Spark's gene therapy price tag: $850,000

Spark Therapeutics has priced its recently approved gene therapy Luxturna to treat a rare form of inherited blindness at $850,000, with a payment structure that could set a precedent for other gene therapies. Spark won a historical first in December when the US Food and Drug Administration approved Luxturna (voretigene neparvovec) to treat children and adults with a retinal dystrophy, caused by a mutation in both copies of the *RPE65* gene, which progresses to complete blindness (*Nat. Biotechnol.* **36**, 6, 2018). Although Luxturna is priced lower than the $1 million estimated by Wall Street analysts, at $425,000 per eye, Spark came under fire from patient advocates. The president and founder of Patients for Affordable Drugs, David Mitchell, said in a statement: "the new payment models are merely a way to disguise a price that is simply too high." To ease the payor pressure, the Philadelphia-based Spark has come up with an outcome-based reimbursement, and is working on an agreement with the Centers for Medicare and Medicaid Services to collect payments over several years. Under the plans, the company will charge insurers for its one-time gene therapy treatment if patients' vision scores in full-field light sensitivity threshold tests improve at 30 and 90 days and at 30 months. The therapy is a modified adeno-associated virus that delivers normal copies of human *RPE65*, which is essential for normal vision, to the retinal cells through a subretinal injection. Luxturna must be given only to patients who have viable retinal cells. In the data supporting the treatment's approval, patients' ability to complete an obstacle course at low light levels improved, compared with a control group. An independent US non-profit organization that evaluates clinical and cost effectiveness of new medicines said on January 12 that despite the money-back strategies proposed by the company, Luxturna's price tag is far too high. The Institute for Clinical and Economic Review stated that only with a significant price discount would Luxturna meet cost-effectiveness standards.

"They're taking Stage IV cancer and turning it into a chronic disease no different than high blood pressure." Tomas Neilan, the director of the cardio-oncology program at Massachusetts General Hospital in Boston alludes to his patient Andy Lindsay, of Ipswich, Massachusetts, who trekked up a 21,000-foot peak in Nepal after his stage IV cancer was treated with a succession of EGFR -targeting drugs. *The New York Times*, 4 January 2018.

"I see the same opportunity now in gene writing that I did in gene reading." John Stuelpnagel, chairman of the board at Inscripta, comments on his company's new CRISPR enzyme, MAD7, from the Madagascar family of enzymes. *Forbes*, 13 December 2017.

Box 1 Synthetic microbes make drugs, fix problems from the gut

Bacteria can be engineered to create medicines *in vivo*, a kind of living drug factory within the body. "It's a relatively new way to harness the power and diversity of synthetic biology to create a new third class of drugs," says Jim Collins, a biomedical engineer at the Massachusetts Institute of Technology in Cambridge, Massachusetts.

The bacteria can be designed to synthesize missing metabolites, produce already approved or entirely new small-molecule drugs, and even act like a miniature artificial immune system, producing a drug when they detect a disease.

"It opens up a new world of possibilities and drug combinations," says Collins.

The Cambridge, Massachusetts–based Synlogic, a synthetic biology company co-founded by Collins, is developing a variety of these living medicines. They have engineered 30 different metabolic pathways in bacteria to replace or supplement those damaged in humans. The bacterial pathways can be engineered to be exponentially more efficient than pathways in human cells. The company recently completed a phase 1 trial on one candidate, which converts ammonia to arginine for patients with a defective urea cycle or other liver diseases. They saw a dose-dependent change in nitrate, a secondary metabolite of arginine, in participants' blood and urine. "We're not trying to fix the microbiome, but change systemic problems from the gut," says JC Gutierrez-Ramos, the company's CEO.

Synlogic has teamed up with the Boston-based Ginkgo Bioworks, a company that designs custom microbes to develop new living medicines for liver and neurological conditions. "The science of the gut–brain and gut–liver axes is now mature enough to bring pharmacology based on them to patients," says Gutierrez-Ramos. Ginkgo's head of business development, Ena Cratsenburg, says the company sees its technology as a kind of operating system, which can be used to build various 'apps' in bacteria. "We are looking for partners with expertise in the 'apps' themselves," she says.

The two companies have begun a nine-month project to optimize one of the candidates in Synlogic's pipeline and will then move on to develop new products. Gutierrez-Ramos sees big opportunities in the collaboration. Gingko's microbe production foundry can quickly create hundreds of different custom microbes for testing. "There are 500 functions in the liver; we could build all 500 in bacteria with Ginkgo," he says. "We could start testing some of the hypotheses around the gut–brain axis."

Collins says he expects the first approved living drugs are not far off. "Within a pretty short horizon we will see bacteria approved as therapeutics," he says. *BO*

of responders' and non-responders' microbiomes using metagenomic sequencing, and found that the 'good' microbiome tended to have more biosynthetic metabolic processes, such as amino acid synthesis, while the 'bad' microbiome tended towards degradation processes. She also found that responders' tumors had more $CD8^+$ T cells, and antigen-presenting cells in general, compared with non-responders. "The bad microbiome resulted in a really cold tumor microenvironment," she says. Wargo then gave germ-free mice fecal transplants from responders. Their systemic immunity improved, and they responded well to checkpoint inhibitors in a melanoma model. "The gut microbiome seems to be influencing and modulating the checkpoint blockade," says Wargo.

Another *Science* paper, from Zitvogel's group, also moved on to human studies. The researchers followed 249 patients treated with anti-PD-1 or anti-PD-L1 drugs, and found that those who had, in addition, taken antibiotics for a variety of common infections, within two months before or one month after starting immunotherapy, had lower survival rates than those who had not (*Science* **359**, 91–97, 2018). The guts of responding patients were enriched in *Akkermansia municiphilia* bacteria, and when that bacterium was given to mice who had received a fecal transplant from a non-responding patient, it restored the animals' response to checkpoint inhibitors.

Bertrand Routy, a hematologist at the Gustave Roussy Institute who worked with Zitvogel on the study, says the exact mechanisms need to be elucidated, but in mice the flora seem to be stimulating interleukin (IL)-12 production, a cytokine involved in recruiting memory T cells to the tumor, as well as in inflammation.

In a third *Science* paper, Gajewski found that in responders' microbiomes *Bifidobacterium longum*, *Collinsella aerofaciens* and *Enterococcus faecium* were abundant. The team collected stool samples from 42 patients before they underwent either anti-PD-1 or anti-CTLA-4 treatment (*Science* **359**, 104–108, 2018).

The upshot from these findings is that a patient's microbiome could become a