Dr Richard Piercy
An approach towards understanding CNM

Dogs have long been man's best friend. Well, we can now extend this partnership to include understanding human disease, since dogs can suffer from the same diseases that we do, including those that effect muscle. It was first recorded back in 1986 that Labrador Retrievers can suffer from a canine form of centronuclear myopathy (CNM). Puppies appear normal at birth, but by the age of 1 year they exhibit tell-'tail' signs of muscle weakness and wasting and biopsies of their muscles confirm their pathology is very similar to the human forms of CNM and to myotubular myopathy (MTM).

Although the bad news is that the dogs suffer similarly to their human counterparts, the good news is that they provide a naturally occurring animal model for CNM/MTM. Scientists can study these dogs to try and find new therapies for both the dog and human form of the condition. In this light, Dr Richard Piercy a Vet and Senior Lecturer at The Royal Veterinary College, Hertfordshire and with his co-applicants Drs Sue Brown, Jan Domin and Cesare Terracciano at Imperial College London have just been awarded £38,548 from The Myotubular Trust, to fund 3 years of research to take this work forward.

What is wrong with these Labrador Retrievers?

The CNM dog has mutations in a gene previously not associated with any known forms of human CNM/MTM. Instead, it has a mutation in a gene called PTPLA, which makes a protein called hydroxyacyl-Co-A dehydrogenase 1 or HACD1 for short. This protein makes a particular type of fat known as phosphoinositides (PIs), which as the name suggests, contains the chemical called phosphate. PIs are important for many aspects of maintaining healthy cells inside our body. For instance, PIs are components of structures known as cell membranes. These line the edge of all the cells in our body, a bit like a sweet wrapper and act as a boundary to keep in the things we need to stay healthy and to keep out the things which make us sick. Membranes have a second function. They can form small, round, sac-like structure, called vesicles. These 'sacs' move substances around a cell in an ordered fashion to keep it happy, in the way that a waiter delivers drinks in a restaurant. PIs are also found in a structure only found in our muscle and no other body tissue such as liver or brain. This is called the T-tubule network. As the name suggests, this is an array of hollow, tube-like structures, which look like penne-shaped pasta. These spread inside the muscle cell, and are involved in controlling the way the muscle contracts. In particular, the T-tubule network is involved with the release of calcium inside the cell, which is needed for strong muscles In the CNM dog, it is thought that the faulty HACD1 gene leads to a loss or reduction in the amount of PI in the cell membranes, T-tubule network and in the vesicles. This leads to both faulty muscle contraction and disrupted movement of the vesicles across the cells i.e. the sweets become unwrapped, your muscles cannot tighten and the waiter drops his drinks! These cellular defects ultimately lead to the characteristic clinical and pathological symptoms associated with CNM/MTM (see http://www.myotubulartrust.com/page1.htm)

What is the connection between canine and human CNM/MTM?

Human CNM/MTM is currently associated with 5 genes (http://www.myotubulartrust.com/page4.htm). The X-linked form of human MTM arises from mutations in the gene MTM1 which produces the protein known as myotubularin which works by removing the phosphate from PIs, such as those generated by the pathway HACD1 is on. So, in canine CNM if less PI is made, myotubularin will have less to work on. Therefore the really exciting link between canine CNM and human MTM is that myotubularin and HACD1 are probably linked in the same pathway in muscle cells, a bit like having to pass through several Tube stations before you reach your final destination. Thus by studying either or both proteins, scientists are likely to generate much information on these diseases.

Proposed research

Dr Piercy is going to use the CNM dog model to try and understand what aspect of muscle function has stopped working properly in this muscle disease. To do this, he is going to take muscle cells from both healthy and CNM dogs, and grow the cells side-by-side in the laboratory for his experiments. He is going to use these cells to look for differences in: (a) cell pathology; (b) how the cells are able to control their calciumneeded for muscle contraction and (c) how muscle cell membrane structure and vesicle movement is affected. It is hoped that the results of this work may suggest therapeutic treatments for dogs and humans alike.

Labrador Retriever CNM website http://www.labradorcnm.com