news

those individuals will accept an HIV test? 'We don't know', said Paltiel. 'But we know that the methods for screening and counselling are critical', added Owens. ' We know for instance that with the traditional methods of screening, a good proportion of people never pick up their results. Rapid tests would be of a great interest to these individuals, since they would get their results quicker'.

'These findings are in line with what the CDC recommended two years ago,' commented Karlie Stanton, spokesperson at the CDC. 'We certainly will take these studies into account in our next HIV testing guidelines', she added. The models do not incorporate certain negative effects of screening. 'We are aware that our analysis does not consider stigma, a critical concern in shaping public perception of HIV', said Paltiel. Acceptance of testing and linkage to care represent a second area for study. 'In addition, we don't really know who will pay for these tests', said Paltiel.

Would these models be applicable to developing African and Asian countries for instance, where HIV kills the most? 'Our study is based on US standards of care and linkage to care', said Paltiel. 'The value of earlier detection is based on the state of the art HAART, the lab facilities allowing to tailor HAART to each individual and the possibility to interfere with further transmission on the disease. 'We are currently working on models applicable to Asian and African countries'. 'Benefit occurs if care is available,' said Owens. 'There is no point testing people if there is no treatment available. Obviously getting treatment to people is absolutely urgent', he added.

References

1 Sanders, G.D. *et al.* (2005) Cost-effectiveness of screening for HIV in the era of highly active antiretroviral therapy. *New Engl. J. Med.* 352, 570–585
2 Paltiel, A.D. *et al.* (2005) Expanded screening for HIV in the United States – an analysis of cost-effectiveness. *New Engl. J. Med.* 352, 586–595

New leukemia drug shows promise against Gleevec resistance

Haroon Ashraf, haroonstuff@hotmail.com

Patients with chronic myelogenous leukemia (CML) resistant to Gleevec, the most successful treatment for the deadly cancer, could have a promising alternative drug in the future, according to early studies by US researchers. CML is caused by the Philadelphia chromosome, an abnormality that produces the BCR-ABL cancer protein. Gleevec works by binding to BCR-ABL and completely blocking its activity, thereby stopping cancer growth.

Synergy

'Our drug [ON012380] works just like Gleevec but by blocking another part of the BCR-ABL protein. It can be combined with Gleevec to create synergy and when patients become resistant to Gleevec, our drug kills 100% of the cancer cells', said lead researcher, Prem Gumireddy, Director of the Fels Institute for Cancer Research at Temple University School of Medicine.

The implication of this study is that clinicians will soon have combination therapies to improve the treatment of CML, said Paul Travers, deputy director of the leukemia charity Anthony Nolan Trust. 'There are other drugs in the pipeline that also target BCR-ABL and which are active against most of the Gleevec-resistant variants but this compound can act synergistically with Gleevec, while the others cannot', said Travers.

Resistance

About 750 people per year in the UK have advanced CML and a small number develop Gleevec resistance within a few years of starting therapy. The actual number of patients who develop resistance depends on the stage of the disease and their previous treatment, said Ken Campbell clinical information officer at the Leukaemia Research Fund. 'In patients put on Gleevec as first-line therapy in the early chronic phase, it is probably no higher than 10%. But in late-stage disease it may be quite high', said Campbell. Currently the alternatives for patients who develop resistance are either to use 'older' drugs alone or in combination or to

temporarily withdraw Gleevec, which may restore sensitivity, said Campbell.

However, Richard Sullivan, Head of Clinical Programmes at Cancer Research UK, said there are likely to be a number of mutations and other mechanisms that cause resistance. 'Doctors would have to genotype resistant patients to see which of many second-line treatments might help them. Screening genes in this way is not straightforward, and may hamper the future use of compounds such as ON012380', he warned. The study was published in the early online edition of *Proceedings of the National Academy of Sciences* [1].

New challenge

Until now scientists have only managed to develop two experimental drugs that could tackle some but not all forms of Gleevec resistance CML. However, both drugs failed to block the activity of a mutant BCR-ABL, called T315I, a more predominant mutation in Gleevec-resistant patients.

When developing their drug, Reddy and colleagues targeted parts of the BCR-ABL protein that didn't appear to be mutating and adapting to Gleevec.

As a result, in human tumour cell and mouse model experiments, the compound called ON012380 induced cell death of all of the known Gleevec-resistant mutants and caused regression of leukemias, said Reddy, who is currently seeking FDA approval to proceed with clinical trials

1359-6446/04/$ – see front matter PII: S1359-6446(04)03404-5

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)

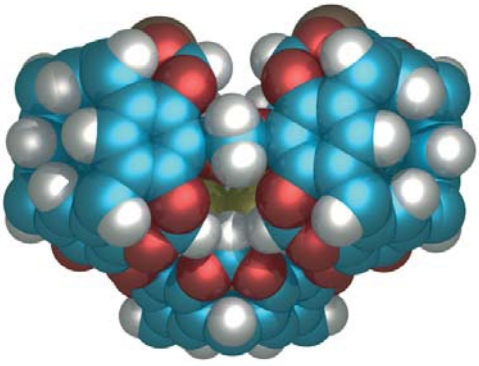
Bowled over by potential for drug delivery

Scott Ewan, scott_ewan@hotmail.com

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

1359-6446/04/$ – see front matter PII: S1359-6446(04)03404-3