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Immunotherapy for Parkinson's disease: a developing therapeutic strategy

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Researchers at the University of California, San Diego, USA, and at Elan Pharmaceuticals, South San Francisco, USA, report that vaccination against abnormal α-synuclein could provide a new approach to the treatment of Parkinson's disease (PD) [1]. 'Because α-synuclein is an intracellular protein, many people thought that antibodies produced by vaccination would not see the abnormal protein,' says lead academic researcher and Professor of Neurosciences and Pathology Eliezer Masliah. 'But we found that antibodies produced in a mouse PD model by immunization with human α-synuclein both recognized abnormal α-synuclein associated with neuronal membranes and targeted it for destruction through the lysosomal degradation pathway.' These results, notes Elan's Chief Scientific Officer and co-author Dale Schenk, 'offer a new and unexpected strategy for the treatment of PD' although any clinical application is likely to be some years down the line.

A new ally in fight against PD

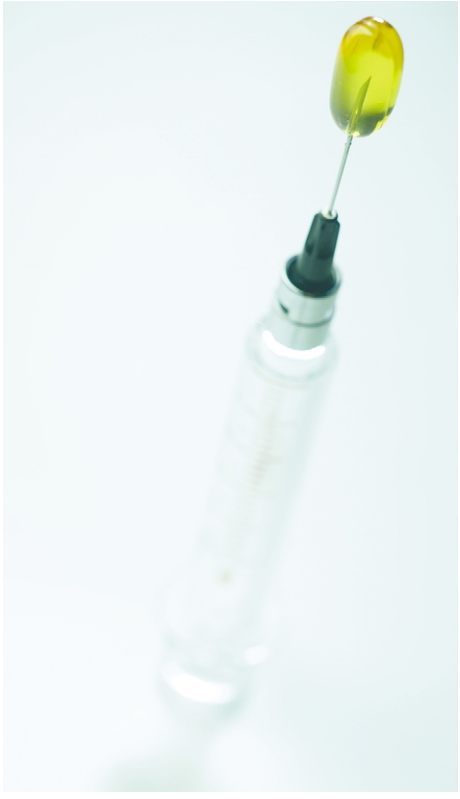
PD is a common neurodegenerative disease caused by the progressive loss of dopaminergic neurons in the substantia nigra. Currently, patients are treated symptomatically but ways to treat the root cause of PD are badly needed. Recent discoveries indicate that the aggregation of soluble α-synuclein into insoluble fibrils lies at the heart of the PD pathological process. These fibrils accumulate in Lewy bodies, the pathological hallmark of PD and other Lewy body diseases. 'We already had experience of using vaccination to treat Alzheimer's disease,' explains Schenk (Elan and Wyeth, Madison, USA, are currently undertaking Phase II clinical trials of passive immunization against beta amyloid), 'so it seemed logical to consider immunization against α-synuclein as a way to tackle PD.'

'This is a unique approach that targets a critical event in the pathogenesis of PD'

When the researchers vaccinated mice transgenic for human α-synuclein, an animal model for PD, with human α-synuclein, the production of relatively high-affinity antibodies reduced the accumulation of aggregated human α-synuclein in neuronal bodies and synapses [1]. The researchers now plan to investigate whether passive immunization with antibodies raised against α-synuclein has similar effects; it might be better to avoid active immunization in a clinical setting, says Masliah, as it might trigger an inflammatory response in the brain.

'This is a unique approach that targets a critical event in the pathogenesis of PD', comments Howard Gendelman, Director of the Center for Neurovirology and Neurodegenerative Disorders at the Nebraska Medical Center, Omaha, USA. However, he cautions, many hurdles must be overcome before clinical applications of the approach can be considered. Overcoming these hurdles will require, among other things, broader analyses of immune system responses to vaccination and the testing of antibody responses in other models of PD.

Anne Messer, Director of the Molecular Genetics Program at the Wadsworth Center, New York State Department of Health, Albany, USA, also describes the Neuron paper as 'intriguing' but notes that in her experience



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with plasmid immunization against huntingtin, the pancreas was more effectively cured than the brain in an animal model of Huntington's disease. 'Before immunization against α-synuclein can be studied clinically,' she notes, 'we need to understand exactly how the antibodies get into the brain.'

Other immunotherapies for PD

Messer and Gendelman have their own approaches to immunotherapy for PD. Messer is developing intrabodies – intracellular antibody fragments that alter the folding or interactions of their target proteins [2] – against α-synuclein. 'So far, we have only tested these intrabodies in tissue culture', she explains, 'and we still need to optimize them before moving into animal models.' However, she is hopeful that the approach will work given that intrabodies against huntingtin partly rescue a *Drosophila* model of Huntington's disease [2].

Gendelman is using immunotherapy to tackle the inflammatory activities associated with PD. 'Like any injury,' he explains, 'neuronal destruction triggered by α-synuclein aggregation drives an immune response that can be deleterious.' Gendelman is trying to control this unwanted side of the immune response in an animal model of PD by using copolymer 1 to affect specific T-cell responses [3].

Harnessing the specificity and the power of the immune system to deal with PD and other neurodegenerative diseases is extremely appealing and potentially valuable, comment both Gendelman and Messer. 'The cancer people have been doing it for 20 years but neuroscientists are only now realising the potential', says Messer. Indeed, interest in immunotherapy for PD is now such that a special session will cover current research at the World Parkinson Congress next year (Feb 22-26, 2006, Washington, DC, USA).

References

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Drugs tailored to race move a step closer to reality

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On June 23, the FDA approved the use of BiDil (Nitromed, Lexington, MA, USA), an orally administered nitric oxide enhancer, for the treatment of heart failure – but only in African Americans. The decision follows the unanimous endorsement of the drug for a limited market by an expert advisory committee a week earlier.

Positive trial results

In 2004, a Phase III trial of BiDil involving involved 1050 African American patients with moderately severe or severe levels of heart failure was halted early because of a significantly higher mortality rate in the placebo group. Patients taking the drug benefited from a 43% reduction in the rate of death from any cause and a 33% relative reduction in the rate of first hospitalization for heart failure. The greater effect seen in African Americans is thought to be due to nitric oxide. Blacks generally have a deficiency of nitric oxide compared with non-African Americans and this plays a greater role in the etiology of their heart failure. BiDil, a fixed dose combination of isosorbide dinitrate (a nitric oxide donor) and hydralazine (an antioxidant and vasodilator agent that protects the nitric oxide formed).

> 'No other drugs ... have been approved as race-targeted'

Race and drug response

'No other drugs, to my knowledge, have been approved as race-targeted' comments Guilherme Suarez-Kurtz (Head of Research at the Division of Pharmacology, Instituto Nacional de Cancer, Rio de Janeiro, Brazil). Differences in clinical effectiveness across population groups have been suggested for other drugs, for example, the antihypertensive losartan (Cozaar®), which carries a warning that its benefits 'do not apply to black patients with hypertension and left ventricular hypertrophy failure… although the blood pressure of black patients is effectively reduced', adds Suarez-Kurtz. Enalapril, known commercially as Vasotec, an ACE inhibitor, also carries a warning that it has less effect on blood pressure in black patients than in non-blacks.

Should race be considered?

So, is developing drugs tailored to work in different ethnic populations viable? 'This question assumes that the criteria used for ethnic categorization parallel biological differences pertinent to drug response, and this is not true', warns Suarez-Kurtz. For example, the Latino or Hispanic category in the US includes several population groups, and a recent study [1] showed that Puerto Ricans and Mexican Americans, the two largest Latino 'ethnic' groups, differ significantly in their response to the bronchodilator drug albuterol and also in the polymorphisms of the β2-adrenergic receptor, which is the target for albuterol´s beneficial effects in asthma. 'The clinical consequences suggest that Mexicans and Puerto Ricans should be considered as separate groups in future drug trials and pharmacogenetic studies of asthma', he says.

The prevalence of the genetic polymorphisms that affect drug response varies across populations but it is extremely

1359-6446/05/$ – see front matter PII:S1359-6446(05)03563-4