FDA approves hereditary blindness gene therapy

The US Food and Drug Administration (FDA) has given the go-ahead to Spark Therapeutics' gene therapy for treating biallelic RPE65-mutation-associated retinal dystrophy. The December 19 approval is the first gene therapy in the US to use an adeno-associated virus for delivery and the first for treating an inherited disease. Voretigene neparvovec, branded as Luxturna, received a unanimous vote of approval from an FDA advisory committee on October 12 (*Nat. Biotechnol.* **35**, 998, 2017). In concert with the milestone approval, the FDA announced that it is developing a policy framework for processing candidate gene therapies. "Next year, we'll begin issuing a suite of disease-specific guidance documents on the development of specific gene therapy products to lay out modern and more efficient parameters—including new clinical measures—for the evaluation and review of gene therapy for different high-priority diseases where the platform is being targeted," FDA Commissioner Scott Gottlieb said in a statement announcing the approval of Luxturna. Biallelic RPE65-mutation-associated retinal dystrophy affects an estimated 1,000–2,000 people in the US. The condition causes progressive sight impairment that leads to near total blindness in almost all patients. Luxturna is a one-time treatment. It is injected into the subretinal space where it delivers a functional copy of RPE65 cDNA to retinal pigment epithelial (RPE) cells, restoring the cells' ability to produce the key retinoid cycle enzyme all-*trans* retinyl ester isomerase. Spark Therapeutics announced that Luxturna will be available in the first quarter of 2018 from retinal surgeons trained by the company. Spark Therapeutics said it will announce pricing in early January. Industry estimates of the price range from $500,000 to $1.5 million, based partly on the $475,000 price tag for Novartis' adoptive chimeric antigen receptor (CAR)-T cell leukemia therapy Kymriah (tisagenlecleucel), which is also a one-time gene therapy treatment. The European Medicines Agency is reviewing Luxturna. Spark Therapeutics has gene therapies for treating hemophilia and neurodegenerative diseases in its pipeline.

"'We have to acknowledge quantitatively, it's the hardest thing we do as a society' and to do that society needs to engage and attract 'the rare geniuses' with appropriate recognition and reward." George D. Yancopoulos, CSO of Regeneron, commenting on the importance of innovative researchers to the biopharma industry at an industry summit in November. (*Forbes*, 30 November 2017)

With a free pass, CRISPR-edited plants reach market in record time

CRISPR–Cas9-edited plants can be cultivated and sold free from regulation, the US Department of Agriculture (USDA) is making increasingly clear. The agency gave a free pass to *Camelina sativa*, or false flax, with enhanced omega-3 oil. And more recently, in October, said that a drought-tolerant soybean variety developed with CRISPR falls outside of its regulatory purview. This *laissez faire* attitude from the agency shaves years and tens of millions of dollars off the cost of bringing a biotech plant to market. "It eliminates that huge barrier to entry for agbiotech companies," says Oliver Peoples, CEO of Woburn, Massachusetts–based Yield10 Bioscience (formerly Metabolix) which developed the camelina.

It would have taken Yield10 at least six years and $30–50 million to test and collect the data necessary to bring genetically engineered camelina through the full USDA regulatory process, says Peoples. "We did this in two years and [USDA's decision] took two months, and I assure you we didn't spend $30 million on it," he says. The company will present its technology to the US Food and Drug Administration's voluntary review process, he says.

Yield10's strategy is to allow CRISPR-Cas9 to make double-stranded breaks in the plant's DNA without a template to direct insertion of a specific DNA sequence. As a result, the plant's own repair mechanisms rejoin the DNA, giving rise to single-nucleotide inactivating insertions in all three copies of the target gene. Peoples would not disclose which gene his company manipulated in camelina.

Camelina oil is used as a biofuel and as a substitute for fish oil in aquaculture. Yield10 will likely make three or four additional edits to the plant line in order to boost camelina's oil content 25%, and translate the technology

Box 1 GM apples now in supermarkets: but how will the public react?

US grocery retailers on November 1 began selling genetically modified (GM) apples that resist browning, making them one of the first consumer-oriented biotech foods to reach the market. The apple's developer, Canadian firm Okanagan Specialty Fruits, a subsidiary of Germantown, Maryland–based Intrexon, is one of a few small companies to succeed in bringing a GM food all the way from discovery to retailers' shelves.

So far, the apples have appeared pre-sliced and packaged in stores in the US Midwest, Southeast and California. Their non-browning trait keeps them fresh-looking without the use of taste-altering preservatives. Okanagan achieved the effect by introducing a transgene to produce RNA designed to silence the expression of at least four browning polyphenol oxidase genes (*Nat. Biotechnol.* **33**, 326–327, 2015).

How have consumers reacted? About 60% say they are likely to buy GM non-browning apples, according to the company's pre-market consumer research, says Neal Carter, founder of Okanagan. Only about 10–15 % of consumers are staunchly against the product, he says, and some of those people change their minds after they've received more information about how the apples were engineered, or after tasting them. "When they get to experience the product, basically all the concerns about genetic engineering go away," Carter says.

Several apple grower associations previously raised concerns about Carter's product, saying it could disrupt the apple market and affect consumers' perception of the wholesomeness of apples. "It was the natural concern of an industry that has a product that is widely accepted to be so healthy," says Jim Bair, president of the US Apple Association in Falls Church, Virginia, an organization that had written to the USDA in 2011 asking it to reject GM apples. US Apple has since changed its position. "The regulatory agencies have confirmed that GM apples are identical to non-GM apples in nutrition, safety and wholesomeness, so consumers can buy and enjoy them without worry," Bair says. Apples are part of a healthy diet, so "anything that potentially expands the marketplace is going to be good for consumers."

Okanagan sells the sliced apples under the brand name "Arctic," and will not label them as GM. Instead, a smartphone-scannable QR code on the bag takes consumers to a website with more information. US regulators approved Okanagan's first apple varieties—Golden Delicious and Granny Smith—in February 2015, and Canadian regulators did the same a month later. *EW*