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Branching out into mix-and-match drug delivery

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Researchers report that dendrimers with single functionalities can be combined together through self-annealing oligonucleotide bridges to form dendrimer clusters with multiple functionalities [1]. This approach, explains James Baker, Ruth Dow Doan Professor of Biologic Nanotechnology at the University of Michigan, Ann Arbor, USA and Chief Science officer of NanoCure, 'means that if you need to deliver drug A to cells carrying receptor X, you can take a dendrimer with a targeting molecule for this receptor and link it to a dendrimer carrying the drug without the need for complicated chemistry.'

Drug delivery in the biotech era

Researchers are constantly trying to design better ways to deliver drugs, particularly drugs based on proteins, DNA and RNA, to their specific target. Polymer therapeutics, in which small-molecule drugs or biotech drugs are linked to artificial polymers, are looking particularly hopeful, with some examples of this type of drug delivery system already entering clinical trials [2].

Among the polymers being investigated for drug delivery are dendrimers – well-defined, water-soluble tree-like molecules [3]. 'Therapeutic agents can be encapsulated within the dendrimer,' explains Mary Cloninger, Professor of Bioorganic and Macromolecular Organic Chemistry at Montana State University, Bozeman, USA. But, because controlled drug release in such non-covalent systems is difficult to achieve, a second approach in which pro-drugs are covalently attached to the dendrimer surface is also being investigated, says Cloninger.

In this approach, multiple functionalities can be attached to the same dendrimer. For example, Baker's team has designed an anti-cancer polyamidoamine (PAMAM) dendrimer in which targeting is achieved through covalent addition of folic acid – tumour cells tend to express more folate receptor than normal cells – and cell killing is produced by the addition of methotrexate. This dendrimer, says Baker, should be tried in patients within two years.

Mix-and-match

Although the single polymer approach is progressing well, 'with each additional chemical synthesis step used on a single dendrimer, the technical problems, including decreased water solubility, low yields, and steric interference of attached functional groups, increase,' says Baker. Furthermore, for each targeting molecule–drug combination a new polymer has to be made. A more adaptable approach, he says, is to have libraries of dendrimers, each with a single functionality, that can be combined as clinically required.

To achieve this flexibility, Baker's team has synthesized two PAMAM dendrimers – one conjugated to folic acid and the other to a fluorescein marker – and then added a complementary oligonucleotide to each dendrimer. 'We simply bring the mixture of dendrimers up to annealing temperature and allow the oligos to link together to form a multifunctional dendrimer cluster,' says Baker. *In vitro* proof-of-principle experiments indicate that the linked dendrimers specifically bind to tumour cells expressing folate receptor and become internalized [1,4].

'This is a new and interesting approach to combining dendrimers with different functionalities,' says Peter Heegaard, Senior Scientist at the Danish Institute of Food and Veterinary Research, Copenhagen, Denmark. 'However, although dendrimers are well-suited to drug delivery, there are some toxicity problems that have to be solved before they can be used clinically.'

Yingjuan Lu, principal scientist at Endocyte, a West Lafayette-based company developing receptor-targeted therapeutics, is also encouraged by Baker's approach. 'There are several folate molecules on the targeting dendrimer so this construct has good binding affinity to tumour cells *in vitro*,' she notes. The next step, she adds, is to test the targeting specificity of these dendrimer clusters *in vivo* and their ability to kill tumours if fluorescein is replaced by an active drug.

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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.

References

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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

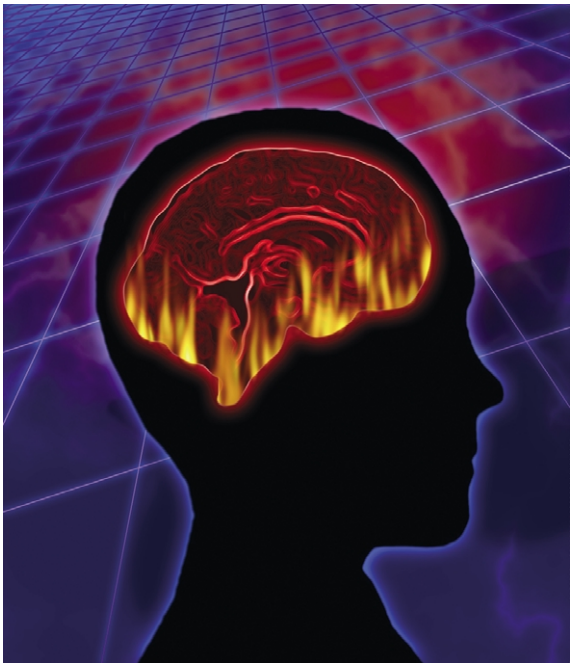
'These results are intriguing and are directly analogous to recent discoveries with minocycline, another anti-bacterial drug in routine human use. This is currently undergoing investigation in Parkinson's disease (PD) for possible neuroprotective effects after promising results in PD animal models,' 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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