

EDITOR'S CHOICE

HUNTINGTON'S DISEASE: new cells for old

The role of neural stem cells in neurodegenerative disorders has been something of a passion of mine for many years, as abnormalities in this process may have important implications for therapy both in terms of innate repair and exogenous cell transplants in disorders of the CNS. Furthermore, understanding the processes of neurogenesis in diseased brains may also provide us with a better understanding of abnormal signalling pathways involved in disease pathogenesis. This new paper from the van der Kooy group raises some very interesting questions on how disease processes may influence stem cell behaviour in one of the neurogenic regions of the adult brain (the subventricular zone [SVZ]) in the R6/2 transgenic mouse model of Huntington's disease. They report that in this mouse, which contains the expanded exon 1 CAG repeat of human Huntington's disease gene:

1. There is an increase in neural precursor cell/neurospheres generated from the SVZ in R6/2 mice compared to wild type with increasing age and the development of symptoms.
2. There is an increase in BrdU in the SVZ 30 days after injection in the R6/2 mice compared to the wild type, implying there is an increase in stem cells at this site which is confirmed using EM and the demonstration of more precursor 'B' cells in the SVZ in the R6/2 mice.
3. There is an increase in proliferation with age which occurs *in vitro* with cloning but only at a time when such abnormalities in proliferation have been seen in the R6/2 mouse *in vivo*.
4. The increase which is seen *in vitro* is clearly primed *in vivo* and cannot be mimicked by growing early stage neurospheres for longer periods of time *in vitro*.
5. There is no change in the fate potential of the precursor cells *in vivo* or *in vitro*.
6. There is a decrease in olfactory bulb BrdU positive cells with an increase the BrdU positive cells in the striatum, suggesting a switch in migration of the stem cells to sites of more pathology.

These series of observations suggest that, with disease progression in this mouse model of Huntington's disease, there is a steady increase in the number of stem cells in the SVZ which, once primed and induced *in vivo*, is maintained *in vitro*. This suggests that the stem cell changes its properties with the evolving disease process in the brain. This would therefore imply that, in neurodegenerative disorders of the CNS, there are signals that cause a fundamental switch in the properties of proliferating neural stem cells which attempts to compensate for the pathology. Obviously if this process can be properly harnessed, then it will have important implications for CNS repair, but the key question remains as to what that signal is and how can we manipulate it to effect better repair in conditions such as Huntington's disease. - **RAB**

Batista CM, Kippin TE, Willaime-Morawek S, Shimabukuro MK, Akamatsu W, van der Kooy D.

A progressive and cell non-autonomous increase in striatal neural stem cells in the Huntington's disease R6/2 mouse.

JOURNAL OF NEUROSCIENCE

2006;26:10452-60.

HUNTINGTON'S DISEASE: up and down or side to side?

Huntington's chorea is characterised by cognitive decline and chorea, but patients often display other deficits, including abnormalities of eye movement. Blekher et al have carried out a detailed and sensitive series of oculomotor tests in a group of patients with HD. Clinical evaluation was carried out using the standardised clinical rating scale UHDRS (Unified Huntington's Disease Rating Scale). The study included 215 individuals grouped into four classes depending on the presence or absence of motor abnormalities representative of HD. All the individuals in this study had a parent affected with HD and followed one of two patterns: they were either at risk of HD but not yet diagnosed or they had been diagnosed with HD within the past two years. Both vertical and horizontal saccadic readings were recorded using a video eye tracking system. Eye movement measures included visually-guided, anti-saccade, predictable, memory-guided (two versions) and fixation tasks. None of the participants reported significant eye problems and all had normal or corrected visual acuity. The authors showed that HD

gene carriers – but not nongene carriers – had impaired saccades and were particularly poor in anti-saccade and memory-guided tasks, and this when standard clinical assessments currently used in HD were normal. The improved sensitivity provided by these quantitative saccadic measures may open a new chapter in the diagnosis of disease onset and also may enable researchers to ascertain whether disease modifying therapies are just that. - **CA**

Blekher T, Johnson SA, Marshall J, White K, Hui S, Weaver M, Gray J, Yee R, Stout JC, Beristain X, Wojcieszek J, Foroud T.

Saccades in presymptomatic and early stages of Huntington disease.

NEUROLOGY

2006;67:394-9.

STROKE: a pit of vipers

If you get bitten by a Malaysian pit viper, you may bleed to death. A key component of the venom is Ancrod which splits fibrinopeptide A from fibrinogen. Ancrod has been used in several trials as a treatment for ischaemic stroke. The previous North American Stroke Treatment with Ancrod Trial (STAT) showed that Ancrod outperformed placebo if given within three hours of a stroke. This study looks at its ability to improve stroke outcome if given later, within six hours. The result, perhaps unsurprisingly given what we know of TPA, is that later treatment is not beneficial. Normally such a pedestrian study would not make it onto the review pages of *ACNR*, but it is the vipers in the last paragraph of the report that merit attention:

"Preliminary data from this trial were first presented at the World Federation of Neurology Congress in London in 2001. Soon thereafter, the sponsor company, which was always supportive of the scientific outcomes of this trial, was sold. In the meantime, data from the study were not fully available to the investigators, and further analysis was difficult. Only with the support of many dedicated investigators and after careful reassessment of the material finally provided, could the members of the executive and safety committees prepare this report on behalf of the investigators. This situation illustrates the understandable but often regrettable divergences between sponsor and investigators' interests, leading to scientific losses and unethical waste of patients' and investigators' efforts. The bias towards easier publication of successful trials, sometimes at too early a stage, is another important issue to consider: the publication of this report is therefore an important recognition of the scientific and medical value of all clinical trials."

The moral is that it is critical that investigators have free access to data accumulated in their trial. It has always amazed me that some investigators are prepared to work in any other way. - **AJC**

Hennerici MG, Kay R, Bogousslavsky J, Lenzi GL, Verstraete M, Orgogozo JM; ESTAT investigators.

Intravenous ancrod for acute ischaemic stroke in the European Stroke Treatment with Ancrod Trial: a randomised controlled trial.

LANCET

2006 Nov 25;368(9550):1871-8.

PARKINSON'S DISEASE: First gene therapy trial

This very short abstract buried at the back of an issue of *Movement Disorders* is one that was presented at the 20th Annual Symposium on the Aetiology, Pathogenesis and Treatment of Parkinson's Disease and Other Movement Disorders. This gives a very brief account (as one would expect) on 12 patients who have received open label unilateral subthalamic viral vector (AAV-GAD) injection as a treatment for their Parkinson's disease. This open label study involves 12 patients with an average age of 58.2 years and in this abstract the authors report on their FDG PET studies using this approach. The strategy involves trying to convert the excitatory subthalamic nucleus to an inhibitory one by changing the phenotype of the projection neurons from this structure and builds on earlier experimental work reported in *Science* in 2002 (see *ACNR* 2.5). Five patients appeared to respond to this virally delivered therapy and seven did not. In those that responded, there were clearly changes in FDG metabolism as one would anticipate, namely a decline in the internal globus pallidum and ventral lateral thalamus ipsilateral to the delivery of the viral vector and increased metabolism in the premotor and supplementary motor regions. These changes appear to correlate with improvements in their UPDRS scores. Whilst this is an abstract, it is important because this is the first ever gene therapy trial in Parkinson's disease and clearly gives us hope that this approach may have a future. - **RAB**

Feigin A, Tang C, Doring M et al.

Gene therapy for Parkinson's disease with subthalamic nucleus AAV-GAD: FDG PET results.

MOVEMENT DISORDERS

2006;21:1543-4.

