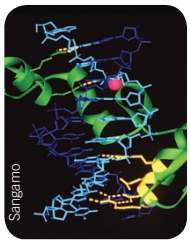
IN brief

One-off therapy for HIV



One of Sangamo's zinc finger nucleases.

The first clinical trial using zinc-finger nucleases to provide long-term resistance to HIV-1 infection has been given the go-ahead by the US Food and Drug Administration. Sangamo BioSciences of Richmond, California, and its clinical partner, the University of Pennsylvania, have begun enrolling the first 12 people in a phase 1 clinical trial to evaluate SB-728-T, a novel zinc-finger DNA-binding nuclease that permanently disrupts the *CCR5* gene on CD4+ T cells (*Nat. Biotechnol.* **26**, 808–816, 2008). CCR5 is the major co-receptor used by HIV-1 to gain entry into T cells. A decade ago, researchers found that a Δ32 deletion in the *CCR5* gene confers resistance to HIV-infection in the 1–2% of humans who are homozygous for this mutation. Since then, small-molecule approaches designed to block the CCR5-HIV interaction have been attempted, and New York–based Pfizer's Selzentry (maraviroc), for instance, a CCR5 antagonist, gained approval in August 2007. But while the virus eventually develops resistance to small molecules, Sangamo's strategy aims to disrupt CCR5 viral entry permanently by modifying CD4+ T cells. The company plans to isolate CD4+ cells from a patient's blood, apply the engineered SB-728-T agent to bind the *CCR5* gene and excise a portion of it, creating a population of T cells with a disrupted CCR5 receptor, which is then injected back into the person. "This is a very clever approach to treating HIV infection, and I think there's a reasonable expectation that it should work," says Ramesh Akkina of Colorado State University in Ft. Collins, who has developed a CCR5-suppressing, small-interfering-RNA agent currently in clinical trials. The real question, Akkina adds, is how long the engrafted T cells will survive in the body and how often the therapy will need to be administered. A treated person will still have many infected T cells in circulation but the modified cells are expected to replicate faster. Dale Ando, Sangamo's chief medical officer, notes that one of the major endpoints for the ongoing trial is whether the modified autologous T cells expand preferentially and eventually dominate circulating T-cell populations. "If we see expansion of these T cells, as we did in our preclinical studies, then we would hope that patients would achieve long-term nonprogressive status." A recent publication (*N. Engl. J. Med.* **360**, 692, 2009), reporting that an HIV-infected patient treated with bone marrow from a CCR5− donor had undetectable viral loads 20 months after transplantation, lends support to the notion that T cells may offer long-term protection against infection.

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Swann in Boston, assuming the US Food and Drug Administration (FDA) will raise questions around yeast-based manufacturing. Indeed, the US regulator is already signaling its intention to closely examine all aspects of biologics manufacturing and equivalence, as demonstrated by the recent regulatory hurdles experienced by Cambridge, Massachusetts–based Genzyme's Lumizyme (alglucosidase-α) and Eli Lilly's Erbitux (cetuximab; **Box 2**)

MBV expects to launch its GlycoFi product MK-2578 in 2012, to have at least five biogenerics in late-stage development by 2012 and launch at least six of these products between 2012 and 2017. The Insmed deal adds granulocyte colony-stimulating factor (G-CSF) to the MBV portfolio: INS19, in phase 3, is a follow-on to Amgen's Neupogen, whereas INS20, a monomethoxypolyethylene glycol–modified (PEGylated) molecule in phase 1, is a follow-on to Amgen's Neulasta (pegfilagrastim; recombinant methionyl human G-CSF). Insmed also gave up two preclinical follow-on molecules: an interferon β1b and an epoetin-α.

Fernandez draws a comparison between follow-on biologics and the emergence of generics. The Hatch-Waxman Act of 1984 spurred the generics industry by carving out a regulatory pathway and an exclusivity period for such drugs. "It took a solid 10 years for the generic industry to get its feet underneath itself. You didn't have any companies with a credible reputation at that time taking on the role of being a generic company in 1984." Fernandez says. With follow-on biologics, however, drug manufacturers like Merck and Pfizer are likely to capitalize on their reputations.

Like Merck, which says it has significantly improved yields using the GlycoFi bioprocess, New York–based Pfizer, through its acquisition of Wyeth, may have a manufacturing advantage. Fernandez says that Wyeth is achieving yields well in excess of the biologics industry average with antibody production at their Grange Castle facility in Dublin. "It gives you a clear opportunity to capitalize" with biogenerics, he believes.

Estimates for the R&D layout for a biogenerics program range from $10–50 million, or less than one-quarter the usual cost of developing a new drug excluding the capital expense of establishing commercial manufacturing. That said, biogenerics "are not going to be a low-cost, high-margin business," says Oppenheimer & Co. analyst Bret Holley, in

Box 1 Obama wants action on biogenerics

President Obama's 2009 budget plan includes a call for access to "generic biologics," which a Congressional Budget Office analysis says could save the government $9.2 billion over 10 years—money it could then use to support the overhaul of the healthcare system. The budget plan supports a period of exclusivity "generally consistent with the principles in the Hatch-Waxman law," or five to seven years of exclusivity for new drugs and three years for new formulations of existing drugs.

Although there is currently no pathway for approval of follow-on biologics, some such drugs—Basel-based Sandoz's Omnitrope, for example—have been filed under applications that contain full data sets on safety and effectiveness, where at least some of the information required for approval comes from prior studies, not conducted by or for the applicant. The biggest sticking point in the current biogenerics regulatory discussion is around the issue of data exclusivity; that is, the period of time before manufacturers could rely on the data from FDA's approval of the 'innovator' biologic to support approval of the follow-on product.

The budget plan supports a period of data exclusivity "generally consistent with the principles in the Hatch-Waxman law," which grants an innovator product 14 years on the market before facing generic competition. Now, the average small molecule is on the market for 13.5 years before it faces competition. A study at Duke University concluded last year that it takes somewhere between 12.9 and 16.2 years for a company to recover its investment in a biologic.

The data exclusivity periods previously proposed for biogenerics have ranged from 12 to 14 years. "I think it's the most contentious item in the debate," says Jim Greenwood, president and CEO of the Biotechnology Industry Organization, which supports a 14-year period. "Data exclusivity not only lays down the foundation for the future of follow-on biologics but for innovative biologics as well. If we don't achieve the right balance between innovation and competition, companies will not be able to afford the gargantuan investment and take the huge risks of developing biologics and be able to recover their costs."