PureTech floats away

The healthcare firm PureTech went public in June raising about $195 million, noteworthy in particular because Boston-based PureTech eschewed NASDAQ in its home country and chose to list on the London Stock Exchange's (LSE's) main market. The reasoning, the company said, was because investors on the London market were already familiar with the company-creation concept behind PureTech. PureTech's initial public offering is also interesting for the company's business model. Similar to biotech venture capitalists (VCs), PureTech focuses on creating startups, except that VCs generally choose from the myriad proposals pitched their way, whereas PureTech builds companies toward a preselected unmet medical need. It evaluates about 650 ideas a year and its list of advisors includes Christopher Viehbacher, former CEO of Paris-based Sanofi; and Robert Langer, PureTech co-founder, professor at Massachusetts Institute of Technology in Cambridge and serial entrepreneur. Run by CEO and co-founder Daphne Zohar, PureTech also differs from VCs in that it usually retains around 80% ownership in its companies. That makes PureTech's goal, Zohar says, the same as a typical biotech's—get products to market. Although PureTech could sell a company or push it public in the manner of a VC, by retaining majority ownership of its projects, PureTech's bottom line benefits directly from its products through revenues, royalties or licensing income. This bottom line is what PureTech's new shareholders will now be watching.

BGI goes head-to-head with Illumina

In June, Complete Genomics of Mountain View, California, unveiled its plans for a turnkey human sequencing platform, the "Revolocity." This $12-million, 1,500-squa-foot behemoth will take human samples (spit or blood) and churn out complete human sequences or exomes at the rate of 10,000 complete sequences per year, claims the company. The new platform moves this wholly owned subsidiary of China's Shenzhen-based BGI from a pure service company into an instrument provider and puts it into direct competition with San Diego–based Illumina and its HiSeq X. This is good thing for the market, according to Mick Watson of Edinburgh Genomics, the University of Edinburgh–based provider of sequencing services. "In reality, Illumina is the only company in this space," he says. Whether the Revolocity will perform up to HiSeq X's standards remains to be seen, however, given a large disparity in read length. Revolocity provides 28 base pair reads, HiSeq X, 150. But with Revolocity comes automation, which will appeal to hospitals wishing to offer genomics to its patients. On the other hand, Illumina has machines in place, global support and a business that works. "For anything to disrupt that, it would have to be a hell of a lot better than the Illumina platform," says Watson. Complete Genomics will be revealing data from Revolocity at the annual meeting of the American Society of Human Genetics, this October in Baltimore.

Oxitec trials GM sterile moth to combat agricultural infestations

The first US caged field studies of a genetically modified (GM) insect for use in agriculture began in July in upstate New York. The GM diamondback moth developed by Oxitec, a spin-out from Oxford University, headquartered in Milton Park, UK, is intended as a tool for crop growers to control infestations without chemical insecticides. Cornell entomologist Anthony Shelton has started testing the transgenic moths, which carry an autocidal gene that causes the insects' female progeny to die before reaching reproductive stage. The results of these trials, and of a handful of others in the works, will provide an indication whether the approach has commercial potential in agriculture and will provide a barometer of attitudes to the release of GM insects that lack a compelling trait for consumers.

Diamondback moth in flight.

Diamondback moths, *Plutella xylostella,* are an invasive species and a global nemesis of brassica vegetables such as broccoli, cabbage, kale, Brussels sprouts and the field crop canola. Diamondback moths cost the global economy an estimated $4–5 billion annually in damaged crops and pest control methods (*J. Econ. Entom.* **105**, 1115–1129, 2012). "The damage the diamondback moth can do is incredible. I've seen whole fields wiped out," says Shelton. The moth has also evolved resistance to over 90 insecticide ingredients, forcing farmers to increase pesticide use, further exacerbating resistance.

Oxitec's solution to this pest is the OX4319L moth. The genetically engineered insect contains a synthetic 'self-limiting' gene encoding tetracycline repressible transcription activator variant (tTAV). At high expression levels this protein ties up cells' transcriptional machinery, shutting down cell function and eventually killing the insect. The tTAV protein also binds and induces the tetracycline operator (tetO) sequences, which in turn increases expression of tTAV. The more tTAV binds to tetO, the more tTAV is produced—a positive feedback system. The moths also carry a fluorescent marker gene (*DsRed2*) that gives the insects color under a certain wavelength of green light, enabling them to be distinguished from wild pests.

To breed large numbers of GM moths, Oxitec feeds the transformed insect lines tetracycline—an antidote to the self-limiting gene—that prevents tTAV from binding with tetO, keeping the insects alive so that they can reproduce. Only females are affected by the self-limiting gene, so when the insects are taken off the tetracycline diet, the females in the breeding population die. The males are then released into the environment to mate with wild female pests. The resulting offspring inherit the self-limiting gene and the females die before they can reproduce, so over time the population dwindles.

The Oxitec moth approach, like its groundbreaking previous work on GM mosquitoes, is similar to the sterile insect technique (SIT), used for over 60 years to deal with screwworm fly, but without the drawback of employing radiation. SIT exposes insects to radiation to render them sterile before their release into the environment to reduce the population. But because radiation affects hundreds of genes, it leaves the insects less fit than their wild competitors. In SIT, separating males and females is also difficult, so both are released into the environment and tend to mate with each other, rather than with the pest population.

Oxitec's moths ought to avoid those pitfalls, although the synthetic gene may still burden the released males with a slight fitness disadvantage compared with their wild pest counterparts. This is one of the questions Shelton will be addressing in his efficacy studies at Cornell's New York State Agricultural Experiment Station in Geneva, New York. His group has set up in a field ten living-room-sized cages with cabbages planted inside. They will release GM male moths into the cages, along with wild male and female moths, to track how competitive the GM males are compared with their wild counterparts, what their mating frequency is and how well they suppress the population.

Results from the caged trials will aid the design of open field trials, slated to be conducted by Shelton next year, says Hadyn Parry, CEO of Oxitec. Funding for the trials has been provided by the US Department of Agriculture's (USDA's) IR-4 Project with support from Oxitec. "This trial is really quite innovative," says Rick Roush, dean of the college of agricultural sciences at Pennsylvania State University in University Park.

Oxitec has engineered two other agricultural insects with gene constructs similar to that in its diamondback moth: the olive fly and the Mediterranean fruit fly, or Medfly. Oxitec tested its Medfly in netted field trials in Africa and has received approval in Brazil to test its Medfly in open-field trials with its partner Moscamed, a state-owned company in Juazeiro. The company is awaiting clearance in Spain to field-test its olive fly, and the *DsRed2* marker gene has already undergone field testing in pink bollworm and mosquito. Most other genetic modification of agricultural pests has been done in a handful of academic laboratories, including that of Al Handler, research geneticist at the USDA's research arm in Gainesville, Florida, who is working on Caribbean fruit fly; Ernst Wimmer, professor of developmental biology at Georg-August-University in Göttingen Germany, who is working on Medfly; and Max Scott, professor of entomology at North Carolina State University in Raleigh, who has transformed a screwworm fly and is awaiting field trial approval in Panama.

Oxitec is also the creator of the world's first field-tested sterile transgenic mosquito—*Aedes aegypti*—aimed at controlling the carrier for dengue fever and other diseases (*Nat. Biotechnol.* **29**, 1034–1037, 2011). These mosquitoes were transformed with a similar construct to that used for diamondback moths and have been tested in open trials in the Cayman Islands, Panama and Brazil. Oxitec's OX513A mosquitos reduced the dengue mosquito population in an area of Juazeiro, Brazil, by 95%, according to a July 2 report (*PLOS Negl. Trop. Dis.* **9**, e0003864, 2015).

Environmental groups criticized the mosquito trials, saying that reducing wild pest populations might create an 'empty niche' that other potentially damaging insects might fill and affect organisms higher in the food chain (*Nat. Biotechnol.* **29**, 9–11, 2011). Oxitec's diamondback moth is facing similar protests from activist groups and an organic growers association, who say the USDA's environmental review of Oxitec's moth was insufficient.

The groups in June sent a letter to the governor of New York and other authorities, requesting that the Cornell trials be stopped. One of their concerns is that GM moths might lay eggs on organic crops, where the female larvae will die and "leave genetically engineered residue behind on the plant," says Anne Ruflin, executive director of the Northeast Organic Farming Association of New York, and a co-signer of the letter.

That residual material could cause organic farmers to lose their USDA organic certification, Ruflin says. USDA inspectors randomly, and sometimes upon suspicion, test farms for contamination by GM and other forbidden materials. If contamination is found, the organic farmer might be asked to develop a plan to eliminate it and later re-inspected to see if that plan was successful, says Ruflin.

But such a scenario is unlikely, says Drew Kershen, an agriculture law professor at the University of Oklahoma in Norman. Even if a USDA inspector encountered GM moth material, an organic grower only has to show that he took reasonable measures to avoid it and that its presence was inadvertent, he says. "End of matter. There is no mandatory requirement for additional plans or tests."

Opposition to the moth trials has puzzled some scientists. "I see this as a green technology," says Scott at North Carolina State University. The technology would reduce pesticide use. The gene won't persist in the environment because it dies out with the insect population, and it is nontoxic to anything that eats the GM moths, he says. Plus, the target is an invasive pest, not a food crop. "This could be an incredibly important advance for human health and the environment," adds Roush. "And not just in Georgia or Florida but in places like Thailand" where the moths would reduce human exposure to pesticides, he says.

Emily Waltz *Nashville, Tennessee*

Around the world in a month