Research Update on Ataxia-Telangiectasia Project from Queensland Institute of Medical Research (QIMR)

Professor Martin Lavin and Dr Tara Roberts

As outlined in Associate Professor Ernst Wolvetang's report we have collaborated with that group to characterise stem cells (iPSC) made from skin biopsies from A-T patients. This project is ongoing and the aim is to use compounds like betamethasone (used to treat A-T patients to improve neurological function) and anti-oxidants to maintain the variability of cerebellar-like cells generated in Ernst's laboratory.

Our major focus is on an animal model to investigate the neurodegeneration in ataxia-telangiectasia (A-T) since mouse models failed to do this we collaborated with Dr Tomoji Mashimo, Kyoto, Japan to generate two rat models which might show the neurodegeneration in the brain. One is called an $Atm^{Mis/Mis}$ generated by point mutations in the Atm gene and the second $Atm^{-/-}$ which causes a knockout of the Atm gene. An outline of the process used to make the $Atm^{Mis/Mis}$ rat appears in figure 1.

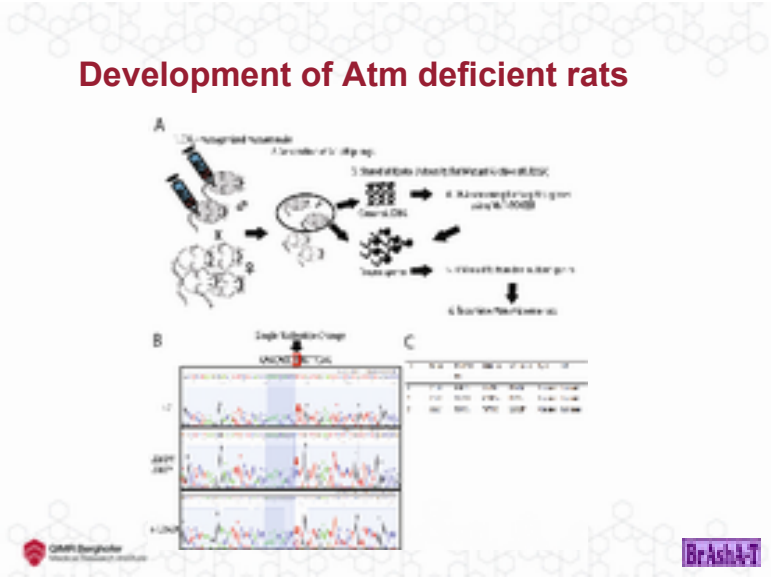

Figure 1 Making the Atm deficient rat

It shows the single nucleotide change that disrupted the Atm gene under B. We have now characterised these Atm mutant rats. The major characteristics are outlined in Fig 2.

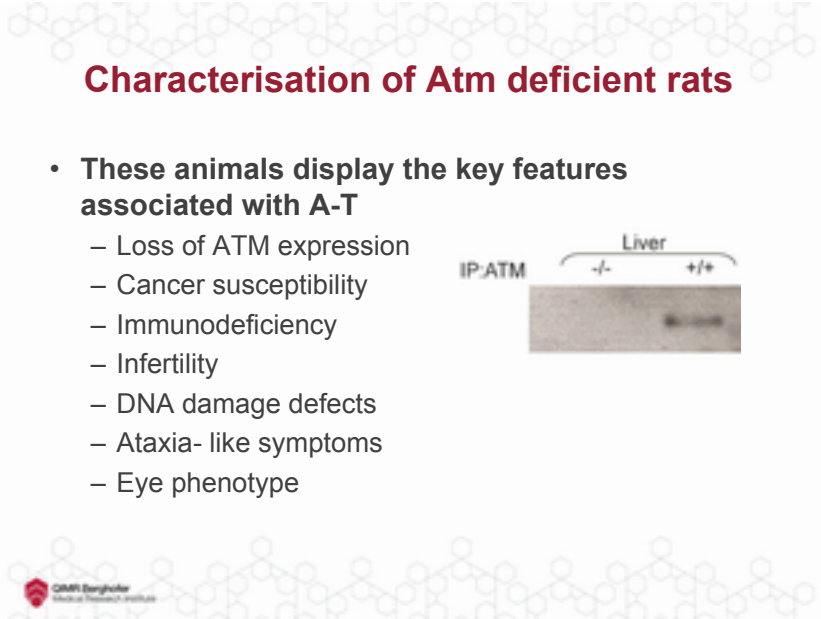

Figure 2 Characterising the Atm mutant rats

It is evident from that figure that Atm deficient rats have the major characteristics seen in the disorder in human patients. This includes ataxia-like symptoms which are described for the first time in an animal model. Pictures of Atm deficient rats displaying these symptoms appear in Fig 3. This is an exciting result since it paves the way for drug screening for compounds that have the potential to prevent or slow the disease in patients.

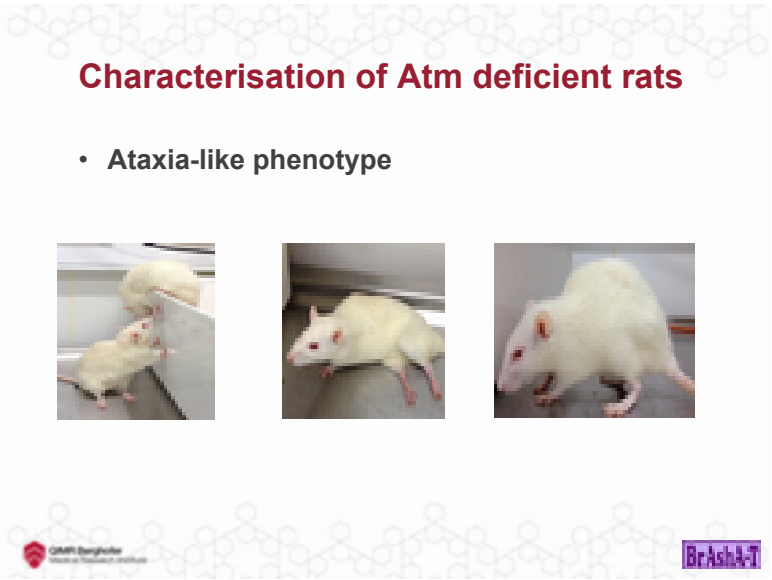

Figure 3 Pictures of Atm deficient rats

We have also observed what we call an “eye phenotype” in Atm mutant rats (Fig 4).

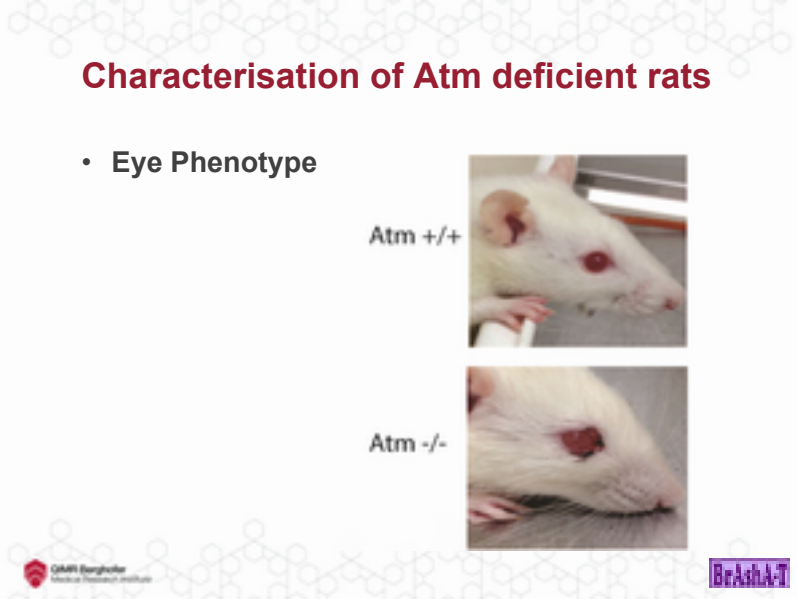

Figure 4 Eye phenotype in Atm mutant rats

The animal in the bottom part of the Figure shows a defect centred around the eye. This condition does not correspond to the telangiectasia (dilated blood vessels) seen in the eyes of patients but may be another manifestation of the same thing.It may be a good model to investigate telangiectasia

We have also undertaken studies on the brains of these Atm rats but find no gross changes. However, more careful observation shows changes in cells called microglia (Fig 5). What is evident is that there are fewer microglia in Atm deficient rat brains and it is evident that these are larger and morphologically different in the Atm deficient animal brains. This is an exciting result since it supports some earlier observations that A-T may be a glial cell disease.

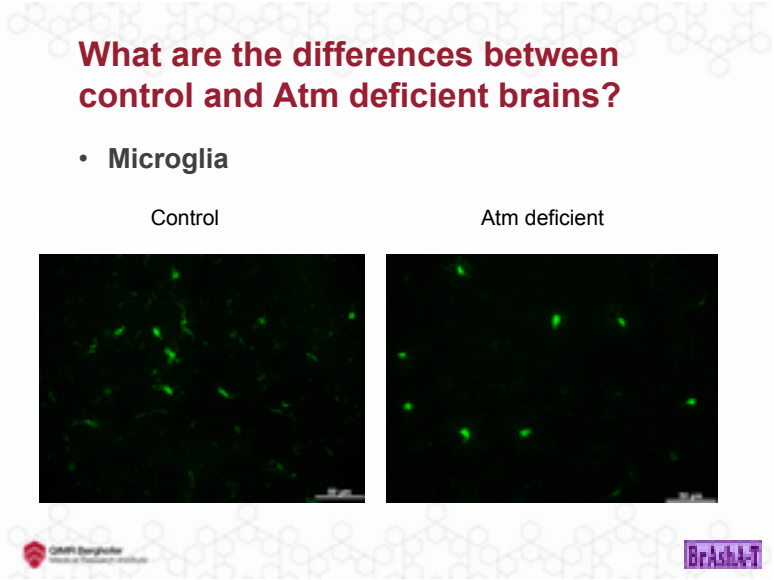

Figure 5 Reduced microglial cells in Atm mutant rats

Our future work will involve investigating the defect in microglial cells in the brains of these animals, isolating spinal cord from Atm deficient rats to determine whether they are losing motor neuron cells and using drugs such as betamethasone to slowdown or prevent the ataxia-like symptoms. Any questions associated with this work should be addressed to Professor Martin Lavin (martin.lavin@qimrberghofer.edu.au) or Dr Tara Roberts (tara.roberts@qimrberghofer.edu.au)