INTRODUCTION

Approximately 1 person in 5 is infected with a parasitic nematode. The relatively benign nematode infections, such as ascariasis, are a health burden for the poor, undernourished populations that are at highest risk. Whereas the filariases can be devastating, Onchocerciasis, for instance, causes blindness in about 30% of affected, untreated individuals [1]. In addition to the human health burden, virtually every major livestock animal is susceptible to infection by parasitic nematodes that reduce agricultural productivity. The nematode parasites cost farmers and ranchers billions of dollars [2]. Drugs that kill nematodes, known as nematocides or, when specifically used to kill parasites, anthelmintics, are the primary means of alleviating the human suffering and preventing the agricultural loss resulting from parasitic nematodes.

Currently used nematocidal compounds were discovered in screens that required no knowledge of the compound’s mechanism of action. While that knowledge is not necessary for antiparasitic drugs to be effective, it has become increasingly important for two reasons. First, the evolution of drug resistance in treated parasites can rapidly compromise the efficacy of nematocides. A better understanding of the action of the drug and the specific genetic changes that can make parasites resistant may help us to manage resistance and maintain the effectiveness of nematocides. Second, as our ability to design new nematocides becomes more sophisticated, an understanding of the mechanism of action of existing, successful compounds will, we hope, help us to identify optimal targets for new drug screens.

That parasites often make poor experimental subjects is an obstacle to their use for studies of nematocides. Parasites usually cannot complete their life cycle in culture and therefore must be bred in and extracted from their hosts. Obtaining sufficient experimental material can be difficult. The technical problems associated with the need to cross parasites in the host, together with the need to use strains that are not genetically homogeneous, limit the genetic analysis of resistance. The ability to transform parasites with genes suspected to play a role in resistance would be useful but is not generally feasible.

Caenorhabditis elegans is a useful model organism from which to learn about nematocides. Although C. elegans is a free-living soil nematode, not a parasite, it offers many compensating experimental advantages. Thousands of C. elegans can be easily grown in a small Petri dish, the life cycle is only 3 days and hermaphrodites can self-fertilize. These qualities of C. elegans simplify screens for rare, recessive genetic mutations that affect drug sensitivity. In addition, the complete cell lineage, which is invariant, is known, the adult anatomy has been reconstructed from serial electron micrographs, and the entire genome has been sequenced. The existence of a complete physical map, consisting of overlapping cosmids and YACs, in combination with the ability to transform worms, makes cloning relatively easy. Finally, electrophysiological techniques that can be applied to C. elegans are useful for studying drugs that target the nervous system. In this review, I will assess the utility of C. elegans for studies of nematocides.

Keywords: nematocides, anthelmintics, nematodes, C. elegans, drug resistance
fewer eggs [6-8]. Worms are more sensitive to BZs at lower temperatures [6]. Treating C. elegans with BZs depletes MTs, as determined by ultrastructure [8,9].

**Genetics of Resistance**

C. elegans strains resistant to mebendazole [10], albendazole [9] and benomyl [6] have been isolated by chemical mutagenesis and selection in the presence of the drug. In a saturated screen, alleles of only one resistance gene, ben-1, were isolated (Table 1) [6,10]. ben-1 is cross-resistant to all the BZs [6,9,10]. The degree of resistance can be greater than 50-fold, depending on the assay and the BZ derivative [6,9]. Null alleles of ben-1 (i.e. alleles that completely eliminate protein expression) are recessive at 15°C and semidominant or dominant at 25°C.

**Molecular Biology**

ben-1 encodes a β tubulin subunit, one of at least 6 β tubulin genes found in C. elegans [6,11]. It belongs to the family of nematode tubulins that form 11 protofilament microtubules (11 PF MTs). This is in contrast to the vertebrate tubulins, which form 15 PF MTs, and to the mec-7-encoded tubulin, which forms the 15 PF MTs found in mechanosensory neurons of C. elegans [8]. At concentrations of BZs that depolymerize MTs in wild-type worms, 11 PF MTs are stable in the ben-1 mutant. Interestingly, 15 PF MTs are not susceptible to BZs. However, a mutation in the mec-7 gene, which eliminates 15 PF MTs in replacement by 11PF MTs that are susceptible [8]. BEN-1* has a phenylalanine at amino acid 200 (F200), which is thought to be necessary for BZ binding [12,13]. In contrast, TUB-1, a β tubulin from C. elegans, has Y200 (the MEC-7 tubulin has F200 but may lack other residues necessary for BZ binding) [6]. Binding of mebendazole to C. elegans MTs in vitro is temperature dependent, which explains the temperature dependence of the drug's effect on worms. In binding studies that used tubulin purified from C. elegans, mebendazole (Bmax specifically bound to MTs was reduced in the ben-1(u107) mutant relative to wild-type [14]. Strikingly, even in worms homozygous for null alleles of ben-1, no other phenotype is apparent, indicating that the BEN-1 tubulin is largely redundant with other tubulins.

**Relevance to Parasites.** In parasites (and fungi), MTs play the same central role in BZ sensitivity and resistance as in C. elegans [3,12,15,16]. BZ treatment disrupts MTs in parasites [17,18]. A decrease in the Bmax of BZ binding to MTs correlates with resistance in Hae monchus contortus [4,15,19] and in Trichostylurus celestiformis [14,20]. Moreover, specific genetic polymorphisms

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* The protein product of a gene is signified by the gene name in capital letters. Thus, BEN-1 is the protein encoded by the ben-1 gene. The mutant allele of a gene is indicated in parenthesis after the gene name.