The stately progress of antibiotics

The push by public authorities in many countries around the world to galvanise more research into new antibiotics is making progress. However, the advances are slow.

According to the Pew Charitable Trusts, a non-profit research organisation based in the US, there were 37 new antibiotics in development in the US as of March 2016 that have the potential to treat serious bacterial infections. These are defined as drugs that attack Gram-negative bacteria or pathogens identified by the government as a serious threat to public health. Of the 37 drugs, 11 were in Phase 1 clinical trials; 13 in Phase 2 and 13 in Phase 3. Historically, about 60% of drugs that enter Phase 3 reach a regulator and are approved. The current pipeline is broader than it has been in the past. But according to the charity, there are still too few candidates to meet future patient needs.[1]

Public authorities in both Europe and the US are taking a multi-pronged approach, starting with restricting the use of antibiotics in food-producing animals, to encouraging healthcare practitioners to ration their use in patient care. They are also encouaraging investment into new antibiotic research through direct grants to research groups and by the provision of regulatory incentives. Both the Food and Drug Administration and the European Medicines Agency have adopted antibiotic-specific guidance for developers while the FDA has a special designation in place for antibiotic and antifungal agents that meet a major health need. Companies can apply for the Qualified Infectious Disease Product (QIDP) designation. If the QIDP-designated product is approved for marketing, then the developer gets an extra five years of market exclusivity.

Who are the developers?

Of the 34 or so companies listed by Pew as having antibiotics in clinical development as of 31 March, only five are large pharmaceutical companies. Most of the developers are small enterprises, many of which are supported by venture capital or other financial institutions. They are pre-revenue, which means they do not generate cash flow from the sale of products on a market.

In order to find out more about the companies behind these statistics, *MedNous* interviewed the chief executive officers of two that fit the Pew profile. They are both located in the UK, but have scientific networks that extend around the globe. Destiny Pharma Ltd of Brighton has an early clinical compound for treating Gram-positive staphylococcal infections, and Auspherix Ltd of Stevenage has a preclinical portfolio of potential Gram-negative agents.

Destiny Pharma Ltd

Destiny recently completed a US Phase 1 study of its drug XF-73 (exeporfinium chloride), the fifth in a series of placebo-controlled studies in human volunteers that confirmed the safety of its compound. The drug is intended to be administered intra-nasally to patients scheduled for surgery in a hospital. The indication for the drug is 'prevention of post-surgical staphylococcal infections.'

"That is an indication for which no existing product is approved," Bill Love, the chief executive, said in the interview.

Destiny's US Phase 1 study was funded by the US National Institute of Allergy and Infectious Diseases (NIAID), which is part of the National Institutes of Health. Company officials were approached by the NIAID at a conference after they had presented clinical data about their compound from their studies in the UK.

"The people from NIAID were interested in our novel approach and the data that we had generated. They invited us to Washington to present to a fuller team," Dr Love recalled.

The application to start the trial was accepted and funding was secured. The trial took place at NIAID centers in Ohio and California.

With the US trial ongoing, the company then applied to the FDA to have XF-73 recognised as a QIDP product. The application was successful, which puts the company in line for additional market access should XF-73 eventually be approved for marketing. More immediately, the designation recognised Destiny's proposed indication for XF-73, which could have broad application across the US healthcare system.

"About half the people coming for surgery in hospitals could benefit from a pre-treatment to prevent post-surgical infection from these bacteria," the executive commented.

An estimated one in three people are carriers of nasal *Staphylococcus aureus*, one of the staphylococcal bacteria. A healthy individual is not harmed by the bacteria. But if he or she enters a hospital for surgery there is a serious risk of infection following the operation. What's more, the bacteria have become resistant to current antibiotics. What Destiny's proposed compound would do is preempt these problems.

Thus far, clinical studies have shown that XF-73 is safe in human volunteers. The US trial and four trials in the UK have enrolled 216 people of which 166 received XF-73 and the remainder received a placebo. Each trial built on the findings of the earlier one, which means that the drug has been investigated at different doses and different dosing frequencies. Dr Love said the trials enabled the company to "develop an optimised approach" to treatment.

Separately, the company conducted a series of *in vitro* tests of XF-73 to find out whether the product could fight off *Staphylococcus aureus* (*S. aureus*) over an extended period of time. The study used a *S. aureus* type known to be resistant to methicillin, a narrow-spectrum antibiotic. They found that XF-73 was able to fend off *S. aureus* despite 55 consecutive days of exposure to the bacteria. By comparison, the bacteria developed resistance to five other marketed antibiotics.[2]

"We performed what is still the world's most stringent and longest resistance test of this type and we have seen no emergence of resistance to XF-73…..We would never say that it [the test] fully predicts what you would find in the clinic, but we are studying that and we believe it [the platform] promises a new range of anti-bacterial products that can have a long clinical lifetime," Dr Love said.

XF-73 is a synthetic dicationic porphyrin derivative that

targets the cell membrane of Gram-positive bacteria. It has shown activity in all the Gram-positive bacteria tested by the company thus far, as well as in some Gram--negative organisms, the executive said. It works by interacting with negatively-charged particles in the cell membrane, causing a rapid membrane depolarisation, leakage of intracellular components, and the death of the bacteria.

According to the company, bacteria die within 15 minutes of exposure to XF-73. This is irrespective of whether they are active or moribund. "Bacteria can become moribund and be in the body without actively multiplying and then pop out and start growing again once antibiotics have cleared from the body. The XF drugs have been shown to be active against bacteria at any growth phase whether they are actively growing or in fact if they are not growing at all," the executive said.

This includes bacteria that are within biofilms. Biofilms are communities of bacteria that can form a jelly-like matrix on the surface of objects such as medical devices. This protects them from most conventional antibiotics. But Destiny claims that its XF drugs reach the bacteria inside biofilms as well.

What's next for the company? The next test of XF-73 will be in Phase 2b trials in a surgical patient population. These studies will predominantly be looking towards a US development pathway, Dr Love said.

Auspherix Ltd

While Destiny Pharma has been working on its technology platform for more than a decade, Auspherix is a relative newcomer to the field. The company was founded in 2013 by a British and a German scientist who were colleagues at the University of Technology Sydney in Australia.

Ian Charles and Dagmar Alber had previously worked together at Arrow Therapeutics, an anti-infective company in the UK that was acquired by AstraZeneca Plc in 2007. They joined forces to found Auspherix, initially raising capital from Australia's Medical Research Commercialisation Fund (MRCF).

Not long after this, they moved the company to the UK where they obtained new financing from Imperial Innovations Group Plc and re-located to the Stevenage Bioscience Catalyst, a hub for startups that is not far from central London. Auspherix's Australian investors stayed with the company.

Auspherix is one of many companies in the world that has successfully found a new purpose for an existing drug. In this case, the compound is auranofin, a drug that was approved for rheumatoid arthritis (RA) in 1985 and has since been overtaken by later generations of RA medicines.

Auranofin has a well-known toxicity profile and is considered safe for human use. It has become a popular target for research, among other things, for repurposing as a medicine for cancer, HIV and bacterial infections.

In an interview, Neil Miller, the chief executive officer, said the company has used its knowledge of medicinal chemistry to modify the compound so that it has activity against both Gram-positive and Gram-negative bacteria. But the focus of the company's work going forward is on developing compounds against Gram-negative organisms. Gram-negative bacteria are the more difficult of the two bacteria classes to target because they have a tough outer membrane surrounding the cell wall. Gram-positive bacteria do not have this second membrane.

"We have intellectual property around new molecules from the same structural class as auranofin….and we have been able to design our molecules to build in Gram-negative activity," Dr Miller said.

Specifically, Auspherix is looking to bring a new molecule to the clinic that would treat complicated urinary tract infections caused by *Escherichia coli*, a Gram-negative pathogen. The company has not disclosed the mechanism of action of its molecules apart from saying that they enter the Gram-negative bacteria and kill it. "We have shown that our molecules are bactericidal so they have a very rapid kill of Gram-negative bacteria," the executive said.

"Our molecules are also renally cleared; they are excreted through the kidneys and therefore that insures that higher concentrations of antibiotic will be present in the kidney and in the bladder and the urine," he said. These are the organs that the company wants to target in seeking to treat complicated urinary tract infections.

The outlook

Table 1 on page 9 gives a list of the drugs in clinical development in the US to treat Gram-negative bacteria as compiled by the Pew Charitable Trusts. The table lists 15 compounds that have possible, or confirmed, activity against these bacteria. In 2012, *MedNous* did a similar survey of the antibiotic pipeline using statistics from the Infectious Diseases Society of America. At this time, there were nine products against Gram-negative bacteria in clinical development. At least two of the products from the 2012 pipeline have gone on to be approved; others are still in development or have been abandoned.

Table 2 on page 9 gives a list of the QIDP-designated products that have been approved by the FDA. This list includes both antibiotics and antifungal agents. The six approved products come from a total of 66 that have received QIDP designation since 2012.

An FDA spokesman told *MedNous* in an email that the introduction of the QIDP designation, which is backed by legislation, has resulted in a "mild uptick" in antibacterial drug development. But the pipeline remains very fragile, he added.

References:

1. "Tracking the Pipeline of Antibiotics in Development," The Pew Charitable Trusts, 12 March 2014.

2. David J. Farrell et al, "Investigation of the Potential for Mutational Resistance to XF-73, Retapamulin, Mupirocin, Fusidic Acid, Daptomycin and Vancomycin in Methicillin-Resistant *Staphylococcus aureus* Isolates during a 55-Passage Study," Antimicrobial Agents and Chemotherapy, March 2011.

This article was researched and written by the editors of *MedNous*.

Table-1 Drugs against Gram-negative bacteria in trials

Source: The Pew Charitable Trusts

Compound	Status	Developer	Drug Class	Potential indications
BAL30072	Phase 1	Basilea Pharmaceutica Ltd	Monosulfactam	Multi-drug resistant Gram-negative bacteria
Zidebactam + cefepime	Phase 1	Wockhardt Ltd	Beta-lactamase inhibitor + beta-lactam	Complicated urinary tract infections
TP-271	Phase 1	Tetraphase Pharmaceuticals	Tetracycline	Community-acquired pneumonia
OP0595	Phase 1	Meiji Seika Pharma	Beta-lactamase inhibitor	Bacterial infections
Ceftaroline + avibactam	Phase 2	AstraZeneca/Allergan	Cephalosporin + beta-lactamase inhibitor	Bacterial infections
Aztreonam + avibactam	Phase 2	AstraZeneca/Allergan	Beta-lactamase inhibitor + monobactam	Complicated intra-abdominal infections
POL7080	Phase 2	Polyphor Ltd	Macrocyle	Bacterial pneumonia
Finafloxacin	Phase 2	MerLion Pharmaceuticals	Fluoroquinolone	Complicated urinary tract infections
S-649266	Phase 3	Shionogi Inc	Cephalosporin	Healthcare-associated pneumonia
Omadacycline	Phase 3	Paratek Pharmaceuticals	Tetracycline	Community- acquired pneumonia
Imipenem/cilastatin + relebactam	Phase 3	Merck & Co Inc	Carbapenem + beta-lactamase inhibitor	Complicated urinary tract infections
Carbavance	Phase 3	Rempex Pharmaceuticals	Meropenem + boronic beta-lactamase inhibitor	Complicated urinary tract infections
Baxdela (delafloxacin)	Phase 3	Melinta Therapeutics	Fluoroquinolone	Acute bacterial skin infection
Eravacycline	Phase 3	Tetraphase Pharmaceuticals	Tetracycline	Complicated intra-abdominal infections
Plazomicin	Phase 3	Achaogen Inc	Aminoglycoside	Complicated urinary tract infections

Table-2 QIDFP -designated drugs approved by the FDA

Source: Food and Drug Administration

Compound	ID	Company	Indication	Date of Approval
Dalvance	NDA 21-883	Durata Therapeutics	Acute bacterial skin infections	23 May 2014
Sivextro	NDA 205435	Cubist Pharmaceuticals	Acute bacterial skin infections	20 June 2014
Orbactiv	NDA 206334	The Medicines Company	Acute bacterial skin infections	6 August 2014
Zerbaxa	NDA 206829	Cubist Pharmaceuticals	Complicated urinary tract infections	19 December 2014
Avycaz	NDA 206494	Cerexa Inc	Complicated intra-abdominal infections	25 February 2015
Cresemba	NDA 207500	Astellas Pharma	Invasive aspergillosis	6 March 2015