trials have not yet been performed,' she explains. Lee suggests that perhaps adhesins could be used as the protein component of a conjugate vaccine coupled to CP5 and CP8 to see if a multicomponent vaccine would be more effective.

Although there are no plans to include staphylococcal proteins, a future generation of the CP vaccine is likely to include an extra polysaccharide. 'The original vaccine, which had just CP5 and CP8, protects against ~85% of all clinically significant *S. aureus* isolates, but inclusion of the recently discovered type 336 should increase this to almost 100%,' says Naso. Lee is less convinced about CP336. 'The composition of the CP336 polysaccharide has not been published, nor have these investigators demonstrated that antibodies to CP336 are protective against *S. aureus* infections,' she points out. Naso, however, counters that Nabi has received a US patent on the CP336 antigen based on both structural data and animal studies and the group is confident that these three CPs should cope with all *S. aureus* infections. 'Other capsular antigens could be added to subsequent generations of the vaccine to address other pathogens such as *Staphylococcus epidermidis* and enterococci,' he adds.

The future

Safety and immunogenicity studies of StaphVax are also planned for other at-risk patient populations. 'If the first-generation vaccine can protect dialysis patients who are immune-compromised and at long-term risk of staphylococcal infections, then the vaccine is also likely to protect against *S. aureus* bacteraemia in more healthy at-risk populations, such as those receiving medical implants, the elderly in extended care facilities, and even surgery patients,' predicts Robbins.

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Caspase inhibitors for liver disease

Jo Whelan, freelance writer

A drug that inhibits apoptosis could be used to treat a range of liver diseases. IDN6556 has been found to be safe and well tolerated in a recent Phase I study, and will soon enter Phase II trials in patients with liver impairment.

Apoptosis is caused by a cascade of intracellular cysteine protease enzymes called caspases (Fig. 1). Too much apoptosis plays a part in conditions as diverse as ischemic injury, neurodegenerative diseases, inflammatory diseases, osteoarthritis, allograft rejection and septic shock. Conversely, insufficient apoptosis is implicated in cancer and autoimmune disease. There is, therefore, great interest in finding drugs to manipulate the pathways that control cell death, and many such products are in clinical trials [1].

Excessive apoptosis also occurs in various liver diseases, including alcoholic hepatitis, hepatitis B and C, Wilson's disease and drug-induced hepatotoxicity [2]. Treatment is problematic: severe acute alcoholic hepatitis is fatal in >50% of cases. Hepatitis C is treated with α-interferon, but this is only effective in ~50% of patients and is expensive.

Broad spectrum

Idun Pharmaceuticals (San Diego, CA, USA) is developing a caspase inhibitor known as IDN6556 that it hopes will prevent liver degeneration by blocking cell-death pathways. In conditions such as acute alcoholic hepatitis, cytokines such as tumor necrosis factor-α (TNF-α) are produced in the liver and bind to so-called 'death receptors' on the surface of hepatocytes. This activates caspase 8, which in turn cleaves and activates the effector caspases – those proteases that bring about the lethal events characteristic of apoptotic cell death [2].

IDN6556 is a small molecule that binds irreversibly to the cysteine residue at the active site of several caspases. 'IDN6556 is designed to inhibit both the initiator caspase, namely caspase 8, and also the downstream caspases in case there is any leak-through,' says Kevin Tomaselli, co-founder and Vice President of Discovery Research at Idun. It is the first broad-spectrum caspase inhibitor to be tested in humans. 'The broad spectrum of action is also advantageous because there are two caspase pathways controlling apoptosis, and we do not yet know which [pathway] is at work in particular disease situations, or whether it is both,' Tomaselli explains. 'With a broad-spectrum drug we can hit both pathways.'

The therapeutic potential of caspase inhibitors in liver disease was demonstrated in studies with a prototype broad-spectrum caspase inhibitor, IDN1965 [2]. Apoptosis-associated liver injury can be induced in mice with anti-Fas antibody.

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This activates Fas (CD95)-receptors, which are closely related to TNF receptors, and causes lethal fulminating hepatitis after ~5 h. Intraperitoneal administration of IDN1965 gave a dose-dependent reduction in liver injury as measured by alanine aminotransferase (ALT) activity. Immunohistochemical and immunoblotting studies showed that the activation and processing of certain caspases was greatly reduced. In survival studies, 70% of mice given anti-Fas alone died within seven days, but there was 100% survival in those given anti-Fas plus either a single dose of IDN1965 or a continuous infusion. The drug also inhibited liver injury when given up to 3 h after the anti-Fas insult. 'When tested in the same model, IDN6556 also showed a strong protective effect on liver cells,' adds Tomaselli.

In a Phase I trial, 50 healthy volunteers were given intravenous doses of IDN6556 four times daily for up to seven days. Full results have not yet been released, but Idun says the drug was well tolerated, producing only mild side effects. Phase II studies are due to begin soon on patients with mild liver impairment, and following this it will be tested in patients with acute alcoholic hepatitis. 'In these trials we will be looking at markers of liver function to measure the extent of liver damage in treated and untreated patients,' says Tomaselli. 'In patients with acute alcoholic hepatitis, we anticipate looking for a reduction in mortality.'

Side effects

Apoptosis is a normal physiological process that has a homeostatic role. Any drug that inhibits this process, therefore, risks causing potentially dangerous side effects, including tumors, associated with the unwanted persistence of cells. However, this is unlikely to be a problem if the duration of treatment is short. 'Our first target with caspase inhibitors will be to protect against organ damage in acute situations such as liver disease, myocardial infarction and stroke,' Tomaselli acknowledges. 'We have to assume that chronic caspase inhibition is more likely to be associated with side effects, and we will need to find out what, if any, those are. But caspase inhibitors could definitely have a potential role in preventing the gradual cell loss seen in chronic conditions such as viral hepatitis and heart failure. The answer might be to inhibit apoptosis chronically but intermittently.'

'Caspase inhibitors are at an early stage of development but have huge potential for acute life-threatening diseases such as liver disease, myocardial infarction and stroke,' says Mark Nuttall, Section Leader, Musculoskeletal Diseases at GlaxoSmithKline (King of Prussia, PA, USA). 'The challenges are to get the inhibitors in and out quickly, and to prove that the salvaged cells retain their function. It is key to measure cell-specific gene or enzyme activities to indicate that they retain function. We also need to thoroughly evaluate any toxicity from short-term exposure. Chronic inhibition, without doubt, has serious safety concerns; these must be evaluated not only in healthy volunteers but also under stressed conditions of infection or injury.'

Idun is also working on caspase inhibitors for neurodegenerative disease and rheumatoid arthritis, and has a clinical candidate for use after myocardial infarction.

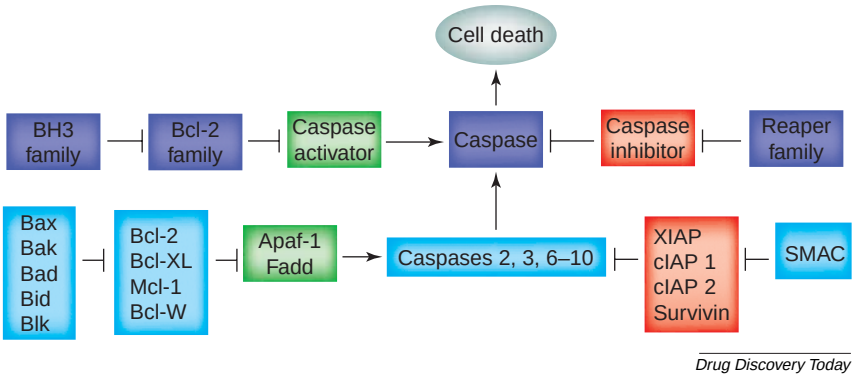

Figure 1. Schematic of the 'core' of the apoptosis pathway in human cells. Caspase proteases are expressed as inactive zymogens in virtually all cells. Caspase activation requires physical association with caspase-activator proteins (green boxes) and simultaneous inhibition of caspase inhibitor proteins (red boxes). Once caspases become active, cell death quickly ensues. Inhibition of caspases with small-molecule protease inhibitors prevents apoptosis. The caspase activation mechanism is inhibited by the Bcl-2 family of proteins. Representative members of each apoptosis gene family are shown in blue boxes.

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