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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

1 Masliah, E. *et al.* (2005) Effects of α-synuclein immunization in a mouse model of Parkinson's disease. *Neuron* 46, 857–868

2 Miller, T.W. and Messer, A. (2005) Intrabody applications in neurological disorders: progress and future prospects. *Mol. Ther.* DOI: 10.1016/j.ymthe (Epubn ahead of print; http://www.asgt.org/member_resources/moleculartherapy.shtml)

3 Benner, E.J. *et al.* (2004) Therapeutic immunization protects dopaminergic neurons in a mouse model of Parkinson's disease. *Proc. Natl Acad. Sci. U. S. A.* 101, 9435–9440

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

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rare for a given polymorphism to be exclusively present or absent in one of the three most-studied continental populations - African, Asian and European. 'In most cases of documented interethnic pharmacogenomic differences, the mean difference between any two populations is substantially smaller than the variation among individuals comprising these populations', explains Suarez-Kurtz. Recognition of interethnic differences in drug response might be useful in the establishment of public health policies and in the design and interpretation of clinical trials. 'More, questionably, such information may also guide clinicians to prospectively evaluate those patients with the greatest probability of expressing a variant genotype', he concludes.

Reference

1 Choudhry, S. *et al.* (2005) Pharmacogenetic differences in response to albuterol between Puerto Ricans and Mexicans with asthma. *Am. J. Respir. Crit. Care Med.*, 171, 563–570

Anticoagulation therapy for stroke

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Anti-clotting drug warfarin might reduce the risk of stroke by more than two-thirds in patients with atrial fibrillation, a condition that puts patients at high risk of stroke, according to US researchers. 'These data suggest that the beneficial effect of warfarin therapy exists not only for patients experiencing atrial fibrillation but also for patients who have a history of atrial fibrillation but who are presumably in sinus rhythm', wrote the team led by David Sherman, University of Texas Health Science Center, San Antonio, USA.

Continued stroke risk

'Anticoagulation therapy should be maintained in patients who have a history of atrial fibrillation and risk factors for stroke, even when the recurrent atrial fibrillation has not been documented', they said in the study published in the *Archives of Internal Medicine*. A large multi-centre study of the two treatments for atrial fibrillation, rate control or sinus rhythm control therapy, found no difference in the risk of death for patients treated with either therapy.

Treatment with warfarin was included in both therapies, although patients in the sinus rhythm control group could stop warfarin after at least four weeks of maintained sinus rhythm while receiving an anti-arrhythmic drug. Patients in atrial fibrillation at the time of stroke had a 60% greater chance of having an ischemic stroke and those taking warfarin at the time of follow up had a 69% decreased risk of an ischemic stroke, found the study.

'Elderly patients who have experienced atrial fibrillation... should be anticoagulated with warfarin regardless of their current rhythm.'

British Heart Foundation Medical Director, Professor Peter Weissberg said the fact that warfarin prevents stroke in atrial fibrillation is well established. 'The surprising finding in this study is that even when the patients were thought to have been returned permanently to normal rhythm, they still had a risk of stroke that was reduced if they continued warfarin', said Weissberg.

'The study suggests that in elderly patients who have experienced atrial fibrillation, they should be anticoagulated with warfarin regardless of their current rhythm. This would require many more patients than is currently the case taking warfarin into old age', he added.

Atrial fibrillation

Atrial fibrillation is an abnormal heart rhythm in which the upper two chambers of the heart beat faster than normal. This can cause unpleasant palpitations and breathlessness. The blood is not pumped out of the heart as well as it should be and can pool and clot. If the blood clot leaves the heart it can lodge in an artery in the brain, causing a stroke.

The team assessed the occurrence and characteristics of strokes in 4060 patients in both treatment groups in the follow-up to the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) study, ranging from two to six years. 211 patients had a stroke, of which 157 had an ischemic stroke, 34 had a primary intraparenchymal haemorrhage, and 24 had a subdural or subarachnoid haemorrhage.

They analyzed the relationship of several variables for risk of ischemic stroke, which is caused by decreased blood flow to a part of the brain, most commonly due to narrowing of blood vessels or an embolism. 84% of the rate control patients and 52% of the sinus rhythm control patients received warfarin throughout the study. 211 patients (8.%) had a stroke event. Ischemic stroke (6.3%) was the most common type. The researchers found seven variables were significantly associated with risk of stroke, including increasing age, female gender, the episode of atrial fibrillation, which qualified the patient for the study lasting two or more days, a history of stroke or TIA (mini-stroke), and a history of diabetes.

The presence of atrial fibrillation was associated with a 60% increase in risk of having an ischemic stroke and the use of warfarin was associated with a 69% decrease in stroke risk. Weissberg said the study pointed to the need for a new prospective trial to provide a definitive answer as to whether warfarin should be continued in patients who have returned to normal rhythm. 'It is important to confirm the findings of the present study before changing treatment policy since warfarin treatment carries substantial risk of bleeding problems, and if adopted outside the carefully monitored environment of a clinical trial, could lead to a lot of problems'.

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