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Invited Article

Anthelmintics: From discovery to resistance II (San Diego, 2016)

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ABSTRACT

The second scientific meeting in the series: "Anthelmintics: From Discovery to Resistance" was held in San Diego in February, 2016. The focus topics of the meeting, related to anthelmintic discovery and resistance, were novel technologies, bioinformatics, commercial interests, anthelmintic modes of action and anthelmintic resistance. Basic scientific, human and veterinary interests were addressed in oral and poster presentations. The delegates were from universities and industries in the US, Europe, Australia and New Zealand. The papers were a great representation of the field, and included the use of *C. elegans* for lead discovery, mechanisms of anthelmintic resistance, nematode neuropeptides, proteases, *B. thuringiensis* crystal protein, nicotinic receptors, emodepside, benzimidazoles, P-glycoproteins, natural products, microfluidic techniques and bioinformatics approaches. The NIH also presented NIAID-specific parasite genomic priorities and initiatives. From these papers we introduce below selected papers with a focus on anthelmintic drug screening and development.

Contents

This special issue of the International Journal for Parasitology: Drugs and Drug Resistance (IJPDDR) contains papers that were presented at a scientific meeting held in San Diego, entitled: 'Anthelmintics: Discovery to Resistance II,' February 9th–12th, 2016. The meeting followed its predecessor: 'Anthelmintics: Discovery to Resistance' that took place in San Francisco, in February, 2016 (Wolstenholme and Martin, 2014) and an earlier meeting on helminth ion-channels in Philadelphia in December, 2011 (Wolstenholme, 2012). With this San Diego meeting we wanted to continue the idea of bringing together biologists, pharmacologists, veterinarians, physicians and discovery scientists from universities and industry, who share interests in anthelmintic discovery and resistance. We also wanted to foster the development and futures of graduate students working in the area of anthelmintic research. We anticipated that we would attract around 80 delegates initially, but eventually secured more than 100 delegates, which was an important encouragement to all of us.

The meeting was held in the Marina Village Center in San Diego which provided a very welcome sunny and warm location in contrast to the winter cold which most delegates came. The location and accommodation worked very well, allowing excellent discussions between the different groups and interests. It was possible to step outside for easy conversations along the shore. The presentations were arranged into themes over four days: there were 25 posters and 56 oral presentations.

In this special issue we have collected papers on anthelmintic drug discovery for publication that were presented at the meeting. The availability of public access drug and drug-like collections for screening is illustrated in the paper of Preston et al. (2016) who screened the Medicines for Malaria's 'Pathogen Box' to identify tolfenpyrad, which has inhibitory effects on the motility of L3 and

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L4 larvae of *Haemonchus contortus.*

The identification and variability of anthelmintic drug targets was a significant topic for a number of papers. Bais and Greenberg (2016), present an interesting paper on the transient receptor potential (TRP) channels of schistosomes. They pointed out that only a few classes of parasite helminth ion channels have been assessed for their pharmacological properties or even their physiology. In their paper they discuss the TRP channel superfamily which shares a common core structure but which are widely diverse in their ion selectivity. Bais and Greenberg (2016), also focus on one of these channels, the SmTRPA channel which has a TRPV1-like pharmacology that could be exploited for therapeutic targeting. A genome-based, single-nucleotide polymorphism (SNP) approach was used by Mani et al. (2016), to examine sequence data of ion channels in *Dirofilaria immitis* from eight different geographical locations: four from macrocyclic lactone (ML) susceptible populations and four from ML-loss of efficacy (LOE) populations. They point out that the SNPs identified may have effects on gene expression, function and resistance selection. Two papers from the laboratory of Jonathan Marchant (Chan et al., 2016a & b) on serotonergic G protein coupled receptors (GPCRs) in flatworms comment on their diversity of flatworm GPCRs for identifying ligands to treat parasitic flatworm infections. They illustrate a novel approach using a genetically encoded cAMP biosensor to resolve the properties of an expressed serotonergic GPCR (S7.1R). In the second of their papers, they demonstrate the use of this approach and describe the pharmacology of an expressed myoexcitatory serotonergic receptor, Sm.5HTRL.

An exciting presentation was the demonstration of a new microfluidic platform for electrophysiological recordings from hookworm and *Ascaris suum* larvae, (Weeks et al., 2016). This platform is based on the Nematrix design that was originally developed for *C. elegans.* The system has been used to examine the electrical activity of the pumping pharynx of feeding *A. suum* L3s and *A. ceylanicum* L4s and can be used to investigate effects of anthelmintics and nematode feeding behavior.

An approach that is being used more frequently in drug design was presented by the lab of Anne Lespine (David et al., 2016) who described the *in silico* analysis of the *C. elegans* P-glycoprotein-1 transporter and its binding to anthelmintics. They observed that avermectin anthelmintics have significantly higher affinity for Cel-Pgp-1, due to the sugar substituent that binds to an area involving H-bonds at Y771 of the inner chamber of the pump. Triclabendazole, closantel and emodepside also bound to overlapping sites in the inner chamber, suggesting that they could compete for Cel-Pgp-1-mediated avermectin transport.

The possible repurposing of flubendazole for filarial treatment was illustrated by the Geary lab. O'Neill et al. (2016), reported an RNAseq study of the effects of flubendazole on adult male *Brugia malayi.* The authors describe effects on genes associated with embryo development and cuticlar components. Their data supports the notion that flubendazole acts predominantly on rapidly dividing cells which may be of use in predicting efficacious flubendazole treatment regimens.

The success of a meeting like ours depends on the financial support and time of many people, in addition to the formal organizers. We thank Dr. Deirdre Joy, program officer at the NIAID for her presentation; our Gold Sponsors: The Burroughs Wellcome Fund and Bayer Animal Health; and our Silver Sponsors: Zoetis, Elanco/Novartis Animal Health, New Biolabs and Nematrix. The views expressed in this special issue do not imply endorsement of commercial practices or organizations. We should also like to thank Jennifer Vit of Iowa State University for handling the registration and finance so efficiently and Melanie Abongwa and Drs. Alan Robertson, Barbara Reaves and Saurabh Verma for their help 'on the ground' in making sure things ran as smoothly as possible. Planning for a third meeting in the series, provisionally to be held in Florida in February 2018, has begun.

Conflict of interest

The authors declare no conflict of interest.

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