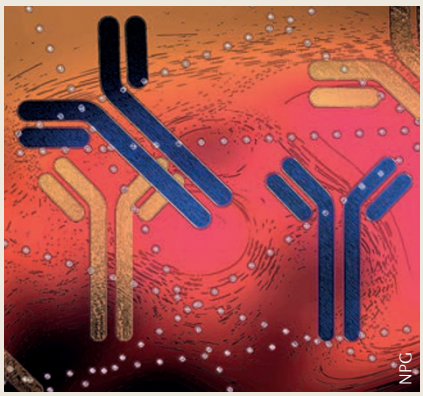
NEWS IN BRIEF

First biosimilar antibody nears US approval



A panel of independent advisors to the FDA voted 21–3 in favour of approving Celltrion and Pfizer's biosimilar version of Johnson & Johnson's tumour necrosis factor (TNF)-specific antibody infliximab. The FDA is expected to make a regulatory decision on the biosimilar therapy in April, when Celltrion and Pfizer's product could become the first biosimilar antibody to be approved in the United States. Although the agency doesn't have to follow the recommendations of its advisors, it usually does.

The FDA gave its first green light to a biosimilar in 2015, when it approved Sandoz's biosimilar of Amgen's filgrastim, a granulocyte colony-stimulating factor (G-CSF), for the treatment of neutropenia. But because antibodies are more complex than proteins like G-CSF, industry is watching the infliximab biosimilar closely for clues about the biosimilar approval pathway.

A key point of discussion at the advisory panel meeting was whether to allow the extrapolation of clinical data in one indication to support approval in another indication. Johnson & Johnson's infliximab is approved for six indications, including rheumatoid arthritis, ankylosing spondylitis, Crohn disease and ulcerative colitis. Celltrion and Pfizer demonstrated clinical biosimilarity for their product only in patients with rheumatoid arthritis and ankylosing spondylitis. The advisory panel voted in favour of allowing extrapolation of this data, backed by analytical data on the biophysical characteristics of the biosimilar, to support approval across all indications.

The European Medicines Agency approved the biosimilar in the European Union in 2013. An approval in the United States would be a further blow for Johnson & Johnson, which sells around US$6.8 billion worth of infliximab each year. Johnson & Johnson is suing Celltrion, however, alleging that the biosimilar will infringe several US patents. This lawsuit could keep the biosimilar off the US market even in the case of an approval.

Many other lucrative biologics will come off patent in the next few years, prompting Janet Woodcock, director of the FDA's Center for Drug Evaluation and Research, to warn last month that the number of biosimilar applications is set to "explode". Other blockbuster antibodies that could see biosimilar competitors in the United States within the next 4 years include AbbVie's TNF-specific adalimumab, Roche's vascular endothelial growth factor (VEGF)-specific bevacizumab and Roche's CD20-specific rituximab (*Nat. Rev. Drug Discov.* **15**, 13–14; 2016).

Asher Mullard

BACE race gains steam

Merck & Co. has completed enrolment of patients into its Phase II/III trial of verubecestat for Alzheimer disease. The drug is the most advanced of the β-secretase (BACE) inhibitors, which prevent the cleavage of amyloid precursor protein. Merck started the 1,960-patient trial in 2012 and now expects trial data in July 2017.

The trial will test the therapeutic potential of a BACE inhibitor in mild-to-moderate Alzheimer disease. The company's ongoing Phase III trial of the drug, which started in 2013, is testing its efficacy in 1,500 patients with prodromal Alzheimer disease.

Two other companies are also in pursuit with BACE inhibitors in Phase II/III trials. They are several years behind Merck, but are looking for efficacy in slightly different patient populations.

In 2014 AstraZeneca started enrolling 2,200 patients into a Phase II/III trial of AZD3293, with a focus on patients with mild Alzheimer disease. AstraZeneca expects final data from the trial in 2019. AstraZeneca is co-developing this drug with Lilly, which dropped its lead BACE inhibitor LY2886721 in 2013 owing to liver toxicity.

In December 2016, Johnson & Johnson became the latest to join the fray, when it started enrolling patients into a Phase II/III trial of JNJ-54861911. The company's 1,650-patient trial will focus on asymptomatic patients who are at risk of developing Alzheimer disease, as assessed by a family history of dementia, the apolipoprotein E (APOE) ε4 risk allele and evidence of amyloid accumulation. Johnson & Johnson expects this trial to complete in 2023.

Eisai has a BACE inhibitor in Phase II trials, and Novartis and Lilly both have BACE inhibitors in Phase I trials.

Asher Mullard

Better screening and disease models needed

Although there have been huge scientific and technical advances in biomedical sciences since the 1950s, the cost of drug development has increased nearly 100-fold in this same timeframe (*Nat Rev. Drug Discov.* **11**, 191–200; 2012). Jack Scannell and Jim Bosley, industry consultants, have now tried to understand these conflicting trends by using a quantitative 'decision-theory' model of the R&D process to explore how the throughput and predictive validity of screening and disease models affect R&D outputs.

Reporting in *PLoS ONE*, they show that large gains from improved throughput of a model can be quickly offset by small decreases in the predictive validity of a model (*PLoS ONE*, 10 Feb 2016). They also hypothesize that "models with high predictive validity are more likely to yield good answers and good treatments, so tend to render themselves and their diseases academically and commercially redundant". The fall in productivity of the pharmaceutical industry, therefore, might be partly due to a decline over time in the availability of sufficiently predictive models for diseases that are of commercial and academic interest to drug hunters.

The authors concede that it is difficult to measure and manage the predictive value of models, but nevertheless make a few suggestions for how to improve the R&D ecosystem. First, they argue that experienced scientists should trust their intuition about the utility of different models but rethink their prioritization of predictive validity, throughput and convenience. Second, research teams need to start capturing, systematizing and communicating information on the predictive validity of the models they use. Third, funders need to invest in empirical studies into the predictive validity of different models.

"The rate of creation of valid screening and disease models may be the major constraint on R&D productivity," they conclude.

Asher Mullard