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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