IN brief

Gilead's $11 billion HCV bet

Gilead Sciences, market leader in human immunodeficiency virus (HIV) drugs, has set out to also dominate the fast-growing hepatitis C virus (HCV) field by acquiring Princeton, New Jersey–based Pharmasset for $11 billion. The valuation is lofty for a company with no drugs on the market, and some have questioned the price paid for Pharmasset's candidate PSI-7977, a nucleotide analog polymerase inhibitor. But New York analyst Phil Nadeau, of Cowen & Co., says "[PSI-7977] is best positioned to be the Viread of HCV." Gilead's Viread (tenofovir) is currently the cornerstone of HIV treatment. The Foster City, California–based large biotech is now wagering that PSI-7977 can transform the treatment paradigm for HCV: the drug candidate is oral and does not require the use of injectable alpha interferon, unlike newly approved protease inhibitors Incivek (telaprevir) and Victrelis (boceprevir) (*Nat. Biotechnol.* **29**, 963–966, 2011) . Strong efficacy data in genotypes 2 and 3 and safety data in genotype 1 indicate a "reasonable likelihood" that the gamble may pay off, Nadeau says. The drug could hit the market in 2014, but would need to earn $3 billion a year for several years to make the acquisition neutral to Gilead shareholders. "Why is it so much money?" Nadeau says. "I think the practical answer is Pharmasset wasn't going to sell itself for less." On January 17, Bristol-Meyers Squibb agreed to pay $2.5 billion for small biotech Inhibitex in Atlanta, and its lead experimental HCV drug INX-189. **Karen Carey**

Affymetrix sued for fraud

Microarray pioneer Affymetrix postponed a $330 million acquisition of eBioscience after an investment firm alleged fraud in the merger terms. The struggling Santa Clara, California–based Affymetrix's attempts to carve out a new strategy were put on pause after San Diego investment firm Tang Capital filed the complaint. Tang claims the maker of genomic analysis tools misrepresented the financing of the acquisition. Affymetrix denied any wrongdoing, but postponed its buyout to the end of January. The proposed purchase of eBiosciences, a firm dealing in flow cytometry and diagnostic reagents for immunology and cancer applications—well outside Affymetrix's core business—creates new commercial opportunities for Affymetrix. Although the company didn't respond to *Nature Biotechnology*'s requests for comment, Doug Schenkel, a senior research analyst in the Cowen Group in New York, said the company had to do something to challenge its steady decline in revenue. Whereas gene expression arrays are still profitable, he said, there is fierce competition, and laboratories are increasingly going over to RNA sequencing, which Affymetrix does not supply. Affy's DNA genotyping products have been outperformed by Illumina's, of San Diego, and its small portfolio of existing oncology products, though promising, is still a "wild card." The eBiociences price tag is "a little rich," says Schenkel, "but it's an asset that can offset the headwind in its core business." **Jennifer Rohn**

are very slow to decline," she says, which adds a layer of difficulty to trial designs.

A subset of patients, however—those with more severe disease—did experience some benefit in an array of neurological indicators. Ted Tenthoff, a managing director and senior research analyst at New York–based securities firm Piper Jaffray, and other observers were unconvinced. Tenthoff viewed the effort to carve out a new primary end point from the unsuccessful phase 2 results as 'data mining', and his firm adopted a more pessimistic view of the company's prospects. "We felt like the risk around SB-509 clinically was too great for the valuation," he says.

Despite such concerns, Sangamo's development team opted to test SB-509 in a more carefully chosen patient cohort. "Looking at the data from the first study, it was very clear—and highly statistically significant based on a retrospective analysis—that there was a group of patients with moderate severity disease who showed the greatest improvement versus placebo," says Lanphier. JDRF renewed their support, providing the funding for the '901' phase 2b trial, which recruited 170 patients with moderate or severe peripheral diabetic neuropathy and incorporated a host of outcome measures, such as the neuropathy impairment score–lower limb, broadly used in clinical settings.

With the results of this latest '901' trial unequivocally disappointing, Sangamo has ceased further development of SB-509. To Lanphier's thinking, the primary culprit, as in previous trials, was that placebo patients simply remained too healthy to observe meaningful relative benefits from treatment. "With the new oral medications that help stabilize blood sugar levels, there's better care for patients in general with type 2 diabetes," he says, "but also there's simply better care for patients who are in a clinical trial." In a press release after the conclusion of the 901 trial, the company noted that the treatment arm achieved neurological improvements equivalent to responders in the 601 trial but that these were masked by the positive response of the placebo arm to routine medical treatment.

Others point out potential technical complications as well, criticizing the decision to deliver SB-509 through a series of intramuscular injections of naked plasmid DNA. "Delivery via plasmid injection hasn't lived up to its promise even in vaccines, which require more limited expression than this therapeutic application," says Carlos Barbas III, a pioneer in the field of zinc-finger engineering at the Scripps Research Institute in La Jolla, California. "I don't think plasmid injection gave SB-509 a fighting chance." Seppo Ylä-Herttuala, whose group at the University of Kuopio in Finland has worked extensively with VEGF-oriented gene therapy, also expressed concern about the chosen method, but acknowledges that choices are limited. "We have two or three other options at the moment, but they all have the same issues related to delivery," he says. Lanphier, however, defends the decision, pointing out that plasmid injection was well suited to Sangamo's primary goal of achieving short bursts of transient expression by means of chronic dosing.

Some also question whether the effects of SB-509 were undercut by insufficient specificity. With only three zinc fingers, the construct targets a nine-base target sequence—far from unique in the human genome. Cell culture and rodent studies showed limited off-target effects, but Ylä-Herttuala is skeptical about those results. "In our hands, with roughly equivalent but non-VEGF zinc-finger constructs, we've seen as many as a hundred genes going up or down," he says.

Although none of these factors alone may explain the failure of SB-509, collectively they appear to have spelled its doom. "They took on a very tough disease with a very tough approach," says Tenthoff.

Sangamo is now moving ahead with its SB-728-T program, which targets chemokine CC-motif receptor 5 (CCR5), a co-receptor for HIV. SB-728-T comprises two endonuclease domains linked to a pair of ZFPs, each containing four zinc-finger motifs (recognizing a total of 24 base pairs in the CCR5 gene). Concerted binding of the DNA induces dimerization of the two endonuclease domains, resulting in a double-stranded break of the CCR5 sequence. This in turn induces cellular DNA repair pathways, most notably the mutagenic nonhomologous end-joining pathway, leading to efficient disruption of the CCR5 gene (*Nat. Biotechnol.* **26**, 808–816, 2008). The approach used for HIV treatment involves the isolation of $CD4^+$ T cells from HIV-positive patients and their treatment *ex vivo* with SB-728. Treated cells are then reinfused in the patient, with the hope that virus-resistant T cells will expand to become the patient's main population.

The company presented phase 1 data this past September at the Interscience Conference on Antimicrobial Agents and Chemotherapy in Chicago, showing potential patient benefit, particularly for one individual who was already heterozygous for the naturally occurring *CCR5Δ32* mutation. The company is embarking on several additional trials, including one that will specifically assess the efficacy of SB-728-T in a larger cohort of heterozygous patients.

In the meantime, Sangamo is likely to remain out of favor with analysts. "The problem that Sangamo faces is not that their results are bad—they're good—but they're phase 1 results," says