Antibacterial antibodies gain traction

First pivotal study win for Merck & Co.'s antibacterial antibody suggests that biologics could at last bring precision medicine to the anti-infective space.

Chris Morrison

Results from a pair of large Phase III studies conducted by Merck & Co. have, for the first time, proved in pivotal trials that an antibody therapy can effectively and safely target a bacterial toxin to ward off infection. The data have energized proponents of developing antibodies to treat bacterial infections, a long-held but frustratingly elusive goal of the biopharma industry.

The immune system evolved to fight infection, points out Aridis Pharmaceuticals CEO Vu Truong, not to fight cancer or cardiovascular disease. And yet, he says, there are not a lot of products on the market that harness immune system components to fight infections. Antibacterial antibodies are a natural first step to address that gap.

They may also offer key benefits over conventional small-molecule antibiotics. As targeted, precision therapies, they are less likely to induce broad resistance among bacteria, and won't disturb the healthy microbiome. Antibodies against bacterial toxins in particular aren't likely to drive resistance at all, because their effects won't "feed back to the genome", says Arsanis CEO Eszter Nagy. They can also be given infrequently (a single injection may be all an intensive care unit (ICU) patient needs, as opposed to multiple daily doses of an antibiotic). And, the use of antibodies alongside traditional antibiotics could have synergistic bacteria-clearing effects.

As a result of these features, there are now at least a dozen antibacterial antibodies in development (TABLE 1). But despite reasons for optimism, difficult clinical pathways and the same regulatory and reimbursement hurdles that have hobbled traditional antibiotic development remain.

Toxins as targets

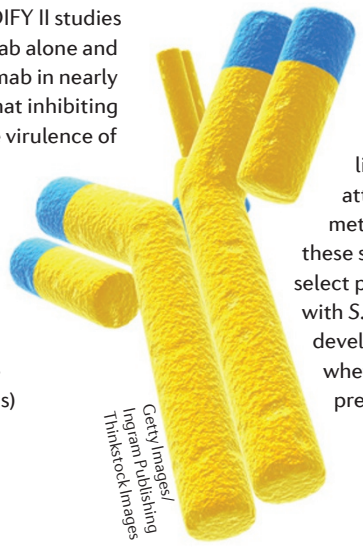
Merck reported at the Interscience Conference of Antimicrobial Agents and Chemotherapy (ICAAC) meeting in September that its two Phase III trials for the monoclonal antibody bezlotoxumab met their primary end points: reduction of *Clostridium difficile* recurrence through 12 weeks, compared with placebo and on top of standard-of-care antibiotics. The company says it will file for approval of the antibody in the United States and European Union during 2015, and the Thomson Reuters Cortellis database shows consensus global sales forecasts of US$350 million by 2020.

Bezlotoxumab works by inhibiting a potentially fatal toxin released by the bacteria, toxin B, which is responsible for the inflammation and cell damage that lead to *C. difficile*'s hallmark pain and diarrhoea symptoms. Merck licensed bezlotoxumab, along with the *C. difficile* toxin A-targeting antibody actoxumab, in 2009 from Medarex (which has since been acquired by Bristol-Myers Squibb) and MassBiologics Laboratory, which is part of the University of Massachusetts Medical School. Interestingly, Merck's evaluation of its Phase III MODIFY I and MODIFY II studies — which tested bezlotoxumab alone and in combination with actoxumab in nearly 2,700 patients — suggests that inhibiting toxin A has no impact on the virulence of the pathogen.

That surprise is indicative of the challenges companies face when selecting bacterial targets for antibody drugs. The move towards narrow-spectrum agents like monoclonal antibodies (mAbs) requires "a change in mindset", says Steve Projan, senior vice president, R&D infectious diseases and vaccines, at AstraZeneca's MedImmune biologics unit. "You hear the term 'precision medicine' in a variety of therapeutic areas but not so much in infectious disease," says Ken Stover, MedImmune senior director of R&D, infectious diseases. "That's because broad spectrum has been the paradigm for so long." And the new mindset requires a deeper understanding of bacterial targets, including the toxins they secrete.

Toxins have been "easier targets", says Todd Black, executive director for basic research in infectious diseases at Merck, but only when they're known primary effectors of disease and when there's a strong association with toxin neutralization and disease prevention, as in the case of *C. difficile*'s toxin B.

Another contender is the *Staphylococcus aureus* alpha-toxin. The alpha-toxin is "the most highly conserved toxin expressed in virtually all strains of *S. aureus*," says Projan, and is produced early in the bacteria's infection cycle to cripple the host's natural immune response to the bug. It also has a pivotal role in staphylococcal infections, including hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP). MedImmune and biotechs like Aridis and Arsanis are attempting to prove the mettle of their antibodies in these settings, where they can select patients who are colonized with *S. aureus* but who have yet to develop pneumonia and see whether a dose of antibody prevents infection.



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This approach is possible in part because of the advent of rapid diagnostics that can identify appropriate therapies for each patient. Projan believes those systems should be (and sometimes are) as easy to use as a Keurig coffee machine.

But deep target biology and the rise of better diagnostics have at times outpaced advances in clinical trial design; choosing the right proving grounds and clinical end points for antibacterial antibodies has also been difficult.

Take the experience of Kalobios, a small biotech that, in partnership with Sanofi, tried to develop an antibody against *Pseudomonas* lung infections in cystic fibrosis (CF) patients. Kalobios learned from its failed Phase II trial that it had set the efficacy bar too high, says Kalobios CSO Geoffrey Yarranton. When CF patients have exacerbations, they lose lung function, so the company set out to show that its exacerbation-reducing drug could improve lung function. But "what we learned is that in dealing with a chronic infection, not an acute infection, it's harder to see an effect", he says. "To reverse [lung function decline] in a 4- or 5-week study is asking a lot."

Kalobios could have looked at inflammatory markers, but reduction of inflammatory markers isn't an "approvable end point", says Yarranton. Dosing the antibody for much longer — a year or two — might have been the way to go, he says, but that's an expensive study for a small biotech. "Chronic indications require chronic dosing, a much longer study, and you need deep pockets to do that," he says. The company has since given up on anti-infectives development, focusing instead on oncology products.

Adding antibody therapies to existing standards of care also means that companies need to demonstrate the superiority of their regimens to standard of care. With small molecules, by contrast, non-inferiority is often enough, says Black.

A difficult regulatory environment for antibacterial therapies in general and the lack of a sustainable commercial model for anti-infective biologics has also slowed the field, says Truong. But "profit margins now look more attractive, the regulatory environment is relaxed, and trial design can be smaller and less expensive", he argues. The alarming rise of antibiotic-resistant bacteria is helping to tip the balance in favour of biologics for infectious disease, he says, especially as antibody developers build up pharmacoeconomic arguments for their therapies. "A pay-for-performance model could make a lot of sense here," says Truong.

Table 1 | **Selected antibacterial antibodies in development**

Drug	Company	Development phase	Indication	Target(s)
Bezlotoxumab	Merck & Co.	III	*C. difficile* infection	*C. difficile* toxin B
MEDI4893	AstraZeneca	IIb	VAP	*S. aureus* alpha-toxin
Salvecin (AR-301)	Aridis Pharmaceuticals	II	HAP and VAP	*S. aureus* alpha-toxin
Panobacumab (AR-101)	Aridis Pharmaceuticals	II	HAP/VAP	*P. aeruginosa* lipopolysaccharide
MEDI3902	AstraZeneca	II	VAP	*P. aeruginosa* Psl and PcrV
Shigamab	Bellus Health	II	Shiga toxin *E. coli*-induced haemolytic uraemic syndrome	*E. coli* shiga toxin type 2
514G3	Xbiotech	I/II	*S. aureus* infections	Undisclosed
ASN100	Arsanis	I	HAP/VAP	*S. aureus* alpha-toxin, and five leukocidin toxins

C. difficile, *Clostridium difficile*; *E. coli*, *Escherichia coli*; HAP, hospital-acquired pneumonia ; mAb, monoclonal antibody; *P. aeruginosa*, *Pseudomonas aeruginosa*; *S. aureus*, *Staphylococcus aureus*; VAP, ventilator-associated pneumonia. Sources: BioMedTracker; company reports.

Multi-prong attacks

That performance — in limiting infections and virulence as well as costs associated with ICU and hospital stays — is beginning to emerge with antibodies like bezlotoxumab. Industry's pipeline of antibody drugs is expanding, and like Merck's initial attempt at lassoing both toxins A and B from *C. difficile*, several candidates aim to bind multiple targets at once — either through mixtures of multiple mAbs or with bispecific antibodies that bind to two distinct targets — as a next-generation strategy to defang particular infections.

Arsanis is simultaneously targeting six *S. aureus* toxins with its lead two-antibody combination, ASN100. Taking advantage of a single conserved epitope on five toxins, one of the two mAbs in this combination product binds alpha-toxin as well as four leukocidin toxins that *S. aureus* produces to kill various immune system components, including macrophages and neutrophils. The second antibody binds a fifth leukocidin that doesn't share the binding epitope of the others. "We understood early on that we needed full coverage," says Nagy. "If you leave even one of these toxins untouched that's sufficient to kill immune cells *in vitro*." Arsanis is on the verge of beginning a government-funded Phase I trial for prevention of VAP, and plans a US- and EU-based Phase II study for mid-2016.

MedImmune is taking a different approach with its MEDI3902, a bispecific antibody that latches on to two distinct targets on the body of the *Pseudomonas aeruginosa* bacteria. One arm of the bispecific binds to Psl exopolysaccharide, a component of the glue-like layer around the bacterium that helps establish and protect it through both immune system evasion and biofilm formation. The other binds the pathogen's type-III secretion system virulence factor PcrV, a needle-like complex on the surface of the bacteria that injects toxins into host cells.

It's not always advantageous to hit two targets using the same molecule, explains Stover. But in the case of MEDI3902, a bispecific made sense because of the short distance between the two targets, he says. The antibody binds Psl with a low affinity, but because the target coats the bacteria and is extremely abundant, even if it slips off it hits another immediately. "Psl keeps the antibody engaged around the bacterium," explains Stover. The interaction with PcrV is high affinity, but there may be only a dozen or so PcrV molecules around the surface of the bacteria. Thanks to the lower-affinity interaction with Psl, MEDI3902 remains in the immediate vicinity of the bacteria and is ready to bind PcrV as soon as it emerges.

The drug is in Phase II trials, with €113 million worth of support from the EU's public–private Innovative Medicines Initiative. The fact that even AstraZeneca's foray into antibacterial antibodies involves considerable public funding is both an indication of the dire public health threat of antibiotic-resistant infections and of industry's assessment of its programmes' remaining risk.