

planned for late 2006. Benitec (Sydney, Australia) also plans to enter Phase I trials with an RNAi-based HIV antiviral in 1H 2006 and a hepatitis C treatment in 2H 2006. In the longer term it is hoped that RNAi could be used to attack cancer cells, and several

compounds are in preclinical development.

References

- 1 Quinlan, E. (2005) ARVO Annual Meeting, 1–5 May, Ft Lauderdale, FL, USA
- 2 Bitko, V. *et al.* (2005) Inhibition of respiratory viruses by nasally administered siRNA. *Nat. Med.* 11, 50–55

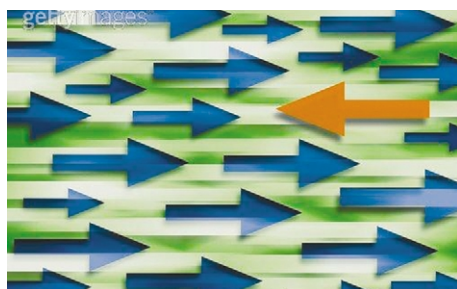
Resisting resistance

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Cancer patients undergoing long-term chemotherapy increasingly endure their tumours developing resistance to the drugs they need. New research by a group led by Bryan Toole, Professor in the Department of Cell Biology and Anatomy, Medical University of South Carolina, USA, have discovered a method of inhibiting a series of reactions leading to the development of drug resistance.

Surprise role for hyaluronan

Resistance to chemotherapeutic drugs normally develops as a result of upregulation of transport proteins that remove the drugs from the cancer cells. The team at South Carolina has elucidated some of the pathways that make this possible – and potentially identified a way to prevent resistance developing.



Toole's group previously showed that small pieces of a polysaccharide – hyaluronan – were able to sensitize previously drug-resistant cancer tissue to a number of chemotherapeutic agents. Hyaluronan is a large polysaccharide that is normally found as part of the structure of the extracellular matrix. As hyaluronan is largely structural in function, it came as a surprise to learn that it has recently been identified as crucial to signalling pathways in the development of tumours. Furthermore, hyaluronan has been shown to stimulate drug

resistance in cancers. It's also been seen that, via a complex signalling pathway, hyaluronan stimulates its own production. Elements of this signalling loop – including hyaluronan itself – stimulate expression the multi-drug transporters that cause drug resistance. 'Effectively, the response to hyaluronan is responsible for drug resistance,' said Toole.

'The oligosaccharides are fairly readily made'

Clear but unproven potential

There's a twist to the tale, however. Toole's group have also been able to inhibit hyaluronan from entering this ever-amplified resistance loop. By taking oligomers of hyaluronan – effectively small pieces of the polysaccharide – the team were able to stop hyaluronan from binding to its natural receptor, CD44, stopping the signalling that leads to resistance. 'The oligomers bind to the same receptor,' Toole added. 'They bind, but don't induce the same reaction.' By displacing the polymer from its receptor, the team have discovered a way to block drug resistance.

Not only do the oligomers block the development of resistance, they have also been shown to sensitize resistant cancer cells to chemotherapeutic drugs, even reverse the malignant properties of cancers. 'This work is

very interesting,' agreed Timothy Hardingham, Professor of Biochemistry at Manchester University, UK. 'And somewhat out of the blue and unpredicted from the known properties and activities of hyaluronan.'

'There is potential for the development of small molecule antagonists at the CD44 receptor,' said Toole, 'but possibilities already exist with peptides.' He continued, 'Peptide hyaluronan mimetics have been around for little while now and can antagonize hyaluronan, but they've not been tested in biological systems yet.' Hardingham agrees; 'There is a clear potential, but as yet unproven scope for translating this to therapy.'

Readily available

Conventional drug development approaches might not be necessary, as the oligosaccharides are not only effective but also, it seems, readily available. 'The oligosaccharides are fairly readily made,' Toole added. 'There's already a hyaluronic acid industry out there, serving the cosmetic industry and for eye and knee surgery. The degradation product would be just as readily available.' The degradation products would serve as a steady supply of hyaluronic oligosaccharide antagonists. 'Hyaluronan can also be made by bacteria – another potential source,' added Toole.

The future for this research, then, might soon be of benefit to patients. Toole continued, 'Using hyaluronan antagonists in combination with regular chemotherapy will allow reduction of chemotherapy dosage, meaning less toxic side effects.'

Reference

- 1 Misra, S. *et al.* (2005) Regulation of MDR1 expression and drug resistance by a positive feedback loop involving hyaluronan, phosphoinositide 3-kinase, and ErbB2. *J. Biol. Chem.* 280, 20310–20315

Cell cycle inhibitors key to neoangiogenesis

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Cancerous tumors insidiously co-opt building blocks for neoangiogenesis – the construction of blood vessels to nourish a growing mass of cells. An emerging picture of the process shows

that cell cycle inhibitors are crucial, and the most recent work now singles out p27 and p130 as key molecules. A collaborative team headed by Andrew Koff at Memorial Sloan-Kettering Cancer Center and David Lyden at Weill Medical College of Cornell University