Thermo Fisher strides into gene therapy

Thermo Fisher Scientific is set to buy viral vector manufacturer Brammer Bio for approximately $1.7 billion, in a move that signals a foray into the gene-therapy field for the life sciences equipment maker. Brammer Bio, which makes viral vectors for use in in vivo and ex vivo gene-therapy clinical trials, was formed in 2016 by the merger of Brammer Biopharmaceuticals and Florida Biologix, a spin-out of the University of Florida. Thermo Fisher Scientific says it will incorporate the viral vector manufacturer, which employs almost 600 people, into its pharma services business. "Gene therapy is an area of increasing focus for our customers and is fast-evolving given its potential to treat a range of genetic disorders," said Thermo Fisher Scientific CEO Marc Casper in a 24 March press release announcing the deal. Thermo Fisher Scientific is no stranger to acquisitions: in 2014 it bought the California-based biotech Life Technologies for approximately $13.6 billion, establishing it as a major player in the genetic testing field (*Nat. Biotechnol.* **31**, 573–574, 2013). Biotech giants are fast snapping up gene-therapy startups. In February, the Swiss pharma giant Roche acquired Spark Therapeutics, the Children's Hospital of Philadelphia startup, whose gene therapy to treat an inherited retinal disease won FDA approval in 2017. And in March, Cambridge, Massachusetts-based Biogen acquired London-based biotech Nightstar Therapeutics, which is also developing gene therapies for inherited retinal diseases.

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"With a science that's moving forward as rapidly as this science is, you want to be able to adapt to new discoveries." David Baltimore advises against a moratorium on genome editing. (*Science News*, 2 April 2019)

"[This] begs the question of what role, if any, does DTC [direct to consumer] testing for these three mutations really play in the healthcare of individuals who either have an indication for testing or are seeking to know their risks." Researchers at Invitae showed that 23andMe's *BRCA* test misses 90% of people with mutations, even some within families with a history of cancer. (*GenomeWeb*, 5 April 2019)

Spark's meteoric rise from hospital-funded spinout to $4.8 billion deal

Roche vows to retain gene therapy leader's culture.

A pediatric hospital spinout responsible for bringing to market in the United States the first gene therapy for treating an inherited disease has been acquired by Swiss pharmaceutical giant Roche. Spark Therapeutics, the Children's Hospital of Philadelphia startup, in 2017 received US Food and Drug Administration approval for Luxturna (voretigene neparvovec-rzyl) to treat an inherited form of retinal dystrophy (*Nat. Biotechnol.* **36,** 6, 2018). The February 25 deal values the five-and-a-half year-old Spark at $4.8 billion, more than twice the company's market valuation before the announcement. Basel-based Roche will keep its target at arm's length in an attempt to preserve what made it an attractive target in the first place, saying that Spark will continue to operate as an independent gene therapy specialist out of its Philadelphia headquarters.

Also on March 4, Biogen acquired Nightstar Therapeutics, a London-based biotech developing gene therapies for rare inherited retinal diseases, for $800 million. This and the Spark deal underscore large companies 'growing appetite for gene therapies, as well as ophthalmic indications' prominence as an early proving ground for these technologies.

With the Spark buyout, Roche gains US rights to Luxturna. The therapy replaces the mutated *RPE65*, a gene encoding the enzyme retinoid isomerohydrolase in the retina, which transduces light into electrical signals. Luxturna recorded $27 million in revenue in its first year on the US market. But Roche's real prize is Spark's gene therapy pipeline—in particular, a pair of treatments for hemophilia A, the most advanced of which should enter phase 3 this year. (Novartis already holds non-US rights to Luxturna and Spark's hemophilia B program is partnered, with Pfizer; Table 1.)

This blood-disorders market is one where Roche has already carved out a lucrative niche: its Hemlibra (emicizumab-kxwh) humanized IgG4 monoclonal antibody for hemophilia A has been a key growth driver

Roche's acquisition of gene therapy developer Spark Therapeutics, founded by researchers from Children's Hospital of Philadelphia, will result in a huge return on the hospital's initial investment. Credit: Spark Therapeutics.

Table 1 | Spark's advanced gene-therapy pipeline

Drug candidate	Clinical stage	Indication	Partner
Luxturna	Marketed	Biallelic RPE65-mutation-associated retinal dystrophy	Novartis
SPK-9001 (fidanacogene elaparvovec)	Phase 3	Hemophilia B	Pfizer
SPK-8011	Phase 2	Hemophilia A	-
SPK-8016	Phase 1/2	Hemophilia A with inhibitors	-
SPK-7001	Phase 1/2	Choroideremia	-
SPK-3006	Preclinical	Pompe disease	-
SPK-1001	Preclinical	Batten disease	-

for the company since its approval in 2017. But until this acquisition Roche lacked a gene therapy in this indication and was potentially vulnerable to the pack of gene therapies gaining ground on the biologics that dominate that field (*Nat. Biotechnol.* **34,** 999–1001, 2016).

Spark's presence in both hemophilia and inherited blindness stems from the work of its scientific founders at the Children's Hospital of Philadelphia (CHOP)'s Center for Cellular and Molecular Therapeutics, established in 2004. Funding for the program that would become Luxturna began at the center in 2005, and the hospital helped conduct its first clinical trial in 2007.

Katherine High, Spark president and head of R&D and founding director of the Center for Cellular and Molecular Therapeutics, has credited the hospital's leadership for the "extraordinary decision" to fund those initial trials, at a time when the future for gene therapy appeared bleak because of safety concerns and a reluctance from the biopharma industry to back companies trying to solve the field's fundamental scientific challenges Despite this, CHOP poured resources into clinical trials and the development of the adeno-associated viral vector to deliver its gene therapies. In October 2013, it staked Spark with $50 million to spin off the technology and gene therapy pipeline from the center, and in 2014 it invested in the company's second venture capital round.

In time the hospital was handsomely rewarded for its investment. Not long after that initial financing burst, Spark went public, raising $185 million—after the offering, CHOP still owned more than a third of the company—and raised several hundred million dollars through follow-on public offerings in 2017. Its financial and scientific success with Spark gives the hospital a key revenue stream to complement its traditional philanthropic and government capital sources and may provide a model for future company formation. CHOP president and CEO Madeline Bell says that for now the hospital is reviewing the acquisition's impact "and will be developing plans to build upon our mission." Meanwhile it retains its focus on gene therapy and will continue to collaborate with Spark.

CHOP's success may prove to be an inspiration. As gene therapy becomes more commonplace, rare disease foundations may take on more of the risk and responsibility of moving these drug candidates along toward FDA approval, says Andrew Lo, director of the Massachusetts Institute of Technology's Laboratory for Financial Engineering. "The complexity of producing these altered viruses and administering them to patients resides at least initially within academic medical centers and research departments," he says. What CHOP and then Spark have been able to do shows that foundations can apply their research dollars to the roots of these diseases, he says, and it wouldn't be shocking if the FDA were approving three to five gene therapies a year in the near future. Patient advocacy groups and philanthropic foundations are taking note, for good reason. "The phrase 'I was blind but now I see' used to be reserved for religious experiences," says Lo. ❐

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Thalassemia gene therapy nears approval

In March, Bluebird Bio received a positive opinion for its gene therapy Zynteglo for β-thalassemia from the European Medicines Agency's advisory body. The next step, approval by the European Commission, is expected this summer. If approved, Zynteglo will be the first gene therapy approval for thalassemia. The recent decision from the agency's Committee for Medicinal Products for Human Use was based on data from several clinical trials, in which 37 patients in total received gene-modified cells. The therapy removes bone marrow cells from the patient and transduces the $CD34^+$ hematopoietic stem cells ex vivo with a BB305 lentiviral vector encoding a functional modified β-globin gene ($\beta^{A\text{-}T87Q}$) under the control of the β-globin enhancer and locus control region. With the modified bone marrow cells, the body can produce functional hemoglobin, which can reduce or eliminate the need for transfusions. Patients with thalassemia, who experience severe anemia due to a mutation in their globin gene, can be treated with bone marrow transplants, but only from HLA-matched donors, which leaves many unable to receive this therapy. Absent that, patients need frequent blood transfusions, which can lead to iron overload and result in organ damage. In the phase 1/2 Northstar trial of ten patients, eight had been transfusion free for a median of 38 months at the conclusion of the trial. Yet to be announced is the likely price tag for Zynteglo. Based on other one-time curative gene therapies, such as Luxturna (*Nat. Biotechnol.* **36**, 291–292, 2018), it is likely to be in the six figures. However, Bluebird floated the idea of annual installments in January at the J.P. Morgan Healthcare Conference. Shortly after, a rival company Sangamo announced their first results in thalassemia using their ex vivo gene editing protocol for a single patient with the most severe form of the disease.

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"**The bar is so low currently that you need a shovel.**" Keolu Fox, a Native Hawaiian and anthropologist at the University of California, San Diego, referring to low representation of non-Europeans in genomic databases. (*Nature*, 16 April 2019)

"**The whole field of developmental genetics has left reptiles in the dust.**" Douglas Menke, University of Georgia. But not anymore. Menke's group created the first gene-edited lizard, an albino, by injecting CRISPR targeting tyrosinase into immature eggs. (*Science*, 1 April, 2019)

"**A crap assay is *not* better than no assay at all.**" Derek Lowe, in agreement with an opinion piece in *STAT* by Adam Rosenberg of Rodin Therapeutics on the limitations of mouse models in neurodegenerative diseases. (*In the Pipeline*, 16 April 2019)