news

Baker has this work underway and if all goes well, his mix-and-match dendrimer approach might move into clinical trials for cancer within 3–4 years. 'We also hope to adapt the approach for other conditions where a specific cell population needs to be killed,' he adds, 'such as autoimmunity and inflammatory diseases.'

Dendrimers for drug discovery

Baker's approach to dendrimer-driven drug delivery also appeals to Cloninger, who describes it as 'creative and interesting.' And, she adds, dendrimer-based chemistry has applications in drug discovery as well as drug delivery. She is currently using carbohydrate-functionalized dendrimers to study protein–carbohydrate interactions. 'Our long-term goal is to understand intercellular recognition processes, such as those involved in the immune response, well enough to be able to devise multivalent therapeutic agents and strategies to correct these processes when they go awry,' she concludes.

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Surprise neuroprotective potential of β-lactam antibiotics

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During a blinded screen of 1040 FDA-approved drugs to try to identify compounds able to stimulate expression of the glutamate transporter, GLT1, β-lactam antibiotics and their semi-synthetic derivatives came out in the top 2% of hits. Previously, no other pharmaceutical has been found to stimulate GLT1 and this discovery could have enormous implications for several neurological disorders. 'This was very unexpected,' explains lead author Jeffrey Rothstein (Professor of Neurology and Neuroscience, Department of Neurology, Johns Hopkins University, Baltimore, MA, USA). 'Pharmaceutical companies were looking for ways to increase transporter functional activity but, thinking about it in retrospect, I know of few examples of research that has been able to get an enzyme to catalyze an activity better. We wanted to increase transporter protein levels, thereby increasing the V_{max}, but we never anticipated the antibiotics capable of this,' he adds.

From random hits to therapeutic possibilities

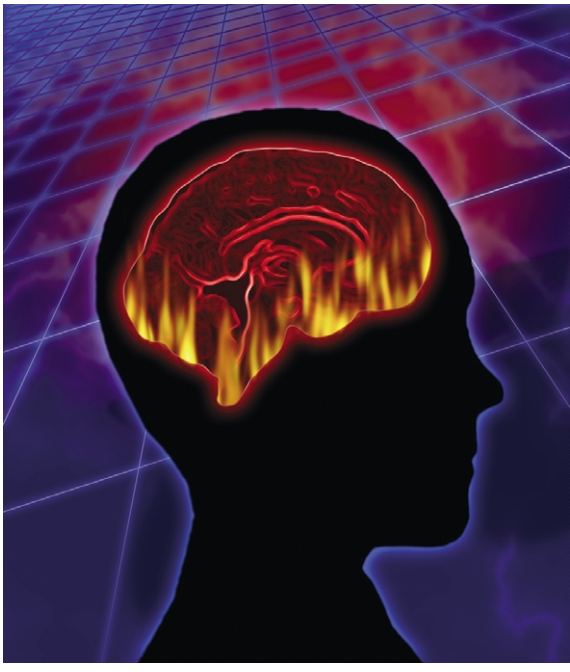
'These results are intriguing and are directly analogous to recent discoveries with minocycline, another anti-bacterial drug in routine human use. This is currently undergoing investigation in Parkinson's disease (PD) for possible neuroprotective effects after promising results in PD animal models,' comments Peter LeWitt, Professor of Neurology at the Clinical Neuroscience Center, Wayne State University School of Medicine (Southfield, Michigan USA). LeWitt regards the study as the culmination of a new type of drug discovery research. 'This finding was not generated by a hypothesis derived from overall understanding of metabolic pathways or major themes of neurodegeneration. It came instead from carefully cataloguing the 'random hits' of various drugs capable of altering genetic expression in ways that can meet therapeutic goals,' he explains.

In vitro* and *in vivo

Rothstein and colleagues followed up their identification of GLT1 stimulators and found that Ceftriaxone was neuroprotective in *in vitro* models of ischaemic injury and motor neuron degeneration. Also, the drug delayed loss of neurons and muscle strength and increased mouse survival in an animal model of amyotrophic lateral sclerosis (ALS). Avital Schurr (Brain Attack Research Laboratory, Department of Anesthesiology, University of Louisville School of Medicine, Louisville, KY, USA) agrees that the study is an excellent one. 'It shows very clearly the advantages of employing both *in vitro* and *in vivo* approaches when screening multiple drugs for their neuroprotective potential,' he says. However, he warns that 'the damaging contribution of this excitatory amino acid during episodes such as cerebral ischaemia is only one factor in a multifactorial brain disorder. Minimizing the damaging effect of glutamate on the ischaemic brain may offer partial protection, but neutralizing its effects cannot be expected to become a 'silver bullet' in brain protection,' he says.

Clinical trials likely

Schurr anticipates a retrospective study to evaluate the neuroprotective potential of β-lactam antibiotics among patients who experienced an ischaemic event while being on one of those drugs. 'Such patients may have exhibited an overall reduction in neurological deficits compared to their cohorts not on β-lactam antibiotics,' he says. This could happen but a clinical trial has already been planned. 'This was done soon after we had our results, the grant was submitted and funding obtained from the National Institutes of Health; the trial is due to start this spring or summer,' reports Rothstein.



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