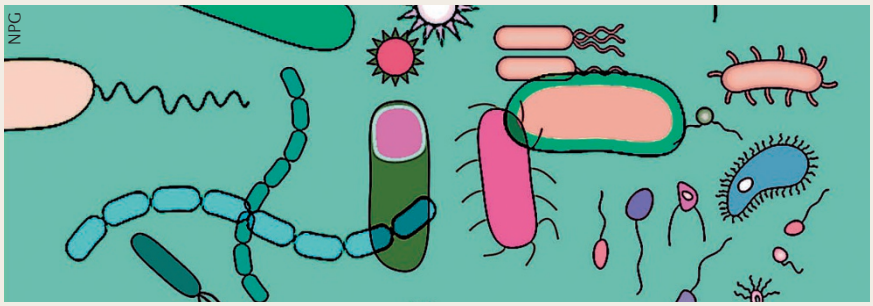
NEWS IN BRIEF



Leading microbiome-based therapeutic falters in Phase II trial

Seres's SER-109 will miss the primary end point in its Phase II trial in patients with *Clostridium difficile* infection, showed an interim analysis of the trial last month. The setback highlights the uncertainty ahead for a burgeoning field of microbiome-based drugs.

Faecal microbiota transplantations are effective for the treatment of *C. difficile* infections, but they require the transfer of minimally processed and uncharacterized faecal matter from healthy donors to recipients (*N. Engl. J. Med.* **368**, 407–415; 2013). By fractionating and processing the stool of healthy volunteers to purify for approximately 50 species of Firmicute spores, Seres hopes that its SER-109 will provide a safer, more palatable, alternative to faecal microbiota transplantation. Seres's orally delivered drug is the first-ever clinically studied synthetic microbiome therapeutic, and it received breakthrough therapy designation from the US FDA in 2015 after producing promising Phase I/II data (*J. Infect Dis.* **214**, 173–181; 2016).

An interim analysis of the 89-subject Phase II trial of the drug recently found, however, that SER-109 is not on track to reduce the relative risk of recurrence of *C. difficile* infection at 8 weeks. Seres's CEO Roger Pomerantz noted that recurrence rates in both the treatment arm and the placebo arm were inconsistent with the company's expectations. Seres did not observe any difference in the adverse event frequency between treatment and placebo. The trial is ongoing, while Seres re-evaluates its development plan for SER-109.

Although there is great excitement over the role of the microbiome in health and disease, the disappointing results show how hard it will be to distil treatment strategies from complex bacterial imbalances.

Asher Mullard

mRNA-based drug approaches Phase I milestone

Moderna and partner AstraZeneca have filed paperwork to advance the first 'secreted protein' mRNA drug into Phase I trials. Initiation of the trial will be an important test for a new drug modality that aims to selectively boost the production of proteins of interest.

The partners' drug, AZD8601, consists of a modified form of the mRNA that encodes vascular endothelial growth factor A (VEGFA). "We believe that using modified mRNA to initiate a strong, local and transient surge of VEGFA expression could help us overcome challenges associated with previous approaches to regulate this protein in tissues," said Marcus Schindler, AstraZeneca's Vice President of Innovative Medicines and Early Development, in a statement. Because VEGFA modulates the fate of cardiac progenitor cells, AZD8601 might provide a regenerative treatment option for patients with heart failure, diabetic wound healing and other ischaemic vascular diseases.

Earlier this year Moderna also advanced mRNA 1440 and mRNA 1851, two infectious disease mRNA vaccines against undisclosed indications, into the clinic. Whereas AZD8601 aims to increase levels of a functional, secreted host protein, mRNA vaccines are typically used to generate pathogenic antigens and the resulting protective antibodies (*Nat. Rev. Drug Discov.*, **15**, 521–522; 2016).

Moderna has been criticized for being tight-lipped about the science behind its mRNA-based drugs (*Nature* **522**, 26–28; 2015). A key question is how they have overcome delivery hurdles to get their drugs into the relevant cell and tissue types. The company has said that it will become more transparent as its programmes move through the clinic. Moderna plans to have six candidates in the clinic by the end of the year. Other areas of interest for Moderna include rare diseases and immuno-oncology (*Nat. Rev. Drug Discov.* **14**, 378–379, 2015). The company is developing candidates independently and in collaboration with industry partners, including Alexion, Merck & Co. and Vertex.

Asher Mullard

EMA rewrites Phase I guidelines in aftermath of FAAH tragedy

The European Medicines Agency (EMA) is proposing a set of changes to its guidelines on how to reduce the risks of first-in-human trials. The agency says a rewrite is needed in part to incorporate lessons learnt from the tragic Phase I first-in-human trial of Bial's BIA 1-2474 earlier this year. One volunteer died and four volunteers were hospitalized owing to adverse effects of the fatty acid amide hydrolase (FAAH) inhibitor. A report by French drug safety regulators found that poor study design likely contributed, noting that doses were escalated too quickly and without taking into account pharmacokinetic data from previously dosed patients.

The EMA also notes that the current guidelines, written in 2007, focus on non-clinical aspects of drug development and single-ascending-dose trials. The EMA plans to update the guidelines to reflect increased use of 'integrated' trial designs that combine multiple substudies (analysing single and multiple ascending doses, food interactions, different age groups and early proof-of-concept end points) into a single first-in-human trial.

Comments on the proposal are due by 30 September 2016. A revised draft guideline is expected by the end of the year.

Separately, the US FDA concluded last month that BIA 1-2474 "exhibits a unique toxicity that does not extend to other drugs in the class". The FDA is currently working with sponsors to establish an appropriate path for other FAAH inhibitors. This could be good news for Johnson & Johnson (J&J), who put its JNJ-42165279 on hold following Bial's Phase I disaster. J&J was testing its Phase II candidate for efficacy in generalized anxiety disorder and major depressive disorder. Pfizer and others have previously tested FAAH inhibitors for pain indications, but many of these companies dropped development of their candidates owing to limited efficacy before the Bial tragedy.

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