IN brief

10,000 rare-disease genomes sequenced

A program to sequence 10,000 whole genomes of people with rare genetic diseases and their biological parents began in October in the UK. The Rare Diseases Genomes Project is a collaboration between sequencing instruments manufacturer Illumina, of San Diego, Cambridge University, UK, and Genomics England, a London-based company set up by the Department of Health in December 2012 with £100 (\$164) million of government funding. The three-year initiative aims to uncover the genes underlying rare genetic diseases to improve diagnosis and treatment. It also serves as a pilot for an ambitious plan to sequence 100,000 genomes within the UK's National Health Service and ultimately introduce genome sequencing data into routine clinical practice. Patients will be recruited from specialist centers at university hospitals across the country. Genomics England has held public meetings to explain its program to patients and clinicians and has the endorsement of rare diseases patients' groups. Mark Palin, spokesman for Genomics England, says that within the limitations of small patient numbers, they hope to build cohorts. "The aim is for the program to have significant impact on understanding of specific rare diseases, but also to use this information to allow us to see how to move forward with the main program." This will include developing information systems to allow clinicians to interpret the data and bring whole-genome sequencing to the bedside. Genomics England is not saying which, or how many, of the estimated 7,500 rare diseases will be covered in its arm of the project, in which 2,000 genomes will be sequenced.

Nuala Moran

IN their words

"For branded companies, this [biosimilars] has been a marginal threat so far. It has been a mid-summer fly that you have to wave away occasionally but which doesn't actually sting," said Andy Smith, chief investment officer at UK's Mann Bioinvest. (*Reuters*, 3 December 2013)

"One of the key ideas that has driven biotechnology stocks into a frothy bubble is the perception that the FDA has become friendlier to companies than it was before. Either that is no longer true or it never really was." Matthew Herper, biotech writer for *Forbes*, comments on Sarepta Therapeutics' revelation that the FDA would not consider accelerated approval for its muscular dystrophy drug eteplirsen, designed for patients with a particular mutation. (*Forbes*, 12 November 2013)

next-generation anti-CD20 antibody with enhanced ADCC function, by modifying the antibody's Fc region to enhance its affinity to the activating FcγIIIa receptor. GlycArt did this by engineering the antibody-producing cell lines to overexpress two glycosylation enzymes—GMP3 and Golgi mannosidase 2. The result was antibodies with bisected nonfucosylated sugars (*Nat. Biotechnol.* 17, 176, 1999). But that was not the only differentiating factor: GlycArt chose to modify a type 2 antibody, which binds to a different epitope on CD20, rather than a type 1 antibody like Rituxan.

Type 1 antibodies are good at engaging complement-dependent cytotoxicity (CDC) and ADCC. But they are not potent mediators of programmed cell death upon binding to CD20, Umaña says. Type 2s, although much less potent at mediating CDC, are more potent at introducing caspase-independent programmed cell death. "We took a gamble," says Umaña, to gain on programmed cell death at the expense of reduced complement-dependent cytotoxicity. Gazyva also appears to enhance antibody-dependent cell phagocytosis, which is mediated by monocytes and neutrophils, more than does Rituxan.

The absence of fucosylated sugars is one possible explanation for Gazyva's superiority. "Defucosylated and high ADCC engineered antibodies outperform their counterparts," says Peter Senter of Seattle Genetics. The Bothell, Washington-based biotech has discovered an oral compound, 2-fluorofucose, that biochemically inhibits the incorporation of fucose into antibody-producing cells *in vitro* and *in vivo*. And if an antibody known to induce anti-tumor responses also has ADCC activity (as is the case, for example, with Rituxan and also Genentech's Herceptin (trastuzumab)), "then we think improving the ADCC activity by defucosylation could ramp up the activity of the antibody," he says. But given differences in the CD20 epitope targeted and the degree to which induction of programmed cell death, ADCC, and CDC are each responsible for Gazyva's greater potency as compared to Rituxan, it's difficult to assess the contribution made by glyco-engineering the molecule. "I am unaware of controlled clinical trials that compare antibodies that differ only in this function," Senter says.

"I believe the approval of GA101 is a particular case," says Alain Beck of the Centre d'Immunologie Pierre Fabre in Saint-Julien-en-Genevois, France. "It is not only due to the specific glyco-engineered portion [of the antibody], but because of the unique epitope that it targets," he says.

Although defucosylation technologies such as GlycArt's and Kyowa Hakko's are more than a decade old, it's

still early days to assess their success, says Beck, because aside from Gazyva and Poteligeo, no such glyco-engineered products are on the market or in phase 3 trials. And even for the two approved antibodies, "it is difficult to really demonstrate that the main part [of their effectiveness] in patients is due to the Fc function and the fucose content," he says.

Other strategies such as antibody-drug conjugates, bispecific antibodies and asymmetrical Fc engineering to enhance Fcγ binding affinity and ADCC may be superseding glyco-engineering approaches.

Indeed, the overall enthusiasm for glyco-engineering may be cooling. Merck, of Whitehouse Station, New Jersey, acquired glyco-engineering specialist GlycoFi, in Lebanon, New Hampshire, in 2006. But as part of an October 2013 company-wide restructuring, Merck is de-emphasizing the GlycoFi operation, turning instead to the development of biosimilars through a collaboration with Samsung Bioepis in Incheon, Republic of Korea.

Roche, for its part, still has the anti-human epidermal growth factor receptor-3 (HER3) RG7116 in early trials. But it stopped its imigatuzumab (GA201) anti-epidermal growth factor receptor (EGFR) program, a potential successor to Erbitux (cetuximab) after the molecule failed to meet its primary endpoint in a phase 2 trial in colorectal cancer. "There is no clear conclusion yet as to why GA201 did not reach its primary endpoint," says Umaña. "Our current assumption is that in solid tumors—in contrast to hematological tumors—sufficient infiltration with immune effector cells can be a limiting factor for the effector cell-mediated efficacy of glyco-engineered antibodies." Although it has not abandoned defucosylation technology, Roche GlycArt is currently developing new antibody-engineering platforms that would bring more immune cells into the tumor and activate them there to counteract the inhibitory mechanisms, he says.

Kyowa Hakko Kirin's BioWa division in La Jolla, California, however, continues to commercialize its POTEILLIGENT host cell line, used for Poteligeo, for defucosylated antibody production. Seattle Genetics has 2-fluorofucose and also a second defucosylation technology in development, which it intends to deploy for antibody production. And a few small companies are also still competing in the space, including Berlin-based Glycotope.

As well, New York-based TG Therapeutics is continuing to develop ublituximab, a CD20-targeted, glyco-engineered antibody, offering enhanced Fc effector function, in phase 2 for CLL. But Gazyva's impressive results have dampened competitors' enthusiasm for developing next-generation anti-CD20 antibodies.

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