DISCOVERY REPORT

An ACS member exclusive

ACS Chemistry for Life®

The future of antibiotics

Bacteria may fuel the next global pandemic. Will we be ready?

Published by c&en

$39.99

The future of antibiotics

After commercial antibiotics emerged in the early 20th century, we began to take for granted the ability to treat bacterial infections. But as bacteria evolved to resist those drugs, pharmaceutical companies have struggled to develop new drugs to challenge the microbes. As a result, the world is facing a public health crisis of drug-resistant bacterial infections.

The fundamental challenge in antibiotic development isn't entirely scientific, even though it certainly isn't easy to stay one step ahead of bacteria with compounds that thwart resistance mechanisms, can be taken up by the body in sufficient quantities, and are amenable to tablet formulation. The bigger problem is how to pay for that work. To avoid bacteria developing ever-better resistance, new antibiotics must be prescribed sparingly. Meanwhile, health care systems are set up to reward volume.

In this Discovery Report, you'll meet the scientists and companies working on the cutting edge of antibiotic drug discovery and antimicrobial science. You'll hear from experts involved in pharmaceutical economics about pilot programs to change the way antibiotics are paid for. You'll read about the path of one antibiotic, Nabriva Therapeutics' Xenleta (lefamulin), from discovery to market.

Contributing editor Brian Owens, an independent journalist who covers health and environment, edited this report with Jyllian Kemsley, C&EN's executive editor for policy and content partnerships. The report includes a reading list of papers and patents curated by our sources, as well as by researchers at the CAS division of the American Chemical Society.

As an ACS member, you get exclusive access to the Discovery Report, a quarterly publication analyzing the new science and technology defining the chemical sciences and our industry. Look for the next one in the fourth quarter of 2020.

Amanda Yarnell

Editorial director, C&EN
@amandayarnell

INSIDE

Published by
c&en

Editors: Brian Owens, Jyllian Kemsley

Contributing writers: Elie Dolgin, Sam Lemonick, Michael McCoy

Creative: Robin Braverman, Yang Ku, Rob Bryson

Copy editor: Michele Arboit

Production: Marsha-Ann Watson, Manny I. Fox Morone

CHEAT SHEET

5 questions and answers about antibiotics

Q. How does antibiotic resistance arise?

» **Bacteria undergo genetic changes** in response to exposure to something that can damage or kill them.

» **Many genes can confer resistance**, and most of them have been around for thousands of years—long before humans started using antibiotics. They have become more common in recent decades, in response to the selective pressure of widespread antibiotic use.

» **Bacteria can acquire new resistance genes** by picking up DNA in the environment (transformation), through DNA transfer by viruses (transduction), or by direct contact with and transfer from another resistant bacteria (conjugation).

Q. How do bacteria resist antibiotics?

» **There are four main mechanisms** of antibiotic resistance: limiting uptake of a drug, modifying a drug target, inactivating a drug through chemical alteration, and pumping a drug out of a cell.

» **Gram-negative bacteria** use all four mechanisms. The structure of the lipopolysaccharide layer in the membranes of gram-negative bacteria helps limit uptake of some drugs.

» **Gram-positive bacteria** don't commonly limit drug uptake and don't have the capacity for some drug efflux mechanisms.

Q. Which bacteria are the biggest threats?

» **The World Health Organization and the US Centers for Disease Control and Prevention** maintain separate lists of the most dangerous resistant bacteria. The lists have significant overlap but are not identical.

» **The WHO's critical pathogens** are carbapenem-resistant *Acinetobacter baumannii*, carbapenem-resistant *Pseudomonas aeruginosa,* and carbapenem-resistant *Enterobacteriaceae* that produce "extended spectrum" enzymes that break down β-lactam compounds.

» **The CDC's urgent threats** are carbapenem-resistant *Acinetobacter*, *Candida auris*, *Clostridioides difficile*, carbapenem-resistant Enterobacteriaceae, and drug-resistant *Neisseria gonorrhoeae*.

Q. What's the biggest challenge in antibiotic development?

» **It's economic:** How can companies turn a profit on drugs that are designed to be used sparingly?

» **In the UK**, a pilot program is testing a subscription-based model in which companies are paid a set annual fee, regardless of how much the drug is prescribed.

» **In the US**, there are moves to ease cost constraints that force hospitals to prescribe older, cheaper drugs when newer, more expensive ones would be more effective. Legislation is also being drafted to provide subscription-style payments.

» **Some have suggested removing the pharmaceutical industry** from the equation altogether and having nonprofits assume the work of developing new antibiotics.

Q. What's next for antibiotic development?

» **Combinations of drugs** with different targets and mechanisms of action may be more effective than single agents and help stave off the development of resistance.

» **New drugs could also target resistance mechanisms**, such as by inhibiting efflux pumps to restore the ability of older drugs to attack bacteria.

» **Artificial intelligence** can be used to identify promising new types of antibiotics, possibly faster and more accurately than humans.

» **Rather than creating more broad-spectrum antibiotics** that act against many kinds of bacteria, some companies are focusing on narrower-spectrum drugs that target a specific species or resistance mechanism.

8 experts working on the frontiers of antibiotic science weigh in on the future of the drug pipeline

Lori Burrows

» **Professor, McMaster University**

Lori Burrows says it is hard to choose which is the most important issue for the future of antibiotic development. "There are so many things wrong now," she says. But some of the biggest challenges are financial. "There is lots of good, grassroots work going on in academic labs and small biotechs, but it's hard to get it to the next level without the backing of big pharma," she says.

Burrows says there are some "flickers of life," in the form of the new $1 billion AMR Action Fund to address antimicrobial resistance. But even that fund is only enough to bring a couple of products to market.

On the scientific side, researchers have concentrated on broad-spectrum antibiotics that act against a wide range of bacteria. An alternative approach gaining popularity is to combine improvements in diagnostics with drugs designed more narrowly to neutralize one specific genus or species. Such an approach ensures that antibiotics aren't misused but are instead prescribed "in an intelligent way to treat the infection we know the person has," Burrows says.

Antibiotic overuse has been a major problem in the response to the COVID-19 pandemic, she says. Because of concerns about secondary bacterial infections, severely ill patients have been given antibiotics that are probably not necessary. "For the amount of secondary infections people are actually getting, they are being way over prescribed, and that is just going to contribute to resistance," Burrows says.

Arnab Chatterjee

» **Vice president of medicinal chemistry, California Institute for Biomedical Research (Calibr)**

Despite concerns that COVID-19 will increase antibiotic resistance, Arnab Chatterjee thinks that the pandemic will ultimately have a significant positive impact on how antibiotics are discovered, tested, and regulated.

One of Calibr's major assets is its drug repurposing library, which allows scientists to search thousands of compounds for potential drugs that have already been through some of the initial steps of discovery and development. Repurposing has seen some success during the pandemic, with remdesivir and other drugs. "This concept allows people to move quickly into the more challenging steps," Chatterjee says.

Calibr has seen increased use of its library in 2020 compared with previous years, and not just for COVID-19. "People are starting to appreciate these tools more now," he says.

The pandemic has also driven a significant transformation of the regulatory environment, Chatterjee says. "I'm excited to see that the way that clinical trials are being conducted has fundamentally changed from last winter to what they will look like this fall," Chatterjee says. The speed and flexibility allowed in clinical trials for COVID-19 therapies and vaccines could also be a benefit in antibiotic work, where unpredictable patient populations make traditional trials difficult. "My great hope is that this will be the working model for antibiotics in the future," he says.

Erin Duffy

» Head of R&D, Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (Carb-X)

One consequence of most major players leaving the antibiotic field over the past several years is that the companies that took their place are much smaller and may not have the in-house expertise needed to move a drug candidate through all the early stages of discovery and clinical development.

That's why Carb-X, a public-private partnership-launched in 2016 to support early-stage drug discovery and clinical development in antibiotics, is more than just a source of much-needed funding for small companies, according to Erin Duffy. "We've always desired to not only fund companies but help them navigate their programs," she says.

Carb-X builds support teams of subject matter experts for each company in its portfolio to help firms think through their plans, troubleshoot problems, and move faster. The organization can also spot issues faced by multiple companies—for example, how to deal with the kidney toxicity that has beset a number of peptide-based programs—and take on the challenge of solving that problem on behalf of all of them, reducing duplication of effort. "Rather than 10 people all hunting around the same problem, let's take a more global approach," Duffy says.

Carl-Fredrik Flach

» Professor, University of Gothenburg

To prescribe antibiotics more accurately, doctors must know what bacteria they face and specifically how those bacteria might resist the drugs. But that knowledge depends on having enough samples from the population to determine which resistance mechanisms bacteria have developed—a time-consuming and expensive process that is difficult to conduct in many parts of the world, according to Carl-Fredrik Flach.

So Flach and his colleagues have devised a faster, cheaper data source: sewage. They have found that bacterial resistance patterns in sewage strongly correlate with resistance patterns in the population that produced the waste. "It provides samples from large numbers of people and can complement traditional clinical surveillance," Flach says. "It can be extremely useful in low- and middle-income countries."

Such a blunt approach can't provide information about which bacteria are infecting individual people, but sewage analysis can guide clinical decisions by giving a statistical measure of resistance risk. Where the risk of resistance is low, older drugs can be used; where the risk is high, newer treatments may be employed.

> **"Rather than 10 people all hunting around the same problem, let's take a more global approach."**

Silas Holland

» Interim director of external affairs, AMR Action Fund

As large pharmaceutical companies backed away from developing new antibiotics in recent years, the public perception was that they weren't doing their part to address a public health crisis, Silas Holland says. So about a year ago, the CEOs of several companies started talking about what they could do to help, and the AMR Action Fund was born. "They wanted to do something valuable," Holland says.

The fund has raised almost $1 billion, which will be invested in smaller companies with the goal of bringing two to four new antibiotics to market within the next 10 years. The fund will provide not just money but access to technical support and expertise in drug discovery and regulatory strategy—proficiencies that are hard to find outside big pharma, Holland says.

A key difference between the AMR Action Fund and other antibiotic development efforts is that it will finance the later stages of clinical development, taking over when companies graduate from programs like Carb-X. "There has been a lot of investment in the early-stage pipeline, and we're starting to see the fruits of that," Holland says. "But if there is no investment in clinical development it's all going to wither on the vine."

Colm Leonard

» Consultant clinical adviser, UK National Institute for Health and Clinical Excellence

The biggest challenge facing pharmaceutical companies developing new antibiotics is that, by design, the drugs will be used sparingly. This makes it difficult to generate much in the way of profits in a field where payments are based on the volume of drugs sold and used.

"When a new antimicrobial comes to market,

PHOTO CREDIT: CECILIA HEDSTRÖM (FLACH)

it is appropriate to avoid large-volume usage to prevent early emergence of resistance," Colm Leonard says, but this leads to low revenues. Since April 2019, three companies that brought new antimicrobials to market have failed.

The UK's National Health Service is testing a unique way of paying for new antibiotics to ensure that the drugs are used responsibly and that the companies are paid enough to stay in business. In a pilot program launched this year, the NHS will pay a flat annual subscription fee to ensure access to a new drug, regardless of how much or how little is actually used. Drug companies will be offered fixed payments annually for an agreed number of years. "This allows appropriate stewardship of the antimicrobial and a return on investment for the company," Leonard says.

But the UK is just a small part of the global market for antibiotics, and the country can't support the companies on its own. "For our work to have the full effect, we need other countries to offer similar incentives in their own domestic markets, which collectively achieve a meaningful incentive for global investment," Leonard says.

Manos Perros

» CEO, Entasis Therapeutics

Despite their vital importance to human health, antibiotics remain a relatively old-fashioned type of treatment. "Patients now have diseases that are very different from 20 years ago, but the drugs are essentially the same," Manos Perros says. People diagnosed with pneumonia, for example, are initially given the same few broad-spectrum drugs, despite the fact that those drugs are no longer effective for some of the resistant strains in circulation.

The pharmaceutical industry needs to take a much more clinical approach to drug discovery, Perros says. Instead of just culturing a new organism from soil or water and looking at what compounds it uses to defend itself, researchers should be tailoring their molecules to attack bacteria in ways that thwart resistance mechanisms.

> **We want products tailored to the bug, not the place of infection.**

This approach will allow antibiotics to become similar to the kinds of personalized, specific drugs that are now common in, for example, cancer treatment—oncologists today wouldn't dream of treating all cancers with the same set of chemotherapy drugs, the way they did in the 1980s. "We want products tailored to the bug, not the place of infection," Perros says. "Physicians don't want another broad-spectrum pneumonia drug; they need something for patients with carbapenem-resistant bacteria."

Matthew Stone

» Deputy director of international standards and science, World Organisation for Animal Health

The World Organisation for Animal Health—commonly known by its historical French acronym, OIE—has three main jobs when it comes to antibiotics, according to Matthew Stone. It oversees an accounting system to estimate the total volume of antibiotics given to animals each year; sets international standards for the prudent and responsible use of antimicrobials; and helps build capacity in veterinary medicine, regulatory processes, and antimicrobial resistance programs in countries worldwide.

Of those jobs, building capacity is probably the most important. In the area of regulatory processes, for instance, the ability of a country to give accurate estimates is more important than what the numbers end up being. "It's not the final numbers that we want to focus on—it's the insights that national veterinary services achieve" through assessment, he says.

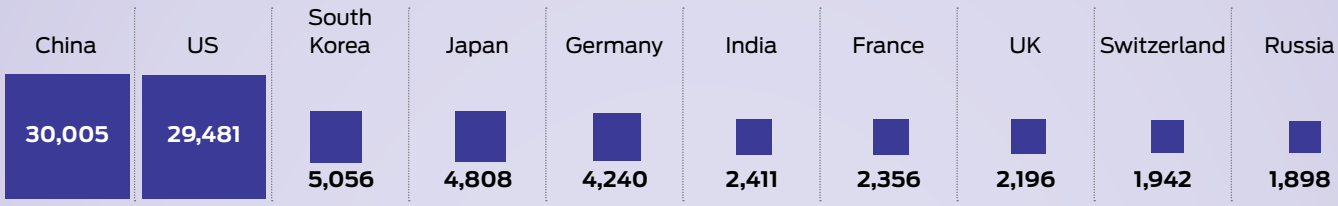
Consequently, the OIE doesn't issue targets to limit antibiotics use. Instead, it encourages countries to collaborate with their agricultural industry to set realistic targets and establish reliable systems to account for antibiotic use. Stone says the UK is a good example of how this can be done well. The country defined reasonable targets, broken down by sector, and is now into its third year of reporting on them. "I'd love to see that in every country," he says.

Who is developing antibacterial treatments?

Global generators

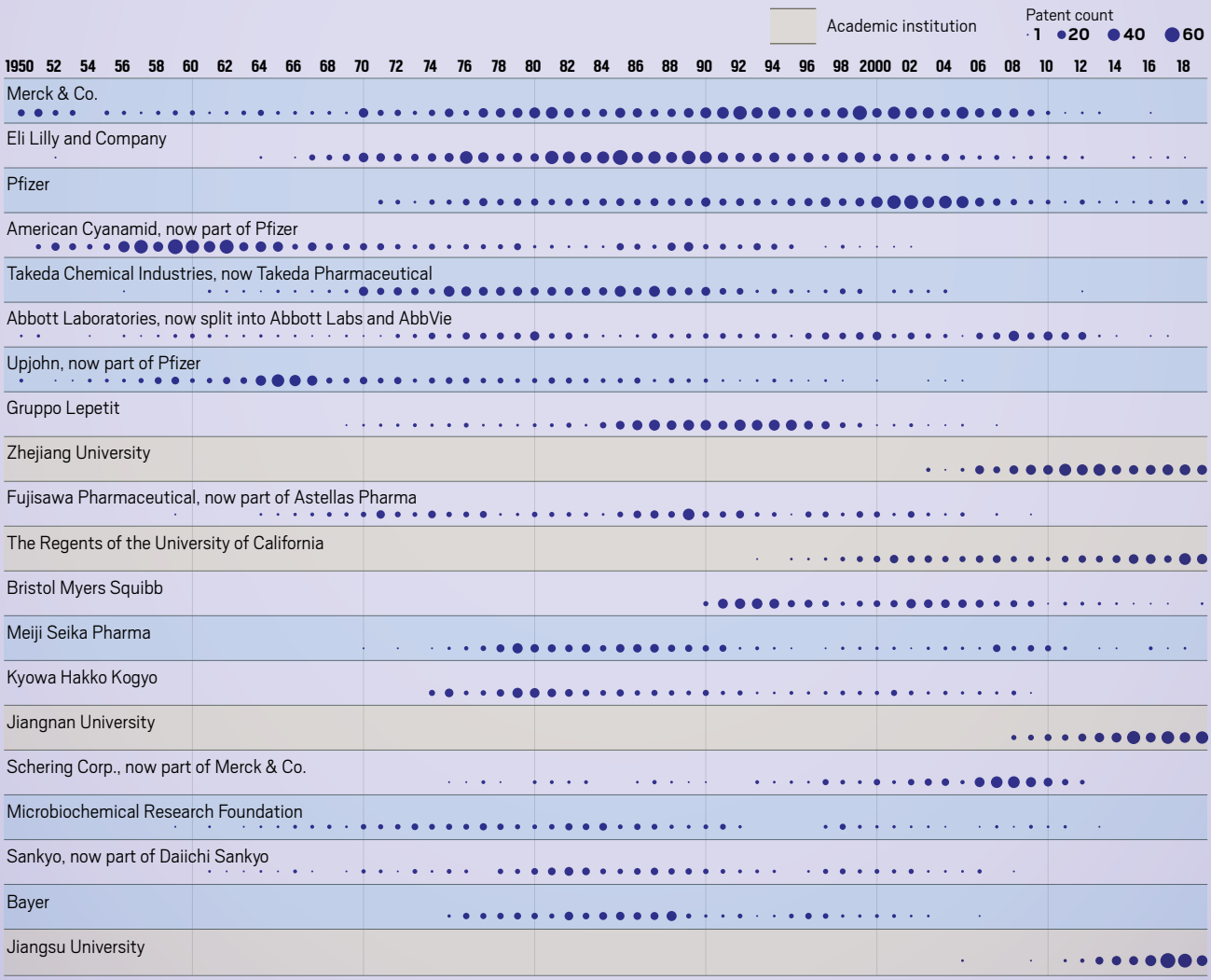
China and the US far outpace other countries in the top 10 for patents published in the past 25 years. The US led the world in annual patent publication until around 2011, when China took over first place.

Number of patents



Source shift

Judging by the top 20 patent assignees, patenting has generally shifted from industry to academia over the past several decades.



Source: CAS, a division of the American Chemical Society.
Note: Patents may be registered in certain territories and administrative regions, and such patents are counted separately from those of corresponding governing nations. Figures for Germany and Russia include patents that were filed in the former East Germany and the Soviet Union, respectively, and published after a long delay.

Preparing for the next pandemic

ELIE DOLGIN, SPECIAL TO C&EN

In the early days of the COVID-19 pandemic, as hospitals became overwhelmed by a crush of severely ill patients with respiratory infections that resembled bacterial pneumonia, doctors began prescribing antibiotics for almost everyone.

Even though the drugs are meant to kill bacteria, not viruses, there was neither the time nor testing capacity to determine the true cause of people's illnesses. And with few good options for treating COVID-19—plus a real risk of secondary infections and claims that a broad-spectrum antibiotic called azithromycin might be helpful—doctors fell back on the drugs they knew best.

The result: widespread overuse of antibiotics. Studies from the first wave of SARS-CoV-2 cases in the US, China, and elsewhere found that over 70% of people diagnosed with COVID-19 received antibiotic therapy, even though fewer than 10% of patients ultimately tested positive for bacterial or fungal coinfections.

Clinical experience and improvements in diagnostic testing have helped reduce the number of unnecessary antibiotic prescriptions, but overuse persists. According to one analysis from Michigan, nearly half of all patients entering the hospital for COVID-19 were still being prescribed "just-in-case" courses of antibiotics several months into the pandemic.

One consequence of COVID-19, therefore, may be that it exacerbated the problem of antimicrobial resistance (AMR) and moved the world that much closer to another pandemic—one caused by drug-defying superbugs. The worldwide death toll from drug-resistant bacterial disease is thought to be at least 700,000 annually according to a 2016 report commissioned by the UK government. The same report predicts that deaths will climb to 10 million by 2050 unless action is taken.

"COVID-19 offers a really clear and vivid example of how an infection, even if you don't get it yourself personally, can wreak havoc on a society," says John Rex, a longtime antimicrobial researcher who now serves as chief medical officer of F2G, an antifungal-drug company. "And now something that sounds kind of boring—preparedness—all of a sudden takes on a whole new meaning."

After nearly 2 decades of fleeing the business of antibiotic discovery, one indication that the world's leading drugmakers are once again taking the issue seriously came in July, when more than 20 companies joined together to launch the AMR Action Fund, a $1 billion initiative aimed at bringing two to four novel antibiotics to market by 2030. The fund was about a year in the making, so companies that had committed to the effort could have pulled out when COVID-19 hit and priorities shifted to advancing new antiviral medicines and vaccines. None did.

CREDIT: SHUTTERSTOCK

In fact, the opposite happened. According to Action Fund spokesperson Silas Holland, "CEOs actually cited COVID-19 as a driver for their investment, since the pandemic has highlighted our continued vulnerability to infectious diseases and the importance of adequately preparing for the predictable and preventable threat of AMR."

But even efforts such as the AMR Action Fund won't be enough to generate the new drugs we need, infectious disease experts and the company executives say. What is required, they argue, is a complete overhaul of the drug reimbursement model for this unique class of therapeutics.

The Action Fund is "kind of a temporizing measure," says Cornelius Clancy, chief of infectious diseases at the VA Pittsburgh Healthcare System. "In the end, it's not going to solve what is the underlying problem with the development pipeline"—namely, how society pays for and values investments in antibiotic innovation.

Drugs of last resort

Novel antibiotics are by design meant to be drugs of last resort, reserved only for the toughest cases when other treatments do not work. That means they "are unlike all the other drugs," Rex points out. "Antibiotics have huge value even when you don't use them."

Our health systems don't value medicines in that way, however. Instead, they simply reward pharmaceutical research and development by paying drug companies for the volume of their product sold. In theory, higher drug costs could offset low volumes, but set the price too high and hospitals—faced with limited budgets and a reimbursement model that bundles payments for in-patient treatments—will never offer new antibiotics. As it is, cost constraints force doctors to routinely prescribe cheaper but less effective antibiotics even when newer agents are warranted.

Consequently, it is perhaps unsurprising that all antibiotics approved in the past decade have had disappointing sales. Several drugmakers that brought new agents to market in recent years have either gone bankrupt or abandoned the pursuit of antibiotics altogether.

Aiming to fix the fundamentally broken marketplace and incentivize the creation of new treatments, a few health-care authorities have begun trials of new payment models that at least to some extent delink profits from sales and instead focus squarely on benefits to public health. In Sweden, for example, the government plans to pay a guaranteed minimum contract each year for certain antibiotics, with the amount tied to the drug volume needed under a plausible medical worst-case scenario. A similar program has also been proposed for Norway.

Meanwhile, in the UK, the National Health Service is embarking on perhaps the world's most ambitious reward scheme to date: a Netflix-style subscription model in which companies are paid an up-front fee for unlimited access to a particular medicine. "This issue of market failure must be addressed," says Dame Sally Davies, who formerly served as England's chief medical officer and is now the UK special envoy on antimicrobial resistance.

"At the moment, we all talk about delinking, but no one has shown it's doable," Davies says. "If we can produce a functioning model, then we've opened the door."

Those involved in the British pilot program are reviewing a range of drug candidates, looking for novel antibiotics that address highly resistant pathogens. Two products will ultimately move forward, and their manufacturers stand to earn up to £100 million each ($130 million) over a decade, with the final amount determined through health economic modeling and expert opinion. If the project is successful, more purchasing arrangements could be negotiated in the years to come.

But what does success look like? "For me, success is finding a model where everyone"—patients, payers, and drugmakers—"feels it's fair," Davies says. And if the program can garner buy-in from those various stakeholders on a national scale, hopefully it can inspire other governments to follow the UK's lead so that, in aggregate, there are sufficient market-based enticements—what economists call pull incentives—to attract significant investment globally in antibiotic research and development.

"Other countries have to join in," says Davies, who is now working with the United Nations to help form a global advisory group focused on AMR-related issues.

Already there are some copycat proposals. In the US, for example, lawmakers in Congress have begun drafting the Pioneering Antimicrobial Subscriptions to End Upsurging Resistance (PASTEUR) Act, which would reward antibiotics manufacturers with subscription contracts of up to $3 billion, paid over 5–10 years. If other countries follow suit, individual drugs could earn enough annually for drug companies to recoup investment costs and earn a profit.

The industry is banking on market-based reforms to have that kind of global snowball effect.

> **"There was a time, a decade or so ago, when this idea of delinking antibiotic R&D and sales was really a quite narrow, academic concept that no one took very seriously."**

Aiming for market reform

The $1 billion AMR Action Fund intends to sustain itself through new market incentives that value public health benefit rather than sales. Its investors include the following:

- Almirall
- Amgen
- Bayer
- Boehringer Ingelheim
- Chugai Pharmaceutical
- Daiichi Sankyo
- Eisai
- Eli Lilly and Company
- GlaxoSmithKline
- Johnson & Johnson
- LEO Pharma
- Lundbeck
- Menarini
- Merck & Co.
- Merck KGaA
- Novartis
- Novo Nordisk
- Novo Nordisk Foundation
- Pfizer
- Roche
- Shionogi
- Takeda Pharmaceutical
- Teva Pharmaceutical
- UCB

Indeed, the $1 billion AMR Action Fund is meant to sustain itself precisely through new reimbursement plans, entry rewards, and other value-based purchasing models—which means that a lot is riding on the success of the British experiment and other yet-to-be implemented payment arrangements.

The AMR Action Fund is a gamble, "a last ditch effort to save the field," says Kevin Outterson, a Boston University law professor who specializes in antibiotics incentives. If the initiative fails, "nobody will invest private money in this field again for a very long time," he says.

Still, he remains more optimistic than ever that drugmakers and governments can collaborate to mend the fragile antibiotics market. "There was a time, a decade or so ago, when this idea of delinking antibiotic R&D and sales was really a quite narrow, academic concept that no one took very seriously," says Outterson, who also leads the Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (Carb-X), a nonprofit partnership designed to fund early development of priority antibiotics. "Today, just about every stakeholder that is involved in this discussion now thinks this is the key piece."

Motives in question

But not every stakeholder. Brad Spellberg is an infectious disease physician and the chief medical officer at the Los Angeles County + University of Southern California Medical Center. For years, he advocated for these types of economic incentives. But last year, his thinking changed. He reasoned that if the public is footing the bill for nearly all antibiotics research and development, what is the industry needed for beyond perhaps manufacturing and drug distribution?

Carb-X, for example, gets its funds from German, UK, and US government agencies as well as private foundations, then passes that money on to companies for drug discovery and development. Then, if subscription contracts or other pull incentives are put into place, the public would be subsidizing up-front research costs to discover antibiotics and padding the profits of pharmaceutical companies on the back end. Why not cut out the industrial middleman?

Writing in the *New England Journal of Medicine* last year, Spellberg called for a complete overhaul of the entrepreneurial model for antibiotics development, arguing instead that nonprofit organizations should take over the task of discovering and developing antibiotics (*N. Engl. J. Med.*, DOI: 10.1056/NEJMp1905589)."The for-profit motive doesn't work," Spellberg says. "You need to have nonprofits in this space."

Spellberg is not alone in this line of thinking. Outterson describes the nonprofit model as "the backup plan" if not enough governments provide market entry rewards and the AMR Action Fund fails. Even economist Jim O'Neill, author of the 2016 UK report that made the case for giving companies around $1 billion for each novel antibiotic they developed, has come around to the idea of eliminating the pharmaceutical industry from the equation, as he wrote recently on Revive, a Global Antibiotic Research and Development Partnership (GARDP) website.

> **"Antibiotics have huge value even when you don't use them."**

GARDP is just such a nonprofit entity, backed by tens of millions of dollars donated by governments and foundations around the world. It is working to deliver five new treatments by 2025 aimed at drug-resistant bacteria responsible for sexually transmitted infections, sepsis in newborns, and hospital-acquired infections.

Spellberg's idea is different, though. "What we need is a group of people whose mission is to continuously discover and develop, at a slow and steady pace, a bullpen of molecules for future unmet needs that can be revved up into development when future problems arise," he says. "Sort of like has happened with COVID."

He points to the example of remdesivir, an antiviral drug that was quickly deployed in the fight against COVID-19 and found to help with patient recovery. Spellberg notes that speedy trials were possible because of scientists' prior legwork identifying compounds with activity against related viruses that had caused earlier outbreaks. Several of the leading vaccine candidates for COVID-19 also come from groups that had been working to address other coronavirus infections and then repurposed their vaccine platforms.

Nobody was necessarily thinking about a future coronavirus sweeping the globe, and any readiness efforts have clearly been insufficient. But the inadvertent preparedness with remdesivir and vaccine technologies has undoubtedly helped save lives.

In Spellberg's vision, a private philanthropist or collection of governments would seed one or more nonprofits with a sizable endowment. Income generated from that endowment would then sustain a small team of drug discoverers, with revenue generated from licensing deals or sales feeding back to support research activities or to further grow the endowment. Spellberg hasn't crunched the numbers to know how much his proposal would cost, but he's confident it would be a pittance compared with the vast sums governments are spending on COVID-19 countermeasures.

The world got caught off-guard with COVID-19, despite the many warning signs—SARS, MERS, bird flu, Ebola—that a pandemic virus would strike again. The rise of drug-resistant microbes is far more predictable and, indeed, probably inevitable. And whether through subscription models or the creation of R&D nonprofits, new ways of thinking are needed today to avoid the next wholly foreseeable pathogen crisis of tomorrow.

Clancy, chief of infectious diseases at the VA Pittsburgh Healthcare System, says, "I'm 100% confident that when we get to the other side of [COVID-19], whenever that is, the antimicrobial issue is going to be there at least as large as it was when we went into this."

Elie Dolgin is a freelance writer based in Massachusetts.

The 20 most-promising companies still in the antibiotics race

Acurx Pharmaceuticals

» **Acurx Pharmaceuticals**
» **www.acurxpharma.com**
» **Based:** White Plains, New York
» **Founded:** 2017
» **Money raised to date:** $10.6 million
» **Key partnerships:** None
» **Strategy:** Acurx Pharmaceuticals focuses on developing drugs that block a molecular target that other companies have struggled to exploit: DNA polymerase IIIC. Its current candidates aim to address gram-positive bacteria listed as priority pathogens by the World Health Organization and US agencies.
» **Why watch:** DNA polymerase IIIC inhibitors have long been a target of the pharmaceutical industry, but previous candidates faced toxicity issues. So far, Acurx's lead candidate has avoided such safety concerns. Acurx has one drug that has reached clinical trials—ibezapolstat for *Clostridioides difficile* began Phase II in July 2020.

BOSTON pharmaceuticals

» **Boston Pharmaceuticals**
» **www.bostonpharmaceuticals.com**
» **Based:** Cambridge, Massachusetts
» **Founded:** 2016
» **Money raised to date:** $600 million
» **Key partnerships:** GlaxoSmithKline, Novartis
» **Strategy:** When pharmaceutical and biotechnology companies around the world drop promising drug candidates, Boston Pharmaceuticals is there to pick them up. The company is not selective about therapeutic area. Instead, it focuses on candidates that have advanced to the point of approval for human clinical trials but no further than Phase II trials.
» **Why watch:** In 2018 the company struck two of its biggest deals to date, acquiring three anti-infectives from Novartis and five from GSK. The most advanced is BOS-228, a former Novartis antibacterial that is in Phase II trials in people with gram-negative bacterial infections.

bugworks

» **Bugworks Research**
» **bugworksresearch.com**
» **Based:** Bangalore, India
» **Founded:** 2014
» **Money raised to date:** $16.5 million
» **Key partnerships:** Carb-X
» **Strategy:** Bugworks Research is working to create broad-spectrum antibiotics that can combat resistant strains of both gram-negative and gram-positive bacteria. It has developed a strategy, ELUDE, to avoid the efflux pumps that bacteria frequently use to evict compounds before they can cause harm.
» **Why watch:** Bugworks has raised funds from seven investors, including a $7.5 million series B round in April 2020. It has three drugs in preclinical development for multidrug-resistant infections.

CrystalGenomics

» **CrystalGenomics**
» **www.crystalgenomics.com/en/index.php**
» **Based:** Seongnam, South Korea
» **Founded:** 2000
» **Money raised to date:** $15.4 million
» **Key partnerships:** None in antibiotics
» **Strategy:** CrystalGenomics uses its proprietary technology to decipher protein structures to design new drug candidates.
» **Why watch:** The firm was selected as one of South Korea's top 10 innovative pharmaceutical companies in 2012 by the country's government and singled out for extra support to help it grow. CrystalGenomics has sent one candidate, fatty acid biosynthesis inhibitor CG-549, through Phase II trials for drug-resistant bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA).

Debiopharm WE DEVELOP FOR PATIENTS

» **Debiopharm International**
» **www.debiopharm.com**
» **Based:** Lausanne, Switzerland
» **Founded:** 1979
» **Money raised to date:** Not available
» **Key partnerships:** Carb-X
» **Strategy:** Debiopharm in-licenses oncology and antibacterial compounds, develops them into medicines, then out-licenses them to large international pharmaceutical companies.
» **Why watch:** The company's afabicin is a first-in-class inhibitor of FabL, an enzyme involved in fatty acid biosynthesis. It has completed Phase II trials for skin infections and is in Phase II trials for bone and joint infections.

ENTASIS THERAPEUTICS

» **Entasis Therapeutics**
» **www.entasistx.com**
» **Based:** Waltham, Massachusetts
» **Founded:** 2015
» **Money raised to date:** $153.2 million
» **Key partnerships:** AstraZeneca, Carb-X
» **Strategy:** Spun out of AstraZeneca in 2015, Entasis focuses on developing antibiotics to overcome mechanisms of resistance. One target is to inhibit β-lactamases, which break down β-lactam

antibiotics such as those in the penicillin and cephalosporin families.
» **Why watch:** The company completed a successful IPO in 2018. Entasis has four drugs in its pipeline, including sulbactam-durlobactam in Phase III trials for multidrug-resistant *Acinetobacter* infections and zoliflodacin in Phase III for gonorrhea.

» **Ginkgo Bioworks**
» **www.ginkgobioworks.com/**
» **Based:** Boston
» **Founded:** 2008
» **Money raised to date:** $789.1 million
» **Key partnerships:** None in antibiotics
» **Strategy:** Ginkgo, self-styled as "the organism company," uses synthetic biology to develop custom microbes to synthesize new molecules for a variety of markets, including sweeteners, cosmetics, crop treatments, and pharmaceuticals.
» **Why watch:** In 2019, Ginkgo acquired from Warp Drive Bio a genome-mining platform that provides it with a huge database of biological information for organism engineering. It intends to use this platform to develop novel classes of antibiotics for drug-resistant infections.

» **Innovation Pharmaceuticals**
» **www.ipharminc.com**
» **Based:** Wakefield, Massachusetts
» **Founded:** 2007
» **Money raised to date:** $1 million
» **Key Partnerships:** Alfasigma
» **Strategy:** Innovation Pharmaceuticals is developing therapies for dermatology, oncology, anti-inflammatory, and antibiotic applications.
» **Why watch:** Innovation's brilacidin is a first-in-class agent that mimics antimicrobial immune system proteins called defensins. Brilacidin is in Phase II trials for skin infections. The drug has also recently shown promise as an antiviral treatment for COVID-19 and is being fast-tracked through clinical trials.

» **Lumen Bioscience**
» **www.lumen.bio/**
» **Based:** Seattle
» **Founded:** 2017
» **Money raised to date:** $65 million
» **Key partnerships:** Bill & Melinda Gates Foundation
» **Strategy:** Lumen uses bioengineered spirulina algae to produce antibodies and other biologic drugs in oral and topical formulations at lower cost than traditional manufacturing methods.
» **Why watch:** Lumen has a neutralizing antibody cocktail in Phase II trials for traveler's diarrhea caused by *Escherichia coli* and *Campylobacter jejuni.* Supported by the Gates Foundation, the product will be made available in the developing world regardless of ability to pay.

» **MGB Biopharma**
» **www.mgb-biopharma.com/**
» **Based:** Glasgow, Scotland
» **Founded:** 2009
» **Money raised to date:** $18.4 million
» **Key Partnerships:** None
» **Strategy:** MGB Biopharma is developing a new class of anti-infective medicines based on compounds that bind to the minor groove of DNA to disrupt gene expression. Bacteria lack any preexisting resistance to this mechanism of action.
» **Why watch:** MGB is supported by eight different investors. The company's lead candidate, MGB-BP-3, successfully completed Phase II trials in May 2020 for *C. difficile.*

» **Microbiotix**
» **www.microbiotix.com**
» **Based:** Worcester, Massachusetts
» **Founded:** 1998
» **Money raised to date:** Not available
» **Key partnerships:** Carb-X, AMR Centre , US Department of Defense
» **Strategy:** Microbiotix focuses on the discovery and development of small-molecule drugs that target serious infectious diseases.
» **Why watch:** Micobiotix has four programs focused on multidrug-resistant bacteria. One targets bacterial virulence through the *Pseudomonas aeruginosa* type III secretion system, which injects proteins into host cells to trigger their death. Another addresses multidrug-resistant *Neisseria gonorrhoeae* by inhibiting the *trans*-translation system that restarts stalled protein biosynthesis. Neither has reached clinical trials yet.

» **MicuRx Pharmaceuticals**
» **micurx.com**
» **Based:** Foster City, California, and Shanghai
» **Founded:** 2007
» **Money raised to date:** $148.4 million
» **Key partnerships:** Carb-X
» **Strategy:** MicuRx develops antibiotics to combat drug-resistant bacterial infections. It couples US research and development with infrastructure and scientific resources in China.
» **Why watch:** The company's hybrid business structure allows it to conduct clinical trials in the US and China in parallel, to accelerate approval and commercialization in both countries. One of its candidates, contezolid, has been submitted for approval in China and has completed Phase II trials in the US and Australia.

» **NovaBiotics**
» **novabiotics.co.uk**
» **Based:** Aberdeen, Scotland
» **Founded:** 2004
» **Money raised to date:** $14.4 million
» **Key partnerships:** Not disclosed
» **Strategy:** NovaBiotics uses rational drug design to develop drug candidates based on the body's own infection-fighting agents, such as molecules that modulate general immune system response to infection.
» **Why watch:** Cysteamine (Nylexa), the company's lead antimicrobial agent, is an adjuvant that "supercharges" the activity of existing antibiotics to which bacteria are resistant or respond poorly, extending their usefulness. Cysteamine is being studied as a treatment for secondary bacterial pneumonia infections associated with severe cases of COVID-19.

» **Procarta Biosystems**
» **www.procartabio.com**
» **Based:** Norwich, England
» **Founded:** 2007
» **Money raised to date:** $14.1 million
» **Key partnerships:** Carb-X
» **Strategy:** Procarta Biosystems is focused on developing a new class of oligonucleotide antimicrobial agents that are active against resistant bacterial strains. The drugs insert into the bacterial genome short pieces of DNA that cause and then block a stress response, a sequence of events that kills the bacteria.
» **Why watch:** The company has raised funds from 10 investors. Procarta's lead product, PRO-202, is in preclinical development to treat complicated urinary tract infections and complicated intra-abdominal infections.

» **Snipr Biome**
» **www.sniprbiome.com**
» **Based:** Copenhagen, Denmark
» **Founded:** 2017
» **Money raised to date:** $50 million
» **Key partnerships:** None
» **Strategy:** Snipr Biome is developing CRISPR-based antibacterial drug candidates for use in difficult-to-treat infections or precision microbiome modulation. The drugs are designed to redirect bacteria's enzymes to chop up their own DNA.
» **Why watch:** The company has more than a dozen patents on its technology and raised $50 million from four investors in a single funding round in 2019.

» **Spero Therapeutics**
» **sperotherapeutics.com**
» **Based:** Cambridge, Massachusetts
» **Founded:** 2013
» **Money raised to date:** $256.4 million
» **Key partnerships:** Biomedical Advanced Research and Development Authority (BARDA), US Department of Defense, Bill & Melinda Gates Medical Research Institute, Carb-X
» **Strategy:** Spero is developing multiple drugs to combat gram-negative, multidrug-resistant bacteria in areas of unmet clinical need or where standard of care is suboptimal, for example, by developing oral antibiotics to treat resistant infections in the community.
» **Why watch:** The company has attracted investment from a number of government agencies and private foundations. It has three products in clinical trials. The most advanced is an oral formulation of tebipenem that was approved in Japan in 2009 for complicated urinary tract infections.

» **Summit Therapeutics**
» **www.summitplc.com**
» **Based:** Abingdon, England
» **Founded:** 2003
» **Money raised to date:** $136.4 million
» **Key partnerships:** BARDA, Roche, Carb-X
» **Strategy:** Summit uses its Discuva platform to identify which genes are essential to a bacterium's survival. The company then designs antibiotics to target the products of those genes. Summit aims to develop antibiotics for high-volume use rather than ones to be held as last-resort treatments.
» **Why watch:** Discuva has generated four candidate drugs, including ridinilazole, which is in Phase III trials for *C. difficile*. Roche is also using the platform to generate an undisclosed number of new leads.

» **Taxis Pharmaceuticals**
» **www.taxispharma.com**
» **Based:** Monmouth Junction, NJ
» **Founded:** 2009
» **Money raised to date:** $3 million
» **Key partnerships:** Carb-X
» **Strategy:** Taxis is focused on disrupting drug resistance mechanisms so that existing antibiotics can again be effective against resistant bacteria.
» **Why watch:** The company has one candidate, TXA709, that has completed Phase I trials as an oral anti-MRSA treatment to be used in conjunction with obsolete antibiotics. It targets a protein involved in bacterial cell division. TXA709 is eligible for fast-track review by the FDA.

» **Vaxdyn**
» **www.vaxdyn.com/products**
» **Based:** Seville, Spain
» **Founded:** 2011
» **Money raised to date:** Not available
» **Key partnerships:** Carb-X
» **Strategy:** Vaxdyn focuses on developing vaccines and monoclonal antibodies to fight drug-resistant bacterial infections.
» **Why watch:** Supported by Carb-X, Vaxdyn is developing KapaVax, a single vaccine against the gram-negative pathogens *Acinetobacter baumannii*, *Klebsiella pneumoniae*, and *P. aeruginosa*. If successful, it could prevent drug-resistant pneumonia in high-risk people and infections in newborns by stimulating maternal immunity.

» **Venatorx Pharmaceuticals**
» **www.venatorx.com**
» **Based:** Malvern, Pennsylvania
» **Founded:** 2010
» **Money raised to date:** $58.9 million
» **Key partnerships:** Carb-X, BARDA
» **Strategy:** Venatorx is focused on the discovery and development of anti-infectives to treat gram-negative multidrug-resistant bacterial infections, with a broad range of resistance mechanisms, including β-lactamases and carbapenemases.
» **Why watch:** The company has two drug candidates in clinical trials: cefepime-taniborbactam in Phase III and the combination of ceftibuten and VNRX-7145 in Phase I, both for carbapenem-resistant pathogens. It also has a program to develop inhibitors of penicillin-binding proteins, which are key for cell wall synthesis, that garnered a contract worth up to $44 million from the National Institute of Allergy and Infectious Diseases.

Note: Companies were included because of the novelty and promise of their methods, amount of capital raised, number of partnerships, and number and identity of investors.

Sources: Crunchbase (accessed August 2020), company websites, news reports.

From discovery to market

MICHAEL MCCOY, C&EN STAFF

In November 2006, Rosemarie Riedl synthesized an antibacterial molecule that she logged into Nabriva Therapeutics' database as BC-3781. It was not just another entry in a compound collection. In 2019, after almost 13 years of development and testing, the US Food and Drug Administration approved that same molecule, lefamulin, for the treatment of community-acquired bacterial pneumonia.

Marketed as Xenleta, lefamulin was the first antibiotic with a novel mechanism of action to win FDA approval for pneumonia in nearly 2 decades. With the help of contract manufacturing firms from across Europe and China, Nabriva took the drug to market without a big pharma partner.

Inventing a drug in its own labs and getting it approved solo is something few biotech firms have done. And yet it won't be enough for the small company. Nabriva must now turn a profit on lefamulin, a goal that has eluded many independent antibiotic developers. Judging from Nabriva's stock price, investors have their doubts that the firm will be in the black anytime soon.

Discovery

Although Nabriva's corporate offices are in the US, and its global headquarters are in Ireland, its research efforts are based in Vienna, where the culture is decidedly more European than American. Riedl, Nabriva's senior director of medicinal chemistry, has been with the company and its predecessor, Sandoz, since earning her PhD in pharmaceutical chemistry. And she's not the only long-tenured employee.

Nabriva chemists scaled up the process for synthesizing lefamulin at the firm's labs in Vienna.

CREDIT: NABRIVA THERAPEUTICS

"The core team has been together for a long, long time," says Werner Heilmayer, Nabriva's vice president for intellectual property and chemistry, manufacturing, and controls. Like Riedl, Heilmayer has been there from the start. He joined Sandoz in 1995 after graduate school and went with Nabriva when it became an independent company in 2006.

That was the year that Novartis, Sandoz's parent company, decided it was done researching and developing new antibiotics, a field that has long been a money pit for big pharma. With about $50 million in financing from venture capital firms and its own venture arm, Novartis set the antibiotic operation off on its own.

As an independent company, Nabriva continued Sandoz's quest for useful derivatives of pleuromutilin, an antibiotic molecule that occurs naturally in an edible mushroom sometimes called *Pleurotus mutilus*.

Pleuromutilin was discovered in the 1950s, and Sandoz launched two semisynthetic derivatives, tiamulin and valnemulin, as veterinary antibiotics in 1979 and 1999, respectively. GlaxoSmithKline (GSK) later succeeded in creating a topical human drug, but systemic human pleuromutilins with a wider potential market eluded drug hunters for decades.

One reason for the lack of success was that, for many years, researchers were focused on finding new β-lactam antibiotics like amoxicillin and cephalosporin, still the most widely used antibiotic class. Drug-company interest in pleuromutilins finally perked up around the turn of the century as bacterial resistance to β-lactams increased,

according to a review paper that Riedl and a colleague, Susanne Paukner, published in 2017 in *Cold Spring Harbor Perspectives in Medicine*.

According to the paper, pleuromutilins work by binding to the peptidyl transferase center on the bacterial ribosome, interfering with protein production and impeding growth. It's a unique mode of action for an antibiotic, even among those that work by blocking bacterial growth. Both mechanistic studies and in vitro experiments show a low potential for resistance to develop.

While pleuromutilin can kill bacteria in the lab, it doesn't have what it takes to make a good drug. Chemists needed to tweak the molecule to improve properties such as how long it lingers in the bloodstream.

A year after Novartis spun off Nabriva, the FDA approved the first human pleuromutilin derivative, GSK's retapamulin. But the skin infection treatment, created by modifying the hydroxyacetyl side chain of pleuromutilin with a bicyclic *N*-methylpiperidine group, only works as an ointment; GSK was unable to put it into a pill or IV bag.

Although Nabriva wasn't first to the market, the company was determined to come up with a systemic drug. When it became independent, the firm didn't have a viable drug candidate of its own. What it did have was a deep knowledge of pleuromutilin chemistry and well-honed skills for making derivatives.

The Nabriva researchers drew on those insights when they, like the chemists at GSK, sought to modify the hydroxyacetyl side chain. Their goal was a modification that would give the natural product the elusive balance of antimicrobial activity, solubility, and metabolic stability needed to turn a molecule into a systemic drug.

Unlike their counterparts at GSK, Riedl and her colleagues didn't have huge compound libraries and combinatorial chemistry machinery at their disposal. Instead, they relied on old-fashioned medicinal chemistry savvy. "We always did dedicated chemistry and synthetic derivatives, compound by compound," Heilmayer says.

In 2006, Riedl tried yet another modification of the side chain: adding an aminohydroxycyclohexyl group. The result was BC-3781, later renamed lefamulin. Riedl's choice of that side chain involved a bit of luck, of course, but mostly it was the culmination of years of carefully directed effort. She describes the moment modestly: "I always had a good feeling about that idea and that it could solve many of the problems we had at the time."

Development

What Riedl actually got was a mixture of diastereomers that had to be separated on a chiral high-performance liquid chromatography column. And even after separation, BC-3781 did not instill a lot of confidence. It was a difficult-to-handle amorphous salt. And the laboratory synthesis required two classical chromatographic purifications. "You cannot have these things on scale," Heilmayer points out.

The Vienna team needed to develop a chirally selective synthesis that avoided chromatography, and a crystalline late-stage intermediate that could be isolated and purified. The team also had to come up with an acceptable salt form. "These were some of the problems we had to solve after discovering lefamulin," Heilmayer says.

The team solved them, and by 2014, lefamulin had successfully completed Phase I and II clinical trials showing it was safe as well as effective in a small group of people with bacterial pneumonias.

Because the Vienna facility didn't operate under the good manufacturing practice standards required by the FDA, Heilmayer had hired the chemistry outsourcing firms Aptuit and Almac to produce the small quantities of active pharmaceutical ingredient (API) needed for those trials.

But Phase III clinical trials and, ultimately, commercialization would be a whole new ball game. New people, new outsourcing partners, and new money would be needed. The company hired a drug industry veteran as CEO and established a US subsidiary in Philadelphia where its clinical development team would be based. In 2015, Nabriva made an initial public offering of stock on the Nasdaq exchange.

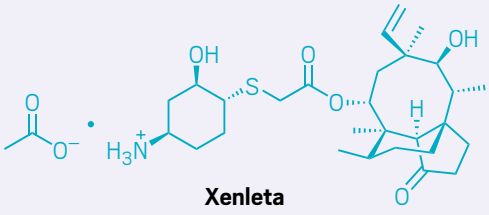
One of the new executives was Steven Gelone, who is now Nabriva's president and chief operating officer, responsible for business development and technical operations. Gelone was a good fit. Earlier in his career as an infectious disease clinician at GSK, he and his colleagues were stymied by Sandoz's robust intellectual property (IP) around pleuromutilin derivatives.

"We kept hitting roadblocks," he recalls. "We just could not solve the problem, in large part because the Sandoz/Novartis team, which ultimately became Nabriva, had an IP portfolio that blocked

> **"Whoever we chose, we had to be highly confident in, because we knew we weren't going to have a second supplier."**

Xenleta at a glance

- **Discovered:** 2006
- **US Food and Drug administration approved:** Aug. 19, 2019
- **European Medicines Agency approved:** July 28, 2020



Xenleta

- **Active ingredient:** Lefamulin
- **Indication:** Community-acquired bacterial pneumonia
- **Mode of action:** Binds to the peptidyl transferase center on the bacterial ribosome, interfering with protein production and impeding growth

Nabriva scientists Rosemarie Riedl (left) and Werner Heilmayer at the firm's facility in Vienna

us from doing some interesting chemistry on one of the key side chains." When Nabriva later offered Gelone a job, he couldn't say no.

Working with the Nabriva executives in the US, Heilmayer looked to secure firms that could manufacture the quantities needed under quality systems that would satisfy inspectors with the FDA and the European Medicines Agency. "Our desire was, as best we could as a small biopharma company, to create a gold-standard supply chain for this product," Gelone says.

The critical synthetic step in lefamulin production is combining pleuromutilin with the aminohydroxycyclohexyl side chain. Heilmayer and his team needed to find large-scale suppliers of pleuromutilin and a chiral building block for the side chain, and a company to join the two pieces into the API. It also needed firms to produce the tablet and intravenous forms of the drug.

For pleuromutilin, Nabriva executives thought they had it easy. Sandoz had pioneered the fermentation of pleuromutilin to produce the two animal antibiotics, and the firm was Nabriva's supplier during clinical development of lefamulin. But in 2014, Eli Lilly and Company acquired the Sandoz/Novartis animal health business. Suddenly, Nabriva was told to look elsewhere for pleuromutilin supply.

Heilmayer had to scramble to find a new company that could supply pleuromutilin at the required purity and with quality systems that would satisfy regulators. He soon settled on the Chinese firm SEL Biochem Xinjiang.

SEL is the world's largest producer of pleuromutilin, using it mainly for its own production of the animal antibiotic tiamulin, according to Grace Xu, a vice president at Zhejiang University Sunny Technology, which owns SEL. For Nabriva, SEL developed a special high-purity version using higher quality standards, Xu says.

For the side chain building block, a cyclohexene carboxylic acid, Nabriva first contracted with an Indian pharmaceutical chemical company, which made it for Nabriva's clinical trials. But because the intermediate is a liquid acid, it had to be shipped from India via sea rather than air, creating an unacceptably weak link in the supply chain, Heilmayer says. So, with approval and commercialization of lefamulin looking more and more likely, Nabriva sought an intermediate supplier closer to home.

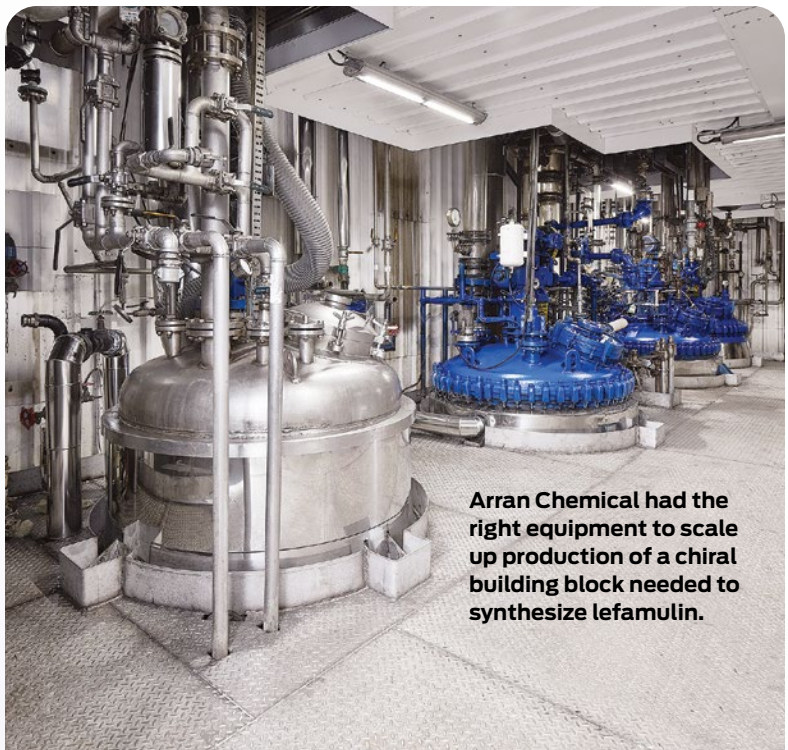
It ended up choosing the Irish firm Arran Chemical, which Almac acquired in 2015. Arran had the right capabilities and equipment, and Heilmayer was impressed that it was able to quote a price for the intermediate lower than what Nabriva paid the Indian firm.

Companies in Ireland have higher labor costs than do those in India, acknowledges Tom Moody, Almac's vice president of technology development and commercialization. To offset them, Arran drew on other strengths. "In Ireland we have to do things efficiently," he says.

Almac, which is based in Northern Ireland, acquired Arran during this period, mainly for its biocatalysis and API building block scale-up skills. Almac had worked with the Irish firm for more than a decade and wanted to bring those capabilities in-house, Moody says. The chiral building block contract with Nabriva was an intriguing sweetener, he adds, because Almac had produced the API in the early days of lefamulin development and formulated it into tablets for administering to patients during clinical trials.

To put the intermediates together into the final lefamulin molecule, Heilmayer and his team settled on the pharmaceutical services firm Hovione at its site in Cork, Ireland, just a 3-h drive from the site in Athlone, Ireland, where Arran makes the side chain.

In choosing Hovione, Nabriva weighed the usual factors of quality, technical fit, timing, and price. But underlying the individual considerations was the knowledge that, unlike a big drug company, Nabriva couldn't afford to hire a second supplier in case things went wrong. "Whoever we chose," Gelone says, "we had to be highly confident in, be-



Arran Chemical had the right equipment to scale up production of a chiral building block needed to synthesize lefamulin.

CREDIT: NABRIVA THERAPEUTICS (SCIENTISTS); ALMAC (FACILITY)

cause we knew we weren't going to have a second supplier when we launched lefamulin."

Hovione, a Portuguese firm, had acquired the Cork facility from Pfizer in 2009. At the time, the plant made only one API—atorvastatin, the active ingredient in Pfizer's cholesterol-lowering drug Lipitor. But by 2014, when Hovione and Nabriva started discussions, Hovione had succeeded in bringing new products to Cork, including several APIs, recalls Paul Downing, general manager of the site. Staffing at the facility had doubled since the acquisition to about 100.

By the time Nabriva and Hovione signed a contract in 2016, it was clear that lefamulin, now in Phase III studies, would need to be made on an accelerated schedule. Hovione typically developed synthetic methods for pharmaceutical chemicals at its pilot plant in Portugal and then produced initial quantities there before transferring the process to the commercial-scale reactors in Cork. "The timeline Nabriva required meant we had to skip the middle piece," Downing says.

Both parties knew that Hovione's job was more than just connecting two molecules. The cyclohexene carboxylic acid from Arran had to be taken through further chemical steps to form the aminohydroxycyclohexyl side chain that Riedl had conceived in 2006. And the hydroxyacetyl group on pleuromutilin has to be activated through an exchange of sulfur for oxygen to form a sulfanylacetyl linker that couples with the side chain.

"It seems simple, but it's actually a very long process that requires care and attention," says Rui Loureiro, Hovione's director of process chemistry development and the lead chemist on the development project. From start to finish, a production campaign takes about 2 months.

One area that called for special attention was phase separation. In lab tests of the reaction in Portugal, process chemists were surprised to find that three phases resulted, rather than the usual two. "We had to understand how you make sure in the plant that you take out the right phase of three phases," Loureiro says.

Another challenge was crystallizing and recrystallizing a molecule with multiple chiral centers. "That's how to ensure that you get the right isomers out of your reaction," Loureiro says.

The API that Hovione manufactures in Cork is the heart of Xenleta, but for people to take it, the white powder has to be turned into tablet and IV forms. For the tablet, Heilmayer turned to Almac again.

Nabriva had first hired Almac in the early 2010s to produce the lefamulin API for Phase I and II clinical trials. At the time, says Tommy Burns, an Almac project services manager, Nabriva took the logical next step in a good relationship and asked Almac's finished drug division to formulate the API into tablets.

Some years later, with clinical successes under its belt, Nabriva came back to Almac looking for tablet manufacturing and packaging for Phase III trials and commercial launch. "Nabriva needed a firm that could help overcome some of the development challenges they faced with the tablet," Burns says.

To be effective, lefamulin needs to be administered in high doses, and 600 mg is tough to squeeze into even a large tablet. Moreover, because the API is sticky, Almac was not able to create a traditional pill with the necessary on-dose product identifier embossed on the surface. Instead, Burns says, Nabriva and Almac worked together to develop a nonstandard pill for which the name is applied with an inkjet printer.

For vials of the drug for intravenous delivery, Nabriva contracted with Patheon's sterile liquid production facility in Monza, Italy. It also tapped Fresenius Kabi's sterile liquid contract manufacturing facility in Halden, Norway, to produce special companion IV bags to which the sterile drug is added.

As Gelone explains, Nabriva scientists realized early in the development of lefamulin that its pH in solution is important and should be maintained. They worked with Fresenius on a bespoke IV bag they created by adding a citrate buffer to the conventional saline bags made in Halden. When a health-care professional pours a vial of Xenleta into the bag, the resulting solution is close to physiologic pH, Gelone says.

In the end, producing and distributing Xenleta requires a supply chain that stretches from China to multiple sites in Europe and, ultimately, the US. Nabriva took the risk of assembling it without knowing if regulators would actually clear the drug, but the bet paid off. The FDA approved Xenleta on Aug. 19, 2019.

"We had the product in the channel and ready for patients 16 days after approval," Gelone says.

Marketing

Nabriva's manufacturing partners continue to refine their processes. At Hovione, for example, Loureiro is eager to develop continuous solvent

CREDIT: NABRIVA THERAPEUTICS

Nabriva hired Hovione to join lefamulin's two key intermediates at this facility in Cork, Ireland.

extraction to decrease the amount of solvent required to recover the API. By his calculation, lefamulin generates 3% less waste than the typical API, but he says Hovione can cut waste further. "We believe there is space to improve the process."

And Burns says Almac is moving the granulation process for Xenleta tablets from pilot to commercial scale. Once the switch is complete, Almac's capacity to manufacture the pills will be markedly higher.

But even as Nabriva's partners streamline production, healthy demand for Xenleta is far from a sure thing.

In the past few years several biotech firms have won FDA approval of new antibiotics that are effective against resistant bacteria, only to find physicians and hospitals reluctant to prescribe them. In 2019 alone, three small antibiotic firms—Melinta Therapeutics, Aradigm, and Achaogen—all declared bankruptcy.

Public health experts say doctors and hospitals need new medicines to fight antibiotic-resistant infections, yet the companies that invent them too often find few customers.

"One of the conundrums that's very unique for anti-infectives is the strong desire to have innovation available but not wanting to use that innovation for fear you're going to ruin it by creating resistance," Gelone says. The health-care community thus thoroughly reviews the differentiating characteristics of a new antibiotic to understand the patients for which it is best suited. "I've run the committees that do it, and the process takes time," he says.

Nabriva contends that Xenleta falls in the right place. Pleuromutilin antibiotics, the firm says, have a lower propensity for resistance than most established antibiotics because they bind to bacterial ribosomes in a unique way and via multiple interactions. And lefamulin has the advantage of being approved in both IV and oral forms, meaning it has the potential to be administered first in a hospital and later at home.

New antibiotics aren't going to be billion-dollar-a-year drugs, Gelone acknowledges. "There has to be a perceived unmet medical need that the physician community believes this product will address," he says. "That's where lefamulin fits in."

Nabriva is finding the process of fitting in to be slow. In April, the company announced that it is laying off its hospital-oriented sales force of 66 people, more than a third of its overall staff. Nabriva described the decision as part of a new strategy of focusing on community health-care professionals. Restrictions on interacting with hospital personnel during the coronavirus pandemic also played a role in the layoffs.

On Aug. 6, Nabriva reported that it had Xenleta sales in the first half of 2020 of only about $100,000. The firm had earlier disclosed that it was in danger of being delisted from the Nasdaq stock market because its shares were trading for less than $1.00. In early 2017 they were changing hands for more than $12.50.

Still, Gelone is optimistic. On July 28, European regulators approved the marketing of Xenleta in the European Union following review by the European Medicines Agency. The drug was also approved in Canada, and Nabriva is working with its partner in China, Sinovant, on approval there. He notes that Xenleta could play a role in treating people infected with the novel coronavirus who also have contracted pneumonia.

In Vienna, Heilmayer and Riedl remain proud of what Nabriva has accomplished. Heilmayer wonders if a larger company would have stuck with the compound through the tougher moments. "They establish certain thresholds, and if you don't achieve these thresholds, the compound is gone," Heilmayer says of big drug firms. "In the biotech world, if you have a challenge you will always look for ways to overcome it."

Today, Heilmayer and Riedl are tackling new challenges. Heilmayer continues to work with Nabriva's outsourcing partners to support and troubleshoot Xenleta manufacturing. In one recent program, they elucidated and synthesized a new impurity encountered during large-scale API manufacturing.

As for Riedl, she and her colleagues are working on next-generation pleuromutilin antibiotics as well as other projects that she is keeping close to the vest. "Stay tuned for the next molecules from Nabriva," she says. ■

This article is reprinted with permission from C&EN. A version of this article was published in C&EN on June 22, 2020, on page 30.

CREDIT: HOVIONE

AI looks for possible antibiotics

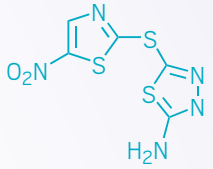
SAM LEMONICK, C&EN STAFF

Antibiotic drugs have been around for less than a century, but the rise of drug-resistant bacterial strains and a dearth of new antibiotics reaching the clinic in recent decades threaten to undermine our ability to beat deadly infections. Using a combination of machine learning and experimentation, researchers say they've identified several molecules that may be effective antibiotics (*Cell* 2020, DOI: 10.1016/j.cell.2020.01.021). Experts applaud the computational approach but say these compounds are not likely to be the drugs we need.

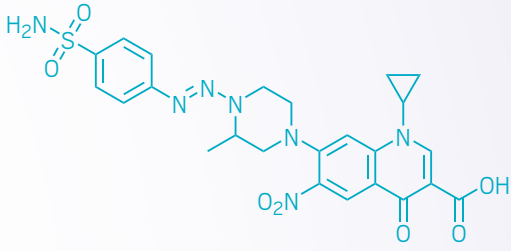
Because bacteria have evolved resistance to some of the most common antibiotics, scientists want to find molecules or structural features that can kill microbes in new ways. Computational chemist Regina Barzilay and bioengineer James J. Collins, both of the Massachusetts Institute of Technology, and colleagues put their heads together and designed a machine-learning approach to find new antibiotics. They trained their algorithms to recognize structural features of different molecules—not just antibiotics—and to predict whether a given structure will inhibit *Escherichia coli* growth.

The researchers found a molecule that they named halicin in the Drug Repurposing Hub, a database of about 6,000 molecules known to be useful against various diseases. The molecule inhibits the enzyme c-Jun N-terminal kinase, which is a target for cancer and other diseases. In mice, halicin treated *Acinetobacter baumannii*–infected skin wounds and *Clostridioides difficile* gut infections. The group also used the machine-learning algorithm to search 100 million molecules from the ZINC15 database and found eight potential antibiotics, including ZINC000100032716, but did not follow up the search with lab tests.

The results show "how much can be achieved when skilled practitioners and machine-learning teams work together," says Günter Klambauer, who leads an artificial intelligence drug discovery lab at Johannes Kepler University. But he criticized the group for training its algorithms on only a couple thousand molecules and looking for just a few biological effects, saying the model could have been stronger with broader training that considered multiple effects.



Halicin



ZINC000100032716

> **It is quite easy to kill bacteria, even the tough ones, with toxic agents—and quite easy to find those.**

Antibiotics experts also praised the group's methods but were unimpressed by halicin, with some arguing that the compound is not the kind of antibiotic doctors need. The nitroaromatic group in the molecule resembles structures in known broad-spectrum antibiotics, and that suggests that how the researchers trained the algorithm was too limited and didn't allow the program to find truly novel structures. Collins says it's fair to point out their molecules' similarities to existing antibiotics but stresses that one of the major values of machine learning is its speed in searching for antibiotic-like molecules. It took their model about 4 days to evaluate more than 100 million molecules.

Several experts questioned whether the group's toxicity predictions were sufficient. "It is quite easy to kill bacteria, even the tough ones, with toxic agents—and quite easy to find those," says antibiotic expert Lynn Silver, who worked at Merck & Co. for 2 decades. But finding drugs is much harder, she says: "Even well-studied antibacterials fail in clinical trials due to toxicity."

Collins says the group is looking to establish partnerships to continue the preclinical evaluation of halicin and the other molecules.

This article is reprinted with permission from C&EN. A version of this article was published in C&EN on March 2/9, 2020, on page 10.

READING LIST

Our picks of the patent and journal literature on antimicrobial resistance and antibiotics

2020

» Theriault, Nicolette, Glenn Tillotson, and Christian E. Sandrock. **"Global Travel and Gram-Negative Bacterial Resistance; Implications on Clinical Management."** *Expert Rev. Anti-Infect. Ther.* (Sept. 9, 2020). https://doi.org/10.1080/14787210.2020.1813022.

» Vaughn, Valerie M., Tejal Gandhi, Lindsay A. Petty, Payal K. Patel, Hallie C. Prescott, Anurag N. Malani, David Ratz, et al. **"Empiric Antibacterial Therapy and Community-Onset Bacterial Co-Infection in Patients Hospitalized with COVID-19: A Multi-Hospital Cohort Study."** *Clin. Inf. Dis.* (Aug. 21, 2020): ciaa1239. https://doi.org/10.1093/cid/ciaa1239.

» Taormina, Gillian, Joseph Campos, John Sweitzer, Adam C. Retchless, Kristy Lunquest, Lucy A. McNamara, Natashia Reese, Maria Karlsson, and Benjamin Hanisch. **"β-Lactamase–Producing, Ciprofloxacin-Resistant *Neisseria meningitidis* Isolated from a 5-Month-Old Boy in the United States."** *J. Pediatr. Infect. Dis. Soc.* (Aug. 3, 2020): piaa085. https://doi.org/10.1093/jpids/piaa085.

» Mercer, Derry K., Marcelo D.T. Torres, Searle S. Duay, Emma Lovie, Laura Simpson, Maren von Köckritz-Blickwede, Cesar de la Fuente-Nunez, Deborah A. O'Neil, and Alfredo M. Angeles-Boza. **"Antimicrobial Susceptibility Testing of Antimicrobial Peptides to Better Predict Efficacy."** *Front. Cell. Infect. Microbiol.* 10 (July 7, 2020): 326. https://doi.org/10.3389/fcimb.2020.00326.

» Huijibers, Patricia M.C., D.G. Joakim Larsson, and Carl-Fredrik Flach. **"Surveillance of Antibiotic Resistant *Escherichia coli* in Human Populations through Urban Wastewater in Ten European Countries."** *Environ. Pollut.* 261 (June 2020). https://doi.org/10.1016/j.envpol.2020.114200.

2019

» Danner, Marie-Claire, Anne Robertson, Volker Behrends, and Julia Reiss. "**Antibiotic Pollution in Surface Fresh Waters: Occurrence and Effects.**" *Sci. Total Environ.* 664 (May 10, 2019): 793–804. https://doi.org/10.1016/j.scitotenv.2019.01.406.

» Abouelhassan, Yasmeen, Aaron T. Garrison, Hongfen Yang, Alejandra Chávez-Riveros, Gena M. Burch, and Robert W. Huigens III. **"Recent Progress in Natural-Product-Inspired Programs Aimed to Address Antibiotic Resistance and Tolerance."** *J. Med. Chem.* 62, no. 17 (April 5, 2019): 7618–42. https://doi.org/10.1021/acs.jmedchem.9b00370.

» Tyers, Mike, and Gerard D. Wright. "**Drug Combinations: A Strategy to Extend the Life of Antibiotics in the 21st Century**" *Nat. Rev. Microbiol.* 17, no. 3 (Jan. 25, 2019): 141–55. https://doi.org/10.1038/s41579-018-0141-x.

» Gupta, Akash, Shazia Mumtaz, Cheng-Hsuan Li, Irshad Hussain, and Vincent M Rotello. **"Combatting Antibiotic-Resistant Bacteria Using Nanomaterials."** *Chem. Soc. Rev.* 48, no. 2 (Jan. 21, 2019): 415–27. https://doi.org/10.1039/C7CS00748E.

» Folgori, Laura, and Julia Bielicki. **"Future Challenges in Pediatric and Neonatal Sepsis: Emerging Pathogens and Antimicrobial Resistance."** *J. Pediatr. Intensive Care* 8, no. 1 (March 2019): 17–24. https://doi.org/10.1055/s-0038-1677535.

» Idorsia Pharmaceuticals. "**Substituted 1,2-Dihydro-3H-pyrrolo[1,2-c]imidazol-3-one Antibacterial Compounds.**" US Patent 10,314,823, filed Sept. 2, 2016, and issued June 11, 2019.

2018

» Wang, Xuejiao, Yuxin Liu, Yiyang Lin, Yuchun Han, Jianbin Huang, Jing Zhou, and Yun Yan. **"Trojan Antibiotics: New Weapons for Fighting Against Drug Resistance."** *ACS Appl. Bio Mater.* 2, no. 1 (Dec. 18, 2018): 447–53. https://doi.org/10.1021/acsabm.8b00648.

» Maier, Lisa, Mihaela Pruteanu, Michael Kuhn, Georg Zeller, Anja Telzerow, Exene Erin Anderson, Ana Rita Brochado, et al. **"Extensive Impact of Non-Antibiotic Drugs on Human Gut Bacteria."** *Nature* 555, no. 7698 (March 19, 2018): 623–28. https://doi.org/10.1038/nature25979.

» Tacconelli, Evelina, Elena Carrara, Alessia Savoldi, Stephan Harbarth, Marc Mendelson, Dominique L. Monnet, Céline Pulcini, et al. **"Discovery, Research, and Development of New Antibiotics: The WHO Priority List of Antibiotic-Resistant Bacteria and Tuberculosis."** *Lancet Infec. Dis.* 18, no. 3 (March 1, 2018): 318–27. https://doi.org/10.1016/S1473-3099(17)30753-3.

2017

» Bristol Myers Squibb Company. **"Compounds Useful as Immunomodulators."** US Patent 9,850,225, filed April 8, 2015, and issued Dec. 26, 2017.

Note: This list was chosen by experts who work in the field, CAS information scientists, and C&EN editorial staff.

ACS
Chemistry for Life®

American Chemical Society

ACS INDUSTRY MEMBER PROGRAMS

help you stay connected to a vibrant community of industry scientists committed to advancing the field of chemistry.

SUBSCRIBE TO THE **ACS INDUSTRY MATTERS NEWSLETTER**

Featuring exclusive ACS interviews with chemical industry executives, career consultants, and other industry leaders who provide valuable insights to help industrial chemists advance their careers.

Preview Industry Matters Content & Subscribe at acs.org/industrynl

ADVANCE WITH ACS CAREER SERVICES

ACS Career Navigator™ helps you stay competitive and advance in your career with personal career consulting, professional education, leadership training, and much more. ACS members get exclusive access to course discounts, an industry salary calculator, and a curated chemistry job board.

Explore resources at acs.org/cnavigator

JOIN THE **ACS INNOVATION HUB LINKEDIN GROUP**

Connect, collaborate, and stay informed about the trends leading chemical innovation, with content and conversation curated by ACS.

Join at bit.ly/ACSinnovationhub

Visit acs.org/industry for more from ACS Industry Member Programs


Download a copy of this
and future reports at
www.acs.org/discoveryreports