Japan's HCV cocktail first

Japan has approved Bristol-Myers Squibb's all-oral hepatitis C virus cocktail for patients with genotype 1 virus (which account for ~70% of infected people). The Daklinza (daclatasvir) and Sunvepra (asunaprevir) regimen, approved in July by the Japanese Ministry of Health, Labor and Welfare, is the first in a number of combinations nearing approval that contain no interferon or ribavirin. Daklinza is a highly selective hepatitis C nonstructural 5A (NS5A) inhibitor and Sunvepra is a novel NS3 protease inhibitor. Elsewhere, the combination has a favorable vote from the European Medicines Agency and a breakthrough therapy designation from the US Food and Drug Administration. The combination equaled Gilead's blockbuster Sovaldi (*Nat. Biotechnol.* **32**, 3–5, 2014) in achieving near 100% 12-week cure rates. Therapies with the shortest treatment times are likely to prevail, so Bristol-Myers is aiming for a four-week therapy combining Daklinza and Sunvepra with Sovaldi. Gilead is also testing its own combinations in-house.

Merck bets on Idenix 'nuke'

Merck agreed to buy Cambridge, Massachusetts–based Idenix Pharmaceuticals for $3.85 billion to boost its portfolio of hepatitis C virus (HCV) products. The New Jersey–based pharma acquired Idenix to get its hands on the biotech's three experimental drugs. Merck's main interest is IDX21437, a nucleotide polymerase inhibitor or 'nuke', that it plans to combine into a triple therapy with two drugs of its own, which work by different mechanisms. The deal underscores pharma's long-term intention to compete with Gilead and others in offering improved drugs for HCV infections.

Long-life agent for hemophilia A

The US FDA approved Biogen Idec's Eloctate for patients with hemophilia A. The June approval was based on data from a clinical trial that showed reduced severity and frequency of bleeding episodes. Eloctate is a recombinant factor VIII molecule attached to the Fc domain of human immunoglobulin G1, which avoids lysosomal degradation and extends the protein's half-life. Eloctate needs one injection every ten days, whereas existing treatments require injections every two to four days. Biogen's other long-lasting agent Alprolix, a recombinant factor IX for hemophilia B treatment, was approved in March (*Nat. Biotechnol.* **32**, 506, 2014). Analysts expect Eloctate to generate annual sales of $1.5 billion by 2019.

> **"[Afrezza is] a very different product, very much a next-generation product."** Matthew J. Pfeffer, CFO of MannKind, compares their recently approved inhaled insulin device to Pfizer's earlier version, Exubera, which was the size of a tennis ball. Afrezza is the size of a referee's whistle. (*The New York Times*, 27 June 2014)

Box 1 Screening resilient individuals for drug targets

Ismail Kola of UCB sees "intellectual convergence" between the NCI and MSKCC initiatives and an innovation challenge, which UCB is running with the help of Innocentive, a Boston-based crowdsourcing platform. The joint challenge is seeking individuals with rare phenotypes that protect against disease or that contribute to rapid healing. At present, UCB and Innocentive are reviewing the submissions they have received—the total is fewer than 100. UCB's recent challenge represents the flip side of another phenotype-based approach focused on negative responders. The company observed that in patients with van Buchem's disease, a very rare condition characterized by excessive bone growth, sclerostin—a negative regulator of bone formation—is underexpressed. That discovery led to UCB's phase 3 sclerostin-targeting antibody for osteoporosis, romosozumab, which it is developing with Amgen, of Thousand Oaks, California. "Let's try to find populations where nature has done the experiment and knocked out a gene that either predisposes to disease or prevents disease," says Kola.

Few drugs have stemmed from a protective phenotype, however, as the individuals lucky enough to have one may not have much need of healthcare, even if they harbor biologically interesting characteristics. "That was the innovation challenge," he says. There are positive exemplars, however. The AIDS crisis did uncover several protective phenotypes, including one, a deletion in C-C chemokine receptor 5 (*CCR5*), which inspired New York–based Pfizer to develop the HIV fusion inhibitor Selzentry (maraviroc). Kola expects more to follow. "What I'm always surprised by is, why others haven't embraced it to the extent that we have?" *CS*

that out," says Conley. At the very least, the analyses should deliver a wealth of new data that will aid clinical trial design and improve clinical decision-making in cancer diagnosis and treatment, even if neither can claim to be a completely definitive effort to uncover all oncogenic drivers in a given population. "There's still a lot of discovery left to be done," says Solit. For example, one recent large-scale mutation analysis, which examined exome sequences from 4,742 tumors across 21 types of cancer, identified 33 new candidate cancer genes (*Nature* **505**, 495–503, 2014).

Initiatives such as The Cancer Genome Atlas (TCGA), which is jointly managed by the NCI and the National Human Genome Research Institute, have already built up a comprehensive catalog of cancer-associated genes, however. The NCI will undertake whole-exome sequencing of about 400 of them, from cancer and normal tissue biopsies taken from each of those chosen to participate. "It's narrow but deep," says Conley. It may also be able to investigate cancers driven by alterations in gene expression rather than by mutations hard-wired into the genome. "We would dearly like to get RNA-seq data if we have enough material," she says. The NCI-Match program, which the NCI will run in cooperation with its newly formed National Clinical Trials Network, will begin recruitment next year and will enroll about 3,000 patients in all. "We are hoping to have access to 20 or 30 agents. Many drug companies are working with us—they have been very helpful," Conley says.

The new MSKCC center will use a system called Integrated Mutation Profiling of Actionable Cancer Targets (IMPACT), developed by its associate director Michael Berger, to analyze patients with solid tumors. The present version of the system, which is based on the Illumina HiSeq sequencing platform, sequences 341 cancer-associated genes from each sample. "We're screening essentially all the known genes," Solit adds. A separate system, jointly developed by MSKCC and Cambridge, Massachusetts–based cancer genomics analysis firm Foundation Medicine, will be used to screen for more than 400 genes in hematologic tumors. Given the high numbers of patients that will be screened, Solit expects even rare mutations to be captured.

Even when the problem is defined at a molecular level, oncologists are working with a moving target, given the inherent genomic instability of cancer. "Not all responses are durable," Subbiah notes. Gaining a rapid—and actionable—understanding of a cancer's resistance mechanisms will therefore become as important as identifying its original oncogenic driver.

From a regulatory standpoint, it is unclear how any of the findings emanating from basket trials or from studies of exceptional responders may be translated into new therapies—particularly when rare mutations involving small patient populations are involved. "That's an issue that everyone is going to have to grapple with," Conley says. "The real question is if you have something that is very relevant, is it feasible to do a randomized, controlled trial?" asks Solit.

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