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JOURNAL OF HUNTINGTON'S DISEASE

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# Large Animal Models of Huntington's Disease Offer New and Promising Research Options

## Sheep, Minipigs Offer Potential Advantages Over Rodents, According to *Journal of Huntington's Disease* Studies

Amsterdam, NL, XX April 2013 – Scientific progress in Huntington's disease (HD) relies upon the availability of appropriate animal models that enable insights into the disease's genetics and/or pathophysiology. Large animal models, such as domesticated farm animals, offer some distinct advantages over rodent models, including a larger brain that is amenable to imaging and intracerebral therapy, longer life-span, and a more human-like neuroarchitecture. Three articles in the latest issue of the *Journal of Huntington's Disease* discuss the potential benefits of using large animal models in HD research and the implications for the development of gene therapy.

A review by Morton and Howland explores the advantages and drawbacks of small and large animal models of HD. In the same issue, Baxa *et al.* highlight the development of a transgenic HD minipig that expresses a human mutant HTT fragment through the central nervous system (CNS) and peripheral tissues in a heritable fashion and manifests neurochemical and reproductive changes with age. In another report, Van der Bom and colleagues describe a technique created with CT and MRI that allows precise intracerebral application of therapeutics to transgenic HD sheep.

Huntington's disease (HD) is an inherited progressive neurological disorder for which there is presently no cure. It is caused by a single dominant gene mutation – an expanded CAG repeat in the HTT gene - leading to expression of mutant huntingtin (HTT) protein. Expression of mutant HTT causes subtle changes in cellular functions, which ultimately results in jerking, uncontrollable movements, progressive psychiatric difficulties, and loss of mental abilities.

The search for new large animal models of HD arises from recognition of some of the practical limitations of rodent and other small animal models. Because neurodegenerative diseases like HD progress over a lifetime, a rodent's short life span excludes the possibility of studying long-term changes. There are also important anatomic differences between the brains of humans and rodents that become especially relevant when studying HD, including the lack of a gyrencephalic (convoluted) cortex, the structure of the basal ganglia, and lack of neuromelanin in the substantia nigra. A rodent's small brain often precludes the use of advanced neuroimaging techniques and it is not clear how intracerebral application of trophic factors, transplant therapies, and gene therapies in small animals might translate to the larger human brain.

"Importantly, these large animal models are being studied for disease phenotypes using sensitive measures that should be highly translatable to the human condition, including MRI and PET imaging, EEG, electrophysiology, molecular analyses including RNAseq, in addition to tests looking at motor

and cognitive function," says Professor A. Jennifer Morton, PhD, of the department of physiology, development and neuroscience at the University of Cambridge. "Moving to larger brained animal models after promising results are obtained in rodents, is a logical (and possibly necessary) step for optimizing delivery and biodistribution, validating on-target mechanism of action, and assessing safety profiles," says Dr. Morton.

As far as non-human primates, there are HD transgenic monkeys but this model faces hurdles such as limited availability, high cost (for purchase and maintenance), and a low rate of infant viability. In addition, there could be practical and ethical challenges arising from keeping a monkey with motor, cognitive, and psychiatric issues for long term, comments Dr. Morton.

Large domesticated farm animals offer some distinct advantages as models of HD. Sheep, for example, are domesticated, docile, live outdoors, are easy to care for, and economical to maintain. A sheep's brain is 50% larger than a monkey's, is gyrencephalic, and has a distinct caudate and putamen. Sheep live long enough to develop progressive neurological diseases and a number of lines of transgenic HD sheep have been developed. HD transgenic sheep express huntingtin protein in the brain and abnormal HD-associated neurochemical changes. These HD sheep have been subject to advanced genomic techniques, and because they carry a human transgene that is expressed at both an mRNA and protein level, they are seen as suitable for testing gene therapy-based reagents directed against human HTT. A further advantage, says Dr. Morton, is that "although sheep have a reputation for being stupid, this is probably undeserved … they have good memories and are capable of learning and remembering new tasks."

In order to advance the use of the HD sheep model, I.M.J. van der Bom, PhD, from the department of radiology at the University of Massachusetts, and colleagues developed a multi-modal technique using skull markings seen with CT imaging and brain anatomy from MR imaging to allow more precise placement of intracerebral cannulae into sheep brain. The technique addresses such potential problems as the tendency for sheep to regurgitate cud and aspirate (which makes anesthesia challenging), develop hyperthermia, and have ear anatomy not conducive to stereotactic placement. With this technique, the authors hope to study the extent of optimal safety, spread and neuronal uptake of adeno-associated virus (AAV) based therapeutics.

"Pigs, and mainly minipigs, represent an optimal model for preclinical drug trials and long-term safety studies," says Jan Motlik, DVM, PhD, DSc, from the Laboratory of Cell Regneration and Plasticity of the Institute of Animal Physiology and Genetics in Libechov, Czech Republic. Advantages include its large brain size and long lifespan. Genetic advances have been made, including defining the porcine genome, with a 96% similarity between the porcine and human huntingtin genes. In addition to well-established methods for pig husbandry, they are economical and have body systems very similar to that of humans.

In the report by Baxa *et al.*, a new HD minipig model is described, using lentiviral infection of porcine embryos. The authors report that they successfully developed a heterozygote transgenic HD minipig that expresses a human mutant HTT fragment throughout the CNS and peripheral tissues through 4 successive generations. The model produces viable offspring, with a total neonatal mortality rate of 17%. The authors reported that one affected HD minipig showed a decline beginning at 16 months of a neuronal phosphoprotein, DARPP32, in the neostriatum, the brain region most affected by HD. A loss of fertility, possibly HD related, was also found.

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**NOTES FOR EDITORS**

"Large Genetic Animal Models of Huntington's Disease," by Jennifer Morton and David S. Howland. DOI 10.3233/JHD-130050.

"A Transgenic Minipig Model of Huntington's Disease," by Monika Baxa, Marian Hruska-Plochan, Stefan Juhas, Petr Vodicka, Antonin Pavlok, Jana Juhasova, Atsushi Miyanohara, Tetsuya Nejime, Jiri Klima, Monika Macakova, Silvia Marsala, Andreas Weiss, Svatava Kubickova, Petra Musilova, Radek Vrtel, Emily M. Sontag, Leslie M. Thompson, Jan Schier, Hana Hansikova, David S. Howland Elena

Cattaneo, Marian Difiglia, Martin Marsala and Jan Motlik. DOI 10.3233/JHD-130001.

“Finding the Striatum in Sheep,” by I.M.J van der Bom, R.P. Moser, G. Gao, E. Mondo, Denice O’Connell, M.J. Gounis, S. McGowan, J. Chaurette, N. Bishop, M.S. Sena-Esteves, C. Mueller, N. Aronin. DOI 10.3233/JHD-130053.

All appear in the *Journal of Huntington’s Disease,* Volume 2/Issue 1 (April 2013), Published by IOS Press.

Full text of the article is available to credentialed journalists. Contact Daphne Watrin, IOS Press, +31 20 688 3355, d.watrin@iospress.nl. Journalists wishing to interview the authors should contact:
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