and Black says that 'preliminary results look promising'.

This is the first dendritic cell vaccine to move into clinical trials, although other teams are in the preliminary stages of examining their potential use for the treatment of other cancers and diseases that activate the immune system such as multiple sclerosis. Black and colleagues are also beginning research into the use of this technique for the treatment of other types of brain tumours, especially in the paediatric population, where it is one of the leading causes of death.

Black and his team are also working to try to improve the current vaccine. 'One of the difficulties of producing a vaccine for brain tumours is that the tumours use several methods to evade the immune system, including directly killing activated T cells,' he explains. 'We are therefore trying to work out a strategy to inhibit this mechanism to make the vaccine even more effective.'

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Trojan antibiotics

Martina Habeck, Freelance writer

Researchers have developed a new technology to design antibiotics against drug-resistant bacteria. From the outside, the novel drugs look like conventional antibiotics, but they carry a potent bactericide hidden within their chemical structure. The lead antibiotic candidate based on this new technology, NB2001, has been shown to be effective *in vitro* and is now being tested in animal models.

According to the WHO, as many as 60% of hospital-acquired infections in the industrialized world are caused by drug-resistant microbes[1]. Bacteria have developed many tricks to resist antibiotic treatment. Often, they produce enzymes that convert the antibiotic drug into an ineffective compound and so much current research is concentrating on developing products that inhibit these resistance enzymes.

Mechanism of new technology

Scientists at NewBiotics (San Diego, CA, USA) have developed a new approach to avoiding the resistance problem by turning the production of the resistance enzyme into a therapeutic advantage as opposed to the usual mechanism of trying to inhibit the enzyme. The general approach involves first identifying the key enzymes in the infectious organisms that play an essential role in the development of drug resistance. They then modify the natural substrate of the enzyme and incorporate a potent toxin into its chemical structure. As a result, the resistance enzyme catalyses the release and activation of the toxin, causing the cell to self-destruct.

Drugs based on this Enzyme Catalyzed Therapeutic Activation (ECTA) technology are not only being developed for treatment of infectious diseases. The approach was originally invented to overcome drug resistance in cancer therapy. NB1011 is in development for the potential treatment of patients with colorectal and breast cancer that have suffered relapse with 5-fluorouracil (5-FU). Preclinical efficacy and toxicology studies look promising, and the compound is now about to enter clinical trials.

Identification of lead candidate

By comparison, the company's anti-infective programme is still in its infancy.

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NewBiotics' scientists designed 35 anti-infective compounds targeted at β-lactamase-producing microbes that are resistant to treatment with β-lactam antibiotics such as penicillin, amoxicillin, ampicillin or cephalosporin. The scientists then screened for the most effective compound by comparing the efficacy of the test compounds with that of ampicillin and of Augmentin (a fixed combination of amoxicillin and clavulanic acid, a β-lactamase inhibitor). The compounds were tested against three *Escherichia coli* strains:

- One ampicillin-sensitive strain that did not produce β-lactamase;
- One ampicillin-resistant strain that produced β-lactamase, but was sensitive to clavulanic acid; and
- One Augmentin-resistant strain that produced β-lactamase and was resistant to clavulanic acid.

Out of these experiments, NB2001 emerged as the most potent compound. NB2001 is a new cephalosporin that carries the well-known bactericide triclosan within its backbone (Fig. 1). According to unpublished company data, the compound was 30-fold more potent than ampicillin in inhibiting the growth of the ampicillin-sensitive *E. coli* strain and 1000-fold more effective against the ampicillin- and Augmentin-resistant bacteria than against sensitive bacteria.

Raymond Poon, Executive VP for Business Development and Operations, says, 'We have also done *in vitro* studies with different isolated bacteria strains that are commonly found in nosocomial infections. We have now started to test NB2001 in mice that have been infected with different isolated bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA).' The team are also planning to look at other animal models of infections as well, mainly bacterial blood and lung infections. 'We are hoping to enter clinical trials within 15 months from now,' added Poon.

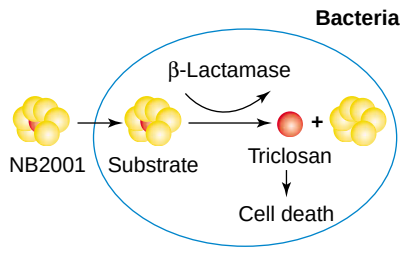

Figure 1. 'Trojan Horse Solution' to antibiotic resistance. NB2001 is a new cephalosporin that carries the bactericide triclosan within its backbone. In non-resistant bacteria, the cephalosporin compound will interfere with cell-wall synthesis and thus inhibit bacterial growth. However, if the bacteria are resistant and produce the resistance enzyme β-lactamase, the enzyme will hydrolyse the β-lactam ring of the cephalosporin compound, thereby triggering the release of triclosan, which will interfere with the bacterial lipid metabolism and cause the cell to self-destruct.

The researchers have not started toxicological studies yet, but as both cephalosporin and triclosan interfere with bacterial pathways and are therefore non-toxic to human cells, they do not expect to see any toxicity as a result of combining the two compounds.

Future promise

Marissa Miller, Antimicrobial Resistance Program Officer at the National Institute of Allergy and Infectious Diseases (NIAID; Bethesda, MD, USA) thinks that: 'This is exciting and certainly looks promising. However, I would like to see the data published in a peer-reviewed journal so we can evaluate how stringently the experiments were carried out.'

Miller is also concerned that bacteria might rapidly develop resistance to the new drug. 'They say the first effect this compound has is inhibition of cell-wall synthesis, but bacteria have found ways to become resistant to this effect. The second effect is the release of triclosan. But triclosan is a common compound in soaps and disinfectives, and there is increasing evidence that bacteria have developed resistance to triclosan.' However, she concludes that: 'ECTA technology is an innovative approach, so hopefully something will come along that will be a hit.'

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