International Journal for Parasitology: Drugs and Drug Resistance 4 (2014) 218–219

Contents lists available at ScienceDirect

International Journal for Parasitology: Drugs and Drug Resistance

journal homepage: www.elsevier.com/locate/ijpddr

Anthelmintics – From Discovery to Resistance

Adrian J. Wolstenholme [a,b,*], Richard J. Martin [c]

[a] Department of Infectious Diseases, University of Georgia, Athens, GA 30602, USA
[b] Center for Tropical and Emerging Global Diseases, University of Georgia, Athens, GA 30602, USA
[c] Department of Biomedical Sciences, Iowa State University, Ames, IA 50011, USA

ARTICLE INFO

Article history:
Available online 22 November 2014

Keywords:
Anthelmintics
Resistance
Drug discovery
Scientific meeting

ABSTRACT

The scientific meeting entitled 'Anthelmintics: From Discovery to Resistance' was held in San Francisco in February 2014. The themes of the meeting were drug discovery, modes of action and resistance. Both human and veterinary parasites were covered in the oral and poster presentations. The attendees were from both academic and industrial backgrounds. In the present article we introduce a number of the papers that emerged from the meeting. Several of the papers covered current drug discovery efforts underway worldwide, with some specific examples focusing on ion channels, protein kinases and cysteine proteases. These efforts included the repurposing of known drugs as well as the discovery of novel actives. Two papers described recently-developed whole-organism screening techniques. Finally, we introduce several papers looking at mechanisms and management of drug resistance in human and veterinary parasites.

In Memorium

Martin John Rogers 1960–2014

While we were preparing this Introduction, we were shocked to hear of the death of John Rogers. John was a program officer in Preclinical Drug Development at the National Institute for Allergy and Infectious Diseases and interacted with many of the US-based scientists at the meeting. His two presentations on how NIH funding worked and what were the best strategies for getting hold of some of it were characteristically helpful, supportive and insightful. John helped many of us over the years and his informed advice and support will be much missed, both personally and professionally. We dedicate this Special Issue to his memory.

This special issue of IJP-Drugs and Drug resistance contains a number of papers that emerged from a scientific meeting entitled 'Anthelmintics: From Discovery to Resistance' that we organized in San Francisco in February 2014. This followed on from a smaller meeting, concentrating on ion channels and anthelmintics, which took place in Philadelphia in December 2011 (Wolstenholme, 2012). In putting together this latest meeting we were driven by a desire to bring together as many groups as possible that were working in this area, whether they were based in academic or industrial settings, whether they concentrated on human or veterinary helminths, and whether those helminths were 'round' or 'flat'. We originally hoped that we could attract 70–80 people; in the event we had to turn a very few late enquiries away as we were nearing the capacity of the room and more than 130 registered, which was extremely gratifying. Those who were there, heard a total of 50 oral presentations over 3 days, and could look at 46 posters presented in two very lively and well-attended sessions.

The oral presentations were loosely arranged into three 'themes'; discovery, modes of action and resistance, with a final session on funding issues and the way forward for the anthelmintic research community. Though there is obviously some overlap between the three areas, we have tried to arrange the contributions to this Special Issue in the same order. However, no-one can do anything without resources and the presentations on funding were possibly the most important topic that was discussed. In this issue, Ramamoorthi et al. (2014) describe The World Intellectual Property Organization (WIPO) Re:Search consortium and how it brings institutions, both academic and commercial, together to form new collaborations, including those focused on anthelmintic drug discovery. In less than three years, more than 90 institutions have joined WIPO Re:Search, leading to over 70 research agree-

* Corresponding author at: Department of Infectious Diseases, 501 D.W. Brooks Drive, Athens, GA 30602, USA. Tel.: +1 706 542 2404.
E-mail address: adrianw@uga.edu (A.J. Wolstenholme).

http://dx.doi.org/10.1016/j.ijpddr.2014.10.001
2211-3207/

ments between Consortium Members, of which 11 are focused on anthelmintics.

Recently, there has been renewed interest in whole-organism screening as part of the drug discovery process and Buckingham et al. (2014) review recent progress in the automation of measuring nematode behaviours, focusing on developments in the application of machine vision, statistical imaging and tracking approaches. Motility, in particular, offers a direct readout of neuromuscular activity and the health of the animal and Storey et al. (2014) describe a modification of the WormAssay system first described by Marcellino et al. (2012) that permits assays to be carried out on microscopic larval stages, such as microfilariae.

Identification and validation of molecular targets remains central to drug discovery efforts and several presentations discussed established and new targets. The enormous success of the macrocyclic lactone anthelmintics has been a fantastic boon to parasite control and so it is fitting that this issue contains discussion of their targets, the glutamate-gated chloride channels (GluCls). The macrocyclic lactones have no activity against trematodes and Lynagh et al. (2014) provide a valuable comparison of nematode and schistosome GluCls, demonstrating that while the flatworm channels may not be affected by ivermectin, the flatworm GluCls are potential as drug targets in their own right. Protein kinases have been investigated as targets for the development of drugs against many conditions, and parasites are no exception. Morel et al. (2014) report studies confirming that inhibition of protein kinases has deleterious effects on schistosomes, thereby highlighting protein kinase B (PKB or Akt) as a novel target for anti-schistosome chemotherapy. Discovery of the essential symbiotic relationship between *Wolbachia* and many species of filarial nematode has opened up many new avenues for research. Lustigman et al. (2014) report that nematode cysteine proteases are required to maintain this symbiosis and that inhibition of their activity hinders microfilarial development and release, and reduces *Wolbachia* DNA levels, suggesting that they have potential as drug targets. *Wolbachia* themselves can be targeted by some existing antibiotics, though these are not suitable for use in mass drug administration programs. Johnston et al. (2014) report progress on drug development for onchocerciasis and lymphatic filariasis by repurposing of existing drugs, which already have regulatory approval. However, Beckmann et al. (2014) provide a cautionary tale of the problems that can be encountered during this process, as the *in vitro* effects of Imatinib, a tyrosine kinase inhibitor, on adult schistosomes could not be replicated *in vivo*. They report that the blood constituents, serum albumin and alpha-1 acid glycoprotein, inhibited the *in vitro* effects.

In parasitology, as in other infectious diseases, it is becoming apparent that 'resistance is inevitable' and that we need to be better at detecting the emergence of resistant helminths and devising strategies to cope with them once they do appear. Mwangi et al. (2014) report the apparent absence of schistosomes with reduced sensitivity to praziquantel in Kenya, but they were able to generate such parasites in the laboratory. They consider that there is a possibility that praziquantel resistance could appear if sufficient selection pressure is applied. The mechanism of such resistance is naturally of great interest and Greenberg (2014) reviews one such possible mechanism, the schistosome P-glycoproteins. The drug efflux transporters may not only modulate sensitivity to praziquantel and other drugs, but they have many other essential physiological roles, which we are only beginning to understand. This might make them drug targets in their own right. But if resistance does appear and become established, what then? Matthews (2014) reviews strategies to mitigate the effects of anthelmintic resistance, specifically in equine parasitic nematodes. She concludes that control of horse nematodes must become less reliant on chemical anthelmintics and make better use of management practices to reduce the environmental impact of infections.

The success of a meeting like this depends on the help of many people, in addition to the formal organizers. First, there is always a need for money and we should like to thank the support we received from Zoetis, New England Biolabs, Merial Ltd and the Burroughs Wellcome Fund, and acknowledge the support received via an R13 award from the NIAID (1R13AI109813-01). The views expressed in this special issue do not necessarily reflect the official policies of the Department of Health and Human Services; nor does mention of trade names, commercial practices or organizations imply endorsement by the US Government. Dr. James McKerrow, Dr. Conor Caffrey, Dr. Judy Sakanari and their colleagues in San Francisco were enormously helpful in many respects and made our jobs much easier. We should also like to thank Jennifer Vit of Iowa State University for handling the registration and finance so efficiently and Dr. Barbara Reaves, Mary Maclean and Melissa Miller for their help 'on the ground' in making sure things ran as smoothly as possible.

Conflict of interest

The authors declare no conflict of interest.

References

Beckmann, S., Long, T., Scheld, C., Geyer, R., Caffrey, C.R., Grevelding, C.G., 2014. Serum albumin and α-1 acid glycoprotein impede the killing of Schistosoma mansoni by the tyrosine kinase inhibitor Imatinib. Int. J. Parasitol.: Drugs Drug Res. 4, 287–295.

Buckingham, S., Frederick, P.A., Sattelle, D., 2014. Automated high-throughput motility analysis in *C. elegans* and parasitic nematodes: applications in the search for new anthelmintics. Int. J. Parasitol.: Drugs Drug Res. 4, 226–232.

Greenberg, R.M., 2014. Schistosome ABC multidrug transporters: from pharmacology to physiology. Int. J. Parasitol.: Drugs Drug Res. 4, 301–309.

Johnston, K.L., Ford, L., Umareddy, I., Townson, S., Specht, S., Pfarr, K., Hoerauf, A., Altmeyer, R., Taylor, M.J., 2014. Repurposing of approved drugs from the human pharmacopoeia to target *Wolbachia* endosymbionts of onchocerciasis and lymphatic filariasis. Int. J. Parasitol.: Drugs Drug Res. 4, 278–286.

Lustigman, S., Melnikow, E., Anand, S.B., Contreras, A., Nandi, V., Liu, J., Bell, A., Unnasch, T.R., Rogers, M.B., Ghedin, E., 2014. Potential involvement of *Brugia malayi* cysteine proteases in the maintenance of the endosymbiotic relationship with *Wolbachia*. Int. J. Parasitol.: Drugs Drug Res. 4, 267–277.

Lynagh, T., Cromer, B.A., Dufour, V., Laube, B., 2014. Comparative pharmacology of flatworm and roundworm glutamate-gated chloride channels: implications for potential anthelmintics. Int. J. Parasitol.: Drugs Drug Res. 4, 244–255.

Marcellino, C., Gut, J., Lim, K.C., Singh, R., McKerrow, J., Sakanari, J., 2012. WormAssay: a novel computer application for whole-plate motion-based screening of macroscopic parasites. PLoS Negl. Trop. Dis. 6, e1494.

Matthews, J., 2014. Mitigating anthelmintic resistance in equine nematodes. Int. J. Parasitol.: Drugs Drug Res. 4, 310–315.

Morel, M., Vanderstraete, M., Cailliau, K., Lescuyer, A., Lancelot, J., Dissous, C., 2014. Compound library screening identified Akt/PKB kinase pathway inhibitors as potential key molecules for the development of new chemotherapeutics against schistosomiasis. Int. J. Parasitol.: Drugs Drug Res. 4, 256–266.

Mwangi, I.N., Sanchez, M.C., Mkoji, G.M., Agola, L.E., Runo, S.M., Cupit, P.M., Cunningham, C., 2014. Praziquantel sensitivity of Kenyan *Schistosoma mansoni* isolates and the generation of a laboratory strain with reduced susceptibility to the drug. Int. J. Parasitol.: Drugs Drug Res. 4, 296–300.

Ramamoorthi, R., Graef, K.M., Dent, J., 2014. WIPO Re:Search: accelerating anthelmintic development through cross-sector partnerships. Int. J. Parasitol.: Drugs Drug Res. 4, 220–225.

Storey, B., Marcellino, C., Miller, M., Maclean, M., Mostafa, E., Howell, S., Sakanari, J., Wolstenholme, A., Kaplan, R., 2014. Utilization of computer processed high definition video imaging for measuring motility of microscopic nematode stages on a quantitative scale: "The Worminator". Int. J. Parasitol.: Drugs Drug Res. 4, 233–243.

Wolstenholme, A.J., 2012. Special issue on anthelmintics and ion channels. Invert. Neurosci. 12, 1.