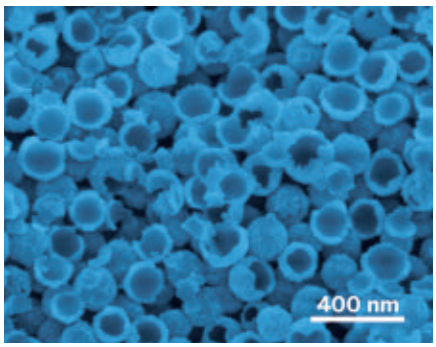
MULTIFACETED Porous particles with distinct body and arms (TEM image and drawing) might one day be used to separately store and deliver incompatible drugs.

In one case, researchers in China boosted the photocatalytic properties of titanium dioxide by preparing a crystalline form of the material with customized morphology and composition. TiO_2 is used extensively as a photocatalyst but suffers from two important shortcomings, explains Tianjin University's Jinlong Gong, who led the study.

Because of the material's band gap—an energy range that's inaccessable for the material's electrons—TiO_2 does not absorb much visible light. That portion of the solar spectrum, therefore, can't be used in applications. In addition, after TiO_2 undergoes light-induced electronic excitation, it often de-excites before the absorbed light can be exploited to trigger decomposition of pollutants or used in other ways.

To address those problems, Gong, Jianwei Lu, Peng Zhang, and coworkers used silica-based templating followed by chemical etching to form cup- or bowl-shaped porous TiO_2 nanocrystals decorated with gold nanoparticles. In a series of control tests using light in the visible range, the group demonstrated that their nanosized TiO_2-gold structures decompose methylene blue, a stand-in for organic pollutants, far more effectively than reference photocatalysts (*Chem. Commun.* 2013, DOI: 10.1039/c3cc42029a).

As Gong explains, the presence of gold boosts TiO_2's ability to harvest visible light. And the unusual cup shape further improves light absorption, aids adsorption and diffusion of pollutant molecules, and helps disperse the nanocups in water, all of which improve photocatalytic activity.



ADAPTED FROM *CHEM. COMMUN.*

BOWLED OVER Decorated with gold nanoparticles, the hollow bowl-shaped titania nanostructures shown in this SEM image are highly active photocatalysts.

Gong stresses that the light-absorbing characteristics of gold nanoparticles can be fine-tuned via particle size, which could lead to customized nanostructures for solar cells and other photo-harvesting applications.

IN ANOTHER RECENT study, Weiyang Li, Yi Cui, and coworkers at Stanford University turned to nanocrystal engineering to come up with a form of sulfur that can be used as a high-performance battery cathode. Sulfur's high charge capacity, which is five times greater than that of common metal oxide cathode materials, could make the abundant element a rock star in the long-lasting lithium battery arena.

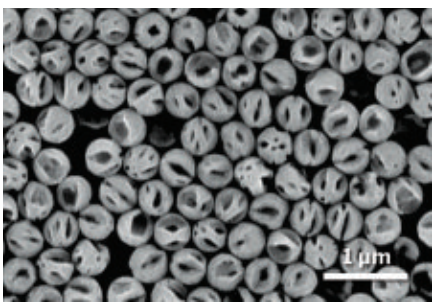
But sulfur-based batteries' ability to hold that high charge fades after just a few charging cycles. There are a number of reasons for the diminished ability. Sulfur-based cathodes in test batteries expand, crack, and slowly disintegrate when they react with lithium, the reaction that generates battery power. And loss of charge capacity also results from cathode reactions that form polysulfide compounds that dissolve in the electrolyte solution, the medium in which lithium ions shuttle between electrodes during battery operation.

The Stanford group approached these problems by using a single-step room-temperature reaction to make polymer-encapsulated hollow sulfur nanospheres. Cui explains that by engineering empty space in the interior of the particles and wrapping them in a polymer, the nanospheres don't expand outward upon lithiation and crack cathodes that contain the nanospheres. In addition, the polymer protects the particles from dissolving, and the

nanoscale size enhances ion and electron transport. Tests show that the custom sulfur particles lead to high charge capacity that resists fading even after hundreds of charge-discharge cycles (*Proc. Natl. Acad. Sci. USA* 2013, DOI: 10.1073/pnas.1220992110).

Meanwhile, a team of researchers led by Ulrich Wiesner of Cornell University has come up with a surfactant-directed colloidal chemistry method for synthesizing porous silica nanoparticles featuring structurally distinct compartments within a single particle. These Jekyll and Hyde particles consist of cagelike crystalline cores with up to four precisely aligned arms protruding from the cores' vertices. The cores' interior channels sit in a cubic arrangement, whereas those in the arms are arranged hexagonally (*Science* 2013, DOI: 10.1126/science.1231391).

The team notes that they can control the extent to which the arms grow simply by adjusting the concentration of one component in the synthesis. They add that differences in the compartments' structures suggest that they could be selectively tailored to have distinct chemical properties. Dual personality in a single particle might be exploited to store incompatible drugs in one place but avoid the incompatibility problem by delivering them on different timescales.



PROC. NATL. ACAD. SCI.

CHARGED UP Polymer-coated hollow sulfur nanospheres (seen in this SEM image) show promise as battery materials.

The studies cause Robert A. Wolkow, a physics professor at the University of Alberta, Edmonton, to think back to his days at Bell Laboratories in the 1980s when Louis E. Brus and Michael L. Steigerwald were conducting some of the earliest nanoparticle investigations. "I admired their pioneering nanoparticle studies and have kept an eye on the area ever since then," Wolkow says. "These most recent advances appear to take substantial steps toward general shape and function control, which further open the door to useful applications." ■

C&EN WEBINARS

Stronger bonds.

Improving your Analysis by Design

Date: May 21st, 2013
Time: 11:00 a.m. EDT / 8:00 a.m. PDT / 16:00 BST / 17:00 CEDT

The development of a chromatographic method for the separation and quantification of a series of components is done routinely in many laboratories. It is often seen as an art and not as a scientific practice. There is a perception that it requires many years to learn the subtleties of column selection and even longer to understand the nuances of mobile phase and pH determination to optimize a separation. The seminar will begin by looking at what key physiochemical properties of the molecules to be separated are important and how this information can be readily obtained and then used to develop a separation. This seminar will also unravel some of the mysteries associated with column selection. The approach will be to combine characterization tests (popularized by Tanaka as a way of fingerprinting some of the key mechanisms that can drive a separation process), with the information gathered from the molecule to predict a separation.

The choice of mobile phase can be critical in optimizing a separation and several key components will be considered including:

- The effect that pH can have on the resolution of critical pairs and as well as peak shape.
- How buffer selection can have an important effect on the robustness of the assay.
- The choice of optimization of organic solvent will be investigated.

Examples will be given throughout the seminar to demonstrate how this approach is effective in providing a quick and robust approach to developing a separation.

Who Should Attend:

- All practicing chromatography method developers
- Analytical scientists who are interested in learning how science can be applied to the art of chromatography

Key Learning Objectives:

- How to optimize column selection
- How to ensure the correct mobile phase is chosen
- How to do some basic troubleshooting of an assay in the method development stage

Speaker

Tony Edge,
R&D Principal, Chromatography Consumables Division,
Thermo Scientific

Moderator

Stu Borman,
Senior Correspondent, C&EN

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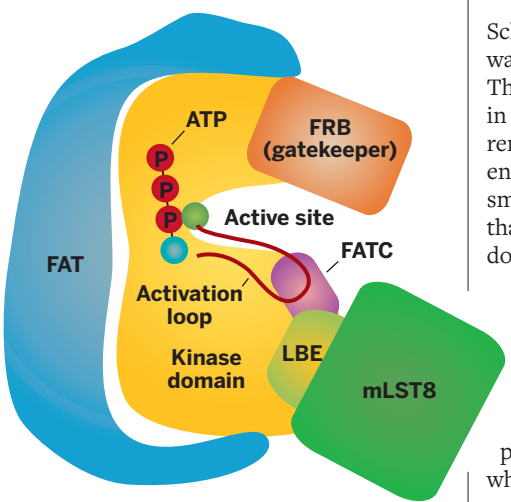
LAYOUT, WORKINGS OF DRUG TARGET FOUND

Researchers obtain structure and propose mechanism of GROWTH-SIGNALING ENZYME mTOR

THE ENZYME mTOR is the target of an approved immunity-suppressing drug as well as drug candidates for cancer and other conditions. Some scientists have longed to know its structure, how it interacts with substrates, and how it catalyzes reactions so they could use the information to develop safer and more powerful mTOR-targeted medications. But it's been difficult to obtain sufficient material suitable for structural analysis.

Nikola P. Pavletich and coworkers at Memorial Sloan-Kettering Cancer Center have now succeeded in obtaining crystals and have analyzed mTOR structurally and mechanistically (*Nature* 2013, DOI: 10.1038/nature12122). The work suggests that one of mTOR's protein domains is a gatekeeper that controls substrates' access to the enzyme's active site.

DARIO ALESSI & YOGESH KULATHU



CAVEAT mTOR mTOR's structure includes FAT, mLST8, LBE, FRB (FKBP12-rapamycin binding), and kinase domains plus an activation loop. The active site includes a magnesium ion (green circle) and ATP (adenosine triphosphate), which provides phosphate for mTOR-catalyzed phosphorylation. FKBP12-rapamycin inhibits mTOR by binding FRB, blocking substrate access to the active site.

mTOR plays a critical role in both cancer and immunity by stimulating production of components needed for protein synthesis and the growth and division of cells, including cancer and immune-system cells. The approved drug that interacts with mTOR is the immunosuppressant rapamycin (sirolimus), a microbial natural product that prevents people's immune systems from rejecting transplanted kidneys, livers, hearts, and other organs.

In 1994, two groups, led by Harvard University chemistry professor Stuart L. Schreiber and Johns Hopkins University neuroscientist Solomon H. Snyder, discovered that rapamycin and a protein called FKBP12 collaborate to bind mTOR and inhibit its activity. The result of those studies was the discovery and naming of mTOR (mammalian target of rapamycin).

"My first impression is 'Wow!'" says Schreiber of the new study. "I've been waiting for years to see these insights." The work by Pavletich and coworkers "fills in critical gaps in our understanding of a remarkable feat of natural selection"—the engagement of a microbial product and a small protein to form a composite surface that targets the huge mTOR and shuts down its operation, he says.

In a *Nature* commentary, Dario R. Alessi and Yogesh Kulathu of the MRC Protein Phosphorylation & Ubiquitylation Unit at the University of Dundee, in Scotland, point out that the function of mTOR in cells is to catalyze the phosphorylation of signaling molecules, which sends signals that tell cells to grow and multiply. "mTOR integrates and interprets all sorts of factors that influence cell growth—including nutrients, stressors, and the outputs of signal-transduction networks—by targeting a multitude of substrates that drive processes such as protein translation, metabolism, and cell division," they explain.

"Research into mTOR-mediated signaling has taken on added urgency since it was discovered that most cancers contain mutations that inappropriately activate this protein," they add. That's why mTOR is a cancer target.

Pavletich and coworkers coaxed human cells to produce mTOR, assembled it with a stabilizing subunit, and identified a truncated version they could crystalize and analyze. The structure enabled them to propose how mTOR works and how its inhibitors achieve their potency and selectivity.

"The solution to the problem is beautiful and elegant," Schreiber says. Normally, mTOR's FRB (FKBP12-rapamycin binding) domain "dangles in front of the kinase domain, luring into the active site certain mTOR substrates." When FKBP12-rapamycin binds FRB, however, the domain "clamps down on the enzyme active site, blocking access to substrates and preventing FRB from playing its normal substrate-recruitment role," Schreiber says. He adds that he would now like to explore new ways to achieve the exquisite target selectivity of small molecules like rapamycin "by exploring ideas that result directly from this important advance."—STU BORMAN

LAB LESSONS FOR RELUCTANT CHEMISTS

ACS MEETING NEWS: Courses aim to engage students who don't know the difference between a beaker and a Bunsen burner

BETHANY HALFORD, C&EN BOSTON

AT THEIR WORST, chemistry courses for nonscience majors are a drag for everyone. The students are there only to get a university-mandated laboratory credit, and the professor is there because someone has to teach the class. But at their best, these so-called nonmajor courses show nonscientists why chemistry is important and let teachers see how outsiders perceive their science. Then the courses give instructors the opportunity to change that perception.

At the American Chemical Society national meeting in New Orleans last month, several educators spoke about their work on such classes. Central to a number of them were innovative laboratory experiments that let students get a taste of the scientific process and how chemists do what they do.

"This approach can really excite students," said Marc L. Richard, a chemistry professor at Richard Stockton College of New Jersey, in Galloway. "You demonstrate how science is done by actually doing it, rather than talking about it or just giving students a demonstration."

During their college careers and beyond, these students will probably take only one or two science classes, Richard noted, so it's important that their experience with science be a positive one that gives them the skills to think about science as they encounter it in the world.

"These students are the people who are going to end up as our lawyers, our businesspeople, and our legislators," said David A. Katz, a chemistry professor at Pima Community College, in Tucson, who organized the symposium. "They don't need a watered-down chemistry course. They need a course that's going to look at how science affects their daily lives."

To that end, Katz has been teaching "Consumer Chemistry" at Pima since 2004. The class meets only in the laboratory, where Katz gives students a brief lecture before launching into an experiment that explores the chemistry they encounter as consumers. "I don't load them down with the basics and take them forward," he said. "Rather, I introduce the chemistry more in context."

DONNA CONNOR

REACHING NEW HEIGHTS Students at the Richard Stockton College of New Jersey study a Mentos and Diet Coke geyser as part of a capstone project.

For example, in one laboratory experiment, the students learn about fats and oils by experimenting with potato chips. They crush the chips and then rinse them with an organic solvent to pull off any oil. They then dry the leftover food and weigh it, ultimately seeing that the weight lost matches up with how much fat the nutritional information says the chips contain.

Students also make a sunscreen lotion and test its ultraviolet-light-absorbing properties, extract the flavor and color additives in candy, and extract essential oils to make perfumes. "I'm always trying to come up with new experiments," Katz told C&EN.

Stockton's "Experiential Chemistry" class also takes place entirely in the laboratory. The course was originally developed by now-retired professor Jonathan Griffiths, and Richard took over teaching it six years ago. "The laboratory experiences are designed to give students initial instructions on how to get started, suggesting measurements or procedures they should follow, but then are open-ended so the students can explore," Richard explained.

AT FIRST, students are simply encouraged to wonder about things. They're taught to make observations and ask questions, even if they don't get any answers. That's because in science the answers aren't always there.

For example, in one laboratory experience students are given a sealed cardboard box containing an object. Their goal is to figure out what the object is. "All the boxes are numbered, but the key that says what's in each box was lost 20 years ago," Richard said. "I have no idea what's in the boxes, and I don't want to know." It's a way of driving home to students that scientists often have to extrapolate information from something they can't probe directly. "I really want them to understand how we practice chemistry and the research process—the idea of making a model, asking questions, and figuring out how to answer them if you're doing an experiment," he explained.

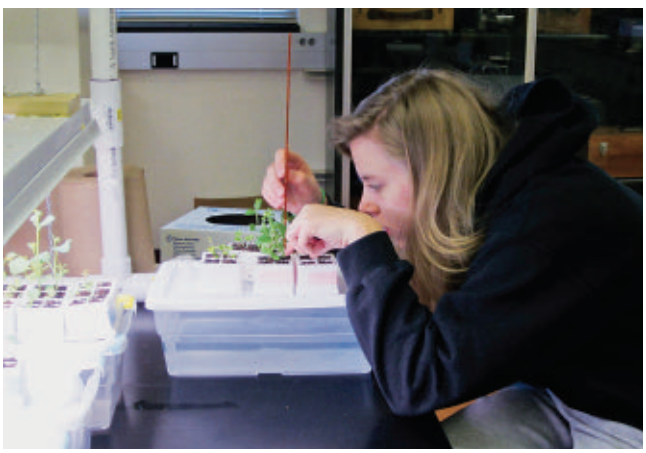
Richard noted that the labs where students get to take home something they've made, such as photochromic plastic or bismuth crystals, are among the most popular. They also serve as a recruiting tool, he added. Other students see what their peers have brought home and get curious about the class.

The course ends with a capstone project, which students design and carry out. "A group of students always wants to work on the Mentos and Diet Coke geyser," Richard said. They explore the explosive combination by trying different sodas, different candies, and various modifications to the Mentos. "Based on feedback, it's pretty clear that after the course students feel they have a better perception of chemistry," Richard said.

"Chemistry departments don't always have opportunities for nonmajors," noted Jennifer E. Mihalick, a chemistry professor at the University of Wisconsin, Oshkosh. "I remember in college hearing about 'Physics for Poets' and 'Rocks for Jocks,' but the chemistry department has such a big service load, that I think it's less common for us to offer a liberal-arts-focused course."

In 2003, Mihalick began teaching "Introduction to the Chemistry of Materials," a course for nonmajors that she teaches with the costume designer from the university's theater department. The class explores the chemistry behind materials that society depends on, such as fabrics, metals, polymers, ceramics, and semiconductors.

KEVIN METZ



GROWING KNOWLEDGE A student at Michigan's Albion College measures plants as part of a semester-long nanoscience experiment.

Mihalick said the labs where students make things are the most popular. In one lab they prepare concrete, and in another they make colored glass using a room-temperature process.

Mihalick enjoys the freedom the class gives her as an educator. "I don't have to cover anything in particular," she said. "I can choose interesting topics right out of the newspaper." For example, when she first taught the course in 2003, classes started just two days after the space shuttle *Columbia* disintegrated on its reentry into Earth's atmosphere. So Mihalick and her students followed the ensuing investigation, learning about the carbon fiber composites in the shuttle's wings.

WHEN ASKED TO CREATE a laboratory course for nonmajor honors students, Kevin Metz, a chemistry professor at Michigan's Albion College, also wanted to address a topic in the news, and so he came up with "Great Issues in Science: Nanoscience."

"I study nanoscience, and these were all students who want to go into policy and law," he said. "I decided I would design a class where we talked not only about what nanoscience is from a physical science perspective but also about the challenges within nanoscience in terms of policy, as well as environmental and sustainability issues."

For the laboratory portion of the class, Metz designed a large open-ended experiment in which the students would synthesize silver nanoparticles and then feed them to *Brassica rapa*, also known as the Wisconsin Fast Plant for its short lifecycle. It was up to the students to design the exposure experiments, determining how large a concentration of nanoparticles they would use.

About half of the plants died because of the way the experiments were designed, Metz said. The half that lived, however, indicated there was no significant difference in height between the plants that were exposed to silver nanoparticles and the control plants. Chemical analysis of the plants' tops revealed silver content, suggesting the plants were pulling the nanoparticles out of the soil.

Metz said that before embarking on the experiment, his nonmajor students had this view that science was simply "a system of buttons you push to get a result. They were shocked to realize it was a long process and the results were heavily dependent on how the scientists worked and how they designed their experiments."

But Metz says his students weren't the only ones who took something away from this course. "I gained perspective on how nonmajor students view science," he said. "Just teaching this one class for nonmajors has influenced how I teach my classes for majors. I find myself talking not only about the nuts and bolts of chemistry but about the broader impacts of science as a process, how we do it, and what the ramifications are." ■

ACADEMIA

Suzanne Fortier has been selected as McGill University's 17th principal and vice chancellor. Her five-year term will begin in September 2013. Most recently, she was president of the Natural Sciences & Engineering Research Council of Canada (NSERC), in Ottawa. Prior to joining NSERC, she served as a vice principal and an associate dean of graduate studies at Queen's University in Kingston, Ontario, where she was also a professor of chemistry.

Jennifer A. Lewis, an internationally recognized leader in the fields of 3-D printing and biomimetic materials, has been appointed as the first Hansjörg Wyss Professor of Biologically Inspired Engineering at the Harvard School of Engineering & Applied Sciences. In addition, she has been named a faculty member of Harvard University's Wyss Institute for Biologically Inspired Engineering. Prior to joining Harvard, Lewis was the Hans Thurnauer Professor of Materials Science & Engineering and director of the Frederick Seitz Materials Research Laboratory at the University of Illinois, Urbana-Champaign.

Victor R. McCrary has been named vice president for research and economic development at Morgan State University in Baltimore. In this newly created position, he will oversee the creation of an enterprise-wide research strategy to increase external research funding and expand the university's intellectual property portfolio in an effort to spark strategic partnerships with industry, government, and other academic institutions. Previously, he had been the business executive for science and technology at Johns Hopkins University's Applied Physics Laboratory.

Krishnan Sadagopan has been named an assistant professor in the chemistry department at Oklahoma State University. Previously he was a postdoctoral research associate at Oxford University. His research focuses on bioanalytical chemistry, biocatalysis, electrochemistry, surface chemistry, biofuel cells, enzyme biosensors, drug screening, and protein detection. **Yolanda Vasquez** has also joined OSU's chemistry department as an assistant professor. Vasquez was a postdoctoral research fellow at Harvard University. She specializes in nanoscience, materials science, tissue engineering, and biomaterials. In addition, **Jimmie Weaver** has been named an assistant professor in OSU's chemistry department. Weaver, who conducted postdoctoral research at Yale University, is focused on organic chemistry, catalysis, material remediation, and development of synthetic methodology.

Wolfgang Voelter has retired from the University of Tübingen, in Germany. He joined the university in 1970, focusing his research on carbohydrate and peptide chemistry. He is credited with more than 800 publications, books, and patents.

BUSINESS

Ben C. Askew has joined SciFluor Life Sciences as vice president of research. Most recently, Askew served as entrepreneur-in-residence for Third Rock Ventures, a venture capital firm focused on building life sciences companies. Founded in 2011, Cambridge, Mass.-based SciFluor is a drug discovery and development company that uses fluorine to accelerate the development of innovative therapeutics.

Magdalena A. Biernat and **Rik Houben** have joined AkzoNobel's surface chemistry group for Europe, the Middle East, India, and Africa as technical project leaders for personal care applications; they are both based in Sempach Station, Switzerland. Biernat recently finished a Ph.D. in biotechnology based on research that began at the Laboratory of Virology at Wageningen University in collaboration with Erasmus Medical Center in Rotterdam, the Netherlands. Houben was previously a senior formulation chemist at Celblos Dermal Research Centre in Singapore.

Cheryl F. Corallo has joined Textum Weaving as its director of sales. Most recently, she served as sales manager for Kuraray Europe in Frankfurt and Kuraray America in Fort Mill, S.C. Textum manufactures engineered specialty and technical fabrics and composites constructed from metal, glass, polymers, ceramic materials, and natural fibers.

Kurt Dinkelacker has been named executive vice president and chief financial officer of Aptuit, a Greenwich, Conn.-based contract research organization serving biotechnology and pharmaceutical companies. Previously, he was an executive vice president and CFO at Retrievex. **Kevin Duffield** has been promoted to vice president of sales and business development for Aptuit. He had been senior director for active pharmaceutical ingredients at the company.

Russell Garlick has become chief scientific officer of SeraCare, which partners with diagnostics researchers, in vitro diagnostics (IVD) manufacturers, and clinical laboratories to provide processed biological materials, specialty human blood products, and other materials and services. Garlick had been cofounder of Life Sciences Group Inc. **Cheri Walker** has joined SeraCare as its chief commercial officer. Prior to joining the company, she consulted with private equity firms and diagnostic and life sciences tools companies. **Ann McCormick** is SeraCare's new chief operating officer. Most recently, she cofounded and managed SeraMetrix Corp. **Joe Kozma** has joined SeraCare as vice president of its IVD Process Solutions unit. Previously, Kozma had been vice president of sales at Serologicals. In addition, **Lisa Alexander** has become SeraCare's vice president of quality and regulatory affairs. Most recently, she was vice president of quality and regulatory affairs at Xcellerex.

Christopher Geiger has been promoted to the position of senior manager within Lockheed Martin's Mission Systems & Training unit. He will be responsible for hardware product engineering for ground and flight training systems. Geiger had been the electrical engineering manager for Lockheed Martin's Global Training & Logistics unit.

Marc van Gerwen has been named global business director for Dow Pharma & Food Solutions (formerly Dow Wolff Cellulosics). He is based in Horgen, Switzerland. Van Gerwen had been marketing and commercial director for Dow Pharma & Food Solutions, which uses plant-based cellulos-

ic technology and companion chemistries to supply products to health care, medical, and industrial markets.

Greg Hertenberger has joined Gelest as product manager for silanes and metal-organic compounds. Most recently, he was an industry manager for coatings, construction materials, and plastics at Ashland Specialty Ingredients. **Matthew Suits** has moved to Gelest to serve as its facilities manager. Previously, he was an engineering and process manager at PB Leiner Gelatins in Davenport, Iowa. **Sean Nichols** has joined Gelest as its purchasing manager. He had been operations manager in the manufacturing division of Haas Group International in West Chester, Pa. In addition, **Adrien Salomon** has been promoted from development engineering manager to production manager at Gelest. **Greg Vuk** has been promoted from shipping and receiving packaging supervisor to logistics manager. With headquarters in Morrisville, Pa., Gelest manufactures organosilicon compounds, metal-organic compounds, and silicones.

David Hogsett has been appointed vice president of research and development and chief technology officer at OPX Biotechnologies. Most recently, he was a vice president of R&D at Mascoma. Based in Boulder, Colo., OPX Biotechnologies is working to make renewable, biobased chemicals and fuels that are more economical and sustainable than existing petroleum-based products.

Eric J. Kaiser has been named Americas business director for Arkema Coating Resins, a global producer of resin products and additives for the coatings industry. Previously, he held sales and marketing positions with Union Carbide and Dow Chemical.

David Maloney has been appointed president and chief operating officer of Equity Solar. Previously, he had been global technology director at DuPont EKC Technology. Based in San Anselmo, Calif., Equity Solar was formed in 2009 to commercialize a patented solar photovoltaic technology licensed from Special Materials Research & Technology.

John Monks has joined Rivertop Renewables as its vice president of business development. Previously, he led business development and sales and marketing teams for ICI, DSM, and Genencor. Based in Missoula, Mont., Rivertop is developing glucaric acid products as effective and cost-competitive replacements for phosphates in the detergent industry and other markets.

Fried Münstermann, president of regional functions and chief financial officer for BASF, will become president of the firm's Global Procurement Competence Center in Ludwigshafen, Germany, effective Aug. 1. He will succeed **Hartwig Michels,** who will become president of the company's European regional division as of Oct. 1. Michels succeeds **Jacques Delmoitiez,** who is retiring. **André Becker,** who is currently senior vice president for global executive human resources, will take over Münstermann's current roles.

Bill Musiak has joined Koch Membrane Systems as its commercial director of water and wastewater for North America. Based in Wilmington, Mass., he will provide leadership to the company's water and wastewater sales force in the U.S., Canada, Mexico, and the Caribbean region. Most recently, Musiak was the commercial director for Pentair X-Flow. Koch Membrane Systems develops membrane technologies for applications in industrial and municipal water and wastewater, food and life sciences, and industrial processes.

Anthony Nigro has been promoted to manager of product development at Halocarbon Products. He had been responsible for the company's inert lubricants business segment and for developing its specialty coatings and electronics fluorochemicals businesses. Based in River Edge, N.J., Halocarbon is a producer of specialty fluorochemicals.

Paul A. (Tony) Novelly has been named chief executive officer of FutureFuel, a manufacturer of custom and performance chemicals and biofuels. **Lee E. Mikles,** who has been both president and CEO since 2005, will retain his position as president.

Sean P. O'Connor has been appointed president and chief executive officer of Nucelis, a specialty chemical company that uses patented technology for modifying cell structure and function. Most recently, O'Connor was president of Chemtura's petroleum additives business unit.

Fernando Tavara has been named president of Sun Chemical Latin America. Most recently, he was vice president of sales. Tavara replaces **Gregory Lawson**, who will retire at the end of 2013. Sun Chemical Latin America is an arm of Parsippany, N.J.-based Sun Chemical, which produces printing inks and pigments for packaging, publications, coatings, plastics, cosmetics, and other industrial applications.

Tavara

Mike Turner has joined Vertellus Specialties as director of its agriculture business segment. Previously, he was vice president and general manager for Universal Fibers Asia in Taicang, China. With headquarters in Indianapolis, Vertellus is a specialty chemical company that produces pyridine and pyridine derivatives for use in many industries.

OTHER ORGANIZATIONS

Margaret E. Kosal has been selected as a fellow for the chief of staff of the Army's inaugural Strategic Studies Group. Kosal, an assistant professor at Georgia Institute of Technology, will join the group as a civilian fellow and will be researching strategic issues for U.S. ground forces and national security. Kosal's research focuses on reducing the threat of weapons of mass destruction and understanding the role of emerging technologies for security. She codirects the Program on Emerging Technology & Security and directs the Program on Biological & Chemical Nonproliferation & Counterterrorism, both of which are part of Georgia Tech's Nunn School's Center for International Strategy, Technology & Policy.

SUSAN J. AINSWORTH *compiles this section. Announcements of new hires and retirements may be sent to s_ainsworth@acs.org.*


DAVID CLEMENTS/LA CROSSE AREA CONVENTION & VISITORS BUREAU

La Crosse, Wis.

2013 GREAT LAKES REGIONAL MEETING

THE LA CROSSE-WINONA Section of the American Chemical Society will host the 2013 Great Lakes Regional Meeting (GLRM) from Wednesday, June 5, through Saturday, June 8. The meeting, which has a theme of "Discovering Chemistry between the Bluffs," will be held at the La Crosse Convention Center and the Radisson Hotel La Crosse in La Crosse, Wis.

The general chairs of the meeting are Jessica Brozek of Hydrite Chemical and Ressano Machado of the University of Wisconsin, La Crosse. Stacy Glidden of Mathy Technology & Engineering is program chair.

Please visit the GLRM 2013 website, glrm-lax.sites.acs.org, for evolving program details, registration, and hotel information.

TECHNICAL PROGRAM. The technical program will cover a wide array of chemistry topics. Planned symposia include "Bio-Energy"; "Bioinorganic Chemistry: Career Highlights of Michael J. Collins," which will feature the Viterbo University professor emeritus of chemistry; "Chemical Education," including high school teacher topics; "Chemistry of Eating Disorders"; "Ethics in Applied Science"; and "Oil Refining: Current Chemicals." In addition, the ACS Division of Small Chemical Businesses will sponsor two sessions: "Resources for Start-Up & Small Businesses" and "True Stories of Success from Entrepreneurs."

GLRM 2013 will also include general sessions in analytical, inorganic, organic, and physical chemistry; biochemistry; and undergraduate research, as well as multiple poster sessions in these and other chemical disciplines.

UNDERGRADUATE PROGRAM. Registered undergraduates are invited to a "Making the Most of Your Regional Meeting Breakfast Social" on Thursday, followed by the undergraduate poster session. That afternoon, Keith Boyer of UW La Crosse; Frank N. Keutsch, UW Madison; and Dylan Millet, University of Minnesota, St. Paul, will present a symposium on atmospheric chemistry.

Students are urged to attend Thursday evening's GLRM 2013 Awards Banquet, at which the undergraduate poster awards will be presented.

GLRM 2013 At A Glance

Dates: June 5–8

Location: La Crosse Convention Center and Radisson Hotel La Crosse in La Crosse, Wis.

Information contacts: Jessica Brozek, general chair, jessica.brozek@hydrite.com; Stacy Glidden, program chair, stacy.glidden@mteservices.com; or John Michael Sophos, ACS Department of Meetings & Expositions, (800) 227-5558, ext. 4608, j_sophos@acs.org

Website: glrm-lax.sites.acs.org

On Friday morning, a career panel featuring Patrick Gorski, Wisconsin State Laboratory of Hygiene; Kirk Moon, Hydrite Chemical; Special Agent Leah Nemetz, Federal Bureau of Investigation Milwaukee Field Office; and Laura Roessler, Elmaro Vineyard, will focus on alternative careers in chemistry.

Registered undergraduates are invited to come to Friday's lunch with an eminent scientist, UW Madison chemistry professor Tehshik P. Yoon.

WORKSHOPS & COURSES. On Thursday morning, the ACS Office of Career Management & Development will present "Finding Your Pathway." The workshop will describe higher education, industry, government, and entrepreneurial careers and hiring trends. It will allow time for participants to inventory their own values, interests, backgrounds, strengths, and weaknesses so that they can select which career pathway they would like to explore in detail.

Also on Thursday morning, the chemical education program will include a workshop on "Resources for Excellence: A Collaborative Project of the 2YC3 [Two-Year College Chemistry Consortium] & the ACS."

An ACS career consultant will hold one-on-one résumé review sessions on Thursday afternoon. Attendees can sign up for appointments at the registration desk on Wednesday evening or during the workshop on Thursday.

An all-day Friday workshop will give "Essential Information & Training for the Chemical Hygiene Officer." This workshop will present details about the position, regulatory requirements, best management practices, risk and exposure assessment, emergency response, and resource materials.

The workshop on "Next-Generation Science Standards" will be held as part of the chemical education program on Saturday morning.

In addition, two ACS Leadership Development System courses will be held during GLRM 2013. "Fostering Innovation" will be offered on Friday afternoon. The course will offer attendees the understanding and tools to tap into their own innovation style and stimulate innovative thinking among their committee members.

"Extraordinary Leaders" will take place all day Saturday. The course will provide a model for effective leadership. Attendees will participate in a 360° review process

that will give them personal feedback on their leadership competencies. They will then use this feedback to create a personal plan for developing leadership strengths.

For additional information and to register for either of these courses, contact Kareem Redmond at (202) 872-6015 or leaders@acs.org.

EVENTS. A variety of social events have been planned for the meeting. Tickets can be purchased through registration or on-site as available. Meeting attendees who have already registered and want to add a ticket can do so by calling John Michael Sophos at (800) 227-5558, ext. 4608.

GLRM 2013 will kick off on Wednesday evening with a plenary lecture by 2012 ACS President Bassam Z. Shakhashiri of UW Madison. He will discuss "The Leadership Role of the ACS in Addressing Grand Global Challenges." The plenary will be followed by a reception during which GLRM 2013 attendees can mingle with Shakhashiri, other members of the ACS Board of Directors in attendance, GLRM 2013 organizing committee members, and others. The plenary session and the reception will be held in the Wisconsin Ballroom at the Radisson.

Tours of the Upper Midwest Environmental Sciences Center will be offered on Thursday. There is no charge for the tours, and transportation will be provided courtesy of the department of chemistry, UW La Crosse. Each tour is limited to 20 people. Participants can sign up for a tour at the time of registration. A limited number of tickets might also be available on-site. For more information about the center, go to www.umesc.usgs.gov/umesc_home.html.

Everyone is invited to attend the Thursday evening GLRM 2013 Awards Reception honoring the recipients of the Division of Chemical Education Great Lakes Region Award for Excellence in High School Teaching, the E. Ann Nalley Great Lakes Region Award for Volunteer Service to the ACS, and the undergraduate poster awards.

The Awards Banquet will follow the reception. Tickets are $32 ($25 for undergraduates).

On Friday evening, attendees are invited to join ACS governance members for a cocktail reception cruise on the *La Crosse Queen* riverboat on the Mississippi. Tickets are $10 (free for undergraduates).

EXHIBITION & SPONSORSHIPS. Industrial and academic booths will be intermixed with the poster boards for the poster sessions on Thursday and Friday. The exhibition area will also serve as Coffee Break Central. Interested potential exhibitors and sponsors are encouraged to visit the meeting webpage to view the floor plan, review the list of existing exhibitors and sponsors, and access the exhibitor and sponsorship registration forms. For additional information, contact Elyse Sorenson at elyse.sorenson@trane.com.

LODGING. A block of rooms has been reserved for GLRM 2013 attendees at the Radisson. Reservations can be made via www.radisson.com/lacrosse/amchem. Alternatively, reservations can be made by calling the hotel at (800) 333-3333 or (608) 784-6680; guests should identify themselves as GLRM 2013 attendees and use the reservation code AMCHEM. Reservations must be made by May 22 in order to guarantee the GLRM 2013 rate. The rate will be honored for stays from June 1 to 10.

REGISTRATION. Meeting registration is available through the GLRM 2013 website. Early-bird registration ends on May 22. Online registration will remain open at the on-site registration rates until June 4.

After June 4, participants must register on-site. On-site registration will take place from 5 to 7 PM on Wednesday, June 5; from 7:30 AM to 5 PM on Thursday and Friday, June 6 and 7; and from 8 to 10 AM on Saturday, June 8.

BILATERAL MEETING ON MOLECULAR MATERIALS

THE INDO-U.S. Symposium on Molecular Materials will take place on July 15–17 at the Indian Institute of Science, in Bangalore. The event is being organized by the Chemical Research Society of India and the American Chemical Society, with funding support from the Indo-U.S. Science & Technology Forum and the Science & Engineering Research Board of India.

The symposium aims to engage scientists from both countries in a global exchange of ideas about materials chemistry and to help the scientists build lasting networks and explore research collaborations. One of the desired outcomes of the symposium is the development of a joint white paper. For more information, visit crsi.org.in/index.php/events/indo-us-symposium.—LW

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- These advertisements are for readers' convenience and are not to be construed as instruments leading to unlawful discrimination.

QUALITY JOBS, QUALITY CHEMISTS

Institut national de la recherche scientifique (INRS) is a research-intensive university offering graduate-level training. One of Canada's leading research universities in terms of grants per professor, INRS brings together some 150 professors and close to 700 students and post-doctoral fellows in its centers in Montreal, Quebec City, Laval, and Varennes. Conducting fundamental research essential to the advancement of science in Quebec as well as internationally, INRS research teams also play a critical role in developing concrete solutions to problems facing our society.

The Centre Énergie Matériaux Télécommunications of INRS is currently seeking a

PROFESSOR-RESEARCHER

ULTRAFAST MATERIALS CHARACTERIZATION

(Tenure-track position – Research Chair – Tier II)

The areas of expertise aimed at, but not limited to, are: time-resolved electron microscopy, electron microscopy, ultrafast electron diffraction, ultrafast characterization of materials, ultra-fast lasers and photonics and their applications in materials science for various areas such as, for example, biomedical and energy.

The candidate should be able to establish collaborations with research teams already in place, while developing or maintaining partnerships with groups outside the Centre. The ability to develop partnerships with companies is particularly valuable.

This position is incorporated within an environment where about forty professors-researchers undertake leading-edge research and training in diverse fields of sustainable energy, advanced materials, ultrafast photonics, telecommunication systems and nanobiotechnology.

The Centre hosts unique major research infrastructure including the Advanced Laser Light Source and the Laboratory of Micro and Nanofabrication, comprising the Infrastructure of Nanostructures and Femtoscience (http://lmn.emt.inrs.ca/EN/inf.htm).

This new position is intended to lead a recent major **$15M** addition, the Infrastructure for Advanced Imaging (IAI), which consists of a time-resolved electron microscope awarded by the Canada Foundation for Innovation (CFI) in the 2012 competition. **This microscope will be unique worldwide.**

REQUIREMENTS:

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- The aptitude for teaching and supervising graduate students and other trainees.
- The ability to work in a multidisciplinary team and within research networks.
- The ability to collaborate with industrial partners.

We actively seek an outstanding candidate who is eligible to be nominated for a Tier II Canada Research Chair.

Potential sources of funding include the Natural Sciences and Engineering Research Council of Canada (NSERC) and the Fonds de recherche du Québec – Nature et technologies (FQRNT).

The Centre is located in Varennes, on the South Shore of Montreal.

The working language of INRS is French. Candidates whose native language is not French are encouraged to apply. The Centre will provide them with all the resources necessary to facilitate their learning of the French language.

Salary and benefits are in accordance with the current collective agreement at INRS.

Interested candidates should submit a full curriculum vitae by e-mail and registered mail, a statement of research interests (max. 3 pages), a statement of teaching philosophy, a copy of their three most representative publications, and the name and coordinates of three references, before **July 15th, 2013**, indicating competition number **DS 13-05** to:

Dr. Federico Rosei, Director, Centre Énergie Matériaux Télécommunications
1650, boul. Lionel-Boulet, Varennes (Québec) J3X 1S2
rosei@emt.inrs.ca

Currently, we plan to hold interviews at the end of August and/or beginning of September 2013.

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POSITION: MATERIALS SCIENTIST (POLYMERS)
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ACADEMIC POSITIONS

RESEARCH SCIENTIST/SCHOLAR I (ELECTRON MICROSCOPIST AND IMAGING SPECIALIST), DEPARTMENT OF CHEMISTRY
COLORADO STATE UNIVERSITY
Fort Collins, Colorado

The position of Electron Microscopist and Imaging Specialist is a full-time, special, 12-month Research Scientist/Scholar I administrative professional position in the CSU Chemistry Department's Central Instrument Facility (CIF) Imaging and X-ray Spectroscopy laboratories. Responsibilities will include providing advanced research services and training for, and routine maintenance of, electron microscopy methods (EM), including ultra-high resolution transmission EM. All instruments in the CIF are available for use by the successful candidate, who will be expected to collaborate with colleagues, staff scientists, faculty, and other principal investigators to advance CSU's primary research, education and service mission. Additional information about the CIF can be found at **http://cif.colostate.edu/.** The successful candidate must have a Ph.D. in a chemistry-related discipline. Familiarity with UHV, EM and X-ray techniques is required and development of collaborations with senior investigators is expected. Familiarity with the chemistry of hard materials, electron energy loss spectroscopy, lithography, and focused ion-beam milling will be considered advantageous. Salary is negotiable and will be commensurate with experience.

For more information or to apply, see **http://cns.natsci.colostate.edu/employment/Chem-EM/.** A full application will include a cover letter, curriculum vitae, and contact information for three professional references. For full consideration, applications must be received by May 27, 2013; however, the search will remain open until a suitable candidate is identified. Anticipated employment start date is July 14, 2013. Files of semifinalists will be available to all Chemistry Department faculty.

CSU is an EO/EA/AA employer. Colorado State University conducts background checks on all final candidates.

ARMSTRONG ATLANTIC STATE UNIVERSITY
Savannah, Georgia
Tenure-Track Assistant Professor—Organic

The Department of Chemistry and Physics at **Armstrong Atlantic State University** in **Savannah, Georgia (http://chemphys.armstrong.edu)** invites applications for a full-time, tenure-track position at the rank of Assistant Professor beginning in August 2013. This position, in our ACS-approved program, requires the candidate to have a Ph.D. in chemistry or a closely related field at the time of appointment. Applicants should possess a strong commitment to excellence in undergraduate teaching and will be expected to develop a scholarly agenda and pursue external funding. Applicants with specialization in organic chemistry are preferred for the tenure track position, however, exceptional candidates in all fields may be considered. For application requirements and a complete description of the position and the department, visit **http://jobs.armstrong.edu.** Application review will begin on May 28, 2013. AA/EOE, open records law state.

ACADEMIC POSITIONS

REWARDING OVERSEAS ELASTOMER TEACHING ASSIGNMENT – EX-PAT INSTRUCTIONAL POSITIONS University Innovation Ventures (UIV) in cooperation with The **University of Akron** Research Foundation is seeking highly qualified candidates with demonstrated leadership and elastomer teaching capabilities to instruct at a new world-class English-based vocational training institute in The Kingdom of Saudi Arabia (KSA). The High Institute for Elastomer Industries (HIEI) opened in September 2012 training technologists to work in the nascent elastomer industry in **Saudi Arabia**: **http://www.hiei.edu.sa/DefaultE.aspx.** Please send your résumé and inquiry to **John Mild – phone: (330) 836-9191 or e-mail John.Mild@Gmail.com.**

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COMPUTERS PLAY SUPER MARIO, STATES ADOPT MICROBES

The Newscripts gang remembers evenings in the late 1980s spent playing games on the **NINTENDO** Entertainment System, guiding a plumber named Mario through mushroom kingdoms. So we were excited to hear about a computer scientist who recently taught his computer how to play Super Mario Bros. and other Nintendo games.

Tom W. Murphy VII works on machine learning, a field of computer science that involves teaching computers how to perform specific tasks. He came up with the idea for the Nintendo project when he reflected on how much more memory his current computer has than the old game system does. "I basically could fit 32 million Nintendos on my computer," he says.

Murphy thought that he could leverage this computing advantage to write a simple computer program that would first figure out the goal of a Nintendo game and then play through it millions of times to find the right combinations of button pushes to win. The computer doesn't actually play with a physical controller. It simulates the signals produced by pressing the buttons.

EVAN-AMOS

Gamer: The old gray Nintendo was *the* video game system of the late 1980s and early '90s.

The program has played about 15 Nintendo games to date, with varying success, Murphy says. For Super Mario Bros., it plays into the third stage of the first level, significantly further than the one minute of game play Murphy used to train the program. But with Tetris, the program doesn't learn the point of the game and just stacks up blocks into ragged pillars. It eventually realizes this Tetris strategy isn't sustainable and pauses the game right before it loses.

Murphy has received interest from other Nintendo fans and computer scientists. A YouTube video he made to explain the program has received about 500,000 views: "It got picked up by a bunch of famous nerds, which was gratifying," he says.

State legislatures show off their pride for their homes by adopting all types of symbols, such as trees, flowers, and, in Massachusetts, even doughnuts.

SHUTTERSTOCK/C&EN

Symbols: Hawaii and Oregon would like to be the first states to adopt an official microbe.

Now Oregon and Hawaii want to honor **STATE MICROBES.**

In February, State Rep. Mark Johnson introduced a resolution in the Oregon House of Representatives to make brewer's yeast, *Saccharomyces cerevisiae*, the official microbe of the state. He thinks the organism serves as a great symbol for the state's thriving craft beer industry. "I'm not aware of another microbe that brings $2.5 billion into Oregon's economy on an annual basis," Johnson says.

The microbe resolution passed the House, 58-0, in April and could get a vote in the state's Senate later this year.

In Hawaii, Stuart P. Donachie, a marine microbiologist at the University of Hawaii, Honolulu, pushed for a resolution to designate *Flavobacterium akiainvivens* the state microbe because it was first found on the islands. Iris Kuo, a high school student working in his lab, discovered the bacterium on decaying akia shrubs, which are native to Hawaii.

State Rep. James K. Tokioka introduced the resolution in the Hawaiian House in January, but the resolution will have to wait until next year to be voted on, Donachie says.

Joan W. Bennett, a microbiologist at Rutgers University, New Brunswick, thinks naming state microbes is a great idea and enjoys thinking up organism-state matches. "It makes for good cocktail party talk at meetings of the American Society for Microbiology," she says.

Bennett hopes adopting state microbes will educate people about the organisms' importance and demonstrate that not all microbes are bad. Donachie agrees: "We should expose everybody to microbes," he says, "in an intellectual context, of course."

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

C&EN WEBINARS

Stronger bonds.

Utilizing Ion Chromatography for Drinking and Wastewater Analysis

Date: May 16, 2013
Time: 11:00 a.m. EDT / 10:00 a.m. CDT / 8:00 a.m. PDT/ 16:00 BST

Although U.S. regulations are cited, the EU and other industrial nations have stringent regulatory requirements for drinking water content. U.S. municipal drinking water and wastewater treatment plants must comply with EPA 300.0 and EPA 300.1 for drinking water requirements. These plants are also known to carry discharge permits by the National Pollution Discharge Elimination System (NPDES). Both cationic and anionic determinations help monitor the primary contaminant specifications. This also includes toxic disinfection byproducts, industrial pollutants and secondary specifications for the acceptable taste of the water. In municipal wastewater, anion and cation determinations ensure that no environmental effects occur as a result of discharging high-salt concentrations into the water system. This webinar demonstrates the advantages of using both ion chromatography and high pressure ion chromatography to separate and quantify common ionic pollutants found in municipal drinking water and wastewater.

Key Learning Objectives:

- Learn about the applications for environmental analysis
- Learn about the importance of regulating certain ionic pollutants in water
- Learn about high pressure ion chromatography and its benefits

Who should attend?

- Analytical chemists working in municipalities, wastewater treatment plants and contract labs
- Environmental analysts interested in EPA Method 300 and 300.1 and others

Speaker

Joachim Weiss,
Technical Director,
Thermo Fisher Scientific,
GmbH

Moderator

Elizabeth K. Wilson,
Senior Editor, C&EN

Hosted by C&EN

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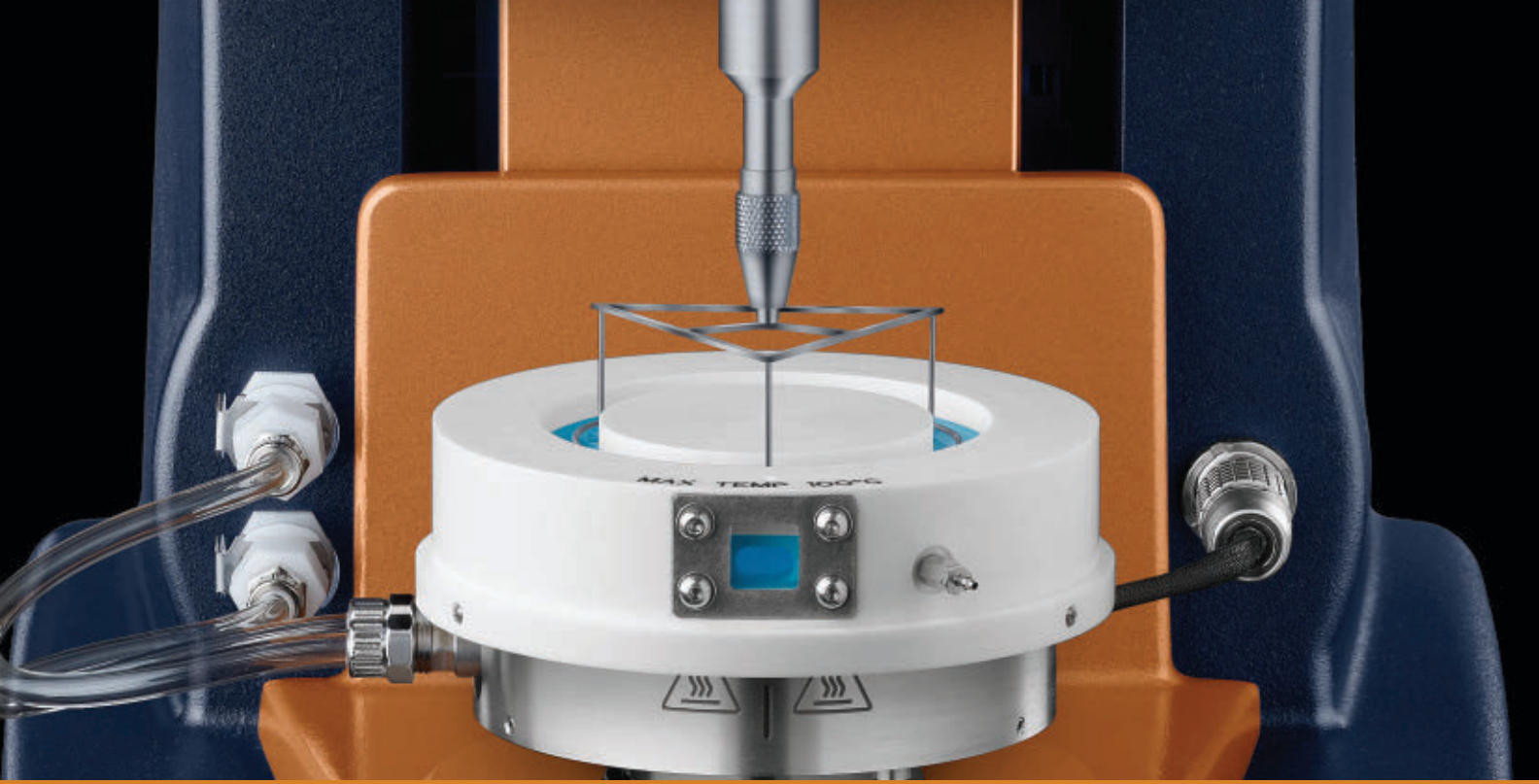

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