oxygen and nutrients to the brain after an ischaemic event, you would basically have a method of stopping the infarction process without having to get things… past a clot that has caused the ischaemic event.'

This idea has proven to be effective in many preclinical experiments performed in cats [1]. According to Shook, the first clinical trial, conducted last year in the USA, confirmed the feasibility of the approach in subjects with very severe ischaemic strokes. In future trials (Phase II), the scientists will look at parameters such as the duration of treatment and the therapeutic time window, which is currently 24 h. If all goes well, the product could be on the market by 2005.

Future potential

According to Brass, all of these approaches show potential but the real test will be whether these compounds are effective in humans. He believes that inhibiting JNK is a promising idea. 'If it works, this would be something that could help people that come in 12 h or a day after the onset of stroke, because programmed cell death does not occur immediately.'

Brass is cautiously enthusiastic when it comes to Revoxyn. 'I think it is a novel idea. I am not sure whether it will work or not but I think it is worth testing in a way that will give us good answers.' He says that part of the challenge is to get the oxygen-carrying fluid inside the brain as well as at the surface of the brain. 'On the other hand,' he concludes, 'a lot of the things we thought would work have not, and it is certainly an innovative approach to try.'

Reference

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A natural antibiotic for cystic fibrosis

Janet Fricker, Freelance writer

A novel antimicrobial peptide, which appears to have a broad spectrum of activity and can overcome drug-resistance problems, has shown promise in Phase I trials for treating patients with cystic fibrosis (CF) [1]. The new compound, iseganan hydrochloride (formerly IB367), which was developed by IntraBiotics Pharmaceuticals (Mountain View, CA, USA), is a synthetic compound based on the natural protegrin peptides found in the human body (Fig. 1).

CF is an autosomal recessive disorder caused by a defective gene on chromosome VII, coding for the cystic fibrosis transmembrane conductance regulator (CFTR) protein. The commonest mutation results in failure of the CFTR protein to reach the surface of the cell leading to abnormal chloride secretion. In the lungs, impaired chloride transport into airways, with excessive absorption of fluid, produces viscous secretions, which interfere with ciliary transport and facilitate infection and inflammation. The mean predictive survival of patients with CF is 31 years [2].

Current therapies

The goal of antibiotic therapy in CF is to reduce the burden of chronic infectious destruction of lung tissue, improve patient well-being and the ability to live independently, and, ultimately, to prolong survival. Recent advances in CF antibiotic therapy have made it possible for patients to inhale antimicrobial drugs, offering advantages over parenterally administered antibiotics because drugs are delivered directly to the site of infection, higher local doses can be achieved than with systemic use, and the normal flora of the gut and urinary tract are less exposed. The first of these drugs was tobramycin solution for inhalation, which was approved by the Food and Drug Administration in 1997. Unfortunately, continued use of this drug has resulted in the development of antibiotic resistance.

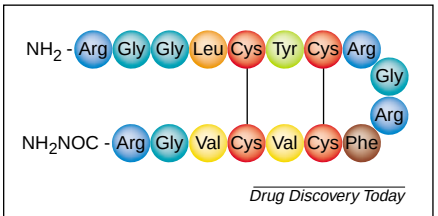

Figure 1. Structure of iseganan HCl. The synthetic antimicrobial peptide consists of a disulfide pleated β-sheet.

Another agent that has been successfully delivered by aerosol is colimycin. Colimycin apparently does not lead to the development of resistance, presumably because of the rapid mechanism of destroying microbial membranes. However, it has a narrow spectrum and can only treat Gram-negative bacteria, leaving Gram-positive bacteria untouched.

Iseganan

'Iseganan represents a significant advance because it possesses the resistance properties of colimycin, with the treatment

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spectrum of tobramycin, killing both Gram-positive and Gram-negative organisms,' says Henry J. Fuchs, Vice-President of Clinical Affairs at IntraBiotics. Resistance properties are a result of iseganan's mechanism of action. The drug rapidly kills microorganisms by disrupting membrane integrity, as opposed to conventional antibiotics, which work by poisoning the metabolic machinery of the cell.

There are many antimicrobial peptides that are part of the natural host-defence response to microorganisms and which have been identified in vertebrates, invertebrates and plants. In mammals, these peptides exist either in phagocytic cells, such as neutrophils, or on epithelial surfaces, such as those lining the airways and gastrointestinal tract.

In 1993, Robert Lehrer from the University of California at Los Angeles (Los Angeles, CA, USA) discovered an antimicrobial peptide that is secreted by porcine neutrophils, which he subsequently named protegrin [3]. Since then, five naturally occurring protegrins have been found and labelled PG1–5.

'Protegrins are extremely hearty, working outside the cell under a wide range of hostile conditions, including high salt concentrations, making them highly relevant for treating CF patients,' says Fuchs. IntraBiotics improved upon PG1, by altering molecules sequentially. The resulting iseganan is based on PG1 but has an amino acid deletion and substitution. 'The result is more active against a broader range of microorganisms, and salt and pH concentrations, than the native sequence,' says Fuchs.

In a rat model of lung infection with *Pseudomonas aeruginosa*, treatment with iseganan (in daily doses of 10, 15 or 50 mg per day) reduced the lung bio burden by 10–1000-times [4]. Meanwhile, in Phase I clinical studies, the investigators concluded that five doses of iseganan at 4.5 mg are safe when administered for 2.5 days to adults with CF. Cough, pharyngitis and chest tightness were the most frequently reported adverse events. However significant changes in pulmonary function tests or sputum bacteria were not detected after five doses. 'This is hardly surprising, since it would probably take a couple of weeks before antibiotics affect the bacteria,' says Fuchs.

The next phase of development will focus on producing a reduction of bacteria in the lungs of people taking iseganan, compared to controls. 'But with the US stock market in such doldrums it's likely to be delayed,' warns Fuchs. ' We're currently conserving cash to ensure we can finish our iseganan oral mucositis programme to take the drug to market in cancer patients.'

Phase III trial

A Phase III randomized, double-blind study of 323 patients undergoing stomatotoxic chemotherapy – presented at the *American Society of Clinical Oncology* (San Francisco, CA, USA) 12–15 May 2001 – showed that iseganan increased the proportion of patients who did not develop oral mucositis by 32%, compared with controls. Iseganan was found to be generally well tolerated, although its use might be associated with a modest excess frequency of oesophagitis and taste disturbance [5].

John Govan, Professor of Microbial Pathogenicity at Edinburgh Medical School (Edinburgh, UK) says: 'Reduction in the lung density of *P. aeruginosa* by iseganan in a rat lung model highlights the therapeutic potential of natural and synthetic antimicrobial peptides. Further research to assess the antimicrobial efficacy of iseganan in CF patients and to investigate other biological functions of these peptides (including immunomodulation and antimicrobial synergy with other airway surface agents) could provide an effective therapeutic weapon against CF pathogens, in particular those resistant to present antimicrobial agents.'

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Dr Joanna Owens, *Drug Discovery Today*, 84 Theobald's Road,
London, UK WC1X 8RR
tel: +44 20 7611 4365, fax: +44 20 7611 4485
e-mail: joanna.owens@drugdiscoverytoday.com