Thesis Abstract & Published Papers

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Project Title:	**PhD: Anthelmintic control in sheep: The cytochrome P450 family in the parasitic nematode *Haemonchus contortus***		
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Abstract:

Haemonchus contortus, a parasitic nematode of sheep, is unsurpassed in its ability to develop resistance to the anthelmintic drugs used as the mainstay of its control. A reduction in drug efficacy Leads to prophylactic and therapeutic failure, resulting in loss of productivity and poor animal welfare. This situation has reached crisis point in the sheep industry, with farms forced to close their sheep enterprises due to an inability to control resistant nematodes.

The mechanisms of anthelmintic resistance are poorly understood for many commonly used drugs. Altered or increased drug metabolism is a possible mechanism, yet has received little attention despite the clear role of xenobiotic metabolism in pesticide resistance in insects. The cytochrome P450s (CYPs) are a large family of drug-metabolising enzymes present in all species. Their expression is induced on exposure to their substrate and over-expression of a single CYP has been shown to confer multi-drug resistance in insects.

The *H. contortus* genome is currently being sequenced and assembled at the Wellcome Trust Sanger Institute, Cambridge. Despite the lack of a completed genome, the public provision of read, contig and supercontig databases has facilitated the identification of 73 partial gene sequences representing a large family of *H. contortus* CYPs. Their constitutive expression is highest in larval stages although adult expression was also detected. The majority of CYPs are most highly expressed in the worm intestine, which is thought to be the main organ of detoxification in nematodes and is consistent with a role in xenobiotic metabolism. A small number of CYPs were more highly expressed in anthelmintic resistant isolates than in an anthelmintic-susceptible isolate and may represent candidate genes for further research. The identification of putative *H. contortus* orthologues of the *Caenorhabditis elegans* nuclear hormone receptors controlling CYP transcription and the cytochrome P450 reductase gene catalysing electron transfer to CYPs suggests that regulatory and functional pathways may be conserved between the species.

Transcriptome analysis using next generation sequencing was undertaken to guide a pilot annotation of 590 Kb genomic sequence. A high degree of conservation was observed between the conceptual translations of *H. contortus* and *C. elegans* genes, although at a genomic level, H. contortus consistently had a larger number and size of introns, which may reflect a larger genome than previously predicted. Gene order was not conserved, although regions of microsynteny were present and a bias for intra-chromosomal rearrangements resulted in putative orthologues frequently residing on the corresponding chromosome in both species. Partial conservation of a number of *C. elegans* operons in *H. contortus* was identified. These findings have important implications for the H. contortus genome project and the transcriptome databases provide a

valuable resource for future global comparisons of gene expression.

Published Papers:

1. **DURING Roz Laing** et al **Characterization of the xenobiotic response of Caenorhabditis elegans to the anthelmintic drug albendazole and the identificationof novel drug glucosside metabolites.** Biochemical Journal 2010 432 (505-514) http://www.biochemj.org/bj/432/bj4320505.htm
2. **Roz Laing** et al. **The transcriptional response of caenorhabditis elegans to ivermectin exposure identifies novel genes involved in the response to reduced food intake.** PLoS ONE 7(2): e31367. http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0031367
3. **Roz Laing** et al**. Annotation of two large contiguous regions from the haemonchus contortus genome using RNA-seq and comparative analysis with caenorhabditis elegans.** PLoS ONE 6(8): e23216 http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0023216