Concerns over the safety of afucosylated antibodies have been, for the most part, theoretical. Companies have nonetheless remained vigilant for signs of increased immunogenicity, altered antibody pharmacokinetics, and any interference with other antibody effector functions. So far, none of these problems have surfaced. "You don't have any systematic defects that accompany defucosylation," says Benjamin. "But it's important to recognize that the antibodies are more potent, and therefore their intrinsic biology does need to be studied and can be different than a fucosylated antibody."

But their potency means that afucosylated antibodies are mostly used to deplete entire cell populations. That carries the risk of collateral damage to other cells. "The challenge here is always to really find the right target," says Kolbeck. "You want something which is really, really specifically expressed on the cell type you are targeting." This may be why Genentech never advanced its afucosylated version of Herceptin (trastuzumab), despite *in vivo* superiority over the original (*Cancer Res.* **70**, 4481–4489, 2010): because the target Her-2 protein is widely expressed on normal cells. (The company declined to comment for this story.) At least three marketed antibodies—Orencia (abatacept), Soliris (eculizumab) and NPlate (romiplostim)—are engineered for the opposite effect, for reduced Fc effector function, to increase their safety margin. Afucosylation, says Strohl, must be used very judiciously. "It's a niche modification," he says.

Bispecific antibodies may be one special case. Indeed, several afucosylated bispecific antibodies in development target proteins that are widely expressed on normal cells (**Table 1**), seemingly violating the specificity deemed essential for their therapeutic use. Strohl, while head of biologics research at Janssen BioTherapeutics, helped develop a bispecific antibody lacking fucose that targets the epidermal growth factor receptor (EGFR) and c-Met for cancer. Although EGFR is widely expressed on normal cells, Janssen's antibody "is built in such a way that it only binds at high affinity cells that have both EGFR and c-Met," says Strohl. "And 90% of those kind of cells, or 80% at least, are going to be cancer cells." Similarly, Merus, in Utrecht, the Netherlands, has two afucosylated anticancer bispecifics in the clinic. "Because we are simultaneously approaching two different epitopes on a tumor, this allows for a more selective targeting," says Merus chief development officer Lex Bakker. "Because of that we are able to put on additional effector mechanisms in the Fc tail."

For all their potency, afucosylated antibodies can't turn a bad target into a good one.

Many strategies exist to engineer antibodies without fucose, although two platforms dominate the commercial market. The Potelligent platform, from Kyowa Kirin's BioWa subsidiary, uses a proprietary CHO (Chinese hamster ovary) cell line genetically engineered to knock out the gene for FUT8, a fucosyltransferase, critical for the assembly of the final Fc fucose. The other platform is GlymaxX technology from ProBioGen in Berlin. This method overexpresses the GDP-6-deoxy-*n*-lyxo-4-hexulose reductase (RMD) enzyme to short-circuit the fucose biosynthetic pathway in antibody production cell lines. Companies that want to develop afucosylated antibodies generally license one or the other, or create their own system if they're able to bypass ProBioGen and BioWa intellectual property.

For all their potency, afucosylated antibodies can't turn a bad target into a good one. "There have been a lot of failures," says Strohl. Genentech's quilizumab, for example, failed a randomized phase 2 trial in asthma (*Respir. Res.* **17**, 29, 2016) and was discontinued. And MedImmune's Fasenra, though it worked in asthma, recently failed to meet its primary endpoint in two phase 3 trials in chronic obstructive pulmonary disease. But such setbacks have not slowed the current wave. "We follow the science," says MedImmune's Kolbeck. "We like what we have seen so far."

Ken Garber *Ann Arbor, Michigan*

First preventive mAb for hereditary angioedema

The US Food and Drug Administration has approved the first monoclonal antibody (mAb) to prevent hereditary angioedema (HEA) attacks. Dublin-based Shire was given the go-ahead in August to market Takhzyro (lanadelumab) as prophylactic treatment for HEA types I and II in patients aged 12 years or older. HEA is a rare but life-threatening genetic disease caused by mutations in the C1 esterase inhibitor gene, which leads to an overactivation of the complement system. This can trigger unpredictable bouts of subcutaneous or submucosal swelling anywhere in the body, potentially leading to blocked airways, and in the gut the attacks can cause intense pain, vomiting and dehydration.

Takhzyro is a human mAb against kallikrein, an enzyme that is elevated in the disease and is known to interact with the complement system. The drug's approval was based on data from four clinical studies, including a 26-week phase 3 trial in 125 patients. They experienced 87% fewer HEA attacks if injected every 2 weeks and 73% fewer if injected every 4 weeks, compared with placebo.

Takhzyro entered Shire's portfolio of HEA therapies when the company acquired Dyax of Burlington, Massachusetts, in 2016 (*Nat. Biotechnol.* **34**, 7, 2016). Shire also owns a portfolio of drugs for treating or preventing HEA attacks, including Firazyr (icatibant), a bradykinin B2 receptor, and Kalbitor (ecallantide), a kallikrein inhibitor. These drugs are self-administered subcutaneously, as is Takhzyro. The latter requires fewer injections than the other approved drugs, which are also more limited in their efficacy and carry more health risks. (Kalbitor is not approved in Europe owing to concerns about anaphylactic events.) These drugs also include attenuated androgens, fibrinolytic agents, and intravenous human or recombinant C1 esterase inhibitors—such as Shire's own Cinryze, CSL Behring's Berinert and Pharming Group's Ruconest.

An oral alternative is also in development. A once-daily selective inhibitor of kallikrein developed by BioCryst Pharmaceuticals is being tested in two phase 3 trials for HAE prevention and in a phase 2 trial for treating acute HAE attacks. If approved, the small molecule BCX7353 could become the first oral—and easiest-to-use—therapy for both HEA treatment and prevention.

Joana Osorio

"**I read the [Health and Human Services] announcement with a great deal of skepticism. My instinct is that this is driven by politics, and is part of the overall effort to stigmatize and eventually criminalize abortion.**" Biomedical law professor Alta Charo of the University of Wisconsin reacts to the announcement that HHS cancelled a contract for fetal tissue. (*BuzzFeed*, 25 September 2018)

"**If a doctor is being paid to market under the cover of professional or academic standing, it looks like an abuse of entrusted power for private gain.**" Brown University's Roy Poses, president of the Foundation for Integrity and Responsibility in Medicine, responds to news that GSK is resuming payments to doctors, which it had stopped after paying a $3 billion fine for illegal marketing and kickbacks. (*STAT*, 10 October 2018)

"**We already tolerate pretty huge levels of inequality and unfairness in this society that we have. And I think that to try to add to that [by editing genes], exacerbate that, just seems wrong.**" Marcy Darnovsky, of the Center for Genetics and Society, responds to the idea that genetic treatments might become a luxury item. (*Healthcare Analytics News*, 20 July 2018)