The benefits of using sheep to model human brain disease

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At present there are no cures for the majority of neurodegenerative disorders of the brain. The ability to study these diseases in animal models allows not only for the elucidation of underlying disease mechanisms but also for the development of effective treatments and- track treatments and therapies for Huntington's Disease (HD) into the clinic.

Huntington's Disease is an inherited late-onset neurological disorder of variable clinical onset but characterised by motor dysfunction, cognitive decline and in some cases severe emotional disturbance. The disease leads inexorably to death some 15–20 years after symptom onset. HD results from an excessive repetition of CAG trinucleotide codons in exon 1 near the 5' end of the IT15 transcript ("interesting transcript 15") gene (4p16.3), which encodes a novel protein called *huntingtin* (HDRCG 1993). Normal individuals have a polyglutamine tract containing 8-39 CAG repeats, whereas HD patients have greater than ~36 (Snell et al. 1993), with the age of onset negatively correlated with repeat length; the greater the number of CAG repeats the earlier the age of onset . The neuropathology of HD is characterised by a striking specificity of degeneration of GABAergic neurons localised mainly to the caudate nucleus and putamen, with the chorea and dementia being related to degeneration of subsets of striatal and cortical neurons respectively (Tippett et al. 2007).

Slow disease course, insidious onset and patient-to- patient variability make human drug trials difficult, requiring many people to be treated for years in order to have statistically significant and clinically relevant outcomes. A precise sheep model could lead to improvements in clinical trials thereby decreasing the risk of late, expensive failures in drug trials. It could also provide an alternate research resource for the

investigation of underlying mechanisms in HD and triplet repeat disorders. Sheep were chosen to model this disease because of their comparable brain structure to that of the human, relatively large body mass to assist with pharmacokinetics, and an extended life span as compared to rodents allowing later disease onset. These features are particularly important for trialling pre-symptomatic treatments.

Using microinjection techniques we generated six founding animals expressing the full length human HD cDNA with 73 CAG repeats. All the animals were kept in Australia in their natural environment. Each animal was chipped, tagged and docked as per normal farming procedure. The docked tails were subsequently taken for analysis. All six animals showed expression of the gene at varying levels, and all showed a single integration site which is advantageous for the genetics of transmission. Four of the founding animals have been bred, with one of the lines (line 4) into the third generation. Preliminary results from offspring from line 4 at seven months of age indicated there to be some changes in the brain that are reminiscent of the human disease. Further analysis of animals at 18 months of age is currently under way, as is the analysis of animals from the remaining lines.

The ability to accurately mimic the human disease in a large animal model could lead to new opportunities for improvements in therapeutic protocols before clinical trials, and so provide a better future for patients of families afflicted by this tragic disease.

References

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