

2006 Workshop – Type V

TYPE V WORKSHOP REPORT AGSD(UK) CONFERENCE OCTOBER 2006

Although it was a long way for many to travel to Bradford we were pleased to welcome five people with McArdle's, plus partners and/or family members making 10 people in all. We welcomed Maurice MacDonald to his first conference, and also Vanessa Gadsby, John Peak, Sioned Williams and myself. Two others plus partners who we thought were coming didn't manage to make it and missed a great day.

Kathryn Wright, the PhD student researching into McArdle's at the Centre for Inherited Neuromuscular Disease, gave an excellent presentation. The AGSD has provided a substantial grant to help fund this research, under the direction of Prof. Glenn Morris. Kathryn explained the scientific background to McArdle's and told us about her research project. The presentation prompted many questions and Kathryn was very willing to interrupt her talk so that we could explore these areas. Kathryn has contributed an article about her research, which appears below.

In the afternoon, after each of us giving a potted introduction to ourselves and our situation, we had a sharing session where we discussed any issues that the individual participants wished to raise. The swapping of experiences was very useful. We covered all kinds of topics from disabled parking and disability living allowance, to coping strategies, diet, exercise regimes, muscle cramps, MedicAlert and many more.

SUMMARY OF WORKSHOP PRESENTATION BY KATHRYN WRIGHT FOR TYPE V

Creating a cell based model of McArdle disease to investigate potential therapies

I began a PhD carrying out research into McArdle disease in October 2005, and have now completed just over a year of the three year research programme, registered with Keele University. I graduated from Cambridge University in 2002 with a degree in Natural Sciences (Specialising in Genetics), and then worked at The Institute for Animal Health, Berkshire, from 2002 to 2005, researching genes that are part of the chicken immune system, which provided really good training in lab techniques.

I work in the Centre for Inherited Neuromuscular Disease based at the Robert Jones and Agnes Hunt Orthopaedic Hospital in Oswestry, Shropshire. The Robert Jones and Agnes Hunt is a specialist NHS Orthopaedic and Rehabilitation Hospital. The group is currently based in the ARC Building, but building work is in progress to create a purpose-built lab.

I am supervised by Prof. Glenn Morris, whose group has experience working on a variety of neuromuscular diseases such as Spinal Muscular Atrophy and Emery Dreyfus Muscular Dystrophy. Also based at the hospital are Prof. Caroline Sewry, who provides a diagnostic service on muscle sections from muscle biopsies using stains and antibodies, and Dr Ros Quinlivan who runs the only UK clinic for McArdle patients.

The aim of my project is to develop cell based models of McArdle disease which can be used to investigate possible therapies. McArdle disease is caused by mutations in the gene which lead to a lack of muscle glycogen phosphorylase. At present there are sheep and cow models with McArdle disease, but they do not have the two mutations which cause McArdle disease in UK patients. There are no cellular or mouse models of the disease.

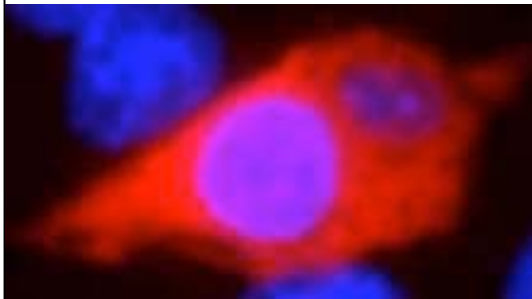
The benefits of a cell based model are that you can do experiments which you couldn't do on humans or animals, it avoids the need to test on animals and it is easier to see direct results of testing potential therapies on the cells.

There are several techniques to create a cell based model (basically "cells with McArdle disease"). Muscle or skin cells from McArdle patients can be grown in the lab. Muscle cells can be taken during a muscle biopsy (only with the donors permission to use it for research)

and this can only be done if the muscle biopsy is being carried out for a medical reason. There is also a method of taking skin cells and making them behave like muscle cells. Normally most cells in the body are constantly dying and being replaced by new cells; which is why your tan fades over time as the brown cells die and fall off. This is a problem with the cells taken from McArdle patients. So if these cells were used for experiments, the experiments could only be done for short time periods and then new cells from a fresh biopsy would be needed.

There are some special types of “immortal” cells which have been used by scientists for years. They don’t die like normal cells, and you can keep growing them for 30 years or more! They can be used to make a model of McArdle disease which can be used for lots of experiments. I obtained these cells and added the DNA for muscle glycogen phosphorylase. In some cells I changed the DNA so that it contained the different mutations which cause McArdle disease in UK patients.

Below are photos of an experiment using immortal cells, which have different DNA in them. The photos are of real cells. The red colour is a technique which shows muscle glycogen phosphorylase has been produced and the blue colour shows where the nucleus (“centre of the cell”) is.



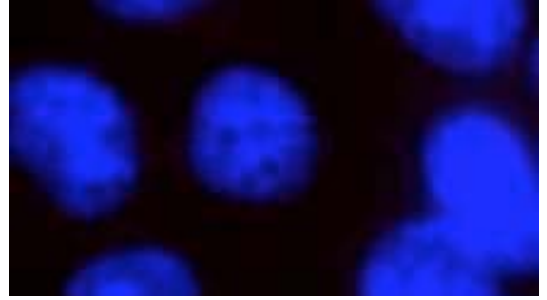
Normal DNA (like an unaffected person)



DNA with R49X mutation which causes McArdle disease



DNA with G204S mutation which causes McArdle disease



No muscle glycogen phosphorylase DNA added to the cells

These are only preliminary results, but it appears that muscle glycogen phosphorylase is only produced if the normal DNA is in the cells. If the DNA has either of the mutations then muscle glycogen phosphorylase does not seem to be produced (shown by the absence of red colour). This is what is believed to happen in patients, which means that these cells are a good model of McArdle disease.

(continued overleaf)

Further research with these cells is now necessary to clarify precisely why the cells with the mutations are not producing muscle glycogen phosphorylase. Future work in this project will involve testing various treatments to try to increase the production of muscle glycogen phosphorylase in the cell based model of McArdle disease.