IN brief

FDA dashes Novo's hopes

Less than a month after the European Medicines Agency granted marketing authorizations for Novo Nordisk's long-acting insulins, Tresiba (insulin degludec) and Ryzodeg (insulin degludec and insulin aspart), the US Food and Drug Administration (FDA) on February 8 rejected their new drug applications. The FDA wants Novo, of Bagsvaerd, Denmark, to conduct a new cardiovascular safety study, after a meta-analysis suggested the drugs may increase the risk of heart attack. As a result, Tresiba's US launch—if it ever happens—could be delayed for several years.

"According to our forecasts, Tresiba [had it been approved] would've earned Novo Nordisk at least $5 billion in the US alone during the period from launch in 2013 to the first half of 2017," says Sebastian Heinzmann, healthcare analyst at Datamonitor in London. "They're not in such a good position after this decision, as the US is by far their biggest market for insulins."

Tresiba's market entry (timed to take place a year ahead of Ryzodeg) was expected to challenge the primacy of Sanofi's long-acting analog Lantus (insulin glargine) before its US patent expires in 2015. Now delayed by a few years, Tresiba will launch into a different market, potentially facing stiff competition from biosimilars being developed by Paris-based Sanofi, Indianapolis-based Eli Lilly, and Mylan of Canonsburg, Pennsylvania, partnered with Biocon of Bangalore, India.

Even in Europe, where it is already available in the UK, Tresiba is unlikely to dominate. Pricing could also limit its use, analysts think, as Novo plans to price Tresiba at a 60–70% premium over Lantus. "It will be tough for the drug to gain traction as the benefits don't really justify such a premium," says Tim Race, pharmaceutical analyst at Deutsche Bank in London.

Tresiba is an insulin analog comprising soluble dihexamers of insulin molecules. It comes in two concentrations, may be flexibly dosed and causes less hypoglycemia than Lantus, especially at night. Tresiba, which has a 24-hour half-life, is the only insulin to form a multihexamer chain when injected, resulting in a soluble depot of insulin. After injection, the individual insulin molecules break away one at a time from the ends of the multihexamers, releasing insulin at a flat rate. According to Heinzmann, however, insulin levels in healthy individuals don't show this peakless profile and many physicians doubt it is really beneficial in clinical practice.

"The main claim is around Tresiba's long profile and low risk of hypoglycemia—an advantage that seems to be statistically, yet not really clinically meaningful for most patients," says Race. "As such, most patients would not switch and thus Tresiba is fighting for new patients and those that have problems with other insulins." *Emma Dorey*

Also, for most PacBio users, Illumina data remain a core component of the workflow, providing high-quality sequence polishing that greatly improves the efficiency of contig assembly while minimizing costs, based on a hybrid technique that Schatz initially helped develop (*Nat. Biotechnol.* **30**, 693–700, 2012). "It's easy to generate a lot of sequence with a HiSeq, and then complement that with PacBio sequencing to interrogate important regions that are not so amenable to sequencing," says Korlach.

Illumina is also 'going long', however. In late 2012, it acquired Moleculo, a San Francisco–based startup with a system for synthesizing long genomic reads from discrete pools of short reads. Their approach isolates and amplifies 8- to 10-kb genomic fragments, which are then broken into barcoded fragments. After Illumina sequencing, these can be reassembled based on their source fragment. For pseudo-long reads, assembly is remarkably swift. "We've worked with something on the order of 20 or so genomes, from a whole variety of different samples," says Geoff Smith, senior director of research for DNA sequencing at Illumina. "We're currently targeting between two and four hours for the analysis."

Moleculo is slated to launch their Moleculo service this summer and a kit by year's end. Several posters at AGBT demonstrated Moleculo technology's effectiveness for the challenging task of generating phased human haplotypes, in which genomic variants are correctly assigned to the proper chromosome within a given pair. Jeremy Schmutz of the HudsonAlpha Biotechnology Institute in Birmingham, Alabama, also presented Moleculo data from a challenging *de novo* genome, the grass *Miscanthus sinensis*, achieving low error rates of 1.2 per 10,000 kb. The platform relies on existing Illumina sequencing technologies that are already widely accessible, and Smith sees this as a key selling point. "The ability to deliver very accurate data at a cost point that makes sense is something that is still an open challenge for long-read sequencing," he says.

For all its speed to market, Moleculo has its limitations. The platform requires PCR amplification, which limits the initial fragment length and can introduce biases, and sequencing still relies on Illumina short reads, which can be hindered by GC-rich or GC-poor regions or baffled by long stretches of tandem repeats, so that gaps may remain a problem. With several months until launch, however, Schatz still sees ample room for growth. "I think we've just begun to scratch the surface with Moleculo," he says.

As an alternative to continuous sequencing, a handful of companies are offering long-range mapping to assemble genomic scaffolds. OpGen and BioNano Genomics, in San Diego, already offer platforms that perform optical mapping of fluorescently labeled DNA, but Nabsys offered a sneak peek of a semiconductor-based platform that it claims will dramatically enhance the speed, scale and precision of genomic mapping. The process entails labeling long DNA strands with short, electronically detectable probes and then passing them through arrays of detectors. "Each strand goes through a single detector on a chip—and the chip has many detectors—at a velocity of over a million bases per second," says Nabsys CEO Barrett Bready. This allows a user to get a clear sense of the distance separating specific sequences of interest, a potentially useful means for fitting together *de novo* genome fragments or getting a handle on large-scale genomic rearrangements within a tumor sample.

At the conference, Keith Robison, of Cambridge, Massachusetts–based Warp Drive Bio, which uses genomics-based approaches to natural products discovery, attended the Nabsys demonstration. He wrote on his blog that the company was able to position their probes on 20-kb fragments with a resolution of nearly 20 base pairs, although these were under fairly controlled experimental conditions (http://omicsomics.blogspot.com/2013/02/agbt-nabsys-unveiled.html). Bready emphasizes that this was only a prelaunch demo, but anticipates hitting the market this year with a low-cost instrument (projected cost ~$50,000) intended initially for *de novo* genome finishing as a complement to existing sequencing platforms. "We're saying second half of 2013 for 100-Mb genomes and smaller, and then for the first half of 2014, targeting genomes of any size," he says.

High-quality data are tantalizing, but these days most scientists are keeping their eyes fixed on the price tag, and long-read sequencing by itself is likely to remain unfeasibly expensive and slow for large eukaryotic genomes. Nevertheless, Korlach remains optimistic and sees a shifting tide. "We were pleased to see that companies that previously were not advocating the value and benefits of long reads are now pursuing strategies of their own to get there," he says. And as scientists with ever more-ambitious projects in nascent fields like metagenomics, pathogen strain typing and cancer genomics bump against the limits of short-read analysis, interest in long reads will keep building.

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