

# New aminosterols from the dogfish shark

Seven new aminosterols, a unique class of polyamine conjugated sterols first discovered in shark tissue (see Box 1), have been isolated from the liver of the dogfish shark (*Squalus acanthias*) and their chemical structures have been determined<sup>1</sup>. Previously described aminosterols are being investigated for their therapeutic potential in several fields of medicine, including cancer, age-related macular degeneration, malaria, obesity and asthma.

## Activities of previously known aminosterols

Squalamine, the first aminosterol discovered by Michael Zasloff (Magainin Pharmaceuticals, PA, USA) and colleagues in 1993 (Ref. 2), is an antibiotic against bacteria such as *Escherichia coli* and strains of *Staphylococcus* and *Streptococcus* with the same potency as ampicillin. It also shows powerful anti-angiogenic activity, a property that could make it invaluable as an anti-cancer drug. Following a successful Phase I/II safety trial in 40 patients in 1999, a Phase II study for non-small-cell lung cancer began in January this year. Zasloff is still highly involved and reports that interim results from the trial could be available by 2001. Additional trials for ovarian cancer and several solid tumours are also in progress and trials for prostate cancer and paediatric cancers are planned. 'Assuming that our clinical studies progress successfully, we would hope to see squalamine available for widespread use in 3–4 years', he predicts.

The anti-angiogenic activity of squalamine could also have potential in the eye condition, age-related macular degeneration (AMD). In one form of

AMD, termed 'wet-AMD', blindness is caused by new blood vessels growing through the back of the eye and damaging the retina. In a mouse model of oxygen-induced retinopathy, squalamine improved retinopathy and inhibited growth factor-stimulated endothelial cell growth<sup>3</sup>. The next step is to evaluate squalamine further and to move to Phase I/II trials early in 2001.

## Current knowledge of the recently discovered aminosterols

Already, the more recently discovered aminosterols are showing potential. Using HTS techniques, Zasloff's team

has identified one aminosterol, MSI1436, that causes profound reversible weight loss in rodents and corrects the diabetic profile of genetically obese mice. 'It is likely that MSI1436 acts on a central target in the brain that involves neural circuits downstream from the leptin receptors,' says Zasloff. Another compound, MSI1437, can inhibit the replication of human lymphocytes *in vitro*.

Yet another compound, MSI1361, dramatically alters the shape of human red cells *in vitro* and is being evaluated as a possible treatment for human malaria. Ray Kaplan (Walter Reed Army

### Box 1. Discovery of the first aminosterols

Work leading up to the discovery of the aminosterols began in the mid-1980s. Michael Zasloff and colleagues (Magainin Pharmaceuticals, PA, USA) had been exploring the tissues of many vertebrates – including frogs, cows and humans – for the presence of antimicrobial substances and had already identified a class of antibiotics called magainins, found predominantly in the skin of frogs. In the early 1990s, Zasloff became intrigued by the shark. 'This fish has a very "incomplete" immune system compared with that of mammals yet rarely succumbs to infection and disease and we decided to investigate what other protective mechanisms could be operating,' he explains.

Such a study required large quantities of material for extraction and the dogfish was chosen as the study species because it was readily available as a food source. A search of its tissues led to the discovery of squalamine, first identified in the dogfish stomach, and then in other tissues. The liver was a particularly rich source, containing 10 µg squalamine per gram of tissue. Before the successful chemical synthesis of squalamine, supplies were obtained solely through extraction of dogfish liver. This work led to the identification of at least 12 structurally related compounds and the determination of their structures.

Sufficient quantities of these compounds were isolated to initiate some limited studies of their activity. 'In one of our early studies, tadpoles were introduced into dilute solutions of each of the pure compounds. Squalamine caused the capillaries of the tail of an animal to regress. Another compound caused an immediate change in the pigmentation of the skin. Others affected, individually, such properties as the secretory activity of the skin, the shape of circulating blood cells, and the activity of its digestive tract,' explains Zasloff. These studies demonstrated that several of these aminosterols had unique biological activities and were not simply metabolic waste products.

Institute of Research, Washington, DC, USA) showed that MSI1361 kills the intra-erythrocytic stages of *Plasmodium falciparum* *in vitro* by lysing the infected red cell [Kaplan, R.M. *et al.* A novel class of steroids isolated from the dogfish shark (*Squalus acanthias*) induce a reversible spherocytosis in normal erythrocytes and kill erythrocytic stages of *Plasmodium falciparum* by inducing lysis of infected erythrocytes. *American Society of Tropical Medicine and Hygiene Meeting*, 7–11 December 1997, Lake Buena Vista, FL, USA, Abstract].

Several of the aminosterol analogues exhibited potent and selective effects on

human T lymphocytes. 'These were subsequently evaluated in animal models of asthma and found to be surprisingly effective', but, admits Zasloff, 'the aminosterol identified as our lead in asthma still requires optimization'. Ideally, a molecule for this indication should be orally available and work is being conducted to improve this property.

## Future prospects for aminosterols

Zasloff is optimistic about the development of all the aminosterols so far described. 'All of them show such potent activity that we expect to develop several useful drugs. I think this may be the most

significant discovery of a novel class of compounds from animal tissues since the prostaglandins; the aminosterols could turn out to be just as important.'

## REFERENCES

- 1 Rao, M. *et al.* Aminosterols from the dogfish shark *Squalus acanthias*. *J. Nat. Prod.* (in press)
- 2 Moore, K.S. *et al.* (1993) Squalamine: an aminosterol antibiotic from the shark. *Proc. Natl. Acad. Sci. U. S. A.* 90, 1354–1358
- 3 Higgins, R.D. *et al.* (2000) Squalamine improves retinal neovascularisation. *Invest. Ophthalmol. Vis. Sci.* 41, 1507–1512

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# E-commerce turns to PriceWaterhouseCoopers

In April 2000, PriceWaterhouseCoopers (PWC; New York, NY, USA) and Ventro Life Sciences (Uxbridge, UK) announced an alliance to create the leading online supplier for laboratory equipment and supplies for the pharmaceutical/biotechnology markets in Europe. The market is currently estimated to be worth US\$7–8 billion. According to Fergus Byrne, PWC's Global Head of Pharmaceutical Consulting, the average major-league pharmaceutical company spends US\$250–350 million to meet its laboratory needs. E-commerce for the life science market seems to be developing into a two-horse race between Ventro – known more widely by the name of their US operating company Chemdex (Mountain View, CA, USA) – and their competitor SciQuest (Research Triangle Park, NC, USA), which has a very similar business model and target audience.

Ventro has turned to PWC for expertise in many areas such as tax, e-commerce regulations and regulatory

compliance. According to Derek McCall, Vice President of Ventro, 'There is a tremendous depth of expertise within the PWC organization that will basically allow us to accelerate the rate at which we can bring this solution to market.'

The Internet is forecast to change the way life science business is performed in Europe – these changes have already happened or are happening in the USA. McCall claims that through the use of an e-procurement solution, pharmaceutical companies could achieve economies of 10–40% in terms of unlocked time, improved purchasing decisions and other benefits.

Ventro already serves the vertical life science marketplace with 1.3 million products listed, 2200 suppliers and 24,000 users (company annual report). Revenue for the Q4 of 1999 was \$20 million. The company also operates in three other vertical healthcare and industrial marketplaces, namely specialty medical products, process plant supply and healthcare supply.

## e-Mission

Ventro specializes in B2B (business-to-business) e-commerce in vertical marketplaces and its corporate mission is to create value on both sides of the supply chain – both for the supplier and for the user enterprise organization. Constraints around B2C (business-to-consumer) e-business are well understood – notably, the poorer penetration of the PC into the home in Europe relative to the US, and the far greater connection and online charges. According to McCall, in the B2B arena, these constraints do not apply, and some projections suggest that Europe could even overtake the US in B2B, with the UK and Germany identified as hotspots for hypergrowth in the next two years.

## Scaleable solutions

Typically, markets suitable for the Ventro approach have a fragmented supplier base without dominant operators. The top ten life science suppliers