MEETING REVIEW

MOLECULAR HELMINTHOLOGY: AN INTEGRATED APPROACH

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In January of 2001, a group of some 125 scientists gathered for a Keystone Symposium entitled “Molecular Helminthology: An Integrated Approach.” The purpose of the symposium was to bring together scientists working on Caenorhabditis elegans, plant nematodes, helminths of veterinary importance, and human helminths. The idea was to get worm-oriented people from different worlds talking to each other in hopes of seeing ideas and technologies flow from one to another.

This Keystone Symposium was the third in a series (last held in 1996) of unique meetings that have focused on multicellular eukaryotic parasites that are a major cause of morbidity in the world. The symposia was designed not just to present recent findings in the field of molecular helminthology but to take advantage of the molecular and genetic systems available from other multicellular eukaryotic worms such as C. elegans. The task was to integrate the vast knowledge available from C. elegans with that available from parasitic helminths and translate that information into relevant directions in the study of parasitic helminths. In particular, the availability of the C. elegans genome sequence and the ease in which genes can now be manipulated in C. elegans provide a conceptual and practical framework to exploit the molecular biology and genetics of C. elegans for parallel studies in parasitic helminths.

The meeting opened with a keynote address by Dr. Paul Sternberg with a discussion of the role of signaling pathways in sexual development and sexual behavior in C. elegans. His studies revealed general principles of signaling networks in helminths and at the same time contributed toward a fundamental understanding of reproductive processes that are needed to envision new classes of antihelminthic drugs. The first session, Helminth Genomes (S. Jones, M. Blaxter, T. Littlewood), focused on the current status of parasite genomes and how they might be exploited using the available approaches utilized by the C. elegans field. It was instructive to be reminded that the C. elegans genome-sequencing project was community driven. The lesson for parasitic worm lovers is that a strong genome network supported by the worm community can accomplish much. In this regard, the C. elegans community has developed a number of high throughput functional genomic projects that attempt to elucidate the function of each gene. M. Blaxter updated the nematode gene discovery efforts and demonstrated the usefulness of the C. elegans information. This information is available at http://www.nematodes.org. T. Littlewood reminded us that studies of phylogeny and evolution provide the history of organisms (Platyhelminths) and is a guide to interpret comparative (e.g., life history, genomic) data. The focus then turned to helminth development. C. elegans studies on sensory neurons (P. Sensgupta) and patterning of male rays by hox genes (S. Emmons) demonstrated the importance of transcriptional regulator families and combinatorial control of gene expression as a basis for development and pattern formation. T. Yoshino updated the audience on in vitro development of intramolluscan stages of trematodes. The intramolluscan stages are obvious targets for the development of genetic and gene manipulation approaches for mechanistic studies of gene function. The identification and demonstration of a role for nuclear receptors in schistosome (P. LoVerde) and nematode (C. Mania) development and the importance of signaling pathways (M. Beall) pointed to novel and helminth-specific targets for drug and vaccine intervention. By focusing on helminth responses to their environment, M. Driscoll discussed touch receptors in C. elegans and J. Appleton the role of Trichinella spiralis N-glycans in epithelial cell invasion. The plant nematode systems (D. Bird, C. Opperman) were then presented as tractable models to study basic mechanisms of host-parasite interactions. A substantial amount of work on the genomics and functional genomics of plant nematodes is well underway. In the section on Helminth Neurobiology, E. Cuppen demonstrated the power of the C. elegans model in studies on G-protein function by using a series of gene manipulation approaches to identify the function of all 25 G-protein subunit genes and the partners with whom they interact. The pathways in which these G proteins interact are currently being defined. This was followed by studies (C. Li) on the flp family of the FMRF amide-related (FaRP) neuropeptide gene family. Interestingly, the results to date suggest that the flp gene family acts on different subsets of neurons having varied and sometimes redundant functions. A. Hart used data mining to identify six new families of neuropeptides in C. elegans and demonstrated the utility of her approach to identify similar genes in parasitic nematodes. Her studies provide an opportunity to address functions of novel neuropeptides in a simple nervous system. A. Maule presented an overview of neuropeptides in parasitic helminths. He reported a higher expression of FaRPs in parasitic nematodes than in schistosomes and proceeded to show that in flatworms FaRPs transmit simple effects compared with nematodes where their effects are more complex. P. Ribeiro focused on monamine receptors in helminths. Using the C. elegans database, she cloned two novel G protein-coupled receptors from schistosomes. Both seem to be surface exposed. Using C. elegans as a model, G. Schad examined the amphidial neuron structure and function in Ancylostoma caninum, Strongyloides stercoralis, and Haemonchus contortus to identify functions that play a role in host-parasite interactions. In this case, C. elegans provided the neural maps and background work, whereas the parasitic nematodes provided biologically medical relevance. T. Geary concluded the session with a provocative talk on the future for antihelminthic drugs. N. Sangster then addressed
the usefulness of *C. elegans* as a model to study drug resistance. He concluded that under certain circumstances *C. elegans* is an excellent model, whereas under other conditions it is probably not as suitable. However, in the former instance, it will greatly contribute to the elucidation of the mechanisms of drug resistance. It is currently the best available model. M. Roos continued the discussion by outlining the genetic and molecular components needed for selection of drug resistance in parasitic helminths. D. Cioli then provided the genetic basis and molecular insights into drug resistance in schistosomes for oxamniquine and hycanthone. Like the previous speakers, he provided evidence of a loss of reproductive fitness in drug-resistant progeny compared with susceptible progeny. T. Day then provided evidence for the development of schistosome resistance to Praziquantel, the primary asset for global control of morbidity resulting from schistosomiasis. The final set of talks focused on the genetics and biochemistry of drug targets. R. Komuniecki compared *C. elegans* and *Ascaris* metabolism, especially mitochondrial metabolism. He also presented work on serotonin receptors in nematodes and the utility of the *C. elegans* model in these studies. M. Selkirk reported on the acetylcholine esterases of nematodes as potential drug targets. Unlike in free-living nematodes, the acetylcholine esterases are secreted into the alimentary tract of their host, where they are thought to interfere with the expulsion response. R. Maizels continued the theme of parasite genes that are involved in immune evasion by presenting data on genes from filarial parasites that interfere with antigen processing and modulation of host cytokine networks. These novel parasite gene products are excellent candidates for drug and vaccine targets.

With this body of information available, a workshop on the Threat of Drug Resistance (N. Sangster, D. Colley, J. Bennett, and P. LoVerde) was held to discuss the five questions.

1. What is the level of the threat of drug resistance in medically important helminthes?
2. How can medical helminthologists capitalize on work from model systems?
3. How applicable are current model systems and what others are needed?
4. Understanding versus tools: what is the capability and where is the balance?
5. What are the biological endpoints to measure drug resistance?

The lively discussion pointed out that single drug assaults run the risk of increasing drug pressure to a point of selecting resistance in the population we are trying to eliminate. It was considered that, with multihost, slow-to-replicate helminths, coupled with some of the drug distribution patterns envisioned (such as regular treatment of high-risk groups and not the general population), drug resistance is not likely to develop rapidly and could take decades. At this point, there is no documented human nematode resistance to drugs, whereas antinematode drug resistance is rampant in animal husbandry, and only a few examples of antischistosome drug resistance have been reported. Nevertheless, although not inevitable, it remains likely that drug resistance by medically important helminths will eventually develop. Thus, we must use this time while effective drugs are available to perform research for developing monitoring technology and new alternative control measures, including drugs and vaccines, that will be needed. Surveillance using newly developed, field applicable monitoring tools and a research pipeline with new control tools will be needed to stay ahead of these wily foes. The development of these tools will depend on a better basic understanding of these worms.

At the Taos meeting, it was clear that some of the technologies that are so productive and interesting in the *C. elegans* world can, with difficulty, be moved into parasitic helminths. The leap to the parasitic worms is being attempted by a few investigators, who are making slow, but important, progress. It was equally clear that research on parasitic worms is going to need its own renaissance of technology and tools, such as gene transfers, gene knock-outs, and RNA interference. These tools, and the manipulations and hypotheses they will allow, are essential for the vitality of parasitic helminthology. One important goal is to attract some of the well-trained young and established *C. elegans*-oriented scientists to work on medically important helminths. Certainly, there are fascinating scientific questions waiting to be answered about this group of organisms. Some of those questions have, as their central theme, the very nature of parasitism. It is amazing what can be accomplished when a group of “worm lovers” representing different worlds come together.

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