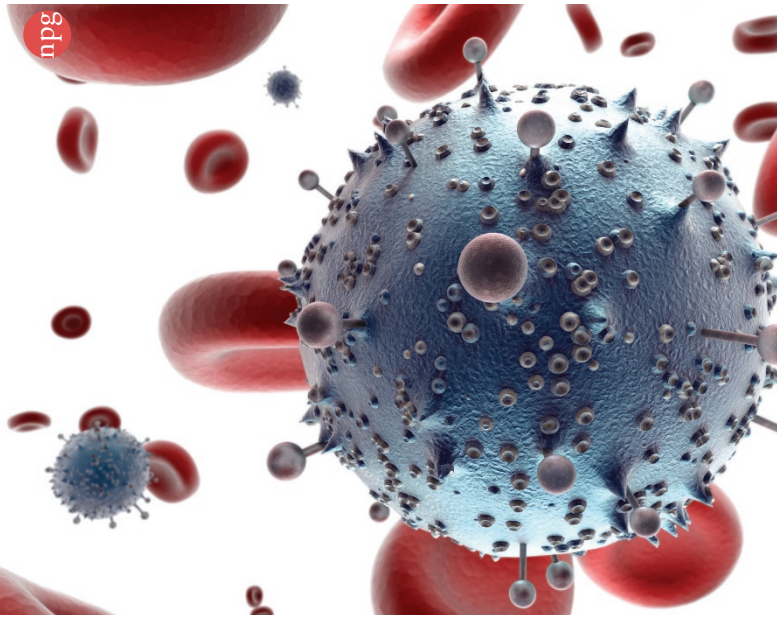
HIV treatment study clears virus, sends Sangamo stock soaring

In early March Sangamo Biosciences saw its share price soar after results from the first clinical study of an HIV treatment program using a zinc finger nuclease (ZFN) appeared in the *New England Journal of Medicine* (*NEJM* **370**, 901–910, 2014). The study showed that infusing HIV-infected individuals with their own CD4 T cells, in which the *CCR5* gene had been altered *ex vivo* using the ZFN method, was safe—in one patient, the treatment drove viral load down to undetectable levels. *CCR5* was targeted because it encodes a co-receptor required for the virus to penetrate the cell, and individuals with a natural *CCR5* mutation are known to resist HIV infection. Sangamo, located in Richmond, California, designed a ZFN pair of proteins, which, by binding *CCR5*, induce an acquired genetic resistance to HIV (*Nat. Biotechnol.* **26**, 808–816, 2008).

All participants in the phase 1 study were on antiretroviral therapy (ART) while receiving the cells with altered *CCR5*, called SB-728-T; four weeks later, half had their ART therapy interrupted for 12 weeks to test the effect of the SB-728-T infusion. The *NEJM* study demonstrates that the modified cells can be safely administered back to the individual; are able to persist and circulate throughout the body to key reservoirs of HIV infection; and survive longer than unmodified cells when antiviral drugs are withdrawn, potentially keeping the virus under control without the use of drugs, says senior author Carl June of the University of Pennsylvania in Philadelphia. The person with undetectable viral load after receiving the cell infusion was later found to have already been carrying a natural mutation of *CCR5* (*CCR5* delta-32) in one allele.

Sangamo's results reinforce the belief that an immunological approach could control HIV infection and eliminate the need for lifelong antiretroviral therapy, he says. In a second study, a phase 1/2 trial reported at the Conference on Retroviruses and Opportunistic Infections in Boston on March 6, preconditioning patients with the chemotherapy cyclophosphamide prior to a single infusion of SB-728-T led to a dose-dependent increase in the engraftment of modified cells and total CD4 cell counts.

In commenting on the potential impact of Sangamo's work on Gilead Sciences, the Foster City, California–based maker of antiretroviral therapies, analyst Michael Yee of RBC Capital Markets in San Francisco noted that it's not clear which subgroup of HIV patients would benefit from SB-28-T therapy. The subgroup of heterozygous *CCR5* delta-32 patients "might be only 5–10% of HIV patients," he said. Further, an accompanying editorial in *NEJM* cautioned that consistently blocking both alleles for *CCR5* using this technology is "not yet tenable" and that the off-target risks are as yet unknown. Nonetheless, Sangamo's stock gained more than 17% the day after the news broke, rising to $22.96 per share, helping pave the way for the pricing of a follow-on stock offering later in March at $22.50, which would add almost $94 million to its coffers. Sangamo has said that with positive data from its phase 2 clinical trials of SB-28-T, it would seek a partner for further development and commercialization. Earlier this year it licensed ZFN technology to Cambridge, Massachusetts–based Biogen Idec for development of therapies for the hemoglobinopathies sickle-cell disease and beta-thalassemia.



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Sangamo's SB-728-T therapy uses a zinc finger nuclease to alter *CCR5* on T cells, which blocks the HIV virus' entry.

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IN brief

Illumina incubates innovators

Illumina launched its Accelerator Program in February to serve as a technology incubator for startup and early-stage companies working on scientifically and commercially promising next-generation sequencing applications. Teams chosen for the Accelerator Program will receive $100,000 from Illumina in the form of reagents, access to sequencers, and 20% of a technician's time, with six months' laboratory space in San Francisco's Mission Bay. Teams will also have access to $100,000 in convertible notes from technology investor Yuri Milner and a $20,000 line of credit from Silicon Valley Bank. For the San Diego company, this scheme provides an opportunity to support entrepreneurs in genomics and contribute toward making genomics more mainstream, an Illumina representative said. Jon Groberg of Macquarie Securities in New York thinks that Illumina's strategy is twofold: first to become the platform of choice for small companies and, second, to have first pick of promising applications. The Accelerator Program provides Illumina with an early insight into the future direction of sequencing, he says. The company has already acquired companies in the applications market: BlueGnome of Cambridge, UK, for cancer and infertility screening, and Verinata of Redwood City, California, for prenatal testing.

Allison Proffitt

Oral immunotherapy approved

The US Food and Drug Administration (FDA) approved Paris-based Stallergenes' Oralair for grass pollen–induced allergic rhinitis on April 1, making it the first oral immunotherapy to reach the US market. Oralair is an under-the-tongue tablet containing a mix of five standardized grass allergens—perennial rye grass, meadow grass, timothy grass, cocksfoot and sweet vernal grass—that mimics patients' natural exposure during the pollen season. Currently, allergy immunotherapies involve 3–5 years of subcutaneous injections. "A sublingual tablet does allow an increased convenience factor," says Sandra Lin, an associate professor of otolaryngology, Johns Hopkins School of Medicine, Baltimore. Still, initial uptake of Oralair may be slow. Jacoba van der Gaag, lead analyst at Datamonitor Healthcare, London, says the biggest barrier is getting the patient to consider immunotherapy in the first place, as symptomatic relief can be easily achieved with over-the-counter medicines, such as antihistamines. Oralair, approved in the EU and Canada, netted Stallergenes €22.2 ($30.7) million in 2013. Also approved by FDA on April 15 is Merck's Grastek, another sublingual immunotherapy, composed of a single grass pollen extract (timothy grass). Grastek is currently sold in Europe as Grazax. Stallergenes has two other oral allergy immunotherapies in late-stage development: Actair, in collaboration with Shionogi of Osaka, Japan, for dust mite–related allergic rhinitis, and Oralair Birch, a recombinant protein synthesized from the DNA-coding region of Betv1a, the major birch pollen allergen, in phase 3.

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