IN brief

First plant-made biologic approved

Carrot cell bioreactors

The US Food and Drug Administration in May approved Elelyso (taliglucerase alfa), an enzyme produced in genetically engineered carrot cells, for treating type 1 Gaucher's disease. This is the first plant-made drug approved by the regulators, and for Israeli company Protalix BioTherapeutics of Carmiel, it is the first product made in their ProCellEx protein expression system to reach the market. The plant cell platform produces recombinant proteins with a glycan and amino acid structure similar to naturally produced human counterparts. Some 10,000 patients worldwide have Gaucher's, a rare genetic disorder in which individuals fail to produce the enzyme glucocerebrosidase. Elelyso, a recombinant form of human glucocerebrosidase, which is injectable, replaces that enzyme and thus prevents lipids from accumulating in organs and tissues, eventually damaging the liver and spleen, leading to low red blood cell and platelet counts, and bone problems. Protalix and US partner Pfizer of New York are pricing Elelyso at a 25% discount from Genzyme's Cerezyme (imiglucerase), the market leader, a price they hope will persuade clinicians and patients to switch. They are also touting this platform for its dependability, pointing to a year-long spate of supply disruptions for comparable enzymes made by Genzyme, wholly owned by Paris-based Sanofi, to treat Gaucher's disease and Fabry's disease (*Nat. Biotechnol.* **28**, 994, 2010). Pfizer and partner are attempting to position Elelyso as the most reliable product on the market launching a "supply continuity program," whereby a 24 months' supply is maintained. They have also developed several programs to help individuals with Gaucher's disease to afford treatments with this new product. It may be too late, however, to gain a significant market share. A year ago, at the height of the supply disruptions affecting Genzyme's enzyme production, the Protalix-Pfizer product stood to gain a majority share, but regulatory delays in approving the plant-based product meant that that opportunity was lost. In a separate development earlier this year, Cambridge, Massachusetts–based Genzyme, a Sanofi company, announced four-year data from a phase 2 clinical trial for an orally administered version of its treatment for type 1 Gaucher's disease, eliglustat tartrate. Ireland-based Shire also has a competing injectable product for treating Gaucher's disease, called Vpriv (velaglucerase alfa). *Jeffrey L Fox*

As well as protecting the drug from degradation—docetaxel, in its native form, is quickly broken down after administration—the nanoparticle needs to evade patients' immune responses. PEGylation, already widely used for stabilizing biologic drugs, is the most commonly used method. "It really creates this hydration shell around the particle. In essence, it looks like water in some ways," says Jeff Hrkach, senior vice president of pharmaceutical sciences at BIND. Early observations of patients with advanced or metastatic cancers indicate responses at dose levels of 30 mg/m^2, well below the traditional 75 mg/m^2 dose used for solvent-based docetaxel. At the other end of the spectrum, BIND-014 does not appear to be hampered by the same dose-limiting toxicities associated with traditional docetaxel therapy. "We're seeing effects you're not expected to see at any dose without killing people," Minick says. The dose-escalation trial is ongoing. "As soon as we have a dose, we intend to start our phase 2 study," he says.

The BIND-014 results are blazing a trail for the new generation of nanoparticle approaches. Elsewhere, the application of nanoparticles to the delivery of short-interfering RNA (siRNA) therapies is at an earlier stage proposition, for multiple reasons. "Some of the challenges include targeting; [but] you also have to maintain activity; you have to ensure there are no off-target effects; and you want to keep the siRNA dose as low as possible," Langer says. Nevertheless, Alnylam reported on April 19 the successful knockdown of the gene encoding proprotein convertase subtilisin/kexin type 9 (PCSK9), an emerging target for managing high cholesterol levels, with a single dose of the siRNA drug ALN-PCS (*Nat. Biotechnol.* **30**, 302–304, 2012). The siRNA molecule is packaged in a cationic lipid nanoparticle (termed MC3) comprising *N*-[(methoxy poly(ethylene glycol)$_{2000}$)carbamoyl]-1,2-dimyristyloxlpropyl-3-amine (PEG-C-DMA), dipalmitoylphosphatidylcholine and synthetic cholesterol (US provisional patent application 61/185,800 2009) to which Cambridge-based Alnylam and its partner Vancouver, British Columbia–based AlCana Technologies have an exclusive license. (It is also the subject of a legal dispute with their erstwhile partner Tekmira Pharmaceuticals, of Burnaby, British Columbia.) MC3 exploits an uptake mechanism based on a liver cell receptor called apolipoprotein E.

The 80-nm ALN-PCS nanoparticle is able to gain access to the liver because of the presence of 'fenestrated' or discontinuous endothelium in the organ, which ordinarily enables it to take up large lipoprotein particles called chylomicrons. It has long been known that tumors, because of their leaky vasculature, are also similarly permeable to nanoparticles, , although this strategy is not generally applicable to all cancers or all stages of cancer. "That is a transient phenomenon in a transient phase of the tumor," says Mauro Ferrari, CEO of the Methodist Hospital Research Institute in Houston, Texas, and the co-founder of several nanotechnology firms. Other tumor therapies can influence this feature as well. "If you give a patient anti-angiogenic therapy, vascular leakiness is the first thing to go," he says. Ferrari is developing a multi-stage delivery technology, analogous to a multi–stage rocket—the starting point is a 600-800nm 'mothership' made from biodegradable nanoporous silicon—which sequentially sheds different components as it nears its target. It could reach the clinic as early as next year.

Efforts to target siRNA nanoparticles to organs other than the liver are less advanced, however. "The heart is not engineered to take up chylomicrons—you need a smaller particle to access that kind of tissue," says Alnylam CEO John Maraganore. "That work is going to need novel materials—and will also greatly benefit from targeting as well." Endosomal release of siRNA, once it is transported across the cell membrane, remains another challenge, which also requires novel materials, he notes. Alnylam is working with several partners on these efforts, including Daniel Anderson and Langer at MIT, with whom it developed a combinatorial library containing 1,536 structurally distinct nanoparticles (*Proc. Natl. Acad. USA* **108**, 12996–13001, 2011).

Alnylam is also working with a Vancouver-based firm, Precision Nanosystems, which is integrating microfluidics technology with a 'bottom-up' self-assembly approach, to develop a stable and scalable population of 1-palmitoyl, 2-oleoyl phosphatidylcholine, cholesterol and the triglyceride triolein nanoparticles in the 20-nm range to target extravascular tissues (*Langmuir* **28**, 3633–3640, 2012). Its NanoAssemblr platform is based on the work of scientific founder Pieter Cullis at the University of British Columbia, in Vancouver. "We can manipulate the mixing conditions to drive the self-assembly and the order of self-assembly," says co-founder and COO Euan Ramsay. "The key [to] this is very, very rapid and controlled mixing." Precision's desktop instrument is currently in testing before commercial release, which is slated for next year, says CEO and