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In The Pipeline

September 2016



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Michael Eisenstein

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MANY ROADS TO THE CLINIC

Michael Eisenstein

THE DRUGS highlighted in this annual C&EN supplement were not selected simply because they were potential billion-dollar blockbusters for their manufacturers—although some of them will be. Instead, this year's Top 40 list was chosen to highlight progress in producing potent therapies for hard-to-treat diseases, transforming new technologies into effective medicines, and tackling urgent public health problems. In short, the drugs highlighted in this supplement were selected because they offer a snapshot of the exciting and innovative science now being done in the realm of clinical research and pharmaceutical development.

Therapeutic antibodies have proven their mettle many times in the past few decades—indeed, five of the ten best-selling drugs from 2015 were antibodies—and these also represent some of the most anticipated agents in the current pipeline. For example, Regeneron and Sanofi's dupilumab offers a far safer and more effective alternative to the potent and toxic immunosuppressant drugs that are currently used to treat severe cases of eczema. Migraine sufferers are anticipating a new road to relief as well, with four different monoclonal-based drugs all demonstrating strong performance in reducing the frequency and duration of headaches.

It can take considerable time for innovations forged in the laboratory to reach patients, and several of the treatments on our roster represent important progress on that front. For example, multiple clinical programs are vying to become the first gene therapy to win approval from the FDA. BioMarin's BMN-270 has demonstrated the potential to normalize clotting in patients with hemophilia A, and the company is hoping to file for accelerated approval next year. This year will also see the first two clinical trials for therapies based on CRISPR/Cas9-mediated gene editing—a remarkable feat, given that the technology has only been in use for around five years.

Researchers are also looking for new targets against old foes. Efforts to develop drugs that delay or halt Alzheimer's by targeting amyloid- β have proven disappointing, but pharma companies are looking for other routes to prevent the accumulation of these neurotoxic protein plaques. Multiple different compounds targeting the β -secretase enzyme (BACE), which is responsible for amyloid- β processing, are now in late-stage clinical trials. Strong preclinical data offer signs of hope—especially if the drugs are given to patients early, before the neurological symptoms of Alzheimer's begin to manifest.

Other drugs on the roster reveal the potential to find effective treatments in seemingly unlikely places. For example, ketamine—generally best known as a veterinary anesthetic and club drug—continues to dazzle psychiatrists and neuroscientists with its capacity to quickly and durably treat the symptoms of major depression, even in patients who fail to respond to existing antidepressants. Several variants of this drug are now in clinical development, that appears to confer all the clinical benefits without the unwanted psychotropic side effects. Similarly, GW Pharmaceuticals has achieved success in treating various forms of pediatric epilepsy with cannabidiol, a compound derived from marijuana that lacks the intoxicating effect of its parent plant.

Vaccine and antibacterial drug development has generally not received the attention it deserves, but this list also recognizes ongoing efforts to bolster the public's defenses against imminent infectious threats. For example, potent new antibiotics such as Achaogen's plazomicin and Shionogi's S-649266 would represent much needed additions to our arsenal for fighting the 'ESKAPE' pathogens—a fearsome cohort of bacterial pathogens that have evolved resistance to many standard drugs. The global research community has also mustered a strong, unified response to the Zika virus, with two vaccine candidates already in clinical trials.

We hope that this supplement offers an interesting and informative window onto the current state of the drug discovery world. If you liked what you saw, or think that we missed something important, please send us a note at CENsupplements@acs.org. Thanks for reading! ■

Michael Eisenstein is a freelance writer and C&EN contributing editor, based in Philadelphia.

TOP 40 DRUGS IN THE PIPELINE



A new wave of antibody-based therapeutics promises to reduce the frequency and duration of headaches for many migraine sufferers.

1. CGRP INHIBITORS

Various companies

Migraine

The fact that there was a time when migraine sufferers would gladly have holes drilled into their skull as treatment says something about their desperation for relief from debilitating headache pain. The modern medical world has thankfully abandoned this treatment, but patients are still stuck with limited options. With the exception of tryptamine-based 'triptans', there are virtually no drugs specifically developed for migraine treatment, and many go entirely without relief. "I would suggest that about 30-40% of patients either cannot tolerate the current standard of care, cannot use it, or it just doesn't work," says Stephen Silberstein, a neurologist specializing in migraine treatment at Thomas Jefferson University.

More than three decades of research into a signaling pathway with an apparently central role in migraine headaches have now culminated in the development of a quartet of effective antibody-based drugs. ALD403 from **Alder Biopharmaceuticals**, TEV-48125 from **Teva Pharmaceuticals** and galcanezumab from **Eli Lilly** each bind and inhibit the calcitonin-gene-related peptide (CGRP),

whereas **Novartis** and **Amgen's** erenumab works by blocking this protein's primary receptor, CGRP1R. CGRP was initially discovered in 1983 and appears to be an important mediator of pain signaling in both the peripheral and central nervous system. However, the details of CGRP function remain poorly understood. "It's a black box—a big mystery," says Silberstein. "All we really know is that CGRP levels go up during a migraine attack, if you induce CGRP it triggers a headache, and if you block CGRP the headache goes away."

This rudimentary knowledge has been sufficient to drive considerable interest in this pathway as a target for drug development. The first generation of therapeutics included a potent small-molecule inhibitor of the CGRP receptor developed by **Merck**. Telcagepant proved effective at preventing and relieving headaches, but the program was subsequently terminated due to concerns over possible liver toxicity. This setback tempered enthusiasm for this class of drugs, according to Silberstein. "The question was whether it was related to the mechanism or whether it was related to the backbone," he

says. More recently, **Allergan** acquired two other small-molecule receptor antagonists developed by Merck, which differ structurally from telcagepant and have not raised any alarms in Phase I or II testing to date.

Nevertheless, the immediate future of migraine therapy appears to lie with antibodies. In June, Amgen presented preliminary Phase II data showing that erenumab had met its endpoint for migraine prevention, reducing the number of monthly days in which patients experienced headaches by 2.4 days relative to placebo. The company anticipates having data from the drug's Phase III trial later this year. Alder also released successful Phase II data this summer, showing that a single dose of ALD403 is effective at delivering a 75% reduction in migraine symptoms relative to placebo, with a pivotal study now underway. Likewise, Teva is currently recruiting for a Phase III of TEV-48125, following the conclusion of two successful Phase II trials showing that their treatment meaningfully reduced both the number and duration of migraine events over the course of a given month. Lilly is also catching up with the others after some delays in its galcanezumab program, following on solid Phase II data.

Regardless of which drug is first to market, patients will be the winners. "I've worked with all of the antibodies, and they appear to be safe and effective, have no major side effects, and they work quite quickly," says Silberstein. In fact, a subset of 'super-responder' patients respond disproportionately well to such treatment. For example, 16% of the patients receiving ALD403 in the drug's recent Phase II trial experienced no migraines during the entire span of the study, whereas no patients in the placebo arm enjoyed the same degree of relief. But as with many aspects of CGRP physiology, the roots of this response remain enigmatic for now.

The biggest open questions in Silberstein's mind are cost—biologic drugs are pricey, and these will regularly be taken for the rest of a patient's life—and long-term safety issues. The drugs appear safe thus far in both preclinical animal studies and human trials, but CGRP is involved in numerous biological processes outside the nervous system, and the broader consequences of tinkering with this signaling cascade remain poorly defined. But for now, he sees the drugs as a likely game-changer. "I'm extremely enthusiastic, there's no question," he says. ■

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The abundance of disease-spreading mosquitoes in tropical and subtropical climates has created the opportunity for a far-reaching pandemic—and this in turn is fueling the race to develop an effective vaccines.

2. ZIKA VACCINES

Various companies

Zika virus

The good news about Zika is that scientists in industry, academia, and government laboratories have mobilized with remarkable rapidity to develop effective countermeasures. More than a dozen vaccine programs have already been announced, with the first clinical trial already in the works and other efforts following close behind. “I think that over the past ten months, the response to Zika has been coordinated quite well in comparison with past outbreaks,” says Pei-Yong Shi, a virologist at the University of Texas Medical Branch.

On the flip side, scientists have been forced to develop their own crash course in Zika biology on the fly, with little known about viral transmission and pathology. The virus was initially identified in Uganda in the 1940s but attracted little interest until it was already on the verge of becoming a crisis. “In total, there were only 13 or 14 documented human infections within the first 60 years—and then all of a sudden, within the past ten years, it became explosive,” says Shi. Precisely how this happened remains a mystery.

Fortunately, Zika has well-studied relatives within the larger family of RNA-based flaviviruses, and the research community has accrued considerable experience in developing vaccines

for such pathogens. For example, robust vaccines have been developed against yellow fever, Japanese encephalitis and, most recently, dengue fever. Common structural features among these viruses could be informative for vaccine developers, but Shi notes that there are also critical differences. For example, like Zika, the West Nile and Japanese encephalitis flaviviruses preferentially infect neurons, but Zika is unique among this viral family in its association with the fetal developmental defects that result in microcephaly. Indeed, the fact that the virus is of greatest risk to this vulnerable population of pregnant women and their unborn children raises yet-unanswered questions regarding which is the safest way to deliver effective immune protection.

The most advanced program at present is from **Inovio Pharmaceuticals** and **GeneOne Life Science**. Inovio’s is a DNA-based vaccine, which encodes a protein found on the surface of the Zika virus; after injection, the DNA is taken up by cells, which produce the protein and thereby train immune cells to recognize the virus. In July, the company initiated the first clinical trial for its GLS-5700 vaccine, which elicited a robust immune response in preclinical studies with both rodents and nonhuman primates. In support of this approach, research-

ers led by Dan Barouch at the Ragon Institute of MGH, MIT, and Harvard have developed an alternative DNA vaccine that provided robust protection in mice against infection by a Zika isolate derived from human patients in Brazil.

Barouch's group obtained similar results with a second vaccine, derived from inactivated Zika particles. This approach will now be developed further by **Sanofi Pasteur**, in partnership with Barouch's collaborators at the Walter Reed Army Institute of Research. These two organizations have previously worked together on a vaccine against dengue, and Sanofi notes that they have built up a considerable infrastructure for performing vaccine studies in Latin America—the current epicenter for the Zika outbreak. **Bharat Biotechnologies** and **Valneva** have also developed inactivated virus-based vaccine approaches, and **NewLink Genetics** is reportedly pursuing a similar program.

In principle, these strategies should all be relatively safe—neither DNA nor a 'dead' virus can replicate or infect cells. However, Shi also sees important trade-offs. "The immune response will not be as robust in many ways, and the immune memory will not be as long as you would wish for," he says. "Usually with those vaccines you need to boost them, which means that you have multiple shots over a few years." An alternative is to elicit a more 'natural' immune response with a live,

attenuated vaccine, which resembles a normal, replicating Zika virus but has been crippled to prevent it from causing cellular damage. For some experts, this approach raises concerns about accidentally triggering disease or an overly-aggressive immune response, and the bar for demonstrating safety is likely to be much higher. On the other hand, it may be the best way to get rapid, enduring protection. "Usually, one shot can protect you for the rest of your life," he says, pointing out the live attenuated yellow fever vaccine as an example.

Shi and colleagues have developed a powerful tool in this effort—a synthetic Zika genome, which they can use to produce and test live viruses with specific genetic modifications. In principle, this should allow them to home in on replication-competent but nonpathogenic variants. "We are taking advantage of the rich experience in live attenuated vaccines in flaviviruses and trying to look at and learn from those," he says. The National Institute of Allergy and Infectious Disease (NIAID) recently collaborated with Brazil's Butantan Institute to develop an effective live-attenuated vaccine for dengue, and aims to pursue a similar program for Zika as well.

For now, Shi points out that scientists still know far too little to confidently predict which strategy will pay off first, and casting a broad net seems the best solution. "At this point, all of these different approaches need to be encouraged in parallel," he says. ■



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Many people with severe depression do not benefit from current drugs, but ketamine could provide rapid and lasting relief for these treatment-resistant patients

3. KETAMINE

Johnson & Johnson

Depression and other mood disorders

Patients grappling with clinical depression must often go through a laborious trial-and-error process to identify a medication that works for their disorder—and for up to one-third, that search will ultimately end in disappointment. For these ‘treatment-resistant’ patients, the outlook has remained bleak. “For 50-plus years, people have been trying to find a new target or mechanism, in both academia and industry, but you usually end up with these me-too kind of drugs based on serotonin or norepinephrine,” says Carlos Zarate, Jr., chief of experimental therapeutics and pathophysiology branch at the National Institute of Mental Health (NIMH). “They’re alternatives, but not clearly superior to one another in terms of efficacy.”

Over the past decade, however, Zarate has been working extensively with ketamine—a compound that he believes could potentially prove transformative for treatment-resistant depression. Unlike conventional antidepressants, which require weeks or months to effect change, ketamine can act within days or even hours. Furthermore, it can address a whole constellation of mood-related symptoms beyond conventional depression.

“There also anti-suicidal ideation effects, anxiolytic effects and effects against anhedonia,” says Zarate. “And all of these things happen really rapidly.”

Ketamine is not new; it was discovered in 1962 and has been in use as a standard anesthetic and sedative in both veterinary and clinical settings since the 1970s, while also achieving notoriety as a popular drug in the club scene. But the exploration of its psychiatric effects only began at the start of the new millennium, with a small study in seven patients demonstrating meaningful improvements in major depression symptoms after a single injection of ketamine, with effects lasting as long as two weeks.

Within the brain, ketamine binds and inhibits the *N*-methyl-D-aspartate (NMDA) receptor, which normally responds to the neurotransmitter glutamate. NMDA signaling is known to play a prominent role in learning and memory, and the abuse of ketamine can have amnesia-inducing effects. The involvement of NMDA in mood and depression is murkier, but numerous other clinical trials have consistently borne out the initial finding

that ketamine rapidly and durably treats many patients who have previously slipped the therapeutic net. One recent analysis of three clinical trials found that two-thirds of the participants achieved a greater than 50% improvement in their symptoms, with side effects that were largely manageable. Particularly promising is ketamine's potential for averting suicide, and clinical studies have shown that the drug can durably control the onset of suicidal thoughts in some patients. "If you can nip it in the bud, you might prevent the behavior from happening," says Zarate, adding that this aspect of ketamine neuropharmacology might help home in on the biological roots of suicidal behavior.

Although ketamine itself is generic, **Johnson & Johnson** has a proprietary version in its clinical pipeline. Ketamine naturally occurs in two mirror-image chemical forms, known as the (R) and (S) enantiomers; Johnson & Johnson has developed a pure formulation of the (S) version, which binds more strongly to the NMDA receptor than the (R) version, under the name esketamine. One potential advantage of their formulation is that it is delivered intranasally, rather than intravenously, making administration much more patient-friendly. Prior studies of such formulations have shown that they can be fast-acting and effective against depression, although no head-to-head comparison against intravenous administration has been published as of yet. Johnson & Johnson currently has a Phase III trial underway.

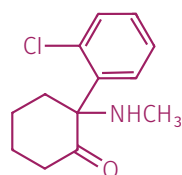
Other companies are exploring nonketamine drugs that still target the NMDA receptor. For example, **Allergan's** rapastinel, which received a Breakthrough Therapy designation from the FDA at the start of 2016, demonstrated the capacity to reduce symptoms of depression for up to a week in a randomized controlled trial. Early clinical data have also shown some promise for *D*-cycloserine, which delivered a meaningful reduction of symptoms in more than half of the patients treated. This compound is currently being developed by Israeli start-up **NeuroRx**, in a formulation that combines it with the antidepres-

sant lurasidone. The company has announced its intention to launch a Phase II/III trial at some point in 2016. On the whole, however, NMDA receptor has yet to prove a fruitful target—one recent review of the published clinical data cited the "ineffectiveness" of most such drugs, with the exception of rapastinel and *D*-cycloserine.

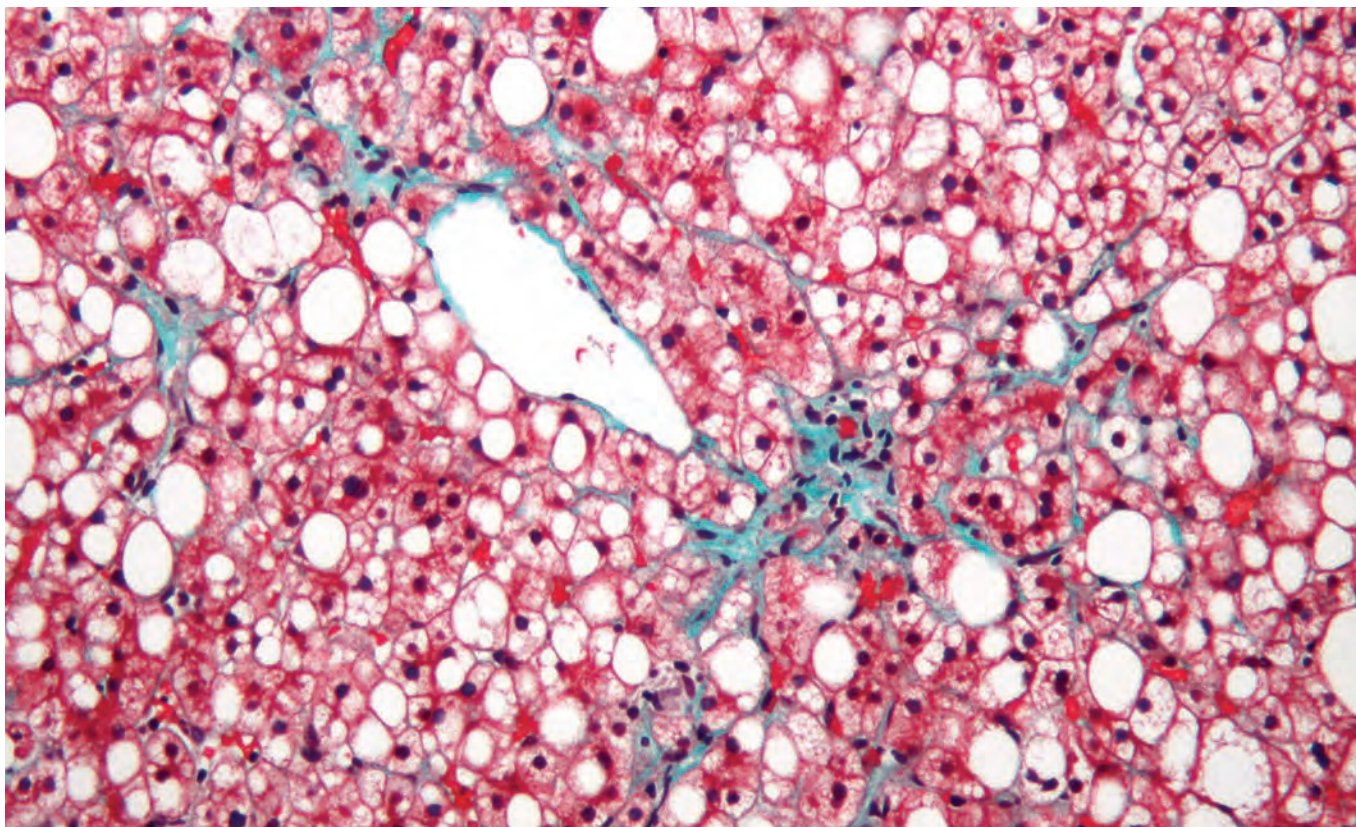
Findings from a recent paper from *Nature* could help explain this. Working with Todd Gould's team at the University of Baltimore, Zarate and colleagues found compelling evidence that ketamine's mood-altering effects are caused by a metabolite of the drug known as hydroxynorketamine (HNK), and are apparently completely independent of the drug's interactions with the NMDA receptor. Instead, HNK seems to act on an alternate glutamate receptor known as the AMPA receptor to exert its depression-modulating effects. If these results translate to

humans, it could form the foundation for a drug that matches ketamine's beneficial effects but without the negative cognitive effects associated with NMDA modulation. Zarate, Gould and colleagues are now hard at work to confirm this. "We've been working on ADME, we've been doing toxicology studies ... everything we can so we can get into humans next year," says Zarate.

In the meantime, the compelling data on ketamine continue to accrue—albeit slowly. "We need larger studies," says Zarate. The clinical community clearly likes what it sees, however, and off-label prescribing is now widespread, with numerous physicians around the country currently dispensing ketamine to patients in need. "There are over a dozen clinics in New York alone ... and there's probably a lot of use that people aren't talking about," says Zarate. Although concerned about the lack of clear prescription guidelines and standards, he is hopeful that clarity will emerge in the near future—particularly if a commercial formulation like esketamine wins FDA approval. "I'm very excited about how quickly the field is moving," he says. ■



Ketamine



The progressive liver damage caused by nonalcoholic steatohepatitis (NASH) has become a leading cause for liver transplants, and many companies are pursuing drugs to halt or reverse the damage.

4. NASH THERAPEUTICS

Various companies

Nonalcoholic steatohepatitis

Twenty-five years ago, it wasn't even on clinicians' radar. Today, nonalcoholic steatohepatitis (NASH) is a battleground for multiple drugs hoping to secure a piece of what some analysts see as a \$35 billion market. According to Arun Sanyal, a professor of gastroenterology and hepatology at Virginia Commonwealth University, the story of NASH began in the 1990s. "Doctors saw that there was an increasing number of people who were coming in with fatty liver disease," says Sanyal. "It was a little bit of a medical curiosity, and nobody knew what it actually was." Over the course of the next few decades, he and other researchers would learn that this condition was closely linked to obesity and diabetes. As the body produces excess levels of fat, the steady build-up of triglycerides in the liver gradually induces cell death, fibrotic scarring and inflammation, which can ultimately give rise to cirrhosis or liver cancer. "There's data now that this is headed toward becoming the leading indication for liver transplant in the US," says Sanyal.

He credits the National Institutes of Health with moving quickly to tackle this newly-identified condition, establishing the NASH Clinical Research Network in 2001 to accelerate the development of new therapies. Today, there are dozens of compounds under clinical development, several of which are in or approaching pivotal trials for treating various aspects of NASH.

One front-runner is obeticholic acid (Ocaliva) from **Intercept Pharmaceuticals**, a drug which won FDA approval for another liver indication, primary biliary cholangitis. Obeticholic acid activates a protein called farnesoid X receptor (FXR), triggering a series of physiological responses that can potentially mitigate NASH progression, including the inhibition of inflammation, fibrosis, and fatty acid production. Its efficacy proved robust enough to support early termination of the Phase II FLINT trial following interim data analysis. "It looks very promising from a liver point of view," says Sanyal. "The FLINT trial also showed that there is a reduction of scarring and fibrosis, which is very encouraging because this informs progression to cirrhosis." However, he also

notes some adverse effects, including severe itching and depletion of healthy LDL cholesterol, although the long-term risks remain to be clarified. The drug is currently in Phase III testing, but Sanyal notes that several other agents with similar mechanisms are also making their way through the pipeline. “If they are true FXR agonists and do not have these side effects, then they could be very attractive molecules,” he says.

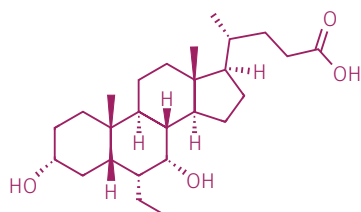
Genfit’s elafibranor goes after an entirely different target, a pair of signaling proteins called peroxisome proliferator-activated receptor (PPAR)- α and $-\delta$, as a means to reduce inflammation and modulate lipid metabolism. A Phase II trial for this drug offered a mixed bag, according to Sanyal. “They did not meet their primary endpoints in the Phase II trial, but a reanalysis found there was a signal that there might be some efficacy,” he says. The newer data suggest that the drug may indeed be beneficial for patients with higher levels of disease activity, and could also reduce the risk of cardiovascular and metabolic complications associated with NASH. The company’s hopes for this drug are now pinned to the results from an ongoing pivotal trial.

Tobira has been looking for a silver lining after failing to meet the primary endpoint in a Phase II trial for its drug, cenicriviroc. Cenicriviroc targets immune signaling as a means to control inflammation but did not manage to meaningfully control disease activity in patients. However, the drug does appear to have a significant impact on liver fibrosis, and Tobira is playing up this drug effect as it prepares to move forward with a Phase III in spite of their apparent Phase II setback.

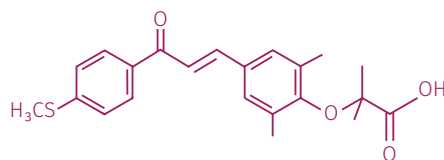
Over the past five years, **Gilead Sciences** has invested heavily in this indication. The company’s most advanced program is a monoclonal antibody called simtuzumab, targeting a protein that contributes to the process of fibrosis. The drug is in the midst of multiple Phase II trials for NASH, although a recent failed trial in idiopathic pulmonary fibrosis may be cause for concern. However, the company has other irons in the fire. These include an alternative FXR agonist, which is currently in Phase II, and a collection of drug candidates that the company acquired from **Nimbus Therapeutics** in a billion-dollar deal. One of these agents, NDI-010976, is particularly intriguing—it was designed via a computational chemistry strategy as an inhibitor for

an enzyme that plays a critical role in the synthesis of fatty acids within the liver. “Reducing de novo lipogenesis alone probably will not have a huge impact, simply because there’s lots of fat from the periphery that’s being dumped into the liver,” says Sanyal. “But in combination with other compounds, reducing the amount of fat would be useful, and there may be some other not-so-obvious potential benefits.” For example, signals triggered by elevated lipid production appear to be an important trigger for late-stage NASH pathology.

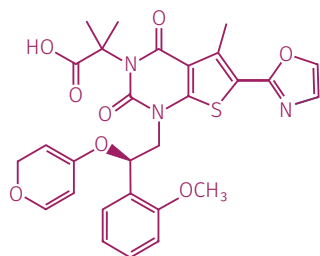
Without question, NASH appears to be a big enough pie for many companies to have a slice, and Sanyal believes that the distinct merits of these various therapeutic strategies will be critical for truly successful treatment. “The future is combination therapies,” he says. “It’s hard to imagine that just hitting a metabolic target will get the job done, especially if inflammation and fibrosis are well established; on the other hand, if you have a fibrotic target, without taking care of the metabolic disturbance, you have not addressed the underlying problem.” ■



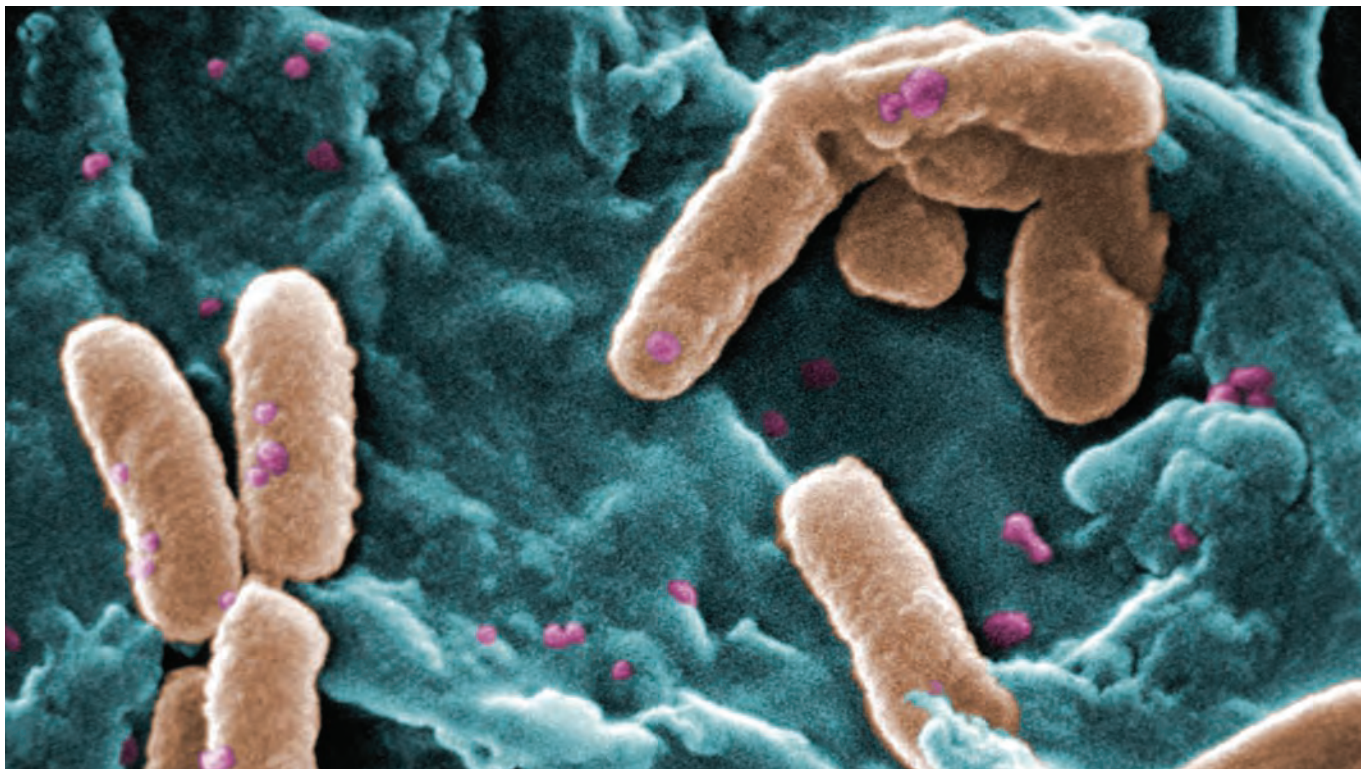
Obeticholic acid



Elafibranor



NDI-010976



The hunt is on for new antibacterial agents that can effectively kill drug-resistant pathogens like *Pseudomonas aeruginosa*.

5. NEXT-GENERATION ANTIBIOTICS

Various companies

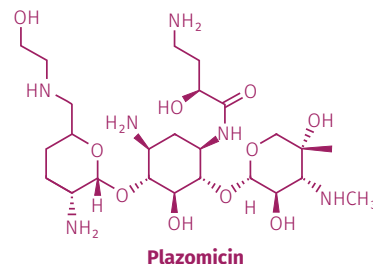
Multidrug-resistant bacterial infection

Decades of overuse and misuse of antibiotic drugs, coupled with stagnation in the drug development world, have led us to the brink of a dire public health crisis. Both government organizations such as the US Centers for Disease Control and Prevention (CDC) and leading microbiological research societies like the Infectious Diseases Society of America (IDSA) have made it clear that the development of new drugs to halt the spread of uncontrollable antibiotic-resistant pathogens must be a research priority.

At present, the pipeline remains limited—as of this past March, the Pew Foundation found that there were only 37 antibiotics in clinical testing against high-risk bacterial pathogens. Nevertheless, new weapons are emerging, and some experts, such as Indiana University microbiologist Karen Bush, see signs of hope. “I’m encouraged by what I’m seeing from small companies,” she says, “although for the most part I haven’t seen the large companies stepping up to the plate.”

If the infectious disease world were to put out a ‘Most Wanted’ poster, it would feature a cohort of bacteria known as the ESKAPE pathogens—an acronym derived from the names

of *Enterococcus*, *Staphylococcus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter*. These various species are responsible for high levels of morbidity and mortality in hospital settings and pose an especially severe risk of acquiring resistance. **Achaogen** has developed a compound called plazomicin, currently in Phase III testing, which may prove broadly effective against these baddies. Plazomicin belongs to the family of aminoglycoside drugs, which inhibit bacterial protein synthesis, and the drug appears to successfully kill bacteria that elude other antibiotics through acquired resistance. Bush notes that the drug’s good performance against *A. baumannii* is particularly



important. “*Acinetobacter* is probably the worst of them,” she says. “There’s not much of anything you can do if you’ve got a colistin-resistant *Acinetobacter* that does not respond to any of your first-line therapies.”

Shionogi is developing another promising ESKAPE-oriented drug candidate, S-649266, a β -lactam antibiotic that interferes with synthesis of the bacterial cell wall, and is currently in Phase III testing. “It covers *Pseudomonas* well and *Acinetobacter* pretty well, and many of the multidrug resistant Enterobacteria,” says Bush. Two drugs belonging to the tetracycline class of antibiotics, which act as inhibitors of protein synthesis, have also entered late-stage testing: omadacycline from

Paratek Pharmaceuticals and eravacycline from **Tetraphase**

Pharmaceuticals. After a strong showing in a Phase III trial for the treatment of intra-abdominal infection, the clinical development of eravacycline was derailed by a failed trial for urinary tract infection. However, Bush notes that the failure may have been attributable to a protocol in which the drug was transitioned from IV to oral administration, whereas the drug has generally fared best when administered entirely by IV. Two new trials are planned.

ESKAPE pathogens aren’t the only threat, however. “People are starting to get concerned because drugs that have been counted on in the past are losing their ability to treat gonorrhea,” says Bush, referring to recent reports of *Neisseria gonorrhoeae* bacteria that can withstand antibiotics

such as ceftriaxone and azithromycin. **Entasis Therapeutics** is gunning for this sexually-transmitted pathogen with zoliflodacin, representing a brand-new class of antibiotics that acts on an enzyme

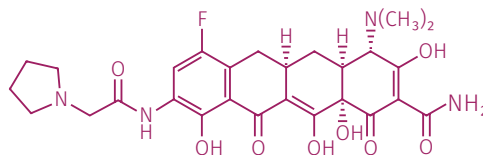
responsible for unwinding DNA strands during the replication process, which the company plans to move to Phase III next year. **Cempra** is also in Phase III testing with solithromycin,

a drug that has demonstrated an ability to kill drug-resistant gonorrhea in laboratory studies. Solithromycin has already proven itself in trials going after the various respiratory bacteria responsible for community-acquired bacterial pneumonia, and Cempra recently filed an NDA with the FDA for this indication.

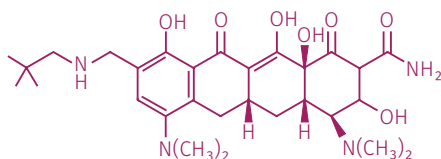
With few exceptions, the most advanced drugs in this space are simply new spins on existing classes of antibiotics, developed to overcome known resistance mechanisms that have already been identified in the wild. But there are a few actual newcomers, such as Entasis’ zoliflodacin and CF-301 from **ContraFect**, which belongs to a cell wall-degrading family of enzymes known as lysins. “That’s something people have looked at for ages,” says Bush. “It’s something that Alexander Fleming was actually looking for when he discovered penicillin!” CF-301 has demonstrated potential in fighting multidrug-resistant *Staphylococcus aureus* (MRSA), and is on track to enter Phase II trials in the near future. New discoveries in the academic world are also bringing new molecules into the arena, such as the MRSA-slaying compound teixobactin, which was isolated from a soil bacterium by researchers at Northeastern University.

That research team recently netted a \$9 million NIH grant to seek out other new antibiotic candidates, and several other major funding initiatives have also been established to fuel innovation in this critical area of drug development, including Europe’s New Drugs for Bad Bugs

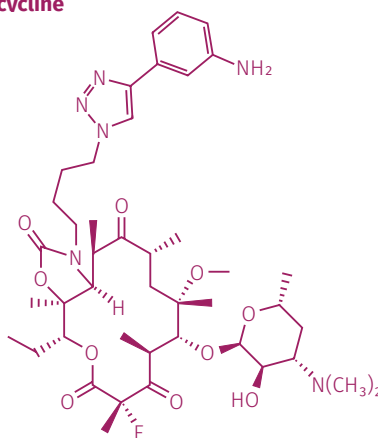
effort and the newly-launched Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) public-private partnership. ■



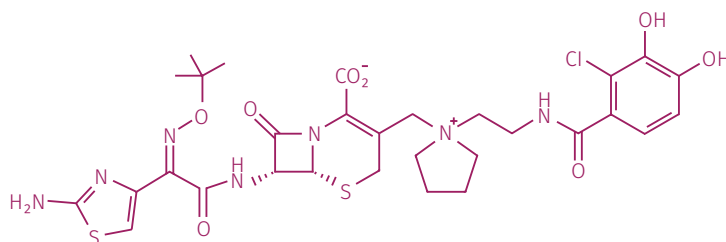
Eravacycline



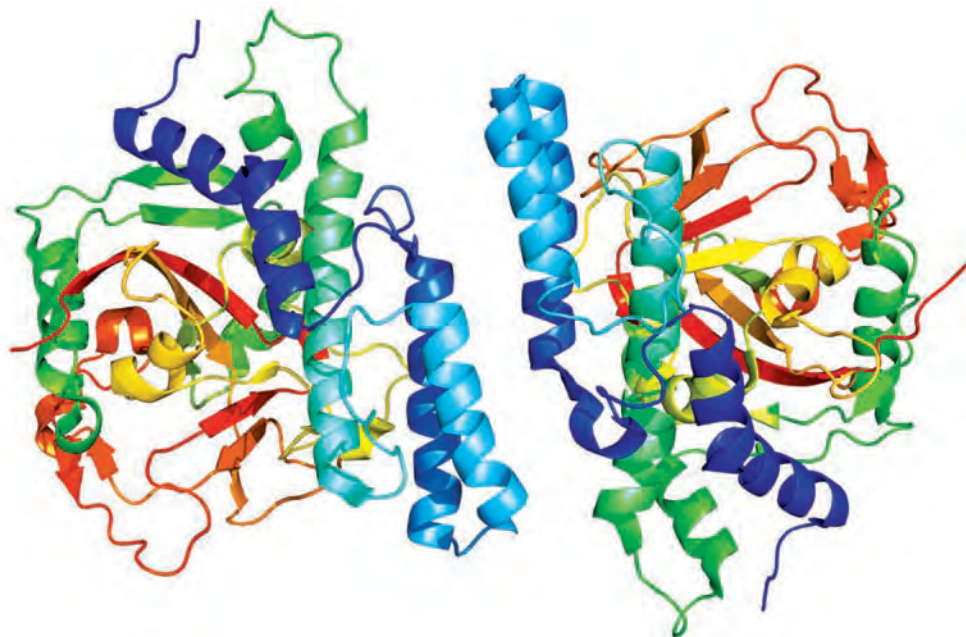
Omadacycline



Solithromycin



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PARP-mediated DNA repair offers a critical survival mechanism for some tumors, making it an appealing target for inhibitor drugs.

6. PARP INHIBITORS

Various companies

Breast, ovarian and other cancers

One of cancer's survival secrets is a hyperactive DNA repair system, which allows tumors to fix genomic damage inflicted by chemotherapy or radiation or otherwise accumulated over the course of countless cycles of proliferation. Enzymes belonging to the poly(ADP ribose) polymerase (PARP) family help coordinate this repair, and researchers have recognized for nearly 40 years that disabling PARP could potentially cripple and kill cancer cells.

As noted in a 2013 C&EN article by Lisa Jarvis ("Pushing Cancer over the Edge"), however, this area of drug discovery has been fraught with setbacks—including a failed Phase II trial for AstraZeneca's olaparib as a treatment for ovarian cancer, which led the company to make the difficult decision to shelve the program. However, lessons learned during this process have given rise to a series of successes in taking down tumors. In fact, AstraZeneca was able to successfully rehabilitate olaparib after identifying a previously overlooked subgroup success story.

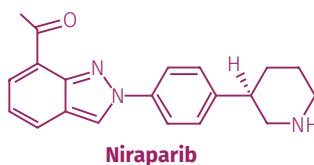
The secret turned out to be going after tumors with mutations in the *BRCA1* or *BRCA2* genes, which encode proteins that facilitate a secondary DNA repair mechanism that can repair the damage arising from PARP inhibition. Patients with this

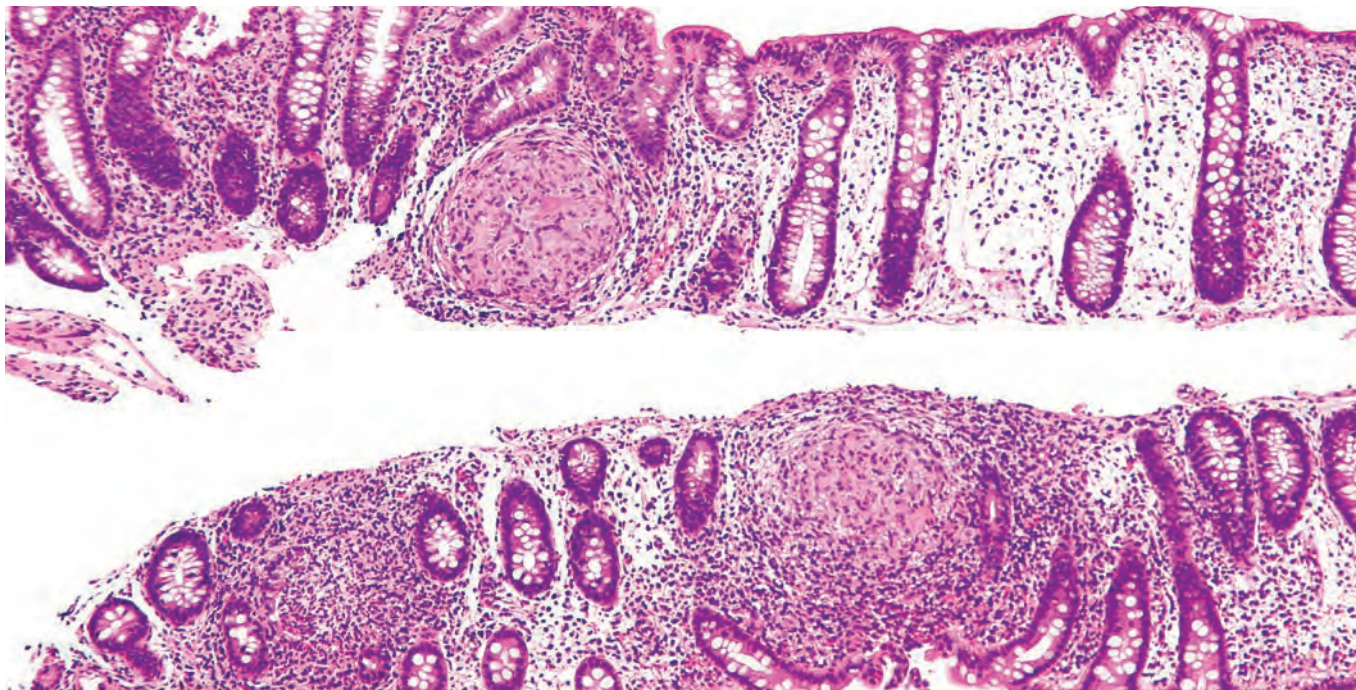
mutation showed a strong response in a subsequent study, and olaparib (now marketed as Lynparza) was approved by the FDA in December 2014 for the treatment of *BRCA*-mutated ovarian cancers that have failed multiple rounds of prior treatment.

Other PARP-targeting drugs have followed close behind. **TESARO** is currently pushing for FDA and EMA approval after a big win in their Phase III trial for niraparib, which extended progression-free survival in ovarian cancer by

more than 15 months relative to placebo in patients with *BRCA* mutations—and by 9.1 months in patients with alternative mutations affecting the same DNA repair pathway. **Medivation's** talazoparib, **Clovis Oncology's** rucaparib and **AbbVie's** veliparib are all in late-stage clinical testing for ovarian cancer as well.

Although the focus for all of these drugs has primarily been ovarian cancer, *BRCA* mutations are often found in breast cancers and, to a lesser degree, in pancreatic, prostate and other tumors. Numerous trials are now underway to assess how olaparib and other PARP inhibitors tackle other cancers with established DNA repair defects, and to determine whether these drugs might be used to increase tumor sensitivity to conventional chemo or radiation therapy. ■





Mongersen selectively reduces levels of a protein that allows the inflammatory response to run wild and inflict damage to the intestinal wall in Crohn's disease.

7. MONGERSEN

Celgene

Crohn's disease

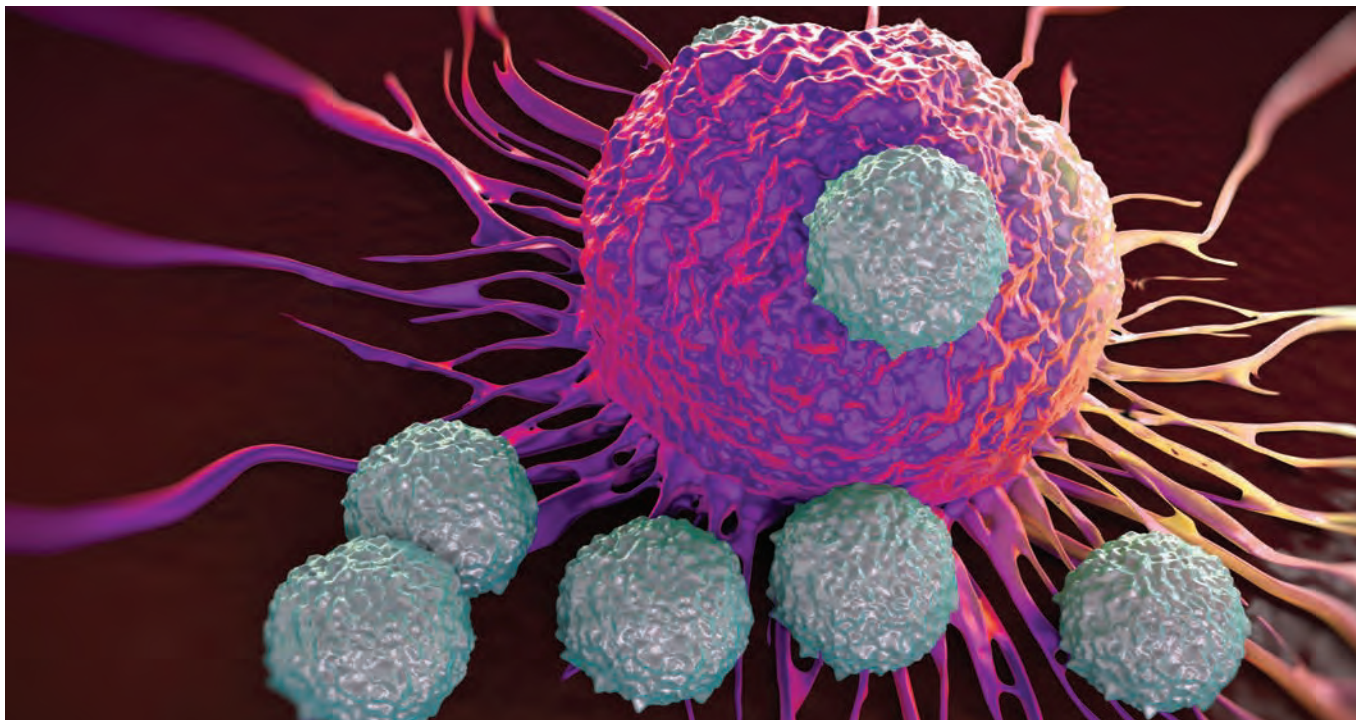
Many patients with moderate to severe Crohn's disease turn to biologic drugs that bind to and inactivate triggers of inflammation. For example, **Abbvie's** Humira or **Janssen's** Remicade are based on antibodies that recognize a protein called tumor necrosis factor- α (TNF α), which provokes the destructive activity of immune cells at the intestinal wall. These agents can drive Crohn's back into remission in many cases, but also suppress other critical functions of the immune system, leaving patients more susceptible to infection. Furthermore, there are questions as to whether these drugs meaningfully improve long-term outcomes for patients.

As an alternative to broadly blocking signals that activate immunity, **Celgene** is hoping to preserve gut health by boosting production of a protein that can help cool down the inflammatory process locally. Many Crohn's disease patients produce abnormally high levels of a protein called SMAD7 in the cells within their intestine. This excess SMAD7 acts as a roadblock to signaling pathways that keep immune cell activation in check. Back in 2001, Italian researcher Giovanni Monteleone, then at the University of Southampton, showed that one could reactivate this pathway by using an 'antisense'-based approach. This method entails the use of single strands of DNA that form double-stranded pairs with a particular messenger RNA—in this

case, encoding SMAD7—and prevent it from being translated into protein. This approach relieves the immunosuppression blockade and thereby helps contain intestinal inflammation.

This work gave rise to the antisense drug mongersen, and a subsequent wave of clinical trials demonstrated enough promise that in 2014, Celgene paid \$710M to acquire the rights for commercial development. So far, the bet seems to be paying off; in a Phase II trial, 55-65% of patients achieved complete remission within two weeks of treatment, depending on the dose given, versus 10% in the placebo group. Remarkably, relief lasted for months in some patients. The drug also appears to be safe, with most adverse events associated with the disease rather than the treatment.

In an editorial from the *New England Journal of Medicine*, gastroenterologist Severine Vermeire of the University Hospitals Leuven in Belgium described the extent of remission seen in the Phase II study as "unprecedented." However, she also raised questions about indicators that the patient population might have exhibited relatively mild—and therefore easier to treat—disease, and suggested that additional outcome data might have provided more robust proof of remission. Phase III trials now underway should help clarify whether this drug lives up to its blockbuster potential. ■



Scientists are testing the effectiveness of virally-delivered CRISPR/Cas9 machinery for the targeted genetic modification of cancer patients' T-cells.

8. CRISPR/CAS9-MODIFIED T-CELLS

**West China Hospital, University of Pennsylvania
Cancer**

The excitement surrounding the use of CRISPR/Cas9 technology for precise, sequence-specific editing of genomic DNA has steadily built to a fever pitch, generating high-impact publications, heavy investments and heated patent disputes—but so far, no clinical trials. This past December, however, C&EN reported that “initial CRISPR/Cas9 cell therapies are predicted to reach the clinic in 2016,” and this has now come to pass, with one study awaiting a formal sign-off from regulators and another poised to begin any day now.

The first announcement came in June, when a team led by University of Pennsylvania oncologist Edward Stadtmauer received authorization to pursue their clinical trial program from the US Recombinant DNA Advisory Committee, a body that oversees any gene therapy-related protocols intended for use in humans. With financial support from the newly-formed Parker Institute for Cancer Immunotherapy, Stadtmauer and colleagues intend to use CRISPR/Cas9 to precisely introduce three targeted edits into T-cells isolated from 18 cancer patients.

The principle of the therapy is largely similar to the ‘chimeric antigen receptor’ (CAR) T-cell approach which is already being employed in clinical trials at UPenn, except using CRISPR/Cas9

rather than viruses to introduce the desired genetic modifications. The modified T-cells will be reprogrammed to aggressively seek and destroy tumor cells, with additional alterations that prevent their activity from being suppressed, and then transplanted back into patients in the hope that they will eradicate the tumor. The protocol still requires approval from the FDA and various institutional review boards, but one of the study’s coordinators, immunologist Carl June, has said that a 2016 start is possible.

Perhaps more unexpected was the news that followed a month later, with the announcement that oncologist Lu You at West China Hospital and his colleagues had already received permission to proceed with their own CRISPR/Cas9 trial, with plans to initiate treatments in August. You’s trial will take a somewhat simpler approach to T-cell modification, using genome editing technology to delete a single gene, encoding an ‘immune checkpoint’ protein called PD-1 that tumors can exploit to thwart attacks by immune cells. The PD-1 pathway is already the target of several successful checkpoint inhibitor drugs, and the hope is that this modification will increase the aggressiveness with which T-cells attack lung tumors after being transplanted back into patients. ■



An immunosuppressive antibody drug can help reduce autoimmune damage to the central nervous system in multiple sclerosis patients.

9. OCRELIZUMAB

Roche (Genentech)

Relapse-remitting and primary-progressive multiple sclerosis

The majority of multiple sclerosis (MS) patients—roughly 85%—are diagnosed with the relapse-remitting form of the disease, in which flare-ups are punctuated by periods of remission. For the remaining fifteen percent, however, the disease manifests as a slow and steady process of neurological degeneration; symptoms of primary-progressive MS occasionally stabilize but do not durably improve. Relapse-remitting MS worsens over time, but there are a variety of treatment options that can delay progression, whereas there are no effective options at present for primary-progressive MS.

This is one of the main reasons that ocrelizumab, a biologic treatment for MS developed by the **Genentech** subsidiary of Roche, is grabbing so much attention. Ocrelizumab is a monoclonal antibody that binds to a protein called CD20 on the surface of antibody-producing B-cells, and thereby helps stave off damage arising from a hyperactive immune response. Roche initially developed this drug as a treatment for other autoimmune conditions, such as lupus and rheumatoid arthritis, but suspended these programs after determining that the drug left patients immunocompromised and vulnerable to infection relative to the benefits that it delivered. However, ocrelizumab has repeatedly displayed considerable promise as a treatment for MS, and in June the FDA granted the drug Priority Review as

a prelude to potential approval for the primary-progressive form of the disease.

This decision came on the heels of a series of Phase III triumphs. In the two OPERA trials, the drug meaningfully reduced the likelihood of disease progression relative to standard interferon treatment in patients with relapse-remitting MS over the course of nearly two years. This was an important general demonstration of the drug's efficacy, but the ORATORIO trial for primary-progressive MS provided robust evidence that the drug could also fight back against this more aggressive form of the disease as well, reducing the risk of progression by 24% relative to placebo. Importantly, the current data suggest that opportunistic infection does not pose the same risk in this treatment regimen as it has for other indications, although longer term studies will be necessary.

Some experts have expressed disappointment that the extent of the effect is not as great against this form of the disease as the strong response seen in relapse-remitting MS, but others are grateful to finally have an option for this subset of patients. In an article from *Nature Biotechnology*, Stanford University neurologist Lawrence Steinman called the drug “an absolute gift—it's the first time that anything's worked in the field.” ■



Doses of 'healthy' intestinal bacteria could prevent the pathogenic bacterium *Clostridium difficile* from making a long-term home in the gut.

10. MICROBIOME-BASED THERAPEUTICS

Various companies

Gastrointestinal disorders

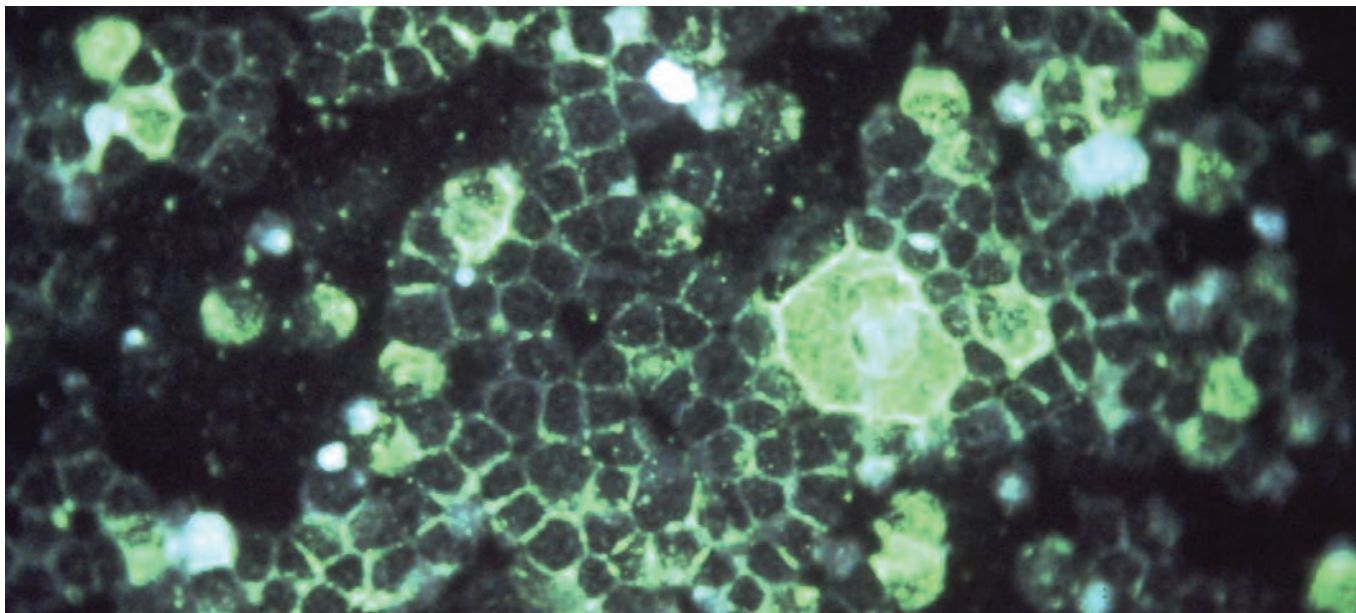
The mainstream media has gotten mileage from the 'gross-out' factor associated with fecal microbial transplantation (FMT) as a treatment for gastrointestinal disorders, but a steady accumulation of clinical and scientific data suggests that there is substance beneath the hype. Several companies are now exploring the curative potential of treatments based on the replacement of health-promoting gut bacteria, as highlighted this past fall in C&EN ("Harnessing the Hordes in the Microbiome").

The greatest FMT success stories to date have come from the treatment of *Clostridium difficile*. In some patients, a course of antibiotics demolishes healthy bacteria living in the colon, and this pathogen expands to fill the void. Taking additional antibiotics may only make things worse. "Most of the antibiotics out there don't kill all of the *C. difficile*," says Sahil Khanna, a gastroenterologist at the Mayo Clinic, "and as you take more antibiotics, you're killing more bacteria that are doing benefit, and your risk of *C. difficile* recurrence tends to increase."

Khanna is collaborating with two companies that are trying to develop standardized microbiome therapies to fight this recurrence. The first, **Seres Therapeutics**, has developed an oral formulation of fecal bacteria that have been collected from healthy donors. Their SER-109 treatment fared well in a single-arm Phase I trial, preventing recurrence in 87% of the patients who received it. However, the company took a major hit after

releasing disappointing Phase II data, with SER-109 showing no apparent efficacy relative to placebo. Some analysts believe this may have been the result of differences between the protocols used in the two trials, and although this represents a setback for Seres, other studies provide broader support for the underlying principles of this treatment approach. **Rebiotix** has pursued a more conventional enema-based delivery system for their FMT approach, and for now, the data look good. "An initial study was done with 30 patients, and again, there was an 87% cure rate," says Khanna, who was involved with the company's Phase I testing. The company plans to release Phase II data in the fall.

Others are pursuing 'curated' selections of bacteria to deliver more targeted relief. In 2015, **Johnson & Johnson** invested \$241 million to license a selected combination of gut bacterial species from **Vedanta Biosciences** known as VE-202. Vedanta cofounder Kenya Honda and colleagues initially identified this collection of bacterial species based on their immunosuppressive properties, and VE-202 is being developed as a means for controlling inflammation in Crohn's disease. From Khanna's perspective, such hand-picked bacterial formulations are likely to be the way forward for diseases other than *C. difficile*, where the roots of microbiome dysfunction are more subtle than the mass destruction inflicted by antibiotic treatment. "We will probably see different products with different formulations for different diseases," he says. ■



Complications from respiratory syncytial virus (RSV) infection are a leading cause of hospitalization in very young children.

11. RSV-F

Novavax

Maternal vaccination against RSV

Respiratory syncytial virus (RSV) is widespread, and virtually every child will be infected with the virus by the age of 2. Early in life, the virus can be a menace rather than a nuisance, causing inflammation of the airways and pneumonia—and in some cases, death. “It is the most common single reason for hospitalization of infants in my hospital and most hospitals in the US,” says Janet Englund, a specialist in pediatric infectious disease at Seattle Children’s Hospital.

In the 1960s, an effort to inoculate infants against RSV ended tragically, with two deaths and numerous hospitalizations—an outcome that Englund describes as a major setback to RSV vaccine-development efforts. As an alternative, **Novavax** is attempting to protect babies by vaccinating mothers during pregnancy. Newborns lack the ability to mount an immune response of their own, but are protected at birth by antibodies acquired from their mothers from the late second trimester onward. “We know that naturally-occurring antibodies go across the placenta quite well, and we think vaccines should work similarly,” says Englund. Indeed, maternal vaccination against diseases like influenza, pertussis, and diphtheria has proven safe and effective enough to win the support of leading health organizations like the CDC.

These are all conventional vaccines that are being administered to moms off-label, but Novavax is gunning for RSV-F to

become the first vaccine to achieve licensure specifically for use in pregnant women. A Phase II trial showed that their formulation, which is based on a well-conserved viral surface protein, elicited a strong immune response in mothers-to-be relative to placebo, with generally mild and localized adverse events. Critically, these antibodies were also readily detectable in newborns, at a level that could confer protection against infection for months after birth.

RSV is a global problem, and this vaccine program is being backed in part by \$89 million from the Gates Foundation as it moves forward with Phase III testing. The vaccine is also being assessed in a separate trial for the elderly, who are vulnerable to RSV, and has been awarded a Fast Track designation by the FDA for this population. The road to licensure is still not defined for maternal vaccines, but Englund notes that the FDA has been proactive in trying to establish a clear path for such programs.

There are some caveats to the maternal vaccination approach. Since antibody transfer peaks in the third trimester, prematurely-born children would not necessarily be protected. Furthermore, maternal antibodies dwindle over time, largely disappearing by four months of age. “But since the peak hospitalization for RSV occurs at two months, that would still potentially help,” says Englund. “It’s not going to get rid of it, but it will certainly help.” ■

12. OLICERIDINE

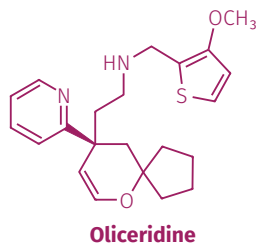
Trevena

Post-surgical pain

Historically, biology textbooks have peddled a rudimentary view of cellular signaling, in which the binding of a ligand either switches its cognate receptor 'on' or 'off.' Needless to say, this is a profound oversimplification—particularly for G protein-coupled receptors (GPCRs), a complex and dynamic family of proteins that is centrally involved in myriad biological functions.

Research from Duke University researcher Robert Lefkowitz showed that not only do GPCRs generate signals through at least two different pathways—transmitted via either G protein or β -arrestin partners—but also that it was possible to activate those receptors in a way that only switches on one pathway but not the other. G protein and β -arrestin signaling can have profoundly different physiological outcomes, and Lefkowitz and members of his laboratory subsequently founded **Trevena** to develop 'biased ligand' drugs that exploit this effect to achieve superior efficacy with reduced risk of adverse effects.

Trevena's flagship clinical program is a drug for postsurgical pain called oliceridine, which binds to the μ -opioid receptor. This receptor is the primary target for some of today's most widely-used painkillers, but these drugs can also trigger nausea, constipation, and respiratory problems. "We had data from the Duke laboratory that the G protein pathway was associated with analgesia, while the β -arrestin pathway was associated with the opioid-related adverse effects," explains Trevena's



chief scientific officer, Michael Lark. Oliceridine was developed with these findings in mind, to act as a safer analgesic that activates the μ -opioid GPCR in a biased fashion to selectively induce G protein signaling.

Trials have provided robust support for this approach, showing that oliceridine can deliver relief with comparable effectiveness to morphine in terms of pain relief, while also reducing the side effect profile associated with the older drug. "We saw very rapid onset of action, very highly effective analgesia in severe pain states, and we were able to show that we have this broad therapeutic window in analgesia versus opioid-related adverse events compared to morphine," says Lark. The data were sufficiently compelling to earn the company a Breakthrough Therapy designation from the FDA in February, and oliceridine is now in a pair of Phase III trials to assess pain relief and tolerability relative to placebo in patients undergoing abdominal surgery and bunionectomy. The company aims to report top-line data from the trials early next year, in preparation for filing with the FDA in 2017.

The company is also developing a second μ -opioid ligand, TRV-734, that acts similar to oliceridine, but can be administered orally rather than intravenously. "This opens up the opportunity to take a biased ligand into chronic dosing," says Lark. A third compound, TRV-250, is designed to selectively activate its target receptor in a way that triggers migraine relief without producing signals that can cause seizure onset, and Lark is bullish about the potential of the company's approach. "I think it's got broad potential applicability to almost any GPCR," he says. ■



A cannabis-derived compound delivers relief from epilepsy without the high.

13. EPIDIOLEX

GW Pharmaceuticals

Epilepsy

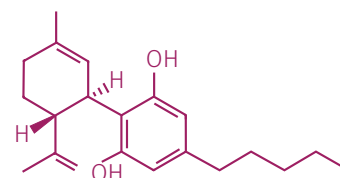
Physicians have known since the mid-19th Century that cannabis can effectively prevent the onset of seizures in epileptic patients—in 1870, English doctor William Gowers reported that treating a man with an extract of *Cannabis indica* gave him six months of relief from the seizures that had plagued him since age 15. By the 1970s, researchers had learned that the chemical component of cannabis primarily responsible for this improvement is cannabidiol. Unfortunately, this area of research would remain stagnant for decades, due in large part to the plant's status as a prohibited drug of abuse.

In 2013, against a backdrop of surging support for the legalization of medical marijuana in the United States, the story of Charlotte Figi reinvigorated interest in this therapeutic approach. Charlotte was afflicted with an untreatable form of congenital epilepsy called Dravet syndrome, which was apparently remedied by an extract prepared from a cannabis strain that is enriched in cannabidiol. **GW Pharmaceuticals**, one of the first companies to actively explore the therapeutic potential of cannabis-derived compounds, subsequently embarked on a clinical program to develop Epidiolex, a cannabidiol-based treatment for epilepsy. Their first trial, an open-label study coordinated by researchers at the University of California at San Francisco, showed that the drug delivered a median 36.5% reduction in seizures over the course of a month in children and young adults with Dravet or Lennox-Gastaut syndrome (another form of congenital epilepsy).

This past spring, GW provided more meaningful support for

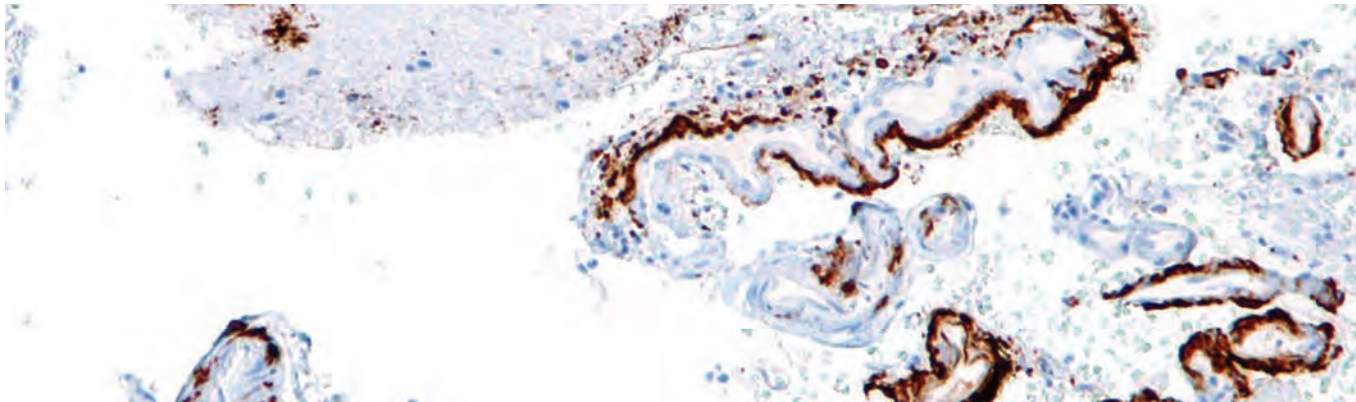
Epidiolex with a pair of randomized controlled trials. In patients with Dravet, the drug delivered a 39% reduction of monthly seizures versus 13% in the control arm; additionally,

Epidiolex proved twice as effective as placebo in reducing seizure frequency in Lennox-Gastaut. Cannabidiol does not bind to the same brain receptors recognized by Δ^9 -tetrahydrocannabinol (THC) and thus does not deliver the potent psychotropic side effects of this other major constituent of cannabis.



Cannabidiol

The drug was associated with increased likelihood of adverse events, and although these were generally mild (such as nausea, diarrhea or vomiting), several patients in each trial experienced serious treatment-related side effects. Additionally, some skeptics note that families living in jurisdictions where medical marijuana is available may prefer to stick with the all-natural option—a cheaper alternative that may offer additional benefits due to so-called 'entourage effects' arising from other beneficial compounds found in the cannabis plant. This isn't an option in many states, however, and GW's stock has climbed strongly on expectations that its potent performance against these debilitating and otherwise untreatable pediatric disorders offers a compelling argument for FDA approval. ■



Drug companies are hoping that inhibition of the enzyme beta-secretase will prevent the accumulation of toxic amyloid plaques in the brains of Alzheimer's patients.

14. β -SECRETASE INHIBITORS

Various companies

Alzheimer's disease

Countless drug development programs have dashed themselves fruitlessly against the rocks of Alzheimer's disease. Nevertheless, researchers in government, industry, and academia diligently continue to search for new therapeutic targets, motivated by the high medical, social and economic costs of this pernicious and widespread disease, which currently afflicts roughly 5.4 million Americans.

One of the latest targets in the cross-hairs is an enzyme known as β -secretase-1 (BACE1), with four major pharmaceutical companies—**Merck, AstraZeneca, Eli Lilly and Johnson & Johnson**—pushing drug candidates into late-stage clinical testing. The treatment strategy is based on the prevailing amyloid hypothesis of Alzheimer's disease, which is based on the idea that the accumulation of a small protein fragment called amyloid- β is the trigger for many of the pathological events that ultimately result in neuronal death. BACE1 is the enzyme that generates amyloid- β from a longer precursor protein, and blocking it should theoretically halt plaque formation.

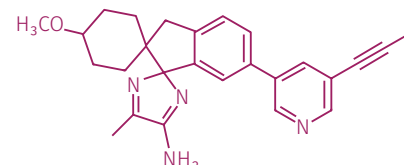
Merck's small-molecule drug verubecestat is the furthest along; the company completed enrollment for its pivotal Phase III trial in January, and expects to finish collecting data next summer. AstraZeneca and Eli Lilly are jointly developing another BACE1 inhibitor called AZD3293, which recently transitioned to Phase III. Johnson & Johnson is further behind in the development of their candidate, JNJ-54861911, which recently began a Phase II/III trial that is not expected to conclude until 2023. These compounds appear to be potent inhibitors—for Merck's compound, a dose as low as 12 mg reduced levels of amyloid- β in the cerebrospinal fluid by more than 50%.

Robert Vassar, a molecular biologist

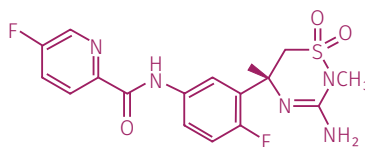
at Northwestern University who led one of the teams that first cloned BACE1, warns that it's possible to have too much of a good thing. "There are many other BACE substrates—I think the current list is close to 100 different substrates in neurons alone," he says. "We need to be cognizant of the normal functions of the BACE enzyme."

He notes that mice lacking BACE entirely have a number of physiological problems, including neurological defects, but adds that moderate reduction of BACE can have a potent effect. "You can get on the order of a 90% reduction in amyloid- β with the equivalent of inhibiting BACE by 50%," says Vassar. Both the Merck and AstraZeneca/Lilly compounds have already passed interim safety analysis, suggesting that adverse events may be manageable if appropriately dosed.

Vassar describes himself as "cautiously optimistic" that BACE will prove an effective target for Alzheimer's. However, he also adds that the preclinical data strongly suggest that early intervention is critical. "Amyloid is building up for decades—at least one or two decades before there are any memory symptoms at all," says Vassar, noting that tackling amyloid production too late in



AZD3293



Verubecestat

the game may have been the undoing of other ambitious trials. Accordingly, all three drugs are being tested in patients with 'mild cognitive impairment', a precursor stage to Alzheimer's, and Johnson & Johnson is striking even earlier with a trial in asymptomatic patients considered at high risk for Alzheimer's. ■

15. BIOSIMILARS

Various companies

Cancer and inflammatory disorders

It began with just a slow trickle, but it appears that the biosimilars floodgate is finally about to open. The EMA has been approving these 'generic' equivalents of off-patent biologic drugs for over a decade now, but biosimilars didn't reach the US market until last year when the FDA approved Zarxio. This was **Sandoz's** version of Neupogen, a recombinant protein drug initially developed by **Amgen** to promote white blood cell growth.

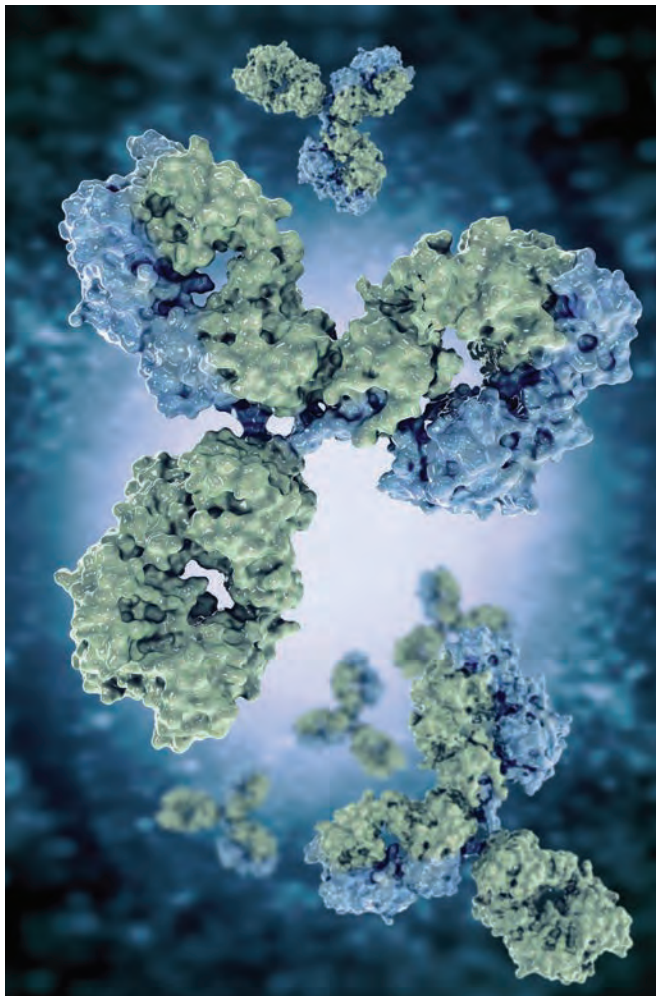
Since then, the agency has subsequently approved Inflectra from **Celltrion**, a biosimilar for **Janssen's** anti-inflammatory antibody drug Remicade. The FDA is also currently on track to sign off on two more anti-inflammatory biosimilars, including a substitute for **Amgen's** Enbrel manufactured by **Novartis**, and Amgen's version of Humira—**AbbVie's** first-ever human antibody therapeutic. In comparison, the EMA has already approved 22 biosimilar drugs—although two of these were subsequently withdrawn.

The FDA's process for approving Inflectra set useful precedents in establishing the burden of proof that future biosimilar applications will need to prove both safety and efficacy. Biosimilars differ considerably from conventional

generics in that they are produced by living cells, and even seemingly subtle variations in the manufacturing process can

potentially have functional consequences—through minor alterations in protein folding or chemical modification, for example. "In addition to the potential for drugs lacking the same efficacy, having too much efficacy or increased potency in the biosimilar agent is a problem," says Cronstein, noting that the EMA has rejected biosimilars that turned out to be 'biobetters', which could potentially create serious dosing issues. Fortunately, a recent study of rheumatology biosimilars suggests that they are generally as safe and effective as their 'parent' drug.

Cronstein notes that many of his colleagues remain hesitant about moving their patients onto these new versions of existing drugs, but believes that lower costs may ultimately prove a major draw—even if the price differential isn't necessarily as great as clinicians might have initially hoped. "The savings will not be nearly as big as those of standard generics," he says. "But a 30–40% reduction in cost is significant for many of these drugs, and I think that's going to be important." ■



After a slow start, a growing number of 'generic' versions of antibodies and other protein-based drugs—known as biosimilars—are now entering the US market.



An antibody-based drug could relieve the pain and itching of eczema without the nasty side-effects associated with more aggressive immunosuppressant treatments.

16. DUPILUMAB

Regeneron Therapeutics/Sanofi

Atopic dermatitis

Atopic dermatitis, also known as eczema, is already hard enough for patients, who have to cope with itchy and damaged skin and often deal with severe psychological and quality of life issues as a consequence. On top of that, existing treatments for severe disease can be debilitating and dangerous—including the potent immunosuppressants cyclosporine and methotrexate, the latter of which is also used to kill cancer.

Riding high on a wave of striking clinical trial data, **Sanofi** and **Regeneron Therapeutics'** monoclonal antibody dupilumab offers the promise of a drug that is both far safer and more efficacious, and clinicians are understandably excited. Steven Feldman, a dermatologist at Wake Forest Baptist Medical Center, draws a parallel to psoriasis. "20 years earlier, we were doing the best we could and didn't even know how poorly we were doing until biologics came along and revolutionized our ability to take care of these patients," he says. "We are on the cusp of the same thing happening in atopic dermatitis."

This antibody binds to a protein that serves as a component of the receptors for interleukin-4 and -13, signaling proteins that have been strongly linked to the pathology of atopic dermatitis.

In April, the company presented Phase III data from two trials showing that treatment with dupilumab essentially eliminated skin lesions in 36-38% of the patients treated, compared with 10% or fewer in the placebo group. Furthermore, roughly half of the patients experienced at least a 75% reduction in the severity of their atopic dermatitis symptoms after being treated with dupilumab either weekly or biweekly.

Subsequent data showed that this level of relief could be sustained for at least 52 weeks. Importantly, all of these patients were suffering from moderate to severe disease that had failed to respond to corticosteroid treatments. "It's a highly effective therapy—certainly compared to what we know about what we have as alternatives," says Feldman. Sanofi and Regeneron are almost certainly hoping that the FDA will feel the same way after reviewing the data—if dupilumab reaches the clinic, some analysts believe the drug could net up to \$5 billion for the two companies, and clinicians are eager for a better option. "If the data are good enough to get it approved, it's going to be enough for me to want to use in my patients with moderate to severe disease before turning to methotrexate and cyclosporine," says Feldman. ■

17. 'UNIVERSAL' INFLUENZA VACCINES

Various companies

Influenza

Every year, researchers working with the World Health Organization (WHO) attempt to predict the future—using global surveillance data to determine which strain of influenza is likely to pose the biggest threat for flu season, and thereby select the correct vaccine. This doesn't always work out. "In the winter of 2014-15, the prediction was wrong, and we had a really bad vaccine where it was pretty much the same protection whether you got it or not," says Francesco Berlanda-Scorza, director of influenza projects at PATH.

The development of a broadly protective vaccine that confers immunity against a diverse array of seasonal strains—and ideally, pandemic viruses that might emerge in the future—has been a long-standing dream in the public health community. "The WHO has said they're trying to set a goal to have a universal vaccine by 2020," says Berlanda-Scorza. Although he is skeptical that this goal will be met in this time-frame, there are numerous programs now underway to make flu vaccination more effective.

Part of the problem with existing vaccines is that they largely elicit a response to the 'head' domain of the viral hemagglutinin (HA) protein, which varies considerably across strains. One possible solution is to develop vaccines based on the 'stalk' domain of this protein, which tends to remain largely unchanged. **Johnson & Johnson** subsidiary **Crucell** has demonstrated that such an approach could elicit a protective immune response in mice and monkeys against a diverse variety of influenza strains. PATH is working with researchers at the Icahn School of Medicine at Mount Sinai on a different approach to generating such an anti-stalk immune response. Their 'chimeric' vaccine entails sequential vaccination with two HA variants with distinctive head domains, but identical stalk domains, and preliminary studies have shown that this vaccine can promote the production of stalk-specific antibodies in humans. This program is now moving toward clinical trials with support from the Gates Foundation and an undisclosed industry partner.

Numerous companies are exploring other viral proteins as a means to elicit protection. Start-up **Imutex** is working with NIAID on plans for a Phase II trial of Flu-V, their combination of peptides from three different viral proteins. Importantly, since this approach is primarily oriented at eliciting a T-cell response to infection, it could greatly reduce the severity of disease but would probably not prevent infection per se. NIAID is also collaborating on a Phase II trial with **BiondVax**, an Israeli company whose M-001 vaccine is primarily intended as a broadly-protective countermeasure against future pandemic strains of avian influenza. In the UK, Oxford University spin-off



Vaccines that induce broad immunity against multiple influenza subtypes could take the guesswork out of flu season preparations, or allow rapid response to emerging pandemic strains.

Vaccitech is also going after a broad immune response with their vaccine approach, in which selected influenza proteins are expressed on the surface of other types of nonpathogenic viruses.

NIH scientists are also pursuing a two-stage approach in which individuals are first 'primed' with a DNA-based influenza vaccine followed by a 'boost' with an inactivated viral vaccine. A recent examination of six participants from this study showed that they produced HA stem-specific antibodies that could effectively protect against a fairly broad range of viral strains. "It works really well and could be a game-changer, but it requires two shots three to six months apart," says Berlanda-Scorza, "and it's already hard to get people to get a one-shot vaccine." ■

18. β -lactamase inhibitors

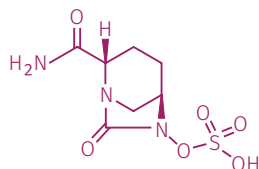
Allergan/Merck/The Medicines Company
Antibiotic-resistant infection

Many of the most commonly used antibiotics are members of the β -lactam family of compounds—and it is perhaps unsurprising that bacteria have come up with sophisticated strategies to defend themselves. What has resulted is something of an arms race—pathogens produced β -lactamase enzymes that can degrade these antibiotics, scientists developed inhibitors to block those enzymes, and the pathogens adapted to produce enzymes that overcome those inhibitors. Some can even fend off the powerful carbapenem antibiotics that are reserved as the final option for fighting infection.

Fortunately, next-generation β -lactamase inhibitors are taking the fight back to the bacteria. The first of these to win approval was avibactam, developed by **Actavis** (which was subsequently acquired by **Allergan**). The FDA was sufficiently convinced to issue approval after a Phase II trial demonstrating that the combination of avibactam and the antibiotic ceftazidime could effectively fend off a variety of severe infection—an unusual event in the antibacterial drug space. The company has since provided further Phase III data in support of this combination, which is marketed as Avycaz. “It covers a reasonable amount of *Pseudomonas* infections, where it’s at least as good as carbapenems,” says Indiana University microbiologist Karen Bush, “and it will cover a number of the carbapenem-resistant *Enterobacteriaceae*.”

Each antibiotic-inhibitor pairing requires separate approval, and Allergan has several other trials underway with different avibactam combinations. One of these, in collaboration with **AstraZeneca**, is testing avibactam with the antibiotic aztreonam, which is potentially well suited for pathogenic bacteria that produce a subset of enzymes known as metallo- β -lactamases. Two other inhibitors are also in the late-stage clinical pipeline. Both **Merck** and **The Medicines Company** are testing their inhibitors with different last-resort carbapenem antibiotics. In June, Merck released strong Phase II data showing that a pairing of their β -lactamase inhibitor relebactam with imipenem was effective in treating urinary tract infection, and two Phase III trials are in the works. The FDA has granted The Medicines Company a Fast Track designation for a combination of inhibitor vaborbactam with antibiotic meropenem, to be marketed as Carbavance, based on its performance to date against the same indication, with Phase III data expected later this year.

Unlike first-generation inhibitors, all three compounds are based on structures that differ considerably from the drugs that are being recognized and destroyed by bacterial enzymes. “I think they’ll have a big impact,” says Bush. “I also think that we’ll see different kinds of resistance mechanisms ... because most of the combinations are using inhibitors that are



Avibactam

not beta-lactams, the bugs will be forced to get a little more creative.” To maximize their durability, she anticipates that most hospitals will likely reserve these combos as an emergency treatment for intensive care unit patients. ■

19. Checkpoint inhibitor combinations

Various companies
Cancer

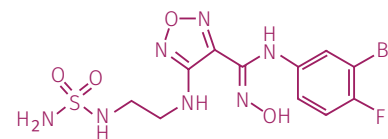
Over the past two years, checkpoint inhibitor drugs have taken the oncology world by storm. Opdivo (nivolumab), from **Bristol-Myers Squibb** (BMS), has now been approved by the FDA for skin, kidney and lung cancer as well as Hodgkin’s lymphoma, and earned the company \$840 million in Q2 of this year. During the same period, Keytruda (pembrolizumab), which has been approved for lung cancer, netted manufacturer **Merck** \$314 million—a three-fold increase over last year.

Both drugs act on a protein called PD-1, a component of a checkpoint pathway that normally prevents the immune system from over-reacting, but which can also be exploited by cancer to defend itself against destruction by B- and T-cells. Keytruda and Opdivo have both proven remarkably effective at shrinking tumors, but drug developers are already looking at novel regimens that might further stack the odds in favor of the patient’s immune system. For example, BMS has numerous trials pairing Opdivo with its first-generation checkpoint inhibitor, Yervoy (ipilimumab), which binds to a separate checkpoint protein known as CTLA-4. In a recently concluded melanoma trial, the combination outperformed either drug alone, and 74% of patients were still responding to the two-drug regimen at the study’s end.

Other therapeutic programs are pursuing new avenues to increase tumor

vulnerability. For example, **Incyte’s** epacadostat inactivates an enzyme called indoleamine-2,3 dioxygenase (IDO), which can establish chemical conditions that impede the anticancer immune response. This approach was highlighted by Lisa Jarvis in C&EN last year (“Using IDO1 Inhibitors to Combat Cancer”). The company is now working with Merck on a Phase III trial that pairs their drug with Keytruda. **NewLink Genetics** also has IDO inhibitor drugs in the pipeline, and BMS acquired **Flexus Biosciences** in 2015 to gain access to the company’s portfolio of IDO inhibitor candidates.

Several other promising targets are at earlier stages of development. **Pfizer’s** utomilumab is an antibody that binds to a T-cell protein called 4-1BB. Rather than inhibiting its target, this antibody acts as an agonist, producing signals that promote T-cell activation, and a combination of this drug with Keytruda elicited a clinical response against various solid tumors in roughly one-quarter of patients treated in a Phase IB trial. Utomilumab is now proceeding to Phase II, as is **Celldex’s**



Epacadostat

varlilumab, which also works by activating an immunostimulatory protein (CD27) and appears to work well when combined with Opdivo. ■

20. Peptidylarginine deiminase (PAD) inhibitors

Bristol-Myers Squibb/Padlock Therapeutics
Rheumatoid arthritis

Even in its infancy, **Padlock Therapeutics** was drawing a lot of attention—indeed, C&EN highlighted the company as one of its ‘Start-ups to Watch’ in late 2015. By March of 2016, the company was less than three years old and still operating entirely in the preclinical world, but **Bristol-Myers Squibb** was nevertheless sufficiently smitten by their therapeutic approach to acquire the company in a \$600M deal.

Padlock’s efforts were centered around founder Paul Thompson’s work with a class of enzymes known as peptidylarginine deiminases (PADs), which modify other proteins by attaching a chemical group known as citrulline. Although this citrullination can play a constructive role in cellular function, rheumatologists have also recognized for decades that citrullinated proteins are a common target for the host cell-attacking autoantibodies produced in rheumatoid arthritis (RA). In fact, this test has become a standard component of the diagnostic work-up. Thompson, a biochemist at the University of Massachusetts Medical School, saw a prime opportunity to intercept disease progression. “These antibodies appear on average four to five years before clinical symptoms, and then the titers get higher and higher until you suddenly hit a threshold and the patients progress to overt RA,” he says. “The idea with inhibiting PADs is that if you get rid of the antigen, you can get rid of the disease.”

Thompson’s laboratory had developed multiple different inhibitors of PAD4, which performed well in a commonly-used rodent model of RA. “We showed efficacy at doses of 10 mg/kg,” he says, “and that was in therapeutic mode, where we started treatment after disease onset.” Padlock had also licensed several PAD4 inhibitors from **GlaxoSmithKline**, including one (GSK199) that similarly alleviated symptoms in the same RA mouse model.

Antibodies against citrullinated proteins are largely an exclusive feature of RA, but PAD inhibitors could still confer clinical benefit in other diseases. Under certain conditions, PADs can initiate a dramatic ‘self-destruct’ process in white blood cells, which results in the ejection of DNA, protein, and other biomolecules to produce what are known as neutrophil extracellular traps (NETs). NETs attract other immune cells, and normally help fight infection but also contribute to the pathology of a variety of diseases. “Inhibition of NET formation correlates with efficacy in models of lupus and atherosclerosis, and there’s some evidence it might even work in cystic fibrosis,” says Thompson. Importantly, inhibition of individual PAD enzymes appears to have no obvious ill effects, and one genetic survey even found that people born without functional PAD2 or PAD4 genes have normal life expectancy.

Although BMS has not yet disclosed their plans for moving forward with PAD inhibitor development, Thompson believes RA will likely remain at the top of the agenda, and believes that the strong interest of the rheumatology community will be a powerful asset. “Rheumatologists are intimately familiar with the presence of these antibodies to citrullinated targets,” he says, “and they’re really interested in getting a PAD inhibitor into the clinic to test this hypothesis.” ■

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Telomerase treatment

21. Imetelstat

Geron/Johnson & Johnson

Myeloproliferative disorders

Cell division gradually erodes the repetitive telomere sequences that cap the ends of the chromosomes; when these become too short, the cell stops dividing. Tumor cells can overcome this proliferative barrier by producing telomerase, a telomere-extending enzyme that is normally inactive in adult cells.

Geron's telomerase inhibitor imetelstat was initially developed for cancer but delivered underwhelming performance against solid tumors. However, the drug has found redemption as a therapeutic option for myeloproliferative disorders, characterized by excessive production of certain blood cell types. In collaboration with Johnson & Johnson subsidiary Janssen, Geron conducted a highly successful Phase II clinical trial for essential thrombocythaemia, achieving a complete response in 16 out of 18 patients with this rare disorder. A second study showed that imetelstat could also benefit patients with myelofibrosis, an often-fatal disorder that is normally treated by bone-marrow transplantation.

Intriguingly, the data suggest that the drug is not altering telomerase activity, but instead acting through an alternative cellular mechanism to halt blood cell proliferation. Regardless of the mechanism, the results have generated considerable excitement, and Geron and Janssen kicked off 2016 with a new Phase II/III trial for myelodysplastic syndrome patients. ■

Antibacterial antibody

22. Bezlotoxumab

Merck

Bacterial infections

Roughly a quarter of patients who manage to initially fend off *Clostridium difficile* with antibiotics will experience a recurrence of infection—setting the stage for even more bouts with this potentially-lethal bacterium down the line. Last September, Merck presented data from two Phase III studies demonstrating that their drug bezlotoxumab could meaningfully reduce the risk of recurrence, and the FDA is currently pondering an approval decision.

This drug is unusual in that it is an antibody-based treatment rather than a conventional antibiotic. Bezlotoxumab specifically binds to toxin B, the bacterial protein that is largely responsible for the disease symptoms associated with *C. difficile* infection. This leaves the pathogen intact while essentially disarming it, preventing the onset of inflammation and tissue damage. In the MODIFY-1 and -2 trials, 15.7-17.4% of patients who received bezlotoxumab alongside antibiotics experienced recurrence versus 25.7-27.6% in the placebo arm. Although they generally found these results compelling, the FDA's Anti-microbial Drugs Advisory Committee has requested additional

information on safety and efficacy before rendering a final decision. ■

Death sentence

23. Venetoclax

AbbVie/Roche

Leukemia

This past April, the FDA gave the nod to venetoclax, a compound from AbbVie and Roche that has delivered dazzling results for certain forms of leukemia. This drug is the first of its kind, a small-molecule agent that promotes cellular suicide by preventing a protein called B-cell lymphoma-2 (BCL-2) from inhibiting the apoptotic cell death pathway. Excessive BCL-2 is a feature of many cancers, and its activity enables tumor cells to proliferate aggressively without triggering the failsafe mechanisms that normally kill off genetically or metabolically defective cells.

Approval was based on the results of two recently concluded Phase II trials, which showed an overall response rate of 79.4% among chronic lymphocytic leukemia patients (CLL). Importantly, these patients all had deletions in chromosome 17, which renders their tumors especially insensitive to chemotherapy. The initial approval is for previously-treated CLL featuring the 17p deletion, but the drug has also received Breakthrough Designation for cases of acute myeloid leukemia (AML) that cannot be treated with conventional chemotherapy, and the company is obtaining promising clinical data for various other blood cancers as well. ■

Fresh start for MS patients

24. Hematopoietic stem cell transplantation

The Ottawa Hospital

Multiple sclerosis

Canadian clinical researchers have shown that aggressive reboot of the immune system can halt—and in some cases even reverse—the progression of multiple sclerosis (MS) for years on end. The villain in this disease is a patient's own hyperactive immune cells, which attack the brain and spinal cord and thereby cause gradual degeneration of neurologic function. Over the past few decades, clinicians have amassed evidence that this crisis might be averted by using chemotherapy to essentially wipe out the defective immune system, and replacing it with blood-forming



A combination of chemotherapy and stem cell transplantation can apparently halt the progression of multiple sclerosis in many patients.

hematopoietic stem cells (HSCs) from a healthy donor.

This regimen is grueling—and potentially fatal—but with high risks come great rewards. In a *Lancet* article from this past June, researchers led by Harold Atkins and Mark Freedman describe a Phase II trial performed with 24 patients suffering from aggressive MS. Although one patient died, the treatment stopped disease progression entirely in 16 of the patients, and eight exhibited measurable and meaningful improvements in their symptoms. Since these results were tabulated three years after the procedure was completed, HSC transplantation might offer hope of an enduring recovery for patients with severe MS. ■

Potent protection

25. Shingrix

GlaxoSmithKline
Shingles virus

Once a person has been infected with varicella zoster virus (VZV), it lingers for a lifetime. Although it often remains latent, VZV will become reactivated in a sizeable subset of individuals, giving rise to the painful disorder known as shingles. There is a vaccine available, **Merck's** Zostavax, but the extent of protection drops considerably in older patients—from around 70% for people in their 50s to less than 40% for those in their 70s. This is a potentially serious problem, given that the elderly are at particular risk for shingles.

GlaxoSmithKline has developed a promising alternative vaccine, which pairs a subunit protein from VZV with a potent new adjuvant. In a large Phase III trial with 14,759 participants, Shingrix offered a consistent defense against shingles across all age groups, with two doses of vaccine delivering an efficacy of 97.2% relative to placebo. Looking beyond Shingrix, GSK's Chairman of Vaccines Moncef Slaoui told *Fierce Pharma* that this trial was also valuable as proof of the potency of their adjuvant, noting that "Shingrix can be the spearheading vaccine to a new generation of elderly vaccines." ■

Keeping hemoglobin in shape

26. GBT440

Global Blood Therapeutics
Sickle-cell disease

Mutations in the gene encoding hemoglobin can produce a defective protein that clumps together, causing red-blood cells to resemble rigid crescents rather than plump donuts. This gives rise to sickle-cell disease, a family of disorders associated with high risk of morbidity and mortality.

Global Blood Therapeutics is going after this condition with a compound that binds to the defective hemoglobin and maintains it in a state that greatly reduces the risk of clumping.

In June, the company presented data from six patients who had been treated with an oral formulation of their compound, GBT440, showing that their drug is effective at preserving

red blood cells, which normally die off rapidly in this disease. Importantly, these beneficial effects were apparent for at least 90 days of treatment, with no evidence that the drug was impeding the release of oxygen from hemoglobin—something that had been an initial safety concern. In late June, the company announced that it would be following up by launching an open-label Phase IIa study in adolescents afflicted with sickle-cell. ■

Retinal repair

27. Voretigene neparvovec

Spark Therapeutics
Inherited retinal dystrophy

This past spring, the European Medicines Agency (EMA) issued its second gene therapy approval to date, for **GlaxoSmithKline's** Strimvelis. In contrast, the FDA has yet to sign off on any such treatments, although **Spark Therapeutics** is making important headway with this regulatory body.

In July, the company published a Phase I trial for voretigene neparvovec, a therapeutic approach that uses a virally delivered gene to repair retinal cells that are malfunctioning as a result of inherited retinal dystrophy. None of the 11 patients experienced any ill effects from the treatment, and ten of the patients experienced improved light sensitivity in the treated eye. This therapy was previously awarded Breakthrough Designation by the FDA, and has also racked up a successful Phase III trial which demonstrated clear improvement in visual function among treated patients relative to the control arm. Spark is currently working towards market approval from the FDA with a 'rolling' biological license application (BLA), and the company has announced its intention to complete the filing process by the end of this year. ■

Strong stomachs

28. IMAB362

Ganymed Pharmaceuticals
Gastric cancer

One of the big surprises at this year's meeting of the American Society for Clinical Oncology (ASCO) came from **Ganymed Pharmaceuticals**, a German biotech specializing in tumor-specific 'ideal monoclonal antibodies'. They presented data from a Phase II trial of IMAB362, which recognizes a protein called claudin 18.2 that is found in high abundance at the interfaces between cancer cells.

In a cohort of patients with claudin 18.2-positive gastric or gastroesophageal cancer, IMAB362 extended median progression-free survival by more than 60% relative to chemotherapy alone—even more impressively, the drug extended overall survival to a median of 13.2 months versus 8.4 months in the arm receiving the current standard of care. This benefit was even more profound for patients with tumors expressing high levels of claudin 18.2, with a median overall survival of 16.7 months.

This could be a valuable new weapon against a cancer that offers a poor prognosis, with a five-year survival rate of less than 30%, and the company is planning to move the drug to Phase III trials next year. IMAB362 might also prove a powerful weapon against other hard-to-treat cancers that over-express claudin 18.2, including pancreatic cancer. ■

Reprogramming polio

29. PVS-RIPO poliovirus

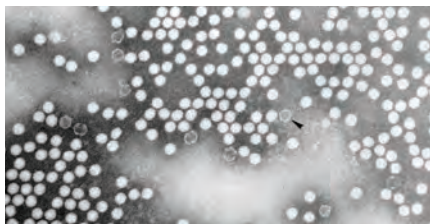
Duke University

Glioblastoma multiforme

Clinical researchers have long been tantalized by the prospect of weaponizing viruses against cancer, although successes to date have been few in number and modest in efficacy. After more than 20 years of effort, researchers at Duke University have now obtained exciting findings from a phase I trial for a lethal form of brain cancer that could help reinvigorate the field.

In the 1990s, Matthias Gromeier and colleagues developed a recombinant poliovirus derivative called PVS-RIPO, which contains sequence elements that were swapped in from human rhinovirus.

The resulting virus loses its capacity to damage healthy neurons, but can infect and kill cancer cells while also eliciting a potent immune response that inflicts further damage on the



Although historically a foe of humanity, scientists have found that poliovirus might also offer a potent weapon against brain tumors.

tumor. In a study coordinated by neuro-oncologist Darell Bigner, PVS-RIPO was injected directly into the brain of 24 patients with glioblastoma multiforme. Although half the patients have died—a sadly typical outcome for this cancer, with a median survival time of 14.6 months—three of the patients have survived 22 months or longer after treatment, and two patients were apparently disease-free as of this past May. Progression was apparently halted in all but one of the surviving patients.

Based on these preliminary but promising findings, the FDA awarded Breakthrough Designation to PVS-RIPO in May, and plans are in the works for an expanded phase I later this year. ■

A valuable vitamin

30. MD1003

MedDay

Multiple sclerosis

That vitamins are generally good for your health is common knowledge, but a vitamin B derivative is also proving its mettle as a surprisingly effective tool for treating MS. In contrast to most drugs now in the MS pipeline, which gener-

ally target the immune system, **MedDay's** formulation of the vitamin biotin is thought to work by directly protecting the health of damaged neurons. This is based on evidence that high doses of biotin boost neuronal metabolic activity and stimulate replacement of the myelin coating that becomes damaged over the course of MS.

In a recently concluded Phase III trial, MedDay showed that 12.6% of progressive MS patients who received their drug, MD1003, exhibited meaningful improvements in their disease symptoms; in contrast, no improvement was seen in the placebo arm of the trial. A parallel trial showed no meaningful improvement in visual symptoms of MS, but both studies demonstrated that the drug was well-tolerated. With a recent infusion of \$38.5 million in Series B funding, the company is planning to file for approval in Europe this year while also embarking on a confirmatory Phase III trial to win over regulators in the US. ■

Eliminating Ebola

31. GS-5734

Gilead Sciences

Ebola

Survivors of infection with Ebola virus are not necessarily entirely out of the woods. There is growing evidence that patients may experience relapse of infection, and there are documented cases of disease transmission via semen up to six months after initial infection.

In collaboration with the US Army Medical Research Institute for Infectious Diseases, **Gilead Sciences** has developed a drug that can potentially thwart the re-emergence of Ebola. After internalizing GS-5734, cells convert it into a molecule that resembles an RNA ribonucleotide. When Ebola viruses attempt to incorporate it into their RNA-based genome, GS-5734 brings the replication process to a grinding halt, preventing the production of new viral particles.

This drug was effective in treating a nurse who experienced a relapse of Ebola, with no virus detectable after two weeks of treatment. Gilead is now working with the governments of the US and Liberia to scale up testing with a trial called PREVAIL, which will recruit male Ebola survivors who have detectable levels of virus in their semen. The drug could be useful for other RNA-based viruses as well, and the World Health Organization is considering it as a tool in the ongoing battle against Zika. ■

Mother's little helper

32. SAGE-547

Sage Therapeutics

Postpartum depression

For as many as 1 in 10 new mothers, the joy of a healthy birth is followed by a protracted bout of postpartum depression. A steady trickle of positive data from **Sage Therapeutics** suggests that their compound SAGE-547 might

offer effective relief to the women who are hardest hit by this debilitating condition.

The drug is based on the naturally occurring hormone allopregnanolone, and was initially developed for the pediatric seizure disorder status epilepticus. However, its action on brain receptors that respond to the neurotransmitter GABA also makes it a promising option for treating depression, which can arise from malfunctions in these receptors. In a tiny preliminary study, the drug essentially eliminated symptoms of depression in all four patients who received treatment within a matter of days. In July, the company announced results from a still small—but placebo-controlled—Phase II trial. Only one of the 11 control patients exhibited meaningful improvement, compared with 7 out of 10 in the treatment arm. The extent of the response was also striking, and well above the reductions in symptom activity seen in many antidepressant trials. Investors are excited, but the experts are waiting to see more patients successfully treated, and the company has now expanded the trial to identify optimal dosing. ■

Giving cancer a STING

33. ADU-S100

Aduro Biotech/Novartis
Cancer

Among the myriad defenses the body maintains against infection is the stimulator of interferon genes (STING) pathway, which triggers an immune response to by-products of bacterial and viral DNA. **Aduro Biotech** is looking to exploit this mechanism to mount a successful counterattack against cancer with a drug candidate that acts as a STING agonist.

ADU-S100 is a synthetic cyclic dinucleotide, emulating a class of molecules that many bacteria use for signaling purposes, and which are known to act as triggers of the STING pathway. In a series of preclinical studies, Aduro and collaborators have shown that STING agonist treatment can provoke an immune response that effectively drives regression of both lymphomas and solid tumors in rodents. These findings attracted the attention of **Novartis**, which has subsequently inked a \$750 million deal with Aduro to collaborate on development and commercialization. Although there are no data available from humans as of yet, Aduro recently initiated a Phase I trial for patients with advanced cancers that are accessible via cutaneous injection. ■

Fistula-fighting fat

34. Expanded adipose stem cells

TiGenix
Crohn's disease

Many of the clinical applications now being explored for stem cell therapies entail the direct replacement of damaged tissues, but stem cells can also potentially

act indirectly to promote tissue repair. This is believed to occur through the production of regeneration-promoting growth factors or modulation of inflammatory pathways, although the details are not fully understood.

TiGenix is looking to treat a variety of different conditions with adult stem cells which have been isolated from the adipose tissue of healthy donors, expanded in culture, and then injected into patients. The company's most advanced clinical program, Cx601, is targeted at the repair of the deep intestinal ulcers that can form as a result of Crohn's disease. The company recently released data from a Phase III trial showing that more than half of patients treated with these allogeneic stem cells achieved durable remission lasting over a year, versus 37.1% in the placebo arm. **Takeda** recently forged a deal with TiGenix totaling over \$400 million, which would grant the Japanese biotech commercialization rights for Cx601 outside the US, and TiGenix has already filed for approval with the EMA. ■

Entry prohibited

35. Ibalizumab

Theratechnologies/TaiMed Biologics
HIV

MAn antibody that interferes with cellular uptake of the human immunodeficiency virus (HIV) could give patients another line of defense when existing antiviral drugs fall short. Ibalizumab is a humanized monoclonal antibody against CD4, HIV's preferred docking site on the surface of immune cells. Interestingly, the antibody does not prevent this initial binding event, but instead appears to interfere with subsequent assembly with the virus's cellular coreceptors, CXCR4 and CCR5.

The drug is being developed collaboratively by **Theratechnologies** and **TaiMed Biologics**, who recently announced a successful outcome for a single-arm Phase III trial in which 33 out of 40 patients met the primary endpoint of reduced viral load. For all of these patients, their infection had already acquired resistance to at least one of the standard antiviral agents. This trial is still ongoing, and the two companies recently completed enrollment for a second Phase III trial that will provide the final data required by the FDA to consider approval. ■

Breaking the cycle

36. CDK4/6 inhibitors

Multiple companies
Cancer

Palbociclib (marketed as Ibrance) from **Pfizer** was first out of the gate, but several other drugs targeting the cyclin-dependent kinase (CDK) 4 and 6 proteins are following close behind in the anticancer pipeline. These two proteins are important cell cycle regulators, helping kick off the round of extensive DNA replication that precedes cell division.

CDK4 and CDK6 work overtime to facilitate proliferation in many cancers, making these closely-related proteins appealing therapeutic targets, and CDK4/6 inhibitor palbociclib won FDA approval last year on the strength of its performance against advanced breast cancer. More recently, **Novartis** stopped its Phase III MONALEESA-2 early after achieving a clear improvement in progression-free survival with ribociclib in the same patient demographic. **Eli Lilly** is somewhat further behind with adamaciclib, but also had positive data to show for its Phase II MONARCH 1 trial. Although all three drugs are duking it out for a common indication, a wide variety of other solid tumors—including lung, skin and brain cancers—also experience cell cycle disruptions that are potentially vulnerable to the same therapeutic approach. ■

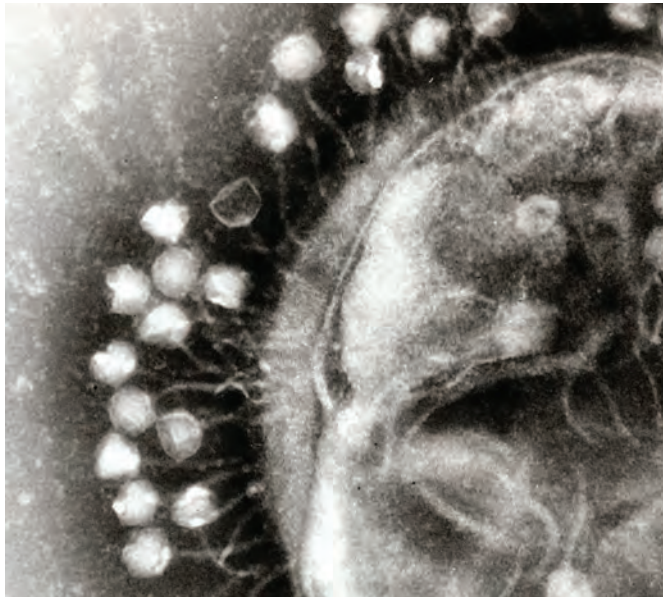
Valiant viruses

37. Bacteriophage therapy

Pherecydes Pharma

Post-burn infection

Even bacteria can perish from an infection, and the idea of using bacteriophage viruses to wage biowarfare on human pathogens is nearly a century old. Indeed, Soviet soldiers routinely used this approach to fighting infection when antibiotics were scarce, although the technique was largely



Cocktails of bacteria-targeting viruses could help fight off infections.

ignored in much of the world. Now, as drug-resistant bacteria gain traction against our existing arsenal of antibiotics, there is renewed interest in so-called 'phage therapy' as an antibacterial countermeasure.

With support from the European Union, the Phagoburn trial is presently testing how well various combinations of bacteriophage strains identified by **Pherecydes Pharma** and produced by **Clean Cells** fend off infections patients at burn units across

Western Europe. Animal testing has suggested that this approach is remarkably safe, and success in fending off *E. coli* and *Pseudomonas aeruginosa* in PhagoBurn could pave the way for the development of viral countermeasures against a host of other resistance-prone and potentially lethal bacteria species. ■

No more bad blood

38. BMN 270

BioMarin

Hemophilia

Mutations in the gene encoding factor VIII leave hemophilia A patients with a reduced ability to form blood clots in the aftermath of an injury. To prevent fatal bleeding, most patients receive regular doses of recombinant factor VIII protein, but **BioMarin** is hoping to provide a long-term fix via gene therapy.

Their BMN-270 treatment uses an adeno-associated viral vector to deliver a working copy of the gene encoding factor VIII to patients. Clinical data released in July provide compelling support for BioMarin's approach; a single dose of BMN-270 was sufficient to restore factor VIII production to essentially normal levels in 6 out of 9 patients with severe hemophilia A after 12 to 28 weeks. Notably, two of the three patients who did not benefit received a lower dose of the therapy. The treatment was associated with a transient increase in liver enzymes, but no serious adverse events arose, and the company is planning a Phase IIb trial for 2017 that it hopes will pave the way for accelerated approval. ■

Undoing SMA

39. Nusinersen

Ionis/Biogen

Spinal muscular atrophy

Spinal muscular atrophy can arise from a change in a single nucleotide, which prevents the proper processing of the messenger RNA produced by the *SMN2* gene. The resulting shortage of working SMN protein results in degeneration of the nerves and muscles and a greatly shortened life expectancy.

Ionis Pharmaceuticals has developed an oligonucleotide-based drug that binds specifically to the segment of *SMN2* RNA where this processing goes wrong, enabling the production of functional protein. In the aftermath of their successful Phase III ENDEAR trial, Ionis' partner **Biogen** has paid out \$75 million for the rights to commercially develop nusinersen. Interim analysis revealed that the drug had sufficiently improved motor function in infants born with SMA to justify early termination of the placebo-controlled trial. As the first treatment for this debilitating disease, nusinersen could become a billion-dollar-drug, and Biogen will be filing for FDA approval later this year. ■

A BET against cancer

40. Bromodomain drugs

Various companies

Cancer

This past spring, **Roche** made a strong investment in bromodomain inhibitors as a promising new strategy for going after various cancers, joining a host of other Big Pharma players and start-ups now crowding the space. This class of compounds interferes with bromodomain and extra-terminal domain (BET) proteins, which recognize their

target genes based on 'epigenetic' chemical modifications at specific sites on the chromosome. Preclinical studies have shown that BET inhibitors can cause cell cycle arrest in various cancers by shutting off key oncogenes.

Roche acquired **Tensha Therapeutics** for \$535 million on the strengths of a BET inhibitor, TEN-010, that shown some promise in early clinical testing. Numerous other companies including **Merck, Abbvie, Incyte, Gilead,** and **Bristol-Myers Squibb** also have clinical trials underway for their own various BET inhibitors, although these are still at too early a stage to discern who might have an edge. ■

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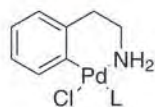


Corporate Headquarters, USA

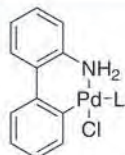


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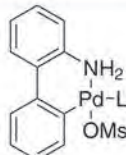
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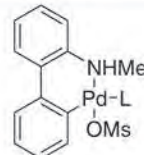
First Generation



Second Generation



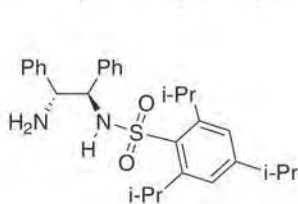
Third Generation



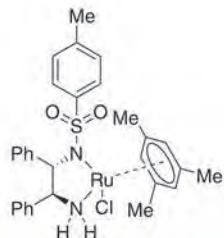
Fourth Generation

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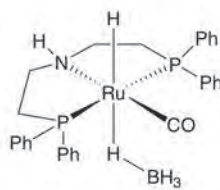
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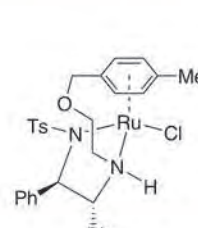
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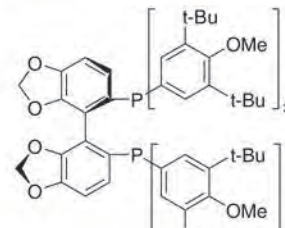
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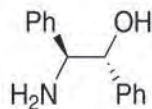


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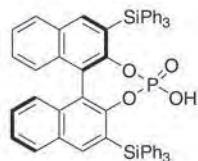


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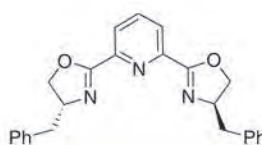
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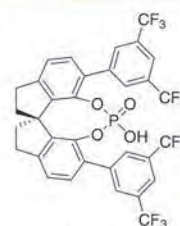
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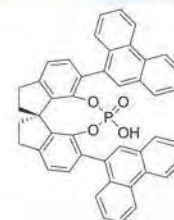
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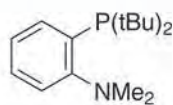


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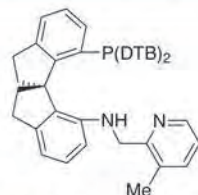


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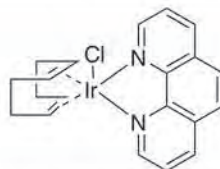
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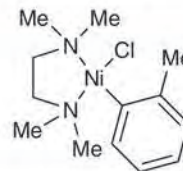
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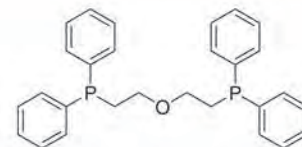
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