Mouse models of neurological conditions provide value when, through their use, new knowledge is generated that can be translated to an understanding of the human condition. This talk will provide background into some of the neurological mouse models, although a survey of all the models is outside the scope. I will discuss the benefits and drawbacks of mouse models with the aim of stimulating discussion in the field about the criteria for choosing and applying models. I will highlight applications of MRI and MRS, and I will include data on advances in molecular imaging and cell tracking (eg, but not inclusive,[13; 27; 34]). There will be some pretty MRI's!

The first step in pre-clinical research is choosing the correct model for the correct question. Animal model research falls largely into 3 types of studies: one is to identify MRI methods that are sensitive and specific to a disease and disease progression (eg development of molecular imaging); a second is to increase our understanding of the disease itself (physiological, biochemical processes); and the third is to use the model for research into treatment options (diet, drugs, etc). Be clear on your goals.

There is a wealth of information on neurological mouse models. In stroke, the models have played a key role in identifying the pathology and the changes in tissue over time[22] They tend to fall into two types. One is that of a normal background strain with a surgical intervention to block the vasculature[13] and the second is where a mouse variant is used to target the impact of manipulating a specific metabolic or organ system.[12] The role of MRI in such animal studies is extensive, and recently reviewed.[14]

Alzheimer's mouse model research plays a major role in studying the specific metabolism associated with tauopathies,[15] and the linkage with human amyloid precursor protein and beta-amyloid metabolism,[11] This research field has benefited greatly from the ability to create transgenic mouse models.[4; 19] Models are used to argue that other aspects of metabolism may be involved, including mitochondrial damage. [21] More recently, model types are being combined, such as linking insulin resistance models with traditional AD models.[10] MRI is often used to detect plaque load.

Multiple sclerosis models have been used to study demyelination, remyelination and inflammation. We recently reviewed many MS models, and the application of MR imaging in MS model research.[24; 25]

The recent increase in attention to mild traumatic brain injury and concussion has led to an increase in activity in this area. The mouse is not the main animal model, but as with other disorders its use will increase as attention to specific genetic or metabolic questions increases.[20]

As noted above, this talk can only skim the surface with respect to the wide range of models available but the literature contains a wealth of information on models covering a range of disorders in including Alzheimer's, Huntington's, Parkinson's, frontotemporal lobar degeneration[9] and psychiatric disorders. The Chakragati mouse mimics aspects of schizophrenia.[6; 33] Some drug exposure and hypercorticosteroids can also mimic aspects of psychiatric disorders, as has been reviewed.[28]

Animal models are critical for drug development and there are many excellent examples in this area concerning the use of animal models in drug discovery. For instance, there is copaxone in multiple sclerosis. [3032] Another is the pipeline of drug development in Alzheimer's disease. [18 16] The FDA has animal use guidelines under the topic "Animal Model Qualification Program" http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284078.htm These guidelines relate to the use of animals in clinical trials themselves. Most of the pre-clinical model testing occurs before clinical trial where the pre-clincial evidence is used to justify a human study.

Genetic models are excellent in that they share the same genetic damage but, perhaps surprisingly, they rarely share the same overall phenotype. From this one can make two points. The first is a reminder that a mouse is not a human and one needs to delve into the specific changes that have occurred.[17] The second is that the knockout mouse model may not be as representative of the human

condition as one might expect. When a gene product is missing throughout development, the body will try to adapt and the extent of such adaptation will vary between species.

A discussion of how to choose and interpret animal models will be included. It is often argued that animal models are not good models of the human disease. There is some truth to this. There are many differences between a mouse and a human. One needs to be very aware of the species and environmental differences that may impact the interpretation of ones results.

Having said that, I would argue that every animal model has specific strengths. One needs to make the distinction that the animal is not a model of the disease itself, but of how a mammalian system responds when exposed to a component of the disease. One should not say, "I chose this model because it is a good model of X, where X is the human disease". Instead, one should say that they chose the model because it represented an aspect of the disease specific to that model.

In conclusion, the combination of applying imaging and molecular imaging to the study of animal disease models has already proven to be a strong research paradigm. Pre-clinical imaging studies of neurological disease models is now one of the key foundations of disease and drug discovery research.

REFERENCES

1. Adamczak, J. and M. Hoehn (2011) In vivo imaging of cell transplants in experimental ischemia. Prog Brain Res **201**: 55-78.
2. Adlard, P. A., B. A. Tran, D. I. Finkelstein, P. M. Desmond, L. A. Johnston, A. I. Bush and G. F. Egan (2014) A review of beta-amyloid neuroimaging in Alzheimer's disease. Front Neurosci **8**: 327.
3. Anthony, D. C., N. R. Sibson, M. A. McAteer, B. Davis and R. P. Choudhury (2011) Detection of brain pathology by magnetic resonance imaging of iron oxide micro-particles. Methods Mol Biol **686**: 213-27.
4. Bilkei-Gorzo, A. (2014) Genetic mouse models of brain ageing and Alzheimer's disease. Pharmacol Ther **142**(2): 244-57.
5. Bryan, K. J., H. Lee, G. Perry, M. A. Smith and G. Casadesus (2009) Transgenic Mouse Models of Alzheimer's Disease: Behavioral Testing and Considerations.
6. Dawe, G. S. and A. K. Ratty (2007) The chakragati mouse: a mouse model for rapid in vivo screening of antipsychotic drug candidates. Biotechnol J **2**(11): 1344-52.
7. Duyckaerts, C., M. C. Potier and B. Delatour (2008) Alzheimer disease models and human neuropathology: similarities and differences. Acta Neuropathol **115**(1): 5-38.
8. Franco, R. and A. Cedazo-Minguez (2014) Successful therapies for Alzheimer's disease: why so many in animal models and none in humans? Front Pharmacol **5**: 146.
9. Gama Sosa, M. A., R. De Gasperi and G. A. Elder (2012) Modeling human neurodegenerative diseases in transgenic systems. Hum Genet **131**(4): 535-63.
10. Gao, C., Y. Liu, L. Li and C. Holscher (2013) New animal models of Alzheimer's disease that display insulin desensitization in the brain. Rev Neurosci **24**(6): 607-15.
11. Hall, A. M. and E. D. Roberson (2012) Mouse models of Alzheimer's disease. Brain Res Bull **88**(1): 3-12.
12. Hossmann, K. A. (2004) Genetically modified animals in molecular stroke research. Acta Neurochir Suppl **89**: 37-45.
13. Hossmann, K. A. (2008) Cerebral ischemia: models, methods and outcomes. Neuropharmacology **55**(3): 257-70.
14. Kallur, T. and M. Hoehn (2011) Experimental stroke research: the contributions of in vivo MRI. Methods Mol Biol **771**: 255-75.
15. Ke, Y. D., A. K. Suchowerska, J. van der Hoven, D. M. De Silva, C. W. Wu, J. van Eersel, A. Ittner and L. M. Ittner Lessons from tau-deficient mice. Int J Alzheimers Dis **2012**: 873270.

16. Kitazawa, M., R. Medeiros and F. M. Laferla (2012) Transgenic mouse models of Alzheimer disease: developing a better model as a tool for therapeutic interventions. Curr Pharm Des **18**(8): 1131-47.
17. LaFerla, F. M. and K. N. Green (2012) Animal models of Alzheimer disease. Cold Spring Harb Perspect Med **2**(11).
18. Li, C., A. Ebrahimi and H. Schluesener (2013) Drug pipeline in neurodegeneration based on transgenic mice models of Alzheimer's disease. Ageing Res Rev **12**(1): 116-40.
19. Lithner, C. U., M. M. Hedberg and A. Nordberg (2011) Transgenic mice as a model for Alzheimer's disease. Curr Alzheimer Res **8**(8): 818-31.
20. Mannix, R., W. P. Meehan, J. Mandeville, P. E. Grant, T. Gray, J. Berglass, J. Zhang, J. Bryant, S. Rezaie, J. Y. Chung, N. V. Peters, C. Lee, L. W. Tien, D. L. Kaplan, M. Feany and M. Whalen (2013) Clinical correlates in an experimental model of repetitive mild brain injury. Ann Neurol **74**(1): 65-75.
21. Martin, L. J. (2012) Biology of mitochondria in neurodegenerative diseases. Prog Mol Biol Transl Sci **107**: 355-415.
22. Mergenthaler, P., U. Dirnagl and A. Meisel (2004) Pathophysiology of stroke: lessons from animal models. Metabolic Brain Disease **19**(3-4): 151-67.
23. Millington, C., S. Sonego, N. Karunaweera, A. Rangel, J. R. Aldrich-Wright, I. L. Campbell, E. Gyengesi and G. Munch (2014) Chronic neuroinflammation in Alzheimer's disease: new perspectives on animal models and promising candidate drugs. Biomed Res Int **2014**: 309129.
24. Nathoo, N., V. W. Yong and J. F. Dunn (2014) Understanding disease processes in multiple sclerosis through magnetic resonance imaging studies in animal models. NeuroImage Clinical **4**: 743-756.
25. Nathoo, N., V. W. Yong and J. F. Dunn (2014) Using magnetic resonance imaging in animal models to guide drug development in multiple sclerosis. Mult Scler **20**(1): 3-11.
26. Petiet, A., B. Delatour and M. Dhenain (2011) Models of neurodegenerative disease - Alzheimer's anatomical and amyloid plaque imaging. Methods Mol Biol **771**: 293-308.
27. Petiet, A., M. Santin, A. Bertrand, C. J. Wiggins, F. Petit, D. Houitte, P. Hantraye, J. Benavides, T. Debeir, T. Rooney and M. Dhenain (2012) Gadolinium-staining reveals amyloid plaques in the brain of Alzheimer's transgenic mice. Neurobiol Aging **33**(8): 1533-44.
28. Poole, D. S., M. S. Oitzl and L. van der Weerd (2011) MRI in animal models of psychiatric disorders. Methods Mol Biol **771**: 309-35.
29. Puzzo, D., L. Lee, A. Palmeri, G. Calabrese and O. Arancio (2014) Behavioral assays with mouse models of Alzheimer's disease: practical considerations and guidelines. Biochem Pharmacol **88**(4): 450-67.
30. Ruggieri, M., C. Avolio, P. Livrea and M. Trojano (2007) Glatiramer acetate in multiple sclerosis: a review. CNS Drug Rev **13**(2): 178-91.
31. Steinman, L. and S. S. Zamvil (2005) Virtues and pitfalls of EAE for the development of therapies for multiple sclerosis. Trends Immunol **26**(11): 565-71.
32. Teitelbaum, D., R. Arnon and M. Sela (1999) Immunomodulation of experimental autoimmune encephalomyelitis by oral administration of copolymer 1. Proc Natl Acad Sci U S A **96**(7): 3842-7.
33. Torres, G., B. H. Hallas, K. W. Gross, J. A. Spernyak and J. M. Horowitz (2008) Magnetic resonance imaging and spectroscopy in a mouse model of schizophrenia. Brain Res Bull **75**(5): 556-61.
34. Wadghiri, Y. Z., J. Li, J. Wang, D. M. Hoang, Y. Sun, H. Xu, W. Tsui, Y. Li, A. Boutajangout, A. Wang, M. de Leon and T. Wisniewski (2013) Detection of amyloid plaques targeted by bifunctional USPIO in Alzheimer's disease transgenic mice using magnetic resonance microimaging. PLoS One **8**(2): e57097.