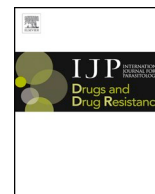




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Anthelmintics – From Discovery to Resistance III (Indian Rocks Beach, FL, 2018)



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ABSTRACT

The third scientific meeting in the series “Anthelmintics: From Discovery to Resistance” was held in Indian Rocks Beach, Florida, at the end of January 2018. The meeting focused on a variety of topics related to the title, including the identification of novel targets and new leads, the mechanism of action of existing drugs and the genetic basis of resistance against them. Throughout there was an emphasis on the exploitation of new technologies and methods to further these aims. The presentations, oral and poster, covered basic, veterinary and medical science with strong participation by both academic and commercial researchers. This special issue contains selected papers from the meeting.

This special issue of the International Journal for Parasitology; Drugs and Drug Resistance (IJPDDR) contains 12 papers that were presented at a scientific meeting held in Indian Rocks Beach, Florida called “Anthelmintics III: From Discovery to Resistance” in from January 30th to February 2nd, 2018. As the name suggests, this third meeting in the series followed two successful previous meetings, held in San Francisco in 2014 and San Diego in 2016 (Martin et al., 2016; Wolstenholme and Martin, 2014). The aim of the meeting was to continue to provide a forum for all those interested in anthelmintic drug discovery, use and resistance to come together and share data and ideas. This included those working in academic and commercial environments, with interests in veterinary and medical parasites, and especially those at an earlier stage of their careers or who might be relatively new to the field. Ninety-eight people registered, from 12 countries and there was at least one attendee from every continent.

The meeting was held at the Holiday Inn, Indian Rocks Beach, which provided a very convenient combination of an on-site meeting room, catering and some very spacious rooms. Though the weather was cooler and wetter than we hoped, the quality of the presentations, discussions and informal interactions was even higher than we expected. There were 46 oral presentations and 33 posters, spread over 10 sessions; each session was chaired by a combination of a graduate student and an established researcher. Each poster presenter was also given one minute to introduce their poster to the meeting, in the always entertaining and occasionally rhyming (sort of) Poster Pitch sessions that have become a feature of these meetings.

The twelve papers in this Special Issue cover many of the themes and specific topics highlighted over the three days of the meeting. In the belief that a better control of parasitic helminth infections relies on a greater understanding of the biology of the basic biology of these organisms, several speakers were invited to explore emerging topics in basic research. Bryant and Hallem (2018) have contributed a thoughtful and exciting review on one such aspect, the involvement of sensory processes in host-recognition by skin-penetrating nematode larvae, such as those of hookworms and *Strongyloides* spp. Much of the excitement in the review comes from the methodology that the authors

have employed in their studies, some of the first applications of transgenesis and CRISPR-Cas9-mediated targeted mutagenesis in parasitic nematodes, techniques that are very likely to become more common in the next few years.

A major component of each of the meetings in this series has been the identification and assessment of potential drug targets that could be exploited in the identification of potential new anthelmintics, and this one was no exception. Bais and Greenberg (2018) provide a comprehensive overview of the transient receptor potential (TRP) channel family of schistosomes. TRP channels have multiple functions in eukaryotes, but the genetics and pharmacology of the schistosome proteins is sufficiently divergent from the mammalian ones to suggest that they might form the basis of selective approaches to control. Inappropriate activation of these calcium-permeable channels has already been exploited to kill target cells, and this could be extended to parasites. Habibi et al. (2018) and Callanan et al. (2018) describe two nematode acetylcholine-gated chloride channels (ACCs), a class of ligand-gated ion channel not found in vertebrates, which have novel pharmacological properties and hence could have potential for development as drug targets. Foster et al. (2018) provide a detailed characterization of a nematode GABA-gated chloride channel. These channels are activated by piperazine and several insecticides are blockers of similar channels, but they have not so far been widely targeted by existing anthelmintics. Charvet et al. (2018) argue that the multiplicity of nicotinic receptors in nematodes provides an opportunity for effective control of parasites resistant to multiple drug classes, and describe potential resistance-breaking compounds that act at a so-far unexploited nicotinic receptor subtype, the N-type.

Once potential drug targets have been identified, then it is necessary to find compounds, which are active against them. Marchant et al. (2018) and Padalino et al. (2018) provide accounts of projects making progress towards generating leads against schistosomes. Marchant et al. (2018) exploit their previous success in expressing a schistosome 5-HT receptor along with a luminescent cAMP biosensor (Chan et al., 2016) to perform structure-activity investigations of 143 compounds containing previously identified alkaloid natural product pharmacophores

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shown to regulate Sm.5HTRL and identify potent 5-HT agonists. These assayed for ex-vivo activity against live worms. Padalino et al. combined bioinformatics, cheminformatics, functional genomics and whole organism approaches to assess the effects of compounds active at a *S. mansoni* lysine specific demethylase homolog as part of a wider effort to develop compounds targeting epigenetic processes in the parasite. Profiling of thiosulfuric acids against mature and juvenile schistosomes identified a compound, TPT sulfonate, which was further characterized by Wolfe et al. (2018). They conclude that the efficacy profile of this drug is competitive with praziquantel, the only anthelmintic currently used for treating schistosomiasis.

There have been speculations that certain anthelmintics work via interactions with the host immune system, including ivermectin (Wolstenholme et al., 2016). Reaves et al. (2018) explore this possibility using an in vitro system with human leukocytes and *Brugia malayi* microfilariae (McCoy et al., 2017). This experimental set-up exhibits considerable variability and the authors demonstrate that this is due to variations in the parasite preps and not in the cells isolated from individual donors. In addition, and perhaps disappointingly, ivermectin and diethylcarbamazine had no effect on gene expression in the leukocytes when they were exposed to the drugs in vitro.

Anthelmintic resistance is a major concern in veterinary parasitology, including in canine heartworm (Bourguinat et al., 2015). Ballesteros et al. (2018) have made progress in identifying molecular markers for resistance to the macrocyclic lactone preventatives in this parasite; they conclude that a 2-SNP model is currently the best fit with the observed drug resistance status of multiple isolates from the United States. Finally, Weeks et al. (2018) exploit their microfluidic device for electrophysiological recordings from the *C. elegans* pharynx (Lockery et al., 2012) to study the effects of various anthelmintics on pharyngeal pumping from susceptible and resistant strains of worm. The system allows for easier incorporation of electrophysiology into many studies on anthelmintics, including parasitic species, as described at the previous Anthelmintics meeting (Weeks et al., 2016).

Meetings such as this require input and help from many people. We should like to thank Katie Gorman and her staff at the Holiday Inn Harborside for their hospitality and efficiency; Jennifer Vit handled the registrations and other financial details with exemplary skill and accuracy. Charlotte Nuttall provided exemplary logistical and presentation support during the meeting. The success of the meeting was greatly increased by the contributions from all those who chaired a session and of course our Scientific Advisory Committee - Cristina Ballesteros (McGill), Conor Caffrey (UC San Diego), Robert Greenberg (University of Pennsylvania), Lindy Holden-Dye (University of Southampton), Paul Selzer (Boehringer-Ingelheim) and Susan Stasiuk (University of Calgary). Very little would have been possible without the generous support of our sponsors, who helped us maintain our tradition of affordability – Bayer Animal Health, Boehringer Ingelheim, Zoetis and New England Biolabs. Thank you to all of you.

Conflicts of interest

The authors declare no conflict of interest.

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