Industry chases pan-genotypic and shorter HCV treatments

Kristoffer Tripplaar / Alamy

Gilead's Sovaldi and its successor Harvoni have drastically reduced HCV infection prevalence. Companies are now looking to shorten treatment time by combining up to four anti-viral agents.

Foster City, California–based Gilead is the first company making strides towards a pan-genotypic therapy for hepatitis C virus (HCV). The giant biotech announced on April 23 positive but still early phase 2 results for a novel combination therapy to treat HCV across all six HCV genotypes (GTs). The same month, the Chicago-based AbbVie and its Watertown, Massachusetts–based partner Enanta Pharmaceuticals reported preliminary results from a phase 2b study with an all oral, four-drug antiviral combination for pan-genotypic treatment of HCV. On May 19, Titusville, New Jersey–based Janssen announced a collaboration with New Haven's Achillion Pharmaceuticals to develop a pan-genotypic oral combination that will include the biotech's NS5A inhibitor ACH-3102. The dramatic success enjoyed by Gilead Sovaldi (sofosbuvir) and more recently Harvoni (ledipasvir and sofosbuvir) have left few gaps in the HCV market. But a pan-genotypic treatment could simplify the treatment options, now a dizzying array of combination genotype matches (**Table 1**), and, if the biotech giant has its way, shorten treatment considerably from the current 12 weeks.

With current regimens resulting in up to 99% cure rates in some subsets of patients, a pan-genotypic, once-a-day single pill regimen is the next far-reaching goal. The HCV therapy landscape has evolved rapidly in the last two years. Gilead's Sovaldi was the first interferon-free nucleotide ('nuc') polymerase inhibitor approved for people infected with HCV GT2 (*Nat. Biotechnol.* **32**, 3–5, 2014) in December 2013. Gilead followed with Harvoni in October 2014, the first noninterferon, nonribavirin, single pill cocktail to treat people infected with HCV GT1, the most frequently isolated variant in the US (*Nat. Biotechnol.* **32**, 1070, 2014). Once-daily Harvoni combines ledipasvir, a nonstructural 5A (NS5A) replication inhibitor, with Sovaldi, and in some patients with low viral loads achieves viral cures in as little as eight weeks.

AbbVie has set out to challenge Sovaldi with its fixed combinations of direct-acting antivirals with distinct mechanisms of action. AbbVie's interferon-free combo regimen Viekirax (ombitasvir—a novel NS5A inhibitor, and protease inhibitors paritaprevir and ritonavir) plus Exviera (dasabuvir), a non-nucleoside polymerase inhibitor, received US Food and Drug Administration (FDA) approval in December 2014 for treating GT1 infections and marketing authorization in January 2015 from the European Commission.

Merck of Kenilworth, New Jersey is also chasing a shortened-treatment, once daily pill for chronic HCV infections. Merck is combining its investigational drugs grazoprevir (a NS3/4A protease inhibitor) and elbasvir (an NS5A inhibitor) with Gilead's Sovaldi in treatment-naive patients infected with HCV GT1 or GT3 in a proof-of-concept, phase 2, open label study.

New York-based Bristol-Myers Squibb's refiled with the FDA the combination of its NS5A inhibitor, Daklinza (daclatasvir) plus Gilead's Sovaldi, in March of this year for GT3 patients. Daklinza, combined with another Bristol-Myers Squibb drug NS3/4A inhibitor Sunvepra (asunaprevir) for GT1, was the first noninterferon regimen approved in Japan.

Between them, HCV therapies on the market provide a cure to a broad swathe of infected patients. "The advances in [HCV] treatment are of historical significance. We have oral-only combinations and cure rates exceeding 95% with very few side effects," says Eugene Schiff, director of the Schiff Center for Liver Diseases at the University of Miami Miller School of Medicine. "I think we have solved the science of how to block replication to cure infection [using] all-oral drug [combinations] without interferon," says Jean-Michel Pawlotsky, of the department of virology at the Henri Mondor University Hospital in Créteil, France.

But Gilead is staying one step ahead. The biotech is assessing whether its next-generation combination can be used for a shorter 6-week course of therapy. The investigational combo includes Sovaldi and two pan-genotypic oral drugs, GS-9857, an NS3/4A protease inhibitor, and GS-5816, an NS5A replication inhibitor that replaces its own narrowly targeted agent ledipasvir in Harvoni.

AbbVie is also heading towards the pan-genotypic, shorter therapy route, having announced preliminary phase 2b data in April on a once-daily pill combining two next-generation HCV agents ABT-493, an NS3/4A protease inhibitor and ABT-530 an NS5A protease inhibitor. Both agents have shown *in vitro* activity against all six HCV genotypes as well as strains that have become resistant to other NS5A inhibitors. The combination resulted in a sustained virologic response (SVR)-12 of 99% among GT1 patients. "We are taking this regimen into phase 3 later this year," says Barry Bernstein, AbbVie's vice president for infectious disease

Cold Spring Harbor in translation

Cold Spring Harbor Laboratory (CSHL) has announced a $120-million cancer therapeutics research partnership with the North Shore-Long Island Jewish Health System. The private, not-for-profit CSHL, renowned for its pioneering basic science, is building its translational capabilities with North Shore, a hospital system with 19 hospitals located nearby, which treats 16,000 cancer patients a year. The partnership will help both the laboratory and hospital break out of their silos, by making CSHL's most promising research more readily available to cancer patients through clinical trials at North Shore facilities. Those trials, in turn, should help advance the research. The alliance will not mean that CSHL is moving away from its roots, according to president and CEO Bruce Stillman, but rather that it will ramp up funding for translational cancer research, which the CSHL has so far been doing on a shoestring budget, Stillman adds. The initial funding will go towards research as well as the development of a new clinical cancer research center at North Shore-LIJ's Cancer Institute and the recruitment and training of additional clinician-scientists.

"Make no mistake about it: these data [whole genome sequencing] will scare people—particularly since they are likely to be framed as a 50% increase in your risk of Disease X. But it's just as likely they won't make a make a difference in your health." H. Gilbert Welch and Wylie Burke in an op-ed piece in which they argue that whole genome sequencing will consume valuable resources and raise more questions than it answers. (*Los Angeles Times*, 27 April 2015)

"The editorial decision to publish this study [on CRISPR-CAS9-mediated human germline editing] should not be viewed as an endorsement of this practice nor an encouragement of similar attempts, but rather the sounding of an alarm to draw immediate attention to the urgent need to rein in applications of gene-editing technologies, especially in the human germ cells or embryos." The editors of *Protein & Cell* explain their decision to publish the first paper describing attempts to edit the human germline. (*Protein & Cell*, 28 April 2015)

"When I give talks, I'm always amazed how often an audience member will cite one of those movies as if it happened!" Hank Greely, speaking of the SciFi movies Gattaca and Jurassic Park. (@HankGreelyLSJU, 28 April 2015)

Table 1 Selected interferon-free HCV agents approved and in development matched with viral genotype

Drug maker	Agents	Genotype	Status
Gilead	Sovaldi (sofosbuvir)	GT2, 3	Approved
	Harvoni (ledipasvir + Sovaldi)	GT1	Approved
	GS-9857, GS-5816 + Sovaldi	GT1–GT6	Phase 2
AbbVie	Viekira Pak (ombitasvir, paritaprevir, ritonavir + dasabuvir)	GT1	Approved
	Viekirax (ombitasvir, paritaprevir, ritonavir) + ribavirin	GT4	Filed
	Viekirax (ombitasvir, paritaprevir, ritonavir) + Exviera (dasabuvir)	GT1 renal-impaired patients	Phase 3b
	ABT493 + ABT-530	GT1–GT6	Phase 2
Merck	Grazoprevir + elbasvir	GT1, 4, 6	Phase 3 (filing planned for mid-2015)
	Grazoprevir + elbasvir in chronic kidney disease	GT1	
	Grazoprevir + elbasvir + Sovaldi	GT1, 3	Phase 2
Bristol-Myers Squibb	Daklinza (daclatasvir) + Sunvepra (asunaprevir)	GT1	Approved (Japan only)
	Daklinza (daclatasvir) + Sovaldi	GT3	Refiled

development. "The plan is to study all six genotypes."

The newer generation therapies aim to cure all genotypes in as little as four weeks, says Phil Nadeau, biotech analyst at New York-based Cowen and Company. "We don't see anything even close to that right now, but that is what [companies] are beginning to strive for."

But an issue with shorter therapy durations is the potential for undertreatment, which can lead to resistance development. Even though there are broad classes of patients—those that have been previously treated, those with cirrhosis, or those with GT3 infections—that are at higher risk for resistance and most likely to need longer therapy duration, it is difficult to predict which individual patients are most at risk. "If we want to achieve very high cure rates at the population level to control infection, it is important to slightly overtreat the population . . . so the difficult-to-treat patients receive sufficient therapy," says Pawlotsky.

Bernstein agrees. "The shortest possible duration is not necessarily in the best interest for patients. We are learning that patients who fail therapy have residual resistance especially to the NS5A [inhibitor], which may persist over time…so we think the initial therapy should be optimized for every patient to give them the best chance of a cure."

Thus far, no single class of drug is necessary for oral combinations to be effective. "It is more important to have multiple agents that are potent and well tolerated than [for the cocktail] to contain any specific agent class," says Bernstein. Still, all of the pan-genotypic combinations in development, including one from Merck in phase 2 for GT1, 2 and 4, contain an NS5A inhibitor.

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Hitting more targets directly has been the guiding principle in HIV therapy. Now companies are building towards one-pill, high-potency HCV regimens, says Pawlotsky. "But this is more of a commercial thing than a medical need," he adds. "We already have what we need if we combine drugs from different companies."

"What analysts are debating now is how long the existing pool of HCV patients will last," says Nadeau. "Gilead recently suggested they will treat 300,000 patients this year. If this number of patients are treated over the next five years, any therapy that comes to market more than five years from now will have a very different opportunity with far fewer patients."

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