Invertebrate Models for Biomedical Research, Testing, and Education

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Abstract

Invertebrate animals have been used as medicinals for 4,000 years and have served as models for research and teaching since the late 1800s. Interest in invertebrate models has increased over the past several decades as the research community has responded to public concerns about the use of vertebrate animals in research. As a result, invertebrates are being evaluated and recognized as models for many diseases and conditions. Their use has led to discoveries in almost every area of biology and medicine—from embryonic development to aging processes. Species range from terrestrial invertebrates such as nematodes and insects to freshwater and marine life including planarians, crustaceans, molluscs, and many others. The most often used models are the fruit fly *Drosophila melanogaster* and the minuscule nematode *Caenorhabditis elegans*. Topics in this article are categorized by biologic system, process, or disease with discussion of associated invertebrate models. Sections on bioactive products discovered from invertebrates follow the models section, and the article concludes with uses of invertebrates in teaching. The models reviewed can serve as references for scientists, researchers, veterinarians, institutional animal care and use committees (IACUCs), and others interested in alternatives to vertebrate animals.

Key Words: animal model; bioactive compound; instructional model; invertebrate

Introduction

History and Highlights of Invertebrate Use in Research

Invertebrate models of human genetics and disease first appeared in the scientific literature in the late 19th century. A search of the National Library of Medicine's PubMed database for the dates 1800–2010 revealed a progressive increase in research involving invertebrates. During 1800–1900, three invertebrate articles appeared. William E. Castle, an animal geneticist, was one of the first researchers to publish studies based on invertebrates—he utilized the sea squirt (*Ciona intestinalis*) as his research model and published his dissertation on this species in 1896.[1] The remaining two articles for the 19th century both appeared in the *Journal of Physiology*; the first reported on the presence of hematoporphyrin in the integument (Munn 1886), the second on respiratory exchange in marine invertebrates (Vernon 1895).

Research with invertebrates increasingly appeared in the scientific literature during the early 1900s, but it was not until the early 1940s that significant numbers of such papers were published. During the period of 1923–1943, 16 papers were based on invertebrate research as compared to nearly 14,000 during 1943–1963. Research with invertebrates showed further expansion in the 1960s, with over 40,000 papers on invertebrates published from 1963 to 1973. Research in the 21st century has continued to show the growing importance of invertebrates in biological and biomedical research: in 2008–2010 PubMed showed 44,000 papers that used invertebrate species as models for studies of genetics and disease and for drug development and testing.

Another mark of the importance of invertebrates to biomedical research is the number of Nobel Prizes awarded to researchers who have used them, whether as their primary model or one of several animal species. Since the first Nobel Prize for Medicine in 1901, 74 of the awards have been based on animal research, and 18 of these included invertebrate species.[2] *Drosophila* was the model for Thomas H. Morgan's discoveries regarding the role of chromosomes in heredity; he was awarded the Nobel Prize for Medicine in 1933 and gave credit to Charles Woodworth and William Castle as pioneers of the *Drosophila* model.[3] *Caenorhabditis elegans'* genome was one of the first to be sequenced and the importance of this organism to scientific advancement is highlighted by three Nobel Prizes awarded in the 21st century. The first, in 2002, was awarded to Sydney Brenner, Robert Horvitz, and John Sulston for their work on similarities in genetic and molecular mechanisms of organ development and programmed cell death between humans and *C. elegans*. Andrew Fire and Craig Mello won the 2006 Nobel Prize for

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[1]Castle's papers are available on the website of the American Philosophical Society (www.amphilsoc.org); this and other websites cited in this article were accessed between November 9, 2010, and April 12, 2011.

[2]Information from www.animalresearch.info/en/medical/nobelprize.

[3]Information about this and other Nobel Prize laureates discussed in this article is available online at http://nobelprize.org/nobel_prizes/medicine/laureates.

their studies with *C. elegans* illustrating the conservation of genes between species and elucidating the fundamental mechanisms of gene regulation (Nass et al. 2008). Most recently, the 2008 Nobel Prize for Chemistry was shared by Martin Chalfie, of Columbia University, for his work with *C. elegans* utilizing the green fluorescent protein (GFP) to facilitate his research on touch sensitivity and gene expression (Grandin 2009).

Applications of Invertebrates in Research

Biomedical research involving the use of animals has been the cornerstone of medical progress for the past several centuries, but ethical concerns about the use of vertebrates, which are more commonly understood to be sentient animals, have led researchers, veterinarians, and others in laboratory animal science to search for alternatives. Invertebrates can serve as replacements for their vertebrate counterparts in many areas of research, testing, and education.

A new area of focus for invertebrate research is drug development, including the discovery of bioactive products from both terrestrial and marine invertebrates. Invertebrates may also play a pivotal role in toxicity and efficacy testing of new pharmaceuticals for both human and animal diseases, sparing vertebrate animals from preliminary testing. As a result of animal rights proponents' pressure on professional, preprofessional, and K–12 schools, the use of live vertebrate animals is rare in education. Invertebrates can serve as alternative teaching subjects, providing students with opportunities to observe behavior, anatomy, physiological principles, pathology, results of genetic manipulation, and mechanisms of drug actions.

To assist researchers, veterinarians, and institutional animal care and use committee (IACUC) members searching for models of specific conditions and diseases, this article is organized by biologic system, process, or disease with discussion of associated invertebrate models. Given the genetic and molecular basis of many of mechanisms and diseases, these topics are discussed in the systematic context with additional models found in the tables (which list models not discussed in the narrative, for reference and to illustrate the breadth of invertebrate use).

Because of their long prominence as research models, *Drosophila* and *C. elegans* are the first subjects of this discussion of invertebrate models.

The Fly and the Worm

Drosophila melanogaster

The fruit fly (*Drosophila melanogaster*) is one of the most studied organisms in the animal kingdom. Cytogenetic research has led to the complete mapping and sequencing of its chromosomes, enabling its use in an array of biological and biomedical investigations (Gilbert 2008). Thanks to the vast number of genetic and molecular tools available for use with *Drosophila*, coupled with similarities in development and behavior, the fruit fly has served as a unique and sensitive model for the study of human genetics and disease (Beckingham et al. 2005). The power of *Drosophila* genetic screens has led to the study of many mutant strains that have helped elucidate visual and behavioral pathways, embryonic patterning, and the development of models for numerous human diseases (Beckingham et al. 2005).

Several databases have been created to contain the genetic records for this tiny but exquisitely precious mine of information. A comparison of one of these databases against over 900 human disease genes (Drysdale and FlyBase Consortium 2008) showed that 714 human disease sequences matched to 548 *Drosophila* genes, of which 153 could be associated with mutant alleles—79 matched to human malignancies and 74 to human neurologic diseases (Reiter et al. 2001).

Drosophila modeling has also been used to express protein products found in human disease and to compare the resulting pathologic condition in the fly to the human counterpart (Beckingham et al. 2005). This approach has yielded positive results in three types of neurodegenerative disease: Alzheimer's, Parkinson's, and polyglutamine diseases such as Huntington's chorea; for each, a fly model has been created and used in research (Bonini and Fortini 2003; Iijima et al. 2004; Iijima and Iijima-Ando 2008).

Drosophila's current and potential uses are expected to transcend virtually every area of biologic study (Gilbert 2008) and to play a role in therapeutic trials for drug candidates targeting many human and animal diseases (Beckingham et al. 2005; Gilbert 2008). Beckingham and colleagues (2005), Gilbert (2008), and Korey (2007) provide excellent reviews of *Drosophila*'s uses in biomedical research.

Caenorhabditis elegans

Caenorhabditis elegans models have many advantages over vertebrate animals for use in biological and biomedical studies. These small worms are highly prolific reproducers with a short generation time, easily grown under laboratory conditions, and inexpensive to care for (Nass et al. 2008; Riddle 1997; Wood 1997). Additionally, *C. elegans* is anatomically simple and has a fully mapped nervous system (White et al. 1976). Humans and *C. elegans* have virtually the same number of genes, and there are many parallels in the ways that these divergent species operate on genetic and molecular levels. As a result, *C. elegans* has become an instrumental model for understanding the molecular mechanisms involved in many human diseases (Nass et al. 2008). It can serve as a model of both forward and reverse genetics, with mutants, transgenics, and knockouts easily created; and worms that express GFP enable in vivo observation of cellular and metabolic processes (Jorgensen and Mango 2002; Nass et al. 2008; Riddle 1997; Wicks et al. 2001).

Caenorhabditis elegans has also been used to study basic biological and physiological processes that are common to all animals (Strange 2007). It has served as a model for Parkinson's, Alzheimer's, and Huntington's disease, diabetes, cancer, immune disorders, and the development and testing of therapeutic agents for these diseases (Artal-Sanz et al. 2006a; Faber et al. 1999; Link 2001; Nass et al. 2008; Pujol et al. 2008). *C. elegans* may someday be the model of choice for in vivo testing of new drugs, including high-throughput screening technologies (Silverman et al. 2009).

Biological Models

Developmental Biology

Invertebrates have been used in the study of embryology since the late 19th century, and several Nobel Prizes have been awarded to scientists who utilized invertebrates in their quest to understand developmental biology. Mechnikov published papers on the embryology of insects during the late 1860s and won the Nobel Prize in 1908. In 1995, the Nobel Prize for Medicine was awarded to three researchers who used *Drosophila* to evaluate genetic control of early embryonic development.

This section provides information on several of the main developmental models; Table 1 lists additional models.

Drosophila melanogaster and Caenorhabditis elegans

A number of invertebrates have been used in developmental biology, but the two primary organisms are *Drosophila* and *C. elegans*, with *Drosophila* most often used. During the past 20-plus years, genetic studies using *Drosophila* have elucidated the regulatory mechanisms that control development of the embryo (Baker and Thummel 2007). Genetic screens in *Drosophila* have led to the discovery of the signaling pathways Notch, Wingless, and Hedgehog and furthered knowledge of vertebrate development and disease (Bier 2005). Genetic alteration of fly embryos has provided information about a variety of biological mechanisms (Shen et al. 2007). Planar cell polarity studies in *Drosophila* and other arthropod embryos have shown that coordination of cell polarization occurs in the development and function of many organs, particularly in epithelial cells such as the gut epithelium, which needs to move secretions (Simons and Mlodzik 2008). *Drosophila* models of planar cell polarity have focused on the development of hair patterns, the eye, and the cochlea and have supported comparisons to mammalian development pathways for each.

Because of the close similarities between *Drosophila* and vertebrate cardiogenesis and the conservation of key genes, the fly's heart serves as an excellent model of cardiac development and disease (Medioni et al. 2009). Study of cardiac development in the fly has led to understanding of the

Table 1 Selected invertebrate models of developmental biology[a]

Model	Species used	References
Bone morphogenic proteins	*Drosophila*	Raftery and Sutherland 2003
Calcium signaling	*Asterina pectinifera*	Santella et al. 2008
Cilia regulation of development pathways	*Caenorhabditis elegans*	Pedersen et al. 2008
Chromatin insulators	*Drosophila*	Gurudatta and Corces 2009
Developmental glycobiology	*Drosophila*	ten Hagen et al. 2009
Formation of the nervous system	*Drosophila*	Kulesa et al. 2009; Quan and Hassan 2005
Gene regulatory networks	*Echinoidea*	Peter and Davidson 2009
MicroRNA function in embryogenesis	*C. elegans*	Wienholds and Plasterk 2005
Nitrous oxide signaling during neural development	*Locusta*, *Schistocerca*, *Acheta*, *Manduca, Drosophila*	Bicker 2007
Pattern signaling and retinal development	*Drosophila*	Baker 2007; Buscarlet and Stifani 2007
Pituitary patterning	*Drosophila*	Veitia and Salazar-Ciudad 2007
Regulatory switches	*Drosophila*	Borok et al. 2010
Semophorin in developing nervous system	Caelifera (grasshopper)	Bonner and O'Connor 2000
Tubulogenesis	*Drosophila*	Kerman et al. 2006

[a]These models are provided for reference; discussion of other models is provided in the text.

molecular and cellular mechanisms that underlie morphogenesis and has elucidated the genetic control of cardiac physiology (Medioni et al. 2009). The *Drosophila* heart model may also play a role in efforts to identify unknown genes and the regulatory networks that contribute to normal heart development and function (Tao and Schulz 2007).

Other aspects of *Drosophila* anatomy and function have proven useful in research. Because of the similarities between *Drosophila* and mammalian mechanisms of hematopoiesis, the fly serves as a model for vertebrate blood cell development (Crozatier and Meister 2007; Crozatier et al. 2007). The developing *Drosophila* eye has been used to study the Notch and tyrosine kinase signaling mechanisms, which direct cell fates during development; recruitment of factors (e.g., transcription factors for gene expression) is important in animal development (Voas and Rebay 2004). The fly's excretory system has been used to study the development and differentiation of the renal system across species (Denholm and Skaer 2009).

In *C. elegans* the pharynx (foregut) has served as a key model for the study of general organ development, with high applicability to vertebrate embryology (Mango 2007). Research on the nematode has clarified the mechanisms of neural cell development by showing that the *C. elegans* gene *sem-4* participates in the control of mesodermal and neuronal cell development (Basson and Horvitz 1996). The gene *lin-9*, which affects signal transduction pathways that control gonadal development in the nematode, has counterparts in many species, making *C. elegans* a useful model for studies of developmental biology and intercellular signaling mechanisms (Beitel et al. 2000). Vulval development in *C. elegans* can be used as a model for understanding the roles of chromatin remodeling in multiple development pathways (Andersen et al. 2006). Additionally, through study of the proteins and genes involved in this development, scientists may be able to recognize how complex proteins could become targets for cancer therapy (Andersen et al. 2006). *C. elegans* has been the primary model used in high-throughput genome scale analysis evaluating the involvement of genes in tissue development (Ge et al. 2006).

Other Invertebrate Species

In recent years deuterostomes and other marine invertebrates, as well as insects, have been increasingly used both to understand the evolution of these organisms and to shed light on developmental processes in higher animals including humans (Arendt et al. 2008; Bicker 2005, 2007; Darling et al. 2005; Holland and Gibson-Brown 2003; Isbister and O'Connor 2000; Lowe 2008; Pourquie 2000; Swalla 2006; Wessel et al. 2010). Grasshoppers (*Dissosteira carolina* and others) have been used to study neural cell development, specifically, the genetics and development of axons through evaluation of grasshopper limb bud growth cones (Isbister and O'Connor 2000). The molecule nitric oxide (NO) is thought to play a role in the regulation of neuronal growth and migration, and gastropod molluscs and embryonic grasshoppers serve as models for elucidating NO signaling pathways (Bicker 2005, 2007).

For over a century the sea squirt (*Ciona intestinalis*) has been used as a model for studying animal development (Holland and Gibson-Brown 2003; Passamaneck and Di Gregorio 2005). This animal may also play an important role in studies to determine how to solve comprehensive gene networks in chordates and evaluate how these networks control development (Davidson 2007). The sea star, or starfish (*Asterias forbesii*), has been utilized in developmental research related to reproductive processes. Basic techniques (e.g., oocyte isolation, microinjection, and polymerase chain reaction) have been developed so that new researchers can easily work with these animals (Wessel et al. 2010). The genome of the starlet sea anemone (*Nematostella vectensis*) has been the focus of a genome project; as a result, this organism has been proposed as a model for molecular and evolutionary biology (Darling et al. 2005). Somitogenesis, a multistep patterning process in vertebrates, has been modeled in a variety of animal models from mice to protostomes and deuterostomes; research with invertebrates has indicated that the genetic machinery responsible for this segmentation is conserved throughout the animal kingdom (Pourquie 2000).

Stem Cell Biology

Stem cell biology has its roots in research performed with invertebrates: *Stammzelle*, the German word for stem cell, was created based on research using crustacean primordial germ cells in the 1890s by the German researcher Valentin Haecker (Kohlmaier and Edgar 2008). Invertebrates continue to be key models for understanding many of the characteristics and genetics of stem cells, including their pluripotency and ability to self-renew through proliferative growth (Kohlmaier and Edgar 2008).

The stem cell niche has been evaluated through study of *Drosophila* gonads. This research has furthered knowledge of the structure of the niche and its ability to produce signaling pathways, which lead to stem cell self-renewal (Lin 2002; Palasz and Kaminski 2009). The germline of *C. elegans*—specifically, its distal tip cell, the foundation for the animal's stem cell niche—has also served as a model for stem cell biology (Byrd and Kimble 2009; Hubbard 2007). Using genetic analysis of *Drosophila* muscle and satellite stem cells, researchers have modeled the biology of vertebrate muscle stem cells (Figeac et al. 2007). Planarians, uniquely, regenerate from their stem cell system and thus serve as a model for gene and stem cell regulation (Agata 2003). Cnidarians (*Hydra, Nematostella*) have been used to study stem cell signaling pathways and other mechanisms of stem cell biology and function (Watanabe et al. 2009).

Endocrine Function and Metabolism

Drosophila, *C. elegans*, and marine invertebrates have been useful in the study of endocrine and metabolic diseases.

Drosophila is an increasingly common model for understanding metabolism across species boundaries (Baker and Thummel 2007). The ability to study the genetics of metabolic function in this small but sensitive model has provided insights into the central regulatory pathways of vertebrates.

Study of the fly has also elucidated the pathogenesis of human metabolic diseases such as diabetes and obesity. *Drosophila* has served as an excellent model for the study of diabetes, lipid metabolism, and other mechanisms of metabolism, including sterol adsorption and trafficking defects that occur in Niemann-Pick type C disease (Baker and Thummel 2007). Both diabetic and obese flies, as well as genetically "lean" and hypoglycemic phenotypes, have been created as models for human disease (Bharucha 2009). *Drosophila* is not suitable for the study of all aspects of human metabolic control; for example, the leptin signaling pathway is not present in the fly. But insulin signaling is very similar in flies and humans, making *Drosophila* an ideal model to study the ways insulin regulates metabolism (Teleman 2009).

Transgenic flies have been developed to study the molecular endocrinology of neuroendocrine signaling and control (Dow 2007). Insulin receptor–like signaling pathways in flies regulate a transcription factor known as DAF-16/FOXO, a "master regulator" of many biological mechanisms (Lin et al. 1997; Ogg et al. 1997). Both *Drosophila* and *C. elegans* can serve as models for clarifying the mechanisms of this transcription factor, which controls lifespan, metabolism, and stress responses, and, in the worm, regulates the dauer stage (when the animal goes into a state of hypometabolism) (Mukhopadhyay et al. 2006). *C. elegans*' dauer stage can be used to model protein targets in the stress responses of higher animals, and study of this stage may lead to recognition of therapeutic targets for human diseases such as ischemia, insulin resistance, neurodegenerative diseases, and cancer (Lant and Storey 2010).

Caenorhabditis elegans has shown promise as a model organism for studying AMPK (5′-AMP-activated protein kinase) signaling (Beale 2008), because it has demonstrated evidence of having AMPK pathways. AMPK is often called "the master metabolic switch" as it plays a key role in regulating metabolism, protein synthesis, and cell growth and in mediating the actions of hormones (Beale 2008). Research into the endocrine signaling pathways and hormone production control in *C. elegans* has yielded insights into similar pathways in humans (Beckstead and Thummel 2006).

Hedgehog signaling studies in *Drosophila*, nematodes, and mice have shown that this pathway inhibits the amount of fat in the body; thus, manipulation of the pathway may be useful in treating hyperlipidemia, obesity, and type 2 diabetes in humans (Suh et al. 2006, 2007). Studying the gene Adipose, Suh and colleagues (2007) determined that both mice (*Adp)* and flies (*adp)* heterozygous for the gene are obese and insulin-resistant, indicating that this gene has an antiadipogenic ability (Gilbert 2008). Other studies have used the fly as a model for human fatty liver disease; the fly oenocyte, which is comparable to the mammalian hepatocyte, participates in lipid metabolism by producing enzymes that lead to ketogenesis (Arquier and Leopold 2007; Downer 1985). In addition to serving as a model for lipid metabolism, the fly may be an effective model both in efforts to discover more genes involved in obesity and diabetes and in the screening of therapeutic agents developed for lipid-based diseases (Gilbert 2008).

Other endocrine models include the silkmoth and the sea squirt. The silkmoth (*Bombyx mori)* has an insulin-related peptide gene that is similar to human preproinsulin (Yoshida et al. 1998). The sea squirt (*Ciona intestinalis*) has many analogues to hormones (e.g., gonadotropin-releasing hormone, insulin, and insulinlike growth factor [IGF]) found in higher animals and thus may prove to be a useful model for understanding the function of these hormones and for the study of neuroendocrinology (Sherwood et al. 2006). And *Drosophila* has insulinlike peptides that serve as hormones, neurotransmitters, and growth factors (Wu and Brown 2006).

Immunology

Allorecognition and Adaptive Immune System

Allorecognition and its molecular basis have been studied in ascidian urochordates such as the sea squirt and the star ascidian (*Botryllus schlosseri*) (Ben-Shlomo 2008). As they most likely share common ancestors with vertebrates, research into their patterns of self-recognition have provided insight into the development of the immune response of vertebrates.

Even though urochordates are not recognized to have an adaptive immune system, some genes in organisms such as *C. intestinalis* are related to those in vertebrates and give rise to adaptive immunity (Du Pasquier et al. 2004). Studies using urochordates and other invertebrate deuterostome model systems have provided information on mechanisms of antigen receptor diversification and immune system development relevant to vertebrates (Eason et al. 2004). Gene rearrangement studies in other species, such as lampreys and molluscs, have also provided information about differences and similarities between adaptive and innate immune systems (Flajnik and Du Pasquier 2004). McKitrick and De Tomaso (2010) provide an excellent review of the molecular mechanisms of allorecognition in *B. schlosseri*.

Both colonial and solitary free-living reef corals such as *Fungia scutaria* show evidence of histocompatibility and allorecognition. Sea anemones from the order Actiniaria also have similar immune systems (Jokiel and Bigger 1994). These animals, along with *B. schlosseri,* can be used to study the evolution of the immune system and could serve as models for screening new therapeutics targeting cellular immunity and transplant rejection. The star ascidian has also been suggested to serve as a model for maternal-fetus allorecognition issues, as the organism has a natural killer (NK) cell similar to human uterine NK cells (Lightner et al. 2008).

Immunity and Response to Infection

Innate immunity is the invertebrate's primary defense against infectious organisms, and this system has similarities to that of vertebrates (Magor et al. 1999). The fly's sensing and signaling cascades during infection have stimulated the use of *Drosophila* as a model for innate immunity and response to infection (Ferrandon et al. 2007; Royet et al. 2005). Similarly, *C. elegans*' innate immunity has been used to study immune defense and the role of cellular stress in an organism's response to infection (Millet and Ewbank 2004). The nematode has also been used to model the activation of genes in response to infection (Gravato-Nobre and Hodgkin 2005). *Octopus maya* has been suggested as a model for immune responsiveness because of its ability to become infected by pathogenic organisms (Van Heukelem 1977).

Macrophages

Invertebrates have played a key role in the history of the macrophage. The term "macrophage" (phagocyte) was coined by Ilya Ilyich Mechnikov, a comparative embryologist and winner of the Nobel Prize in 1908. He observed in starfish larvae a group of cells that had unusual characteristics—the ability to move in tissue: after introducing small rose thorns into the larvae, he noted the next morning that the thorns were surrounded by the mobile cells. He further studied this phenomenon using the freshwater flea (*Daphnia magna*), exposing it to fungal spores: the spores were attacked and isolated by the *Daphnia* macrophages.

Macrophage-like cells are present in many species of invertebrates. Often they originate from mesenchymal, endothelial, or fibroblastic cells that differentiate into phagocytes (Naito 2008). For example, *Hydra*, a member of the phylum Cnidaria, has cells with phagocytic capability that play a role in the animal's ability to recognize "self" (Bosch and David 1986; Kobayakawa and Koizumi 1997; Naito 2008) and, thus, make it a useful model of graft rejection. Molluscs also have cells that can act as macrophages, but the origin of these cells is mesenchymal, not hematopoietic, indicating divergent paths of differentiation (Naito 2008).

Neuroimmunology

Neuropeptides can transfer information from the nervous system to the immune system, perhaps serving as regulators of immune response (Stefano et al. 1991, 1996, 1998). Opioid peptides are present in the neural tissues of several molluscs, including the blue mussel (*Mytilus edulis*) (Stefano and Leung 1982) and the garden snail (*Helix aspersa*) (Marchand and Dubois 1986), and are involved in immune processes. These animals can thus serve as models to explore connections between the immune system and neural regulation (Liu 2008).

Infectious Disease

Viruses have been found in the genome of many species including invertebrates (Becker 2000). The gypsy element, which infects *Drosophila,* was the first retrovirus recognized in invertebrates and may be an ancestral precursor of vertebrate retroviruses (Pelisson et al. 2002). The gene *flamenco* modulates *gypsy* in *Drosophila*, and the interaction of the two genes has provided an excellent model for the study of the genetic relationships between virus and host (Bucheton 1995).

Drosophila has also served as a model for other host-parasite relationships—for example, as a host for the *Burkholderia cepacia* complex (Bcc), a group of bacteria that contribute to severe health risks among humans with cystic fibrosis (Castonguay-Vanier et al. 2010). Bcc studies performed in *Drosophila* showed similar virulence patterns to those observed in mammals, indicating that the fly is a useful alternative model for such studies (Castonguay-Vanier et al. 2010).

Virulence screening for agents with biological warfare potential may be possible in *Drosophila*. Recently, genome-wide virulence screens were performed for *Francisella novicida* using *Drosophila* as the host. Researchers identified many similarities in gene function between flies and mammals but also found that a considerable number of the virulence factors that play a role in mammals do not in the insect model (Ahlund et al. 2010).

Pathogenic fungi have been studied in worms and insects. Several major fungal pathogens (e.g., Aspergillus, Candida, Cryptococcus) infect and kill roundworms, fruit flies, and wax moths. Because the genes that modulate virulence in these invertebrates are remarkably similar to those of humans, these three species have been evaluated as alternatives to mammalian models of fungal disease (Chamilos et al. 2007). Researchers have specifically used *C. elegans* to study bacterial and fungal virulence, pathogenicity, and mechanisms of host defense against invaders (Fuchs and Mylonakis 2006). Conservation of virulence mechanisms between roundworms, fruit flies, and wax moths and higher animals has led to the increased use of these and other invertebrates in virulence studies (O'Callaghan and Vergunst 2010).

Because of the similarities between human and invertebrate infections, insects are considered a model of choice for studying opportunistic microorganisms. Insect models can allow for rapid screening of potentially opportunistic infections while minimizing concerns about the ethics of vertebrate animal experimentation (Scully and Bidochka 2006). O'Callagan and Vergunst (2010) provide a review of the use of *Drosophila* and *C. elegans* as models for infectious disease.

Other invertebrates used to model infectious disease include *Daphnia* and marine shrimp species. *Daphnia* is recognized as a model system to study host-parasite interactions for diversity of parasites, from bacteria to helminths (Ebert 2008). Study of viral diseases in marine shrimp has

led to discovery of RNA interference–based therapies that may result in similar therapies for viral diseases of higher animals, including humans (Krishnan et al. 2009).

Memory, Learning, and Behavior

The California sea slug (*Aplysia californica*; Glanzman 2006, 2008, 2009), opalescent sea slug (*Hermissenda crassicornis*; Alkon 1987), and pond snail (*Lymnaea stagnalis*; Lukowiak et al. 1996)—all gastropod molluscs—have served as models in studies of neuronal mechanisms of learning and memory. Such studies have also used many cephalopod molluscs, especially the coleoid group, which includes octopuses, cuttlefishes, and squids.

The octopus has been an effective model in studies of behavioral communication. Octopuses use body color and tentacle positions to indicate their attitude toward approaching prey or other octopi (Pribram 1973)—their stance and color are comparable to the facial expressions and body language of monkeys and humans. Octopi have also proven useful in reversal learning experiments, with comparable results to similar studies in rats (Sutherland and Mackintosh 1971).

The chambered nautilus (*Nautilus pompilius*), one of the most ancient cephalopods, has been used in Pavlovian conditioning studies (Crook and Basil 2008), and *Aplysia* and *H. crassicornis* have been used to study classical and operant conditioning (Baxter and Byrne 2006). Studies in *Aplysia* have led to elucidation of the molecular mechanisms involved in all phases of implicit memory (Hawkins et al. 2006), and the mud flat crab (*Chasmagnathus convexus*) has served as a model in similar studies (Romano et al. 2006). Decapod crustaceans have been used to study aggressive behaviors (Barron and Robinson 2008).

Among insects, honeybees (*Apis mellifera*) have a long and rich history as research models—Aristotle studied them and recorded his observations of their behavior (Elekonich and Roberts 2005). More recently, von Frisch (1967) studied the bee's behavior and communication through dance. Even though the brain of the honeybee is less than 1 cubic millimeter in diameter, it is very accessible for study and can serve as a model for many higher-order cognitive processes (Giurfa 2006, 2007). Investigators have studied learning, memory, and sensory processing by focusing on honeybee patterns of navigation and foraging, as bees follow several routes to and from their nest to their preferred blossoms, requiring them to recall memory sequences and respond to memory cues (Chittka et al. 1999; Collett 2005; Menzel 1999; Menzel and Giurfa 2006). Furthermore, the complete sequencing of the honeybee genome makes this tiny creature an excellent research model (Menzel et al. 2006). The study of gene expression and of the endocrine, metabolic, and neural physiology of bee colonies is revealing how these and other animals respond to their environment (Elekonich and Roberts 2005). Scientists are also studying neural mechanisms of reward reinforcement in honeybees (Gil et al. 2007).

Ants have been used to study the molecular genetics of social behavior and adaptation (Robinson et al. 1997) and to discover associative links between long-term memory and visual stimuli (Collett and Collett 2002). In the cricket (*Gryllus bimaculatus*), the sensory system and ability to respond to environmental stimuli have been compared to the complex responses of vertebrates to their environments (Jacobs et al. 2008). *Drosophila* has served as a model for olfactory learning and memory, partly because of the ability to chemically mutate genes in this organism (Glanzman 2005; McGuire et al. 2005). With the ability to manipulate *Drosophila* genes and to model aggressive behavior and its genetic basis (Robin et al. 2007), study of the fly may lead to understanding of the genetic and molecular basis of human emotions (Iliadi 2009). The fly also serves as a model of several human cognitive disorders and may be useful in the evaluation of drug therapies for them (Skoulakis and Grammenoudi 2006).

C. elegans has been the subject of studies on the behavior and genetics of habituation, the use of long- and short-term memory for learning (Giles and Rankin 2009), and the neural and molecular mechanisms of behavior (Schafer 2005; Sengupta and Samuel 2009). Its dauer stage serves as a model for the molecular mechanisms behind stress response behavior (Lant and Storey 2010).

Musculoskeletal Disease

The metabolism of proteins in the flight muscles of the tobacco hornworm (*Manduca sexta*) has been studied (Tischler et al. 1990), and the species has been used in space flight research to understand the effects of low gravity on muscles. Studies using both *Drosophila* and *C. elegans* have enhanced understanding of muscle formation and degeneration (Kim et al. 2008); for example, research with *C. elegans* contributed to knowledge of regulatory muscle proteins and the maintenance of muscle under certain physiological and pathological conditions (Kim et al. 2008). Striated muscles of the leech (*Pontobdella muricata*) have dystrophin-associated proteins that have striking similarities to those in humans; thus, leeches and other annelids may be useful in the study of interaction sites for muscular dystrophy–associated proteins (Royuela et al. 2001).

Neural and Neuromuscular Systems and Disease

Drosophila and C. elegans

The fruit fly and the nematode are the primary invertebrate models for many areas of neurobiological study.

Work with *Drosophila* has a long history and includes the cloning of the first potassium channel; demonstration of transient receptor potential (TRP) channels through cloning of *trp*; discovery of the genes responsible for the biological

clock; and studies of courtship behavior, sleep patterns, learning, alcoholism, and aggression (Foltenyi et al. 2007; Gilbert 2008; Grosjean et al. 2008; Vosshall 2007). The fly serves as a model for many specific disorders. For example, there is a homologue or orthologue in *Drosophila* for most of the approximately 300 genes that participate in human retardation (Inlow and Restifo 2004), so the mysteries surrounding Fragile X retardation may be unraveled through study of the fruit fly model (Pan and Broadie 2007). *Drosophila* models will also play a vital role in the identification and evaluation of new therapies for neurological diseases, providing a preliminary animal model before the use of mammals (Marsh and Thompson 2004, 2006; Whitworth et al. 2006).

C. elegans is an important model for understanding the pathophysiology and molecular mechanisms of neurodegenerative diseases such as Alzheimer's, Parkinson's, and Huntington's (Johnson et al. 2010; Troulinaki and Tavernarakis 2005).

Tauopathies

Drosophila and *C. elegans* have served as models for Alzheimer's disease and other tauopathies (Crowther et al. 2005; Luheshi et al. 2007; Wheeler et al. 2010). Alzheimer's is postulated to result from amyloid toxicity that initiates aggregation of proteins into amyloid fibrils (Luheshi et al. 2007). In the fly model, Crowther and Luheshi found that protein aggregation in fly brains leads to dysfunction of neurons and neuronal degeneration, which progresses to memory loss and shortened lifespan, hallmark symptoms of Alzheimer's (Crowther et al. 2005; Luheshi et al. 2007). Transgenic *C. elegans* created to express human beta amyloid peptide (Abeta) develop intracellular deposits with the classical Alzheimer's amyloid fibrillar component, indicating the usefulness of this organism in the study of Alzheimer's (Link et al. 2001). The introduction of mutant human tau into *Aplysia* neurons grown in culture induced neuropathologic lesions typical of Alzheimer's, indicating that *Aplysia* can serve as a model for this disease (Shemesh and Spira 2010).

Drosophila is contributing to knowledge of Niemann-Pick type C (NPC), a tauopathy in which an overabundance of free cholesterol in the brain leads to neurodegeneration (Patterson 2003; Vance 2006). The pathogenesis of NPC is not well understood, but if either *NPC1* or *NPC2* is mutated in the human, NPC is likely to result (Patterson 2003). To determine whether the fly could serve as a model of NPC, researchers reviewed the fly database (flybase.org) and identified potential NPC models (Fluegel et al. 2006; Huang et al. 2005). As in humans, the presence of *npc1* is necessary for sterol homeostasis; when it is mutated, the flies show molting defects. Study of *Npc1a* function in the fly has led researchers to hypothesize that *NPC1* may play a vital role in the transport of sterol to the endoplasmic reticulum and mitochondria (Huang et al. 2005). *Drosophila* also contains a family of *Npc2a* genes whose mutation results in neurodegeneration (Huang et al. 2007). Similarities between NPC in flies and humans suggest that the fruit fly can also serve as a therapeutic test model for this devastating disease (Gilbert 2008).

Parkinson's, Huntington's, and Other Neurological Diseases

The discovery of *Drosophila* homologues of Parkinson's-associated loci has resulted in the use of pink1 and parkin fly mutants as models for Parkinson's disease (PD) (Greene et al. 2003; Laurent 1999; Pesah et al. 2004). PD has also been studied using *C. elegans*, which has not only dopamine neurons, receptors, transporters, and the enzymes that catabolize dopamine (Nass et al. 2002, 2008; Nass and Blakely 2003; Sulston et al. 1975; Wintle and Van Tol 2001), but also orthologues of most of the human Parkinson's genes (Nass et al. 2008). As a result, various genetic manipulations with worms have produced models of the genetics and molecular pathways of Parkinson's. For example, *C. elegans* has been used in human gene expression assays to identify genes associated with PD. The genes are overexpressed in dopamine neurons; if they are PD-associated, the worms show signs of neurodegeneration (Berkowitz et al. 2008). Mitochondrial dysfunction plays a role in the pathology of PD (Korey 2007), and work with the *C. elegans* model has contributed to understanding of intercompartmental proteostasis and its role in cellular function (Kirstein-Miles and Morimoto 2010). Both *Drosophila* and *C. elegans* have been proposed as alternatives to vertebrate animals in the screening of drugs with therapeutic potential for PD (Pienaar et al. 2010).

Drosophila models show promise for elucidating many other neurodegenerative diseases including Huntington's (HD) (Gilbert 2008) and neuronal ceroid lipofuscinoses (NCL), neurodegenerative disorders associated with accumulations of cellular material and the formation of inclusions in lysosomes (Korey 2007). Research using *Drosophila* homologues for HD and NCL has assisted efforts to understand the pathogenesis of both diseases (Korey 2007).

Fly homologues have also been found for several hereditary spastic paraplegias (HSPs), disorders that exhibit symptoms such as progressive weakness of the legs due to axonal degeneration (Korey 2007). For example, Kennedy's disease results in progressive muscle atrophy and weakness in males and is caused by an androgen receptor (AR) mutation. Research on flies on which an AR-like gene is overexpressed in photoreceptor neurons may prove useful in the development of therapeutic approaches for Kennedy's disease (Matsumoto et al. 2005).

Transgenic *Drosophila* models exist for Alzheimer's, Fragile X, HD, Kennedy's, Machado-Joseph, NCL, spinocerebellar ataxia, and spinal and bulbar musculoatrophy (Celotto and Palladino 2005). An unusual use of transgenic technology in flies has been the production of a transgenic, prion-induced neurodegenerative disease in *Drosophila*. The

resulting "mad fly" disease, characterized by locomotor dysfunction and shortened lifespan, is similar to Gerstmann-Sträussler-Scheinker syndrome, an inherited prion disease in humans (Chandran and Lewis 2007).

Human mitochondrial encephalomyopathy disorders include neuropathy, ataxia, retinitis pigmentosa, Leigh syndrome, and familial bilateral striatal necrosis, all of which have components of neurological and muscular dysfunction coupled with tissue degeneration (Korey 2007). A number of fly mutants have phenotypes that can be directly related to the symptoms observed in this complex set of disorders. For example, flies with *mt:ATPase6* mutation show shortened lifespan, progressive degeneration of flight muscles, and neural dysfunction (Celotto et al. 2006). Indicative of even closer correlation with the human disease, these animals have mitochondrial dysfunction and reduced ATP (adenosine triphosphate) production, both of which characterize the human disease.

Recent reviews of *Drosophila* models of neurodegenerative diseases are available (Lu 2009; Lu and Vogel 2009).

Other Invertebrate Models

Because of their giant axons, fibers, and synapses, octopi and squid are often used as research and teaching models for neurobiology (Grant et al. 2006; Van Heukelem 1977). The Yucatan octopus (*O. maya*), which can easily be grown under laboratory conditions, is used as both a teaching and research model for comparative psychology and neurobiology (Van Heukelem 1977). Additionally, octopi and squids are excellent models for neural electrophysiology, neurochemistry, and neurosecretion (Packard 1972; Sanders et al. 1975; Young 1967, 1971). Research utilizing the long-finned squid (*Loligo pealei*) in nerve conduction studies garnered Andrew Huxley and Alan Hodgkin the 1963 Nobel Prize for Medicine. Because of its giant fiber system, *Loligo* has also been proposed as a model for neurodegeneration and dementia (Grant et al. 2006). The somatogastric nervous system of decapod crustaceans (e.g., lobsters, crayfish, and crabs) can be used for modeling the neuromodulator actions of vertebrates (Stein 2009).

The brain of freshwater planarians (Platyhelminthes) may appear to be very simple in comparison to that of humans, but these organisms have many neural genes and transcription factors that are homologous to those that cause pathology in humans. Furthermore, planarians are known for their ability to regenerate—even their central nervous system (CNS)—and researchers using gene silencing techniques hope to elucidate the molecular mechanisms and genes that enable the animal's regeneration (Cebria 2007). Understanding this process may yield important information for treating human CNS injuries and disease.

The highly sensitive auditory system of the cricket can be an effective model in studies of the development of dendrites and their response to injury (Horch et al. 2009). The cricket has also contributed to the understanding of adult neurogenesis (the production of new neurons throughout life), which occurs in most species including humans (Cayre et al. 2007).

Pathophysiology

Aging and Healthspan

C. elegans has been used to study genetic regulation of lifespan. Some *C. elegans* are endowed with multiple copies of the gene *sir-2.1* (counterparts occur in humans), which works in combination with the transcription factor DAF-16 to produce greater longevity. The longevity is based on 14-3-3 proteins, which activate a pathway that increases resistance to both oxidative and genotoxic stress (Berdichevsky et al. 2006). Evolution of lifespan and the biology of aging have also been studied extensively in *Drosophila* (Grotewiel et al. 2005).

Other models have been established in *Drosophila* and *C. elegans* to evaluate insulin/IGF-1 signaling (IIS) pathways, the role of the intestine in germline signaling, and the ablation of germline precursors in longevity—all of which are involved in the regulation of lifespan (Mukhopadhyay and Tissenbaum 2007). In one study, germline precursors were ablated in *C. elegans*, which lived up to 60% longer than their unaltered counterparts (Hsin and Kenyon 1999). Because the IIS pathway participates in regulating lifespan in both invertebrates and mammals, *Drosophila* and *C. elegans* are effective models to study this pathway and the mechanisms through which it can increase lifespan (Giannakou and Partridge 2007; Piper et al. 2008). The Yucatan octopus has also been suggested as a model for healthspan and the effects of aging (Van Heukelem 1977).

Many studies using invertebrates have focused on the beneficial effects of reduced caloric intake on lifespan (Kennedy et al. 2007; Masoro 2005). Similar studies in mice, flies, and monkeys have shown rejuvenation of the immune system when the animals were subjected to caloric restriction (Nikolich-Zugich and Messaoudi 2005), thus providing the opportunity for extended life. Additional models of aging and lifespan are shown in Table 2.

Apoptosis

The word apoptosis translated from the Greek means "falling or dropping off" and was used by the Greeks to refer to petals and leaves falling from flowers and trees (Collins English Dictionary 2009). It was not until 1842 that the German scientist Carl Vogt described the modern-day pathological process of apoptosis after studying the tadpole of the midwife toad (*Alytes obstetricans*) (Vogt 1842). The term then fell into disuse until 1965, when John Foxton Ross Kerr of Australia recognized apoptosis, as distinguished from traumatic cell death, while performing electron microscopy of rat liver cells affected by acute injury (Kerr 1965). Kerr's

Table 2 Other disease models[a]

Model	Species used	References
Age-related cardiac disease	*Drosophila*	Ocorr et al. 2007a,b
Aging	Bivalves, *Drosophila, Caenorhabditis elegans*, *Macrostomum lignano* (flat worm)	Abele et al. 2009; Ballard 2005; Ballard et al. 2007; Berryman et al. 2008; Brys et al. 2007; Campisi and Vijg 2009; Grotewiel et al. 2005; Guarente 2007; Johnson 2008; Mouton et al. 2009; Partridge 2008; Philipp and Abele 2010; Wolff and Dillin 2006
Angiogenesis/vasculogenesis	*Hirudo medicinalis*	de Eguileor et al. 2004
Autophagy	*Drosophila, C. elegans,* Platyhelminthes	Kang and Avery 2010; Kourtis and Tavernarakis 2009; Tettamanti et al. 2008
Axon guidance regulators	*Drosophila*	Duman-Scheel 2009
Caloric restriction/diet	*C. elegans, Drosophila*	Chen and Guarente 2007; Guarente 2007; Morck and Pilon 2007; Partridge et al. 2005, 2008; Piper and Bartke 2008; Pletcher et al. 2005
Ehlers-Danlos syndrome	Echinoderms	Szulgit 2007
Epilepsy	*Drosophila, C. elegans*	Baraban 2007
Freeze tolerance	Various species of insects	Sinclair and Renault 2010
Hypoxia	*Drosophila, Daphnia magna, C. elegans*	Gorr et al. 2006; Romero et al. 2007
Lymphangioleiomyomatosis	*Drosophila*	Juvet et al. 2007
Mitochondria-associated diseases	*C. elegans*	Ventura et al. 2006
Postural control	*Clione* (mollusc)	Deliagina and Orlovsky 2002; Deliagina et al. 2007
Sleep regulation	*Drosophila*	Cirelli 2009
Stem cell roles in cancer	*Drosophila, C. elegans*	Januschke and Gonzalez 2008; Nimmo and Slack 2009
Testicular cancer	*Drosophila*	Browne et al. 2005
Tumor metastasis	*Drosophila*	Jang et al. 2007; Naora and Montell 2005
Tumor suppression	*Drosophila*	Vaccari and Bilder 2009
Wound healing	*Hirudo medicinalis, Drosophila, C. elegans*	Grimaldi et al. 2006; Jane et al. 2005; Michaux et al. 2001

[a]These models are provided for reference; discussion of other models is provided in the text.

later work with colleagues Jeffrey Searle, Andrew Wyllie, and Alastair Currie furthered understanding of the role of apoptosis in both normal and disease processes (Kerr et al. 1972; O'Rourke and Ellem 2000).

Subsequent study of *C. elegans* was pivotal in the quest for understanding the genetics of apoptosis. The 2002 Nobel Prize in Medicine was awarded to three researchers—Sydney Brenner, H. Robert Horvitz, and John E. Sulston—for their work on genetic regulation of organ development and programmed cell death, for which their primary model was *C. elegans*. They were also able to determine that similar genes are present in humans to control apoptosis.

Pathways for apoptosis are conserved throughout most of the animal kingdom, from invertebrates to humans, but *C. elegans* and *Drosophila* remain models of choice, especially for genetic, biochemical, and molecular-mechanistic studies (Bao et al. 2005; He et al. 2009; Xu et al. 2009). Moths are also useful in the study of apoptosis and in particular programmed cell death in skeletal muscles (Schwartz 2008). Tumor necrosis factor (TNF), a cytokine involved in programmed cell death, has functional analogies in the earthworm *Eisenia foetida*. The worm counterpart to mammalian TNF, while not homologous, has similarities in function based in lecithinlike activity/domains (Beschin et al. 2004), so the earthworm may be a useful model for studying apoptosis.

Cancer

Drosophila and *C. elegans* are long-established models for the study of neoplastic diseases. Because the pathways of

gene functions in the two species have many similarities to those in humans, the study of these organisms has provided much insight into tumorigenesis in both humans and animals (Gateff and Schneiderman 1967, 1969; Gilbert 2008; Kirienko et al. 2010; Saito and van den Heuvel 2002).

Genetics. Many genetic mutations in the fly lead to uncontrolled cell division, neoplasia, and death (Gateff and Schneiderman 1967, 1969; Gilbert 2008). As a result, *Drosophila* is a useful model for gene regulation, particularly tumor suppressor genes (TSGs) and oncogenes (Brumby and Richardson 2005; Gilbert 2008; Menut et al. 2007). Similarly, *C. elegans* is also an excellent model for cancer including the study of apoptosis, cell cycle progression, growth factor signaling, genome stability, and mechanisms of invasion and metastasis (Kirienko el al. 2010). Studies with *C. elegans* have provided important clues about the function of homologous oncogenes and TSGs in humans. Genomewide RNA interference screens in *C. elegans* have facilitated the identification of new cancer gene candidates and how they function in the pathogenesis of cancer (Poulin et al. 2004). Understanding how multiple genes function together to create a cascade of events provides opportunities for identifying therapeutic agents that can target genes contributing to cancer. *C. elegans* thus may serve as a key model in screening potential cancer therapeutic agents (Saito and van den Heuvel 2002).

A specific genetic screen has been developed to delineate neoplastic TSGs that provide control over cell polarity and proliferation (Menut et al. 2007). Hippo, a kinase, modulates a chain of events that lead to expression of genes involved in cell proliferation and growth regulation (Badouel et al. 2009). Study of the Hippo pathway in flies has identified close similarities to the same pathway in mammalian species (Buttitta and Edgar 2007). In flies, mutations in *hippo* can lead to epithelial cell proliferation in several tissues—and play a role in managing apoptosis—so cancer researchers can add *Drosophila* to their arsenal as a model for studying control of cell proliferation (Gilbert 2008). Both *Drosophila* and *C. elegans* have also served as models for evaluating the role of *FOXO* genes in cancer; FOXO factors affect many physiological processes, including differentiation of cells, tumor suppression, cell-cycle arrest, and apoptosis (Arden 2008).

RUNX (runt-related) genes in humans regulate a number of processes—control of cellular proliferation, maintenance of stem cells, development of specific cell lineages, and regulation of cell differentiation; disruption of the genes leads to pathology and often cancer. RUNX transcription factors have been studied in *Drosophila*, *C. elegans*, and the purple sea urchin (*Strongylocentrotus purpuratus*) (Braun and Woollard 2009).

Drosophila is also being used to evaluate the roles of axon guidance genes, such as *Netrin* and *Deleted in Colorectal Cancer* (*dcc*), for which the human counterparts are implicated in causative mechanisms of human cancer. These models may prove useful in developing cancer therapeutic agents (Duman-Scheel 2009).

Table 3 shows other invertebrate models for genetic studies.

Molecular and Cellular Biology. Asymmetric cell division (the generation two different daughter cells from a single cell) plays a role in the development of cancer. The mechanisms of such division and its potential to lead to tumorigenesis have been modeled in both *C. elegans* and *Drosophila* (Chartier et al. 2010), but the embryo of *C. elegans* has served as the primary model for understanding asymmetric cell division in cancer—in particular, determining stem cell function and tumorigenesis in humans (Hyenne et al. 2010).

Molecular control of cell migration and tumor metastasis has been modeled in *Drosophila* (Jang et al. 2007). For example, a model for ovarian cancer metastasis has been evaluated in *Drosophila* based on the migration of ovarian border cells (Naora and Montell 2005). Human ovarian cells and fly border cells have many similarities: both are controlled by steroid hormones; during development, each can show characteristics of epithelial and mesenchymal cells; and both can migrate to other sites to form cell nests (Gilbert 2008; Naora and Montell 2005). Several genes and proteins have been identified in border cell migration in flies. The proteins, which also occur in women, have been tested in vitro on ovarian cancer cells and the cytopathology observed. Unlike cancer cells, border cell migration represents a normal process in flies—it ends without harm to the animal (Gilbert 2008; Naora and Montell 2005). Further studies in flies may assist in determining the factors that turn off cell migration and may lead to an understanding of ovarian cancer metastasis and, ultimately, methods to prevent it. Border cell migration may also serve as a biological assay for the development of treatments for ovarian cancer (Gilbert 2008).

Drosophila has also been used to understand the concept of cell competition, whereby cells of different genotypes are located next to each other and compete for proliferative advantage. In cancer, the abnormal cells dominate the normal; thus, cell competition may play a role in cancer development (Baker and Li 2008). Planarians also have found a niche in cancer research. These tiny organisms have been studied to understand the molecular biology and genetics of cancer as well as the possible role of regeneration in causing or curing cancer (Oviedo and Beane 2009).

Table 2 lists additional cancer models.

Substance Abuse

Drosophila and *C. elegans* have been used to study the genetic and behavioral mechanisms of cocaine, alcohol, and nicotine addiction (Schafer 2004; Wolf and Heberlein 2003). In addition, the pond snail has been used to study cocaine addiction and therapies to treat or prevent it; changes in learning and memory in the snail can be easily evaluated and demonstration of impairment is readily observed (Carter et al. 2006). The honeybee is another model for studying cocaine addiction. Bees fed low levels of cocaine show altered patterns in their foraging dance and removal of cocaine from their diet results in withdrawal effects (Barron et al. 2009).

Table 3 Genetic models[a]

Model	Species used	References
Behavior	*Drosophila*	Jasinska and Freimer 2009; Mackay and Anholt 2007
Chromosome speciation	*Drosophila,* mosquitoes	Ayala and Coluzzi 2005
Cocaine-related behaviors	*Drosophila*	Heberlein et al. 2009
Complex traits	*Drosophila*	Mackay and Anholt 2006
CT/CGRP[b]	*Pecten maximus, Haliotis tuberculata, Crassostrea gigas, Drosophila*	Lafont et al. 2007
Gene perturbations	*Caenorhabditis elegans*	Borgwardt 2008
Gene regulation	*C. elegans, Drosophila*	Ercan and Lieb 2009; Large and Mathies 2007; Mendjan and Akhtar 2007
Genetic interaction networks	*C. elegans*	Lehner 2007
Meiosis	*C. elegans*	Colaiacovo 2006; Schvarzstein et al. 2010
Mitochondrial DNA	*Mytilus edulis, M. galloprovincialis, Venerupis philippinarum, Lampsilis, Inversidens japanensis*	Breton et al. 2007
Muscle development	*Drosophila*	Maqbool and Jagla 2007
Myoblast fusion	*Drosophila*	Richardson et al. 2008
Noncoding RNA	*Drosophila*	Deng and Meller 2006
p53	*C. elegans, Drosophila*	Lu and Abrams 2006
RNA silencing	*Drosophila*	Kavi et al. 2005
Sleep	*C. elegans, Drosophila*	Andretic et al. 2008
Spindle assembly and regulation	*Drosophila*	Buchman and Tsai 2007; Doubilet and McKim 2007
Telomere protection	*Drosophila*	Cenci et al. 2005
Transposable elements	*Drosophila*	Le Rouzic and Deceliere 2005
Tumor susceptibility gene (TSG) 101	*Drosophila*	Herz and Bergmann 2009
Wnt	*Drosophila*	Bejsovec 2006

[a]These models are provided for reference; discussion of other models is provided in the text.
[b]CT/CGRP, calcitonin/calcitonin gene-related peptide

Ethanol response has been studied in several invertebrates. Research on ethanol sensitivity and tolerance in *Drosophila* revealed genes that are directly linked to the behavioral responses of the inebriated flies (Berger et al. 2008). Work with intoxicated *Drosophila* has shed light on the specific neurons that mediate observed behaviors (Scholz 2009). The honeybee has also been proposed as a model of alcoholism and its effects. After consuming concentrations of ethanol up to 20% of their diet (Abramson et al. 2000), the honeybee's behavior changes in ways similar to those observed in vertebrates, with effects on locomotion and learning. The social bee may also be appropriate to study alcohol influence on language, social interaction, development, and learning (Abramson et al. 2000). *C. elegans* has also served as a model of alcoholism (Dolganiuc and Szabo 2009).

Toxicology

Pharmaceutical research requires the detection of adverse reactions to new drugs as early in development as possible. A number of in vitro tests are available (e.g., cell culture, tissue-slice) but do not always translate to animal model systems or relate to clinical experience. Invertebrates can be used as models for many toxicological studies and can bridge the gap between in vitro models and vertebrate animal studies. Close similarities to vertebrate response, rapid reproduction rate, cheap cost, and ease of housing and care have made invertebrates key organisms in toxicologic screens (Avanesian et al. 2009). The literature shows numerous examples of the use of invertebrates in toxicity evaluations; the most commonly used organisms are *C. elegans*, *Drosophila*, and the water flea.

The nematode has proven to be an excellent model for use in toxicology studies, drug development, and research on environmental toxicology due to its mapped genome and simple nervous system (Williams et al. 2000). Because of its genetic and cellular similarities to humans, *C. elegans* is an important model for high-throughput screening of therapeutic agents for human diseases (Nass et al. 2008). It can be used in both LD50 (lethal dose, 50%) and behavioral paradigms (Dhawan et al. 1999), and it shows results comparable to those of mouse systems (Williams et al. 2000). The worm has been used for evaluations of genetic and environmental toxicology, neurotoxicolgy, and high-throughput experiments to screen for molecular and genetic targets of chemical toxicity. Neurotoxicity can also be modeled in *Drosophila* and various species of cockroaches (Peterson et al. 2008). All of these organisms provide simple and inexpensive alternatives to mammals for evaluating the toxicity of new pharmaceuticals (Artal-Sanz et al. 2006; Leung et al. 2008).

Both the sludge worm (*Tubifex tubifex*) and *D. magna* can also be used as models in preliminary toxicology screening, including LD50 evaluations (Devillers and Devillers 2009). Because of *Daphnia*'s sensitivity to toxicants, it is also used in water quality monitoring to identify the presence of contaminants (Martins el al. 2007). In addition, the mussel has been used to study organophosphate toxicity and proposed as an additional biomarker for pollution (Brown et al. 2004).

Drosophila has proved to be a useful model in drug-feeding experiments to evaluate new antiepileptic drugs (Ackermann et al. 2008). Drug delivery, however, is a major challenge when using *Drosophila* as it is very difficult to standardize the amount of drug consumed in a fly's diet (Avanesian et al. 2009); other options, such as microinjection in the abdomen, have been proposed (Dzitoyeva et al. 2003). In spite of the drug delivery challenge, a number of studies have used *Drosophila* in toxicological evaluations (Ackermann et al. 2008; Avanesian et al. 2009; Gupta et al. 2007b; Patnaik and Tripathy 1992).

Endocrine-active chemicals are present in the environment and some therapeutic agents have endocrine effects; in both cases, these compounds disrupt normal endocrine function in mammals. Changes in sperm counts, breast cancer, congenital abnormalities of the genitalia, and other pathologic conditions in humans are linked to these chemicals and therapeutic agents. Invertebrates can be used to study endocrine effects of drugs and environmental contaminants (Avanesian et al. 2009; Duft et al. 2007; Gupta et al. 2007b; Patnaik and Tripathy 1992; Tatarazako and Oda 2007). For example, researchers have observed adverse reproductive effects in *Drosophila* adults and cell lines exposed to a variety of insecticides (Gupta et al. 2007b; Patnaik and Tripathy 1992). Similarly, Avanesian and colleagues (2009) studied methotrexate toxicity in flies and found ovarian impairment comparable to that observed in mammalian models. The freshwater mud snail (*Potamopyrgus antipodarum*) and *Daphnia* have also served as models for the assessment of environmental chemicals (Duft et al. 2007; Tatarazako and Oda 2007). Many gender-related differences in toxicant effects have been noted in humans, and these effects can be modeled in many different invertebrates including insects, nematodes, crustaceans, molluscs, corals, and echinoderms (McClellan-Green et al. 2007).

Environmental impacts on the lysosomal-autophagic system have been studied in bivalve molluscs (Moore et al. 2006). Environmental metal contamination can be monitored in various insects, as metal accumulates in chitinous exoskeleton and is incorporated into insects' internal issues (Hare 1992). Additionally, many aquatic species serve as biomarkers for organic xenobiotic and metal contamination in both fresh and saltwater (Rainbow 2007; Raisuddin et al. 2007; Sarkar et al. 2006).

"The Five Senses"

Hearing

The Johnston's organ, located in the antenna of *Drosophila,* is the counterpart of the mammalian ear. Similarities in the genes involved in development of the hearing structures of flies and mammals have led to speculation that study of fly hearing may provide insights into deafness in humans (Boekhoff-Falk 2005). The role and function of TRP channels, present in both flies and vertebrates, have been evaluated in flies to provide a model system to study vertebrate inner ear disorders that affect hearing and balance (Cuajungco et al. 2007). The creation of mechanical models has enabled modeling of auditory transducer dynamics, which will be used to test auditory performance in both vertebrates and *Drosophila* (Nadrowski and Gopfert 2009).

Olfaction

There are many similarities—structural, functional, and physiologic—between the olfactory systems of vertebrates and insects (Kay and Stopfer 2006), making insects excellent models for the study of olfaction. Vertebrates use their noses to smell, whereas insects have antennae; however, both structures have specialized epithelium lined with ciliated olfactory receptor neurons (ORNs) that respond to odorants (Hallem et al. 2006; Kay and Stopfer 2006; Malnic et al. 1999; Rospars et al. 2003). From the ORNs, both vertebrates and insects send neural processes to the brain—the insect's antennal lobe and the vertebrate's olfactory bulb (Kay and Stopfer 2006; Laurent 1999). Investigators have studied insect olfactory systems to understand interactions between animals and their environment (de Bruyne and Baker 2008). Other studies have focused on odor processing and the capacity to detect odor blends using moths and honeybees (Lei and Vickers 2008), and *C. elegans* and *Drosophila* have been models in olfactory signaling research (Kaupp 2010; Nakagawa and Vosshall 2009).

Decapod crustaceans can serve as olfactory system models because the cellular and morphological organization of their olfactory system has many similarities to the human

olfactory pathway. In many decapod crustaceans, neurogenesis occurs in the olfactory system throughout life, so these animals are being used to study lifelong neurogenesis, with the aim of understanding how it occurs (Sandeman and Sandeman 2003; Schmidt 2007). This research may elucidate methods to stimulate neurogenesis in humans to treat neurological diseases or injuries.

All organisms are exposed to an enormous diversity of chemicals in the environment, and understanding the way the nervous system recognizes and responds to these chemical signals is challenging. The chemosensory system of insects has become an important area of research, and *Drosophila* is the primary model under study (Benton 2008). Crustaceans are also effective models for the study of chemoreception, which is based in their olfactory system (Derby and Sorensen 2008).

Taste and Satiation

Researchers study *Drosophila* to understand taste perception and the neural circuits (in particular one called *hugin*) that affect feeding behavior. An organism's decision, whether human or fly, is basically to eat or not to eat; the mechanisms in the brain that prompt this decision are similar (Amrein and Thorne 2005; Melcher et al. 2007).

Touch and Temperature Sensing

Responses to mechanical forces, including touch, are poorly understood at the molecular level. Touch-sensitive mutants of *C. elegans* have been created and the defective genes studied to help identify sensory components that affect the cells that sense gentle touch (Bounoutas and Chalfie 2007).

All animals have the ability to detect changes in environmental temperature based on the presence of neuronal and molecular substrates that affect thermosensation. The three primary models for studies of thermosensation are the mouse, *C. elegans*, and *Drosophila* (McKemy 2007). Investigators have also studied thermosensing in *C. elegans* to understand the molecular and cellular basis for neural plasticity (Mori et al. 2007).

Vision

In the 1930s, horseshoe crabs (*Limulus polyphemus)* were used by Haldan K. Hartline and C.H. Graham as their model for studying the optic nerve, and in 1967 Hartline, Ragnar Granit, and George Wald were awarded the Nobel Prize in Medicine for their research into visual processes of the eye. Hartline's *Limulus* model continues to serve as an excellent model for vision research because of its complex ocular-neural network. Limuli have large, easily accessible retinal neurons, allowing for electrophysiological study. Study of the horseshoe crab has provided insight into the operation of human vision, particularly adaptation to light and lateral inhibition (Liu and Passaglia 2009).

Octopuses have also been used in vision research. Their sucker chemotactile systems have been compared to the mammalian eye (Packard 1972; Sanders et al. 1975; Young 1967, 1971).

Other Models

Space Biology

Invertebrates are useful in studying the effects of ionizing radiation, both on earth and in space. *C. elegans* has been effectively used in microbeam irradiation studies to evaluate bystander effects (Bertucci et al. 2009), to study the long-term effects of radiation exposure in space travel, and to evaluate the gravitational effects of space travel on muscle gene expression (Zhao et al. 2005). It has also been used to study natural space radiation exposure, and the resulting mutants have been genetically evaluated (Nelson et al. 1994). Tardigrades (water bears, moss piglets) have also served as models for open space research, because they have the ability to survive desiccation, extreme cold, and radiation, all of which occur in space. Additional invertebrate species showing potential for use in outer space biological experiments are the sleeping chironomid (*Polypedilum vanderplanki*), the brine shrimp (*Artemia salina* and *A. franciscana*), and several types of rotifers, which are commonly called "wheel animals" (Jonsson 2007).

Symbiosis

Throughout nature, symbiotic relationships between organisms contribute to survival and the ability to flourish. Even humans are dependent on lowly microorganisms, which contribute to nutrition and defense. The relationship between host and microbe has been modeled through invertebrates, which have a diverse set of associated microorganisms (Chaston and Goodrich-Blair 2010). The primary model systems in such research are insects and nematodes. The former include various species of termites (Hongoh et al. 2005; Ohkuma 2008; Yang et al. 2005), the honeycomb moth (*Galleria mellonella*; Gouge and Snyder 2006; Walsh and Webster 2003), the tobacco hornworm (*Manduca sexta*; van der Hoeven et al. 2008), the Asian gypsy moth (*Lymantria dispar*; Broderick et al. 2004), and *Drosophila* (Ryu et al. 2008). The nematode *Steinernema carpocapsae* and its association with the bacterium *Xenorhabdus nematophila* have been used as a model for symbiotic relationships (Goodrich-Blair 2007).

Bioactive Products

Biomaterials and Biomimetics

Baculovirus

Baculovirus-insect cell expression systems have enabled the production of recombinant proteins for use in research

(Jarvis 2003), making it possible for investigators with basic molecular biology background to produce their protein of choice very simply. Moths and butterflies are the most common species used for the cell culture system (Jarvis 2003).

Luciferase

Bioluminescence, the ability of a living organism to produce light, results from a biochemical reaction where oxygenation of luciferin, a substrate, occurs through the action of the enzyme luciferase (Day et al. 2004). Many organisms can produce bioluminescence, but the animal most studied and used for biomedical research applications is the firefly or lightning beetle (*Photinus pyralis*). Light in beetles is produced in "lanterns," organs containing photocytes that are layered between two rows of cells. Uric acid crystals in the cell layers reflect the light produced by the photocytes (Fraga 2008; Hastings and Wilson 1976; Hastings 1983, 1989a,b). During the late 1800s, Raphael Dubois, a French physiologist, studied the biochemical properties of bioluminescence in these insects and created a luminescent solution by crushing their abdomens and mixing the crushed organs in cold water (Harvey 1957; McCapra 1982).

Luciferases have been incorporated into many in vitro molecular assays to allow evaluation of gene expression in transformed cell lines (Contag et al. 1998, 2000; de Wet et al. 1987; Lim et al. 2009; Sherf and Wood 1994; Takakuwa et al. 1997; Wood et al. 1989; Wood 1995; Zhang et al. 1994, 2008). In addition to the firefly and other beetles, luciferases have been isolated from the sea pansy (*Renilla reniformis*) and jellyfish (*Aequorea victoria*) and used as reporters in mammalian cells and in other types of animal studies (Contag et al. 2000). Cloning of image reporters, such as the *luc* gene, is allowing researchers to study transcriptional regulation, signal transduction, protein-protein interactions, tumor transformation, cell trafficking, and targeted drug actions in living animals without invasive techniques (Gross and Piwnica-Worms 2005).

Silk Products

For centuries silk fibers were the primary source of suture materials, but in recent years synthetic materials have dominated the market. Studies of silkworm fibers have shown biocompatibility between silk and the commonly used biomaterials polylactic acid and collagen (Altman et al. 2003). As a result, silk and silklike fibrous proteins from the silkworm (*B. mori*), the golden orb web spider (*Nephila clavipes*), diadem spider (*Araneus diadematus*), and other insects are being considered for use in biomedical applications such as tissue scaffolding for joint repair (Altman et al. 2003). The design of silk-inspired polymers and proteins and their uses in bioengineering and biotechnology are reviewed by Hardy and Scheibel (2009).

Biomimetics

Biomimetics is the study of a living organism to create a device, either medical or nonmedical, by applying information gained from the organism. Invertebrates have been useful models in this area of applied research. For example, the study of marine ragworms (*Nereis virens* and *N. diversicolor*) supported the development of a new endoscope based on the ragworm's ability to move in slippery substrates, similar to mucus in the gastrointestinal tract (Hesselberg 2007).

Drug Discovery

Invertebrates have been used for many centuries for their medicinal properties. In the western hemisphere, the leech (*Hirudo medicinalis*) was used for bloodletting of patients with many different disorders and maggots were (and sometimes still are) used for cleaning wounds. In the East, the Chinese valued the sea cucumber for its ability to cure many human diseases (Kelly 2005).

A wide range of invertebrate species—from insects to marine life—serve as reservoirs of bioactive compounds, but marine life accounts for the largest number: over 14,000 pharmacologically active compounds have been identified from marine plants and animals (Adrian 2007), 961 of them in 2007 alone (Blunt et al. 2009). Bis(indole) and tris(indole) alkaloids are among the most commonly isolated compounds and show high biological activity, with potential as pharmaceutical agents (Gupta et al. 2007a). These alkaloids have a wide range of effects including antimicrobial (bacterial, fungal, viral), antiparricidal, anticancer, anti-inflammatory, antiproliferative, and antiserotonin activity, and RNA and DNA synthesis inhibition. In addition to the discovery of pharmacologically active compounds, invertebrates such as snails and sea anemones are being used in the creation of antisera used in humans (Redwan 2009). Excellent reviews are available of the many species studied, compounds identified, and their biological activities (Blunt et al. 2009; Gupta et al. 2007a; Kelly 2005).

While marine invertebrates are proving to be outstanding sources of pharmaceuticals, the harvesting of marine life, especially by third-world countries to sell species to pharmaceutical companies, is decimating native populations. There is significant concern among conservationists that such overexploitation of marine animals is going to result in the extinction of many (Duckworth et al. 2003; Lawrence et al. 2010). Fortunately, many countries are initiating aquaculture programs for the cultivation of marine invertebrates to spare wild populations while providing new means of revenue for their societies (Kelly 2005). As research and development with bioactive compounds move forward, global measures to ensure species protection and welfare will be critical.

Anticoagulants

Tick anticoagulant peptide and other natural anticoagulants have been isolated from hematophagous invertebrates and

testing of these products in mammalian animal models of thrombosis and atherosclerosis has shown that they have potent anticoagulant properties (Fioravanti et al. 1993; Ragosta et al. 1994; Schaffer et al. 1991; Schwartz et al. 1996; Sitko et al. 1992). Ticks and similar organisms may thus serve as sources of natural inhibitors in the design of improved anticoagulants (Corral-Rodriguez et al. 2009) and antithrombotics (Koh and Kini 2009). Evaluation of hirudin, a natural thrombin inhibitor present in the blood-sucking leech, for use in the management of thromboembolic diseases (Markwardt 2002) has resulted in the creation of two recombinant versions of hirudin (Lepirudin and Desirudin) that are now on the market for use in humans. Lepirudin has found a second niche as an effective treatment for angina (Redwan 2009).

Sulfated fucans and galactans (homopolysaccharides) isolated from marine invertebrates have powerful natural pharmacological actions that can be therapeutically effective in humans (Pomin 2009) as anticoagulants (Farias et al. 2000; Mourao and Pereira 1999; Mourao 2004; Pereira et al. 1999), antithrombotics (Berteau and Mulloy 2003; Mourao and Pereira 1999; Mourao 2004), and anti-inflammatories (Berteau and Mulloy 2003). The main source organisms for fucans and galactans are the sea cucumber, sea urchin, and ascidians (Pomin 2009).

Antimicrobials

In 2005, Salzet reported the identification of over 30 neuropeptide-derived antimicrobials from such diverse invertebrate species as shrimp, fly maggots, mosquitoes, scorpions, horseshoe crabs, sea cucumbers, and numerous other marine invertebrates (Lawrence et al. 2010; Salzet 2005). Chemokine binding proteins (CBPs), lectins that have been isolated from the sea worms *Chaetopterus variopedatus* and *Laxus oneistus*, have potential as antivirals as research has shown that they can inhibit HIV infection in cells and prevent virus transmission from infected to unaffected T cells (Balzarini 2006). HIV-inhibitory compounds have also been isolated from soft corrals (*Lobophytum* sp.) from the Philippines (Rashid et al. 2000). Sulfated fucans and galactans from marine invertebrates can also serve as antivirals (Harrop et al. 1992).

Other antimicrobial peptides isolated from invertebrates have other bioactive properties (Bulet et al. 2004). Cecropin A, identified in the silkmoth (*Hyalophora cecropia*) and the mosquito (*Anopheles gambiae*), has antibacterial and antifungal properties and lyses yeast cells. Stomoxyn, from the stable fly (*Stomoxys calcitrans*), is toxic to bacteria and fungi and has lytic effects on trypanosomes. Similar peptides have been isolated from fire ants (*Pachycondylas goeldii*), termites (*P. spiniger*), and the spiders *Oxyopes kitabensis* and *Cupiennius salei*. Two bioactive peptides with multiple uses have been identified in the stalked sea squirt (*Styela clava*) (Bulet et al. 2004).

Cancer

Over the past 10 years, a number of compounds originating from marine invertebrates have entered preclinical and clinical development as cancer therapeutics (Adrian 2007; Jimeno 2002). C-nucleosides from the Caribbean sponge (e.g., *Cryptotethya crypta*) served as the chemical model for synthesis of Cytarabine, which is used in the treatment of leukemia and lymphoma (Schwartsmann et al. 2003). Compounds in clinical development include didemnins, Kahalalide F, hemiasterlin, dolastatins, cemadotin, soblidotin, bryostatins, ecteinascidin-743, and aplidine (Rawat et al. 2006; Schwartsmann et al. 2003). Many of these compounds are still being evaluated clinically; others (e.g., bryostatin 1) have been removed from trials because of severe side effects (Singh et al. 2008). Bonnard and colleagues (2010) recently reported the discovery of antitumor promoters in two types of Comorian soft corals; they are under investigation for potential use in cancer therapy. Sulfated fucans and galactans from marine invertebrates have also been recognized to have antimetastatic properties (Coombe et al. 1987).

Immune Protectors

Parasite colonization can provide protection from immune-mediated diseases. Studies in mice colonized with helminths showed that the animals were protected when challenged with colitis, asthma, encephalitis, and diabetes (Elliott et al. 2007). Similarly, clinical trials have shown that helminth exposure can reduce the symptoms of ulcerative colitis and Crohn's disease in human patients by altering immune response. The effects on the immune response may result from the induction of regulatory T cell activity (Weinstock et al. 2005). Induced helminth infections may some day be used to treat many inflammatory and immune-mediated diseases (McKay 2009).

Pain

Cone snail (*Conus* sp.) venom, known as conotoxin, can alleviate pain and prevent or treat epilepsy. Based on the number of species of cone snails and the number of conopeptides each can produce, it is expected that 70,000 different conotoxins will be characterized and tested for therapeutic potential (Ekberg et al. 2008). Evaluation of conotoxins in mammalian animal models has led to numerous applications, including use as antinociceptives, antiepileptics, neuroprotectives, and cardioprotectives. Conopeptides may also find use as therapeutic agents for cancer and neuromuscular and psychiatric disorders (Han et al. 2008). The drug Prialt, a derivative of conotoxin, has been approved for and is being used to treat intractable pain (Lee et al. 2010); it has a potency 800 times that of morphine (Xia et al. 2010).

Sunscreens and Antioxidants

A wide variety of marine organisms can be used to obtain effective sunscreens and antioxidants. Mycosporinelike amino acids (MAAs), prevalent in corals, have the ability to

absorb UV rays and serve as natural sunscreens in marine animals (Dunlap et al. 1999); synthetic sunscreens have been developed based on these MAAs (Dunlap et al. 1995, 1999; Karentz et al. 1991).

Marine invertebrates, either independently or in symbiotic relationship with bacteria, also produce potent antioxidants (Dunlap et al. 1999). These antioxidants have potential biomedical applications, ranging from use as food supplements to cosmetic additives and chemopreventives in oxidative stress-related disease.

Harvest of Bioactive Products from Sponges

Marine sponges contain a circular proteoglycan called "spongican" that is involved in species-specific cell adhesion, resulting in cell aggregation (Fernandez-Busquets and Burger 2003). There are many similarities between the responses of cell aggregation in sponges and processes in humans. For example, both human platelets and sponge cells respond similarly to stimuli that either inhibit or accelerate aggregation (Philip et al. 1992). Because of the cell-aggregation response, sponges can be used to study both inflammation and anti-inflammatory compounds and may serve as models in anti-inflammatory drug development (Dunham et al. 1985).

Spongicans may also be useful in the study and treatment of specific human diseases; for example, a derivative of spongican has been shown to block replication of HIV, indicating potential as a treatment for HIV infection (MacKenzie et al. 2000). Sponges may also serve as a model to evaluate treatment for Alzheimer's and other amyloid disorders, as spongicans affect amyloid fibrils by causing aggregation, thus helping block the characteristic lesions of Alzheimer's (McLaurin et al. 1999).

Spongin is a protein that makes up the fibrous skeleton of sponges and may have potential uses in the treatment of osteoarthritis and other degenerative bone diseases (Kim et al. 2009). Spiculogenesis creates sponge skeleton and has been studied to find new approaches to treat dental and bone disease. It is initiated by the enzyme silicatein, beginning the process of creating silica nanoparticles that fuse in layers around a central protein filament of silicatein and silintaphin-1, which serves as the scaffolding protein (Muller et al. 2009). This process has led to the development of synthetic biomaterials containing recombinant silicatein and silintaphin-1, which have been used to induce biosilica-mediated regeneration for tooth and bone defects. The assembly of silica nanoparticles by the action of silicatein and silintaphin-1 results in the synthesis of light waves; these nanoparticles could serve as an alternative to fiberoptics in biomedical applications (Muller et al. 2009).

Sponges of the genus *Spongosorites* contain several bis(indole) alkaloids that have potent antifungal properties and produce moderate cytotoxicity in cancer cell lines (Oh et al. 2006). Stevensine, an alkaloid metabolite with antitumor properties, is produced by the sponge *Axinella corrugata*, which is being laboratory raised to create sufficient quantities of Stevensine without affecting natural-living specimens (Duckworth et al. 2003).

Invertebrate Models in Teaching

For most of the history of biological, medical, veterinary, and agricultural teaching, vertebrate species have been the models of choice because of their close similarities to humans and other target species. For example, veterinary colleges have used vertebrates to help students understand physiology, pharmacology, and pathology and practice surgery and clinical care. Similarly, colleges of medicine have used turtles, rats, dogs, and other vertebrates to teach medical students the fundamentals of physiology, pharmacology, and other aspects of medicine. But fewer vertebrate animals are being used in teaching as pressure from animal rights activists has led many medical and veterinary programs to reduce or even eliminate the use of animals, despite students' expressed concerns about the lack of hands-on experience with living animals.

In K–12 teaching, many animals commonly used in the past have been extensively harvested or, among wild populations, decimated by disease. Reduced numbers of some species have led to the animals' being listed as endangered, which means that these animals cannot be taken from the wild. As a result of all of these factors, fewer vertebrate animals are available or used for study by K–12, college, and professional students.

Invertebrate species can serve as substitutes for vertebrates in some, but not all, educational experiences for students. The wide range of animals available for study, the vast populations available either in the wild or from laboratory suppliers, their similarities to (and differences from) vertebrates, the ease of keeping them, and the low cost of acquisition and maintenance—all contribute to their value as experimental subjects (Deyrup-Olsen and Linder 1991).

A number of books and scientific articles document the varied uses of invertebrates in teaching; Deyrup-Olsen and Linder (1991) provide a concise review of the uses of invertebrates in teaching physiology. Additionally, a number of examples of the use of invertebrates in teaching K–12 and college-level students are available on the Internet. Following are some of the many examples of the use of invertebrates in teaching (with websites as available; also see Smith 2011, in this issue):

- In lieu of the frog sciatic nerve preparation for demonstrating action potentials, recordings from cockroaches (*Periplaneta* sp.) can be substituted.
- Crayfish (*Procambarus* sp. and *Pasifastacus* sp.) are effective for modeling the effects of changing environmental temperature on metabolic rate (Casterlin and Reynolds 1977).
- Circulation and the heart can be observed in *Mercenaria* clams (Florey 1968a; Greenberg 1965) and crayfish (Florey 1968b).

- *Aplysia* is an effective model for teaching physiology and neuroscience.
- Mussels are useful for demonstrating muscle function (Hoyle 1968).
- Mussel and clam gills can be used to study the function of cilia, including the effects of environmental toxicants on cilia (Deyrup-Olsen and Linder 1991; Hoar and Hickman 1983).
- The tobacco hornworm (*Manduca sexta*) can be used to observe the active transport of ions in the midgut, serving as an alternative to frog skin preparations (Deyrup-Olsen and Linder 1991).
- Bryn Mawr College has developed the "Serendip" program (http://serendip.brynmawr.edu), providing a hands-on guide to teaching middle and high school biology. The classes include Invertebrate Diversity, for which students purchase earthworms, snails, and arthropods from pet stores and use them for class activities.
- Oklahoma State University offers a class called Laboratory of Comparative Psychology and Behavioral Biology, using honeybees, houseflies, carpenter ants, and crabs, to teach students about the neuronal mechanisms of learning and memory (http://psychology.okstate.edu/faculty/abramson).
- The University of Southern California teaches a month-long short course in Antarctica, where students study invertebrates to learn about the adaptations of animals, including humans, in extreme environments (http://antarctica.usc.edu).
- Lafayette College has included invertebrate research opportunities for undergraduates in its curriculum for a number of years (Sherma and Fried 1987).
- Johns Hopkins University School of Medicine uses *C. elegans* as a molecular model to teach undergraduate students about congenital mysasthenic syndromes (Kaas et al. 2010).
- And the University of Arizona offers research projects for students to study biological processes and disease using *C. elegans,* black flies, mosquitoes, cockroaches, shrimp, and others.

Because of the growing culture of invertebrates for food, medicinal purposes, and pets, a number of veterinary colleges offer invertebrate classes to teach students how to provide care for invertebrates (e.g., North Carolina State University's Invertebrate Medicine; www.cvm.ncsu.edu/conted/invert.html). In addition, veterinary schools are teaching conservation medicine (Veterinary Examiner 2009), particularly targeting marine life. Marine invertebrates, so necessary for their biologically active properties, will open new avenues of practice for veterinarians, allowing the veterinary profession to provide additional contributions to environmental protection and animal welfare.

Many of the invertebrate species and models discussed in this article have also been used in teaching to help students learn about basic biological processes. Advanced students can also use invertebrates to learn about genetics, developmental biology, cancer, and other areas of study. However, there remain teaching activities, such as learning and practicing surgical techniques or working with livestock in animal science or wildlife biology curricula, for which vertebrate animals will remain the models of choice.

Conclusions

There is a long and illustrious history of invertebrates as models for research, testing, and education. Use of *Drosophila* for genetic studies was established in the early 20th century, and the fly has since become one of the most prolific models for mammalian disease. Similarly, *C. elegans*' parallels with mammalian genetics and molecular biology have made the worm a vital model for understanding the molecular mechanisms involved in disease. While *Drosophila* and *C. elegans* remain the two most studied organisms, there is no paucity of information about other invertebrates. Many terrestrial and marine organisms serve as models for human disease and provide nonvertebrate alternatives for preliminary toxicology and efficacy studies, as evidenced by the examples in this article and its extensive bibliography, coupled with the 300,000-plus articles on invertebrate use available through PubMed and other databases.

Similarly, invertebrates have many uses in education, offering a wealth of educational opportunities throughout the spectrum from K–12 classes to professional and graduate curriculums without having to rely on vertebrate species. However, vertebrate animals in teaching are still necessary, so that students at all levels can learn from hands-on encounters with the animals they will work with during their careers or with which they will share their lives as companions and friends. And professional students must have the opportunity to observe and practice techniques in living animals so that they can ethically practice their professions—for the welfare of both humans and animals.

For all uses of animals, IACUCs, veterinarians, members of the scientific community, governmental regulators, and the public must balance ethical concerns about the use of animals with the needs of society. There is also an ethical responsibility to question the use of higher animals—in research, testing, and teaching programs and in the evaluation of protocols. Invertebrate models provide rich opportunities for learning about and practicing ethical animal care and use by meeting the first and most critical principle of Russell and Burch's Three Rs—replacement.

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