news

Study limitations

Campbell warned that the study was done with cell lines and not with fresh cells from CML patients. 'In the past cell line results with other drugs have not always panned out with fresh cells or clinically.' Furthermore, manipulation of the cell lines might have changed their response to the new drug, suggested Campbell.

'The 'resistant' cells were produced artificially by inserting a mutation into cell-line derived cells – this may or may not be a valid model of *in vivo* resistance', he said.

Meanwhile, Travers queried the authors' observations that their compound was active against another kinase, Lyn, and that some Gleevec resistance arises through dysregulation of Lyn. 'One has to ask what the effect of Lyn inhibition in normal cells would be, and this is not dealt with in the study.' Furthermore, the researchers use a nude mouse animal model, which lacks T cells and is immunodeficient, said Travers, whereas the likely detrimental effects of Lyn inhibition will be on immune cells. The animal model is therefore not adequate to determine the likely side-effects of the drug, he warned.

Reference

1 Gumireddy, K. *et al.* (2005) A non-ATP competitive inhibitor of BCR-ABL overrides imatinib resistance. *Proc. Natl. Acad. Sci. U. S. A.* doi: 10.1073_pnas.0408283102 (Epub. ahead of print; http://www.pnas.org)

Bowled over by potential for drug delivery

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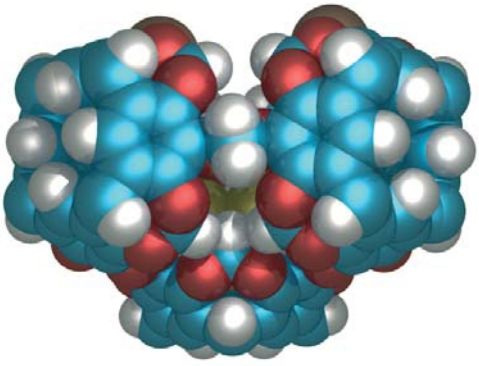
Getting drugs to where they are needed is a headache for modern drug discovery. A recent development by researchers at the two of Australia's leading universities shows the potential for carrying drugs to their site of action. The development of so-called 'superbowl' molecules could soon be used to deliver a wide range of drug molecules to specific parts of the body.

Self-assembling cages

First created to act like naturally occurring transport molecules, bowl-shaped molecules were initially synthesized in the 1980s, and pioneered by researchers like Jerry Atwood at the University of Missouri-Columbia. 'Atwood's work inspired us,' said Michael Sherburn of the Australian National University. Sherburn's group, including scientists from the University of Sydney, developed the new superbowl molecules. 'Atwood came up with an unusual self-assembling molecular array of six relatively large bowl molecules, which came together to encircle a large, roughly spherical, volume of space.' Said Sherburn. '[Atwood] first patented the notion of using these arrays in a drug delivery context,' continued Sherburn. 'But these self-assembling cages were non-covalently bound, had limited stability, and dissociated easily, particularly in solution.'



Gating mechanism

The new superbowls developed by the Australian team have some subtle differences, meaning that a wider range of applications is open to them. Atwood's structures consist of up to six non-covalently linked structures. The superbowls described in the Australian research are inherently more stable. Five identical bowl-shaped subunits are covalently linked to form an open superbowl.

Around the hole on top of the superbowl it's been possible to include a gating mechanism to help guest molecules in and out of the superbowl. 'Nature hates a vacuum,' added Sherburn. 'The interior of the superbowl is never empty. In their development, solvents were always present inside. To encapsulate a molecule, the superbowl just needs to be exposed to it.' This has been demonstrated with a range of molecules, and work is ongoing to encapsulate others. 'We've only worked with fairly boring molecules so far', added Sherburn, 'the largest so far being tetra-*n*-octylammonium bromide, which has a strong binding constant.' Despite the lack of direct interest in this particular molecule, it is significant in that it is comparable in size to many drug molecules, adding impetus to the drive behind using the superbowls in therapies.

Looking for the right key

Extending the current research into the future, Jacob Irwin of the University of Warwick (who was involved in earlier stages of this research) sees many possibilities for further enhancing the capabilities of the 'superbowls.' 'The subunits are linked by short $-OCH_2O-$ groups. These could be extended to allow the superbowl to accommodate different shapes or sizes of drugs.' The binding pockets within the superbowls are currently chemically fixed, somewhat limiting the functional groups, and thus the drugs that could potentially bind there, but identifying them could pose problems. 'It's similar to the lock and key principle for binding drugs to proteins, like looking for the right key to fit your lock,' said Irwin. 'The system could be computer-modelled, however, to help develop better guests.'

Looking at the 'targeting' capabilities of the 'superbowls,' further potential arises from the options to chemically modify the side chains projecting from the 'superbowls.' 'There are side chains that can be altered to change the superbowls' properties,' added Sherburn. 'In our paper, the side chains are simple alkyl chains to maximise solvent solubility, but an obvious modification could be to replace these or aromatic rings with sugar molecules to enhance water solubility.' 'Binding to antibodies is another possibility. The technology is already in place to facilitate this, but it's still science fiction at the moment.'

Reference

1 Barrett, E.S. *et al.* (2004) Superbowl container molecules. *J. Am. Chem. Soc.* 126, 16747–16749

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