IN brief

Dynavax trial halted

Berkeley, California-based Dynavax announced April 17 that the FDA is requesting preclinical and clinical safety data on two investigational new drug applications for its hepatitis B vaccine, Heplisav, which combines an immunostimulatory sequence (ISS 1018) with hepatitis B antigen. Trials with Heplisav were halted last month in response to a serious adverse effect report from a phase 3 trial comparing Heplisav to a marketed hepatitis B vaccine, Engerix-B, sold by GlaxoSmithKline in London. (Merck, of Whitehead Station, New Jersey, which has the only other marketed hepatitis B vaccine, called Recombivax, is partnered with Dynavax on Heplisav.) After receiving two doses of Heplisav, one subject was preliminarily diagnosed with Wegener's granulomatosis, an autoimmune disease characterized by inflammation of the vasculature. Though dosing in that trial was complete, Dynavax halted a phase 2 trial of patients with end-stage renal disease. Early results for Heplisav had looked promising. A trial report in November 2006 that compared the product with Engerix-B showed that a larger percentage of recipients on Dynavex responded with what appeared to be a more robust response with fewer doses of vaccine (98.5% seroprotection versus 25% after two doses). It's not clear what caused the serious adverse effect, but immunostimulatory sequences—short oligodeoxynucleotides containing at least one internal unmethylated CpG—stimulate innate immunity by interacting with Toll-like receptors on immune cells, like the pathogen-associated molecular patterns they were designed to resemble. Immunomodulatory molecules sometimes raise safety concerns, owing to the possibility of inducing autoimmunity or causing the overproduction of inflammatory molecules, but this is the first serious adverse effect potentially related to Heplisav, 5,000 doses of which have been injected into 2,500 subjects in seven trials over the last ten years. In addition, at least 50 other clinical trials using immunostimulatory sequences have been reported to http//:clinicaltrials.gov/, ten using ISS 1018 in Heplisav. Eyal Raz, professor of medicine at University of California at San Diego, founder of Dynavax (though he no longer has ties to the company), says that although immunostimulatory sequences given to people with preclinical disease might "take it up a notch," he feels this is unlikely, given that they have been used in humans for over a decade.
—Laura DeFrancesco

IN their words

"It's sort of like saying all birds don't fly when you are studying a penguin."

John Maraganore, CEO of Alnylam (Cambridge, MA) on a study published in *Nature* suggesting that at least some RNAi drugs being tested in clinical trials actually work, not by silencing genes, but by activating the immune system. (*The New York Times*, April 2, 2008)

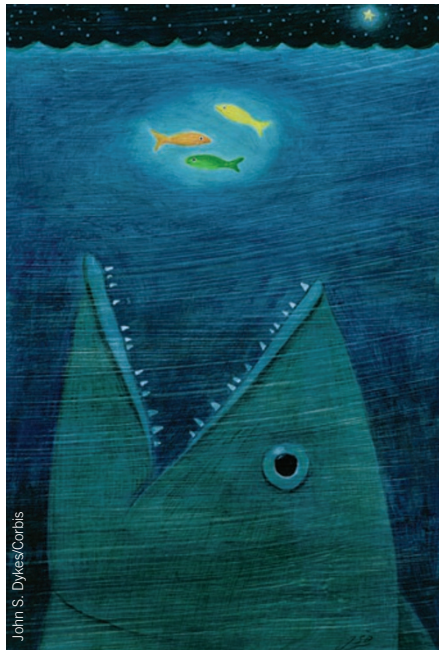
No way out for small public firms?

Although buyouts of private biotech firms leaped in 2007, exceeding the 2006 value by more than three times, the dollars spent purchasing public biotech companies rose by only 50%. And if the London-based AstraZeneca's $15.6 billion purchase of MedImmune is excluded, the aggregate dollar value of public biotech acquisitions in 2007 drops below the previous year's level.

These kinds of numbers (see **Table 1**) suggest a problem for small and mid-cap public companies. They now face slim chances of relieving cash shortages by accessing today's volatile public markets, and their most likely acquirers—big pharma firms—are less interested in larger public companies that carry regulatory barriers, additional sites and large workforces (though Japan's biggest pharma, Takeda, is interested enough to pay $8.8 billion for Millennium, of Cambridge, Massachusetts). That means uncertainty for today's unprofitable public biotechs: there is no cash to pull in, and the investors can't get out.

In current acquisitions, "pharma firms don't necessarily want to buy the company; they want to get hold of the relevant intellectual property and product programs, which they will then transfer internally," says Kate Bingham of London-based SV Life Sciences Advisers, adding that private companies are easier to buy because they're "smaller and more virtual with few staff and sites," without the "burdensome requirements" of public reporting, US Securities and Exchange Commission filings and Sarbanes-Oxley compliance. Moreover, says Bingham, private companies with early-stage products are seen as less of a gamble, because any failure at the US Food and Drug Administration is cheaper and further in the future than it would be with a more mature public company with later-stage products.

Even favorable clinical data may not help the foundering public firms, says Genghis Lloyd-Harris, partner at London-based Abingworth Management. He notes that, in the current bear market, quoted biotech companies' share prices tend to slump, even when they announce good news. "Ironically, good news creates increased liquidity, leading some investors to rush for the exits on the back of it," he says.



It has been smaller private firms, rather than public biotechs, that have been gobbled up by big pharma.

What should happen in this environment is mid-level mergers, but Lloyd-Harris believes that the opposite will happen. "The pace of biotech-to-biotech mergers is slowing, because CEOs tend to batten down the hatches in a market like this," he says. Conscious that their firm's share price is seriously depressed, they fear that a merger may sell their investors short, although that's irrational because most companies with which they would merge also would have a depressed share price. "But the boards of both companies frequently have blinkers on that stops them negotiating a deal," says Lloyd-Harris.

Perhaps the way forward for public biotechs under shareholder pressure is to be more realistic on valuations. Lehman

Table 1 Takeovers of public & private biotech firms, 2005–2007

Year	Public firms (total $ value/number)	Private firms (total $ value/number)
2005	8.6 billion/14	3.8 billion/62
2006	23.5 billion/14	2.6 billion/59
2007	23.1 billion/15[a]	8.7 billion/59

[a]Excludes AstraZeneca/MedImmune event.

Data sources: Lehman Brothers, BioCentury