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### Control of P-glycoprotein in both host and parasite for an improvement of anthelmintic treatment

The presence of large numbers roundworms in domestic livestock can lead to ill thrift, loss in productivity and in severe cases death of the animal. A key problem in the control of gastro-intestinal parasites of ruminants is the maintenance of anthelmintic efficacy in the face of increasing resistance. The increased presence of worms that are able to survive treatment to all of the available chemicals has lead to interest in studying the specific and non specific mechanisms by which this happens.

One important step in such studies is to obtain reliable tests to estimate the effects of both anthelmintics and potential modulators of the mechanisms of resistance. The drugs act on the roundworms in a variety of ways; effecting biochemical pathways, disrupting cell division or by causing paralysis of the worm. Laboratory tests can examine the effects of drugs and inhibitors on the normal behaviour of various development stages of the roundworms life cycle and thus investigate effects on egg development, larval development or feeding and larval motility.

A second objective is to better understand the mechanisms, mainly non specific, that have been previously identified as potential factors in treatment failure. The results from our studies suggested that these non specific pathways are important at all stages of development within the worm's life cycle in allowing them to cope with drug exposure. Also it has been shown that these mechanisms are important in both drug resistant and sensitive worms and that they are important at handling all classes of drugs. In addition, it has been demonstrated that the increased activity of a membrane protein, P-glycoprotein (Pgp) facilitates the elimination of drugs from both hosts and parasites alike by acting as a cellular pump. Thus, one of the strategies to improve the use of anthelmintics is to increase their concentration (bioavailability) in both the host and the parasite by targeting the Pgp with inhibitors. We have developed tools aiming at selecting Pgp inhibitors in Pgp-overexpressing vertebrate cells, further testing them *in vivo* for their ability to increase drug concentrations in sheep infected with an anthelmintic resistant parasites (collaborative study). At Moredun Research Institute work has primarily focussed on the effect of the macrocyclic lactone drugs alone and in combination with biochemical and energy transport pathways inhibitors in the parasites such as verapamil hydrochloride and piperonyl butoxide. In INRA, other groups of anthelmintics have been studied in both vertebrate cells and nematodes associated or not with pumps modulators. Promising results have been obtained in nematodes developing *in vitro*.

Work in the future will focus on determining whether the results that have been observed in the laboratory can be replicated in infected host animals.