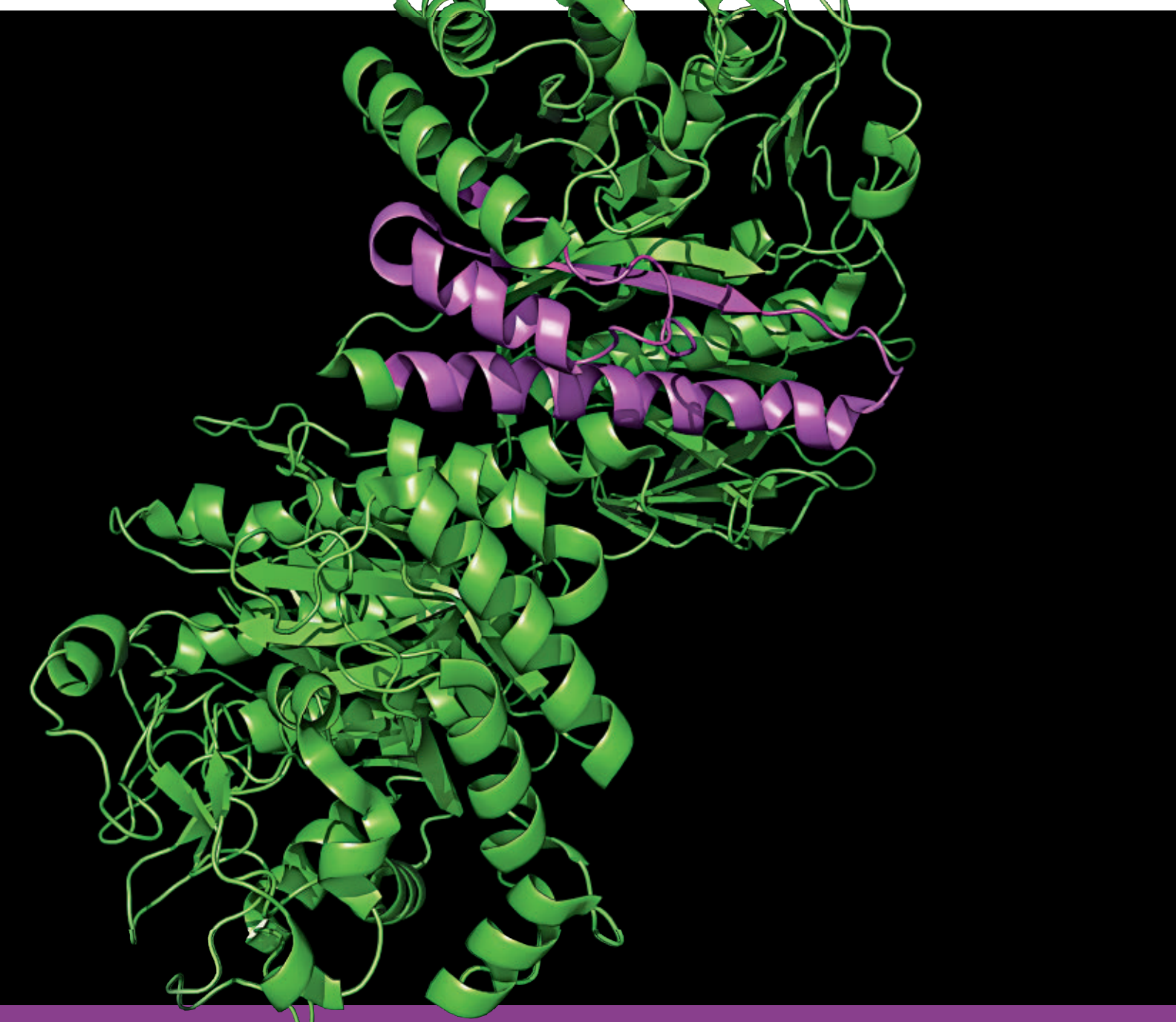
MAY 30, 2011

C&EN

CHEMICAL & ENGINEERING NEWS

SUSTAINABILITY
United Nations' efforts founder **P.39**

WOODWARD REDUX
Notes on conducting materials published **P.46**



FINE CHEMICALS

Suppliers help create new peptide drugs **P.13**

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C&EN

CHEMICAL & ENGINEERING NEWS

Serving the chemical, life sciences, and laboratory worlds

COVER STORY

PEPTIDE THERAPEUTICS

Drug class's stock rises as firms solve the problems of stability, delivery, and manufacture.

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QUOTE OF THE WEEK

"You can't hire a team of scientists to do your shopping for you."

JESSICA ALBA; CELEBRITY SPOKESWOMAN; SAFER CHEMICALS, HEALTHY FAMILIES PAGE 28

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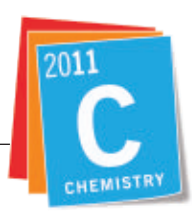
COVER: *An identified peptide fragment, or Phylomer (purple), sits within its host bacterial protein (green). Phylogica*



& THIS WEEK ONLINE

cen-online.org/thisweek

Old Paint Increases Lead Bioavailability

The dust sitting around a home can contain lead from construction materials, old paint, and other materials. Canadian government researchers recently surveyed lead in house dust across the country and found that houses with old paint have more bioavailable lead in the dust.

SHUTTERSTOCK

cenm.ag/env36

Microfluidic Chip Identifies Microbes

Doctors often wish for quick diagnostic tests to identify disease-causing microbes by their genetic fingerprints. Now researchers have designed a microfluidic chip that could provide an all-in-one, sensitive method to detect specific viruses or bacteria in patient samples.

cenm.ag/anl27

Conserving Canada's Valuables

Canada may not be rife with Roman ruins and Rembrandt masterpieces, but the country's art and artifacts keep scientists busy at the Canadian Conservation Institute. C&EN Senior Editor Sarah Everts gets a peek at the institute's research on the paint chemistry of Canadian artists and on preserving leather work from the country's indigenous peoples.

cenm.ag/blg15

Severe Bleeding: When Clotting Isn't Enough

At this month's Mid-Atlantic Regional Meeting of the American Chemical Society, news came of a novel technology to fight profuse bleeding. A Maryland-based start-up called Remedium Technologies is developing wound dressings based on a chemically modified chitosan, a biopolymer that can be scavenged from waste shells of shrimp or crabs. Remedium's CEO started the company while still in graduate school.

cenm.ag/blg16

C&EN IN THE CLASSROOM

AS A HIGH SCHOOL science teacher and a member of ACS, I use C&EN as one of my primary sources for keeping up with current science.

Last summer, I thought this would be a great resource to bring awareness of cutting-edge science to my classroom for the 2010–11 academic year. It would also help to answer the inevitable question: "When are we ever going to need this in the real world?" I also hoped it would spark discussion and, in some, even a desire to become a part of the exciting world of research science.

As the academic year wraps up, I conclude that sharing some of the articles that have appeared in C&EN has been a resounding success. "Fighting Friction" was a class favorite (C&EN, Oct. 11, 2010, page 14). Students appreciated the real-world applications of the theory that was presented by the text, while also being introduced to new ideas—particularly nanotechnology. None of the students had even heard of nanotechnology at that point!

This almost unbelievable unfamiliarity with nanotechnology touched off a year that has been filled with exposure to how nanotechnology has quietly begun to infiltrate our everyday world and how it may have a profound effect on our future. We wrap up the semester with "Moving Up the Food Chain," examining how nanomaterials may impact our health and environment (C&EN, March 14, page 44). From my students and me, thanks for the most stimulating year of science any of us has had in a long time.

Senetta Bancroft
Derby, Kan.

SAYING NO TO NUCLEAR

AS MUCH AS I agree with Rudy Baum on so many issues, his knee-jerk defense of nuclear safety requires a reply from me (C&EN, March 21, page 5). The reaction to this massive accident was not hysteria but a reasoned reaction by nonscientists who realize that they have been conned.

As for safety and cost, just look at the third law of thermodynamics. A simplified version is that it becomes more and more difficult the closer you come to perfection. In effect, reasonable safety can be achieved only at exorbitant cost. The insurance industry knows this, in their way, in that they would never have given construction loans nor will they now without the Price-Anderson Act, which limits their liability to $375 million. Consider this amount a mere pittance for any of the known spills.

I could give examples of half-lives of the deadliest isotopes or compare what this means for cleanup of contaminated land, but suffice it to say that every study has shown that there are other ways of addressing global warming more cheaply and, most important, faster than nuclear energy.

Emil Lawton
Sherman Oaks, Calif.

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The Value Of R&D

AS SCIENTISTS, members of the American Chemical Society understand innately the value of R&D and the importance of government funding of R&D.

It's not always obvious that nonscientists—a category that encompasses most politicians—share that understanding. Thus I was heartened to learn that the person who is perhaps America's most influential economist, Federal Reserve Chairman Ben S. Bernanke, had given a major speech titled "Promoting Research and Development: The Government's Role" in mid-May.

Bernanke gave the keynote address at a two-day conference on "New Building Blocks for Jobs and Economic Growth" sponsored by the Conference Board. Bernanke noted that "the effective commercial application of new ideas involves much more than just pure research. Many other factors are relevant, including the extent of market competition, the intellectual property regime, and the availability of financing for innovative enterprises. That said, the tendency of the market to supply too little of certain types of R&D provides a rationale for government intervention; and no matter how good the policy environment, ultimately, big new ideas are often rooted in well-executed R&D."

Bernanke went on to observe that "the primary economic rationale for a government role in R&D is that, absent such intervention, the private market would not adequately supply certain types of research. The argument, which applies particularly strongly to basic or fundamental research, is that the full economic value of a scientific advance is unlikely to accrue to the discoverer, especially if the new knowledge can be replicated or disseminated at low cost. ... If many people are able to exploit, or otherwise benefit from, research done by others, then the total or social return to research may be higher on average than the private return to those who bear the costs and risks of innovation. As a result, market forces will lead to underinvestment in R&D from society's perspective, providing a rationale for government intervention."

Although it might be possible to correct this situation through stronger intellectual property protection, Bernanke said, "this approach has significant drawbacks of its own ... in that strict limitations on the free use of new ideas would inhibit both further research and the development of valuable commercial applications."

"Is government support of R&D today at the 'right' level?" Bernanke asked. The question isn't easily answered, but he noted two trends: Since the 1970s, R&D spending by the federal government has decreased as a share of GDP, and the share of R&D spending targeted to basic research has also been declining. "These two trends ... are related, as government R&D spending tends to be more heavily weighted toward basic research and science. The declining emphasis on basic research is somewhat concerning because fundamental research is ultimately the source of most innovation, albeit often with long lags."

Bernanke discussed approaches government can take to support R&D, including "direct funding of government research facilities, grants to university or private-sector researchers, contracts for specific projects, and tax incentives." He went on to observe that "the challenge to policymakers is to encourage experimentation and a greater diversity of approaches while simultaneously ensuring that an effective peer-review process is in place to guide funding toward high-quality science." Nevertheless, he continued, "however it is channeled, government support for innovation and R&D will be more effective if it is thought of as a long-run investment. Gestation lags from basic research to commercial application to the ultimate economic benefits can be very long. ... Thus, governments that choose to provide support for R&D are likely to get better results if that support is stable, avoiding a pattern of feast or famine."

Major battles are looming in Congress over the 2012 budget. The budgets of many agencies that support R&D saw increases in 2010 that have been carried over for the most part into 2011. In their zeal to cut budget deficits, I hope members of Congress heed Bernanke's caution on the pitfalls of feast or famine funding of R&D.

Thanks for reading.

Editor-in-chief

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

C&EN news of the week

MAY 30, 2011 EDITED BY WILLIAM G. SCHULZ & KIMBERLY R. TWAMBLY

UBIQUITINS IN FOUR-PART HARMONY

BIOMACROMOLECULAR SYNTHESIS: Tetraubiquitin is the longest protein made chemically

BY CHEMICALLY PREPARING a four-membered chain of ubiquitin proteins for the first time, a research team has not only opened the door to a better understanding of the role of polyubiquitins in biology but also set a new size record for chemical synthesis of proteins.

Different types of polyubiquitins have different cellular functions, such as ferrying unneeded proteins to the proteasome, the cell's recycling center. There are seven homogeneous polyubiquitins, consisting of individual units linked to one another via the same lysine residue. But there are also innumerable possibilities for mixed-linkage types of polyubiquitins.

Scientists would love to better understand the relationship between polyubiquitin structure and function. But this has been difficult because polyubiquitins are hard to synthesize. Enzymatic techniques have yielded only a few types of homogeneous tetraubiquitins.

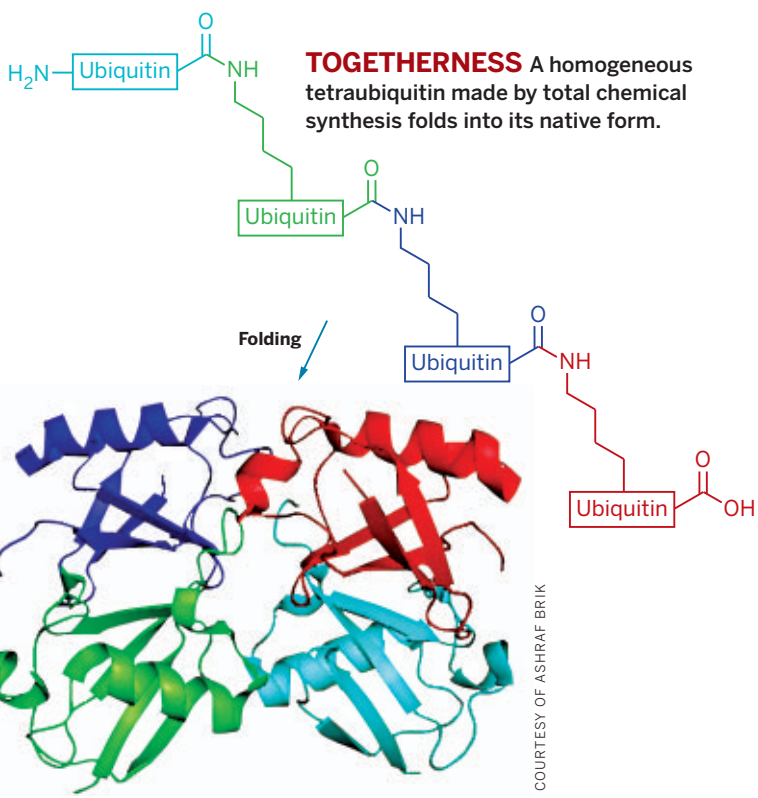
Tetraubiquitins are of particular interest because they are believed to be the smallest polyubiquitins that are active biologically. For instance, homogeneous tetraubiquitin attaches to proteins to mark them for disposal by the proteasome. But polyubiquitins this large have not previously been made by chemical synthesis, which has the potential to produce versions that are much more customized than those accessible enzymatically.

Chemical synthesis has until now been restricted to diubiquitins, which several groups created last year (C&EN, Oct. 11, 2010, page 36). One group, led by protein synthesis specialist Ashraf Brik of Ben-Gurion University of the Negev, in Israel, prepared all seven types of homogeneous lysine-linked diubiquitin chains (*Angew. Chem. Int. Ed.*, DOI: 10.1002/anie.201003763).

Now, Brik and coworkers report having extended that work by using a similar chemical approach to synthesize a homogeneous tetraubiquitin (*Angew. Chem. Int. Ed.*, DOI: 10.1002/anie.201101920). Prior to this feat, the largest protein molecules prepared by total chemical synthesis had about 200 residues. Tetraubiquitin has 306, making the new structure the largest protein made chemically.

The researchers believe the technique can be further extended to other types of homogeneous and mixed-linkage tetraubiquitins and perhaps longer polyubiquitins as well. "By using chemical synthesis, virtually unlimited variations" would be accessible, the researchers write in their latest paper. "This would lead to unraveling of the thus-far unattainable details of ubiquitin biology."

"The limited availability of polyubiquitin chains of defined lengths and linkage composition certainly has been a major impediment to the ubiquitin field," comments polyubiquitin expert Robert E. Cohen of Colorado State University. "The total chemical synthesis approach that's now been developed may provide the ultimate solution."



TOGETHERNESS A homogeneous tetraubiquitin made by total chemical synthesis folds into its native form.

COURTESY OF ASHRAF BRIK

To make tetraubiquitin, Brik and coworkers first tried a convergent approach—synthesizing two diubiquitins and combining them—which they thought might be more efficient than linear synthesis. But they ran into problems and ended up using linear synthesis to connect four ubiquitin units with native isopeptide bonds at 5% isolated yield. They then showed that the synthesized tetraubiquitin folds into its native protein form.

In principle, the approach "offers complete flexibility with respect to ubiquitin-ubiquitin linkage type and has the potential for incorporation of nonnatural amino acids and other modifications," Cohen notes. "It could have an enormous impact on the field."—STU BORMAN

STREAMLINING REGULATION

GOVERNMENT: Agencies offer plans for cutting costs, paperwork for businesses

Obama talks with Sunstein (left) and Senior Adviser Valerie Jarrett.

PETE SOUZA/WHITE HOUSE/NEWSCOM

THE WHITE HOUSE last week unveiled plans from 30 government agencies to cut the cost and paperwork needed to comply with federal regulations. The plans are in response to President Barack Obama's January directive to agencies to weed out outdated regulations and ensure that those on the books promote economic growth and job creation while protecting public health and welfare (C&EN, Jan. 24, page 10).

Cass R. Sunstein, Obama's regulatory gatekeeper, says this first round of reforms will save hundreds of millions of dollars in annual compliance costs and tens of millions of hours in reporting burdens. The changes could ring up billions of dollars in savings for U.S. businesses in coming years, he adds.

Major themes in the plans are scaling back or eliminating government paperwork that businesses must fill out and switching from paper to electronic reporting.

For instance, the Environmental Protection Agency's plan includes electronic online reporting for pesticide and commercial chemical makers to provide health and safety data that EPA requires. With this change, companies would no longer have to submit six paper copies of certain information under the Toxic Substances Control Act. Also, the Food & Drug Administration plans to look at revising regulations to allow electronic submission of clinical-study data for drug trials, postmarket reporting for drugs and biological products, and registration and listing of drugs and medical devices.

Meanwhile, the Departments of Commerce and State plan to lead a series of reforms to lower barriers to exports of U.S.-made products, Sunstein says. And an upcoming rule from the Occupational Safety & Health Administration will switch the U.S. to an international hazard communication system for chemicals used in the workplace. This single change will save businesses more than $500 million per year in regulatory costs, he says.

Jacob J. Lew, director of the White House Office of Management & Budget, says more reforms are coming. "This is not a one-time project. This is the beginning of what will become a new way of doing business. Every year, we'll keep looking at the regulations that are on the books," Lew says.—CHERYL HOGUE

VERTEX HEPATITIS DRUG IS APPROVED

PHARMACEUTICALS: Stage is set for a heated competition between Vertex and Merck

VERTEX

IN A MAJOR ADVANCE for people with hepatitis C virus, FDA has approved Vertex Pharmaceuticals' Incivek, a protease inhibitor that, when added to the current treatment regimen, significantly improves hepatitis cure rates. Earlier this month, Merck & Co. got the regulatory nod for its own protease inhibitor, Victrelis, setting up for a battle over the HCV market.

The first drug launched out of Vertex' labs, Incivek is the culmination of more than 20 years of work and some $4 billion in R&D investment, CEO Matthew W. Emmens told analysts on a call to discuss the approval. "Our researchers didn't pick an easy disease to tackle," he said.

Industry watchers have been expecting Incivek, known generically as telaprevir, to be more successful than Victrelis (boceprevir). Although the two drugs have never been tested in a head-to-head trial, clinical studies suggest that the Vertex drug is more effective at eradicating the infection and works faster.

Now, with more information on how FDA will allow the drugs' use, their relative prices, and the companies' marketing strategies, the competition is shaping up. Incivek will cost $49,200 for the full treatment course, and Victrelis will cost between $31,000 and $44,000. Vertex and Merck have unveiled assistance programs to offset the co-pays that insured patients will face.

"Based on our examination of the labels, we think Incivek could be viewed to have a meaningful edge," Leerink Swann stock analyst Howard Liang told investors. He added that the drug would be taken for a shorter period and with fewer pills per day. Unlike Victrelis patients, most Incivek patients do not need to take additional medicine for drug-related anemia.

The stakes in the HCV market are high: ISI Group analyst Mark Schoenebaum estimates Incivek alone will bring in $1.75 billion in sales in 2012.

Merck, however, is hoping to gain an advantage by marketing its drug in combination with the existing HCV regimen, PEGylated interferon and ribavirin. The company recently unveiled a pact with Roche, which will promote Victrelis alongside its PEGylated interferon product, Pegasys.—LISA JARVIS

METALS RECYCLING FALLS SHORT

SUSTAINABILITY: Recycling rates must rise to conserve, maintain resources, UN report says

A **UNITED NATIONS** analysis shows that less than one-third of 60 economically important metals are recycled globally at rates of greater than 50%, according to a report released on May 26. More than half of the metals surveyed are recycled at rates of less than 1%.

"Recycling is very important for a resource-efficient economy," and metals recycling must increase within the next decade to conserve and maintain resources, says Matthias Buchert, who heads the Infrastructure & Enterprises Division of the Institute for Applied Ecology at the European research institution Öko-Institut.

Buchert was part of the group that put together the report, "Recycling Rates of Metals: A Status Report," for the UN Environment Program's International Resource Panel. The panel released another report this month on decoupling economic growth from resource consumption (see page 40).

The goal of the metals recycling report was to document "the amounts of metals that are not recycled and are available to be brought back into the economy by improved recycling rates," the report's preface says. "It provides governments and industry the relevant baseline information to make more intelligent and targeted decisions on metals management."

The report indicates that most lead is recycled. Lead is primarily used in vehicle and industrial batteries. And iron and other components of steel, such as chromium, nickel, and manganese, have recycling rates that are higher than 50%.

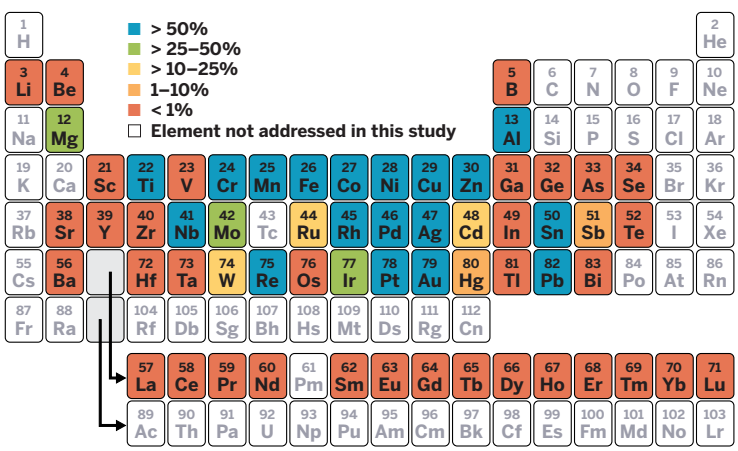
In contrast, recycling rates fall below 1% for lithium, used in rechargeable batteries; cerium, used in catalysts; and indium, used in semiconductors and light-emitting diodes.

Part of the reason for the low recycling rates of some metals is that they're used in products in low concentrations, Buchert notes. For example, collectively, there's a lot of indium in flat-screen computer monitors worldwide, "but per square meter it's not so much," Buchert says. "It's very often a challenge to get these small but very precious concentrations out of complex waste streams."

Buchert is hopeful that metal recycling rates will improve substantially in the next decade. One key indicator, he says, is rising prices for rare-earth metals, principally the lanthanides. When metal prices are low, there is less incentive to recycle. As prices go up, recycling becomes more cost-effective, he notes.

The report is available online at unep.org/resourcepanel/publications/recyclingratesofmetals/tabid/56073/default.aspx.—JYLLIAN KEMSLEY

REUSE STATS Global postconsumer recycling rates for many metals show lots of room for improvement.



SOURCE: UN Environment Program

PHARMACEUTICALS Lilly creates new company to assume U.S. rights for sepsis drug

Eli Lilly & Co. has joined with Care Capital and NovaQuest Capital to create a new critical care medicines company called BioCritica. Based in central Indiana, the biotech firm has U.S. rights to Lilly's antisepsis drug Xigris.

BioCritica will take over U.S. development and marketing of Xigris, a recombinant glycoprotein approved in the U.S. in late 2001 and in Europe in 2002. At that time, Lilly was banking on Xigris—along with older products Evista, Gemzar, and Zyprexa—for its growth. But Xigris sales peaked at $215 million in 2005 and by last year were down to $104 million.

"We are confident that BioCritica will help realize the full potential for Xigris, while working to develop new critical care medicines," Lilly CEO John C. Lechleiter said when announcing the venture.

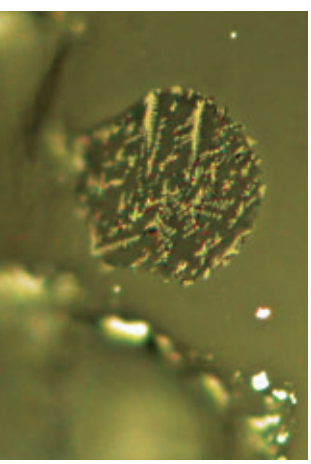
In addition to Xigris in the U.S., BioCritica gets rights to potentially acquire several Lilly compounds in preclinical development and an option to possibly acquire rights to Xigris outside the U.S. In return, Lilly gets an equity stake in BioCritica, a supply agreement, and royalties on U.S. sales of Xigris.

Indiana Economic Development Corp. and the state's public-private life sciences initiative, BioCrossroads, are lending support as well. IEDC has offered up to $2.9 million in tax credits and $175,000 in training grants. BioCritica expects to create about 70 jobs once it finds a headquarters site.—ANN THAYER

WATERY MAGMA FROM THE MOON

MOON'S ORIGIN: High levels of water found in ancient lunar magma bubbles add twist to giant-impact theory

Found inside a lunar soil sample, this bubble of preserved magma, 30 μm in diameter, contains high levels of water.



THOMAS WEINREICH/BROWN U

A NEW STUDY of preserved bubbles of magma trapped in ancient moon rocks shows the magma contains 100 times more water than that found in previous moon rock analyses and carries a profile of volatiles closely resembling those found in Earth's upper mantle.

This finding may require a retooling of theories of the moon's formation, say geochemist Erik H. Hauri, at the Carnegie Institution of Washington; Alberto E. Saal, geological sciences professor at Brown University; James Van Orman, geological sciences professor at Case Western Reserve University; and their colleagues, who performed the study (*Science*, DOI: 10.1126/science.1204626).

The reigning theory of moon formation, called the giant-impact theory, holds that a Mars-sized chunk of rock slammed into the nascent Earth billions of years ago, expelling debris that quickly lost its volatile compounds and formed a dry moon. Using the more sophisticated analytical technology developed in the past decade, however, several recent studies of moon rocks have found more water than expected.

In the new study, the researchers focused on a sample, brought back in 1972 by astronauts on Apollo 17, known as "orange soil" for its stark orange contrast with typical grayish moon rocks. The orange soil was formed at the foot of a lava fountain around 3.6 billion years ago.

The group used ion microprobe analysis to look at the magma melt bubble trapped inside the orange-soil crystals. In addition to the startling high levels of water, the samples also contain high levels of fluorine, sulfur, and chlorine. The group says that to explain the findings scientists will need to come up with mechanisms by which volatiles could have been retained during the moon's formation.

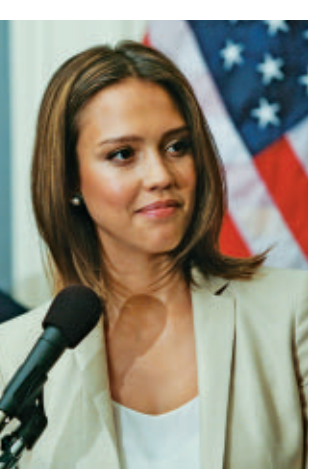
"This work is definitely an important element for all the theories of the origin of the moon," says Francis Albarède, geochemistry professor at École Normale Supérieure in Lyon, France. "Of course, this great finding should be treated with some caution," he notes, pointing out that the orange soil is unique among hundreds of lunar samples brought back by the Apollo missions and may represent only local conditions.

Other possible mechanisms that don't necessarily interfere with the giant-impact theory could be invoked to explain the samples' water content, Albarède adds, including impacts from volatile-rich asteroids fertilizing the local mantle with water.—ELIZABETH WILSON

STAR POWER FOR SAFE CHEMICALS

REGULATION: Congress hears from celebrity Jessica Alba on revising the Toxic Substances Control Act

Alba traveled to the Capitol to focus attention on TSCA reform.



NEWSCOM

DISCUSSIONS ABOUT modernizing the 35-year-old federal chemical control law have, thus far, been decidedly unsexy. Now, Hollywood star Jessica Alba is injecting pizazz into efforts to overhaul the Toxic Substances Control Act (TSCA).

Alba appeared in Washington, D.C., last week to support a bill (S. 847) sponsored by Sen. Frank R. Lautenberg (D-N.J.) to rewrite TSCA.

Star of the television series "Dark Angel" and the films "Fantastic Four" and "Sin City," Alba is the new spokeswoman for Safer Chemicals, Healthy Families. That coalition is lobbying for revisions to TSCA that go significantly beyond reforms supported by chemical manufacturers. The coalition consists of environmental and health activists, parents' organizations, health care providers, and companies seeking safer substances for the products they use, make, or sell.

Speaking at a news conference at the Capitol, Alba called for Congress to overhaul TSCA. "Like many other moms out there, I try to buy safe products for my family, but that can't be the only solution. You can't hire a team of scientists to do your shopping for you," she said. "At some point the government has to step in and ensure that chemicals are safe before our children are exposed to them."

Andy Igrejas, campaign director for Safer Chemicals, Healthy Families, said, "Jessica is the perfect spokesperson for the mom power that is driving this campaign."

"Jessica Alba is helping to deliver a message from America's mothers: Untested chemicals belong in labs, not in the bodies of our children," Lautenberg said. He contended that his bill "would ensure that the chemicals we are exposed to every day have been tested and proven safe for mothers, children, and all Americans."

In response, Scott Jensen, spokesman for the American Chemistry Council, an association of chemical manufacturers, said, "We agree that the Toxic Substances Control Act needs to be modernized to further ensure the safe use of chemicals and the innovation of new products."

Lautenberg, chairman of the Senate Environment & Public Works Subcommittee on Superfund, Toxics & Environmental Health, said he intends to push for legislative action on S. 847 this summer.—CHERYL HOGUE

Your Nominations, Please!

The American Chemical Society (ACS) Has Just Established a New Award Recognizing Underrepresented Minorities in Chemistry for Excellence in Research & Development

We're looking to promote the participation of under-represented minorities in chemistry by identifying and recognizing a distinguished minority chemist who has made significant contributions to chemical research.

The award will consist of:

- A $2,000 award and travel expenses to an ACS meeting where the awardee will give a presentation on their research.
- An opportunity to give a talk at two minority-serving institutions to discuss their work and visit with students, faculty, and administrators to assist outreach efforts to interest students in careers in chemistry.

So caucus with your colleagues and then submit the following to diversity@acs.org:

1. A brief explanation of why the nominee should be considered for the award, specifically identifying his/her contribution to chemical research and its significance.
2. A list of publications or other documentation demonstrating the impact of the research.
3. A biographical sketch of the nominee.
4. Three letters of support from scientific colleagues familiar with the nominee's work.

The deadline for submitting nominations for this inaugural award is June 15, 2011.

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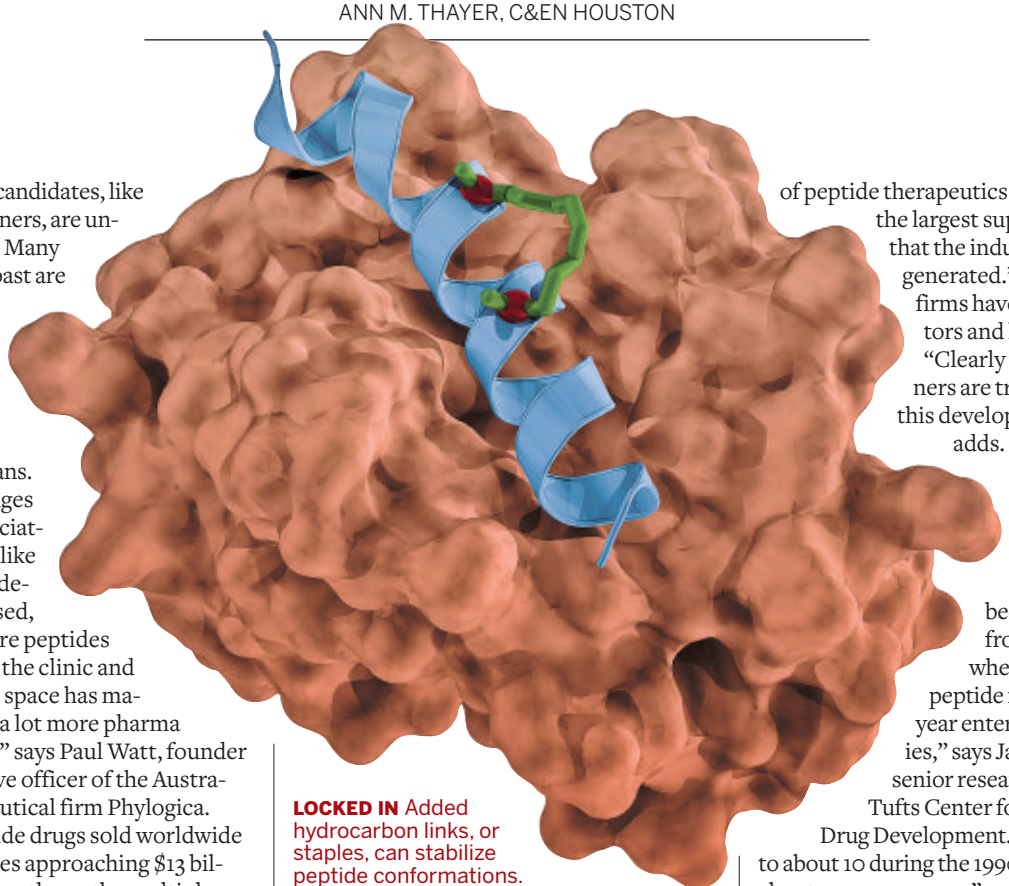
Small firms develop better **PEPTIDE DRUG CANDIDATES** to expand this pharmaceutical class and attract big pharma partners

ANN M. THAYER, C&EN HOUSTON



AILERON THERAPEUTICS

LOCKED IN Added hydrocarbon links, or staples, can stabilize peptide conformations.

PEPTIDE DRUG candidates, like long-distance runners, are undergoing training. Many more than in the past are trying to build the muscle and endurance to reach the finish line. And a few wins along the way are bringing out the fans.

"As the challenges traditionally associated with peptides, like stabilization and delivery, are addressed, and more and more peptides progress through the clinic and are marketed, the space has matured and there's a lot more pharma industry interest," says Paul Watt, founder and chief executive officer of the Australian biopharmaceutical firm Phylogica.

About 60 peptide drugs sold worldwide had combined sales approaching $13 billion in 2010. Among these, the multiple sclerosis therapy Copaxone and the hormone-related products leuprolide, octreotide, and goserelin have annual sales of more than $1 billion each.

Nearly half of approved peptide drugs are older generics, many of which are based on natural products. Newer products, such as Eli Lilly & Co.'s recombinant osteoporosis therapy Forteo and Amylin Pharmaceuticals and Lilly's synthesized diabetes drug Byetta, are fast approaching the $1 billion milestone.

Peptides play central roles in bodily processes. The advantages they can offer as drugs—such as specificity, potency, and low toxicity—are well-known, but they have stumbled over practical hurdles such as poor stability, short half-life, and being readily digested by protein-eating enzymes in the body. Executives at small peptide discovery companies say they have found solutions that are making fans of some big pharmaceutical firms.

Indeed, more large companies are evaluating peptides as part of their drug development strategy, says Joseph A. Yanchik III, CEO of Cambridge, Mass.-based Aileron Therapeutics. "They understand that if you can unlock certain fundamental limitations of peptide therapeutics you might have the largest superclass of drugs that the industry has ever generated." As a result, small firms have attracted investors and large R&D deals. "Clearly the pharma partners are trying to accelerate this development," Yanchik adds.

About 140 peptide drug candidates are in clinical development. "There's been a decent uptick from the 1980s when about five new peptide molecules per year entered clinical studies," says Janice M. Reichert, senior research fellow at the Tufts Center for the Study of Drug Development. "That went up to about 10 during the 1990s, and we're at about 17 per year now."

Reichert's figures come from a study she conducted for the Peptide Therapeutics Foundation, which promotes peptide R&D. The nonprofit group's sponsors are Amylin, Ferring Pharmaceuticals, Ipsen, Pfizer's CovX unit, and the peptide contract manufacturer PolyPeptide Group.

Greater use of peptide drugs over the past two decades also reflects an acceptance of injected therapies by doctors and patients, Reichert points out. Depending on the disease indication, other delivery

"Who would have ever thought that Gila monster saliva would be a good place to look for a type 2 diabetes drug?"

routes are being explored, including oral forms. Advances in delivery technology are expected to have a major impact on peptide drug development.

Approved peptide drugs and those in development fall into many therapeutic areas, with oncology, metabolic disorders, and cardiovascular disease on top. Most disease targets are extracellular, and these are dominated by G-protein-coupled receptors.

"There is a lot of research being done on cell-penetrating peptides, but this hasn't yet translated into a large number of molecules with intracellular targets," Reichert says. Only about 10% of clinical-stage peptide candidates are aiming for the hard-to-hit, albeit plentiful, intracellular targets.

INTRACELLULAR TARGETS, among those often labeled as "undruggable," are challenging for two reasons, Watt explains. The first is the difficulty of simply getting the peptide into the cell. Adjusting the number of charged amino acids in a sequence, for example, is one way to make peptides pass through membranes. Then, once inside, peptide structures, such as those held together with disulfide bridges, may unravel in the reducing environment.

Phylogica, the result of a collaboration between Australia's Telethon Institute for Child Health Research and the Fox Chase Cancer Center in Philadelphia, works around these obstacles. "Many of our structures are very stable but are not constrained by disulfide bonds and therefore could remain stably folded even inside cells," Watt says. Small enough to cross cell walls, these rigid structures maintain the desired conformation for binding, but unlike linear peptides, they may resist being chewed up by protease enzymes.

Working with Roche, Phylogica has identified peptides that can both travel into cells and deliver cargo. "Some of these have no structural resemblance to other well-characterized cell-penetrating peptides," Watt points out.

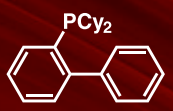
Similarly, intracellular delivery is a goal of KAI Pharmaceuticals and AngioChem, which specifically goes after blood-brain barrier targets. And last year, Compugen began offering an in silico process to predict cell-penetrating structures through which it has found 20 such peptides.

Founded in 2001, Phylogica has signed three partnerships with major pharmaceutical companies over the past 18 months, according to Chief Financial Officer Nick Woolf. The company has a deal worth up to $100 million to find antibiotic peptides with AstraZeneca's biologics unit, MedImmune, and another on therapeutic peptide vaccines with Pfizer that could bring in $135 million. It recently extended its collaboration with Roche to evaluate the potential for peptide delivery to the brain.

Relying on nature to provide a range of evolutionarily stable structures, Phylogica finds peptides that it calls Phylomers within bacterial protein fragments. To create libraries of these protein pieces, the sequenced genomes of diverse bacteria, primarily extremophiles, are fragmented. The genes are then expressed to create random, yet overlapping, peptide libraries.

The libraries can be screened for a desired phenotype, such as killing cancer cells, or for binding to a known target. Once an active Phylomer is found, "we are able to isolate the sequence that encoded

ALDRICH Chemistry



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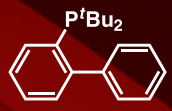

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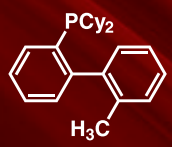

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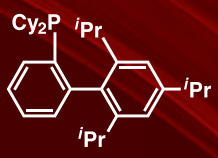

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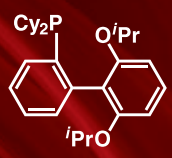

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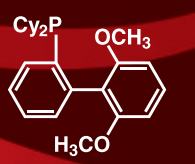

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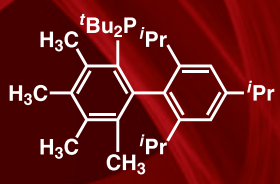

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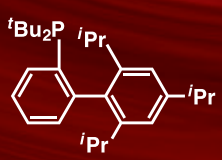

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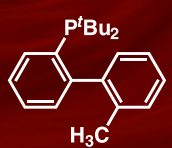

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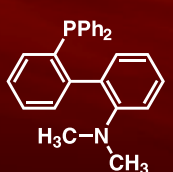

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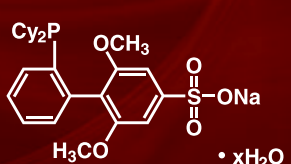

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SIGMA-ALDRICH

the peptide and then order it as a synthetic peptide from a manufacturer," Watt says. "We then test the isolated peptide for the activity we selected for in the first place."

Although Phylogica has found peptides that bind with picomolar affinity, it can further optimize them via mutagenesis of the gene sequence and chemical modification. "Since every screen yields sets of structurally related peptides, we can fast-track the structure-activity lead optimization process," Watt says. "The screens provide very powerful bioinformatic clues for where to focus mutagenesis without disrupting the peptide scaffold."

Amino acids also can be replaced with functionalized or nonnatural ones to improve a peptide's stability, activity, and half-life. The entire sequence can even be synthesized in reverse order—to form so-called retro-inverso peptides—using D-amino acids, which is a way to stabilize peptides and make them resistant to proteolysis, Watt says.

Ranging from 15 to 80 amino acids, but averaging about 30, Phylomers are small enough to be made cost-effectively by chemical synthesis, Watt says. At this size, they are amenable to noninjectable delivery methods. Phylogica's experience so far has been with intranasal routes. Pointing to four marketed intranasal peptide drugs, Watt sees potential for success.

OTHER COMPANIES screen as well. With two marketed peptides, the diabetes drugs Symlin and Byetta, Amylin has amassed a library of peptide hormones. In collaboration with Lilly, it is developing nasal and transdermal forms of Byetta. An injectable long-acting version made by linking the peptide to Alkermes' biopolymer microspheres faces regulatory delays in the U.S. but has been recommended for approval in Europe. In the obesity area, under a deal initially valued at up to $1 billion, Amylin has been working with Takeda Pharmaceutical, but in March the partners halted a clinical study on their lead project to investigate the possible neutralizing effect of antibodies on the tested drug combination.

Affymax, once part of GlaxoSmithKline, also has been working with Takeda since 2006 to develop the anemia treatment peginesatide (once known as Hematide). Arising from Affymax' recombinant library, the synthetic peptide is PEGylated for stability and extended half-life. And Cambridge, Mass.-based Dyax screens for peptide candidates using phage display libraries, which it has licensed to many big pharma firms. In 2010, Dyax launched the angioedema peptide drug Kalbitor.

According to Tufts's Reichert, only about 10% of peptide drugs in development have been modified through means such as PEGylation, lipidation, radiolabeling, or conjugation to a small molecule, antibody, or protein. "But it seems to be a growing area as the technology advances," she says.

Phylogica recently agreed to work with Pepscan Therapeutics in the Netherlands to use that firm's technology for chemically linking peptides to scaffolds that will keep them in biologically active conformations. Under a European Union grant, Pepscan also is working with Copenhagen-based Zealand Pharma to create dual-action pep-

tides. On its own, Zealand has licensed peptide drug candidates to Pfizer, Helsinn Healthcare, and Sanofi, although Pfizer returned its compound after deciding to exit cardiovascular R&D.

On the list of successful synthetic peptide drugs are five originally found in venoms, which are highly complex mixtures of potent and selective bioactive compounds. Although it makes sense that venom-based peptides, such as Prialt, act as anesthetics, "who would have ever thought that Gila monster saliva would be a good place to look for a type 2 diabetes drug?" remarks Jason Moss, a business development technical manager at peptide supplier Bachem Americas, referring to Byetta.

As the five products show, venom-derived peptides don't just act like venom but are useful against different disease targets. "These peptides have been designed evolutionarily to sit on receptors," Moss says about their potency and stability. To broaden access to them, Bachem has partnered with Atheris Laboratories, a Swiss peptide and protein drug discovery firm. Bachem offers Atheris' venom libraries in microplates, under the name Melusine, for screening.

Atheris can provide mixed or species-specific collections. Rather than supply pure venoms, which are too potent for cell assays and too complex to characterize, Atheris fractionates them using high-performance liquid chromatography, Moss explains. "It makes venoms a lot easier to screen for drug discovery and development."

When hits are found, Atheris can identify the active component and provide lead optimization for customers. "If a customer wants to develop a molecule, Bachem can prepare a research-grade batch synthetically to make sure it is identical and has the same activity," Moss says. After that, "we can provide material for preclinical and clinical development." Most peptides are made by chemical synthesis.

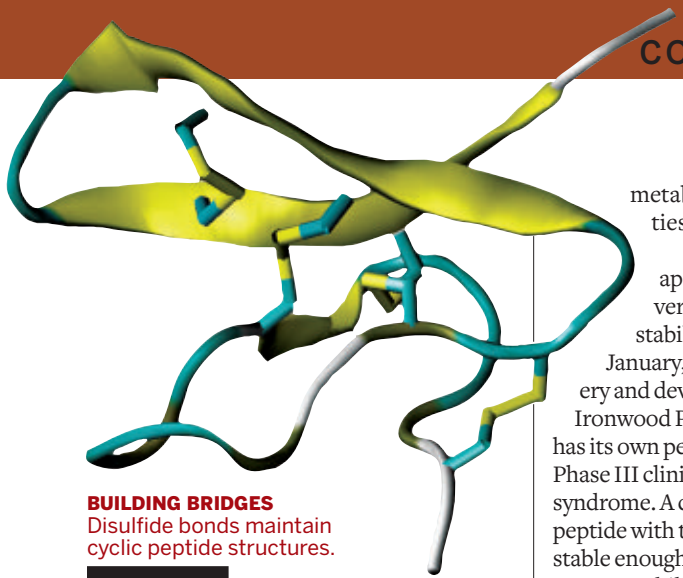
The fact that peptides can be manufactured at large scales under regulatory compliance has helped advance peptides as drugs themselves, rather than just as leads for small-molecule development,

TOXIC ORIGINS

Several successful peptide drugs have their roots in venoms

DRUG	MOLECULE	ORIGIN	DISEASE	COMPANY
Aggrastat (tirofiban)	Peptidomimetic	Saw-scaled viper	Angina/heart attack	Medicure
Byetta (exenatide)	Peptide	Gila monster	Type 2 diabetes	Amylin/Eli Lilly & Co.
Capoten (captopril)	Peptidomimetic	Brazilian lancehead snake	Hypertension	Bristol-Myers Squibb
Integrilin (eptifibatide)	Cyclic peptide	Southeastern pygmy rattlesnake	Ischemic stroke	Millennium Pharmaceuticals
Prialt (ziconotide)	Miniprotein	Magician's cone snail	Chronic pain	Elan/Azur Pharma

SOURCES: Bachem, Atheris Laboratories



BUILDING BRIDGES
Disulfide bonds maintain cyclic peptide structures.

PROTAGONIST THERAPEUTICS

Moss suggests. "If you look at the history of peptide therapeutics from natural sources, many are 20 to 30 amino acids in size with one or two, sometimes three, disulfide bonds." Such structures are synthetically manageable, he says.

Protagonist Therapeutics focuses on disulfide-rich peptides, or DRPs, ranging from eight to 40 amino acids. "DRPs address the major disadvantage of peptides, that of biological stability," CEO Dinesh Patel says. Founded in Australia but headquartered in Redwood City, Calif., the company combines rational drug design and computational tools to identify DRPs, phage display libraries for expression and screening, and medicinal chemistry to optimize the structures and activity.

TAPPING INTO a diverse set of DRPs, Protagonist can identify leads against almost any kind of target in a de novo fashion, Patel claims. "If we have structural information on a target, then we will try to mimic what may be the best fit into the binding site," he says. "If that is not available, we have created generic libraries that capture all different sizes and shapes offered by DRPs to screen against a target."

Protagonist aims at targets not approached satisfactorily either by biologics or small molecules. "We are trying to grab the best of both worlds," Patel says. "We want them to have the potency of biologics, but because of their engineered stability, we want them to have the pharmacokinetics and absorption, distribution, metabolism, and excretion properties of small molecules."

Although many peptides fall apart in the stomach, "we are very, very confident in the oral stability of DRPs," Patel says. In January, Protagonist entered a discovery and development collaboration with Ironwood Pharmaceuticals. Ironwood has its own peptide drug, linaclotide, in Phase III clinical trials for irritable bowel syndrome. A cysteine-rich, 18-amino acid peptide with three disulfide bridges, it is stable enough to be taken orally.

Permeability is another requirement to make peptide drugs bioavailable. If small enough, they may be able to move unaided through the wall of the gastrointestinal tract. If not, permeability or absorption enhancers might be required. "In some instances, you might not want permeability if the targets are confined to the GI tract," Patel explains. "In this case, you can convert low permeability into a huge advantage and have a very specific drug with an excellent safety profile."

Aileron Therapeutics has developed a tool kit of stabilization technologies to retain peptides in the desired conformation. Initially, it used olefin metathesis to form hydrocarbon links, or staples, across functionalized amino acids in α-helices. The company has since licensed other chemistries and has developed its own technology.

Although α-helices are involved in many drug-target interactions, the company is not limited to that structure, Chief Scientific Officer Tomi K. Sawyer says. "Stapling chemistry comes with incorporating novel or nonnatural amino acids, but we like to leverage as much of nature's original sequence as possible to take advantage of the high specificity peptides have for their targets, whether they are enzymes, receptors, or protein-protein interactions."

Aileron's targets are largely intracellular. The firm often starts with structural information on the target to design a peptide ligand, but it may also use diversity-based approaches for lead optimization, Sawyer says. Modifications of analogs can help fine-tune target specificity and cellular activity. "We are building into the same sequence both cell-penetrating ability and the pharmacophore to bind to a specific target, while being metabolically stable. So you get all the features needed for a drug," he says.

"The really powerful feature of stapled peptides is that they have extraordinarily good pharmacokinetic properties right from the start," Sawyer adds. "We believe we can go neck and neck, certainly in terms of potency, with any small molecules."

Such features are making pharma firms "recalibrate their thinking" about what's possible with peptide drugs, Sawyer says. In 2010, Aileron signed a deal with Roche worth $25 million up front and up to $1.1 billion in potential milestones. The program is focused on undruggable targets in infectious and metabolic diseases and oncology.

In 2009, Aileron attracted investments from the corporate venture funds of Lilly, GSK, Novartis, and Roche. The Novartis and GSK funds have also invested in Bicycle Therapeutics, a U.K.-based firm that creates chemically constrained peptides. And Lilly has backed Protagonist and Sutro Biopharma, which is developing new peptide manufacturing methods.

Advances in manufacturing that make peptides more economically feasible have

APPROVED PRODUCTS

Numerous large sellers are among peptide-based drugs marketed in the past 10 years

GENERIC NAME	TRADE NAME	DISEASE TARGET	COMPANY	2010 SALES ($ MILLIONS)
Teriparatide	Forteo	Osteoporosis	Eli Lilly & Co.	$830
Exenatide	Byetta	Type 2 diabetes	Amylin/Lilly	710
Liraglutide	Victoza	Type 2 diabetes	Novo Nordisk	416
Lanreotide	Somatuline	Growth disorders	Ipsen	228
Pramlintide	Symlin	Diabetes	Amylin	92
Enfuvirtide	Fuzeon	HIV	Roche/ Trimeris	88
Ziconotide	Prialt	Pain	Elan/Azur Pharma	20[a]
Icatibant	Firazyr	Angioedema	Shire	11
Ecallantide	Kalbitor	Angioedema	Dyax	9
Tesamorelin	Egrifta	Lipodystrophy	EMD Serono	na
Degarelix	Firmagon	Prostate cancer	Ferring	na
Mifamurtide	Mepact	Bone cancer	Takeda	na
Nesiritide	Natrecor	Heart failure	Johnson & Johnson	na

NOTE: Includes U.S. and non-U.S. approvals. **a** C&EN estimate. **na** = not available.

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helped small companies, Yanchik suggests. "Technologies allow us to do things today that would have been very difficult even 10 years ago." As a result, potential partners are expressing fewer concerns about whether new peptide drug candidates can be made.

Creating a helical structure, for example, takes at least 10 amino acids, and longer peptides may contain 40 or more. "There are pragmatic limits of how long you need to go to achieve target specificity versus how long you can go before your manufacturing cost of goods becomes a little bit high," Sawyer says. "And you better make sure that the market you are looking at will be able to accommodate the more expensive, longer peptide."

Inserting stapling modifications doesn't compromise the scale or chemical yield, and the cyclization chemistry is very efficient, Sawyer claims. Aileron has developed manufacturing capabilities over its five years in operation.

"One of the pleasant surprises of the platform has been the ability to scale up the stapled peptide technology," Yanchik says. Although the company can produce research-grade and higher quantities, it has gone to outside firms to test production under current good manufacturing practices.

OTHER PEPTIDE drug firms can do even more of their own manufacturing. Ferring is a Swiss peptide drug company that began by extracting peptide hormones from animal sources and modifying them. In the 1960s, it developed methods for chemical synthesis and now has several production facilities. With its acquisition of BioTechnology General in 2005, it also gained recombinant manufacturing methods.

Similarly, Unigene Laboratories combines its recombinant manufacturing capabilities with drug delivery and formulation technologies to develop new peptide products. It has supplied salmon calcitonin to Novartis for osteoarthritis and osteoporosis products in development and has licensed its production technology to the drug company as well.

Unigene also developed Fortical, a nasal calcitonin product marketed by Upsher-Smith Laboratories. It has licensed an oral form to Tarsa Therapeutics, in which it holds a 25% stake. And, for many years it has worked with GSK under an agreement worth up to $145 million to develop an oral formulation of a recombinantly produced parathyroid hormone analog for treating osteoporosis.

Those in the race indicate that discovery, development, and manufacturing challenges are increasingly being met. If there is any remaining skepticism to overcome, it is around regulatory approval. "Peptides do seem to take longer in regulatory review, averaging about two years," Reichert says. Questions tend to fall in the chemistry, manufacturing, and control areas.

Nonetheless, proponents are optimistic about peptide drugs playing a bigger role, especially against undruggable targets. According to Protagonist's Patel, "Just like biologics are now grasping a larger footprint at the expense of small molecules, similarly as we go forward I believe peptides are going to have a larger footprint at the expense of both biologics and small molecules." ■

POLYPEPTIDE GROUP

MAKING PEPTIDES AT LARGE SCALE

EFFICIENT SYNTHESIS is helping to renew interest in the peptide drug market

ANN M. THAYER, C&EN HOUSTON

CUSTOM PEPTIDE manufacturers speak fondly of Fuzeon, a 36-amino acid HIV fusion inhibitor that has been on the market since 2003. It's not because the drug, developed by Trimeris and Roche, is a blockbuster. In fact, many call it a flop because runaway sales of the high-priced treatment never materialized.

They like it because, to be effective, the daily dose of the poorly stable peptide is a hefty 180 mg. That dose makes Fuzeon one of a few peptide drugs to have been made in near-ton annual quantities. And beyond sheer volume, they like that it proved large-scale production of a long peptide is possible.

Fuzeon production broke ground in terms of equipment and process design. To couple that many amino acids takes a huge number of synthetic steps and massive amounts of raw materials. "All the amino acid suppliers had to gear up to supply that manufacturing effort, which brought the costs down for everyone," says Jim Hampton, executive vice president of business development at peptide supplier AmbioPharm in North Augusta, S.C.

Roche has stopped R&D on HIV and, in a restructuring move, put its Roche Colorado peptide manufacturing site up for sale. But its interest in peptide drugs seems to be growing, and like many big pharma firms it is collaborating with peptide discovery companies (see page 13).

As a result, the peptide ingredient market is growing as well, and drug developers are asking custom manufacturers to make the newest generation of peptide drug candidates. Although these peptides are longer and more complex than earlier ones, technical improvements and economies of scale have made production faster and more cost-effective. By harnessing multiple synthetic and recombinant techniques, contract manufacturers are helping turn peptides into affordable and effective drugs.

"Peptides have been around for a long time, but only recently have come into prominence because research has led to the development of more robust molecules," says Ipshita Chakraborty, senior research analyst with the market research firm Frost & Sullivan. "It's now possible to generate stable peptides, and the therapeutic peptide sector is venturing into new disease areas." About 60 peptide drugs are on the market, and nearly 10 times that are in preclinical and clinical development.

BIG TIME Manufacturers are making more peptides in larger quantities.

Today, 36 amino acids is about the average peptide length that suppliers are being asked to make. "The choice of production technology depends on the quantities that are needed and on potential challenges related to the peptide sequence," says Johan Devenyns, general manager of Solvay's Peptisyntha business.

SOLUTION-PHASE chemistry is usually favored for peptides that are fewer than 15 amino acids long and for quantities greater than 100 kg. When it comes to complex or longer amino acid sequences, solid-phase chemical synthesis usually wins. Peptides, or what some call miniproteins, of 50 amino acids and longer can often be made by recombinant means.

"Peptide manufacturing is substantially more expensive than manufacturing small molecules, but it's still often less expensive than using recombinant procedures for quantities under 50 to 100 kg," says Rodney Lax, senior director of business development in North America at PolyPeptide Group, which operates facilities in the U.S., Europe, and India. Making a peptide for clinical trials using recombinant methods can be up to an order of magnitude more expensive than chemical synthesis, he says.

A solid-phase process generally is the fastest and cheapest to develop, peptide suppliers tell C&EN. Solution-phase processes, despite the name, can actually require less solvent and also might avoid the need for chromatographic purification. Increasingly popular are hybrid approaches that combine solid- and solution-phase steps to make shorter fragments that are coupled to make bigger peptides.

Peptide active pharmaceutical ingredients (APIs) generally are made at the tens-of-kilograms scale, with about a dozen at the 100-kg-per-year level. Fifteen years ago, "a kilogram was just an unthinkable amount of peptide to have to make," Hampton says. Today, leading manufacturers operate reaction vessels of up to a few thousand liters in size. "In peptide terms, this is huge," Hampton says.

Solid-phase peptide synthesis involves sequentially coupling protected amino acids on a support. In the past five years, increased sourcing of raw materials from

"Peptides have been around for a long time, but only recently have come into prominence."

low-cost countries has significantly reduced costs for solid-phase synthesis, Hampton says. "Companies may derivatize them in the U.S. or Europe, but they are buying the basic amino acids from China."

Founded in 2007, AmbioPharm has a business model of offering low-cost peptides made under current Good Manufacturing Practices (cGMP). In addition to a South Carolina facility it acquired from the former UCB-Bioproducts, the company runs a cGMP plant in China. "The first step will be making generics because it will be a while before the world is ready for new chemical entities coming 100% out of China," Hampton predicts.

Similarly, PolyPeptide is shifting some of its generic products to a facility it built near Mumbai, Lax says. "Most customers who are developing proprietary peptides, however, would prefer to keep them close to home in the U.S. or Europe."

Generic peptide drugs are under the most price pressure but remain an important part of the market, suppliers say. "About half of peptide APIs are produced captively by pharma companies," Devenyns says, which leaves the rest open to contract manufacturers. "The addressable market opportunity for peptide APIs is on the order of $500 million per year," he estimates. About 20 peptide drug candidates enter clinical trials each year, and anywhere from zero to three typically get approved.

Several peptide drugs will lose patent protection in the next five years, including Fuzeon and the large-volume anticoagulants Integrilin (eptifibatide) and Angiomax (bivalirudin). "The peptide market is still a relatively young one, but there are some very well established generics," Frost's Chakraborty says.

According to Hampton, many peptide manufacturers are opting to make bulk eptifibatide, a relatively simple cyclic heptapeptide, but only a few, such as AmbioPharm and Teva Pharmaceutical Industries are tackling the 20-amino acid bivalirudin. Both have completed drug master files. Teva became a significant competitor after buying the peptide drug firm CoGenesys in 2008.

PEPTISYNTHA TAKES a "common fragment" approach to making some generic peptides. After identifying shared sequences among peptides, it can achieve economies of scale by pooling their syntheses. The company is adding a large-scale cGMP solid-phase peptide plant at its Brussels site, where it already has industrial-scale solution-phase capabilities. The company also practices solid-phase synthesis in Torrance, Calif.

For short peptides, Peptisyntha has developed a process to precipitate APIs at desired purity levels that avoids the need

for chromatography. "We've also further developed our specific know-how in the area of lyophilization," Devenyns adds, to improve productivity and control product morphology.

"Control over drug substance quality and morphology is becoming increasingly important to ascertain bioavailability and manage drug substance stability for new engineered-release peptide therapeutics," says Mimoun Ayoub, Peptisyntha's vice president of global business and strategic development. And most opportunities will stem from developing new dosage forms and improving drug delivery.

Drug delivery firms are learning to formulate peptides for nasal, oral, and transdermal delivery. "If we find a drug delivery platform that is applicable to a wide range of peptides, it is really going to open doors and make peptide therapeutics of much greater interest," Lax says.

Conjugation is also used to increase target specificity or extend half-lives. "Peptides are actually bridging the two worlds of small and large molecules," says Stefan Stoffel, head of Lonza's chemical manufacturing business. In its work, the Swiss company is seeing more antibody-drug conjugates and cell-penetrating peptides linked to cytotoxic drugs.

Requests for PEGylated peptides are on the rise as well. "We are being asked to make large quantities of these nowadays, as well as other conjugates," PolyPeptide's Lax says.

How a peptide will be formulated or delivered may have to be addressed during its actual synthesis. Peptide manufacturers also need to design their syntheses to make the more complex cyclic or constrained structures that developers are creating for better stability. These factors are frequently dealt with through backbone modifications or the insertion of nonnatural and functionalized amino acids in the sequence.

PRODUCING PEPTIDES that are cyclic or contain nonnatural amino acids is "pretty sophisticated," Devenyns says. Cyclic peptides can be formed, for example, by installing internal disulfide bridges across cysteine residues or by creating hydrocarbon links between functional groups.

Having these functionalities in place may require using customized amino acid derivatives, which some peptide producers also make. "We have in-house manufacturing of special complex building blocks and can design them to the exact purity that we need," says Philip Ottiger, president of Bachem Americas, part of Switzerland's Bachem Group.

Developing a robust, large-scale manufacturing process can be challenging but is doable depending on the number of modifications, explains Jason Moss, a business development technical manager at Bachem, which has several production sites in the U.S. and Europe. "It can be a perfect storm of functional groups where any individual one won't be that big a deal from a process chemistry perspective, but having the combination could require a lot of effort," he says. Synthesis might call for multiple protecting groups and novel coupling and oxidation chemistries. First

synthesized as linear, many peptides are subsequently folded stepwise to get the right connectivity and shape.

Subtle changes to the peptide structure can make a process scalable and economically feasible—or not. "A peptide could have one amino acid, for example, where a gram of it would take six months to make and cost $100,000, but a slight one-carbon change makes it one that's $1,000 per kg," Moss explains.

Peptide synthesis is highly sequence dependent, and method development and analytical characterization are critical as the process grows in complexity, suppliers point out. Synthetic routes must be broken down to determine, for example, where fragment solubility and racemization might be problems.

As the number of amino acids rises, so, too, does the number of potential impurities, many of which will be almost identical to the final product. "The dream is to be able to crystallize the desired peptide within the expected specifications without going through a purification by high-performance liquid chromatography," Lonza's Stoffel says. "We still have a long way to go in achieving this goal, and challenges remain in the purification stages to remove critical impurities that are close to the APIs."

FURTHER WORK is needed to minimize the loss of desired APIs during primary and secondary purifications, Stoffel says. "In the generic field or in the development of a second-generation product, the impurity profile match is critical from a regulatory point of view and is a challenge for the process development chemists."

Scalability, rather than the underlying chemistry, is the main aspect of peptide synthesis that has changed over the past five years, contends Firuz Shakoori, director of sales at American Peptide in Sunnyvale, Calif. "Companies now are capable of making large quantities of drug substance in a single batch, and the size of purification columns has increased drastically," he says.

American Peptide has added four purification suites in recent years, and it has plans for new solution- and solid-phase

AMERICAN PEPTIDE

synthesis suites. It offers research-grade peptides from a facility in Sunnyvale and has cGMP production in Vista, Calif. Ito Life Sciences, part of Japan's Otsuka Chemical, has owned the firm since 2008.

As companies are scaling up to make larger volumes of peptides, the industry is consolidating into a core group of players, many with multiple sites and technologies. In 2007, PolyPeptide acquired Isochem's

CLEANING UP Chromatographic purification is a key step to remove impurities in peptide production.

NeoMPS business. Lonza bought UCB-Bioproducts in 2006. More recently, Diosynth became part of Fujifilm and Corden Pharma acquired Genzyme Pharmaceuticals.

With sites in Belgium, Switzerland, China, and the Czech Republic, Lonza may be the only large-scale peptide supplier to offer both chemical synthesis and recombinant production. According to Stoffel, "An estimated 8% of peptides use recombinant processes, which are mainly managed by pharma in-house production."

Drug developer Unigene Laboratories, for example, focuses on recombinant peptide manufacturing at its cGMP plant in Boonton, N.J. After expressing a peptide in *Escherichia coli,* its process includes an in vitro enzymatic amidation of the peptide tail to enhance stability, activity, and bioavailability. Its technology is being used to make development-stage products and has been licensed to Novartis.

THE MAIN ADVANTAGE chemical synthesis has over recombinant methods lies in the ability to insert unusual amino acids into a sequence, Bachem's Ottiger points out. This step is a prelude to creating peptides that can be specially cyclized or conjugated to other entities. Companies such as La Jolla, Calif.-based Ambrx are conducting research to create cell-based systems that can handle nonnatural amino acids.

Taking another approach, Sutro Biopharma in South San Francisco has developed biochemical protein synthesis in a cell-free system. Components of the system include a DNA template that encodes the desired peptide, a ribosomal extract as the synthesis machinery, amino acids, and an energy source, explains Chief Scientific Officer Trevor Hallam. Nonnatural amino acids can be incorporated by using transfer RNAs to deliver them at the appropriate point as the template is decoded.

"We can actually put a lot of chemical functionality into these, including reactive amino acids to let us do chemistry on the product," Hallam says. The desired peptide is produced quickly, and proper folding can be promoted by controlling the chemical and physical environment. The product also can be easily separated, he adds.

Sutro's goal is to make peptides that are inaccessible because they are not expressed by cells, cannot be isolated, or are insoluble. This year, the company entered a multiyear collaboration with Pfizer. "At the moment we are preparing to build clean rooms so we can actually work to cGMP. Our plan is to be setting up to produce clinical-trial materials by early next year," Hallam says.

Although peptide manufacturers fall into two camps—chemical synthesis or recombinant production—most observers believe this dichotomy will disappear. But rather than one approach supplanting another, they are likely to complement each other or even merge. "The demarcation line between peptides and minproteins will disappear as well because there will be chemical synthesis of much larger proteins and more recombinant manufacture of shorter peptides," Lax says. ■

DOW IS PROMOTING INCINERATION

Dow Chemical is recycling plastic the old-fashioned way: It's burning it. The company has wrapped up a trial at its Midland, Mich., headquarters in which it incinerated 578 lb of linear low-density polyethylene film waste from its nearby extrusion laboratories. The firm was able to recover 96% of the energy from the plastic, the equivalent, it says, of about 11.1 million Btu of natural gas. Dow suggests that incineration is a viable alternative to the landfill for those plastics that aren't commercially recycled. It also asserts that waste-to-energy is an underused scheme in the U.S. compared with Europe, where the practice is fairly common. "The U.S. lags behind many other countries that capture trapped energy from recovered materials," says Jeff Wooster, plastics sustainability leader for Dow's North American plastics business.—AHT

TWO DIE AT SHINTECH PLANT IN LOUISIANA

Two workers died on May 22 while commissioning a new vinyl chloride plant at Shintech's complex in Plaquemine, La. The workers—Shintech employee Tommy Rivet and contractor Tory Sanchez—had climbed into a vessel on the site. "We believe they were in a nitrogen atmosphere and inhaled nitrogen," says a Shintech spokesman. The company is starting up chlorine, ethylene dichloride, and vinyl chloride plants at the site. The incident is the first fatal accident for Shintech, a subsidiary of Japan's Shin-Etsu Chemical, in its 37 years in the U.S.—AHT

DUPONT REGROUPS TO ABSORB DANISCO

DuPont has formed two new business units—industrial biosciences and nutrition and health—to account for its recent acquisition of the Danish enzymes and food ingredients company Danisco. To be headed by James C. Collins Jr., industrial biosciences will be a $1 billion-a-year business that includes Danisco's Genencor enzymes division and DuPont Applied Biosciences. Nutrition and health, headed by Craig F. Binetti, will combine Danisco Food Ingredients with DuPont's existing nutrition and health business. It will have $3 billion in annual sales.—MM

BIG CHEMICAL MERGERS ON TRACK TO RISE

Deal-making activity in the first quarter of 2011 suggests that chemical companies will move quickly to close deals this year and that many acquisitions will have price tags of more than $1 billion. PricewaterhouseCoopers, an accounting and advisory services firm, reports that the number of announced chemical deals dropped 16% compared with the first quarter of last year but that the number of deals worth more than $1 billion shot up to 35 from 19. Private equity buyers increased their share of deals to 23%, the highest in five years. Two of the largest announced deals in the quarter were Berkshire Hathaway's bid for Lubrizol of about $9.7 billion and DuPont's acquisition of Danisco for $6.6 billion. PwC forecasts that deals will close faster this year than during the downturn. The firm reports more competition among buyers due to a return to solid balance sheets, increased confidence in demand, and improved lending conditions. In addition, potential buyers are vying with bidders from companies in developing countries such as China.—MMB

HEMP CHAIR RELIES ON RESIN FROM BASF

What's being called the world's first one-piece chair made of natural fibers was showcased at Material Vision 2011, an architectural materials exhibition held last week in Frankfurt, Germany. The chair, designed by Berlin-based Werner Aisslinger, is made of hemp, kenaf, and a water-based thermoset acrylic resin from BASF. It is more than 75% natural fiber, BASF says.—MM

BASF

CHEMTURA FORMS BROMINE ALLIANCE

Chemtura has signed a letter of intent to form an alliance in bromine and brominated derivatives with Chennai, India-based Archean Group. Beginning in 2012, Chemtura will market bromine from Archean's chemical facility in the state of Gujarat, where the Indian firm plans to produce potassium sulfate fertilizer from seawater. Bromine will be a by-product of the process. In a second phase, the two firms will build what they are calling a "world class" bromine facility. Eventually, they also plan to construct a factory to make brominated derivatives such as flame retardants. Chemtura currently gets bromine from Arkansas brines and the Dead Sea.—MSR

INVISTA WILL EXPAND SPANDEX IN BRAZIL

Invista, the former DuPont fibers unit now owned by Koch Industries, is expanding capacity for Lycra brand spandex fiber at its plant in Paulínia, Brazil. The $100 million project will be completed in 2012. The company is the only spandex producer in Brazil, making Lycra fibers in Paulínia and Supplex fabrics in Americana. Earlier this month, Invista's joint venture in Foshan, China, completed a project that doubled spandex capacity there.—AHT

LIQUID METAL BATTERY GETS GATES FUNDING

Liquid Metal Battery, founded by MIT materials chemistry professor Donald R. Sadoway, has received venture funding from philanthropist and investor Bill Gates. Targeting stationary energy sources, such as wind or solar installations, the start-up is developing a battery that contains all-liquid cathode, anode, and electrolyte. Sadoway tells C&EN that Liquid Metal Battery has a second, unidentified sponsor. French oil giant Total previously backed Sadoway's research at MIT with a $4 million grant.—MMB

BASF SLATES TDI PLANT FOR EUROPE

Becoming the second German firm to plan a toluene diisocyanate (TDI) plant in Europe, BASF says it will build a 300,000-metric-ton-per-year TDI facility in Antwerp, Belgium, or Ludwigshafen, Germany, by 2014. The plant will be the world's largest single-train facility for the polyurethane precursor, BASF says, and will be integrated with key raw materials. A year ago, Bayer announced it would build a 300,000-metric-ton TDI plant in Dormagen, Germany, based on new technology that cuts energy use by 60%. Start-up is also planned for 2014.—MM

IDEMITSU BIDS FOR AGROCHEMICAL FIRM

Japan's Idemitsu Kosan will bid for SDS Biotech, an agrochemical producer listed on the Tokyo Stock Exchange, in an offer that values SDS at $92 million. At a minimum, Idemitsu will aim to acquire the 53% stake in SDS held by the private equity firm MH Capital Partners. Buying SDS, which has an established base of foreign customers, would support Idemitsu's goal of expanding sales of biological pesticides it has developed. It would also add a line of chemical pesticides. Established in 1968, SDS supplies fungicides and herbicides for use in vegetable and rice cultivation.—JFT

ALMAC

Almac CEO Alan Armstrong (from left), McClay, and Mitchell at the opening of Almac's North American headquarters.

ALMAC TOASTS ITS U.S. HEADQUARTERS

Almac, the Northern Ireland-based drug development services company, marked the opening of its North American headquarters in Souderton, Pa., earlier this month. On hand were former Sen. George J. Mitchell, who chaired the 1998 Northern Ireland Peace Agreement, and Lady Heather McClay, the widow of Almac founder Sir Allen McClay. The $120 million headquarters comprises a three-story administration building and facilities for production, analysis, and distribution of clinical-trial supplies. It houses about 800 employees, including some 300 new hires.—RM

ACCELRYS HAS ANOTHER LAB NOTEBOOK DEAL

Approximately one year after acquiring Symyx, a leading supplier of electronic laboratory notebooks (ELNs), research software firm Accelrys will acquire Swedish ELN maker Contur for about $13 million. Contur's Web-browser-based notebooks for small and medium-sized commercial and academic labs complement Symyx' ELNs, which are used largely in FDA-validated laboratories in the pharmaceutical industry, says Accelrys CEO Max Carnecchia. Accelrys will market Symyx and Contur ELNs in conjunction with its Pipeline Pilot scientific informatics platform.—RM

VALEANT AND WATSON BUY INTO GENERICS

Looking to spend its money after failing to take over Cephalon, Valeant Pharmaceuticals will acquire the specialty drug firm AB Sanitas for about $443 million in cash. Based in Kaunas, Lithuania, Sanitas sells branded generic drugs throughout Central and Eastern Europe. Valeant expects its sales to reach more than $140 million this year. Separately, Watson Pharmaceuticals has bought the generic drug maker Specifar Pharmaceuticals for $562 million. The Greek firm had 2010 sales of about $120 million.—AMT

BUSINESS ROUNDUP

SYNGENTA will spend $71 million to construct a new research facility adjacent to its existing campus in Research Triangle Park, N.C. To open in the second half of 2012, the center will focus on discovering and developing agronomic traits to help plants better tolerate climate variability and drought stress.

HUNTSMAN CORP. has licensed technology for the production of propylene oxide and methyl *tert*-butyl ether to China's Yantai Wanhua Polyurethanes. Wanhua plans to use the technology in a world-scale plant set to open late in 2012.

NOVOZYMES and China's Meihua Group will develop a process for turning agricultural residues into sugars that can be fermented to yield amino acids. The companies seek a process that yields lysine, glutamic acid, and threonine, all commonly used as food additives. Meihua is one of China's leading monosodium glutamate producers.

GEORGIA-PACIFIC Chemicals will expand a plant in Lufkin, Texas, that produces resins used in making proppants, which are coated sand grains used to extract oil and gas via hydraulic fracturing. The firm says it is exploring other opportunities to expand proppant output.

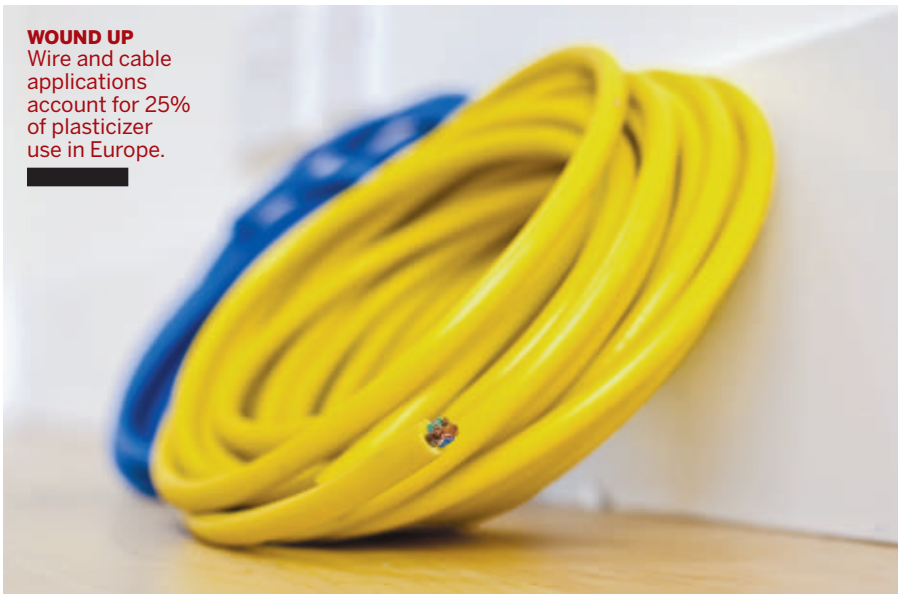
AKZONOBEL has opened a research laboratory in Deventer, the Netherlands, that will house more than 200 top researchers. The facility is one of six global R&D centers that are working with the firm's businesses to boost sales of innovative products from 9% of sales to more than 15% of sales by 2015.

CERES, a developer of seeds for energy crops, has filed for an initial public offering of stock worth up to $100 million. In its filing with the Securities & Exchange Commission, the company says its first product will be sweet sorghum that can extend the operating season of Brazilian sugarcane-to-ethanol mills.

SIGMA-ALDRICH has purchased Brazil's Vetec Química Fina, a supplier of specialty chemicals for academic and industrial markets. The acquisition will add more than 3,000 products used in lab and manufacturing applications. Vetec has more than 200 employees at its Xerem site near Rio de Janeiro.

JOHNSON & Johnson's Cilag division has agreed to buy Rinza, Russia's leading over-the-counter cough and cold medicine brand, from Mumbai-based J.B. Chemicals & Pharmaceuticals for $260 million. Cilag also gets the number two cold medicine in Russia.

PAR Pharmaceutical has agreed to buy privately held Edict Pharmaceuticals, based in Chennai, India, for up to $38 million in cash and some repayment of debt. Edict develops and makes solid oral-dosage forms of generic drugs with a focus on niche first-to-file, first-to-market formulations.



EUROPEAN COUNCIL OF VINYL MANUFACTURERS

WOUND UP Wire and cable applications account for 25% of plasticizer use in Europe.

PHTHALATES FACE MURKY FUTURE

As Europe moves toward a **BAN ON SOME PHTHALATES,** producers of the plasticizers look to diversify

PAIGE MARIE MORSE, C&EN MUNICH

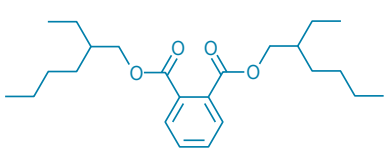
CONCERN ABOUT the use of phthalates as plasticizers for polyvinyl chloride has persisted for several years. The perception, right or wrong, that some phthalates could have reproductive toxicity in humans has led to reduced use in the U.S. and Europe. And the planned European Union phaseout of three phthalates could be the death knell for these products.

Chemical producers are not bowing out quietly. France-based Arkema is leading a consortium of European producers intent on getting approval for continued regional use of one of the products targeted for phaseout, di(2-ethylhexyl) phthalate. Known as DEHP, it is the largest-volume phthalate globally. At the same time, chemical associations in Europe and the U.S. are trying to combat what they see as misperceptions about these products by clarifying research findings and redefining product types.

But as these activities proceed, phthalate producers are positioning themselves to survive any market upheaval. Most have begun to produce alternative phthalates, and some are exploring new plasticizers to add flexibility and softness to vinyl. PVC compounders and end users, meanwhile, are just trying to keep up with all of the changes.

"The plethora of products now available has made the overall plasticizers market much more complex than it used to be," says Ross Law, R&D manager at Ineos Compounds. Law, who reformulates and develops products for Europe and the U.S., says, "It is a challenge for a compounder in terms of logistics."

More than 12 billion lb of plasticizers is sold globally each year, with 96% used to produce flexible PVC. DEHP represents about 40% of that volume, according to data from SRI Consulting, but regional use varies significantly. In the U.S. and Europe, DEHP consumption has been falling as it is displaced, primarily by higher molecular weight phthalates. In Europe, which consumes one-fifth of global phthalates output, DEHP represents about 15% of plasticizer sales, down from nearly 40% a decade ago.



Di(2-ethylhexyl) phthalate (DEHP)

Plasticizers are used primarily in durable applications, such as wire and cable insulation and coatings, roofing materials, and flooring, according to the European Council for Plasticizers & Intermediates (ECPI), a division of the European Chemical Industry Council (CEFIC). Only 4% of plasticizers used in Europe end up in so-called sensitive applications such as medical bags and tubing, food packaging, and toys.

And it is largely concern about these sensitive applications that has raised consumer alarm and prompted regulatory changes in recent years. "It is mostly the weight of the legislation that forces converters to seek other choices that have less paperwork and hassle attached to them," notes Maggie Saykali, sector manager for plasticizers at ECPI, adding that concern for the welfare of their workers and clients is also a factor.

The European Union banned the use of the lower molecular weight phthalates DEHP, di(*n*-butyl) phthalate, and benzylbutyl phthalate in cosmetic applications in 2004. Restrictions on use in toys and child-care articles followed in 2007. The EU also restricted DEHP use in food-contact materials for fatty foods or in single-use applications in 2007.

U.S. LAWMAKERS placed a permanent ban on these products in toys and child-care articles in 2008. A temporary restriction on the higher molecular weight phthalates di(*n*-octyl) phthalate, diisononyl phthalate, and diisodecyl phthalate in these applications is in place until a science panel completes its review, which is expected in mid-2012. No similar constraints on cosmetics or food-contact materials exist in the U.S., although they could happen soon, warns Steve Risotto, senior director of the Phthalate Esters Panel at the American Chemistry Council, a U.S. industry trade organization. The Consumer Product Safety Commission and the Environmental Protection Agency are reviewing phthalates, and Risotto expects an update in the next two years. "It is difficult to predict the impact of these activities at this point," he adds.

The EU's latest action is to phase out DEHP and the di(*n*-butyl) and benzylbutyl phthalates by February 2015 under the region's Registration, Evaluation, Authorization & Restriction of Chemical substances (REACH) program, unless businesses can show that the compounds do

not pose a risk to human health or the environment (C&EN, Feb. 28, page 10). As a first step, a consortium of European DEHP producers—Arkema, Perstorp, Polynt, Zak, Deza, Oltchim, and Boryszew—is compiling information on its safe use in current PVC applications.

Arkema was the lead registrant for DEHP through the REACH registration process last year and is leading this next step. "Arkema remains very committed to DEHP," spokeswoman Sybille Chaix says. "There is no single general-purpose plasticizer that can be used across such a wide range of applications."

Producers are also expected to file for similar coverage for the other two targeted phthalates. Requests for authorization must be submitted to the European Chemicals Agency, which implements REACH, by August 2013. Additionally, importers of articles containing the targeted phthalates must notify the agency beginning next month.

One application that receives a lot of media coverage is medical devices. DEHP is the dominant plasticizer used in products such as blood bags and dialysis tubing because its performance goes beyond just softening PVC. "DEHP increases the stability of blood," ECPI's Saykali explains, "which is very helpful when shipping blood to warmer climates" or when it needs to be stored for a long period of time. She also highlights the antikink properties of PVC tubing made with DEHP.

MEDICAL DEVICE applications are overseen by the health and consumer protection division of the European Commission, the executive body of the EU. This means that the potential ban through REACH will have no impact on these applications. In its 2008 report on DEHP, the EU Scientific Committee on Emerging & Newly Identified Health Risks found no conclusive evidence of harmful effects from DEHP exposure; at the same time, the committee acknowledged the high value of flexible PVC in medical devices. Plasticizer producers and PVC compounders have been working to find an alternative product for medical uses, but none has yet provided this breadth of performance.

For industrial applications, replacements for DEHP include higher molecular weight phthalates such as diisononyl phthalate (DINP), diisodecyl phthalate (DIDP), and dipropylheptyl phthalate (DPHP), which have low volatility, fewer toxicity concerns,

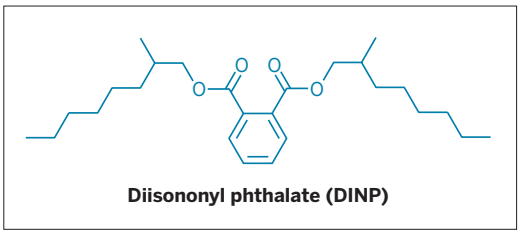
and are assumed to migrate less in final formulations.

To highlight these differences, industry experts now separate phthalates into two distinct classes according to the length of the carbon backbone of the precursor alcohol, Saykali says. The lower molecular weight products, including DEHP and the dibutyl and benzylbutyl esters, are made from alcohols with a backbone of three to six carbons.

The so-called high phthalates, such as DINP, have more than six carbons in the backbone. The reproductive toxicity concerns are confined to the "low" phthalates, Saykali stresses.

Working with the American Chemistry Council, CEFIC launched a public awareness campaign in 2010 to clarify the differences between the phthalate esters. "There has been a lot of confusion in the past year because of everything happening on the REACH front," Saykali explains, "so we started this ambitious program to convey the facts, not emotions, in language that is easy to understand."

Some of this confusion has been created by companies that are lax in naming conventions and use general terms in their marketing. For example, DEHP is often referred to as DOP, for dioctyl phthalate, a misnomer because DEHP is not made from a linear C_8 alcohol but rather a branched C_8 alcohol, 2-ethylhexanol. Differentiating between the six- and eight-carbon chains is critical to distinguishing between low and high phthalates. Additionally, some marketing documents state that new materials are "phthalate-free" when they are actually higher molecular weight phthalates. Such misinformation makes the clarification story more difficult, especially with a lay public that struggles just to pronounce the word "phthalate," let alone understand molecular-weight distinctions.


Diisononyl phthalate (DINP)

PRODUCERS OF all types of plasticizers are trying to refine the phthalates message, either to clarify why the larger derivatives are better or to explain why alternative chemicals offer a preferred solution.

"It is important to understand that not all phthalates are created equal," says Paul J. Galasso, global advocacy director at ExxonMobil Chemical. The company produces several higher molecular weight phthalates, including DINP and DIDP, which are used primarily in durable goods such as flooring, roofing, and wire and cable insulation.

"DINP and DIDP are among the most thoroughly tested phthalates in the world," Galasso claims, "with ExxonMobil proactively investing over $30 million and three decades in testing these products." These chemicals were some of the earliest products registered under REACH because of the long history of testing.

Germany-based Evonik Industries is another producer of DINP and says the product continues to gain market share. "Europe is seeing a major shift to DINP," says Norbert Scholz, vice president of product stewardship at Evonik. ECPI data reflect this progress: Together, DINP, DIDP, and DPHP now account for 75% of the plasticizer market in Europe.

Evonik also produces the related isononyl benzoate, which Scholz says is especially useful as a secondary plasticizer to facilitate processing.

"The high phthalates have a clean bill when it comes to toxicity," says Jerker Olsson, oxo vice president at Sweden's Perstorp. "The debate today is on the total phthalate family, when in fact the concern is with the 2-ethylhexyl derivative only."

Perstorp had been a major producer of DEHP, but it has gradually reduced output in recent years, shifting its resources to DPHP. The company recently announced that it will build new plants for DPHP and the precursor alcohol at its Stenungsund, Sweden, site by 2014. According to Olsson, marketing efforts are targeting large DEHP applications including wire and cable and flooring. The company will cease making DEHP within five years, he adds.

BASF halted its DEHP production in 2005 and now manufactures a variety of higher molecular weight phthalates and plasticizers based on other chemistries. Spokesman Andreas Gryger reports that interest in nonphthalate plasticizers has increased sharply because of regulatory activity. BASF's most well-known alternative, diisononyl cyclohexane-1,2-dicarboxylate, is a saturated version of DINP that goes by the acronym DINCH. BASF also markets

adipates, trimellitates, and other aliphatic carboxylic acid derivatives as phthalate replacements.

Another German firm, Oxea, switched to making alternative plasticizers after ending DEHP production in 2009. The company launched di(2-octyl) adipate in 2009 and added trioctyl trimellitate last year. It is upping its capacity for these specialty esters by 40% later this year and plans to build a second unit at its Oberhausen, Germany, site in 2012. "People are asking for phthalate-free products, so we are investing in new capacity to make sure that the product is available," says Jacco de Haas, Oxea global marketing manager for specialty esters.

Similarly, Eastman Chemical has announced that it will exit low phthalates, ceasing production of diethyl phthalate and dibutyl phthalate by the end of the year. The company is focusing instead on benzoate and terephthalate alternatives.

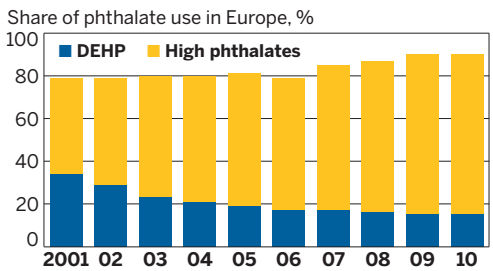
And the latest plasticizers are those based on renewable materials. Roquette's customers are showing interest in starch-derived products, says Franck Thumerel, the firm's business development manager. "First, they want a product that is phthalate-free; then they request our product because it is biobased." Roquette received REACH approval for its first isosorbide diester product in April and is currently testing it with customers.

With the growth of alternative plasticizers, PVC compounders have to juggle multiple choices. "Cost versus benefit is the key issue," Ineos' Law says, noting that high prices for alternative products have pushed him to use other formulating tools to keep costs down.

And when alternatives are developed, customers do not always follow, says Ted Fisher, general manager at Michigan-based Harman Corp., which produces flexible vinyl products for consumer and industrial markets. "We developed nonphthalate formulations a few years ago, but demand has been very limited, going primarily to specialty applications with regulatory requirements."

Like these formulators, chemical companies know that being alert to end-user needs is necessary. "The industry is trying to listen," Perstorp's Olsson says. "You cannot sit by and stubbornly say that the scientific basis shows the products are not dangerous, because you will lose that battle in the end." ■

SHIFTING ROLES **Use of higher molecular weight phthalates is rising in Europe at the expense of DEHP.**



NOTE: Remaining volume is other phthalates. **DEHP** = di(2-ethylhexyl) phthalate.
SOURCE: European Council for Plasticizers & Intermediates

INDENA

WITH CARE A worker handles a cytotoxic and high-potency compound in a glove box at Indena's Settala, Italy, site.

INDENA STEPS UP

EXTRACTS AND API PRODUCER makes its own drug discoveries to keep ahead of competitors

MARC S. REISCH, C&EN NORTHEAST NEWS BUREAU

READINESS TO ADAPT to changing times and market conditions has enabled Indena, a privately held Italian medicinal and nutritional plant extracts specialist, to survive for 90 years.

The company's annual sales grew to $200 million mainly by making custom active pharmaceutical ingredients (APIs) for drug firms and standardized plant extracts for nutritional supplement makers. Now it is conducting internal research programs to discover, patent, and license its own drugs. And it has started up a new business to make single-dose nutritional supplements for sale by prescription in Italy.

Over many years, explains Dario Bonacorsi, the company's president, Indena became expert in scaling up the extraction and purification of APIs from plant sources. Success led to a long list of process patents. But such patents are no guarantee that a customer will buy only from Indena.

"As you know, others can develop processes of their own to compete at lower cost," says Bonacorsi, a Ph.D. electrical engineer and a 30-year veteran of the company. Players include not only U.S. and European fine chemicals makers but also a host of new Asian firms that often bring to market lower cost products.

A little more than 10 years ago, Bonacorsi started to dedicate a portion of Indena's R&D budget to develop new chemical entities. One, a taxane known as ortataxel, is a drug for solid tumors in Phase II clinical trials. Licensed to Spectrum Pharmaceuticals in 2007, the drug is in the same family as paclitaxel, the pioneering ovarian and breast cancer treatment derived from the yew tree.

Indena is developing two other novel entities, both derivatives of colchicine, an extract from the autumn crocus. One has potential as a muscle relaxant and is licensed to an Italian drug firm. The other is a cytotoxic molecule that may be useful to treat colon tumors and has been licensed to Celegene via Abraxis Bioscience.

In addition, Indena is developing a DNA-derived therapeutic oncology vaccine from animal and human cell sources for which it has recently filed an Investigational New Drug Application. As evidence of its potential, Bonacorsi notes that the U.S. Food & Drug Administration last year approved Dendreon's Provenge (sipuleucel-T), the first vaccine for metastatic prostate cancer. Indena also has high hopes for a therapeutic aid to counter the effects of radiation on cancer patients, which it is also developing on its own.

IN WORKING ON these and other potentially useful molecules, Indena does much of the phytochemistry research it is known for at its Settala, Italy, production and R&D complex, Bonacorsi says. For efficacy testing, it joins with outside academic and clinical researchers including the University of Texas M.D. Anderson Cancer Center, in Houston, and Karmanos Cancer Institute, in Detroit.

In nutritional supplements too, the firm has taken a new approach. Although it continues to supply standardized extracts to nutritional supplement formulators, Indena has just introduced what Bonacorsi calls a line of "ethical supplements." They are meant to be sold by prescription through pharmacies under a label incorporating the names of the firm's founders: Carlo Boccaccio Inverni and Biagio Alberto Della Beffa.

The first of the supplements helps people lose weight and stay on a diet. "Developed with a pharmaceutical attitude," the ingredients are obtained from edible plants, Bonacorsi says. They promote a feeling of satiety, help regulate blood sugar levels, and act as a diuretic.

Bonacorsi attributes Indena's current focus on its own patented discoveries to a rough period in the pharmaceutical and nutritional supplements markets that began around 2000. Like many lean periods,

Indena At A Glance

Headquarters: Milan, Italy
Sales: $200 million
R&D spending: $16 million
Employees: 700

BUSINESSES
(% of total sales):

Pharmaceuticals (65%): Extracts and active pharmaceutical ingredients for medicines

Nutraceuticals (30%): Extracts of fruits and herbs such as bilberry, ginseng, green tea, and saw palmetto

Cosmetics (5%): Plant extracts for skin and hair care products

NOTE: Figures are for 2010.

"The mass market is not interested in quality but in low prices."

this one came after a time of plenty.

In 1992, Bristol-Myers Squibb (BMS) gained approval to market paclitaxel, known as Taxol, in the U.S. and Canada. At first, huge quantities of the endangered Pacific yew tree were needed to make the drug. However, scientists discovered that it could instead be made from an intermediate obtained from needles of *Taxus baccata*, the common English yew. BMS turned to Indena, which had developed a process to extract the intermediate, 10-deacetylbaccatin (10-DAB).

The relationship was profitable for Indena until 2000, when BMS lost patent protection on its process for making paclitaxel and generics began to enter the market. "Overnight, BMS decreased the price of Taxol by 70% to keep volumes high," Bonacorsi says. Indena had to accept the new reality. "We kept our 10-DAB volumes, but we had to review our prices," he says.

A similar decline occurred in the nutraceutical market. In the mid-1980s, Indena began to develop a market in the U.S. for nutritional supplements based on extracts from plants such as *Gingko biloba*, ginseng, grape seed, and saw palmetto. Until then, most dietary supplements sold over the counter in the U.S. were vitamins and minerals.

"We practically transferred to the U.S. ingredients that in Europe were considered active pharmaceutical products and were produced according to Good Manufacturing Practices," Bonacorsi says. And in doing so, "we created quite a nice market for ourselves and our customers." Initially, the supplements market grew through specialty shops, mail order, and direct-to-consumer sales.

THEN, AT ABOUT the same time that paclitaxel went generic, mass market retailers became interested in the supplements category. "It was a disaster for Indena," Bonacorsi recalls. "The mass market is not interested in quality but in low prices." Chinese and Indian producers entered the U.S. nutritional supplement market and "our sales decreased dramatically," he says.

Indena's balance sheet took a hit, Bonacorsi says, but the firm had sufficient capital on hand to weather the storm. It also had—and still has—no bank debt. "We are still private because we don't need to bring in outside capital," he explains. Heirs of one of Indena's founders, Della Beffa, still control and guide the firm, he notes.

Now, by discovering its own new drugs the firm expects to move beyond traditional custom manufacturing and gain revenues from royalties and option fees, Bonacorsi says. Spectrum, for instance, paid Indena $2.8 million when it first licensed ortataxel and promised to make milestone and royalty payments.

With the new line of ethical dietary

INDENA (BOTH)

PROCESSED Reaction vessels at Indena facility in Settala.

supplements, Bonacorsi says, Indena has patented both the extracts and the process to make them. The branded products should be shielded somewhat from price competition, he says, and are candidates for licensing to markets outside of Italy.

James R. Bruno, president of Chemical & Pharmaceutical Solutions, a pharmaceutical industry consulting firm, says Indena's work on taxane derivatives "plays well into their strengths," which include the ability to make high-purity extracts and handle highly potent compounds.

However, Bruno is skeptical of Indena's plan to compete in the dietary supplements area with prescription extracts. As an example, he says St. John's wort, an herbal treatment for depression, is St. John's wort whether it is sold over the counter or by prescription. He doubts a company can command a significantly higher price for the prescription version.

Bonacorsi

For Indena, selling plant-derived nutritional supplements by prescription revives a business model the firm undertook in the 1960s when it was known as Inverni Della Beffa and sold prescription pharmaceuticals. The pharmaceutical business was sold in the mid-1990s to Synthelabo, now part of Sanofi-Aventis. The name Indena—short for Industria Derivati Naturali—came into use in the mid-1980s to identify the extracts and API businesses.

IDB Holdings, Indena's parent, recently reacquired the Inverni Della Beffa name. In Italy, "it's a souvenir brand" that will provide traction in the nutritional supplement business, Bonacorsi tells C&EN. He says Indena has done the research needed to back the diet aid. "You need strong evidence to sell this way," he notes.

Although the supplement product line is important, Bonacorsi says Indena's future will be increasingly dependent on its own new ethical pharmaceutical discoveries.

In a moment of optimism, Bonacorsi predicts that success with such products could double Indena sales in five years. But then he recalls the ebbs and flows the firm has seen in the past and moderates his outlook. "The world is changing so quickly," Bonacorsi says, "we would be happy with 10% annual growth." ■

SHELL

RUBBER SOURCE View of the Shell petrochemical complex in Singapore.

RUBBER IS BOOMING IN SOUTHEAST ASIA

ELASTOMER PRODUCERS set up shop in Singapore and Thailand

JEAN-FRANÇOIS TREMBLAY, C&EN HONG KONG

SEVERAL JAPANESE companies and Germany's Lanxess are breaking ground in Singapore and Thailand to build major new plants to produce advanced elastomers for making tires. The companies are muscling into Southeast Asia because of its growing tire production and the availability of hard-to-get raw materials from local refineries.

Announcements from the rubber producers have come fast and furious over the past year. In May 2010, Lanxess said it would go ahead with a $575 million investment, the largest project in its history, to build a butyl rubber plant in Singapore. Butyl rubber offers high impermeability to air and is used in tire inner tubes.

Then Japanese firms started to announce that they, too, would build tire rubber plants in Singapore, a country where no international tire manufacturer has production facilities.

In October, Asahi Kasei said it would build a plant producing solution-polymerized styrene-butadiene rubber (S-SBR) with an initial capacity of 50,000 metric tons per year in Singapore. S-SBR is another key rubber in high-end tires. Asahi was followed a month later by Sumitomo Chemical, which said it was setting up a 40,000-metric-ton S-SBR plant in Singapore, where it already operates a petrochemical complex. And last December, Zeon declared that it was building, also in Singapore, an S-SBR plant with an initial capacity of between 30,000 and 40,000 metric tons.

After a few months' hiatus, in March, JSR announced it would build an S-SBR plant with an initial capacity of 50,000 metric tons in Map Ta Phut, Thailand. JSR, which claims to be the world's leading producer of S-SBR, says the plant may later be expanded to 100,000 metric tons.

The sequence of announcements raises eyebrows, but the explanation is straightforward, according to Hiroshi Yoshida, general manager of Asahi Kasei's synthetic rubber division. "There is a global shortage of butadiene, and in the future it will become tighter and tighter," he states.

In Singapore, he says, Asahi Kasei was able to negotiate a long-term butadiene supply contract with Shell, which operates a refinery in the city state and completed construction of a naphtha-based ethylene cracker there in May 2010.

As part of its expansion, Shell built a 155,000-metric-ton butadiene extraction facility. The supply agreement, based on a pricing formula linked to the price of crude oil, is what made it possible for Asahi Kasei to build the plant, Yoshida adds. Similar to the Japanese producers, Lanxess said it selected Singapore largely because of an agreement with Shell to obtain isobutene, the key raw material for butyl rubber.

There aren't many new sources of butadiene in the world, explains Samuel Liew, an Asia-region olefins and elastomers analyst at the consulting firm Chemical Market Associates. The Middle East is not an option because most petrochemical complexes there are based on natural gas, and butadiene is produced in significant quantities only by crackers that run on naphtha or other liquid raw materials. Likewise, the two ethylene crackers recently announced for the U.S. will be fed by natural gas.

China is building several naphtha crackers, but the country is not an attractive location for producers of advanced rubbers. First, Liew says, China plays a lesser role in the international tire market since the Obama Administration imposed U.S. import tariffs on Chinese tires last year. "That has definitely affected the cost of Chinese tires," he says.

MORE IMPORTANT, rubber producers are keen to protect the know-how behind making S-SBR, a technology that Chinese manufacturers have yet to master. The risk of intellectual property loss is great in China because foreign petrochemical producers normally cannot invest in the country without a local partner, Liew explains, and partnership could compromise control of the technology. "If China starts to export S-SBR, Asahi, JSR, and the others will not

"If China starts to export S-SBR, Asahi, JSR, and the others will not be able to define their advantage in the marketplace."

be able to define their advantage in the marketplace," he says.

Used in the production of tire treads, S-SBR is a rubber that few companies know how to make. S-SBR allows tire manufacturers to attain the seemingly contradictory goals of fuel efficiency and strong wet grip. Fueled by increasing concern about energy conservation, global demand for S-SBR is booming, says Nobu Koshiba, president of JSR Corp.

In 2010, Koshiba explains, Japan implemented a voluntary labeling system for tires that rates them for rolling resistance and wet grip performance. A similar labeling system will come into effect in Europe in 2012. "In Germany, for instance, drivers go at high speed on wet surfaces, but they also want high fuel efficiency on dry roads," he says. High-performance tires with S-SBR treads are increasingly sold as standard items on new cars, Koshiba says.

Not all S-SBRs are the same in terms of performance, Asahi's Yoshida says. Asahi's S-SBR, he claims, is more successful than its competitors' at eliminating the traditional trade-off between fuel efficiency and adherence to the road surface.

Generally, a tire manufacturer will create blends of rubbers from several suppliers to produce specific models. Asahi, Yoshida claims, supplies S-SBR to the world's 10 largest tire manufacturers. "We're the first choice of some manufacturers, but not others." Asahi, he adds, is constantly developing new rubber characteristics by working closely with tire companies.

RUBBER BAND

Several companies are planning to open Asian facilities in 2013

	LOCATION	PRODUCT	CAPACITY (METRIC TONS) PHASE 1	CAPACITY (METRIC TONS) PHASE 2	SCHEDULED 2013 OPENING
Asahi	Singapore	S-SBR	50,000	50,000	June
JSR Corp.	Thailand	S-SBR	50,000	50,000	June
Lanxess	Singapore	Butyl rubber	100,000	Not planned	Early in the year
Sumitomo	Singapore	S-SBR	40,000	Not planned	Late in the year
Zeon	Singapore	S-SBR	30,000–40,000	30,000–40,000	July

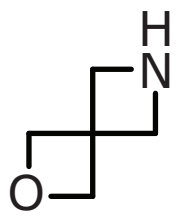
S-SBR = solution-polymerized styrene-butadiene rubber. **SOURCE:** Company reports

It was a coup for JSR to set itself up in Thailand, Koshiba contends. Not only is Thailand, unlike Singapore, a major tire producer, but the cost of setting up chemical plants in that country is lower. "We quickly ruled out Singapore," he says. The company has a 49% partner in Thailand's Bangkok Synthetics, with which it previously collaborated on business ventures. Bangkok Synthetics' major role in the venture is to supply butadiene, JSR says.

Additional sources of butadiene in Asia should appear in coming years. Indonesia's Chandra Asri has started construction of a butadiene unit that it expects will come on-line in 2013. In Malaysia, Petronas just announced an oil refinery and petrochemical complex that would supply the C_4 fractions necessary for butadiene and isobutene production (C&EN, May 23, page 9). Chances are the two companies are already being courted by the world's big rubber producers. ■

SYNTHONIX©

ELEMENTS OF PROGRESS™



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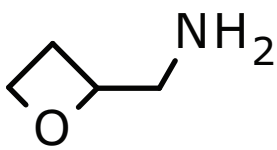

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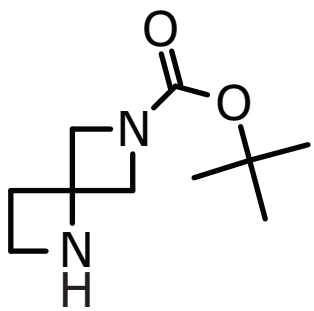

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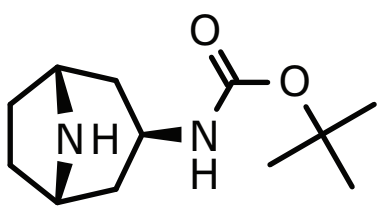

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Building Blocks for Grown Ups

CLIMATE PANEL ADOPTS NEW POLICIES

The Intergovernmental Panel on Climate Change (IPCC) is making changes to improve its scientific integrity. The move comes in part because of mistakes discovered in the panel's 2007 assessment, including the incorrect statement that Himalayan glaciers would melt away by 2035. Last year, the InterAcademy Council, a coalition of national scientific academies, recommended changes to IPCC to address these and other issues (C&EN, Sept. 6, 2010, page 15). At a meeting in mid-May, IPCC adopted a procedure for evaluating and correcting errors in its assessments. The group also established a standardized method for addressing scientific uncertainties in its reports, and it approved a new conflict-of-interest policy. In addition, the panel set a benchmark for scientific literature used for its assessments. This gives priority to peer-reviewed studies but recognizes that reports from governments, industry, and research institutions may provide crucial data even if they aren't peer reviewed. It states that magazines and newspapers are generally not valid sources of scientific information and bans the use of material from broadcast media, blogs, social networking sites, and personal communications of scientific results.—CH

EU BANS CADMIUM IN JEWELRY, PLASTICS

The European Union has banned the use of cadmium in jewelry and all plastic products effective Dec. 20, according to an amendment added to the chemicals law Registration, Evaluation, Authorization & Restriction of Chemical substances (REACH). Cadmium is a known human carcinogen and is toxic to aquatic organisms. Previously it was used in plastics as a coloring agent and stabilizer. It has been banned in the EU in most plastics since 1992 but was allowed in some polyvinyl chloride because alternatives were unavailable. The European PVC industry has since found alternatives to cadmium. The legislation will allow low levels of cadmium in a limited number of construction materials that are made from PVC waste to encourage recycling. The ban on cadmium in jewelry is intended to protect consumers, particularly children, from the toxic metal, which has been increasingly showing up in inexpensive costume jewelry imported from China. The legislation also bans cadmium in brazing sticks, which are used to join dissimilar metals in applications such as steam engines for model trains, because of the fumes released during the brazing process.—BEE

HOUSE BILL WOULD ANALYZE EPA RULES

A bill that would require the Obama Administration to evaluate the cumulative economic impacts of EPA regulations was approved last week by the House of Representatives Energy & Commerce Committee's Energy & Power Subcommittee. The legislation (H.R. 1705) would create an interagency committee to analyze how EPA rules governing air and water quality impact the nation's global economic competitiveness. The panel would also study the costs and benefits of the regulations to consumers, small businesses, state and local governments, labor markets, and agriculture. The proposal is strongly supported by the petrochemical industry. "Conducting a cost-benefit analysis of EPA regulations is an important first step to identify burdensome regulations that do little or no good but can inflict tremendous harm on American families, workers, and businesses," says Charles T. Drevna, president of the National Petrochemical & Refiners Association, an industry trade group. The legislation now goes to the full Energy & Commerce Committee for consideration.—GH

PESTICIDE RESIDUE DATA RELEASED

Only a small fraction of food and water tested in 2009 contained pesticide residues that exceeded safety limits set by EPA, a report from USDA's Agricultural Marketing Service concludes. The annual Pesticide Data Program report provides a snapshot of the levels of pesticides found on numerous foods including fresh and processed fruits and vegetables, beef, catfish, and rice, as well as treated and untreated drinking water. Samples were collected and analyzed in 12 states in 2009. Only 0.3% of the samples contained pesticide residues that exceeded EPA limits, and 2.7% of the samples contained residues of pesticides with no established limits. The data are used by EPA to assess dietary exposure to pesticides and by other agencies to help facilitate trade of U.S. agricultural products. They are also used by environmental and consumer advocacy groups to warn people about foods that contain particularly high levels of pesticides. The Environmental Working Group, in particular, has been pushing USDA to release the data in a more timely fashion.—BEE

U.S. ARMY

The final 1-ton container of mustard agent undergoes disposal at the Anniston Army Depot.

ARMY DEPOT DESTROYS CHEMICAL WEAPONS

The Anniston Chemical Agent Disposal Facility in Alabama has completed the destruction of its stockpile of mustard agent stored in 1-ton containers, according to the U.S. Army. The disposal campaign, which took about two months, involved the elimination of 108 containers that together held more than 18,300 gal of mustard agent, a chemical that causes severe burns and blisters on exposed skin. "Even though the ton-container campaign was relatively brief, we put in the same planning, preparations, and attention to detail as with any previous campaign," says Kenneth R. Ankrom, plant manager. "Safety and environmental compliance remain our top priority regardless of the campaign duration." The Alabama depot began incinerating chemical warfare materials in August 2003. Since then, operators have processed 638,225 nerve agent- and mustard agent-filled munitions and containers.—GH

MARK GARTEN/UN PHOTO

WORLD LEADER UN Secretary-General Ban (center) addressed the Commission on Sustainable Development.

WHITHER SUSTAINABLE DEVELOPMENT?

Recent failure of UN talks raises concerns over likelihood of success of efforts to create a **GREEN ECONOMY**

CHERYL HOGUE, C&EN WASHINGTON

THE UNITED NATIONS is revving up for a major conference next year that it hopes will set the stage for a global green economy. That meeting, the UN Conference on Sustainable Development, commemorates and builds on the work of the 1992 Earth Summit, a highly influential meeting held in Rio de Janeiro that brought together scores of global leaders who signed the world's first treaties on climate change and biodiversity protection. In addition, governments attending the summit endorsed an agenda for sustainable development.

In the past 15 years, it has led to the creation of two new international treaties on chemicals and a global strategy for helping countries that lack a regulatory system to manage chemicals.

But given what happened at UN headquarters in New York City in mid-May, the outlook for the 2012 conference is not good. The negative omen came when negotiators attending the UN Commission on Sustainable Development meeting walked away from the table on the morning of May 14, several hours after the two-week gathering was scheduled to end on May 13. Discussions broke down, and completed—or nearly completed—draft agreements on commercial chemicals, waste management, mining, transportation, and sustainable patterns of consumption and production were abandoned. The causes were disputes over the definition of "green economy" and provisions for financial and technology assistance.

This wasn't the first stalemate for annual negotiations by the Commission on Sustainable Development, which was established at the Earth Summit to continue the work begun at that meeting. In 2007, the commission's talks also failed to produce agreement.

The current deadlock left in limbo a long-anticipated international agreement: a 10-year global action plan to create sustainable patterns of production and consumption. UN countries agreed in 2002 that they would create this plan of action. UN Secretary-General Ban Ki-moon has emphasized the importance of the action plan to transform current patterns of protection and consumption and reverse trends of excessive resource use. Negotiators finished work on the document at the May meeting, but it is not official because the commission did not adopt it.

Countries represented at the May meeting also agreed on policy options for managing commercial chemicals. Speaking on behalf of a coalition of more than 130 developing nations—called the Group of 77—Silvia Merega, an Argentine diplomat, told the commission that the benefits of commercial substances for developing nations "cannot be overemphasized. However, the main challenge that developing countries face lies in the local capacity to manage production, effective uses of chemicals, prevention of chemical hazards, and protection of the environment as well as in promoting corporate, social, and environmental responsibility." In their discussions, negotiators recognized a major transformation within this sector, namely that commercial production of chemicals is shifting to developing countries, some of which lack the know-how and money to manage this industry effectively.

BUT THE CHEMICALS talks ran into fatal snags on how best to help developing countries surmount these challenges through funding, training, and technology. In UN parlance, these types of assistance are collectively called "means of implementation." The G-77 and China—which is not a member of the G-77 but generally joins the coalition in policy stances—were at loggerheads with industrialized countries over what this assistance should include and how it should be provided. The bloc's argument was that simply establishing worldwide consensus on commercial chemicals does no good if many developing nations

"Our vision must be clear—a sustainable green economy that protects the health of the environment."

lack the wherewithal to implement these policies. They want the industrialized world to support these efforts with money and other aid.

Industrialized nations—notably the U.S.—balked at calls for funding made not just in the chemicals sector discussions, but throughout the commission's meeting. Several of these countries pointed out that they are facing serious economic problems at home. For instance, John M. Matuszak, chief of the U.S. State Department's Sustainable Development & Multilateral Affairs Division, told the commission as it kicked off its recent meeting that "the U.S., as with many other countries, is actively cutting budgets to reduce our deficit and cannot make new financial commitments or support costly new initiatives." Instead, governments, the private sector, and others must engage effectively to "leverage our collective resources" to help the developing world on sustainable development issues, Matuszak said.

RESOURCES

Boosting Efficiency While Curbing Environmental Harm

To foster sustainability, the world's economy needs to do a lot more with a lot less, according to a new report from the United Nations. At the same time, pollution and ecological destruction from extracting and using natural resources must decline, the report says.

Driving the need for these changes is the growing global appetite for a smorgasbord of resources: fossil fuels, metals including rare-earths, water, fertile soil, and construction supplies such as cement.

"Global resource consumption is exploding. It's not a trend that is in any way sustainable," says Ernst U. von Weizsäcker, cochair of the International Resource Panel (IRP), which produced the report. "Prosperity and well-being do not depend on consuming ever-greater quantities of resources," says von Weizsäcker, who is also dean of environmental science and management at the University of California, Santa Barbara.


Khosla

PAULO FILGUEIRAS/UN PHOTO

Formed by the UN Environment Program (UNEP) in 2007, IRP is composed of researchers who are providing independent scientific assessments about the sustainable use of natural resources and the environmental impacts of their use. It is analogous to the Intergovernmental Panel on Climate Change.

The report, released on May 12 in conjunction with the UN Commission on Sustainable Development's annual meeting, explores what IRP calls "decoupling." The panel applies this term to separating the rate of economic activity from the rates of resource use and environmental degradation.

One goal of decoupling is to use fewer resources per unit of economic output—for instance, requiring less energy, water, or land for a set amount of industrial or agricultural production. A second goal is to shrink the environmental impact of resource use of an economic activity, such as reducing pollution from mining operations or curbing carbon dioxide emissions from transportation. Decoupling, the report points out, is not the same as an absolute reduction in uses of resources.

In essence, decoupling is about replacing debt-financed consumption with sustainability-oriented investments in innovation as the primary driver of the world's economy, explains Mark Swilling, a lead author of the IRP decoupling report.

Some decoupling takes place as a part of economic evolution. For example, over the past century, the global economy grew faster than the use of resources. The world saw an eightfold increase in use of resources while, overall, gross domestic product rose 25-fold, says Swilling, who is academic director of the Sustainability Institute at the University of Stellenbosch, in South Africa.

Innovation in the private sector helps decouple economic progress from the need to use more resources, Swilling says. But achieving sustainability will necessitate additional efforts, he adds.

"Decoupling will require significant changes in government policies, corporate behavior, and consumption patterns by the public," the report says. But the report doesn't suggest options for new policies and technologies. Those will come in other IRP publications, including one on metals (see page9).

Swilling

PAULO FILGUEIRAS/UN PHOTO

The panel is preparing future reports on how to apply the concept of decoupling to a number of key areas: technologies to curb emissions of greenhouse gases, recycling, land and soil, and water. The panel's work is part of UNEP's Green Economy Initiative, which aims to link a revived world economy to reductions in ecosystem degradation, water scarcity, and dependence on fossil fuels.

Decoupling the world economy from resource uses and their impacts is "profoundly important for life on Earth," says Ashok Khosla, cochair of IRP and president of the International Union for the Conservation of Nature. There will be "devastating consequences" if the world fails to act on this issue, Khosla said.

The report is available online at unep.org/resourcepanel.

Although arguments over funding and related means of implementation will almost certainly carry over to the 2012 gathering, another obstacle may pose a bigger threat to the success of the upcoming conference. At the commission's meeting this month, the G-77 and China steadfastly opposed use of the phrase "green economy" in any documents, saying there was no agreed-on definition for it.

THIS DEBATE over the term green economy is "not a welcome sign" for the meeting next year, said Jeffrey Barber, executive director of Integrative Strategies Forum, a nonprofit citizens group that works on sustainable development issues. That's because one of the two major focuses of the 2012 conference, which will be held in Rio, is "a green economy in the context of sustainable development and poverty eradication." The second main theme of next year's meeting is governance for sustainable development.

For some developing countries, a main sticking point is whether a green economy must involve significantly lower emissions of carbon dioxide, a major greenhouse gas. Emerging economies, including India, China, South Africa, and Brazil, are increasing their emissions of CO_2 as they rapidly industrialize.

But that's not the only dispute related to defining a green economy. The European Union is recommending that a transition to a green economy include the removal of environmentally harmful subsidies and the use of incentives for more environmentally friendly goods. Some developing countries balk at this notion. For instance, a delegate from India told the commission that requirements for green products may distort free flow of global trade and erect barriers to some products. Importing countries' environmental standards, subsidies, and market incentives for green goods could limit the ability of developing countries that export to achieve their sustainability goals, the Indian representative added.

UN chief Ban either was unaware of the developing countries' concern about the term green economy or chose to dismiss it when he addressed the commission on May 13. Looking ahead to the 2012 conference, which the UN has dubbed "Rio + 20," Ban said, "Our vision must be clear—a sustainable green economy that protects the health of the environment." A green economy, he said, must support development "through growth in income, decent work, and poverty eradication." ■

CAPTURING CARBON DIOXIDE

Senators question cost, lack of applications for GREENHOUSE GAS STORAGE plans

RESEARCHERS AND lawmakers alike are looking for ways to reduce the amount of carbon dioxide released into the atmosphere because of its contribution to global climate change. Work to develop feasible carbon capture and sequestration (CCS) technologies is still ongoing, and methods to turn the CO_2 into a resource for other industrial applications, such as enhanced oil recovery, are years away from becoming reality. This was the less than satisfying message delivered to senators during a hearing earlier this month.

The goal of the Senate Energy & Natural Resources Committee hearing was to get feedback on a pair of CCS bills that have been reintroduced in the Senate. In discussing the legislation, the witnesses described potential uses for captured CO_2 but noted that such options either are not cost-effective or are technically challenging.

Of the two bills, discussion of S. 699—an amendment to the Energy Policy Act of 2005 that would allow the Department of Energy to provide technical and financial help to 10 commercial-scale projects on integrated CCS systems—dominated the hearing. The second bill (S. 757), which garnered less interest from the senators, provides incentives to encourage the development and implementation of technology to capture significant amounts of CO_2 from dilute sources using direct air capture.

A key issue for the senators was to understand the cost and purpose of commercial CCS systems. The systems covered by S. 699 are designed to capture more than 1 million tons of CO_2 per year from industrial sources and then inject, monitor, and geologically store it.

Earlier in the week of the CCS hearing, the committee heard testimony from oil and gas industry executives on how they were having trouble getting CO_2 for enhanced oil recovery. The industry uses CO_2 and other gases to expand a reservoir and push more oil into a production wellbore. With this concern fresh in their minds, senators, including committee Chair Jeff Bingaman Jr. (D-N.M.) and Joseph Manchin III (D-W.Va.), asked why R&D endeavors to capture and sequester millions of tons of CO_2 from industrial sources hadn't considered applications of the gas in enhanced oil recovery.

Scott M. Klara, deputy director of the National Energy Technology Laboratory, explained that using CO_2 captured by CCS systems is prohibitively expensive. NETL, which is the DOE lab charged with managing laboratory and field-based R&D projects on CCS, has a small portfolio of research projects that are studying the conversion of CO_2 into other chemical products. But, Klara said, the stability of CO_2 requires high-pressure and high-temperature processes that make the conversion of the gas into other products very expensive. Storing CO_2, although also costly, is the cheaper alternative.

UP IN SMOKE Lawmakers want information about the cost and potential applications of CO_2 captured from industrial sources such as coal-fired power plants.

SHUTTERSTOCK

"Two big issues in getting the technology to go forward for CCS are cost and liability," Sen. John H. Hoeven III (R-N.D.) noted. The liability issue is covered in the S. 699 bill, but the cost issue is still left dangling. "We've got to find a way to address the cost aspect where we use this CO_2 in a productive way," he said. Hoeven wasn't buying into the use of captured CO_2 in the enhanced oil recovery application because the technology is still 10 years away from being feasible. He wanted ideas of more immediate uses for the CO_2 that would help offset the cost of CCS.

KLARA AGREED there is a need to reduce the cost of CCS technologies, but he couldn't offer immediate suggestions. Currently, CO_2 purchased for enhanced oil recovery costs between $10 and $30 per ton of gas, he said. With the best CCS technology currently available, "it will cost you $60 a ton or more," Klara stated. He said NETL is looking into technologies to drive the costs of CO_2 capture down by two-thirds so the oil and gas industry could consider using CO_2 obtained by CCS in the future.

Sallie E. Greenberg, assistant director of the Illinois State Geological Survey, pointed out that the purity of the CO_2—whether it is free of volatile organic compounds and other contaminants—is a critical factor in using it for chemical processing. She also said transportation infrastructure is a consideration to "get anthropogenic CO_2 from locations where it is being produced to places where you're going to be doing [enhanced oil recovery]."

Her comment caused Hoeven to push his point that unless CO_2 is soon turned into a usable product, the cost for CCS will not drop. But Klara argued that even if applications, such as turning CO_2 into plastics, did take off, they would hardly help drive down CCS's cost because they would use only a small amount of captured CO_2.

Manchin asked whether implementation of CCS technologies would affect the nation's competitiveness by increasing the price of energy. If U.S. energy costs rise because of having to use CCS technology in places such as coal-powered utilities, it gives countries like India and China that have cheaper energy a competitive advantage, he stated.

Because of these concerns, Manchin asked: "Why would we lose more jobs because of our high cost of manufacturing when we don't have the proven technology, and why should we put money" into research to develop the technology that will make the U.S. less competitive? No one had a response.—RAJENDRANI MUKHOPADHYAY

JOHN SCHWAB

An advocate for mentoring young organic chemists will **RETIRE FROM NIH** this month

BRITT E. ERICKSON, C&EN WASHINGTON

ONE OF ORGANIC chemistry's staunchest allies at the National Institutes of Health is leaving; finding a replacement with the same passion for organic chemistry could be difficult.

For the past 15 years, John M. Schwab has been overseeing extramural grants in organic synthesis, chemical biology, and natural products chemistry at NIH. Many people in the organic chemistry community consider him a hero for spearheading a mentoring workshop for junior faculty and for promoting organic chemistry as an integral component of biomedical research.

Schwab will retire on May 31 from his role as a program director at the National Institute of General Medical Sciences, the leading NIH institute for the support of chemical research. C&EN sat down with him earlier this month to talk about his work at NIGMS and how organic chemistry has changed over the past decade and a half.

BRITT ERICKSON/C&EN

WRAPPING UP Schwab looks forward to spending more time playing his guitar.

Of all the aspects of his job, Schwab takes the most pride in mentoring young researchers. When he arrived at NIH in the mid-1990s, "the number of grants and grantees in organic chemistry was going down almost to zero," he tells C&EN. The decline "correlated with the aging of the grantee population. You could see the number of young investigators steadily dropping toward zero," he says.

That alarming trend led Schwab and Michael P. Doyle, a chemistry professor at the University of Maryland, College Park, to launch an annual NIGMS-supported mentoring workshop for junior faculty in organic chemistry and chemical biology. The first workshop was held in 2005.

One of the lessons young faculty learn at the workshop is how to sell a project to peer reviewers. Good communication skills are "very important and underappreciated," Schwab says. The workshop also aims to enhance skills that are not typically taught to graduate students and postdocs, such as "knowing how to motivate and get the most out of your coworkers, navigating departmental politics, and managing research collaborations," Schwab notes.

Schwab was trained in natural product biosynthesis and enzymology, or as he puts it, "somewhere between organic chemistry and biochemistry." However, most of the grants that come across his desk involve organic synthesis and synthetic methodology. Because he didn't receive formal training as a synthetic organic chemist, Schwab says he's been able to maintain impartiality and open-mindedness in dealing with applicants and grantees.

Much has changed in organic chemistry since Schwab joined NIGMS. In the mid-1990s people tended to place "heroic syntheses of very complex molecules" on a pedestal, he says. Since then, he notes, just making molecules is no longer enough; the molecules have to be useful.

As a result, peer reviewers are now questioning the biomedical relevance of every proposed synthetic methodology. One way that organic chemists can more readily identify potential applications is to collaborate with biologists, Schwab says. Such collaborations are much more common today than in the 1990s, he notes.

Another change is the employment outlook for organic chemistry graduates. "In the past, chemistry departments could turn out as many synthetic chemists as they wanted because pharma hired people who were trained very deeply, albeit fairly narrowly, in organic synthesis," Schwab says. "But these days pharma isn't doing much hiring in the U.S., if any. There are relatively few jobs now for people who are trained in this way."

Chemistry departments must keep pace with the changing workforce and train their students broadly, Schwab stresses. "I think we need to be very much involved with our graduate students and postdocs to understand what their career goals are and to help them be realistic about preparation for the careers that will be there," he says. Departments should support alternative career paths such as journalism, law, or policy, he points out. "I think it is going to be very important that people be flexible."

FOR STUDENTS still interested in pharma careers, Schwab notes, related jobs are moving to East Asia and South Asia. With that in mind, he says, "an understanding of foreign cultures and foreign languages would be useful" when job hunting.

The most gratifying part of his job has been his interactions with the organic chemistry community, Schwab tells C&EN. Many of those stemmed from the mentoring workshop, but many more took place during his day-to-day work on the telephone, by e-mail, or at meetings.

If he could do it all over again, Schwab says, he would have pushed for an initiative in natural products discovery at NIH much earlier in his tenure than he did. Natural products chemistry "has been a very hard sell in the NIH system because it is discovery driven and not hypothesis driven," he notes. Nonetheless, natural products are extremely important because they have inherent biological activity, he says.

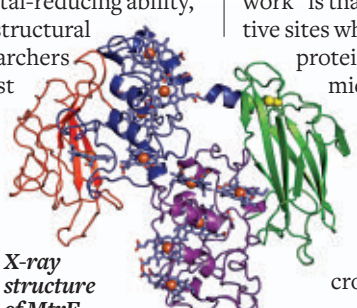
After he leaves NIH, Schwab plans to remain involved in the mentoring workshop, do some consulting, and continue to serve on C&EN's advisory board. He will also spend much more time playing backup guitar in an old-time string band. "I'll be leaving May 31 in time for the music festival season," he remarks. ■

ORGANIC LAYER SMOOTHS DIELECTRIC FILMS

Depositing a few layers of organic molecules on graphene enables subsequently deposited oxide layers to be grown without imperfections, according to a study published in *ACS Nano* (DOI: 10.1021/nn201414d). The investigation identifies a fabrication step that can improve the quality of insulating layers crucial to the performance of graphene-based electronic devices. To exploit graphene for use as a field-effect transistor electrode, this ultrathin carbon film needs to be selectively coated with smooth, thin, and defect-free layers of insulating materials known as high-*k* dielectrics. Graphene's hydrophobicity and inertness, however, prevent dielectrics such as alumina and hafnia from being deposited on graphene smoothly and uniformly. Some surface treatments have been shown to improve the deposition process, but they tend to degrade graphene's structure and electronic properties. A team of researchers, led by Northwestern University's Mark C. Hersam, has shown that those problems can be overcome by growing one or two monolayers of a perylene dianhydride compound, PTCDA, on graphene before depositing films of alumina and hafnia. According to the team, surface analysis and electrical measurements show that dielectric films grown that way are highly uniform and conformal, and that the graphene remains undamaged.—MJ

MICROBE'S PROTEIN STRUCTURE ELUCIDATED

Shewanella oneidensis, a bacterium admired by biologists for its metal-reducing ability, just gave up one of its structural secrets, thanks to researchers at the University of East Anglia, in England, and Pacific Northwest National Laboratory. The scientists report the first X-ray crystallography structure of a protein in the complex that is responsible for shuttling electrons from the microbe's innards to solution (*Proc. Natl. Acad. Sci. USA*, DOI: 10.1073/pnas.1017200108). The protein, called MtrF, sits on the outermost membrane of *S. oneidensis*, and knowledge of its configuration should enable more efficient use of the bacterium in microbial fuel cells and future industrial redox reactions. Together, two of MtrF's four domains contain 10 heme groups, which are arranged in a staggered cross structure that conducts electrons. "The brilliant finding" in this work "is that there appear to be three active sites where electrons can exit the protein," says Jeffrey A. Gralnick, a microbiologist at the University of Minnesota, Twin Cities. Electrons can leave directly from the cross tip, the research team shows, and they can potentially leave via shuttle molecules, such as flavins, from each of the cross's arms.—LKW



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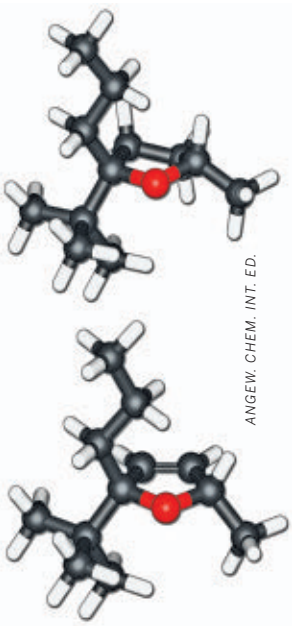
X-ray structure of MtrF shows the cross configuration of the protein's 10 heme groups (orange spheres are iron atoms), which form a conductive "wire."

PULLING OUT PROTEIN COMPLEXES

Many of a biological cell's most important activities are orchestrated by collections of proteins that form macromolecular complexes, but studying these protein powwows is far from simple. Now researchers, led by Taekjip Ha, a biophysicist at the University of Illinois, Urbana-Champaign, have developed a new way to capture these complexes for detailed study. Referred to as single-molecule pull-down (SiMPull), the method relies on capturing a "prey" protein from the complex via an antibody, and then pulling the protein and all of its binding cohorts out of a cell or tissue extract and depositing the analytes on a surface, where the assembly can be studied with single-molecule fluorescence microscopy (*Nature*, DOI: 10.1038/nature10016). Unlike its competitor, the long-standing western blot method, SiMPull can be performed in 30 minutes rather than several hours, it does not require any preparatory purification steps, and further biochemical studies on the proteins can be undertaken after the extraction step. In addition, the technique can isolate very low abundance protein complexes and can sometimes provide quantitative information about the numbers of unique proteins in the complex.—SE

SNIFFING OUT BLACK-CURRANT STRUCTURES

The secret behind the trendy aroma of black currant may be all about puckering up—five-membered ring puckering, that is. A team at Swiss fragrance firm Givaudan and RWTH Aachen University in Germany has shown that the structure and shape of an ingredient in black-currant scents influence its olfactory properties (*Angew. Chem. Int. Ed.*, DOI: 10.1002/anie.201100937). Black currant, or cassis in French, is a berry from a plant native to Europe and Asia, and its scent has enjoyed a new surge of popularity with the success of products such as DKNY Be Delicious perfume. The cassis aroma is highly dependent on the stereochemistry of its substituent compounds, and Givaudan chemist Philip Kraft wanted to see whether that held true for Cassyrane, a proprietary black-currant odorant introduced by Givaudan in 2010. With Aachen's Wolfgang Stahl and colleagues, he combined quantum chemistry calculations with microwave spectroscopy to determine gas-phase structures of Cassyrane stereoisomers and derivatives. They found that stereochemistry at Cassyrane's number five carbon determines whether the molecule smells like cassis, and that puckering of the odorant's furan ring enhances its fruity cassis character.—CD



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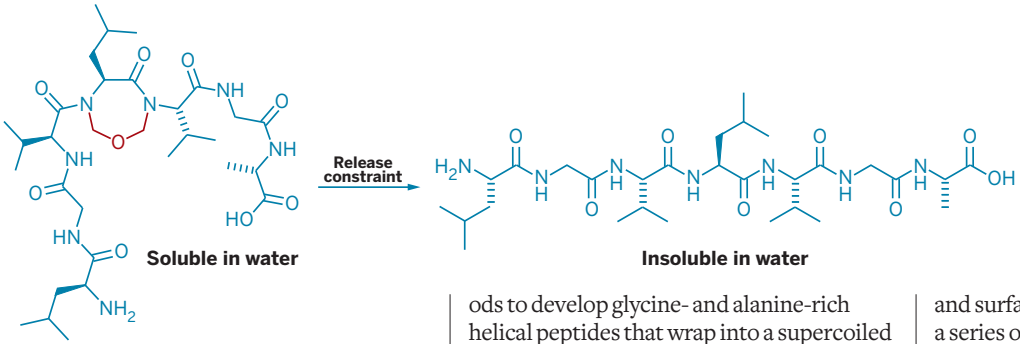
A Cassyrane derivative with a puckered ring (top) has a stronger odor than a compound with a flat ring (bottom).



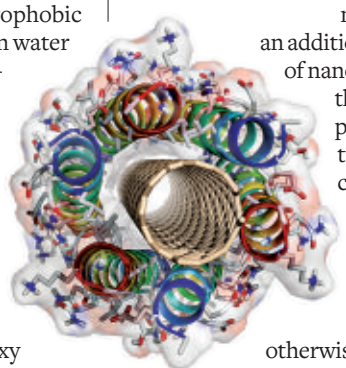
Linking adjacent amino acids reversibly with a dimethyleneoxy group (red) enhances water solubility and inhibits aggregation, making peptides easier to work with in syntheses.

MOLECULAR CONSTRAINT INHIBITS PEPTIDE AGGREGATION

Researchers have devised a way to use isonitrile chemistry to constrain peptides reversibly, making them water soluble and easier to work with in syntheses (*J. Am. Chem. Soc.*, DOI: 10.1021/ja2023898). The constraint, a dimethyleneoxy group that creates a seven-membered ring that includes nitrogens on two adjacent amino acids, causes the peptides to bend, permitting the two ends to fold together. The folding satisfies the peptides' hydrophobic needs, thus making them soluble in water and discouraging them from forming aggregates with other peptide molecules. The constraint can then be released chemically, causing the peptides to unfold into their usual water-insoluble and aggregation-prone selves. Xiangyang Wu, Peter K. Park, and Samuel J. Danishefsky of Sloan-Kettering Institute for Cancer Research install the dimethyleneoxy constraints by using an isonitrile and carboxylic acid reaction developed earlier by Danishefsky's group. The tendency of peptides and proteins to form aggregates not only leads to conditions like Alzheimer's disease but also makes them hard to manage synthetically. The new approach "points to a direction that could help solve that problem" for synthetic chemists, Danishefsky says.—SB

PEPTIDE-NANOTUBE ASSEMBLIES CREATE SUPERSTRUCTURES

Coating carbon nanotubes with peptides can produce structurally specific, tunable macromolecular assemblies, University of Pennsylvania researchers report (*Science*, DOI: 10.1126/science.1198841). Led by biochemistry professor William F. DeGrado, the group used computational design methods to develop glycine- and alanine-rich helical peptides that wrap into a supercoiled layer around single-walled carbon nanotubes. Glycine or alanine groups are needed on one side of a peptide helix to interface with the nanotube, while residues at helical interfaces direct assembly. Other amino acids in the peptides can be altered to modulate the solubility or stability of the constructs, or functionalize the surface. In one case, DeGrado and colleagues nucleated gold nanoclusters on the surface of a peptide-coated nanotube, creating an additional ordered layer of nanoparticles on top of the peptide layer. The peptides can also be tuned to bind to specific nanotube geometries. The overall approach provides a way to create defined and controllable structures on an otherwise featureless surface, the authors say.—JK



A model structure shows glycine-rich peptides wrapping around a carbon nanotube; blue-to-red coloring on the peptide helices indicates N-to-C terminal direction.

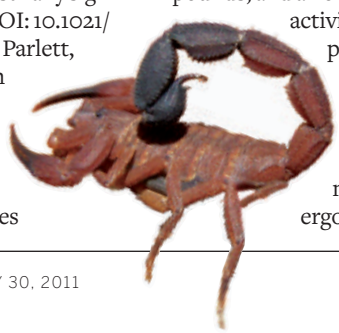
SCIENCE

KEY CATALYST SUPPORT PARAMETERS IDENTIFIED

By conducting a detailed comparison of silica materials used as palladium-catalyst supports, researchers in the U.K. have uncovered key criteria that make some supports far superior to others in selective alcohol oxidations. The team also identified the catalytically active species that mediate conversion of allylic alcohols to the corresponding aldehydes, an industrially significant process (*ACS Catal.*, DOI: 10.1021/cs200145n). Christopher M. A. Parlett, Adam F. Lee, and Karen Wilson of Cardiff University, Wales, and coworkers in England prepared palladium catalysts on four types of silica that widely vary in pore architectures and surface areas (200–950 m^2/g). Through a series of microscopy, spectroscopy, and other types of measurements that probed the catalysts and monitored formation of cinnamaldehyde and separately crotonaldehyde, the team found that the best supports feature the highest surface areas and a three-dimensional network of interconnected channels. Some high-surface-area silicas lack 3-D interconnectivity, which is needed for maximizing palladium dispersion and enhancing mass transport, the group says. Additionally, they found that Pd^{2+} species (PdO) are responsible for the rate-limiting oxidative dehydrogenation step.—MJ

SCORPION VENOM UNFRIENDLY TO FUNGI

Scorpion toxins may be a new source of potential fungicides, researchers in Brazil and Venezuela report (*J. Agric. Food Chem.*, DOI: 10.1021/jf200486t). The venom that scorpions inject into their victims contains a soup of peptides that wreak havoc on cell membranes. Scientists have noted that scorpions often spray themselves with their own venom to rid themselves of opportunistic fungal infections. But although over 500 compounds in two different scorpion species have been identified, their antifungal properties haven't been tested. So, Gina D'Suze and Galax Joya at Instituto Venezolano de Investigaciones Científicas in Caracas, Venezuela, and colleagues investigated, thinking the compounds could be useful for the agrochemical industry, since fungal infections cause 35% of crop loss worldwide. The group selected seven molecules, six of them peptides, from the common South American scorpion *Tityus discrepans*. They exposed fungus *Macrophomina phaseolina*, which attacks bean plants, to the compounds, and all of them showed antifungal activity. The authors posit three possible mechanisms by which the molecules attack fungi: by inhibiting fungal esterases, affecting sodium membrane permeability, and inhibiting ergosterol synthesis.—EKW



CARLOS SEVCIK

WOODWARD'S UNFINISHED WORK

More than 30 years after his death, a selection of R. B. Woodward's **NOTES ON CONDUCTING MATERIALS** is published

BETHANY HALFORD, C&EN NORTHEAST NEWS BUREAU

STACKED NEATLY in a cardboard box, Eric Woodward has exactly 699 pages of decades-old notes written by his father. Most people would describe a box of their parents' old notes as little more than sentimental ephemera or even junk bound for the trash bin. But most people aren't the children of Robert Burns Woodward, the acclaimed Harvard University chemistry professor and 1965 Nobel Laureate in Chemistry.

Many of the pages have yellowed with age, but to those in the chemical community, the contents of that modest cardboard box are a veritable treasure trove. They are Woodward's notes on conducting materials—a project that he clearly spent a considerable amount of time thinking about but that resulted in only two papers (*Proc. R. Soc. Lond. A* **1979**, *366*, 23; *J. Am. Chem. Soc.* **1981**, *103*, 1540), the latter of which was published posthumously.

Now, more than 30 years after his death, a selection of Woodward's ideas in this area are being made public in a perspective article in *Tetrahedron* (DOI: 10.1016/j.tet.2011.05.004). The paper features two dozen drawings and notes from the famed organic chemist, best known for his total syntheses of natural products such as chlorophyll and strychnine and his theoretical work on pericyclic reactions.

"In the last three years of his life, R. B. Woodward was gripped by the idea of designing and synthesizing an organic superconductor," writes Roald Hoffmann, a Cornell University professor who collaborated with Woodward on some of the work, in a preface to the publication. "The evidence to that creative obsession (and I use the word in its most positive sense) is to be found in the hundreds of meticulous drawings of molecules he left behind at his untimely death in 1979." At that time, Hoffmann notes, organic conducting materials and organic superconductors were hot topics, but "no one had yet made an organic superconductor of any transition temperature of note."

Although it's difficult to pin down precisely when Woodward began to think about organic conductors and superconductors—for none of the 699 pages bears a date—Eric Woodward believes that his father's interest in the area emerged as early as 1967 or 1968.

He vividly recalls one evening when he was a teenager: "My father arrived punctually at home at 6:25 every night for dinner. One night we sat down and he said, 'I've had an inspiration. I think I can make a room-temperature superconductor.' He described how that would be a material

NOTEWORTHY A collage of notes on organic conducting materials by Woodward, shown in his office in 1978.

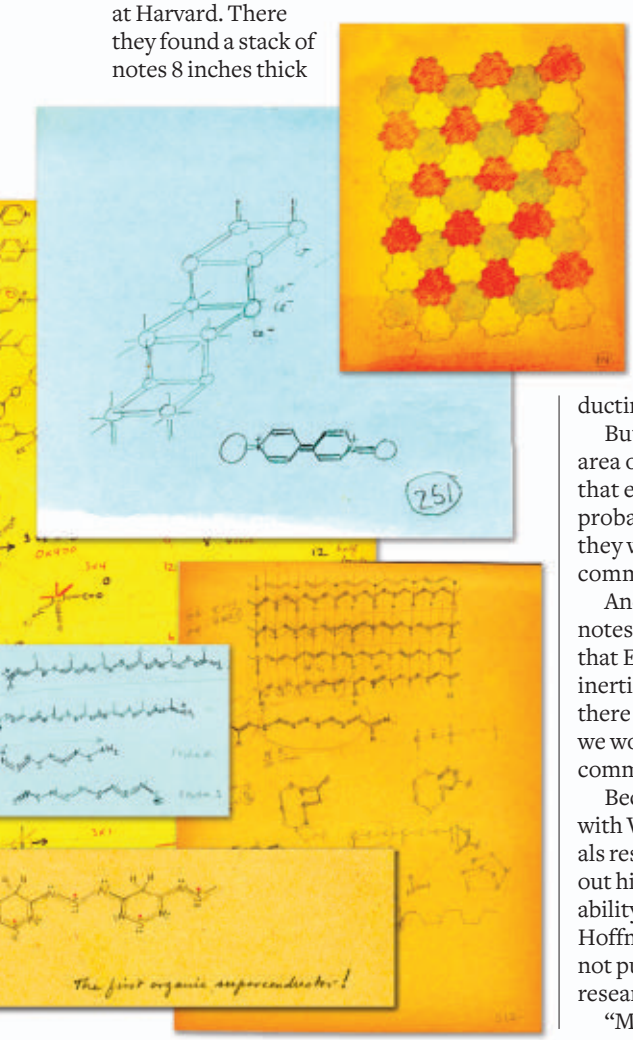
WOODWARD PHOTO: IAN FLEMING; NOTES: COURTESY OF THE WOODWARD FAMILY

"In the last three years of his life, R. B. Woodward was gripped by the idea of designing and synthesizing an organic superconductor."

that loses no energy as it conducts electricity over large distances and how that would change the world," Eric remembers. "He rarely would say anything about chemistry, but this day he was particularly inspired."

To skip to the end of the story, little came of Woodward's inspiration in the area of superconductivity and conducting materials. He tried to get his team at the Woodward Research Institute in Basel to work on the project, his son recalls, but was largely frustrated by the results, or lack thereof.

WHEN WOODWARD died in 1979, his two youngest children, Eric and Crystal, were tasked with cleaning out his office at Harvard. There they found a stack of notes 8 inches thick about conducting materials, written on everything from photocopy paper to blue paper to hotel stationery.



"One of the big challenges after my father died was figuring out what do with all his chemical drawings," Crystal says. "They're intellectual and scientifically full of the thought process, and they're artistically very beautiful."

Most of Woodward's notes went to the Harvard University Archives. But the notes on conducting materials were never part of a Harvard research effort, Eric says, so he and his sister kept them. "I was hoping there were still some unexplored nuggets of brilliance in this work that hadn't been realized yet," he says, but neither of them was a chemist, so they couldn't be sure.

"It didn't seem that we were sitting on a gold mine, but we didn't know," Crystal says.

So they turned to Robert M. Williams for advice. Williams, now a chemistry professor at Colorado State University, was at the time a postdoc in the Woodward group and a close family friend. "I looked at these notes—sometime in 1979—and I was blown away by the sheer magnitude and the depth at which he was thinking about conducting materials," Williams remembers.

But the notes were far from Williams' area of expertise. He told Eric and Crystal that even though he thought they were probably of great historical significance, they were unlikely to contain anything of commercial value.

And then, nothing happened with the notes for quite a number of years, a fact that Eric says had "much more to do with inertia than anything else. If we really felt there was commercial value in the notes, we would have been pushing to get some commercial result," he explains.

Because Hoffmann had collaborated with Woodward on the conducting materials research, Eric and Crystal also sought out his thoughts on the commercial viability of the ideas in the notes. "Roald Hoffmann's opinion was a major part in my not pursuing other people to take on the research," Eric says.

"My opinion is that there is nothing patentable in there," Hoffmann tells C&EN, "but I speak from a background of not owning a single patent."

Still, Williams remembered the notes and would, year after year, pester Eric to find a way to preserve them for the chemical community.

By 2000, the paper was starting to deteriorate, and Williams remembers telling Eric, "In the future, these notes may be viewed as a very interesting historical footnote to your dad's career, but if the notes decompose into a pile of confetti dust in the box you've been keeping them in, they're going to be worth nothing to anybody."

The Woodwards finally agreed that the notes should be digitally preserved, and Williams paid Eric's two daughters, then 15 and 12, to digitally scan each of the 699 pages. Williams also asked Eric and Crystal if he might seek out an author to put together a paper on the ideas contained in the notes. Ideally, he says, he was looking for someone who had been a student of Woodward's, to alleviate any concerns the Woodward children had about someone stealing their father's ideas.

At the suggestion of then *Tetrahedron* editor and Yale University chemistry professor Harry H. Wasserman, Williams approached Michael P. Cava, a chemistry professor at the University of Alabama who had worked as a postdoc with Woodward on the synthesis of strychnine. Independent of Woodward, Cava's research focus as a principal investigator had moved into the arena of organic conducting materials. Along with his long-term research associate M. V. Lakshmikantham, Cava sifted through Woodward's notes and pulled together some analysis of Woodward's ideas in this area.

THE WRITING and editing of the paper took longer than anyone imagined, Williams says, and, sadly, both Cava and Lakshmikantham passed away before it was submitted for publication.

The paper focuses largely on Woodward's ideas about poly(thiazyl) systems, $(SN)_x$, and their isoelectronic organic variants $(SCR)_x$. Hoffmann believes that Woodward was initially inspired by some of the papers on poly(thiazyl) systems

that were published in the 1970s. "I think Woodward also read William Little's simple account of how the interaction of electronic motions and molecular vibrations might create superconductivity," he tells C&EN. Although there were physicists and a few chemists working in the area, Woodward thought his expertise in organic chemistry could bring new insight to the field, Hoffmann adds.

Little's paper in *Scientific American* (**1965,** *212,* 21) strongly influenced many working in the field of organic conducting materials, notes Fred Wudl, a chemistry professor at the University of California, Santa Barbara, who studies organic electronics and did postdoctoral research with Woodward in the late 1960s. Like Cava, Wudl's interest in organic electronics developed independently of Woodward's.

The new *Tetrahedron* perspective "is an unusual glimpse into Woodward's thinking at the height of the pursuit for organic superconductors by chemists and physicists," says Wudl, who notes that Woodward's ideas were quite clever for the time.

"In commenting about this manuscript, one cannot apply the current concepts and mechanisms that have evolved since Woodward's interest in the area," Wudl notes. "It is, however, clear that he had very similar ideas to those of the few organic, inorganic, and physical chemists who were researching in the field at the time, and he would very likely have eventually developed novel conjugated polymers and two-dimensional solids with unusual electronic properties."

"This is incredibly interesting as an insight into the thought process. It's great the notes are finally seeing the light of day."

The *Tetrahedron* perspective only hints at how deeply Woodward was thinking about conducting materials, according to Williams. "Cava commented on only 10 to 15% of the actual structural content in the notes," he says. "Woodward started with ideas about nitrogen- and sulfur-containing heterocycles and other polymers, and then his thoughts drifted to metal-containing polymers and metal-containing lattices and then mixtures of heterocycles and metals and all types of things."

"He was thinking at top creativity level," Hoffmann adds. "That's what those hundreds of blue and yellow pages testify to." But Hoffmann also thinks the notes point toward Woodward's desire to stake out new territory.

"In a broader sense, the question I think could be asked: Was Woodward looking for a different direction to exercise his well-developed and exhibited talent for synthesis other than making natural products?" Hoffmann wonders. "Stepping outside natural products was a natural thing for him. He was interested in making theoretically interesting molecules," Hoffmann says, pointing to Woodward's role in the discovery of ferrocene and his work on the 7-norbornadienyl cation with University of California, Los Angeles, chemistry professor Saul Winstein.

Still, such interests didn't always translate to work at the bench. "I had hints that he had difficulty convincing Harvard graduate students and postdocs to work on the project," Hoffmann says of Woodward's ideas on organic conducting materials.

Jeffrey I. Seeman, a chemical historian at the University of Richmond who has been studying Woodward, says, "Woodward made and saved pages and pages of handwritten notes on major research projects such as orbital symmetry, but 699 extant pages on organic conducting materials is extraordinary, even for Woodward." He adds, "What is interesting, even perplexing, is the extent to which there are so many notes and apparently so little experimental work done."

BUT IT'S DIFFICULT to assess just how hard Woodward tried to convince his graduate students and postdocs at Harvard to work on the project.

David Wenkert, now a professor of physiology at Michigan State University,

was one such graduate student. Part of Wenkert's doctoral thesis research was published in Woodward's posthumous *JACS* paper. That paper described a novel heterocycle that was synthesized as a side product while the researchers were trying to prepare some of the polymers Woodward was interested in.

Wenkert recalls visiting Woodward one day in either 1976 or 1977 to speak with him about problems he was having on another project. "He brought up this idea that he had just come up with as a project for me to work on," Wenkert remembers. "He started jotting down for me some of the initial ideas he had and the theory behind them for conductors that had the potential to be superconductors," he says. "He had asked me not to talk to anybody about it, and I never have."

When Wenkert returned to Woodward's office a few weeks later, he saw that Woodward's thoughts had expanded to 2-D polymers that stemmed from the same idea. Around that time, he recalls, "people suddenly saw Woodward in the library at night. They didn't know what was up. But I kind of figured that he was working on this project."

Aside from the work that was ultimately published in *JACS*, Wenkert declined to do research on the conducting polymers. "Practically, I didn't think this was a project I could work on and get a Ph.D. thesis out of, given my lack of experience in polymer chemistry," he says.

Still, Wenkert says, "it was just incredible for me to be able to see the beginning of an idea of his that he then developed. I thought it was amazing. To me it was the most intellectually stimulating interaction that I ever had with him. I still have the notes somewhere in my basement."

AS FOR THE 699 PAGES of notes in the cardboard box, the future is uncertain. Now that the notes have been scanned, it's theoretically possible they could be made available to the public, but both Eric and Crystal Woodward say there are no plans to do so at the moment. "But no plans not to either," Eric says. "In other words, it's an open question."

Both Williams and Hoffmann hope the scanned notes will someday find a home on the Web where everyone will have access to them, either through the Harvard University Archives, the Chemical Heritage Foundation, or some other entity. "My wish is that they'd become a permanent, accessible treasure for the chemical community," Williams says.

For now, the paper will have to suffice for those wishing to get a glimpse of Woodward's unfinished work in organic conducting materials. "I think the most important thing is just to get some of the visual images out there so the chemical community can see what Woodward was doing in his last days," Williams remarks.

"I think this is incredibly interesting as an insight into the thought process. We just don't see this very often," Hoffmann adds. "It's great that the notes are finally seeing the light of day. I think ultimately Woodward believed that the true achievements of this world are the gifts of knowledge we give to other people." ■

SYNTHESIS SEES INFLATIONARY PUSH

Historical analysis of inflated **YIELD AND PURITY DATA** in organic synthesis papers points to pressure to produce high-impact results

STEPHEN K. RITTER, C&EN WASHINGTON

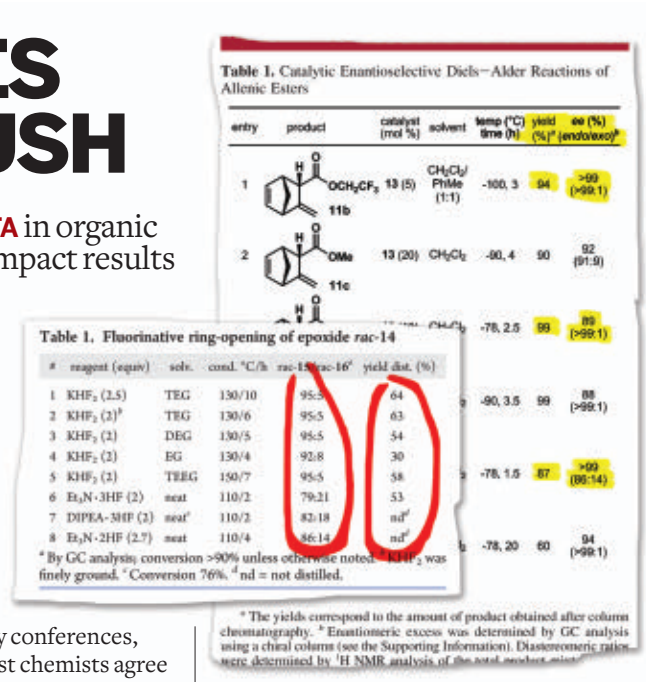


Table 1. Catalytic Enantioselective Diels–Alder Reactions of Allenic Esters

entry	product	catalyst (mol %)	solvent	temp (°C) time (h)	yield (%)[a]	ee (%) endo/exo[b]
1	11b	13 (5)	CH_2Cl_2/PhMe (1:1)	-100, 3	94	>99 (>99:1)
2	11c	13 (20)	CH_2Cl_2	-90, 4	90	92 (91:9)
				-78, 2.5	99	89 (>99:1)
				-90, 3.5	99	88 (>99:1)
				-78, 1.5	87	>99 (86:14)
				-78, 20	60	94 (>99:1)

[a] The yields correspond to the amount of product obtained after column chromatography. [b] Enantiomeric excess was determined by GC analysis using a chiral column (see the Supporting Information). Diastereomeric ratios were determined by ^{1}H NMR analysis of the crude product mixture.

Table 1. Fluorinative ring-opening of epoxide *rac*-14

#	reagent (equiv)	solv.	cond. °C/h	*rac*-15	*rac*-16[a]	yield dist. (%)
1	KHF_2 (2.5)	TEG	130/10	95:5		64
2	KHF_2 (2)[b]	TEG	130/6	95:5		63
3	KHF_2 (2)	DEG	130/5	95:5		54
4	KHF_2 (2)	EG	130/4	92:8		30
5	KHF_2 (2)	TEEG	150/7	95:5		58
6	$Et_3N \cdot 3HF$ (2)	neat	110/2	79:21		53
7	DIPEA·3HF (2)	neat[c]	110/2	82:18		nd[d]
8	$Et_3N \cdot 2HF$ (2.7)	neat	110/4	86:14		nd[d]

[a] By GC analysis; conversion >90% unless otherwise noted. [b] KHF_2 was finely ground. [c] Conversion 76%. [d] nd = not distilled.

FINE PRINT REQUIRED Chemists report yields and isomer ratios in different forms, as these samples show (*Org. Lett.*, DOI: 10.1021/ol1004802, right; *Org. Process Res. Dev.*, DOI: 10.1021/op200019k, left). Reporting extraordinary values is now coming under greater scrutiny.

MOST CHEMISTS have gone into the lab at some point in their careers with a new chemical recipe in hand, only to be perplexed when it doesn't turn out as described in the paper from which it was torn. Organic chemists Tomas Hudlicky and Martina Wernerova of Brock University, in St. Catharines, Ontario, recently decided to dig a little deeper into one facet of this phenomenon: inaccurate reporting of isolated product yields, ratios of diastereomers, and enantiomeric excess values in organic synthesis papers (*Synlett,* DOI: 10.1055/s-0030-1259018).

In comparing organic papers published from 1955 to 1980 and from 1980 to 2005, Hudlicky determined that reports of nearly perfect yields and remarkable enantioselectivities were common in the recent period but rare before 1980. To support the findings, Hudlicky and Wernerova conducted volumetric experiments on sample reactions, measuring differences between the actual content of materials and the experimentally measured values for yields and isomer ratios to determine the practical limits and relative errors in reporting such data.

The inflationary trend in yield and other data is occasionally a topic of informal conversation at chemistry conferences, Hudlicky tells C&EN. Most chemists agree that reported yields above 95%, isomer ratios above 200:1, and enantiomeric excesses above 99% aren't realistic. For example, a couple percent yield can be lost just in extractions and product purifications, let alone from incomplete reactions and weighing errors.

"Such reports at best may be attributed to the inability of the authors and research personnel to determine accurately the true content of the sample under scrutiny, and at worst to deliberate manipulation of research data," Hudlicky and Wernerova write.

The reasons for inflated yields and ratios are many, Hudlicky says, but the key ones include pressure on the research community to produce high-quality, high-impact research on smaller scale reactions at a fast pace. He suggests that principal investigators may not be adequately reviewing the

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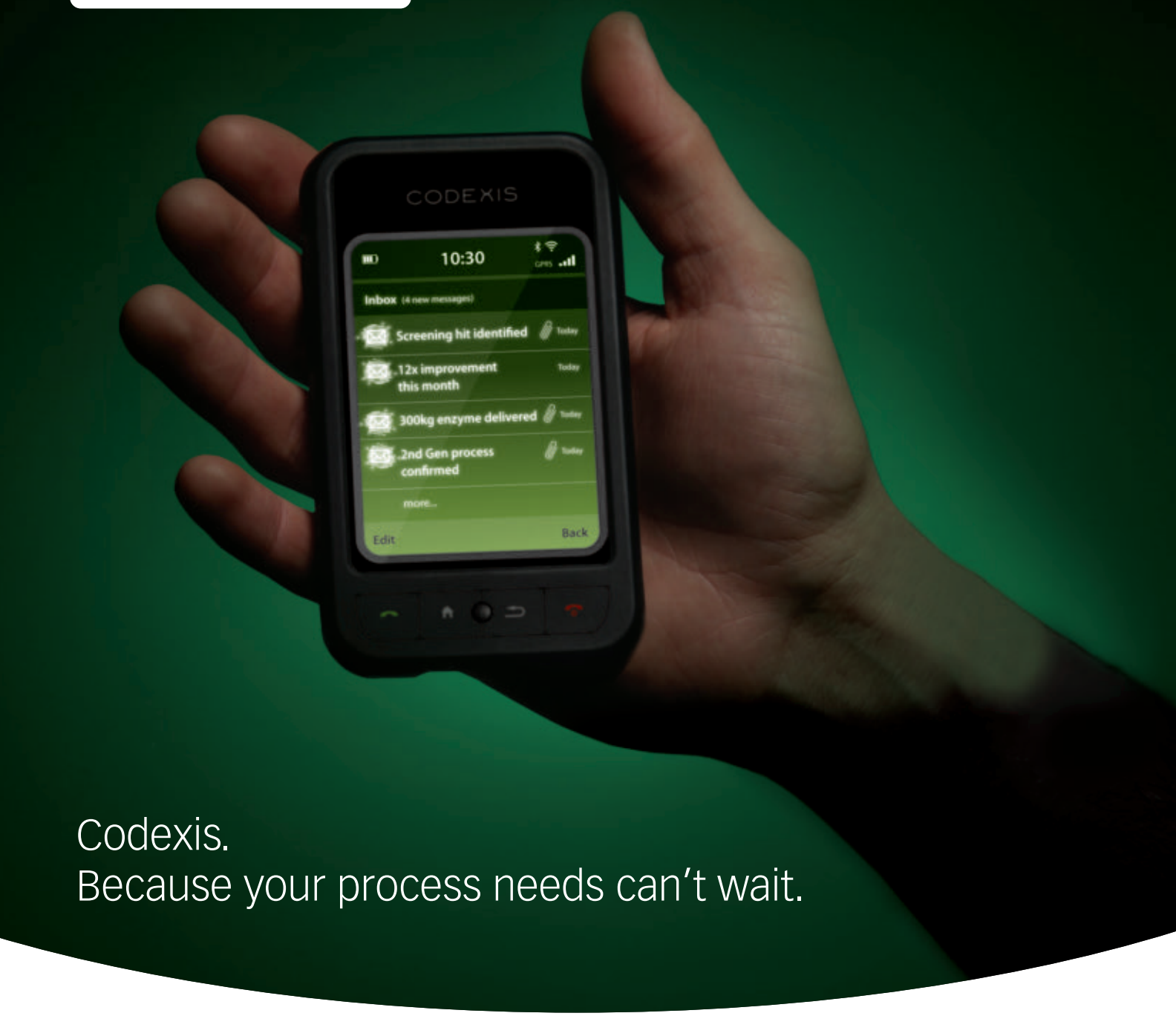

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research conducted in their labs, academic researchers may not have the training needed or the equipment and financial resources needed, and referees and editors may not be adequately scrutinizing submitted papers.

"People continue to engage in self-deception regarding the reality of experimental work," Hudlicky adds. "Most of the time they have no idea what they actually are measuring." For example, reporting 99% yields following chromatography "is an outright ridiculous situation," he points out.

The *Synlett* analysis "has made quite an impact," Hudlicky says. He has received hundreds of e-mails, he notes, that agree something needs to be done about this issue. There has also been discussion about the paper in chemistry blogs.

Trevor Laird, editor of the American Chemical Society journal *Organic Process Research & Development* and founder of industrial chemistry consulting firm Scientific Update, agrees with Hudlicky and Wernerova's assessment and commented on it in an editorial (*Org. Process Res. Dev.*, DOI: 10.1021/op2000404). Laird says researchers should be wary of literature data claiming quantitative yields.

"In industry we know how easily final products can be contaminated with inorganic salts, which do not show up in NMR or HPLC nonquantitative analyses, and this is why residue on ignition or sulfated ash tests are routine for final products in industry," Laird writes. But such tests are rarely carried out in academic laboratories, he adds.

Laird suggests that most papers in *OPR&D* come from industrial process chemistry labs that are more likely to report quantitative measurements that have been repeated many times by different experimenters. As a consequence, he says, they should be reproducible in the lab and on a larger scale than experiments reported in most journals.

For their part, Hudlicky and Wernerova used as a yardstick *Organic Syntheses*, the highly respected independent open-access journal in which experiments are separately checked by referees before publication and yields rarely exceed 95%.

Hudlicky and Wernerova offer a few remedies for overstated yields and ratios: Authors could either provide evidence of a standard calibration and the method used or insert a disclaimer indicating that the values have not been validated, authors could report a range of yields when multiple experiments are carried out, and journal editors could reject papers when the reported yields are deemed unrealistic.

Amos B. Smith III, editor of the ACS journal *Organic Letters* and a chemistry professor at the University of Pennsylvania, finds Hudlicky and Wernerova's observations "timely and important," and he is taking their message to heart. After reading the *Synlett* paper, Smith asked his associate editors and members of his editorial advisory board to read it and consider how they might follow up on the suggestions.

THE ISSUE OF OVERSTATING yields and isomer ratios "is not a revelation in the organic research community," Smith says. "It is bogus to report 100% yields and enantiomerically pure products. But we understand that when someone reports very high yields and ratios, it means the results are pretty good."

Smith adds that, at least in the academic community, which is the major source of research papers, no one has the resources anymore to spend a huge effort to nail down yields and ratios with high precision. He says that in lieu of costly elemental analyses, using NMR or chromatographic techniques is reasonable. But researchers do need to clearly state how they obtained their data, Smith notes; that information typically appears in the fine print of data tables or in the online supporting information.

"This issue is well worth giving additional consideration and having our students think about it," Smith says. "Where possible we should tighten up reporting data, so long as the process is not so onerous that it impedes new discoveries."

It turns out Hudlicky is well-known in the organic community for voicing his opinions. Several years ago he commented in a C&EN letter to the editor that the use of catchy titles and adjectives that hype up the content of organic synthesis papers had "gone through the roof" (C&EN, April 4, 2005, page 6). Back then, Hudlicky did a literature search and found that descriptors such as new, novel, efficient, concise, facile, and practical were proliferating.

"If 1% of such claims were true, there would be no problems in organic chemistry left unsolved," Hudlicky wrote. "Such claims are in stark contrast to the actual content of articles so advertised." He suggested that it would be prudent of journals to agree on a policy to ban the use of these descriptors. Hudlicky has now incorporated the hyperbole and the inflated yield and ratio issues into a one-day short course on research integrity that he teaches.

Hudlicky says his intentions are only for the good—he pleads guilty himself of reporting unrealistic yields in the past. Getting these issues more out in the open so the organic community can reflect on them in greater detail, he says, should help improve experimental reproducibility and facilitate chemical advances, as well as improve the credibility of researchers. ■

IMPROVING VACCINES AIMED AT CANCER

Scientists use various ways to strengthen immune response to **CARBOHYDRATE CANCER ANTIGENS**

STU BORMAN, C&EN WASHINGTON

CARBOHYDRATE-BASED vaccines are widely used to prevent infectious diseases, but their use to fight cancer has so far proved problematic. To increase the chance of success, researchers are pursuing a number of avenues that have a common goal: enhance carbohydrates' ability to induce the human immune system to mount an effective fight against cancer.

Carbohydrates are studded all over the surfaces of human cells, where they help with essential functions ranging from protein transport and cell-cell recognition to signal transduction and cell adhesion. Those on cancer cells are different from those on normal cells, making it possible to distinguish the cancerous ones. Researchers hope to use carbohydrate vaccines to get the immune system to attack and kill cancer cells while leaving normal cells alone.

Unfortunately for vaccine designers, the immune system doesn't pay a lot of attention to cell-surface carbohydrates, normal or not.

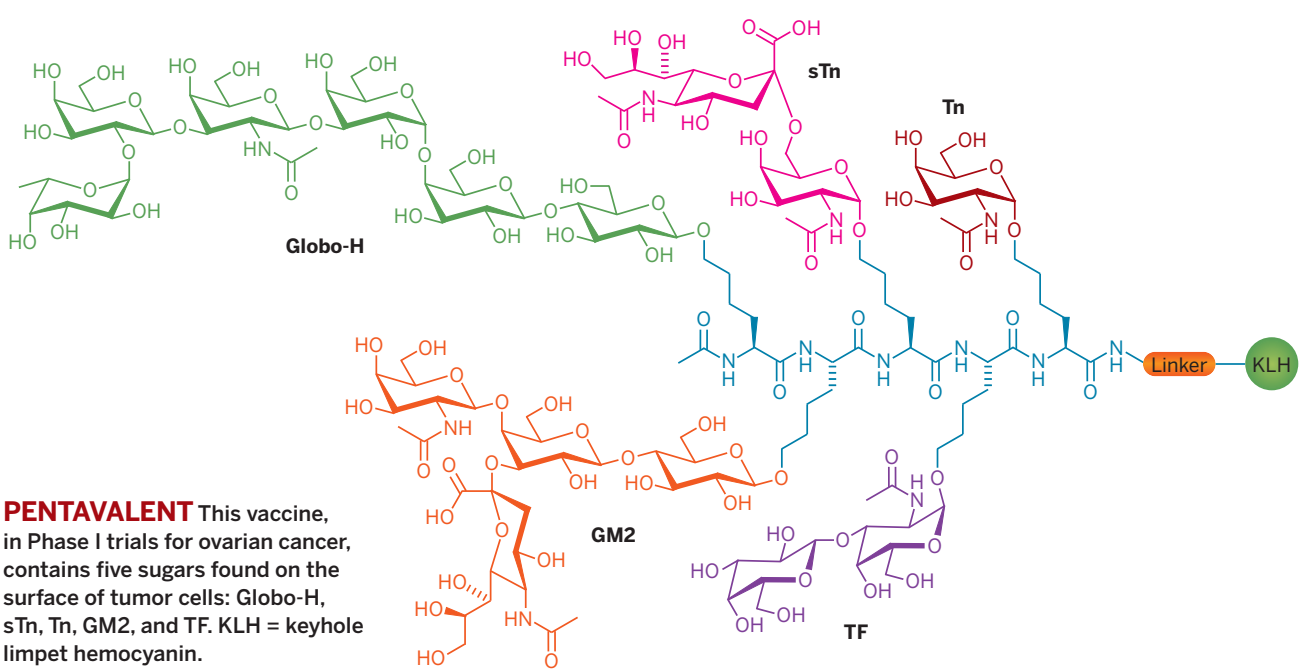
"If you vaccinate someone with a carbohydrate tumor antigen, you're not likely to get much immune response at all," says glycopeptide vaccine specialist Steven J. Sucheck of the University of Toledo. And if an immune reaction ensues, he says, the antibodies generated in response to the carbohydrate will usually be weak.

To generate strong antibodies, scientists typically conjugate a carbohydrate antigen to a protein "carrier." This route has been effective for antibacterial vaccines—a number of which have long been commercially available and are widely used, including carbohydrate-based vaccines by companies like Wyeth Pharmaceuticals, Sanofi Pasteur, and Merck & Co., against bacteria that cause pneumonia, meningitis, and other conditions.

But carbohydrate vaccines against cancer have not yet "worked out quite as well" as those against bacteria, Sucheck says. In fact, no carbohydrate-based anticancer vaccine has yet been approved for public use. Some scientists believe that anticancer vaccines have failed because both antibody and killer T-cell responses are needed to prevent cancer. Even though carbohydrate antigens induce antibodies, the antigens typically don't elicit the killer T cells that do much of the immune system's dirty work.

SCIENTISTS ARE THUS racing to devise ways to raise the immune response to carbohydrates. Strategies include engineering cancer cells to display carbohydrates that are more likely to trigger an immune response; devising new types of carriers, ranging from polysaccharides to nanoparticles, that enhance a carbohydrate antigen's immune response; using additives known as adjuvants to boost the immune response to antigens conjugated to conventional carrier proteins; and constructing polyvalent vaccines that include multiple carbohydrate antigens.

Carbohydrate vaccines based on strategies like these are being tested in human clinical trials and are showing promising results. Scientists in the field have high hopes for the success of one or more of these approaches.

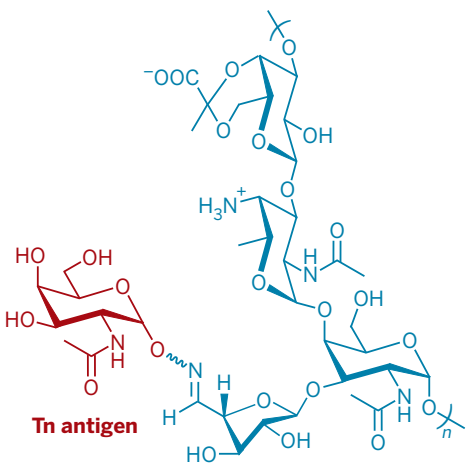


PENTAVALENT This vaccine, in Phase I trials for ovarian cancer, contains five sugars found on the surface of tumor cells: Globo-H, sTn, Tn, GM2, and TF. KLH = keyhole limpet hemocyanin.

Wayne State University carbohydrate immunotherapeutics specialist Zhongwu Guo's preferred strategy focuses on engineering cancer cells to express sugars that could better attract the immune system's attention. To do so, his team inoculates cancerous animals with chemically modified carbohydrate cancer antigens. After the animals develop an immune response to the modified antigens, the researchers feed the animals a compound that their cancer cells can use to produce the same type of cell-surface chemical modification. The animals' immune systems are then able to attack the modified cancer cells selectively.

The researchers demonstrated the concept by derivatizing carbohydrate antigens expressed on surfaces of melanoma, breast cancer, and prostate cancer cells with *N*-phenylacetyl groups. Animals fed with these antigen derivatives produced an immune response to the modified antigens. The researchers then fed the animals *N*-phenylacetylated mannosamine, which added *N*-phenylacetyl groups to the carbohydrate antigens on surfaces of their cancer cells. The animals' immune systems then attacked the modified cancer cells.

CANDIDATE Conjugation to a zwitterionic polysaccharide carrier boosts the immune response to the tumor antigen Tn (red).



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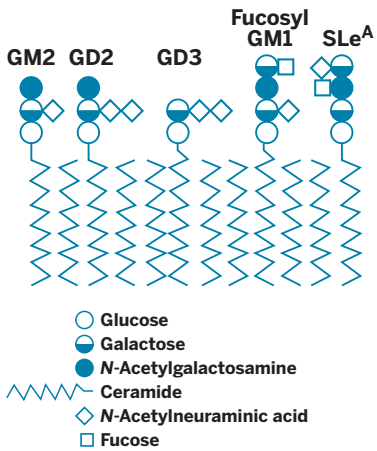
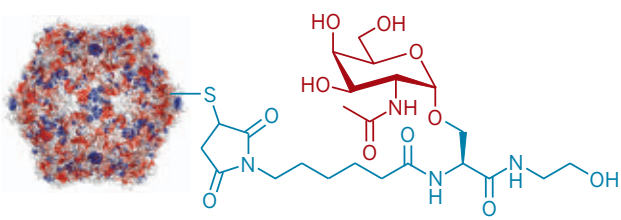


GANGLIOSIDES Carbohydrate antigens of the ganglioside class—GM2, GD2, GD3, fucosyl GM1, and SLe^A (sialyl Lewis A)—are overexpressed on, and attached by ceramide lipid tails to, cancer cells. Protein-conjugated versions of each of these antigens have been investigated as cancer vaccines.

QIAN WANG



GOING VIRAL The immune response to the carbohydrate cancer antigen Tn (red) is enhanced by a vaccine in which 60 copies of the antigen are attached to the surface of a virus.

"We proved that the new immunotherapy can effectively control metastatic melanoma," Guo says. "The results have not been published because larger scale animal experiments are in progress." A company is interested in the technique and has been negotiating with Wayne State to license it, he adds.

A MORE CONVENTIONAL way to improve the immune response to carbohydrates has been to covalently attach the sugars to standard carrier proteins such as keyhole limpet hemocyanin (KLH). But the fate of Biomira's Theratope, a carbohydrate-KLH conjugate vaccine that failed clinical trials a few years ago, showed that carbohydrate-protein conjugation does not necessarily a successful carbohydrate vaccine make. Researchers are experimenting with a variety of carrier alternatives.

For example, carbohydrates conjugated with viruses and virus-like particles are being developed by synthetic chemist Xuefei Huang of Michigan State University, bioorganic chemist Qian Wang of the University of South Carolina, virus chemist M. G. Finn

of Scripps Research Institute, and coworkers.

The researchers figured that multivalent displays of tumor-associated carbohydrate antigens could boost the normally weak immune response to these sugars. To test the idea, they synthesized the carbohydrate tumor antigen Tn and conjugated 60 copies of it to cowpea mosaic virus, which is noninfectious in humans. The outer shell of cowpea mosaic virus has 60 identical protein subunits, and the researchers used those as Tn attachment points.

Their experiments show that Tn-virus conjugates elicit high levels of high-powered antibodies that recognize breast cancer cells. The group's preliminary studies also suggest that carbohydrate-virus conjugates slow the growth of tumors in mice, "which is very encouraging," Huang says. His team is now working to further boost the immune response by eliciting killer T cells. Polyvalent conjugates of other carbohydrate antigens with viruslike particles have given similar results, Finn notes, and he and others recently received a grant to further advance the technology.

Zwitterionic polysaccharides are also being used as alternative carriers to strengthen the immune response to carbohydrates. Pioneered about a decade ago as immune-system activators by professor of medicine Dennis L. Kasper of Harvard Medical School, zwitterionic polysaccharides are carbohydrate polymers containing alternating positive and negative charges on adjacent monosaccharide units. Kasper and others have found that they can be used in place of proteins as antigen carriers.

ZWITTERIONIC polysaccharides could skirt a key problem with conventional protein conjugates of carbohydrate antigens: Such carrier proteins often possess their own inherent immune-triggering abilities. This tends to divert the immune system's full attention from the carbohydrate, lessening the immune response it generates. Combining carbohydrate antigens with zwitterionic polysaccharides might eliminate this problem because the resulting conjugates are entirely carbohydrate-based.

Indeed, carbohydrate vaccine specialist Peter R. Andreana of Wayne State University and coworkers have found that carbohydrate-polysaccharide conjugates elicit both arms of the immune system—strong antibodies and killer T cells. They are currently testing the efficacy of their all-carbohydrate-based cancer vaccines in mouse cancer models.

Meanwhile other groups are testing three-component vaccines. Synthetic carbohydrate chemist Geert-Jan Boons of the University of Georgia and coworkers have created fully synthetic vaccines with three components: human epithelial type 1 mucin (MUC1) glycopeptide, an immunity-activating poliovirus-based peptide, and a bacterially derived lipopeptide adjuvant.

The three-part conjugates elicit strong antibodies and killer T cells that can neutralize cancer cells. The vaccine is efficacious in a mouse model for breast cancer, Boons says. And the team is preparing for Phase I/II clinical trials in collaboration with the Mayo Clinic.

Sucheck's group has also been synthesizing three-part conjugate vaccine candidates. On the basis of findings by glycobiologist Jeffrey C. Gildersleeve of the National Cancer Institute (NCI), Frederick, Md., and coworkers that humans develop high levels of antibodies against the carbohydrate rhamnose, Sucheck and coworkers are testing a conjugate of Tn antigen with an immune-activating peptide called YAF and rhamnose. They are also studying multivalent conjugate vaccines made from MUC1 glycopeptides, adjuvant, and rhamnose.

A group led by Joseph J. Barchi Jr., a structural glycoconjugate chemist at NCI, is developing yet another type of replacement for carrier proteins—nanoparticles. By attaching an antibody-inducing peptide and a MUC4 glycopeptide form of the disaccharide cancer antigen TF separately to gold nanoparticles, Barchi and coworkers have been able to raise antibodies that recognize both TF and the TF-glycopeptides.

"I WANTED TO SEE if you could create immunity on a nanocarrier like gold and at the same time go against the paradigm of needing to covalently conjugate carbohydrate antigens to carrier proteins like KLH," Barchi says. However, immune responses induced by the conjugates have so far been weak and nonprotective, he notes. His team continues to optimize the conjugates' construction in hopes of boosting the immune response to them.

MULTIPLICITY

A handful of polyvalent carbohydrate anticancer vaccines are currently being tested in people

CONSTRUCT TYPE	SPONSOR	CLINCAL TRIAL PHASE	CANCER TYPE
Ganglioside trimolecular trivalent	MabVax Therapeutics	Phase II	Sarcoma
Pentamolecular pentavalent	National Institutes of Health	Phase II	Ovarian
Ganglioside bimolecular bivalent	MabVax Therapeutics	Phase I/II	Neuroblastoma
Unimolecular pentavalent	Memorial Sloan-Kettering Cancer Center	Phase I	Ovarian

NOTE: In all four vaccines, carbohydrate antigens are conjugated to the carrier protein keyhole limpet hemocyanin and QS-21 adjuvant is included.

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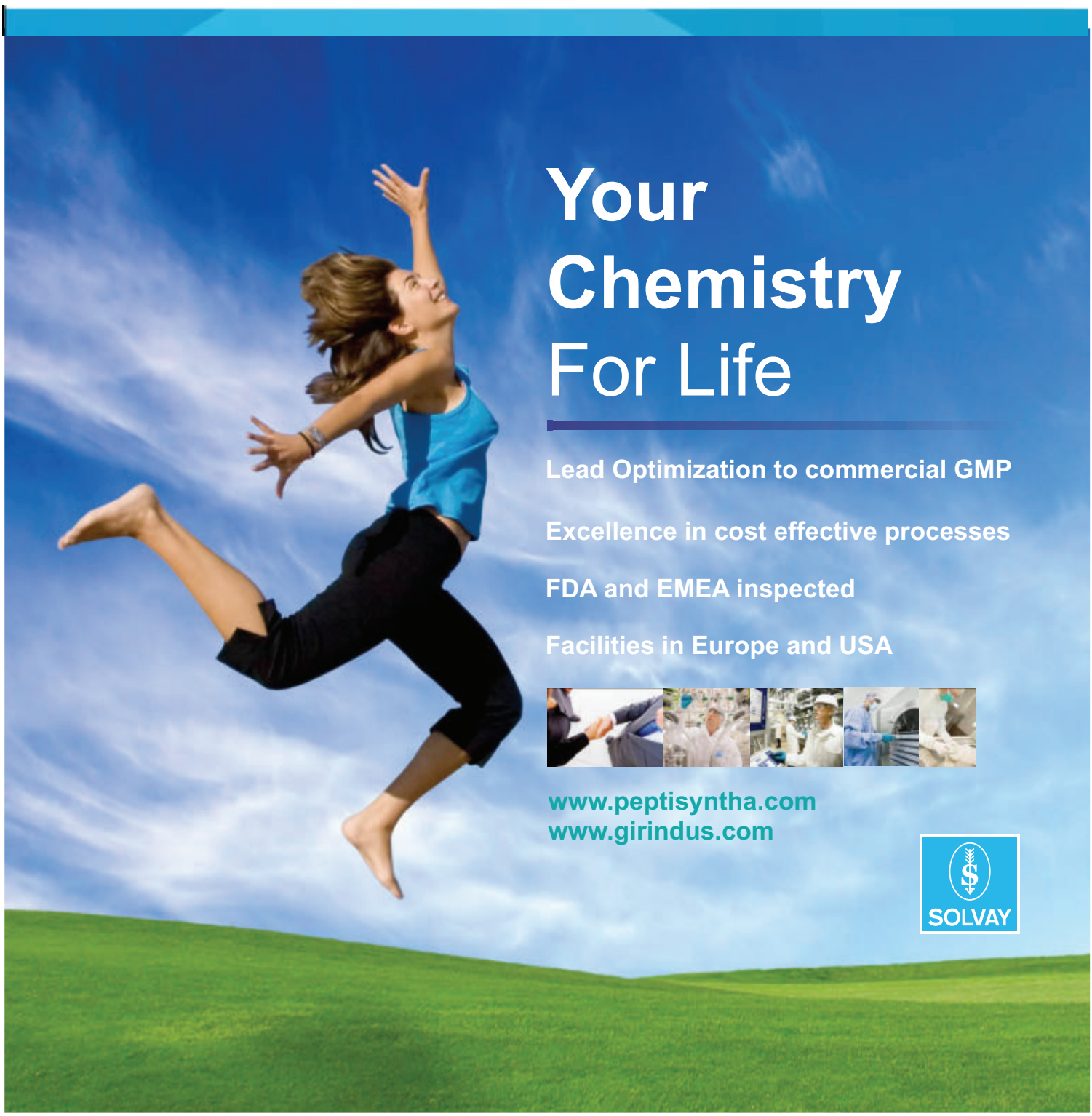

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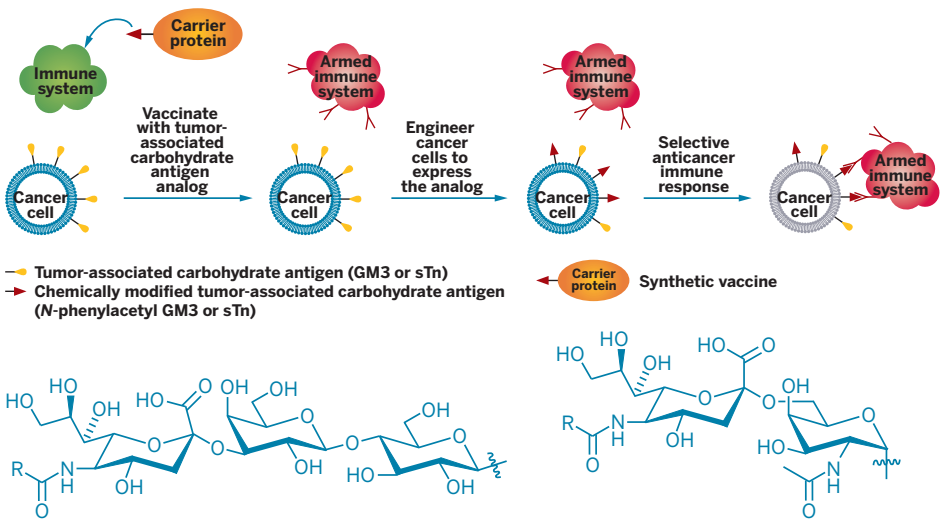
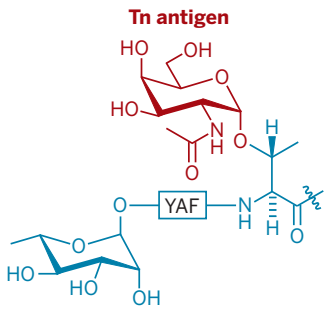
IMMUNE BOOST Guo's experimental vaccine uses *N*-phenylacetylated versions of tumor-associated carbohydrate antigens GM3 or sTn to develop an immune response in animals with cancer. Administering reagents that cause the modified antigens to appear on cancer cells makes those cells susceptible to selective attack by the animals' immune system.



SOURCE: Zhongwu Guo

THREE-PART STRUCTURE Sucheck and coworkers are trying to heighten the immune response to the carbohydrate tumor antigen Tn (red) by conjugating it to the peptide YAF and the sugar rhamnose.



Ultimately, the test of carbohydrate vaccines will come not from in vitro experiments but from human clinical trials. One group that has gone farther than most in testing carbohydrate vaccines in humans is that of Philip O. Livingston, head of tumor vaccinology at Memorial Sloan-Kettering Cancer Center, New York City.

LIVINGSTON and coworkers focus on vaccines that induce immunity against cell-surface glycolipids known as gangliosides and other carbohydrate antigens overexpressed on cancer cells. Their formulations consist of carbohydrate antigens conjugated to KLH and include the naturally occurring tree-bark component QS-21 as an adjuvant. Some of the group's vaccines are polyvalent, incorporating different types of antigens in the same formulation.

MabVax Therapeutics, San Diego, has organized Phase II trials of the group's trivalent ganglioside vaccine in sarcoma patients and Phase I/II trials of its bivalent ganglioside vaccine in neuroblastoma patients, and the National Institutes of Health has organized Phase II trials of its multimolecular pentavalent carbohydrate vaccine in ovarian cancer patients. Livingston, a MabVax shareholder and scientific adviser, hopes these trials will validate KLH conjugation, QS-21 adjuvant, and polyvalency in carbohydrate vaccines.

Meanwhile, Memorial Sloan-Kettering Cancer Center synthetic and carbohydrate chemist Samuel J. Danishefsky and coworkers have developed a single-molecule polyvalent vaccine consisting of five different carbohydrate antigens conjugated to KLH and including QS-21 adjuvant. A Phase I trial of this vaccine in ovarian cancer patients began last year. Danishefsky believes this to be the most complex fully synthetic vaccine ever to enter clinical trials.

Danishefsky's group earlier synthesized a univalent vaccine based on the carbohydrate antigen Globo-H. That vaccine is in Taiwanese Phase II/III trials against metastatic breast cancer.

Such clinical trials "are the kind of studies that build confidence in the field," Toledo's Sucheck says.

"I think we're close to figuring out what's going to be required to make carbohydrate-based cancer vaccines a success," Wayne State's Andreana says. As researchers continue to zero in on the best peptides, proteins, lipids, adjuvants, polymers, nanoparticles, and other substances to enhance the immune response to carbohydrates, he says, "I think we're right on the tail of really getting to cancer and eradicating it." ■

Redefining The Kilogram And Mole

PETER F. RUSCH, CHAIR, COMMITTEE ON NOMENCLATURE, TERMINOLOGY & SYMBOLS

BECAUSE OF THE possible mass change of the international prototype kilogram—the last of the International System of Units (SI) base units still defined by a physical artifact—the metrology community proposed a redefinition of the kilogram. This proposal led to a recommendation to redefine other SI base units, including the kelvin, ampere, and mole. Definitions of the second, meter (or metre), and candela will remain unchanged, although they will be worded differently. The new "fixed constant" definitions will rely on values of physical constants recognized as invariants of nature.

COURTESY OF PETER RUSCH

The new "fixed constant" definitions will rely on values of physical constants recognized as invariants of nature.

Definitions of SI base units are approved by the General Conference on Weights & Measures (CGPM), a treaty organization founded in 1875 by the Metre Convention, of which the U.S. is a member state. CGPM convenes every four years and is scheduled to meet this October.

Prior to going to CGPM, work is done by bureaus and committees in preparation for the conference. For chemists, the International Committee for Weights & Measures (CIPM) is a primary focus as its stated principal task is to promote worldwide uniformity in units of measurement, either through direct action or by submitting draft resolutions to CGPM.

CIPM works through consultative committees, one of which is the Consultative Committee for Units (CCU). Recent deliberations of CCU have lacked strong engagement on the part of the U.S. chemistry community, so the American Chemical Society's Committee on Nomenclature, Terminology & Symbols has undertaken the task of determining what is being proposed and what it means to chemistry.

The work of CCU is now mostly complete, and a draft resolution for CIPM to present to CGPM is now available with the following definitions:

"The kilogram, kg, is the unit of mass; its magnitude is set by fixing the numerical value of the Planck constant to be equal to exactly 6.626068 ... $\times 10^{-34}$ when it is expressed in the unit s^{-1} m^2 kg which is equal to J s.

"The mole, mol, is the unit of amount of substance of a specified elementary entity, which may be an atom, molecule, ion, electron, any other particle or a specified group of such particles; its magnitude is set by fixing the numerical value of the Avogadro constant to be equal to exactly 6.022141 ... $\times 10^{23}$ when it is expressed in the unit mol^{-1}."

The ellipses in the definitions are intentional at this time as the final resolution awaits the most recent, accurate values of the constants to be used when the final resolution is presented to CGPM.

THE DEFINITIONS themselves do not explain how each constant is related to the unit it defines. This is intentional because CCU believes that the method of "realizing the definition"—that is, connecting the constant to the unit—should not be specified. Development of new methods for doing so may come at any time and may be quite different from what is used today. Still, the definition would remain valid because it is independent of the method.

The proposed definition of the kilogram offers some challenges because it is not obvious how Planck's constant is related to the kilogram. Making that relationship today requires the use of a watt balance, an elaborate electromagnetic device for determining mass using a combination of constants including the noninvariant gravitational constant. Only a few of these complex, expensive instruments exist today. In practice, chemists rely on secondary standards for mass, and that won't change. Accordingly, it matters little to chemists what instrument is used to calibrate the secondary standards, so long as their mass is accurate.

The definition of the mole is more problematic. Currently, the definition is connected directly to the mass of a carbon-12 isotope and the kilogram. According to the current definition, the mass of carbon-12 is an absolute invariant of nature. In the proposed definition, the value of Avogadro's constant is the fixed invariant of nature, leaving the mass of carbon-12 to be determined experimentally. Using metrological methods and the best accepted values of other constants, it is calculated that the mass of carbon-12 will have an uncertainty of 1.4×10^{-9} u (u is the unified atomic mass unit). Since all atomic weights are currently defined on carbon-12 as 12 u exactly, all atomic weights will change by small amounts.

For many chemical practices, this is an insignificant difference from the current 12 u exactly. In fact, average atomic weights often change as isotopic distributions become better known.

For chemical practice at the atomic level, however, this difference can be considerable. In particular, the mass spectrometry community is concerned about the loss of the carbon-12 standard of 12 u exactly. Currently assessed in parts-per-billion charge-to-mass ratios, MS results will be subject to recalculation each time the carbon-12 mass is more precisely determined.

Proposed definitions of the SI base units will wait until the 2015 CGPM for possible adoption. In the meantime, all of the constituents of the chemical enterprise have the time and the opportunity to review the proposals and evaluate their impact on the practice of chemistry. ■

MOLDOVA

Chemistry professor **VASILE GUTSANU** has lived through Soviet and independent rule

JYLLIAN KEMSLEY, C&EN WEST COAST NEWS BUREAU

Population
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No. of ACS members
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TOP SUBJECTS in chemistry publications: Semiconductors; inorganic, physical, and food chemistry

SOURCES: CIA World Factbook, Chemical Abstracts Service

ONE DAY WHEN Vasile Gutsanu was a teenager in his native Moldova, he read in a magazine about the discovery of a new elementary nuclear particle. "I was surprised," Gutsanu says. "I knew that the atomic nucleus consists of protons, neutrons, and electrons. It was so clear and simple. The discovery changed my view on atomic structure"—and on science.

Gutsanu's teachers, he says, had presented science as a closed system of knowledge. Reading about the new particle opened his eyes to the fact that science is continually evolving, he says. Gutsanu went on to study chemistry, earning a Ph.D. from Moldova State University in 1974. He worked at the Moldova Academy of Sciences as a researcher for several years before taking faculty positions at several universities. In 1993, he earned a higher doctorate—a D.Sc. in chemistry—from Moldova State University.

Today, Gutsanu is a chemistry professor at Moldova State University, and he says that one of the things he tries to emphasize to his students is that chemistry is a creative, constantly developing endeavor. Gutsanu teaches physical chemistry to undergraduates, as well as special topics courses for seniors and graduate students. Overall, the university's Faculty of Chemistry & Chemical Technology includes about 60 faculty members who teach about 400 undergraduate and 100 graduate students.

Although teaching is Gutsanu's main focus, he also researches the properties of ionic polymers. His recent work explores the formation and properties of ultrafine metallic compounds sequestered in cross-linked, strongly basic polymers (*J. Appl. Polym. Sci.*, DOI: 10.1002/app.32615). The polymer-metal complexes create a new system that can function as a sorbent or catalyst, he says.

Gutsanu's career has spanned two epochs of Moldovan history: Moldova, which is sandwiched between Romania and Ukraine, was part of the Soviet Union until the country declared independence in 1991. Under the Soviet regime, Moldova was known for research on coordination and quantum chemistry. Scientists had access to chemicals, but instrumentation was limited, Gutsanu says. Now, both are expensive and can be difficult to source.

COURTESY OF VASILE GUTSANU

MOLDOVAN Gutsanu (far right) stands with graduate students and colleagues in a lab at Moldova State University.

Instrumentation at Moldova State University is typically purchased for educational purposes, so Gutsanu and his colleagues must collaborate with other institutions to gain access to techniques such as electron paramagnetic resonance spectroscopy, X-ray spectroscopy, and electron microscopy.

GUTSANU NOTES that under Soviet rule, scientists didn't have the opportunity to communicate and collaborate with foreign colleagues. He now holds the distinction of being the only American Chemical Society member living in Moldova. He joined ACS in part to be more informed about what is happening in the world of chemical science, he says. Gutsanu's native language is Moldovan, which is essentially the same as Romanian; he also speaks Russian, Ukranian, and "a little" English.

According to the CIA World Factbook, Moldova is one of the poorest countries in Europe, with an economy heavily dependent on agriculture—in particular fruits, vegetables, wine, and tobacco. Chemistry graduates who stay in Moldova typically work in education, the food or electrical industries, medical institutions, or ecology, Gutsanu says. Others leave. "Quite a few of our graduates are now working as chemists, researchers, and lecturers in France, Germany, Canada, and the U.S.," Gutsanu says. Such a "brain drain" is endemic to countries in Southeast Europe, according to the 2010 Science Report by the United Nations Educational, Scientific & Cultural Organization.

Moldova has also faced significant political uncertainty in recent years: Three elections in 2009 and 2010 failed to give any party or coalition enough votes in the Moldovan Parliament to elect a president. As the country continues its transition from a socialist to a market-based economy, there are deep divisions among its people, Gutsanu says. "Most people want the country to join the European Union in the future," he says, but others are nostalgic for the past and are against EU membership. Gutsanu hopes that the country will come together soon to agree on a path to economic development that will improve the quality of life for everyone.

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ROGUE ROBOT, ENERGETIC PICNICKING, FIRE WALKING IN SYNC

The ceremonial opening pitch of a Major League Baseball game is often the scene of disaster. Celebrities such as singer Mariah Carey and track legend Carl Lewis have become famous for flubbing that game-starting throw to home plate.

These poor performances from untrained pitchers aren't surprising, but it does raise a few eyebrows when a robot designed for the task comes up short.

PHILLIEBOT—a contraption with three wheels, a computer brain, and a carbon-fiber-scoop arm propelled by a pressurized cylinder—pitched a ball into the dirt about 5 feet in front of home plate to start an April 20 game between the Philadelphia Phillies and the Milwaukee Brewers. The robot was created by engineering students from the University of Pennsylvania's General Robotics, Automation, Sensing & Perception Laboratory to celebrate Science Day at the Phillies' ballpark.

In a postgame report by KYW Newsradio, the engineering team defended their mechanical buddy, which took two months to build. All of their practice runs went smoothly, the engineers said, but they turned PhillieBot's pressure down because they were warned not to hurt the Phillie Phanatic, the team's beloved mascot, who awaited the pitch behind home plate.

To see video of PhillieBot in action, go to the Newscripts blog (cenblog.org/newscripts).

Another student-designed contraption getting attention these days is a solar-powered **PICNIC TABLE** on the campus of Catholic University of America, in Washington, D.C. Having installed more than 1,000 solar panels on its rooftops in 2009, the university is a major proponent of solar energy. So it held a competition early last year that asked students to combine their design skills and their photovoltaic know-how to create a solar sitting place.

The winning design, which features a cantilevered solar canopy that supplies enough power to the picnic table for students to plug in a few laptops and iPods at any given time, was recently unveiled on Catholic's campus. A computer display screen, although it has yet to be installed inside the canopy's central Plexiglas tower, will eventually educate users about the wattage the device produces, says Lindsey Dickes, a member of the winning design team.

"When users plug in their personal electronics to the table, they will be able to immediately see the effect that the electrical load has on the system," Dickes tells Newscripts.

Catholic awarded the six-member team $3,000 for its extracurricular work. Dickes says she applied her portion toward a well-deserved vacation.

If Newscripts readers don't get a charge out of solar panels, they might get heated over the results of a recently published study on a fire-walking ritual held annually in San Pedro Manrique, a rural village in Spain. An international team of researchers found that fire walkers crossing a 7-meter-long bed of coals with a surface temperature of 677 °C raised not only their own **HEART RATES** but also those of loved ones watching in the crowd (*Proc. Natl. Acad. Sci. USA,* DOI: 10.1073/pnas.1016955108).

The scientists outfitted 38 participants with heart rate monitors and recorded data during both the ritual and the procession beforehand. Spectators who were friends or relatives of the walkers had heart rate patterns that synchronized with the person walking on the hot coals; nonrelated spectators on the sideline did not.

Dimitris Xygalatas, an anthropologist at Denmark's Aarhus University and research team member, tells Newscripts that the group is now planning similar experiments in Mauritius. The Cavadee ceremony there, he says, involves participants piercing themselves with needles, hooks, and skewers.

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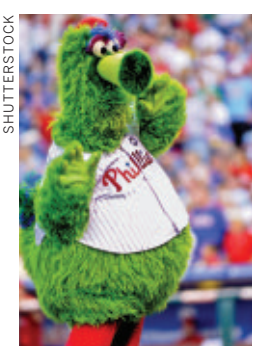

DIMITRIS XYGALATAS

Phillie Phanatic: Handle with care. Piggyback: Ritual fire walker carries a passenger.

LAUREN K. WOLF *wrote this column. Please send comments and suggestions to newscripts@acs.org.*

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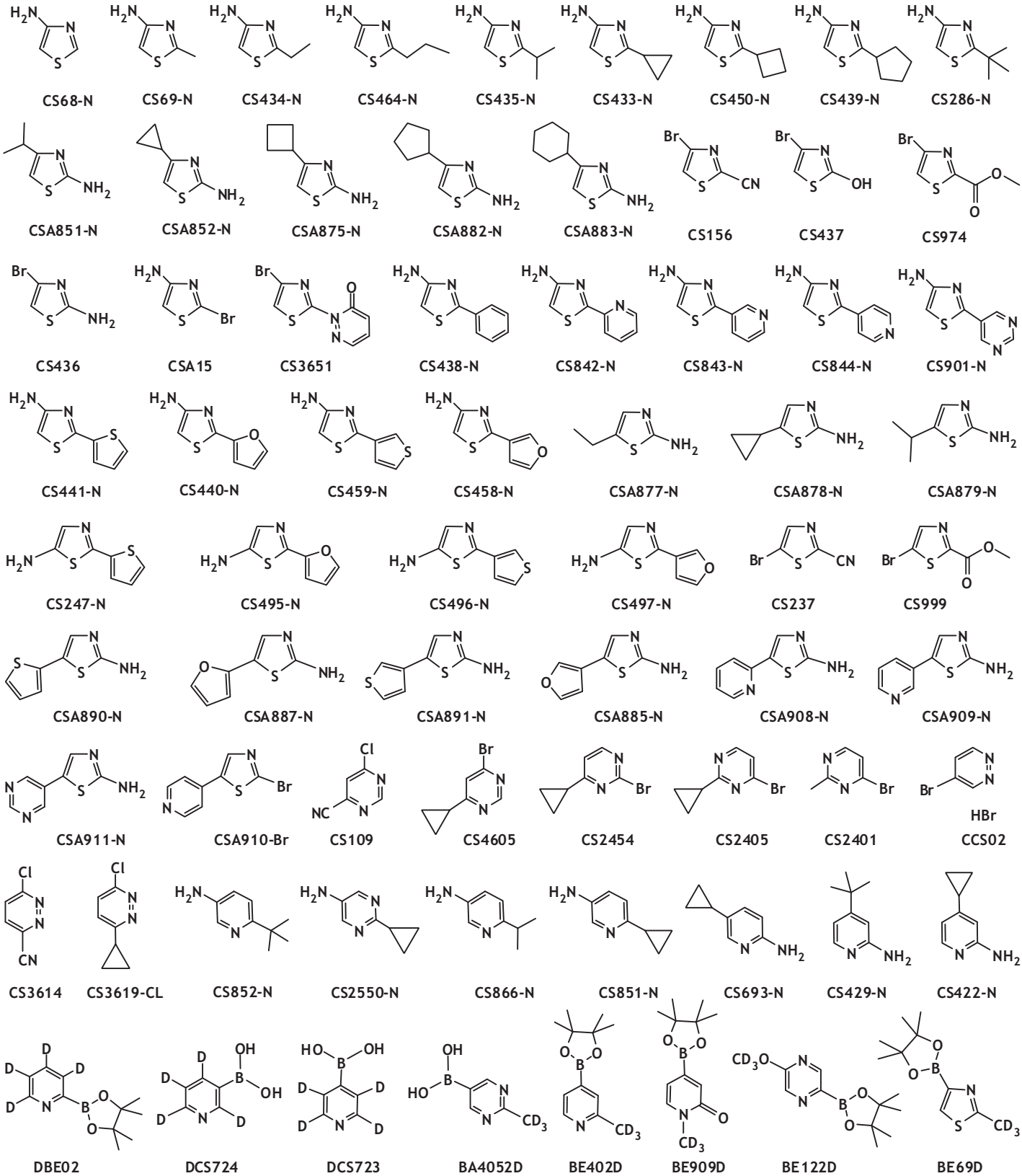

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