Part One
Drug Discovery Approaches
Target Identification and Mechanism-Based Screening for Anthelmintics: Application of Veterinary Antiparasitic Research Programs to Search for New Antiparasitic Drugs for Human Indications

Timothy G. Geary*, Debra J. Woods, Tracey Williams, and Solomon Nwaka

Abstract

Anthelmintic discovery in the veterinary pharmaceutical industry has succeeded only through screening synthetic compounds and fermentation products against whole parasites in culture or in host animals. Following trends in the parent, and much larger, human pharmaceutical industry, many programs have been developed in the past 20 years to exploit mechanism-based screening strategies for the identification of new leads in this therapeutic area. This strategy relies on the robust identification of parasite proteins as targets for chemotherapeutic intervention and their subsequent validation. Expanding access to sequenced genomes of parasitic nematodes will facilitate identification of genes that encode putative drug targets. Of particular relevance will be those that are shared among nematodes of veterinary and human importance. These targets offer the best chance for finding new molecules with potential utility in both arenas and provide an opportunity for collaboration and synergy between the two sectors. Validation of these gene products as drug targets will require advances in functional genomics methods for parasites. Expanded capacities for parasite-based physiological and biochemical experiments are also likely to be needed. While mechanism-based approaches remain an attractive alternative to organism-based strategies for broad-spectrum anthelmintic discovery, proof-of-concept for the platform is still needed.

Introduction

Screening for antiparasitic drugs as a scientific exercise can be traced to the early work of Ehrlich, who screened a collection of synthetic dyes for trypanocidal activity in mice with the aim of allowing the importation of European horses and
cattle into the African colonies of Germany prior to 1900 (see Refs. [1, 2]). This was perhaps the first example of a screen of a collection of chemicals for any therapeutic indication; Ehrlich’s efforts at drug discovery seem to have begun with a veterinary parasite as target, but led to the introduction of the first anti-infective drugs for use in humans. Thus, the process by which drugs introduced into veterinary practice for parasite control were adopted for use in humans has a long history.

The motivation to discover “modern” antiparasitic drugs for the animal health industry can be traced to the introduction of sulfaquinoxaline for the prevention of mortality and morbidity due to poultry coccidiosis in the late 1940s, phenothiazine (1930s) and piperazine (1950s) as veterinary anthelmintics, and the chlorinated hydrocarbons and organophosphates as ectoparasiticides in the 1940s and 1950s. Diethylcarbamazine was discovered as an agent for use in human filariasis within the same time-frame, being developed for veterinary practice for heartworm prevention some time later. It is important to note that all these drugs were first used in humans – not necessarily for parasites – prior to being adopted for veterinary use. Their utility for controlling parasites in animals paved the way for the institution of systematic screening of chemical collections for new synthetic antiparasitic drugs for veterinary application. Their use in clinical settings proved that chemotherapeutic control of parasites which plagued livestock and poultry was economically rewarding for the manufacturer, the veterinarian, and the farmer.

The general flow of antiparasitic drugs from human to veterinary application (Table 1.1) reversed over time. For anthelmintics, the reversal began with the discovery of thiabendazole for veterinary medicine in the 1960s (Table 1.2), which was later introduced for treatment of various gastrointestinal (GI) nematodes in humans. This pattern was repeated for the nicotinic cholinergic agonists (pyrantel, levamisole), the second generation benzimidazoles, particularly albendazole and mebendazole, and ivermectin (and, potentially, related macrocyclic lactones). In contrast, antiprotozoal drugs have not moved as easily between the sectors (Table 1.2) or continue to flow in the opposite direction, a situation that primarily reflects the

<table>
<thead>
<tr>
<th>Drug</th>
<th>Human use</th>
<th>Veterinary use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diethylcarbamazine</td>
<td>Filariasis</td>
<td>Heartworm prophylaxis</td>
</tr>
<tr>
<td>Arsenicals</td>
<td>Trypanosomiasis, onchocerciasis</td>
<td>Heartworm therapy</td>
</tr>
<tr>
<td>Piperazine</td>
<td>Gout (discontinued)</td>
<td>GI nematodes</td>
</tr>
<tr>
<td>Phenothiazine</td>
<td>Malaria/mosquito control</td>
<td>GI nematodes</td>
</tr>
<tr>
<td>Sulfa antibiotics</td>
<td>Bacteria</td>
<td>Poultry coccidiosis</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Anaerobic microbes</td>
<td>Giardiasis</td>
</tr>
<tr>
<td>Buparvoquone</td>
<td>Malaria</td>
<td>Theileriosis</td>
</tr>
<tr>
<td>Halofuginone</td>
<td>Malaria</td>
<td>Poultry coccidiosis</td>
</tr>
</tbody>
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differences in the major species of protozoal pathogens of animals compared to 
humans (see below).

Potential for Veterinary → Human Transfer of new Antiparasitic Drugs

Like most of the pharmaceutical industry, animal health companies underwent a 
considerable reduction in abundance over the past 20 years from mergers and 
acquisitions [3, 4]. This led to a net reduction in investment in antiparasitic drug 
discovery, with a consequent focus of efforts on the most profitable sectors of the 
animal health market [5]. As a result, priorities for veterinary parasite control now 
diverge more extensively from those of human medicine. A summary of current 
emphasis on types of parasites targeted for drug discovery for human versus veterinary 
applications is shown in Box 1.1. It is worth noting in this context that there may be a

<table>
<thead>
<tr>
<th>Drug</th>
<th>Veterinary indication</th>
<th>Human indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzimidazoles</td>
<td>Anthelmintic/antiprotozoal</td>
<td>Nematodes, protozoa</td>
</tr>
<tr>
<td>Pyrantel/levamisole</td>
<td>GI Nematodes, Lungworms</td>
<td>Nematodes</td>
</tr>
<tr>
<td>Praziquantel</td>
<td>Cestodes</td>
<td>Schistosomiasis</td>
</tr>
<tr>
<td>Ivermectin</td>
<td>Heartworm prophylaxis</td>
<td>Filariaiias</td>
</tr>
<tr>
<td>Nitazoxanide</td>
<td>Sarcocystis in horses</td>
<td>Protozoa, nematodes</td>
</tr>
<tr>
<td>Moxidectin</td>
<td>Nematodes, ectoparasites</td>
<td>Onchocerciasis (in development)</td>
</tr>
<tr>
<td>Emodepside</td>
<td>Nematodes</td>
<td>Onchocerciasis (investigation)</td>
</tr>
</tbody>
</table>

Table 1.2 Antiparasitic drugs introduced into human use from veterinary interest.

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Box 1.1: Areas of synergism/overlap based on current trends in discovery investment

<table>
<thead>
<tr>
<th>Parasite Group</th>
<th>Veterinary Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apicomplexan protozoa:</td>
<td>human ↑, veterinary ↓</td>
</tr>
<tr>
<td>Kinetoplastids:</td>
<td>human ↑, veterinary ↓</td>
</tr>
<tr>
<td>Giardia/ameba/Cryptosporidium:</td>
<td>human ↓, veterinary ↓</td>
</tr>
<tr>
<td>Trematodes:</td>
<td>human ↔, veterinary ↔</td>
</tr>
<tr>
<td>Filarial nematodes:</td>
<td>human ↑, veterinary ↔</td>
</tr>
<tr>
<td>GI nematodes:</td>
<td>human ↓, veterinary ↑</td>
</tr>
</tbody>
</table>

This box illustrates the potential for flow of compounds in each direction as discovery efforts 
continue.

↑: relatively high interest and activity in discovering new drugs.
↔: modest interest/activity.
↓: minimal or declining interest/activity.
resumption of drug transfer for parasites from the human to the veterinary side in the future. This situation may benefit both areas, as described below.

**Protozoan Parasites**

A renaissance has occurred in the attention of public and private funders to the discovery of new drugs for protozoal parasites that infect humans. The primary targets for chemotherapy include the Apicomplexan malaria parasites (*Plasmodium* spp.), kinetoplastids such as *Leishmania* spp., *Trypanosoma brucei* and *T. cruzi*, *Entamoeba histolytica*, *Giardia lamblia*, *Toxoplasma gondii*, *Trichomonas vaginalis*, and *Cryptosporidium parvum*. Based on prevalence and pathogenicity, these drug discovery efforts are considerably weighted to malaria and the kinetoplastids [6–12]. In contrast, the primary protozoal target for veterinary medicine is a distinct group of Apicomplexans, the *Eimeria* spp. of poultry, with additional interest in phylogenetically related parasites (*Neospora caninum*, *Sarcocystis neurona*) and in *Giardia* spp. and *Cryptosporidium* spp. [3]. However, dedicated antiprotozoal discovery programs are no longer common in the animal health pharmaceutical industry (vaccine discovery is more prevalent at this time), and so future drugs for these infections will likely flow from human to veterinary use. Current work in this area on the human side is heavily focused on mechanism-based, as opposed to whole-organism, high-throughput screening. The extent of target overlap is likely to be reasonably good across the human/veterinary species divide, though target choice in the human-focused projects does not routinely include an assessment of relevance for parasite species of strictly veterinary importance. Inclusion of this factor as a criterion for prioritization could provide a for-profit component that would appeal to potential animal health partners, with benefits similar to those anticipated in the anthelmintic arena (see below).

**Ectoparasites**

Indications for the use of ectoparasiticides in human medicine are far fewer than for veterinary clientele, which in turn is a much smaller market than agricultural applications. The flow of these compounds has typically been from agriculture to animal health to human applications, with the exception of DDT, which was first developed for use in humans. The use of ivermectin for the treatment of head lice and scabies is an example of an ectoparasiticide developed for animals being adopted for humans. However, the current economic driving force for this arena is so small that discovery programs in animal health sectors typically do not include a component that addresses possible human uses. From the human medical perspective, the temporally limited (as opposed to chronic) use of these products and the relatively low number of infestations in the West make the cost–benefit analysis in terms of registration unrewarding. This situation may change if head lice and scabies develop more extreme resistance to available ectoparasiticides, including ivermectin.
Trematodes

These considerations suggest that the primary influence of animal health drug discovery research on human medicine will continue to be in the anthelmintic arena. More specifically, this will be largely restricted to drugs that primarily affect nematodes. The only flatworm of economic significance in veterinary medicine is the liver fluke, *Fasciola hepatica*. This parasite is important in some areas, but is not enough of a production problem in livestock to warrant dedicated screening in most animal health companies, even though resistance is emerging to the best available drug, triclabendazole (which is not even registered in the USA). Although *F. hepatica* is a significant human pathogen in some regions, it has not proven to be sufficiently prevalent to elicit a dedicated discovery effort for it. Instead, work on flatworms in the human sector focuses on *Schistosoma* spp., currently controlled by a single drug (praziquantel). In the absence of rigorously documented cases of praziquantel resistant schistosomes, investment in new antischistosomal drug discovery has been somewhat limited compared to the efforts mounted against protozoa. This situation may be changing in light of the Helminth Drug Initiative recently developed by WHO/TDR [13], which aims to reinforce and advance screening for new antischistosomal drugs. As for protozoan parasites, this effort may discover compounds that can be adopted for use against liver flukes in veterinary medicine.

Nematodes

Further analysis of the impact of veterinary antiparasitic drug discovery programs will be restricted to nematocides. Historically, the discovery of nematocides for use in animals or humans was based on low-throughput systems that employed infected animals as the primary screen. These assays were labor-intensive, slow to attain the final read-out and used relatively large amounts of experimental compounds. Even so, it remains true that at least the prototype of every available anthelmintic class, including emodepside, the paraherquamides, and the newest class, the AADs, was discovered by screening in infected animals or worms in culture. Nonetheless, there has been a marked shift of strategy in the animal health industry to emphasize discovery programs based on targets, or high-throughput, mechanism-based screening [14].

The initial change from screening in infected animals to tests run on organisms in culture was motivated primarily by the need for animal health operations to fit into the evolving discovery paradigms adopted by their parent companies. This meant a marked reduction in the amount of chemicals used in a screen (to adapt to new parameters for compound synthesis in medicinal chemistry programs) as well as a reduction in animal use and in labor costs associated with screening. In addition, there were concerns that *in vivo* screens might fail to detect truly interesting actives that are false negatives due to insufficient potency or pharmaceutical inadequacy.
Unfortunately, screening against parasites or the free-living species *Caenorhabditis elegans* in culture, while vastly increasing throughput and radically diminishing the amount of compound needed for primary screening, was not very successful in revealing new anthelmintic templates. Indeed, these procedures led to a very high rate of false positives, as many compounds were noted to kill nematodes in culture, but very few (almost none) were subsequently found to be active in infected animal models. As resources were typically insufficient to permit experiments designed to determine why *in vitro* actives routinely failed *in vivo*, improvements in the screening stream designed to reduce the incidence of false positives were not possible. A new approach was clearly needed, and it was incompatible with standard industry practices to return to the era of screening in infected animals. In keeping with drug discovery for human medicine, mechanism-based approaches came into vogue [14].

The drive to move from organism to target-based screens was based on several factors. One factor was the motivation to capitalize on biology-based intellectual property (IP); screens using infected animals or organisms in culture barred few competitors from an area and can only exploit chemistry-based IP. Mechanism-based screens can restrict the discovery activities of competitors by taking advantage of investments made in understanding the physiology and molecular pathology of diseases and infectious pathogens that dominate Western human medicine. In addition, advances in chemical technology, such as combinatorial chemistry, made it possible to synthesize thousands of molecules at a time in small amounts; organism-based screens were ill-equipped to test either the number or the small amount of available compounds. Advances in computational chemistry and structure-based drug design meant that the traditional whole-organism blind-screen approaches became seen as intellectually unchallenging and out of step with the times. Finally, whole-organism approaches are labor-intensive compared to mechanism-based strategies; the incorporation of mechanism-based screening allowed a relatively small team of screeners to evaluate hundreds of thousands of compounds against multiple targets in a matter of weeks. The combination of vastly increased throughput with lowered labor costs made this an irresistible strategy, validated by expert scientific opinion. To date, however, it is undeniably true that the adoption of this overall strategy has not led to an increase in the number of new chemical entities registered for use in humans. For our topic, it is crucial to stress again that at least the prototype of all commercially available anthelmintics was discovered in whole-organism assays, despite at least two decades using the more modern approaches to discovery. What does this bode for the switch to more modern screening platforms? We can use the neuropeptide area as an example (see page 12).

**Discovery Synergies**

Discovery programs in animal health companies can contribute to the discovery and development of drugs for use in humans in several ways. The most obvious is the
direct transfer of veterinary-approved drugs to human medical use, as was the case for ivermectin and albendazole, among others. It may happen again with compounds such as moxidectin or emodepside. In these cases, human clinical trials are still required for registration, but much of the basic registration package will already be available. It should be noted that this transfer does not directly benefit the animal health partner.

Failing that happy occurrence, another synergy can occur through the donation of selective compound collections to discovery efforts targeted at human parasites. Most animal health companies have been engaged in antiparasitic drug discovery for decades and have assembled a set of compounds with activity at some level of screening. The set may consist of thousands of compounds. These compounds were not commercialized for a variety of reasons, but they offer an enriched set of potential leads that can be tested in screens relevant for human parasites, either in mechanism-based assays or against whole organisms in culture. Such a transfer has occurred already as part of a TDR program to incorporate contributions from industrial sources into drug discovery processes [10, 11, 13]. A key component in the transfer is the negotiation of an agreement on IP for the compounds, which has been accomplished by TDR in several cases that can serve to facilitate additional agreements with other companies [10]. Activity of these “set aside” compounds in a human parasite-targeted screening stream may reawaken interest in the template in the animal health partner, providing a potential economic return on the collaboration.

This factor is particularly relevant in light of the recent history of anthelmintic discovery in the animal health industry. The extraordinary clinical utility of ivermectin and subsequent macrocyclic lactones set the bar for commercial introduction of new anthelmintics to the veterinary market at a very high level [3, 4]. This led to economic decisions in animal health companies to shelve molecules that were potentially useful but clearly inferior to the macrocyclic lactones discovered during the course of screening. Increasing concerns about macrocyclic lactone resistance in veterinary medicine has led to renewed interest in these shelved molecules; as research into them is revived, new leads may emerge from once-discarded molecules or templates.

In the most basic example of potential synergy, animal health programs can contribute screening models and expertise to human parasite discovery efforts. These operations would screen the chemical collections of the industrial partner, providing unprecedented and otherwise unattainable access to chemical space for a human parasite target. In addition to screens employing whole organisms (parasitic or free-living), high-throughput, mechanism-based assays for targets of broad interest in nematodes (for other kinds of parasites as well) can be operated cooperatively. Expertise in design, performance, decision strategies and information management for such screens can be contributed by the animal health partner. Hits identified in the screen can be of interest to both partners or to either separately, depending on activity in subsequent screens. Importantly, agreements with animal health companies enable the onsite training of external scientists in this technology, which can broaden its expert use in non-industrial centers [10].
Post-Discovery Synergies

The conversion of hits from a high-throughput, mechanism-based screen to a legitimate lead compound with activity in animals against target parasite species has rarely (if ever) been attained. This is also a significant issue for drug discovery in other therapeutic areas [15, 16] and represents a major concern for the current discovery paradigm. Whereas it is quite easy to propose targets for mechanism-based screens, it is a very difficult thing to convert a target to a molecule with activity in vivo, let alone a drug. The multidisciplinary studies needed to generate a lead from a hit are commonly undertaken in industrial settings; the internal expertise in drug metabolism, pharmacokinetics, pharmacodynamics, formulation, and pharmaceutical chemistry is difficult (though not impossible) to assemble outside of a for-profit institution. The availability of this expertise and the associated experimental platforms and systems in animal health companies can be an enormous benefit to lead generation for human parasite indications if hits can be generated through screening. This is especially important for testing of compounds against parasites in animal models. The early phases of hit-to-lead generation overlap for a compound with activity against nematodes of both human and veterinary medical importance, representing a significant cost benefit for the human-oriented program.

Despite advances in high-density chemical synthesis for analog generation, medicinal chemistry remains the largest expense in drug discovery. In some respects, the role of screening and subsequent bioassays is simply to focus a company’s medicinal chemistry resources on the most promising hits or lead series. Medicinal chemistry is an asset that must be applied in any lead-finding program. The most advanced research in this area is based in industry, and the cooperation of animal health companies in providing facilities and training for sponsored scientists to work in this milieu has great benefits [10]. Again, negotiating an agreement on ownership of and rights to compounds produced by the sponsored scientists are critical to ensure full access to the industrial expertise and facilities, but these have been successfully executed.

Additional contributions can be realized from mutually beneficial early development programs. This is unquestionably the case if the same compound is selected for use in humans and animals, but much can be gained from a shared effort even if different compounds are chosen for the two indications. Preliminary pharmaceutical chemical work (stability), advanced formulation, ADME, and toxicology will have at least some overlap. Importantly, research in process chemistry and manufacturing can be integrated, as both therapeutic areas demand the lowest cost of goods possible. Insofar as data from a veterinary-driven development program can be used to support development and registration of a compound for human use, there will be a significant cost savings in the human component; this may tip the balance sheet in favor of development by lowering the cost-recovery break-even point.

Although direct discovery of antiparasitic drugs intended primarily for use in humans is not a primary goal for major human pharmaceutical companies in the
West, work on neglected tropical diseases does occur in this sector [11]. Considerable expertise in running human clinical trials is available in these organizations and at least some have pursued or are pursuing development of existing drugs for use against human parasites (e.g., azithromycin for malaria [17]). The ability to potentially tap into these resources as part of an advanced development and registration collaboration involving the animal health component of a major pharmaceutical company is a substantial attraction to such arrangements.

As discussed above, compounds identified in screening operations for parasites of human interest (malaria or schistosomes in particular) may be adopted by animal health companies for development for the treatment of Apicomplexan parasites or trematodes of veterinary importance. Collaboration in the development stream illustrated for anthelmintics would provide similar benefits for leads flowing in the opposite direction and could favorably affect the costs of development that might otherwise limit or restrict the human-oriented pathway. This kind of interaction could be facilitated by the negotiation of agreements to funnel antimalarial or schistosomicidal actives to an animal health company for evaluation. Whether this kind of agreement is possible would depend to some extent on IP issues pertaining to the ownership of compounds screened for activity against human parasites. The potential of a revenue stream based on royalties from veterinary sales should not be discounted, even if the amounts are not likely to be large.

**Cautions**

Genomics-based approaches are a natural point of overlap between veterinary and human parasiticide discovery. Efforts to deduce useful anthelmintic drug targets by genome-based analysis [18–25] are of great potential value. However, there are several caveats to the adoption of this strategy in addition to the failure to demonstrate proof-of-concept to date for antiparasitic drug discovery (no marketed products discovered by this approach).

Perhaps the greatest concern is that little research on the biology of potential drug targets has been done in nematodes. Parasitic species are difficult to maintain in the laboratory, and functional studies on the physiology and biochemistry of these organisms have never been abundant and are decreasing in frequency. The plethora of targets identifiable in genomics approaches are difficult to prioritize by functional significance in the target organisms. This conundrum is particularly relevant for protein targets of uncertain function, based on annotation.

A second concern is that a fairly large proportion of nematode genes seem to be species-specific [26]. In the veterinary realm, this is not too critical, since breadth of spectrum is an essential feature for commercial success and thus species-specific targets are not pursued. However, targets unique to adult filariae may be worthy of
pursuit, since narrow-spectrum drugs for the control and potential eradication of lymphatic filariasis and/or onchocerciasis (river blindness) would be of high value – from a public health, if not economic, perspective. The lack of facile functional genomics approaches for parasitic nematodes means that validation of potential drug targets is only possible if they are present and serve the same role in *C. elegans*. Genes unique to filariae clearly fall outside of this category, as do genes that may encode proteins necessary for parasitism in general in this phylum [27]. At this time, there are no readily available techniques for validating such proteins as drug targets.

Another concern pertains to the difficulty of prioritizing candidate drug targets by biological validation. Such efforts rely primarily on methods to knock-down the function of target genes in *C. elegans*, primarily by RNA interference [19, 20, 25]. Such techniques are not reliably available in parasitic nematodes [28]; and their full exploitation will require labor-intensive work in animal models (which are not available for key species in human medicine). Another problem is that it is quite difficult to analyze gain-of-function changes in target proteins even in *C. elegans*. There are no convenient methods for genome-wide protocols to induce gain-of-function mutations. However, most currently marketed anthelmintics are agonists, the effects of which cannot be duplicated or predicted by RNAi. This is also true for newer anthelmintics; emodepside opens a K⁺ channel [29] and the AADs are atypical nicotinic cholinergic agonists [30]. Neither target would have been prioritized for screening based on an RNAi filter. More basic research on nematode biology is needed to provide a robust platform for prioritizing drug targets.

A final concern is that targets are typically highly valued for screening if homologs are absent from mammals. This strategy is, on the surface, highly rational as it may help assure parasite–host specificity. However, commercially available anthelmintics target GABA receptors, nicotinic acetylcholine receptors, and β-tubulin, which are very highly conserved indeed; and macrocyclic lactones target glutamate-gated Cl⁻ channels but are also excellent agonists of their GABA-gated relatives. A discovery strategy that would have failed to discover most of the commercially available drugs in this class should be endorsed with great caution. It should also reinforce faith in the power of medicinal chemistry to safely exploit even very small differences in protein structure.

An Example

A project conducted at Upjohn/Pharmacia/Pfizer illustrates some of the issues that pertain to the adoption of mechanism-based screening in anthelmintic discovery. As noted, relatively little basic research has been done on parasite biology, especially in nematodes, with the goal of identifying drug targets. As a consequence, the animal health industry had to conduct this research itself. This is in marked contrast to the situation in industrial drug discovery for major human indications, for which
governments and other institutions fund a great deal of research, the results of which can be readily translated into mechanism-based, high-throughput screens by companies.

Beginning in the 1980s, research on nematode neurobiology revealed the presence of a family of neuropeptides related to the snail tetrapeptide FMRFamide that were very widely distributed in nematodes and other invertebrates, but were rare in vertebrates (see Ref. [31] for review). Based on their distribution and very potent neuromuscular physiology (primarily studied in *Ascaris suum*), the receptors for these FMRFamide-like peptides (FLPs) were chosen for high-throughput screening to identify non-peptide agonists or antagonists for evaluation as candidate anthelmintics [32]. A very-high-throughput screening campaign more than 15 years after inception of the program identified a relatively small number of validated hits [33], none of which have advanced to the market. Until an anthelmintic is commercialized, from this screen or from another mechanism-based approach, one must consider the strategy an unrewarded experiment to date.

The consequences of failure in a screening campaign can be profound, given the disparity of resources available in animal health companies compared to human-focused companies. The resources needed to develop and implement a mechanism-based screening program, from physiology to bioinformatics/genomics to screen construction, can represent a significant proportion of the typical R&D budget of an animal health company. This situation may discourage investment on HTS systems for veterinary targets and requires that such programs be integrated with less costly and potentially less risky whole-organism approaches. It also motivates collaboration between human and veterinary medical programs to spread the investment risk as broadly as possible. It is essential to recognize that, as long as parent pharmaceutical companies rely on mechanism-based screening approaches for drug discovery, animal health companies must participate in the process. The crucial task is how to ensure the best chance for success.

**Conclusion**

Bidirectional flow of antiparasitic compounds, leads, and hits between animal health companies and organizations devoted to discovery of drugs for human parasitoses offers many mutual benefits. For protozoa and trematode infections, the direction of this flow in the near term is likely to be from human to veterinary indications. The existence of multidisciplinary expertise in animal health companies can benefit the human development path if the same or similar compounds are chosen for advancement in the two fields. For nematocide discovery, synergies between the two areas are evident from target identification to screening to development toward registration. Fortunately, the benefits of collaboration with industrial partners have reinvigorated current efforts to discover new anthelmintics [10]. The results of this new enterprise are eagerly awaited.
References


