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Where can I find out more?

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Primer

Platyhelminthes

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Platyhelminthes (flatworms) have captivated the imagination of biologists for centuries. Indeed, planarian flatworms were used as experimental models decades before *Caenorhabditis elegans* became known as 'the worm'. Although planarians experienced a brief fall from grace, with the advent of molecular tools, planarians, such as *Schmidtea mediterranea*, have emerged in recent years as powerful models to study the basis of stem cell regulation and tissue regeneration. Flatworms are not just everyone's favorite experimental subjects from high school biology — they also include some of nature's most successful parasites, many of which have plagued humans throughout our history. This Primer will focus on several aspects of the remarkable biology found throughout the phylum Platyhelminthes.

Basic flatworm biology

Platyhelminthes (*platy* = flat and *helminth* = worm), or simply 'flatworms', are dorsoventrally flattened and bilaterally symmetrical worms (Figure 1A,B). Often speculated in the classic literature to represent primitive basal bilaterians, modern molecular phylogenetic analyses place the Platyhelminthes within the Lophotrochozoa, a clade of invertebrate animals that includes annelids (segmented worms) and mollusks. Free-living members of the phylum, the so-called turbellaria, are largely restricted to marine and freshwater environments; however, some taxa, such as land planarians (Figure 1B), are capable of inhabiting warm humid terrestrial habitats. Turbellarian flatworms are almost entirely carnivorous, scavenging on the remains of dead animals or in some cases tracking, capturing, and killing their prey. Although these free-living taxa have evolved to thrive in a variety of habitats worldwide, the most successful group of flatworms without question belong to the Neodermata. This group of obligate parasites includes both flukes and tapeworms that together are responsible for a significant disease burden in livestock and humans throughout the world.

Given the diversity of flatworms it is difficult to make sweeping generalizations that unite all members of the phylum. However, unlike most bilaterians, flatworms lack a coelom and possess a 'blind gut' where food enters and exits via the same orifice (that is to say, they have no anus). Flatworms are also dorsoventrally flattened, ensuring the diffusion of oxygen and nutrients to their tissues. Despite this constraint, the absence of a cuticle, exoskeleton or shell has allowed these soft-bodied worms to adopt a dizzying array of shapes, body plans and sizes (Figure 1B–O). Many free-living flatworms are microscopic, but some can reach >10 centimeters in length (for example, land planarians; Figure 1B). These variations in body sizes and shapes are even more exaggerated among members of the Neodermata. Indeed, larval Neodermata rarely resemble the adult parasite (Figure 2), and tapeworms, arguably the most notorious of all Neodermata, can reach tens of meters in length growing inside their hosts (Figure 1K,L).

The outer surface of turbellarian flatworms is typically lined with a simple epidermis comprised of a single layer of columnar epithelium that sits on top of a basement membrane and several layers of muscles. This epithelium is usually ciliated, allowing these worms to swim through the water column or to 'glide' over the substrate. Flatworms lack a circulatory system but possess a primitive excretory system (protonephridia) and an array of secretory organs that aid in digestion, protection from predators, locomotion, prey capture and the prevention of desiccation in terrestrial environments. These worms also possess a well-organized central nervous system, consisting of an anteriorly positioned brain that interfaces with a peripheral nervous system and a variety of sensory organs, including pigmented 'eye-like' photoreceptors in many taxa (such as freshwater planarians; Figure 1C–E,I). Despite the seemingly

primitive appearance of the flatworm nervous system, studies have shown that the brains of freshwater planarians are quite complex, divided into distinct anatomical regions comprised of molecularly diverse cell types. This neural complexity allows flatworms to integrate a variety of sensory cues (touch, smell, taste, temperature, water flow and light) and perform relatively 'complex' behaviors, such as hunting. These worms even appear to have some capacity for associative learning.

Reproduction and development

With a few notable exceptions (such as the schistosomes; Figure 1O), flatworms sexually reproduce as cross-fertilizing hermaphrodites. Usually, adult worms simultaneously possess both male and female gonads along with associated ducts, glands and copulatory organs. Often times mating is as simple as the exchange of sperm between two willing parties; in other cases sperm exchange can be a violent endeavor. For example, some marine polyclads (Polycladia) practice 'hypodermic insemination' where they inject their partners with a sharpened penis depositing sperm beneath their partner's skin. Some such polyclads also engage in 'penis fencing' where the worms square off and attempt to inject their opponent with sperm while simultaneously avoiding the wrath of their rival's penis.

Following fertilization, flatworms produce egg capsules containing fertilized oocytes. There are, however, important differences in the types of egg capsules generated between members of the phylum. Basal turbellarians produce entolecithal eggs, typical of other animals, in which yolk material is deposited inside the oocyte. In contrast, members of the Euneoophora (Figure 1A) produce ectolecithal eggs, where specialized organs produce yolk cells that are deposited into the egg with the fertilized oocyte. With some exceptions, the production of ectolecithal eggs coincides with the abandonment of the spiral mode of embryonic cleavage observed in basal flatworms (and most lophotrochozoans). Instead, in order to utilize the extra-embryonic yolk many Euneoophora have adopted strange adaptations to their embryonic development. This is typified in developing planarian embryos that undergo 'blastomere anarchy', where the early blastomeres separate from one another and undergo subsequent divisions. Some of these blastomeres eventually generate a transient embryonic pharynx and intestine responsible for assimilating yolk in the center of the embryo. Following embryonic development, with the exception of some marine polyclads that can form pelagic larvae, most turbellarians directly develop to adulthood without intervening larval stages. As will be detailed below, the path from egg to adulthood is extremely complicated for members of the Neodermata.

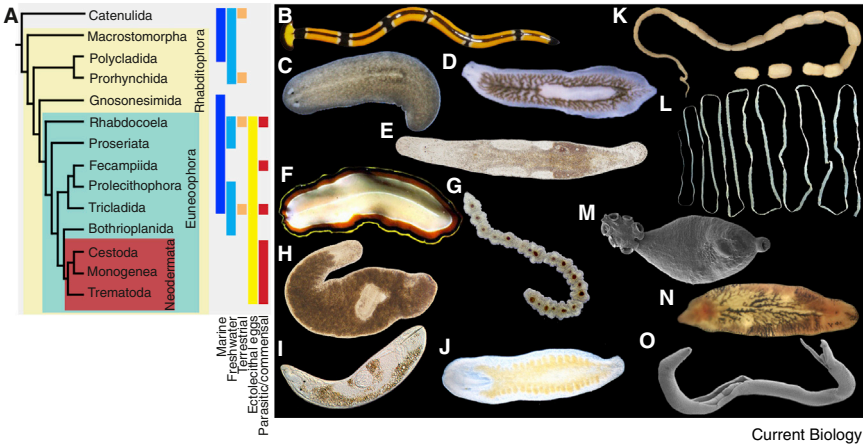

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Figure 1. The diversity of the Platyhelminthes.
(A) A phylogenetic tree showing the relationships of the Platyhelminthes. Orders are shown for everything except the Neodermata, for which Classes are shown. The habitats and traits of the groups are shown to the right. Phylogenetic tree adapted from Laumer *et al*. (2015) Elife *4,* e05503. (B–N) Images of various free-living and parasitic flatworms. (B) Land planarian, Tricladida *Bipalium* sp. (credit, B. Dupont, Creative Commons). (C) Freshwater planarian, Tricladida *Schimidtea mediterranea.* (D) Freshwater planarian, Tricladida *Procotyla fluviatilis* (credit, J. Sikes). (E) Macrostomorpha *Macrostomum ligano* (credit, D. Vizoso, Creative Commons). (F) Polycladida *Pseudoceros bimarginatus* (credit, M. Litvaitis, Creative Commons). (G) Catenulida *Catenula lemnae* (credit, C. Laumer, Creative Commons). (H) Bothrioplanida *Bothrioplana semperi* (credit, C. Laumer, Creative Commons). (I) Rhabdocoela *Gyratrix hermaphroditus* (credit, C. Laumer, Creative Commons). (J) Prorhynchida *Geocentrophora applanata* (credit, C. Laumer). (K) Dog tapeworm, Cestoda *Dipylidium caninum* (credit, Centers for Disease Control). (L) Beef tapeworm, Cestoda *Taenia saginata* (credit, Centers for Disease Control). (M) Monogenea *Protopolystoma xenopodis* (adapted from Theunissen *et al.* (2014). Parasite *21*, 20; Creative Commons). (N) Trematoda *Fasciola hepatica* (credit, K. Hoffmann and A. Chakroborty). (O) Trematoda *Schistosoma mansoni.*

The undisputed champions in this arena are the freshwater planarians that can regenerate from virtually any amputation. For more than a century, this regenerative prowess has attracted the attention of experimental biologists, including Thomas Hunt Morgan (of *Drosophila* fame), who did seminal work on planarians at the turn of the 20th century. In fact, one of Morgan's oft-cited contributions to the field is his observation that a planarian can regenerate from tissue fragments as small as 1/279th the size of an intact worm!

Where it has been carefully studied, the regenerative abilities of flatworms rely on a population of stem cells called neoblasts. Following injury, neoblasts migrate to the site of the wound and differentiate, forming an unpigmented structure known as the blastema. Inside the blastema neoblasts differentiate and ultimately restore amputated tissues. Based on data from planarians, neoblasts appear to be pluripotent cells capable of giving rise to all three germ layers. Indeed, transplantation studies have shown that a single planarian neoblast

Regeneration and stem cells

It is impossible to discuss flatworms without mentioning their unparalleled regenerative abilities, which are widespread throughout the phylum. Indeed, from the Catenulida to the Neodermata many flatworm groups have members possessing the ability to regenerate following injury.

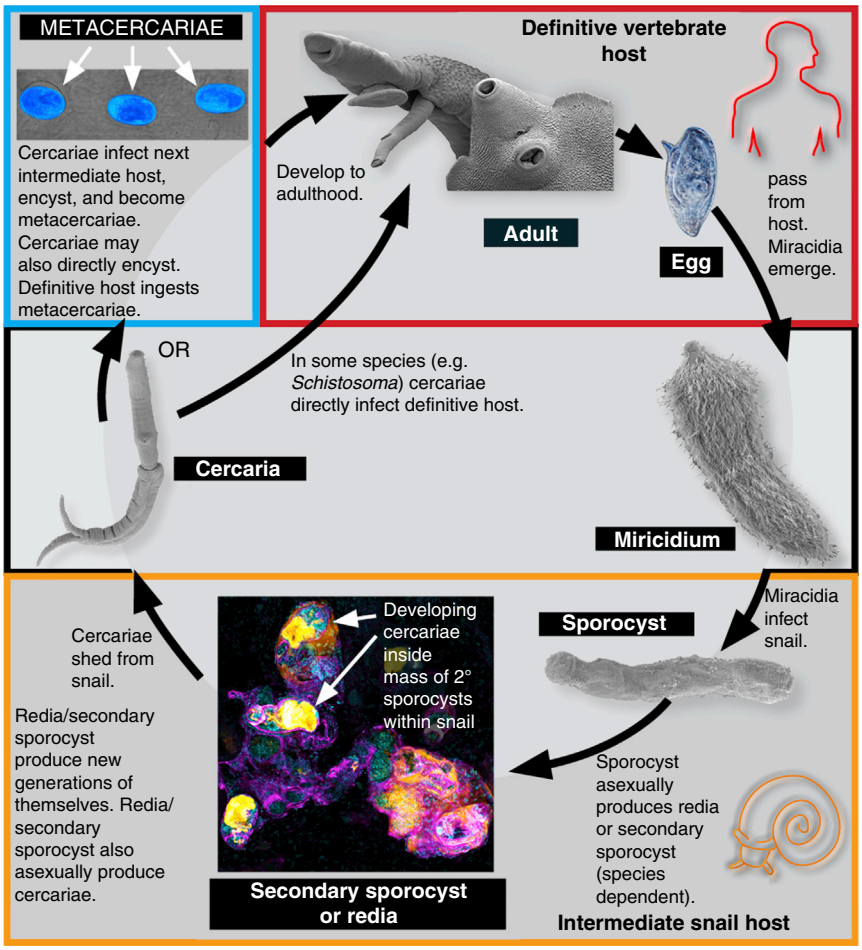

Figure 2. The complex lifecycles of digenetic trematodes.
Miracidia emerge from eggs and infect a specific species of snail. Once inside the snail, miracidia transform into sporocysts. Specialized cells inside sporocysts, called germinal cells, undergo embryogenesis and produce either secondary (2°) sporocysts or redia, depending on the trematode species. Redia and 2° sporocysts are similar, except redia have the capacity to feed on the snail's tissues. Germinal cells inside 2° sporocysts/redia undergo new rounds of embryogenesis producing either cercariae or 2° sporocysts/redia. Usually cercariae can infect a second intermediate host and encyst as metacercariae, encyst as metacercariae on vegetation, or directly infect a definitive host. Images: metacercariae, *Apophallus* in coho salmon muscle (credit, M. Kent), adult *S. mansoni* (back) and *Fasciola hepatica* (front, credit, K. Hoffmann and A. Chakroborty), other stages are all *S. mansoni* (credit, J. Collins and A. Vieira).

has the capacity to restore every tissue in the worm. Traditionally neoblasts have been defined morphologically as small proliferative somatic cells with a high nuclear to cytoplasmic ratio. However, more recent molecular studies have demonstrated that not all planarian neoblasts are created equal — they are heterogeneous in regards to the genes they express and the cell types they are responsible for renewing. Although nearly all work on neoblasts has been done in planarians, molecular approaches are also being applied to study the neoblasts of other free-living (for example, *Macrostomum*; Figure 1E) and parasitic (such as *Schistosoma*; Figure 1O) taxa. It will be interesting to see how similar neoblasts are throughout the phylum with regards to their molecular fingerprint and developmental potential.

Although neoblast-like cells have been found in virtually every flatworm that has been examined, there are plenty of taxa that possess only limited (or no) ability to regenerate amputated tissues. Asking why some taxa cannot regenerate is as intriguing and informative as asking why some possess regenerative potential. For instance, dendrocoelid planarians, such as *Procotyla fluviatilis* (Figure 1D), can only regenerate new heads when amputated within the anterior third of their body. More posterior amputations result in worms that heal their wounds yet never regenerate a new head. Recent work has shown that by perturbing β-catenin, effectively suppressing Wnt signaling, these regeneration-deficient fragments can regenerate new heads complete with a functional central nervous system. Such studies highlight how modifying the activity of a single gene can unleash an untapped reservoir of regenerative potential. These studies also provide hope that there may be untapped regenerative potential lurking in our own bodies that could one day be exploited therapeutically.

One obvious advantage of regeneration is the ability to endure virtually any insult that nature can muster. However, a variety of flatworm species also lean on their regenerative abilities as a reproductive strategy. In addition to sexual reproduction, many flatworms can reproduce asexually. In planarians this is accomplished by transverse fission where the worm will attach to the substrate and literally pull itself in two with each half regenerating a new worm. Some groups, such as Catenulida, do not necessary bother pulling themselves apart and instead will form chains of asexual progeny, called zooids (Figure 1G). Interestingly, sexual and asexual modes of reproduction are not mutually exclusive, as environmental cues (for example, the time of year) can influence which mode the animal uses. In planarians, there are even bizarre examples where simply feeding an asexually reproducing worm extracts of a sexually reproducing worm can induce sexualization. There appears to be a clear correlation between the ability to reproduce asexually and regenerative capacity. Some groups, such as polyclads and the dendrocoelid planarians mentioned above, do not asexually reproduce and have only limited regenerative abilities when compared to flatworms capable of asexual reproduction (such as planarians and *Stenostomum*). Therefore, it is possible that the ability

of flatworms to regenerate is an added bonus of the ability to asexually reproduce.

Neoblasts are not just essential for regeneration — they are also required for homeostatic tissue maintenance. Indeed, planarians without neoblasts will die within the course of a few weeks because they are unable to renew their tissues. This ability of neoblasts to support robust homeostatic tissue maintenance likely explains the often-extreme longevity of flatworms, which can survive for years in the laboratory. An asexually reproducing clone of the Catenulid *Stenostomum tenuicauda* was reported to survive for >10 years in culture. Clonal populations of planarians can similarly be propagated for decades (by asexual reproduction or amputation) in the laboratory without ever sexually reproducing. Indeed, an asexual strain of the planarian *Schmidtea mediterranea* derived from a single worm has been propagated in laboratories for more than a decade with no signs of aging. Although it is difficult to determine the lifespan of many free-living flatworms in the wild, some parasitic flatworms have been observed to thrive for decades in their hosts. For example, people infected with *Schistosoma* blood flukes can harbor adult parasites (which do not replicate in the host) for >30 years after leaving endemic regions. Similarly, some tapeworms, such as the beef tapeworm *Taenia saginata* (Figure 1L), appear to have the capacity to live for the entire duration of their host's life. In such cases, it is not clear that these tapeworms are truly limited by the lifespan of their host. Indeed, the tapeworm *Hymenolepis diminuta,* whose rat host only lives for ~2 years, could be maintained for 14 years by serially transplanting the worms to young rat hosts. Since neoblasts are present not only in free-living flatworms, but also in the Neodermata, it is likely that neoblasts can help explain the longevity of these parasites as well.

Flatworms as parasites

Parasitic nematodes and flatworms, usually referred to as 'helminths' in parasitology circles, include some of nature's most successful

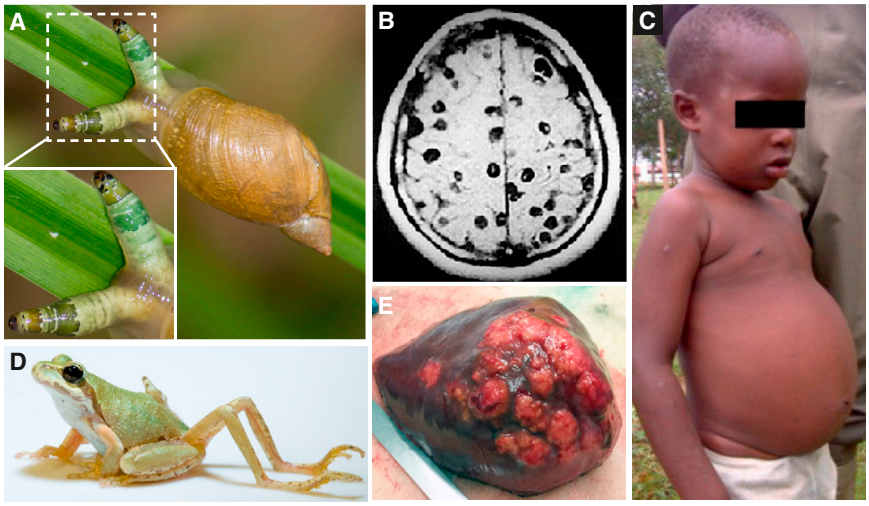

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Figure 3. Parasitic platyhelminthes and their hosts.
(A) *Leucochloridium* sporocyst inside snail tentacle, this sporocyst will pulsate rhythmically (credit, iNaturalist.org, Creative Commons). (B) Cystocerca in a human brain (adapted from Evans *et al.* (1997). Emerging infectious diseases *3,* 403–405; Creative Commons). (C) Child with ascites due to schistosomiasis (adapted from Stothard *et al.* (2013). Trends Parasitol. *29,* 197–205; Creative Commons). (D) Pacific chorus frog with deformed extra hind limbs due to *Ribeiroia* infection (credit, D. Herasimtschuk, Freshwaters Illustrated). (E) Human liver with cysts of *Echinococcus* (credit, C. Issing and K. Brehm).

pathogens. However, in contrast to the nematodes, where parasitism has evolved independently several times, all parasitic flatworms that infect vertebrates (Neodermata) hail from a single evolutionary event. Since the Neodermata are thought to infect every vertebrate on earth, it has been argued that these worms represent the single most successful transition to parasitism in the animal kingdom. This is not to say that there are not isolated cases of commensalism and parasitism in non-neodermatan flatworms (Figure 1A). However, the success of non-neodermatan flatworms as parasites, in terms of species number and host range, is dwarfed by that of the Neodermata. In fact, most flatworm species are Neodermata. The Trematoda alone include nearly 20,000 described species!

Aside from being obligate parasites of vertebrates, the Neodermata are united by the fact they have dispensed with the ciliated epidermis found in their free-living relatives. Instead, as their name would suggest, the Neodermata (*neo* = new, *derm* = skin) have evolved a novel epidermis, a structure known as the tegument. This tegument is a syncytium (a single, multinucleated cell) that covers the entire surface of these worms. The importance of the tegument for the success of these parasites cannot be overstated. As an uninterrupted syncytium, the tegument forms a protective barrier that guards the parasite against the host immune system and from the extremes they encounter living in the digestive system, blood, or internal organs of their host. The tegument also serves as a conduit for the worms to acquire nutrients. Indeed, the Cestodes do not have an intestine and instead rely on their tegument to steal nutrients from their host. Since the tegument aids in so many critical parasite-specific functions, and is not found in any free-living taxa, it is widely considered to be the key innovation that led to the evolution of parasitism in these animals.

While parasitism is the rule among the Neodermata, there are countless variations in parasitic strategies. Some are ectoparasitic, like the Monogenea that live on the gills or skin of aquatic vertebrates, whereas others are endoparasitic, like the Cestoda or Trematoda that live inside the digestive tract, blood, or internal organs of aquatic and terrestrial vertebrates. The

inseparable bond with its host creates a number of barriers for the success of any parasite. First and foremost: how to reproduce and transmit offspring to a new host. Addressing this issue has led these worms to develop amazing developmental and reproductive strategies. For example, the extreme length of many cestodes (tapeworms) is due to the perpetual birth of segments, called proglottids, from the parasites' attachment organ known as the scolex (Figure 1K,L). These proglottids each contain a complete set of male and female reproductive organs that copulate, eventually filling the proglottid with eggs. These gravid proglottids will eventually fall off and pass from the host to be eaten by another host. This strategy allows tapeworms to generate massive numbers of eggs that can be spread over a large geographic area.

Most Neodermata also rely on complex life cycles to ensure their successful transmission. Indeed, with the exception of the Monogenea, most Neodermata exploit a variety of invertebrate or vertebrate intermediate hosts before sexually reproducing inside their definitive host. The most complex of these lifecycles are those of the digenetic trematodes (Trematoda; Figure 2). Following hatching from the egg, larval trematodes, called miracidia, infect a snail intermediate host. Inside the snail, miracidia eventually undergo multiple rounds of asexual reproduction generating potentially millions of infective cercariae. This intramolluscan amplification is a key step of this life cycle since it dramatically enhances the probability these parasites will be transmitted to their next host. Interestingly, the cells fueling this asexual amplification share a number of molecular similarities with the neoblasts found in other flatworms, highlighting yet another role for these stem cells in the amazing biology of flatworms. In some species, cercariae directly infect the definitive host and develop to adulthood. However, in most cases cercariae encyst as metacercariae inside the tissue of a second intermediate host or in the environment. When these metacercariae reach the digestive tract of the definitive host, the encysted metacercariae will mature and sexually reproduce. The reliance of these parasites on intermediate hosts has led to some of the most remarkable adaptations in nature. For example, *Leucochloridium* forms a pulsating green and yellow-striped sac of larvae inside the tentacles of its snail intermediate host (Figure 3A), making the snail an eye-catching snack for the birds that serve as the definitive host. Even more bizarre are the *Ribeiroia.* The cercariae of these parasites infect tadpoles and alter the development of the frog's hind limbs (Figure 3D). These deformed frogs are virtually helpless to escape being eaten by the parasite's definitive bird host.

Although it would seem impossible given their complicated life cycles, neodermatans are among the most successful human pathogens, responsible for 4 of the 17 neglected tropical diseases targeted by the World Health Organization. Cestodes cause life-threatening diseases such as neurocysticercosis and echinococcosis, in which larval tapeworms form cysts inside human tissues (Figure 3B,E). Trematodes such as *Clonorchis sinensis* and *Opisthorchis viverrini* are among the few pathogens known to cause cancer. The most serious and widespread parasitic flatworms are trematodes of the genus *Schistosoma* (Figure 3C). These parasites infect over 200 million people in the developing world and claim the lives of more than 200,000 every year. As is the case with many parasitic diseases, treatment options for diseases caused by parasitic flatworms are limited to a small number of drugs. However, the availability of genome sequences for the most serious parasitic flatworms and a growing molecular toolbox makes this an exciting era to explore the biology of these fascinating parasites. Certainly, understanding more about the complex biology of these animals will expedite the discovery of the next generation of therapeutics.

Conclusion

Whether it is the regeneration and asexual reproduction observed in free-living taxa, the bizarre embryonic development of many Neoophora, or the complex lifecycles of the Neodermata, flatworms possess a remarkable ability to mold their developmental trajectories to their environmental circumstances. Although this developmental plasticity is key to the success of so many flatworms, molecular studies into these processes are only in their infancy. Clearly, these gaps in our knowledge necessitate a larger effort to understand this important biology, not just in model flatworms like planarians, but also in free-living and parasitic worms from across the phylum.

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