

## 2007 - Progress Report Workpackage 4

### The Molecular Basis of Macrocyclic Lactone Resistance

#### Work carried in 2007

The macrocyclic lactones are the most important group of anti-parasite agents in use today, and include drugs such as ivermectin, doramectin and moxidectin. The aim of the research in this Workpackage is to elucidate the way(s) in which worms become resistant to these drugs so that we can devise better tests for resistance. This work is still at an early stage and this year we have concentrated on two major aims.

1) We are trying to produce better defined 'strains' of drug-resistant worms, especially of *Ostertagia ostertagi* and *Haemonchus contortus*. One of the major problems we face is that parasitic worms are genetically very variable, even though they all look the same! This makes finding the differences between them that are associated with drug resistance very difficult. For *O. ostertagi*, good progress has been made, and the Gent team has produced an isolate which is quite resistant to normal doses of ivermectin. Producing a well-defined strain of resistant *H. contortus* has been more difficult, and the Bristol workers have been held up by the restrictions imposed as a result of the foot-and-mouth outbreaks in the UK.

2) Our major aim has been to try and find differences between the resistant and susceptible worms that we do have available, by examining their DNA and the proteins they produce. So far, this has mostly focussed on those genes and proteins that we think might be involved in resistance (a candidate gene approach), but we are also preparing to carry out some experiments on a wider range of genes. Already, some possible changes have been identified in a *H. contortus* gene very similar to one already implicated in resistance in a 'model' worm, *C. elegans*, and these changes are being actively followed up. This involves studying as many worms from a wide geographical area as possible to see if the sequence changes correlate in any way with drug resistance. We are also examining possible changes in the proteins produced by the resistant worms: it is clear that different strains of worms do express slightly different proteins, but whether this is due to geographical variations or to drug resistance is still under active investigation. We are also looking at whether resistant worms are better at inactivating the drug than susceptible ones. A detailed comparison of ivermectin-resistant *Teladorsagia circumcincta* with susceptible worms is being undertaken. Our knowledge of the genetics and molecular biology of this important parasite is much less advanced than it is for *H. contortus* and so a lot of basic research is also being undertaken to provide a platform for further studies. It is already clear that these parasites have some important differences, and it may be that they all become resistant in different ways. One disappointing result is that a candidate resistance-associated sequence change, previously reported from *Cooperia oncophora*, has been eliminated as a mechanism of resistance in any of the species we study – including *C. oncophora*.