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# Ivermectin 20 years on: maturation of a wonder drug

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**Ivermectin has been on the veterinary market for almost a quarter of a century and has been approved for human use for 18 years. Its use has revolutionized the treatment of nematode and arthropod parasites in animals and has provided hope for the control or even eradication of filariases in humans. Although much remains to be learned about how the drug works and how resistance to it will develop, it has earned the title of 'wonder drug'.**

## Origin of ivermectin

Ivermectin, the first commercially available macrocyclic lactone endectocide, was discovered in a screening program at Merck (http://www.merck.com/) in the mid-1970s [1]. The origin of the drug perhaps foretold its remarkable impact on both veterinary and human medical practice. Historically, drugs derived from bacterial or fungal fermentations had found application as anticancer or antibacterial agents. The only reason for screening fermentations for antiparasitic activity was the belief of Satoshi Ōmura of the Kitasato Institute (http://www.kitasato.or.jp/rcb/eng/intro.html) [2,3] that fermentation products had broader therapeutic relevance, coupled with the willingness of the Merck parasitology team to take the risk of investing in this possibility. The results transformed the therapy of parasitic infections and revolutionized the animal-health pharmaceutical industry. The purpose of this brief article is to update a review of ivermectin that was published in the first issue of *Parasitology Today* [4], focusing on the major developments that have happened since then.

## Veterinary antiparasitic chemotherapy

Anthelmintic drugs such as the benzimidazoles, levamisole, pyrantel and morantel had changed management strategies for optimizing nematode control in livestock and companion-animal veterinary practice since the 1960s. The introduction of ivermectin in 1981 elevated worm control to new levels. The unprecedented combination of potency, spectrum (which included nematodes and ectoparasites such as fleas, ticks, lice, mites and flies) and persistence opened new markets and new management options for parasite control. In particular, the remarkable lipophilicity and potency (intrinsic potency $<1$ nM for many species) enabled new routes of

application of the drug that had enormous economic impact on livestock production. By 1985, injectable formulations of ivermectin were available for livestock, which greatly reduced labor costs associated with dosing. The subsequent introduction of oral formulations, slow-release products and, most notably, a topical (pour-on) formulation for livestock in the late 1980s further lowered the labor costs of dosing and enhanced the acceptance of routine worm-control programs in livestock operations.

By 1985, the impact of ivermectin on veterinary medicine was already apparent. Of special importance was the ability of the drug to prevent heartworm infections in dogs dosed on a monthly basis. This property has since protected tens of millions of pets from infection with *Dirofilaria immitis*. Similarly, monthly treatment protected cattle, sheep, swine and horses from a broad variety of insect and nematode parasites. Hundreds of millions of large animals have since been treated with ivermectin.

In response to these successes, animal-health companies, recognizing the market niche for persistent parasite control, developed and introduced ivermectin analogs, including moxidectin, milbemycin oxime, doramectin, selamectin, abamectin and eprinomectin, each of which has (subtly) distinct properties relevant for treatment. In addition, consumer expectations for persistent action led to the ready acceptance of month-long treatments for ectoparasite control (especially fleas and ticks) on dogs and cats, beginning with the inhibitors of chitin synthesis, such as lufenuron. Consequently, sales and profits of some animal-health companies soared. This situation then changed again as patent protection for ivermectin was lost and generic products entered the veterinary market. Subsequently, a wave of consolidation occurred as less-profitable companies lost the ability to compete. The excellent therapeutic profile of the macrocyclic lactones raised the bar for the introduction of new anthelmintics to an almost impossible level. Thus, many companies reduced or eliminated investment in research programs devoted to parasite control. The consequences of this decision will be realized as resistance to the macrocyclic lactones becomes more common (see later) [5].

## Human antiparasitic chemotherapy

Ivermectin had not been introduced into human medicine in 1985. After its use for preventing the development of

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symptoms of infection with *Onchocerca volvulus* became apparent, Merck initiated a remarkable give-away program to deliver ivermectin to Africa and South America. This act spurred other international pharmaceutical companies to follow suit, as evidenced by the donation of albendazole (along with ivermectin) for control of lymphatic filariasis. Based on the undeniable benefits of these programs [6,7], a renewed interest in tropical medicine has evolved in the pharmaceutical industry, and it began with ivermectin.

## Advances in pharmacology

Initial work on the mechanism of action of ivermectin focused on its ability to open γ-aminobutyric acid (GABA)-gated $Cl^-$ channels [4]. The drug has potent activity at GABA receptors in both invertebrates and mammals, and GABA was known to be the primary inhibitory neurotransmitter in the nematode somatic neuromuscular system. However, subsequent work by Merck scientists identified glutamate-gated $Cl^-$ channels as the more likely physiological targets of ivermectin and related drugs [8,9]. This previously unrecognized class of ligand-gated channels is absent from vertebrates but has key roles in both insects and nematodes.

Experiments performed with the free-living nematode *Caenorhabditis elegans* emphasize the primary importance of glutamate receptors in the mechanism of action of ivermectin. Extremely high-level resistance to ivermectin is achieved in this organism after loss-of-function mutations in three genes encoding distinct but related glutamate-gated $Cl^-$ channel subunits [10]. These results suggest that GABA-gated $Cl^-$ channels are of minor importance in the pharmacology of ivermectin in nematodes. It is not known how closely the biology of *C. elegans* mimics that of parasites and, therefore, the question of whether this situation pertains to parasitic nematodes is unresolved [9,11,12].

Although ivermectin paralyzes body-wall muscle in nematodes, more-potent effects occur on the pharynx. The importance of somatic versus pharyngeal muscle paralysis in mediating the antiparasitic effects of the drug on gastrointestinal parasites has not been fully resolved [13]. Both effects could have a role; high parasite exposure, occurring shortly after dosing, might achieve efficacy by paralyzing body-wall muscle, whereas persistent efficacy observed at low blood and tissue drug levels could be due to starvation.

Parasite–host selectivity in the actions of ivermectin is not simply a consequence of the absence from vertebrates of glutamate-gated $Cl^-$ channels, given the well-documented sensitivity to the drug of mammalian GABA receptors. It was known early that ivermectin gained only limited access to the mammalian central nervous system (CNS), the location of GABA-gated $Cl^-$ channels, but the manner in which this compartmental exclusion was attained was not known [14]. Recent work has illuminated the basis of the rare, severe ivermectin toxicity observed in a small number of dog breeds, particularly collies. Collies homozygous for a loss-of-function mutation in the gene encoding a multiple-drug resistance P-glycoprotein drug pump (*mdr1*) show the toxic response [15]. Discovery of

this pump – which, at least partly, generates the blood–brain barrier that restricts the entry of many drugs and other chemicals into the CNS – was made in *mdr1*-mutant mice following treatment with ivermectin for a mite infestation [16].

Although ivermectin has proven to be impressively safe in humans treated in onchocerciasis-control programs, a small number of severe, even fatal, events has occurred [17]. The basis of this unexpected pathology remains unresolved [18], although it has been tied to the presence of high levels of *Loa loa* microfilariae in the affected patients [17]. These reactions are so rare as to seem idiosyncratic. It is not readily apparent that *Loa* microfilarial loads *per se* should account for an event that is, seemingly, all or nothing; that is, there does not seem to be a graded CNS response to ivermectin treatment, which one might expect if the killing of *Loa* microfilarial stages were the primary cause. It is possible that the reaction is due, at least in part, to the restricted geographical presence of loss-of-function *mdr1* alleles, as in collies [18], although this hypothesis has not been proven [19].

## Threats of resistance

In 1985, resistance to ivermectin in parasites was an unrealized threat. Since then, the inevitable appearance of ivermectin-resistant parasites has occurred. It has been a particular bane in small ruminants, arising in regions that rely on intensive anthelmintic treatment to optimize animal productivity and then, essentially, spreading globally [20]. Of more concern is that resistance has appeared in parasites of cattle, particularly *Cooperia* spp. [20], with productivity consequences. Very recently, reports of macrocyclic lactone-resistant *Cooperia onco-phora* in US cattle have appeared at parasitology conferences. If these findings are confirmed and extended, the time could be right for the development of a new class of anthelmintic.

However, there are no reports of ivermectin-resistant heartworms, or ivermectin-resistant large or small strongyles in horses. Although there are suspicions that ivermectin resistance might have been selected in *O. volvulus* [21], proof at the pharmacological or genetic level remains to be obtained. The picture is complicated by the fact that the molecular basis of resistance to ivermectin is not understood in any parasites [22]. It is not yet clear whether work done on glutamate receptor mutations in *C. elegans* [10] will be relevant. A recent report about *C. oncophora* suggests that mutations in glutamate receptor subunits might be associated with ivermectin resistance [23]. Although the results must be extended to other parasite species and isolates, it is a positive development in this arena.

## The next 20 years

Much remains to be learned about ivermectin and related drugs. Priorities for research include developing a thorough understanding of the basis of resistance to ivermectin in the field. A molecular marker for resistance to this drug (if, indeed, a single genotype is found to underlie the phenotype in all species) will be of inestimable help in monitoring the spread of the phenotype and

will aid the understanding of why it occurs differentially in various species of parasite in different hosts.

How ivermectin works (and whether other macrocyclic lactones mimic its mechanism of action precisely) must be determined in full. Although it seems that glutamate receptors are the primary target of these drugs in nematodes, work with the fruit fly *Drosophila melanogaster* suggests that the distinction between GABA and glutamate receptors might not be straightforward [24]. Determining whether similar subunit co-mingling also occurs in nematodes should be a high priority. Where the various ligand-gated Cl⁻ channels are expressed in nematodes, the physiological roles that they have and how conserved they are across the phylum Nematoda remain to be resolved at the experimental level. Developing an understanding of how ivermectin really works in parasites at the molecular level will reveal much about the basic biology of these organisms.

The ultimate maturation of a drug might occur when it can be used as a tool to investigate biological processes. Particularly intriguing in this regard is the effect of ivermectin on microfilariae. It has long been noted that this drug has little obvious effect on microfilariae at pharmacologically relevant concentrations but, instead, seems to require an immune response for efficacy [25]. It has been hypothesized that ivermectin works in this situation by interfering with the ability of microfilariae to evade the host immune response [18]. Further work in this area might illuminate fundamental aspects of this intricate host–parasite relationship.

The era of ivermectin and the other macrocyclic lactones is far from over. New kinds of compound might be needed for resistant parasites, but the macrocyclic lactones will remain mainstays of antiparasite chemotherapy in animals, including humans, especially as (cheaper) generic versions proliferate. Ivermectin has come a long way since 1985 and is rightly accorded the title of 'wonder drug'.

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