# NEWS IN BRIEF

## First *in vivo* gene-editing drugs enter the clinic

Sangamo Therapeutics has started dosing patients with gene-editing drugs that are administered directly into the blood.

Sangamo's zinc finger nucleases (ZFNs) are enzymes that selectively bind, cleave and enable the directed repair of DNA to knock genes both in and out of patient genomes. In 2011, their first clinical application of a ZFN-based drug relied on *ex vivo* gene editing; researchers harvested T cells from HIV-positive patients, edited the cells to disrupt the *CCR5* gene, and then re-infused these back into the patients in the hopes that the engineered cells would evade infection.

The company's new ZFN products are now designed to edit genes *in vivo*. In a landmark first *in vivo* gene-editing trial, patients with the rare lysosomal storage disease mucopolysaccharidosis II (MPS II) received SB-913 intravenously. The drug traffics to the liver, where it inserts a functioning copy of the *IDS* gene, under the control of the strong albumin promoter, into the genomes of liver cells.

"We are at the start of a new frontier of genomic medicine," says Sandy Macrae, CEO of Sangamo Therapeutics.

The company is also recruiting patients into trials of two other *in vivo* ZFNs. SB-318 inserts a copy of the *IDUA* gene into liver cells, for MPS I. SB-FIX inserts a copy of the gene that encodes factor IX, into liver cells, for haemophilia B.

Other biotechs are gearing up to launch clinical trials of CRISPR-based drugs, which promise more precise and efficient gene-editing activity. CRISPR Therapeutics and Vertex Pharmaceuticals are readying a trial of CTX001, an *ex vivo* treatment for β-thalassaemia. Editas Medicine is preparing a phase I trial of its lead product, an *in vivo* treatment for Leber congenital amaurosis. Editas CEO Katrine Bosley recently credited lessons learned with ZFNs as a key to CRISPR's rapid race to the clinic (*Nat. Rev. Drug Discov.* **16**, 672–673; 2017).

*Asher Mullard*

## Boehringer Ingelheim experiments with open-access chemical probes

Boehringer Ingelheim launched a platform to share well-characterized preclinical compounds with the biomedical community. These can be used as probes to explore mechanistic and phenotypic biology.

The company is currently offering nearly 20 molecular probes through its opnME portal for free, without intellectual property restrictions. These probes act on various targets, including aurora B, autotaxin, soluble epoxide hydrolase and SYK. Targets include kinases, GPCRs, ion channels and epigenetic actors from across cardiometabolic, respiratory, oncology, central nervous system and immunology therapeutic areas.

A subset of probes will only be available through collaborative research projects with Boehringer Ingelheim scientists. They are currently soliciting research proposals to test an SGLT6 inhibitor, for example.

"Working together with scientists across the world, we can accelerate research in a wide range of biomedical research areas," says Clive Wood, senior vice-president of Discovery Research at Boehringer Ingelheim. "This exciting new initiative further expands Boehringer Ingelheim's global external innovation footprint and will help unlock the full potential of some of our most interesting compounds."

The company also launched a search tool called BI Miner that can simultaneously search the scientific literature, patent databases and clinical trial resources for therapeutic targets and drug discovery concepts.

Boehringer Ingelheim is also a member of the Structural Genomics Consortium, a public–private partnership of academic groups and pharmaceutical companies that has released nearly 60 probes to the biomedical community.

The Chemical Probes Portal, a free resource that reviews chemical probes, currently ranks only around 125 compounds as high-quality chemical probes. They also list around 250 'historic compounds' that are not sufficiently selective or potent for such use.

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## Sage gets an antidepressant lift

Sage Therapeutics' lead antidepressant brexanolone generated positive results in two phase III trials for postpartum depression, and a next-generation candidate with similar properties passed a smaller phase II trial for major depressive disorder.

Brexanolone is an intravenous formulation of the steroid allopregnanolone, which is thought to affect mood by acting as a positive allosteric modulator of the $GABA_A$ receptor. In November, two phase III trials of the drug in 226 women with postpartum depression met the primary end point of reduction of Hamilton Rating Scale for Depression (HAM-D) scores at 60 hours. Treatment reduced HAM-D scores by 14–20 points, compared to reductions of 12–14 points by placebo.

The treatment effect was modest compared with the 12-point difference that was observed during phase II trials. But the company pointed to the rapid onset of action as a major selling point for the drug, and the firm's share price jumped by 50% on these results. The HAM-D reduction with brexanolone was maintained at 30 days, but was no longer significantly different to placebo at this time point, a failure that the company attributed to variability in the placebo arm.

The company plans to file for regulatory approval of the drug in 2018.

These findings were bolstered in December by phase II results with SAGE217, which has similar properties to brexanolone but is orally available. In an 89-patient phase II trial, SAGE217 reduced HAM-D scores by 18 points at day 15, compared with a reduction of 11 points for placebo. By week 6, the effect was no longer statistically different. Sage's share price jumped again on these results, by another 70%, to US$161.

Phase II trials of SAGE217 in essential tremor and in Parkinson disease are ongoing. Brexanolone failed in a pivotal epilepsy trial earlier this year, despite promising prior phase II results in this indication.

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