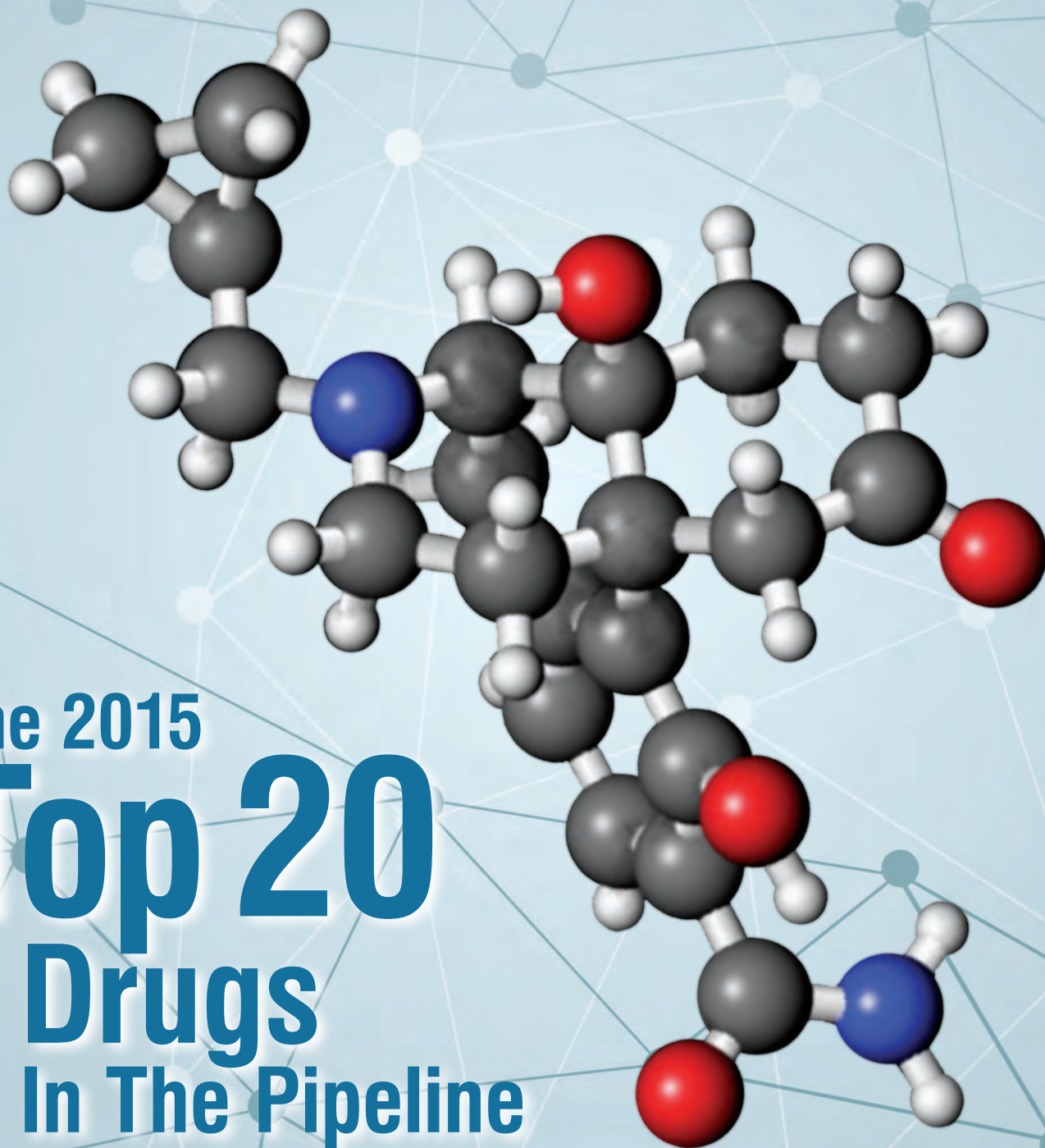


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September 2015



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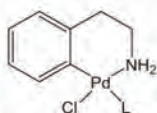


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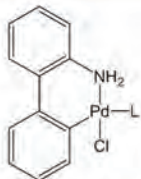


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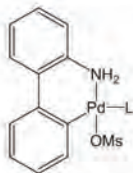
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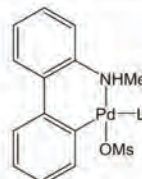
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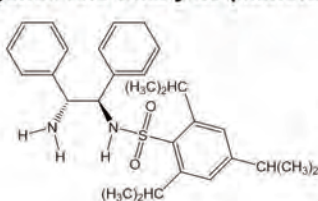
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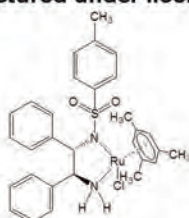
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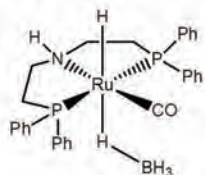
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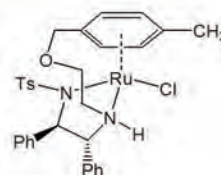
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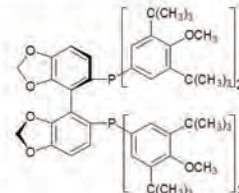
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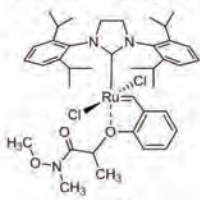


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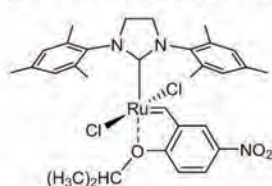


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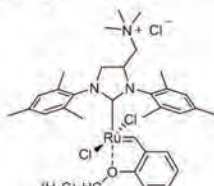
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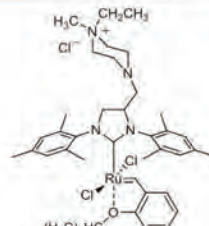
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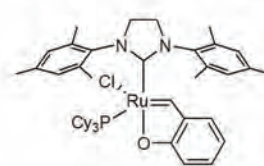
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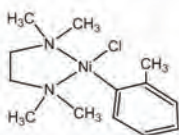


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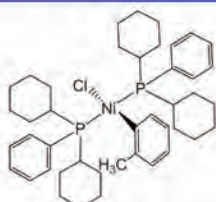


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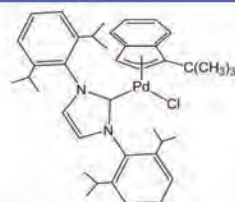
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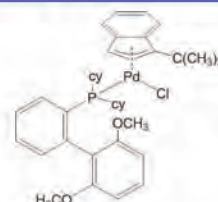
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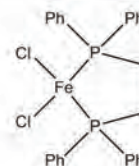
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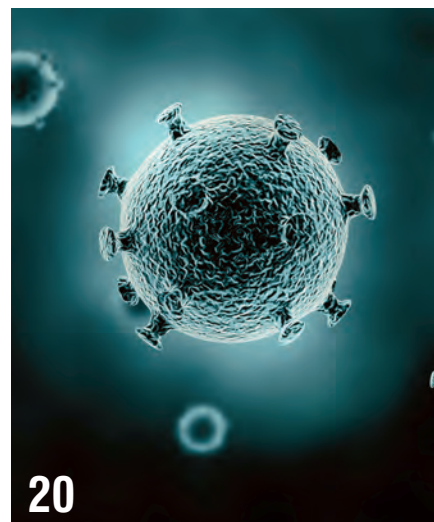
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Correction

This issue was updated on Dec. 2, 2015, to correct the labels of the sugar molecules on the diagram on p. 19 and to correct the structure of samidorphan on p. 22. We have also acknowledged that teixobactin (p. 29) was discovered by NovoBiotic Pharmaceuticals, not Northeastern University as previously stated.

Cover image: Structure of samidorphan. Created by Digital World Biology® with its Molecule World™ app on the iPad and exported using Molecule World's camera feature. Shutterstock/C&EN

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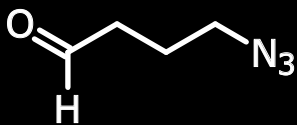
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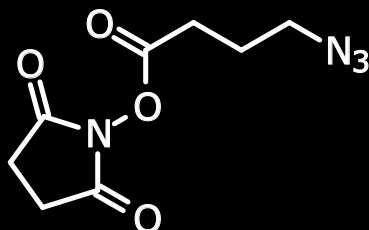
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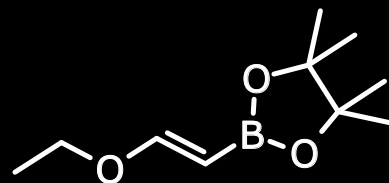
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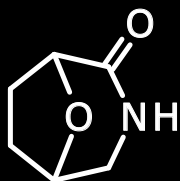
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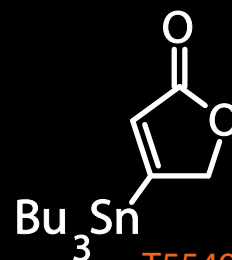
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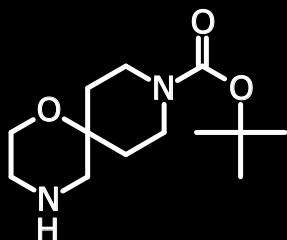
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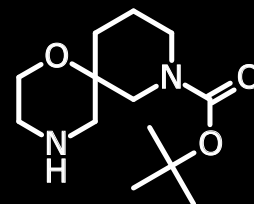


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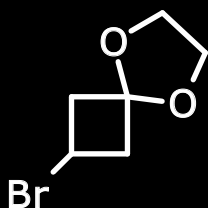


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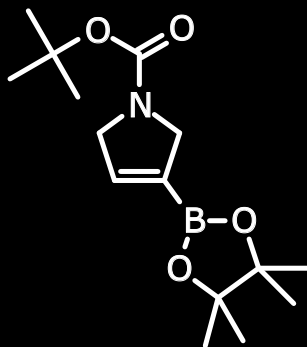
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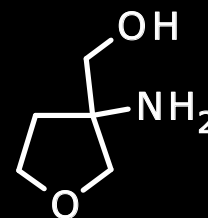
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PUBLISHER'S NOTE

Pipeline Promises

LAST YEAR, a 3D model of Gilead's Solvadi graced the cover of C&EN's special report on the Top 50 Drugs of 2014. Based on the critical reception that supplement received, we wanted to revisit the theme this year. However, for a slight variation, we've chosen to focus on drugs that are "in the pipeline" (to borrow the title of Derek Lowe's must-read blog).

For this report, we tasked contributing editor Dr. Nina Notman to identify 20 of the most promising new drugs—small molecules, monoclonals, various genetic constructs—that look poised to win approval in the coming years and have a profound effect on human health, from rare diseases to common cancers. In the supplement introduction, Nina outlines her criteria for drug selection, but notes that putting these in a rank order is, by definition, a little arbitrary.

Regardless of whether you think we have overpraised or under-appreciated certain drugs in this report, there is no denying the excitement surrounding new forms of drug discovery. Names like Juno Therapeutics and Editas Medicine did not exist a few years ago, and yet here they are already, with novel and potentially revolutionary drugs and technologies bringing hope to patients. Bluebird Bio did not exist a few years ago either, although that's because the firm was previously known as Genetix Pharmaceuticals. The prospect of gene therapy providing clinical benefit is remarkable given the severe setback the field suffered following the death of volunteer patient Jesse Gelsinger in 1999.

I'd like to thank Nina—a frequent contributor to *Chemistry World* magazine—for her debut contributions to C&EN. And we thank the companies who have chosen to support production of this supplement by advertising. We can assure you, based on experiences last year, that this will be one of the most read publications from C&EN over the course of 2015.

Doubtless you will be able to keep track on the progress of many of these molecules in the pages of C&EN, as we wait with baited breath to see if their promise is fulfilled.

Best Wishes



Kevin Davies, PhD
Publisher, C&EN

A RARE TREAT

Nina Notman

WELCOME TO a 2015 snapshot of the most exciting drug candidates currently in the biopharma pipeline.

We believe that these 20 drugs (or groups of similar drugs) all have the potential to be hugely successful if and when they win approval. Our reasons for selecting these over the hundreds if not thousands of prospects inching their way through preclinical or clinical studies are varied. These drugs might impact huge numbers of people whose lives they could potentially improve or save. Some offer hope of a viable treatment for a rare disease where currently there is none. Others utilize some breathtakingly clever and novel science, where one can only hope that clinical application matches the fundamental research.

Potential earning capability was also considered during the selection of the top 20. But while each drug (or group of drugs) has had to earn its (or their) place in this supplement, the precise ranking itself is somewhat arbitrary.

Genes and Therapy

It is estimated that nearly 40% of people will be diagnosed with cancer at some point during their lives. It is therefore not surprising that approaches to boosting the oncology toolbox continue to dominate the drug pipeline—as reflected in our top 20 rankings. Five of our 20 selected drugs are targeting various types of cancer. Approaches that help the body's own immune system to kill off cancerous cells—the so-called immunotherapies—are undoubtedly generating the biggest buzz.

Ways to correct faulty, disease-causing genes also feature heavily. Gene therapy has been in development and clinical trials for decades, but after years of setbacks, in November 2012 the first of these was finally approved in Europe. No gene therapies have yet been given the green light by the U.S. Food & Drug Administration (FDA), but this is thought to be imminent and companies are scrambling to be first over the line.

Among them is Spark Therapeutics, which is injecting a modified virus armed with a corrected gene (called SKP-RPE65) into the eyes of patients with a severe genetic eye disorder. Here the gene correction process is occurring inside the body but many of the gene therapies in the pipeline are *ex vivo*, meaning cells are genetically modified outside of the body. Bluebird Bio is hoping its LentiGlobin BB305 will be the first approved gene therapy of this type.

Also highlighted in this year's top 20 list is the highly touted

CRISPR/Cas9 gene editing technique, which is still in the very early stages of development. The ability of CRISPR/Cas9 to snip out and replace faulty genes means it could potentially revolutionize the already revolutionary gene therapy.

Much closer to the market is a first-in-class drug that can patch over a faulty gene. BioMarin Pharmaceutical's drisapersen has the potential to transform and extend the lives of some boys with Duchenne Muscular Dystrophy, and could be approved by the end of 2015. Sarepta Therapeutics' eteplirsen—with the same mode of action—is just two months behind in the approval process.

Meanwhile, Alnylam Pharmaceutical's patisiran may well become the first small interfering RNA therapeutic approved for market. This gene silencing drug turns off the faulty genes that cause a rare genetic liver disease.

Drugs for rare diseases—such as the above genetic disorders—are hot business at the moment. They cost less to put through clinical trials (thanks to small trial sizes) than other diseases, have an advantage at regulatory review due to a lack of alternative treatments and can command extremely high prices when they do hit the market for the same reason. According to industry analysts EvaluatePharma, the average cost of drugs for rare diseases is six times more per patient than that of other drugs. By 2020, it is estimated that drugs for rare diseases will account for 19% of the total share of (non-generic) prescription drug sales, amounting to \$176 billion per year.

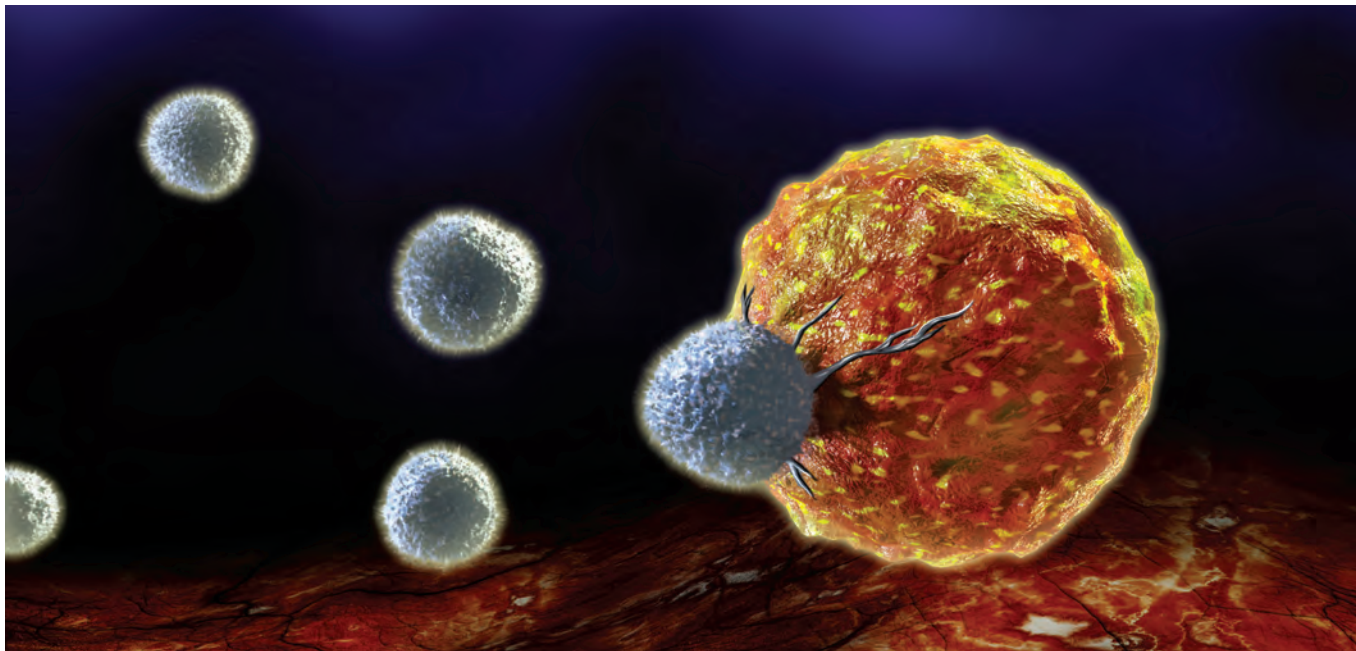
Many of the more traditional type of big money-making drugs in the pipeline—the potential blockbusters, that could earn their makers over \$1 billion per year—were also selected for highlighting in this report, including drug combinations for treating hepatitis C and HIV, and monoclonal antibodies for slowing Alzheimer's disease progression.

We hope you enjoy this special C&EN supplement. How did we do? Did we pick a fair representation? Please tell us which drugs you would have put on this list, and why, by writing to CENsupplements@acs.org.

Nina Notman PhD is a contributing editor for this C&EN Supplement. Nina is a freelance science writer and editor based in Salisbury, UK. ■

TOP 20 DRUGS IN THE PIPELINE

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Immune checkpoint modulators outsmart cancer cells by re-enabling the body's T cells to hunt down and kill these interlopers.

1. IMMUNE CHECKPOINT MODULATORS

Genentech, AstraZeneca, Bristol-Myers Squibb, and Merck & Co.

Various cancers

Cancer is a sneaky disease. It can evade and confuse T cells, switching off the body's natural immune response to cancerous cells. Drugs that can remove the brakes cancer puts on T cells are being widely explored as a way to combat one of the world's biggest killers. With the brakes off, T cells can once again hunt down and destroy their enemy.

Three of these so-called immune checkpoint modulators are now on the market, with many more expected to follow. Combinations of checkpoint modulators with both other checkpoint modulators and different therapeutic types are also generating exciting results in pre-clinical and clinical trials.

Breaking the body's immune tolerance to cancer will equal big bucks. This is expected to become a crowded and frenzied marketplace. Industry analysts EvaluatePharma predict that the global annual cancer drug market will expand an average of 10% per year for the next five years to reach more than \$153 billion in 2020. Drugs targeting the PD-1 (programmed cell death protein 1) pathway are expected to account for nearly a quarter of this growth.

The first immune checkpoint modulator to market did not target this pathway. Yervoy blocks the CTLA-4 receptor instead and was approved for treating advanced melanoma in 2011. This drug, made by **Bristol-Myers Squibb (BMS)**, currently earns \$1.3 billion per year.

PD-1 is a receptor on the surface of T cells that binds the ligand PD-L1. This constitutes an immune checkpoint, playing a vital role in regulating the strength of an immune response to invaders. Cancer cells are, however, able to confuse it by expressing PD-L1 themselves to sneakily instruct T cells not to attack them. In 2014, the first two PD-1 inhibitors gained US Food & Drug Administration (FDA) approval. These block the PD-1 receptors from cancer's trickery, and hence the T cells stay switched on.

Merck & Co.'s monoclonal antibody Keytruda was first PD-1 inhibitor out the gate, approved for treating advanced melanoma in September 2014. EvaluatePharma predict that annual worldwide sales of this immunotherapy will reach nearly \$5 billion in 2020. Former president Jimmy Carter recently an-

nounced that he was embarking on treatment with Keytruda following his diagnosis with melanoma, which has spread to his liver and brain.

BMS's Opdivo was next to market, approved for advanced melanoma in December 2014 and for lung cancer in March 2015. Opdivo is predicted to rake in over \$8 billion per year in 2020, making it the second highest selling oncology drug worldwide.

Immune Pipeline

Some of the most exciting checkpoint modulators in the pipeline are PD-L1 inhibitors, designed to interfere with the PD-L1 ligand rather than the receptor, but still blocking the interaction on T cells. **Genentech** has an investigational drug candidate, atezolizumab, in Phase III clinical trials. It is also being trialed in combination with a range of different approved and not yet approved cancer treatments, including the blockbuster drug Tarceva and another type of checkpoint modulator—an agonist rather than an inhibitor—MOXR0916. These trials are looking at treating various cancers and Genentech has the coveted FDA breakthrough therapy designation for use in bladder and lung cancer. The first filing for FDA approval is expected for lung cancer in early 2016, with filings for other cancers to follow. EvaluatePharma predicts this immunotherapy will earn more than \$2 billion per year by 2020.

Another anti-PD-L1 candidate for which there are high hopes is **AstraZeneca's** durvalumab. This monoclonal antibody is also in Phase III trials, both alone and in combination with other drugs, again for various cancer types.

It is in these drug combinations that most of the clinical excitement lies, because the premise behind these checkpoint modulators as cancer-busting agents has a flaw: a significant one. The likelihood of success depends on whether the patient has an underlying immune response, which is being blocked by cancerous cells expressing PD-L1.

"A clinical response will follow if you have an immune response that's just held in check by PD-L1 and then you come in with an inhibitor that unclogs the gears of the immune system so it can work efficiently," explains James Gulley, head of immunotherapy at the National Cancer Institute. Many patients do not have this, and for them pairing checkpoint inhibitors with other therapeutics that are able to kick start an underlying immune response may be the key to success.

Gulley draws comparisons with HIV, which was not brought under control until the advent of cocktails of three or more drugs. "I think that with these immunotherapies, in order to get the maximum benefit out of them, we are going to need to find rational partners for combination therapies that will address all the different aspects needed to kill the tumor cells," he says.

These partners could be other drugs, not necessarily checkpoint modulators, or vaccines. One potential approach in early stage trials is to target the enzyme indoleamine-2,3-

dioxygenase that plays a role in immune suppression. (Research on this enzyme was summarized by Lisa Jarvis in C&EN, "Using IDO1 Inhibitors To Combat Cancer," April 6, 2015; issue 14, pp.10–14.)

BMS grabbed the headlines earlier this year when it showed that a combination of its two checkpoint modulators—Yervoy and Opdivo—outperformed either drug on its own in a Phase III trial involving 945 patients with advanced melanoma. The third of the patients taking Yervoy alone reported an average time to disease progression of 2.9 months; for Opdivo it was 6.9 months; but for those taking the combined regimen, it was 11.5 months. Another important finding from this study was that patients with an underlying immune response had an average time to disease progression of around 14 months for both Opdivo alone or in combination with Yervoy, compared with 3.9 months for Yervoy alone. This means that this subset of patients could just be given Opdivo alone, avoiding the serious side effects reported for the combination therapy.

Merck has also subscribed to the combination approach, embarking on a massive program of combination trials with its PD-1 inhibitor Keytruda in collaboration with other drug companies and researchers. Partners announced so far include **Immune Design** and **Dynavax Technologies Corporation**. ■



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Emily Whitehead was the first child to undergo CAR T-cell immunotherapy.

2. CAR T-CELL IMMUNOTHERAPY

Novartis, Juno Therapeutics, Kite Pharma, and others

Various blood cancers

In 2012, the parents of six-year-old Emily Whitehead made an extraordinarily brave decision. Emily had been diagnosed with acute lymphoblastic leukemia (ALL) almost two years earlier, and all approved treatment options had failed to keep her cancer in remission. With time running out, Emily's parents were offered the option of enrolling their daughter on a Phase I clinical trial. The risks were high; this type of treatment had only been tested on a handful of patients, and never before on a child.

Emily underwent CAR (chimeric antigen receptor) T-cell immunotherapy in April 2012. The first step of this process was to remove some of her T cells and genetically-modify them to fit a cancer cell tracking device. These cells were then multiplied before being returned to her body to hunt down and kill their prey: cancer cells.

CAR T-cell immunotherapy has been under exploration since the late 1980s, but it wasn't until 2011 that interest in the area exploded. The trigger came from Carl June's lab at the Abramson Cancer Center, University of Pennsylvania. His team

has treated three advanced chronic lymphoid leukemia patients with genetically-engineered versions of their own T cells. Within three weeks, the cancerous cells had disappeared and two patients showed sustained remissions. "When people started to see these really spectacular clinical results a frenzy of interest developed," explains John Maher, head of the CAR mechanics research group at King's College, London.

Further small-scale trials, mostly on patients with advanced ALL (Emily's cancer) or lymphoma were equally successful. Many patients saw their cancers completely disappear and remain cancer-free for prolonged periods. Emily is still cancer free more than three years after her initial treatment.

CAR T-cell therapy is, however, only currently suitable for blood cancers. "For solid tumors, where most of the cancer is, we're not seeing anything like the same level of efficacy with this technology," Maher says. He and many others are trying to address this.

The most successful outcomes so far have been from tackling cancerous B-cells, by targeting the CD-19 antigen

exclusively found on B-cell surfaces. CD-19 is the target of **Novartis'** lead product, CTL019. (This was the treatment Emily received.) CTL019 is now in Phase II clinical trials. In June, it was reported that 13 of 19 lymphoma patients being treated as part of this trial had responded to the therapy. In 11 of these patients, the cancer became undetectable while the other two had a partial response. Novartis is working in collaboration with University of Pennsylvania researchers on developing this product, which has been awarded breakthrough therapy designation by the FDA. Novartis plans to file to use CTL019 to treat ALL in 2016 and for diffuse large B-cell lymphoma in 2017.

The process of transforming a patient's T cells in this procedure is far from simple. First, the patient's T cells need to be transported to a manufacturing facility where a viral vector is used to insert the gene coding for a certain type of CAR. These CARs—which form on the surface of the T cell—contain an antibody domain that recognizes the CD-19 protein. The CAR T-cells are then grown in a bioreactor until they number in the billions, and shipped back to the clinic. The patient is given chemotherapy to reduce their white blood cell count, making space for the CAR T-cells that are then infused back into their blood. (See Lisa Jarvis' report on this week-long manufacturing process, "The Immune System Fights Back," in C&EN, October 6, 2014; issue 40, pp.12–19.)

Much work will be needed to improve the efficiency and costs of this process before CAR T-cell therapy can be offered on a large scale. "Scaling that kind of activity up does cause people to scratch their heads a lot," agrees Maher. **Pfizer** and **Cellceptis** are working together to develop an approach that uses donor T cells modified to be suitable for a broad patient population. As Jarvis reported last year, this set-up requires a gene-editing technology to precisely snip out DNA segments coding for proteins that would cause patients to reject them. This universal approach is still in the early stages of development.

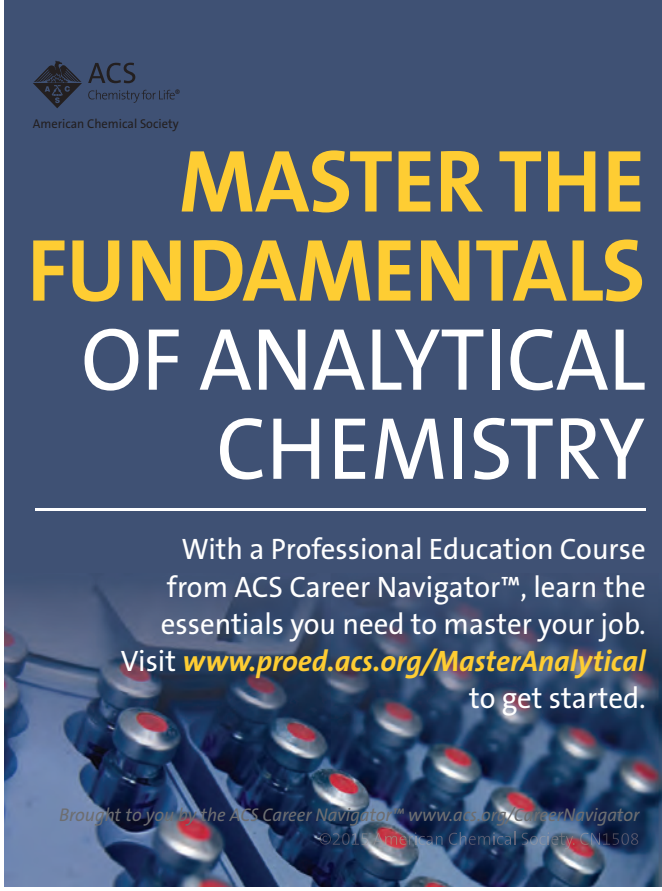
The companies snapping closest to Novartis' heels as it heads towards FDA approval are the biotech start-ups **Juno Therapeutics** and **Kite Pharma**. Juno has a handful of CAR T-cell candidates in Phase I and Phase I/II trials for various cancers. As well as targeting CD-19, some of these target other tumor antigens such as Wilms tumor antigen 1. In May, Juno reported updated Phase I results for its most advanced drug candidate: the CD-19 targeting JCAR015. An 87% complete remission rate was reported for 38 adult ALL patients. In July, Juno announced it would be initiating a pivotal Phase II study trialing JCAR015 with relapsed/refractory ALL. JCAR015 has FDA breakthrough therapy designation, and the company plans to file for registration by late 2016 or early 2017. Kite also has a pair of CD-19 targeting CAR T-cell therapies in Phase I and Phase I/II clinical trials for a range of blood cancers with similarly promising results being reported.

As the quest continues to overcome manufacturing challenges and apply CAR T-cell therapy to solid cancers, safety

remains a concern. The biggest sting in the tail of CAR T-cell therapy is the potential to over activate the immune system, causing cytokine release syndrome. T cells, modified or not, unleash cytokines whilst attacking target cells and too many of these proteins inside the body can be very serious, sometimes fatally so.

Cytokine release syndrome is a fairly common problem during CAR T-cell therapy, but the effects are generally manageable. Emily, however, became critically ill and was admitted to intensive care where doctors administered a rheumatoid arthritis drug to bring her immune response under control. Not all trial patients have been so lucky, with Juno reporting a couple deaths from this syndrome during its trials. Carefully controlling the dose is one possible answer to reducing the likelihood and severity of the syndrome.

Collaboration is fast becoming the name of the game in this field. Pairings announced in 2014 included **GlaxoSmithKline/Adaptimmune** and Kite/National Institutes of Health. So far this year, collaborations with gene editing CRISPR-focused start-ups are in vogue with Novartis/**Intellia Therapeutics** and Juno/**Editas Medicine** teaming up. Gene editing knowhow is also one of the reasons given for the collaboration between Kite and **Bluebird Bio** announced in May 2015. ■



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Gilead hopes its latest hepatitis C combination drug emulates the success of Harvoni. This photo shows Gilead's R&D team receiving a 2015 ACS Heroes of Chemistry Award for the development of Harvoni.

3. DIRECT ACTING ANTIVIRAL AGENTS

Merck & Co., Gilead, and Achillion Pharmaceuticals

Hepatitis C

Treatment of the hepatitis C virus has undergone a revolution in recent years with huge improvements in both efficacy and side-effect reduction. More new drug combinations are now nearing the marketplace. It is hoped that these will not only keep raising treatment success rates for all genotypes of the disease, but also simplify treatment selection and restart the price wars that have currently pushed the most effective drugs out of the reach of many.

Curing this virus was once a rather unpleasant hit-and-miss affair. A combination of interferon and the antiviral ribavirin were used for up to a year, with nasty side effects and no certainty of success. Since 2011, the market has exploded with better options (although success rates still depend on which genetic variant of the disease the patient has). First to gain FDA approval were two protease inhibitors—**Vertex's** Incivek and **Merck & Co.'s** Victrelis—that were used alongside interferon and ribavirin. Although these heralded a massive advance in treating Hepatitis C, they were soon superseded by **Gilead's** Sovaldi and then interferon- and ritonavir-free oral drug combinations.

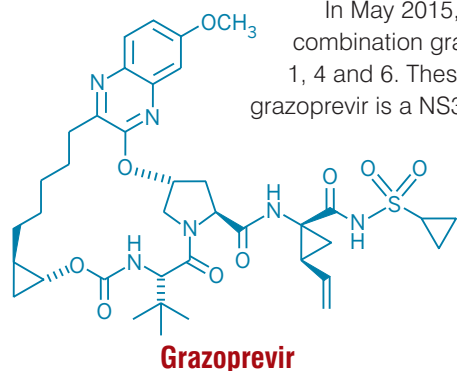
Gilead's Harvoni (containing Sovaldi and ledipasvir) was the first of these to gain approval in October 2014, with reported cure rates of 94 to 99%. The company received a prestigious 2015 American Chemical Society Heroes of Chemistry Award for developing this drug combination at the ACS national meeting in Boston last month. In late 2014 and early 2015, other combinations were approved including **AbbVie's** Viekira Pak (ombitasvir, paritaprevir, and ritonavir, co-packaged with dasabuvir). Again these report near perfect cure rates. These drugs are all direct-acting antiviral agents that interfere with the hepatitis C virus life cycle by suppressing viral replication. Sovaldi and dasabuvir are both inhibitors of its NS5B polymerase enzyme; ledipasvir and ombitasvir both inhibit the NS5A protein; paritaprevir is a NS3/4A protease inhibitor; and ritonavir inhibits the actions of liver enzymes thus slowing down the body's breakdown of the protease inhibitors in the tablet.

The prices for these drug combinations are all high. The sticker price for Harvoni, for example, is \$1,350 a pill—mean-

TOP 20 DRUGS IN THE PIPELINE

ing an overall cost of \$94,500 for a typical 12-week treatment. Multiple studies have shown that, although pricey, they are highly cost effective, in terms of money saved in future healthcare costs if patients were to remain infected with the virus, explains Maria Ascano, an infectious diseases analyst for Decision Resources. However health insurance companies are still balking at the cost and therefore restricting access to the drugs.

"You must have a certain [liver] fibrosis level and have [previously failed] treatment experience and so on," explains Ascano. Price wars have also broken out between the two main suppliers, Gilead and Abbvie. "The price wars have evolved so that there are now exclusivity agreements," Ascano says. This further limits patient choice to which drugs they can take. (See Rick Mullin, "High Noon at the Pharma Pricing Corral," C&EN, February 16, 2015; issue 7, pp.16–20.)



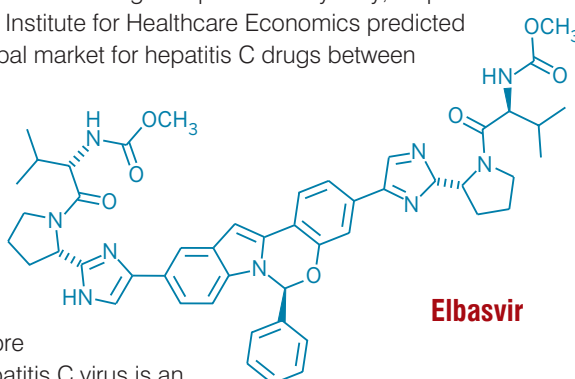
In May 2015, Merck filed for approval to use the drug combination grazoprevir/elbasvir for treating genotypes 1, 4 and 6. These are both direct acting antiviral agents: grazoprevir is a NS3/4A protease inhibitor, elbasvir a NS5A inhibitor. This combination has FDA breakthrough therapy designation.

"If approved, it is hoped that Merck would come in and shake everything up by undercutting everybody," explains Ascano. "If they do that, it might get rid of these exclusivities and then restart a price war where prices plummet because of increased competition. That is what a lot of physicians and experts

are hoping will happen."

Another investigative drug combination generating a buzz is Gilead's GS-9857/ Sovaldi/GS-5816 (GS-9857 is a NS3/4A protease inhibitor and GS-5816 an NS5A inhibitor). This treatment is showing promising results in Phase I and Phase II studies, and is aiming to be the first pan-genotypic drug combination for hepatitis C to market. Currently physicians carefully select treatments that suit the genotype of the disease their patient has, but a pan-genotypic drug would eliminate the need to do this. "Just like single tablet regimens do, it just makes things simpler for everybody," explains Ascano.

A 2014 report from the IMS Institute for Healthcare Economics predicted a greater than \$100 billion global market for hepatitis C drugs between 2014 and 2018. It was also estimated that by 2018 the US will have treated approximately 500,000 patients infected with hepatitis C. This represents only approximately 9-14% of patients infected with the virus in the country. It's therefore not difficult to see why the hepatitis C virus is an appealing target for drug companies.



One pharma giant after a bigger stake of the market share is **Johnson & Johnson**. It already has a hepatitis C drug, Olysio, on the market, which is used in combination with Sovaldi for some patient populations. In May 2015, it announced a partnership with small biotech **Achillion Pharmaceuticals** to develop and commercialize Achillion's pipeline hepatitis C drugs, including ACH-3102, ACH-3422 and sovalprevir. This pairing is aiming for a super simple, but highly effective pan-genotypic oral drug regime. ■

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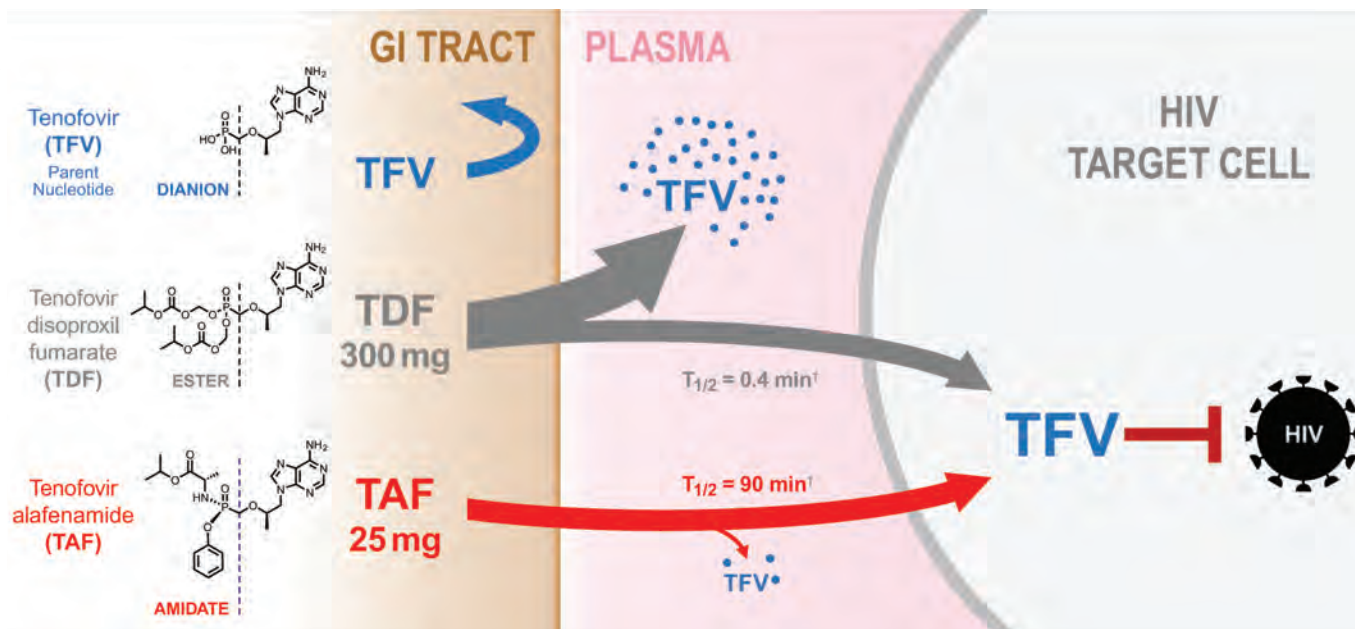


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Viread and TAF are both pro-drugs of the antiviral agent tenofovir.

4. TENOFOVIR ALAFENAMIDE (TAF)

Gilead

HIV

The gold standard treatment for HIV is currently once-daily single-tablet regimens. The transition over the last decade or so away from needing to take multiple pills, multiple times a day means the virus is now viewed as a highly manageable chronic infection rather than the death sentence it once was. With extremely high efficacy rates being the norm and patients living for much longer, drug companies are starting to focus on fine tuning and addressing niggles with the drug side effects. Now one of the most successful drugs to date—**Gilead's Viread**—is set to get an upgrade.

HIV is currently a \$10-billion/year market. According to Gilead, 70% of newly-diagnosed HIV patients in the US are currently prescribed one of its single-tablet regimens. Viread (tenofovir disoproxil fumarate) is a staple in all of these regimens. It is a nucleotide analogue inhibitor that blocks reverse transcriptase, an enzyme crucial for the replication of the HIV genome. Whilst highly effective with a good safety profile, patients taking Viread are still at risk of mild-to-moderate kidney toxicity and a decrease in bone mineral density has been observed in some patient populations. Clinical trials show that Viread 2.0—known as tenofovir alafenamide or TAF—is significantly less likely to cause these issues. TAF has also demonstrated high antiviral efficacy at less than a tenth of the dose of Viread.

Gilead now has three drug combinations containing TAF, in a direct swap with Viread, awaiting FDA approval. “Gilead is taking every compound that they market currently as a combination with Viread and converting it to a TAF,” explains Maria Ascano, an infectious diseases analyst for Decision Resources. The FDA is expected to decide on the first of these—a combination of the HIV integrase inhibitor elvitegravir, cobicistat (a boosting agent that inhibits the liver enzymes that metabolize elvitegravir), the nucleoside reverse transcriptase inhibitor emtricitabine, and TAF—in late 2015. The Viread version of this combination is called Stribild.

An FDA decision is due next April on the combination of emtricitabine and tenofovir alafenamide. The Viread version of this one, Truvada, is a blockbuster drug. The new drug application for the third combination, containing the non-nucleoside reverse transcriptase inhibitor rilpivirine, emtricitabine, and TAF, was filed in July. (Complera is the Viread version of this combination.) A priority review voucher was used for this combination meaning the anticipated target action date is just six months after the FDA accepts the filing.

As well as improving the safety profile for those already taking one of Viread's combination regimens, the new combinations will also allow patients with unmet needs (owing to being at high risk for renal toxicity or bone loss) to be treated.

"HIV-infected patients are now living just as long as uninfected individuals. That means the patient population is getting older and is therefore naturally at risk for renal failure and for women bone loss," Ascano says. The substitution of TAF will open up Gilead's current drug combinations for safe use by these patients.

Both Viread and TAF are pro-drugs of tenofovir, and it is where in the body they are converted into this active form that explains their different efficacies and side effects. Both are absorbed from the gastrointestinal into the blood plasma. Viread converts here, whereas TAF travels on into immune cells before converting into tenofovir.

Efficient Delivery

"TAF delivers tenofovir more efficiently to target tissue than Viread," explains a Gilead spokesperson. "In clinical trials in combination with other antiviral agents, this more precise targeting allows TAF to achieve high antiviral efficacy at a dose less than one-tenth that of Viread. And with less active drug in the blood, TAF-based regimens may provide a favorable renal and bone safety profile versus Viread-based regimens."

It isn't just upgrading Viread that Gilead has its eye on for TAF. It is also being explored in a new drug combination with emtricitabine, cobicistat, and **Janssen's** protease inhibitor Prezista. Janssen is responsible for the development of this regimen, currently in Phase III clinical trials. If approved, this

would be the first protease-containing single-tablet regime available to patients.

Although TAF is set to burst onto the market in the very near future, there have been accusations that Gilead has been dragging its feet over getting this drug to market. "You could definitely say that Gilead could have accelerated TAF's development, given that it does have a much safer profile than Viread," says Ascano. "But the timing for TAF is actually quite well placed here."

At first the focus was on developing highly effective drugs, once achieved drug companies moved to simplifying therapy with single-dose regimes, and now the focus is on minimizing adverse effects that are related to the therapies, she explains. "I think that the treatment landscape has gotten to the point where TAF can shine as a new improvement." Gilead is also exploring using TAF as a preventative drug. Its Viread-based blockbuster Truvada is the only drug currently approved for pre-exposure prophylaxis, taken by people deemed to be at substantial risk of contracting HIV. Gilead is preliminarily exploring substituting Viread for TAF for this purpose too.

"A novel, investigational fixed-dose combination of emtricitabine/TAF is currently being evaluated in an animal preclinical study to determine its potential implications for HIV pre-exposure prophylaxis. Gilead will evaluate these data in order to determine next steps," says the Gilead spokesperson. "It is not yet known if emtricitabine/TAF is effective for pre-exposure prophylaxis." ■

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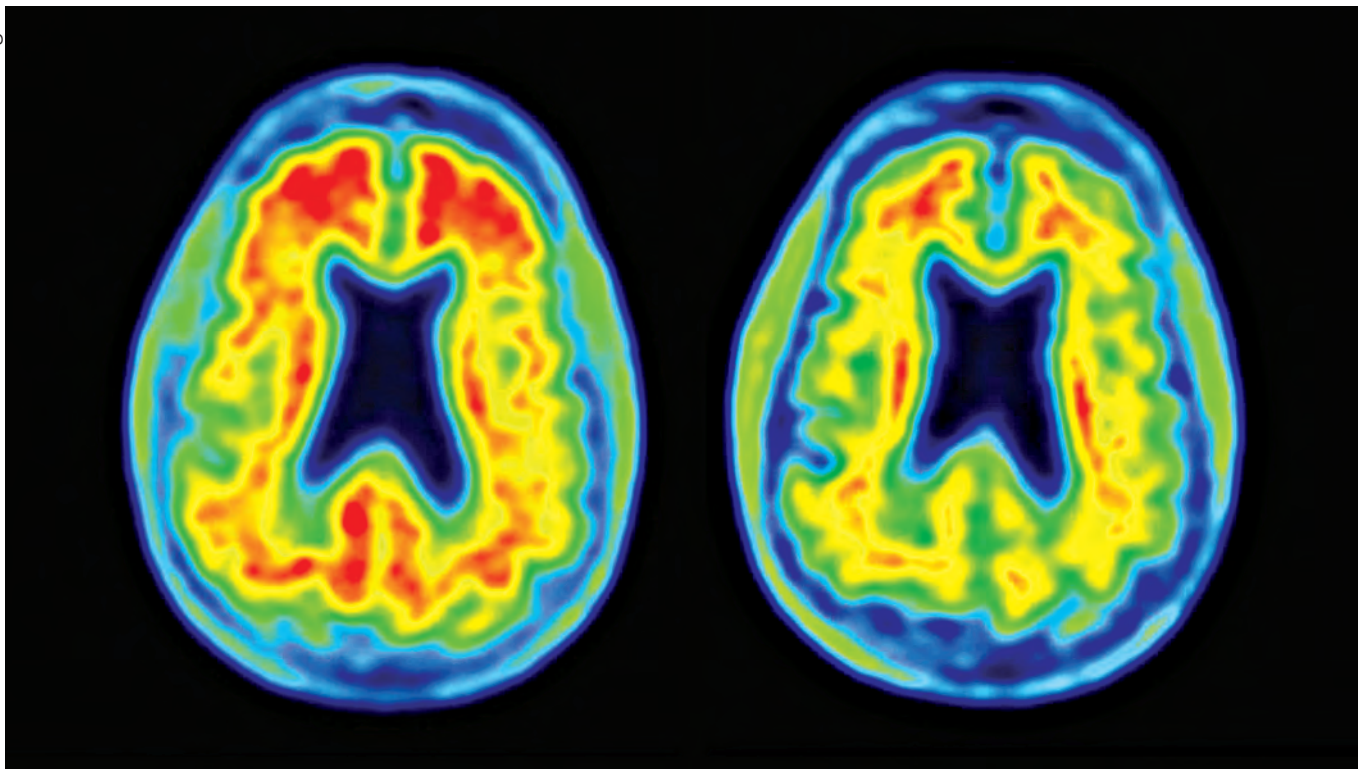
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Biogen's aducanumab significantly reduced the amount of amyloid (in red) in the brains of people with early-stage Alzheimer's. Left, pretreatment. Right, after 54 weeks of the drug.

5. ADUCANUMAB AND SOLANEZUMAB

Biogen and Eli Lilly & Co.

Alzheimer's disease

An estimated 5.3 million people in the US currently have Alzheimer's disease. By 2050, this figure is projected to nearly triple unless a medical breakthrough to prevent or cure the disease is unearthed. **Biogen** and **Eli Lilly & Co.** are now taking baby steps towards this end goal, as both have disease-modifying drug candidates in Phase III clinical trials. There is hope that these monoclonal antibodies can slow down disease progression. Currently the best on offer for Alzheimer's patients is a handful of medicines that ease their symptoms for a year or two.

Analysts are projecting that the global market for Alzheimer's treatment will expand from \$4.9 billion in 2013 to \$13.3 billion by 2023, thanks to these and other disease-modifying drugs in the pipeline.

Both Biogen and Lilly's monoclonal antibodies are designed to be amyloid- β -busters. Amyloid- β is a sticky protein that aggregates together into telltale plaques and clumps inside the brains of Alzheimer's patients. Accumulation of this protein is thought to be one of the main drivers of the disease, with

both plaques and the smaller clumps causing disruption and destruction of nerve cells.

"These drugs are felt to bind to various forms of the amyloid- β protein in the patient's brain," explains Dennis Selkoe, a leading neurologist and Alzheimer's expert at Brigham and Women's Hospital and Harvard Medical School. The two antibodies are not however targeting the same forms of amyloid. Lilly's solanezumab binds to soluble monomeric forms of amyloid- β (before they clump together), whereas Biogen's aducanumab binds to soluble oligomers and amyloid plaques. These bound amyloid- β then leave the brain, possibly with the aid of microglia scavenger cells.

Solanezumab is expected to be the first to market, with a Phase III clinical trial due to report in October 2016. This drug has failed two rounds of Phase III trials previously, but participating patients in the milder stages of the disease did appear to benefit. It is this patient subset that the drug is being trialed on now.

In July, Lilly released further results in support of the decision not to give up on solanezumab. 1,300 patients were given the

antibody for a further two years following an earlier failed Phase III study. In the subset of patients taking the placebo, the disease was slightly more progressed than in those that took solanezumab from the start. (If the drug was only treating symptoms, no difference between the two groups would be expected.) These results therefore suggest solanezumab has a disease-modifying effect. "The effect of solanezumab was small, it wasn't as robust as we saw with aducanumab," explains Selkoe.

Attacking Amyloid

It is aducanumab that is causing the biggest buzz within the medical community. In December 2014, Biogen reported that, following a preliminary analysis of Phase Ib clinical trial data, aducanumab would be skipping Phase II studies and starting Phase III trials imminently.

"This is the first time an investigational drug for Alzheimer's disease has demonstrated a statistically significant reduction on amyloid plaque as well as a statistically significant slowing of clinical impairment in patients with prodromal or mild disease," said Alfred Sandrock, Biogen's chief medical officer when announcing the move. They also showed that this effect was dose dependent: a higher dose equaled more plaque removed from the brains and better performance on cognitive tests. "Based on these results, we are advancing the aducanumab clinical program to Phase III with plans to initiate enrolment later this year."

Genentech also has a potential amyloid- β -busting agent inching its way through clinical trials: crenezumab. This antibody has two failed Phase II trials under its belt. Again, in the failed trials an effect was seen in the patients in the earlier



threes of the disease. A Phase I study to assess the safety of higher doses in people with mild-to-moderate Alzheimer's was launched in January.

The common theme seen in all these trials is that anti-amyloid- β agents perform better when a patient is in the early stages of the disease. This is problematic because the protein starts accumulating in the brain 15 years before symptoms appear and, even once the patient is symptomatic, doctors can struggle to distinguish early stage Alzheimer's from other forms of dementia. As Lisa Jarvis recently reported in C&EN ("The Next Chapter in Treating Alzheimer's," June 1, 2015; issue 22, pp. 11–15), combinations of therapeutic approaches may be the answer to successfully treating this disease.

The neuronal protein tau is being eyed up as a potential co-target. In the brains of Alzheimer's patients, tau collapses into twisted strands called tangles that hinder the communication between neurons. Amyloid- β is known to trigger tau's tangle formation, but how isn't yet understood. It is hoped that a drug that targets tau maybe more suitable in later stages of the disease than those that bind amyloid- β .

Some drugs that target tau are already in development. For example, **TauRx Therapeutics** currently has a methylene blue compound LMTX in two Phase III clinical trials. The company says that the Phase II trial results suggested the treatment could delay the progression of cognitive decline in mild-to-moderate Alzheimer's. The results of both Phase III studies are expected in 2016. No trials combining drugs to bust amyloid- β alongside tau have yet been started. ■

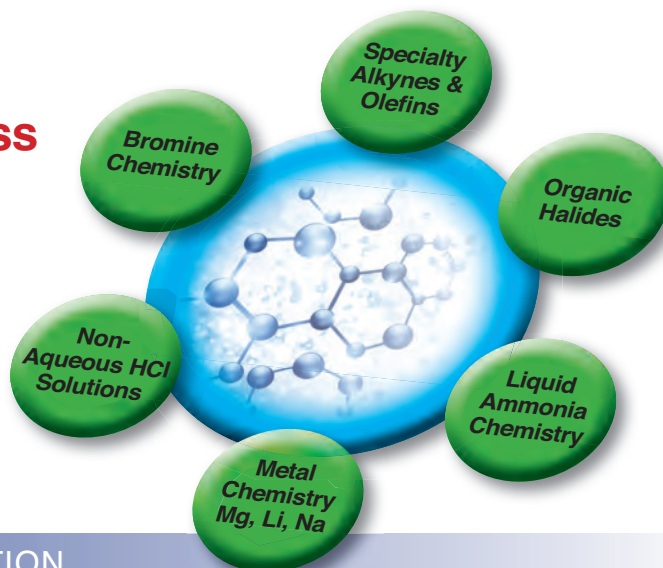
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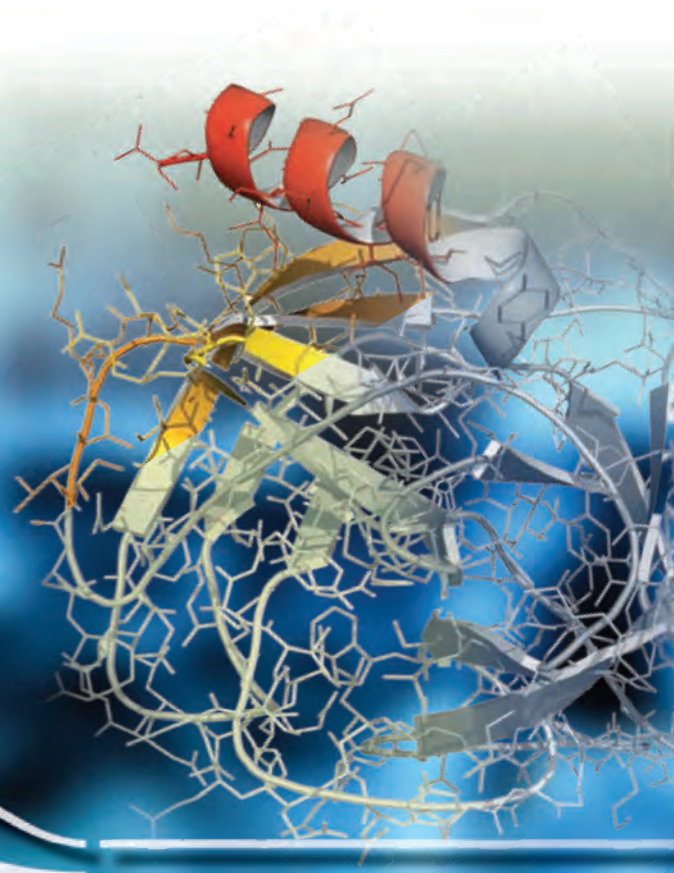
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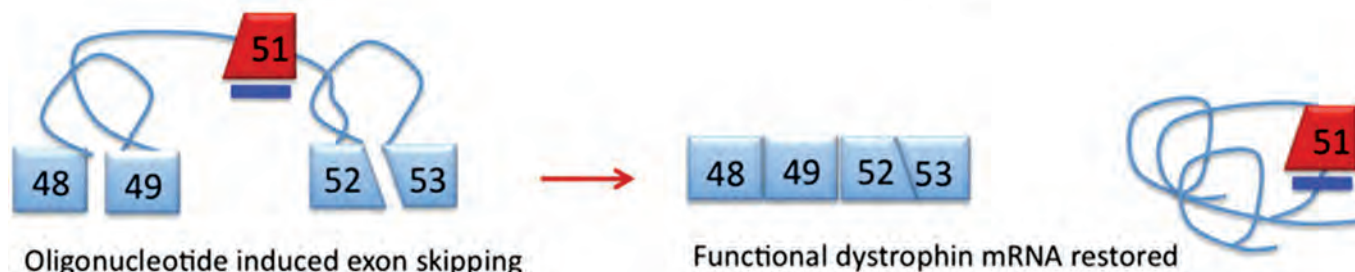


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Exon-skipping drugs allow the ribosome to skip over a deleted exon and continue translating the functional protein.

6. DRISAPERSEN, ETEPLIRSEN, AND TRANSLARNA

BioMarin Pharmaceutical, Sarepta Therapeutics, and PTC Therapeutics

Duchenne Muscular Dystrophy

Duchenne muscular dystrophy (DMD) is a rare hereditary disease affecting approximately one in every 3,500 males born. It is caused by a mutation in the gene on the X chromosome that codes for an essential protein for muscle fiber function—dystrophin. A lack of dystrophin causes muscles to suffer progressive damage. Patients are usually diagnosed by the age of six, wheelchair bound by their teens and unlikely to survive beyond their early 30s. There is no approved disease-modifying treatment and the current treatment regime of steroids does little to slow disease progression.

This was the fate facing 16-year-old DMD patient Austin McNary until late last year. In 2011, his younger affected brother Max (then age 8) had been selected to take part in a Phase II clinical trial of a new class of drug that target the root cause of the subset of the disease. Max's symptoms started to improve after just 16 weeks and soon he no longer needed a wheelchair. While Austin's disease was too advanced for him to qualify for the same trial as Max, the family was hopeful that he could be granted access to the same drug. It took more than three heart-breaking years, of watching one child get better as the other got worse, before Austin got his hands on the drug. His treatment started in November 2014 and, as with his brother Max, improvements in his physical capabilities are already being reported.

The drug being taken by the McNary brothers is an exon 51-skipping drug called eteplirsen that is being developed by **Sarepta Therapeutics**. Eteplirsen is currently sitting the FDA's in-tray awaiting a decision on whether it should be approved for use in the approximately 13% of DMD patients that may benefit from a drug that skips this region of the gene that codes for dystrophin.

There are a number of different subsets of the disease. The dystrophin gene is one of the longest in the human genome, made up of 79 coding regions or exons. In the majority of DMD sufferers, one or more of these protein-coding exons has been

deleted, preventing the protein from being formed. Exon-skipping drugs are designed to allow the ribosome to skip over a deleted exon and continue translating the protein in a shortened but functional form. While patients' prognosis will improve significantly, some symptoms would remain due to the protein being in a shortened form.

Eteplirsen is an antisense oligonucleotide designed to patch over exon 51. And it isn't the only drug currently racing to market that targets this same subset of DMD patients. **BioMarin Pharmaceutical** has a drug called drisapersen that works in the same way, two months ahead in the FDA approval pile.

Sarepta's antisense oligonucleotide is a phosphorodiamidate morpholino oligomer (PMO). These oligomers have the same nucleic acid bases as RNA, but are bound to six-sided morpholine rings instead of five-sided ribose rings. As well as the exon-51 skipping variety eteplirsen, Sarepta has another seven PMO drug candidates in preclinical development designed to skip different exons in the dystrophin gene. As many as 60% of DMD patients might benefit from this kind of exon-skipping therapy.

Drisapersen's antisense oligonucleotide has a modification in the 2' position called 2'-O-methylated phosphorothioate (2'OMePS). BioMarin has three similar drug candidates in earlier development for skipping different exons in the dystrophin gene.

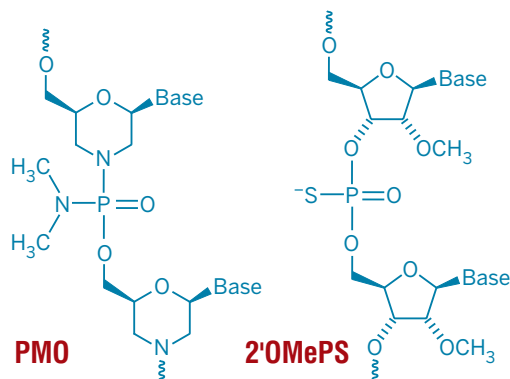
Nikhilesh Sanyal, an immunology analyst for GlobalData, says that an FDA panel is likely to consider these two new drug applications together, as it has little prior experience of this rare disease. "These drugs are most likely going to be reviewed somewhat together, side by side, if not completely in parallel," Sanyal explains. Both drugs have been undergoing a rolling approval process with FDA that is likely to increase likelihood of them making it to market. Sanyal predicts that drisapersen will launch in the US in December 2015/January 2016 and eteplirsen in February/March 2016.

The journey of DMD drugs to market have been hindered by

a lack of basic understanding of disease progression, making it hard to know whether a potential drug is improving matters (see Lisa Jarvis, C&EN, "Help for Boys with Duchenne Muscular Dystrophy," July 21, 2014; issue 29, pp. 17–20.) Although FDA approval of these two DMD drugs is widely expected, neither drug has completed Phase III trials. "It is highly uncommon that a regulatory agency conditionally approves a drug based on Phase IIb data," explains Sanyal. The rush to market is being permitted due because of the unmet need treating DMD. "Both companies are still working on their Phase III studies," he confirms.

Potential patients and their families fear that these drugs could be withdrawn if Phase III studies show unfavorable results—even if it is working for them personally. Those fears are not unfounded; drisapersen has already failed one Phase III study. Drisapersen was developed by **Prosensa**, but this trial was sponsored by **GlaxoSmithKline**. The trial failure caused GSK to dump the drug program. BioMarin believes differently, having acquired Prosensa to capture this asset in November 2014.

These exon-skipping drugs are expected to cost upwards of \$200,000 per year per patient. Sanyal predicts that drisapersen and eteplirsen will generate approximately \$214 million and \$189



million in sales, respectively, from the six major pharmaceutical markets (U.S., France, Germany, Italy, Spain, and the U.K.) in 2019. Eteplirsen predictions are lower due to unresolved patent-related issues in the EU.

Drisapersen and eteplirsen are not the only drugs on the horizon for DMD sufferers. In August 2014, **PTC Therapeutics'** Translarna was awarded conditional approval in Europe, again based on Phase IIb results. This is a small molecule that addresses 10-15% of DMD patients with a "nonsense" mutation that causes protein production to stop before completion. Translarna allows RNA to read through the mutation to build the protein. "Translarna essentially set the trend of early approval based on Phase IIb data," explains Sanyal. PTC has now expected to win approval in the US around the end of 2015.

Further down the drug pipeline are several other drug candidates addressing these and other subsets of the DMD population. The DMD market is set to witness a remarkable growth in the next five years, says Sanyal. He predicts that the market will rise from less than \$10 million annually to close to \$1 billion by 2019. ■

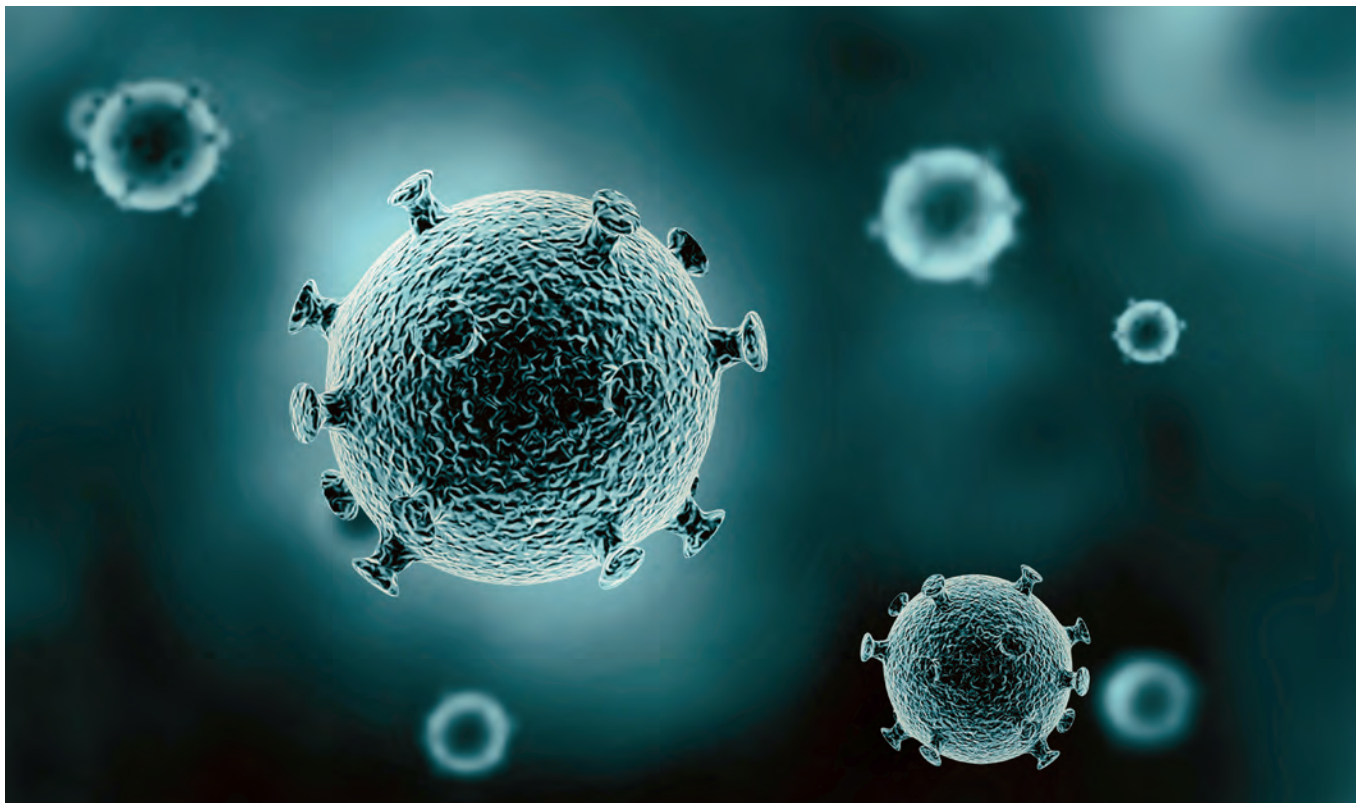
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A modified HIV virus can insert a therapeutic gene into a hematopoietic stem cell.

7. LENTIGLOBIN BB305

Bluebird Bio

Beta-thalassemia and sickle cell disease

Bluebird Bio is emerging as one of the favorites in the race to become the first gene therapy to be approved by the FDA. This biotech's widely-publicized goal is to cure, or at least dramatically transform, severe genetic diseases through one-off treatments.

"In my opinion they are the best at viral-based ex vivo gene therapy," says Eric Schmidt, a biotech analyst for Cowen & Co. This process involves removing hematopoietic stem cells from a patient, using a modified virus to insert a therapeutic gene, and then returning the cells to the patient where the cells' own machinery should now be able to build the functional protein.

The diseases most suited to gene therapy are those caused by mutations in single genes and Bluebird is currently tackling three of these: sickle cell disease, beta-thalassemia and childhood cerebral adrenoleukodystrophy (CCALD).

Sickle cell disease affects some 25 million people globally. It is caused by a mutation in the gene that codes for

beta-globin, a subunit of hemoglobin. The mutant hemoglobin is a long, rigid molecule, causing red blood cells to bend into a sickle shape. Pain episodes and chronic anemia are signature symptoms, and treatment options are limited. Many children with the disease are reliant on regular blood transfusions.

Beta-thalassemia is another common recessive disorder, with global prevalence estimated at 288,000 people. Patients with beta-thalassemia do not make enough, or any, beta-globin leading to anemia, and typically require regular blood transfusions throughout their lives.

For both these diseases a bone marrow transplant offers the only potential cure, but there are problems finding suitable donors and safety concerns. Bluebird is hopeful that its LentiGlobin BB305 will offer an alternative potential cure that is safer and suitable for all. A handful of patients with both these diseases have now been treated using this investigational drug, with positive results so far.

In June, Bluebird announced it had treated its first ever

patient—a 13-year-old French boy—with severe sickle-cell disease using LentiGlobin. Six months after treatment, the proportion of healthy hemoglobin in the teenager was rising steadily and accounted for 45% of overall hemoglobin production. Only 30% is believed to be needed to modify the disease symptoms. It was also reported that the boy had been free of blood transfusions for more than three months.

As part of this same Phase I/II trial, two beta-thalassemia major patients were also treated. As of May, neither had required a blood transplant for 16 and 14 months, respectively. A second Phase I/II study for beta-thalassemia major has treated five patients so far, and Bluebird has stated that the early results look promising. No safety concerns have been reported and LentiGlobin has been granted FDA's coveted breakthrough therapy designation.

Fantastic Voyage

Bluebird is using the popular HIV-derived lentiviral vector in these trials. First the virus is stripped of any components that can cause HIV, and then a normal functioning beta-globin gene is inserted. Stem cells are then collected from the patient and exposed to the lentiviral vector. The virus inserts the functional beta-globin gene into the DNA of the stem cells. The remainder of the patients stem cells are then removed using chemotherapy, before the modified stem cells are returned to the patient. These corrected stem cells should grow and multiply, effectively becoming the source for healthy blood stem cells for the rest of the patient's life and therefore minimize the need for blood transfusions.

For CCALD trials, Bluebird is using a different investigational drug that works similarly to LentiGlobin. This drug Lenti-D is Bluebird's most advanced product candidate and is currently in Phase II/III clinical studies. One in 20,000 boys born worldwide has adrenoleukodystrophy (ALD)—the disease featured in the film *Lorenzo's Oil*—and the most severe form CCALD accounts for 30 to 40% of those patients. CCALD is caused by a single mutation in the ABCD-1 gene on the X chromosome that encodes the ALD protein. Long-chain fatty acids build up in the brain causing damage to nerve cells. Symptoms typically appear in childhood. A stem cell or bone marrow transplant is the only currently available option to halt disease progression.

Lenti-D contains a functioning copy of the ABCD-1 gene packaged in an HIV-derived lentiviral vector. The process of getting the hematopoietic stem cells containing this modified gene into the patient is the same as for LentiGlobin. Once inside the body, the goal is that the new blood stem cells become a permanent source of new cells able to produce the ALD protein and therefore halt the progression of the patient's CCALD. Early trials saw Lenti-D halt disease progression in all four participating patients.

These treatments are extremely expensive—stem cells have to be removed from each patient, treated and then returned to the body. As with the CAR T-cell therapies currently

in clinical trials to treat various cancers, it is hard at this stage to see how commercial-scale manufacture of these gene therapies will be achieved cost effectively. Another financial concern is that these diseases are relatively rare and the treatments are—by design—one off. This means drug may need to be priced extremely highly to recoup R&D and treatment costs plus turn enough of a profit to satisfy investors.

"Bluebird hasn't really discussed prices, but I would be very surprised if LentiGlobin wasn't over \$1 million per therapy," says Cowen & Co.'s Schmidt. "You could certainly justify a very high price tag to payers given how expensive it is to treat these patients with current standard of care, and also how poor in many ways the current standard of care is relative to the benefits they would get with LentiGlobin."

Schmidt says it is hard to predict when LentiGlobin could make it to market, but approval is possible within the next two to three years. "They have got excellent efficacy from the five or so patients that have now been treated and the remaining risk from the program comes from safety. I'd like to see another 20 or 30 patients be safely treated before we can know how good a therapy this is going to be," he says. ■

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Over 16 million people in the US are diagnosed with major depressive disorder every year.

8. ALKS 5461, ESKETAMINE, AND RAPASTINEL

Alkermes, Johnson & Johnson, and Naurex

Major depressive disorder

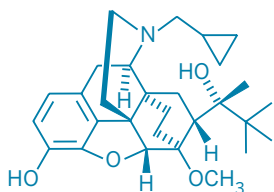
The outlook for patients with a severe form of depression may finally be looking up, thanks to a handful of fast-acting drugs in late stage trials. With generics crowding the antidepressant space, many major pharmaceutical companies have walked away from this multi-billion dollar global market. However a significant unmet medical need remains.

More than 16 million people are diagnosed with major depressive disorder in the US each year. Only a third of these will respond to initial antidepressant treatment involving either selective serotonin reuptake inhibitors or serotonin and norepinephrine reuptake inhibitors. In addition, these drugs typically take six to 12 weeks to start working. This is too long for severely depressed patients, who may be at high risk of suicide. Currently the only approved fast-acting treatments are transcranial magnetic stimulation and electro-convulsive therapy. The new

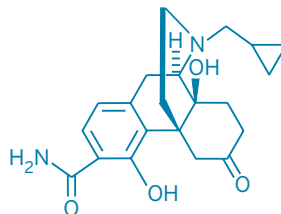
drugs in the pipeline start taking effect in a matter of hours and are showing high levels of efficacy in clinical trials.

Alkermes' ALKS 5461, the most advanced of these investigative drugs, works on the brain's opioid receptors. Natural opiates such as endorphins bind to opioid receptors in the brain, making people feel happy (explaining why opioid drugs such

as heroin give users a certain euphoric feeling). ALKS 5461, which has an FDA fast-track designation, is a combination of buprenorphine (approved as a pain medication and for treating opioid addiction) and the investigational drug samidorphan. Both drugs act on the μ -opioid receptors: buprenorphine acts as a



Buprenorphine



Samidorphan

partial agonist and samidorphan as an antagonist. (Agonistic behavior alone can lead to addiction.) The two drugs are designed to work together to attenuate buprenorphine's μ -agonist effects and therefore reduce the risk of addiction. "Patients feel

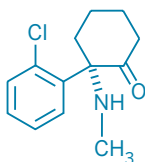
better without the abuse side effects,” explains Edny Inui, a scientific analyst specializing in depression at BioMedTracker.

ALKS 5461, an oral once-daily medication, is currently in Phase III trials in patients who have responded inadequately to standard therapies. Approximately 1,500 patients will be taking part in these studies, with the first results announced in June. This small 66-patient study supported the findings of the Phase II trials, with patients reporting a significant reduction in depressive symptoms by the end of the first week of treatment. Just over half these patients were feeling well after taking the drug for eight weeks. Alkermes expects to file with the FDA by early 2017.

Feeling Good

Meanwhile other companies are looking to mimic the feel good effect of ketamine. This party drug blocks the brain's NMDA (N-methyl-d-aspartate) receptors, a component of the glutamate pathway indicated in depression and anxiety. Ketamine is approved for use as an anesthetic and pain killer, and trials have found it to be an extremely effective and fast working treatment for depression. Companies are now scrambling to develop a patentable drug that works on the NMDA receptor, without causing the delusions and hallucinations that can occur when taking ketamine in high doses.

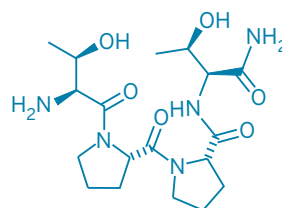
Johnson & Johnson's Janssen research unit is developing a nasal spray called esketamine, again for treatment-resistant patients. Esketamine, the S enantiomer of ketamine, has the coveted FDA breakthrough therapy designation. In ongoing Phase II trials, clinically significant improvements of depressive symptoms have been reported. Recruitment for a Phase III trial



Esketamine

began in August, with an FDA filing expected in 2017.

Naurex is also interested in developing NMDA receptor modulators: with two in clinical trials. The furthest forward, also with FDA fast track designation, is rapastinel. “The Phase III program for rapastinel is to start in 2016,” says Inui. Rapastinel is given as a once-weekly injection, and in Phase II trials was shown to demonstrate a statistically significant reduction in depressive symptoms within two hours that lasts at least a week between doses. The second NMDA receptor modulator Naurex is developing is NRX-1074. This investigative drug is in



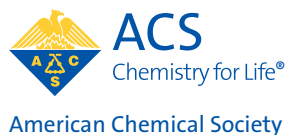
Rapastinel

Phase II trials, and the intention is that it will be taken orally.

In July, the drug giant **Allergan** announced it would buy Naurex for \$560 million to get its hands on these assets. “Naurex's unique pipeline comprises compounds that utilize a new mechanism to target areas of significant unmet medical need in

major depressive disorder. These highly differentiated compounds will immediately bolster our exceptional mental health pipeline,” said Allergan's chief executive Brent Saunders when announcing the acquisition.

Vistagen also has an oral NMDA receptor modulator, AV101, in development, although at an earlier stage, with a Phase II trial, funded by the National Institutes of Health, due to start in September. The other notable potential NMDA receptor modulator is a nasal spray being in preclinical development by newly launched Turing Pharmaceuticals, with clinical trials hopefully starting by the end of this year. ■



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9. CANCER METABOLISM-TARGETING DRUGS

Agios Pharmaceuticals/Celgene, Cornerstone Pharmaceuticals, and Calithera Biosciences,
Various cancers

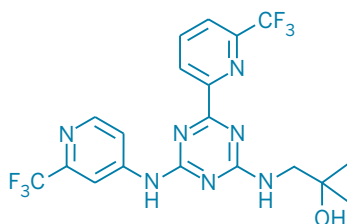
Since the 1920s it has been known that the metabolism of cancer cells is different to that of normal cells. Now, a handful of drug makers are hoping to take advantage of this quirk to add a new class of compounds to the cancer drug arsenal.

Agios Pharmaceuticals is one such company, with three investigative drugs that selectively disrupt cancer cell metabolism in clinical trials. The targets chosen by Agios are mutant variants of the metabolic enzymes isocitrate dehydrogenase 1 (IDH1) and isocitrate dehydrogenase 2 (IDH2). The normal version of these enzymes participate in standard cell metabolism, but when mutated they switch roles to ramp up the production of 2-hydroxyglutarate (2HG) instead. Too much 2HG alters a cell's genetic programming meaning that—instead of maturing—it remains primitive and proliferates rapidly.

The drugs being developed by Agios are IDH mutant inhibitors. “When we inhibit the levels of 2HG, by inhibiting the enzyme, the cells then revert and undergo differentiation into cells that behaves like normal cells,” explains Scott Biller, the company's chief scientific officer, formerly with Novartis. “It's a very novel mechanism.” By design these drugs are only suitable for cancers that have mutations in either IDH1 or IDH2 genes, and these are more prevalent in some cancers than others. For instance, about 25% of acute myeloid leukemia (AML) has either the IDH1 or IDH2 mutation and over 75% of low-grade glioma has the IDH1 mutation.

Agios has been testing their once-daily pills on a range of different blood cancers and solid tumors, in patients with no approved treatment options remaining. On average, Biller says his team is seeing complete remission rates close to 20%. More patients are reporting partial remissions. He calls the response rate “very encouraging.” The durability of the response has also been praised. “We have patients getting out to 16 months [without relapse] on these pills who really had no other treatment options,” Biller says.

The most advanced of the three Agios' investigative drugs is the IDH2 mutant inhibitor AG-221. A Phase III trial in patients with relapsed or refractory AML, who harbor an IDH2 mutation,



AG-221

is scheduled to start by the end of this year. Agios also has an IDH1 mutant inhibitor AG-120 expected to start Phase III trials in 2016. Trailing behind is AG-881, a compound that can inhibit the actions of both mutant IDH1 and IDH2 enzymes. This drug is particularly exciting because it fully penetrates the blood-brain barrier. Phase I trials with this investigative drug, which Agios refers to as “a potential second-generation molecule”, started in June.

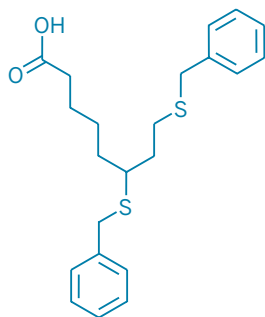
All three of these small-molecule drugs are being developed in collaboration with Celgene. The structure of AG-221 (a substituted triazine) was revealed for the first time at the American Chemical Society national meeting last month in Boston, as reported by Bethany Halford in C&EN (September 2015; issue 38 pp. 38–40).

Precision Medicines

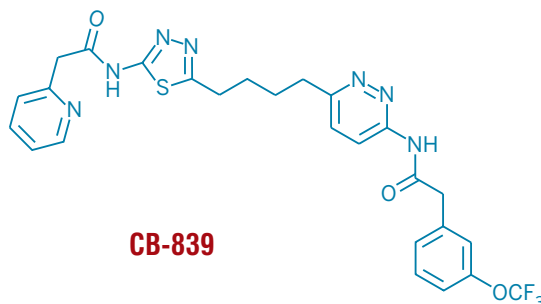
These are precision, or highly customized, medicines. The patients undergo a genetic test to check their cancer has the relevant mutation before they are enrolled on a trial. “We can tell by the genetics of the tumor that the patient is either likely to respond or likely not to respond, then only put the likely responders on the drug,” explains Biller. Agios is also developing new diagnostic tests in parallel with their drugs.

Cornerstone Pharmaceuticals, meanwhile, has a drug candidate CPI-613 that can simultaneously disrupt pyruvate dehydrogenase (PDH) and alpha ketoglutarate dehydrogenase (KGDH). These are both crucial mitochondrial enzymes for the metabolism in cancerous cells, but not normal cells. Disrupting the function of these enzymes cuts off a cancer cell's mitochondrial energy supply, causing the cell to die.

PDH and KGDH is a metabolic change seen across most types of cancers. This means that—unlike Agios' drug candidates—CPI-613 could potentially be useful for the majority of cancer types. In the first Phase I clinical trial, CPI-613 was test-



CPI-613



CB-839

ed on patients with 21 different types of cancer, including typical blood cancers and solid tumors. "We saw evidence of a response in pretty much every indication," says Robert Shorr, Cornerstone's chief scientific officer.

The drug is now in a number of Phase I, I/II and II trials for various cancers including AML, lung cancer, and pancreatic cancer. "Studies so far show that our drug can be given chronically to patients, safely maintaining a stable disease or better for periods starting to meet the definition of cure," says Shorr. "We have that kind of data for eight different indications of cancer."

Cornerstone is also trialing CPI-613 in combination with other drugs. It is now widely accepted that the best way to kill off cancer for good may be to hit it with several different drug types at once. The chemotherapy drugs bendamustine hydrochloride and fluorouracil, and the immunotherapy rituximab, are all being trialed with CPI-613. Agios also says it is exploring possible combinations of their IDH mutant inhibitors with both approved and not yet approved drugs, although no such combinations are yet in clinical trials.

Calithera Biosciences also plan to test its investigative cancer-metabolism targeting drug CB-839 in combination with other therapies. Phase II trials of CB-839 combinations are planned to start in late 2015 or early 2016. CB-839 is another small-molecule enzyme inhibitor; here it is glutaminase that is being blocked. Some types of tumor show a dramatic rise in the uptake of glutamine compared to normal cells. Glutaminase converts glutamine to glutamate, and preventing the formation of glutamate has been shown to lead to a substantial reduction in cell growth or induces cell death in certain types of cancer cells.

Cancers currently being explored in Phase I trials with CB-839 include AML, breast cancer, and lung cancer. Calithera are also looking at identifying relevant biomarkers to allow clinicians to predict which patients will be sensitive to treatment with CB-839. ■



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10. CRISPR/CAS9 GENE EDITING

Caribou Biosciences, Editas Medicine, CRISPR Therapeutics, and Intellia Therapeutics,
Various diseases

While anticipation mounts that the FDA may rubber stamp a gene therapy technique for the first time within the next couple of years, excitement about a new, simple and highly-precise gene editing technique is reaching fever pitch.

The CRISPR/Cas9 system can cut-and-paste sections of DNA in the nucleus of cells with exquisite accuracy and relative ease.

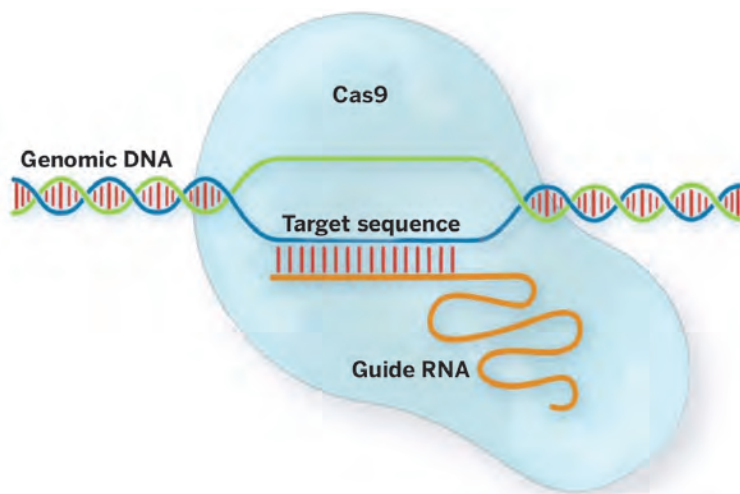
It is being explored for rewriting flawed genes in a growing number of organisms from bacteria to humans. However it is in human therapeutics where much of the hope and hype is located. This summer, *The Economist* and *Wired* both published feature articles highlighting the potential of this gene editing technique.

Start-up biotech companies exploring the use of CRISPR/Cas9 to treat human diseases have attracted more than \$300 million in funding so far. With this financial interest coupled with a highly publicized patent row and ethical concerns, it's easy to forget that no cell edited using CRISPR/Cas9 has actually been placed back in a human yet. All work so far has been done in a petri dish.

Jennifer Doudna at the University of California, Berkeley is one of the technique's pioneers. "I think things are moving very fast and, barring any bumps in the road, I wouldn't be surprised to see within a year applications to the FDA to do an initial, very limited, clinical trial," she told C&EN.

CRISPR/Cas9 only burst onto the scene a few years ago, but it is not the first gene editing approach to be developed. It is however the cheapest and easiest to use. The system is comprised of a small customized piece of RNA called a CRISPR (short for clustered regularly interspaced short palindromic repeat) that guides the DNA-snipping enzyme Cas9 (CRISPR-associated protein 9) to the section of a cell's DNA that requires editing. Sometimes snipping out the flawed gene is enough, and sometimes a new functioning gene is added in its place. The technique mimics how bacteria detect and then destroy the DNA of attacking viruses.

Adapted from OriGene Technologies



A guide RNA directs the Cas9 enzyme to the target DNA sequence. Cas9 cuts both strands of the DNA, priming the gene for editing.

Doudna predicts that the first human trials will involve hematopoietic stem cells. The cells would be removed from a patient, the DNA edited to correct for a genetic flaw, and then returned to the patient where they should act as a source of fully functioning stem cells for the remainder of the patient's life. Various similar one-off genetic correction treatments are already in development. The advantage of the CRISPR/Cas9

approach is the theoretically unlimited control over which genes are deleted or changed. Diseases caused by single mutations are widely expected to be the first to reach clinical trials.

No one has tried returning CRISPR/Cas9-edited cells to any animals yet. However, a comparable set-up with an earlier gene editing technique that utilizes zinc-finger nucleases enzymes is in Phase II clinical trials. **Sangamo Biosciences** are disrupting the CCR5 gene in T cells. This gene codes for a surface protein used by the HIV virus to enter these immune cells. In the Phase I trial, 12 patients had their T cells edited and returned to their body. Six then stopped their usual anti-viral drug regimen. The HIV levels in these patients were found to rebound more slowly than normal, and the modified T cells were seen to decline far slower than the unmodified T cells. These results suggest that the edited T cells are immune to the HIV virus. "This is one of the really exciting initial uses of genome engineering," says Doudna. Some research teams are already preliminarily looking at using CRISPR/Cas9 to disrupt this gene for this purpose.

Editing the genes in a patient's T cells before returning them to the body is also of interest for cancer treatment. In early 2015, two CRISPR-focused biotech companies announced collaborations with companies working on the experimental oncology approach CAR T-cell immunotherapy (see above). "Engineering T cells that could target tumors seems very, very appealing," Doudna says.

The biotech companies working with CRISPR/Cas9 for therapeutics are being secretive about what other diseases they are tackling. Other ex vivo applications being explored

include inherited blood diseases such as sickle cell disease and therapeutic protein production to treat conditions such as cystic fibrosis. Longer term in vivo applications—where the therapeutics are administered directly into the body—include targeting genes in cells in the eye, muscle, lung and central nervous system.

A cluster of biotech companies focused on the CRISPR technique have emerged in the last four years, attracting considerable support from both eminent scientists and financial backers. The first off the block was **Caribou Biosciences** in 2011. Caribou, which has a wider scope than just therapeutics, has raised \$11 million. Editas Medicine was founded in November 2013 with an initial \$43 million. In May, it received \$25 million upfront from Juno as part of the pair's CAR T-cell therapy collaboration. Then in August, Editas announced it had secured an extra \$120 million from a large group of investors including Bill Gates.

CRISPR Therapeutics, founded by researcher Emmanuelle Charpentier, also launched in 2013 and has so far secured \$89 million in two rounds of funding. The fourth significant player in this field is **Intellia Therapeutics**, founded in November 2014. Intellia secured \$15 million in its first round and received a further undisclosed amount from Novartis when agreeing to collaborate on CAR T-cell therapy.

Doudna is a scientific co-founder of Caribou, Editas and Intellia. She has now cut ties with Editas, thanks to fallout

over conflicting patent claims with another of the company's scientific co-founders, Feng Zhang at Massachusetts Institute of Technology.

Further controversy in this field surrounds the possibility of editing the genome of human embryos. In April, Chinese scientists reported an attempt to use CRISPR/Cas9 to edit the gene responsible for beta-thalassemia in non-viable human embryos. The attempt was largely unsuccessful, but it triggered a huge uproar about the ethics of these types of experiments. Permanently editing genes in embryos, sperms or eggs means the change will be passed on to future generations. This is not the case in the therapeutics applications discussed above. The ethics of this so called human germ-line editing is hotly debated. As Britt Erickson reported in C&EN in June ("Editing of Human Embryo Genes Raises Ethics Questions," June 29, 2015; issue 26, pp. 20–21), leading scientists including Doudna are now scrambling to address these ethical concerns, in part to avoid the bickering negatively impacting less controversial uses of the technology.

Even without the lingering controversy, there is a lot that needs to be ironed out before this technology can hit the market. Scientific matters that still need addressing include how to safely and efficiently get the CRISPR/Cas9 complex into cells both ex vivo and in vivo, and the possibility of the wrong sections of the genome being targeted and then edited. ■

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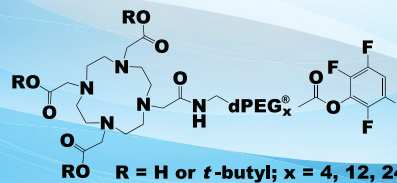
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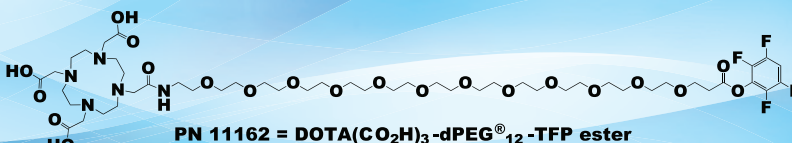
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The Hot Zone

11. ZMapp, TKM-Ebola, and rVSV-ZEBOV

Mapp Biopharmaceutical, Tekmira Pharmaceuticals, and Merck & Co.

Ebola

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The current Ebola outbreak is coming to an end. Just a handful of new cases each week are now being reported to the World Health Organization (WHO). With nearly 28,000 cases reported during this outbreak so far, and over 11,000 patients dead, the frustration over the absence of any proven treatments for this virus is entirely justified.

Since WHO gave the go-ahead in August 2014 for experimental drugs to be used to bring this outbreak under control, companies have been scrambling to start clinical trials with various treatments. For the most part, however, bureaucracy and logistical problems have hindered progress. (Lisa Jarvis and Bethany Halford reported on the push to get the drugs into the field in C&EN, "Unraveling Ebola," December 1, 2014; issue 48, pp. 8–15.)

The two most promising drug candidates, shown to be effective in monkeys, are **Mapp Biopharmaceuticals'** ZMapp and **Tekmira Pharmaceuticals'** TKM-Ebola. ZMapp is a cocktail of three antibodies grown in tobacco plants. A Phase II clinical trial using ZMapp started in Liberia in February. TKM-Ebola is a synthetic small interfering RNA therapeutic. A Phase II trial of this drug started in Sierra Leone in March. No results from either of these trials have been reported yet.

Ebola was back in the headlines in July, when a Phase III vaccine trial in Guinea reported 100% prevention rate. These were the interim results of a study assessing the efficacy of **Merck & Co.'s** rVSV-ZEBOV vaccine in more than 4,000 participants. All individuals were protected within six to 10 days of receiving the vaccination.

Novel Antibiotic

12. Teixobactin

NovoBiotic Pharmaceuticals

Bacterial infections

A new antibacterial molecule with a novel mechanism of action has been unearthed by U.S. academics at Northeastern University. Teixobactin—a cyclic depsipeptide—is believed to work in a way that makes it difficult for bacteria to develop resistance to it. This is being viewed by many as a step towards a new class of antibiotics that could potentially tackle the growing problem of antibiotic resistance.

Teixobactin was discovered using a new route of culturing bacteria in soil that can grow previously unculturable colonies. This molecule was shown to be able to protect mice from lethal doses of the superbug MRSA, but hasn't yet been tested in humans. Kim Lewis, who led the discovery team, has speculated that teixobactin could be in clinical trials within two years. (Bethany Halford reported on this breakthrough in C&EN, "Novel Bacteria Fighter Unearthed," January 12, 2015; issue 2, p. 3.)

The Eyes Have It

13. SPK-RPE65

Spark Therapeutics

Leber congenital amaurosis

A gene therapy for treating Leber congenital amaurosis (LCA)—a rare inherited retinal dystrophy caused by mutations in the RPE65 gene—will shortly be completing a pivotal Phase III clinical trial. LCA is estimated to affect approximately one in every 81,000 people, with 20% of blind children thought to suffer from this disease.

SPK-RPE65 is being injected directly into the retinas of trial patients using a vector based on an adeno-associated virus. The final results from this trial are expected in the second half of 2015. **Spark Therapeutics** hopes to follow that by filing with the FDA in 2016. If given the thumbs up, this one-off treatment will become the first gene therapy to be approved in the U.S. SPK-RPE65 has FDA breakthrough therapy designation for treating night blindness in patients with LCA.

RNAi Ringleader

14. Patisiran

Alnylam Pharmaceuticals,

Transthyretin mediated amyloidosis

Patisiran is widely expected to become one of the first RNA interference (RNAi) therapeutics to win FDA approval. This would signal the end to the rollercoaster ride this gene silencing technique has been on since it was first developed around 15 years ago.

Transthyretin (TTR)-mediated amyloidosis is a rare, inherited, progressive, and often fatal disease caused by mutations in the TTR gene. Patisiran is designed to turn the mutant genes off in the liver, and therefore prevent the TTR proteins that are known to drive disease progression from being translated.

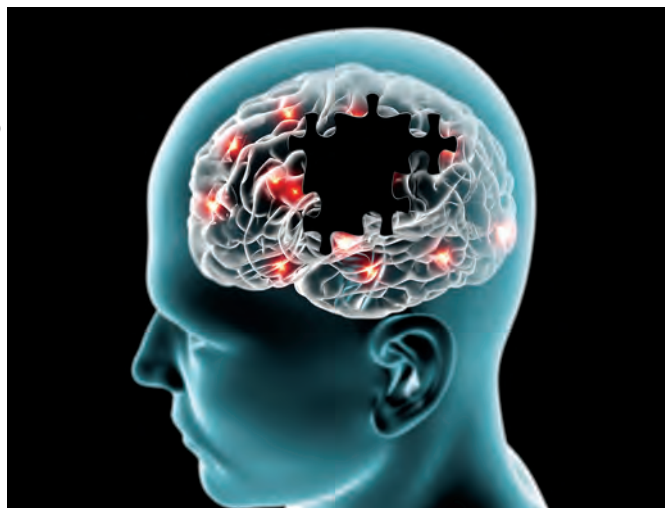
An ongoing Phase II trial has reported robust gene knock-downs for more than a year accompanied by disease stabilization (and in some cases improvement). **Alnylam Pharmaceuticals** is expected to report results from a pivotal Phase III trial in 2017.

Alzheimer's Agitation

15. AVP-786

Avanir Pharmaceuticals/Concert Pharmaceuticals,
Alzheimer's disease agitation

Shutterstock



The idea of improving known drugs by replacing selected hydrogen atoms with deuterium has been knocking around for years, but none have yet reached the market. AVP-786—a combination of deuterium-substituted dextromethorphan (a cough suppressant) and an ultra-low dose of quinidine (used to treat abnormal heart rhythms and malaria)—is aiming to be the first past the gate, a collaboration between neurological disease specialists **Avanir Pharmaceuticals** and **Concert Pharmaceuticals**, which developed the deuterium substitution technology.

Deuterium is a heavier atom than hydrogen, which forms stronger bonds with carbon. The theory behind deuterated drugs is they should retain the activity, potency and selectivity of the undeuterated versions, whilst changing some properties that could improve safety, efficacy and tolerability of the molecules.

Phase III trials of VP-786 for treating agitation in Alzheimer's disease patients are scheduled to start this fall.

Anti-Asthma Antibody

16. Dupilumab

Regeneron/Sanofi
Asthma

A potentially groundbreaking new asthma drug entered Phase III clinical trials in April. Designed by **Regeneron** and being co-developed with **Sanofi**, dupilumab reduces the risk of an asthma attack by 87% in patients for whom existing medications couldn't control their condition. This investigative drug is administered every two weeks by injection, and the current trial will run until the summer of 2017.

Dupilumab is a monoclonal antibody that blocks the actions of both interleukin 4 and interleukin 13, cytokines implicated as potential causes of allergic inflammation. The drug is also being tested against other inflammation conditions including as an emollient for treating eczema and as a nasal spray for chronic sinusitis.

MS Immunity

17. Ozanimod

Receptos
Multiple sclerosis

An investigative immunotherapy for treating multiple sclerosis is storming its way through clinical trials, generating high hopes that it may prove to be a safer option than a currently available top drug with the same mode of action.

Multiple sclerosis is thought to be an immune disease, and **Receptos'** ozanimod impacts the immune system by modulating the sphingosine-1-phosphate 1 receptor pathway. **Novartis'** Gilenya, which works in the same way, has cardiac side effects and early clinical trials suggest these are less of a problem with ozanimod. Two Phase III trials are now being carried out with this drug, both due to finish in 2017.

In July, **Celgene** said it would pay approximately \$7.2 billion to buy Receptos with ozanimod cited as the key driver for the acquisition. Celgene expects ozanimod to have peak annual sales of \$4 to \$6 billion.

Targeting PARP

18. Veliparib

AbbVie
Breast cancer and lung cancer

An investigational drug that targets the Achilles' heel of certain cancer types is generating promising results in clinical trials against both breast cancer and lung cancer. Veliparib is a poly (ADP ribose) polymerase (PARP) inhibitor. The first drug of this type—**AstraZeneca's** olaparib—was approved for use in ovarian cancer treatment by the FDA in December 2014.

PARP inhibitors work on cancers caused by a faulty BRCA1 or BRCA2 gene. Cancerous cells of this type depend on the PARP protein to carry out DNA repairs. If PARP is blocked, cancer cells can't repair themselves and die. Drugs with this mode of action should increase the effectiveness of common DNA-damaging therapies such as chemotherapy or radiation.

Following promising Phase II results, **AbbVie's** veliparib is in Phase III trials in combination with chemotherapeutic medicines such as carboplatin for both breast cancer and small cell lung cancer. (See Lisa Jarvis' in-depth report on PARP inhibitors in C&EN, "Pushing Cancer Over The Edge," June 17, 2013; issue 24, pp. 13–18.)

Killing Cancer STAT

19. BBI608

Boston Biomedical

Various solid cancers

Another potential way to give chemotherapy or radiation a helping hand is to combine them with a drug that blocks the growth of cancerous cells by inhibiting specific proteins needed for them to grow. Most cancer treatments target proliferating cells, and do not eradicate cancer stem cells. These can lead to the cancer reoccurring or migrating to another site in the body.

Boston Biomedical is focused on targeting cancer stem cell pathways. Its lead product BBI608 is in a Phase III trial in

combination with paclitaxel in patients with gastric and gastroesophageal junction cancer. The trial is scheduled to complete in 2017. BBI608 is designed to inhibit cancer stem cell pathways by targeting STAT3, a protein that plays a fundamental role in converting normal cells to cancerous cells.

Liver Lifeline

20. Obeticholic acid

Intercept Pharmaceuticals,

Primary biliary cirrhosis

The first new drug for treating primary biliary cirrhosis for more than two decades is awaiting FDA approval. In June, **Intercept Pharmaceuticals** filed to use obeticholic acid both as a standalone therapy, for patients unable to tolerate the drug ursodeoxycholic acid (UDCA), and in combination with UDCA for those with an inadequate response to this drug alone.

UDCA is the only currently approved therapy for treating this rare liver disease that can progress to cirrhosis and liver failure. The disease primarily results from the autoimmune destruction of the bile ducts that transport bile acids out of the liver. Obeticholic acid is a first-in-class bile acid analogue that selectively binds to and activates the farnesoid X receptor, thus reducing natural bile acid production. Analysts have projected that, if approved, annual sales of this drug could approach \$3 billion by 2020. ■

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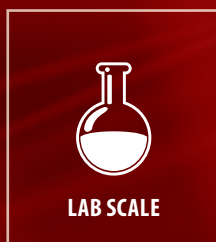
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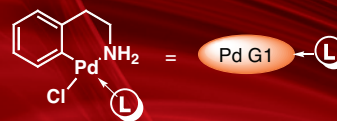


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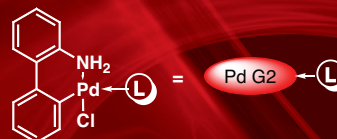
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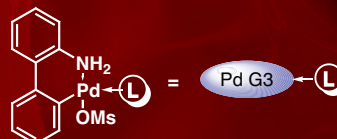
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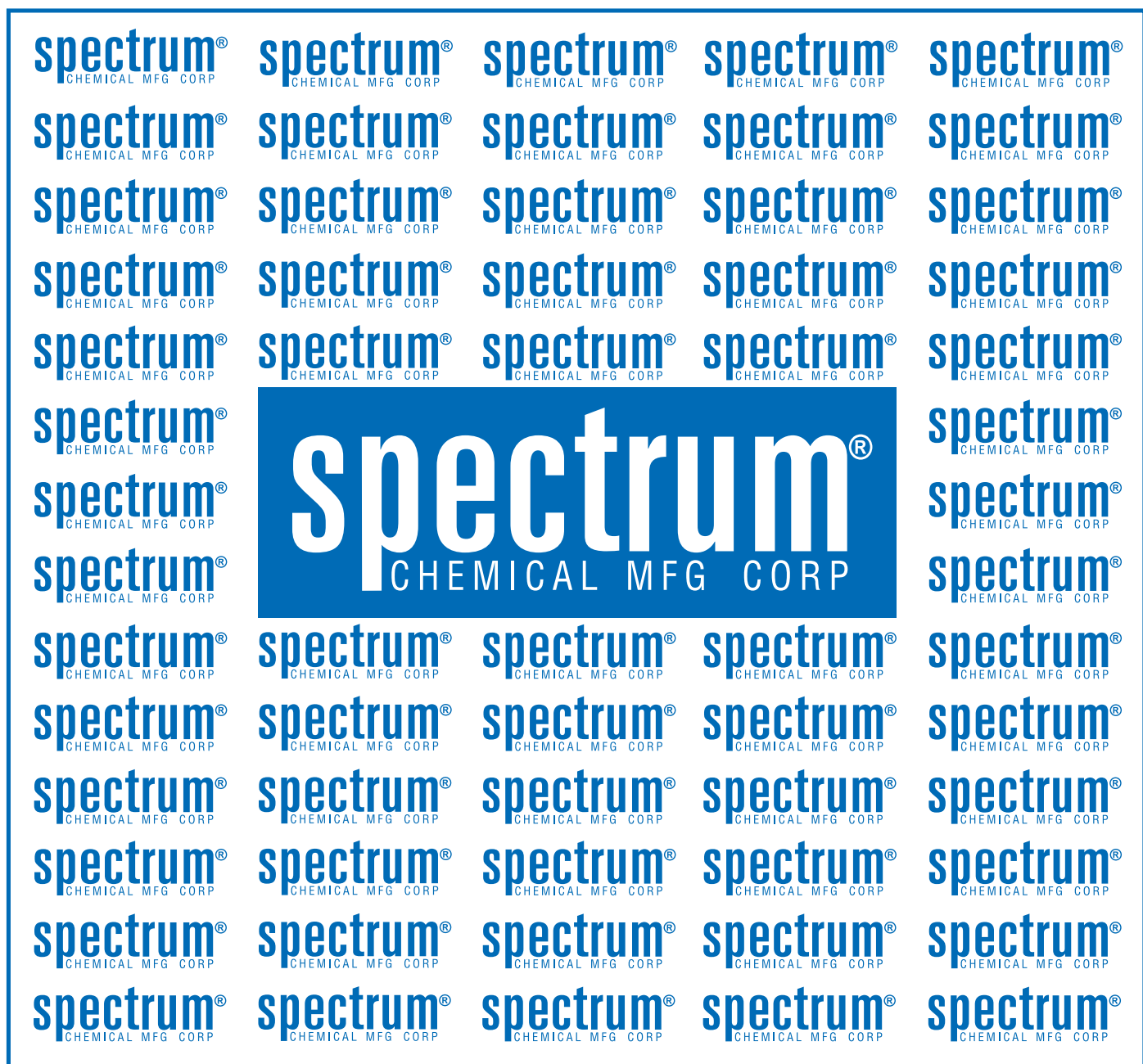


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