Getting the nano-needle

A novel type of drug that kills cancer or bacterial cells by punching a hole in them, acting like a tiny needle, could soon be possible according to a US research team. The team has designed an artificial ion channel that works just like the critical proteins that pit the surface of every cell and control the molecular traffic across the cell membrane. The model channel will not only help researchers explore how the real things work and how they accomplish their high selectivity for different chemical species, but could be designed to target specific diseased cells and kill them.

Understanding exactly how ion channels work is, according to Dr George Gokel (Department of Molecular Biology and Pharmacology, Washington University School of Medicine, St Louis, MO, USA), "One of the hottest areas of modern biology because channels are important in neural transmission as well as in controlling ion concentrations and in communication between cells". A significant amount is known about which channels transport which ions – calcium, sodium, potassium and chloride – but researchers have not until now been in a position to emulate the transport processes very effectively in the laboratory.

Gokel and his team have now devised a simple synthetic channel based on the ring-shaped macrocyclic molecules known as crown ethers stacked together. The team recently reported their latest results (*J. Chem. Soc., Chem. Commun.* 1997, 1145–1146) and have shown that their model can slip itself into a phospholipid bilayer much like the ion-channel proteins naturally sit in the membrane of almost every cell.

In tests of the functioning of their artificial channel, the researchers have achieved about 3:1 potassium over sodium selectivities so far. They have also had success in transporting caesium ions, although these particular results are not yet published.

"Gokel's membrane channel mimics are remarkable because they combine structural simplicity with functional efficiency," enthuses supramolecular chemist Dr Prasanna de Silva (Queen's University, Belfast, UK), "single channel events akin to membrane channel proteins are possible and the structural simplicity will allow them to synthesize related structures for further evaluation."

The long-term goal is to develop new drugs based on the artificial channels. Gokel explains, "If a model channel compound could be made tissue selective, perhaps by appending a peptide, fatty acid or steroid, the channel could insinuate into selected bilayers." The transport of a selected ion through this channel would have a deleterious effect on the cell, and if that happened to be a cancer or bacterial cell then the channel would be a targeted therapeutic agent. Pathogenic cells have little if anything in their chemical defences that would allow them to develop resistance to such an attack.

Gokel points out that such agents would not be limited to cancer and bacterial infections. Cystic fibrosis (CF) is intimately linked to chloride ion transport by natural protein, and so the so-called chloride transporter channel might be used to redress the balance in CF patients although this, he confesses, is a very distant goal.

The team is now trying to enhance selectivity of their channels as well as studying the effects of changing the size of the macrocyclic rings and adding 'gates' to the openings to the channels.

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In short ...

Researchers from **NeXstar Pharmaceuticals** presented results from the first US Phase I clinical trial for the proprietary antibiotic MiKasome (a liposomal formulation of the antibiotic amikacin) at the 35th Annual Meeting of the Infectious Diseases Society of America (IDSA) in San Francisco. The Phase I study was conducted at the Stanford Medical Center (Stanford, CA, USA). Overall conclusions of the study were that: at the doses studied, MiKasome did not cause toxicity or impairment to the kidneys, to hearing function or to balance; MiKasome's half-life is longer than reported for any other liposome formulation; and relatively constant antibiotic levels appear to be maintained with once weekly dosing.

Dr Michael R. Pavia, a member of the *Drug Discovery Today* Editorial Board, has joined **Millennium Pharmaceuticals, Inc.** (Cambridge, MA, USA) as Chief Technology Officer. Pavia was formerly Vice President of Research at the Cambridge research site of **Sphinx Pharmaceuticals** (A Division of Eli Lilly).

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