PNAS PERSPECTIVE OPEN ACCESS

From nematode to Nobel: How community-shared resources fueled the rise of *Caenorhabditis elegans* as a research organism

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Edited by Iva Greenwald, Columbia University, New York, NY; received September 21, 2025; accepted October 16, 2025

Experimental organisms such as the nematode *Caenorhabditis elegans* are fundamental to biological discovery. The success of *C. elegans* research has been greatly enabled by infrastructure that allows thousands of scientists to share and access research materials and unpublished information efficiently. Here, we celebrate the worm by interweaving vignettes describing four Nobel Prize–winning discoveries with descriptions of how the major NIH-supported research resources—the *Caenorhabditis* Genetics Center, WormBase, and WormAtlas—provide invaluable support for all *C. elegans* research. The synergy between investigation and the availability of shared resources for the *C. elegans* community is a paradigm for all model organism research, and the continued support of such community research resources will be essential for maximizing impactful discoveries in the future.

Caenorhabditis elegans | model organism research | WormBase | WormAtlas | *Caenorhabditis* Genetics Center (CGC)

Much of what we know about human biology comes not from direct study of humans, but from other organisms. Animal models provide unparalleled experimental access to fundamental biological processes that are shared across evolution, including with humans. The logic is simple but profound: if a mechanism is ancient and conserved, then uncovering it in other organisms provides insight into our own biology. This has proven true time and again—discoveries in yeast, flies, worms, and mice have illuminated the foundations of human development, physiology, and disease. The best-established models share certain features including the ease of cultivation, a rapid life cycle, relative simplicity, and accessibility to genetic and genomic analysis and manipulation. These features facilitate both basic research and exploration of potential translational applications in a controlled and cost-effective way, free of many of the ethical concerns that apply to any research using humans and human tissues. But these organisms are not simply substitutes or models used to study known human biology. Often, as outlined below, they are the source of new discoveries that illuminate unforeseen aspects of human biology.

A Brief History of *Caenorhabditis elegans* as a Model Organism and the "Worm Community"

The use of *C. elegans* to dissect biological truths originated in the visionary thinking of Sydney Brenner. After an extraordinary career defining fundamental principles of molecular biology, by the early 1960s Brenner was searching for a relatively simple animal where these principles could be applied to understand mechanisms controlling development and nervous system function. He chose *C. elegans* for its simpler anatomy and development and more rapid life cycle than the well-established model organism, *Drosophila melanogaster*. While considered by some to be an odd career move at the time, Brenner's decision propelled a little-known roundworm into a juggernaut of biomedical research (Fig. 1). Since Brenner's seminal publication establishing the worm as a genetic system (2), research into *C. elegans* has grown continuously and now includes fundamental discoveries in myriad areas, including landmark discoveries recognized by four Nobel Prizes.

Brenner's use of *C. elegans* attracted many researchers, several of whom established projects that produced an unprecedented look at an entire multicellular organism: mapping the entire cell lineage from the single cell to the adult stage (3), describing the cellular wiring diagram (all visible chemical and gap-junctions) for the entire 302-neuron nervous system (4), and developing a genetic and physical map of the genome as a prelude to generating the first complete DNA sequence of an animal (5). The worm's genome is compact, yet it encodes essential regulatory machinery found in humans.

The development of common resources and the belief that research findings and mutant strains should be freely shared has propelled worm research to the forefront. This community spirit was alive early on with Bob Edgar's establishment in 1975 of "The Worm Breeder's Gazette," a newsletter for sharing information prior to publication. The communal approach

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Author contributions: A.E.R. conceived and organized the paper; V.R.A., M.C., A.L.D., A.Z.F., D.H.H., H.R.H., C.C.M., G.R., N.E.S., P.W.S., and A.E.R. wrote the paper.

The authors declare no competing interest.

This article is a PNAS Direct Submission.

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Published November 24, 2025.

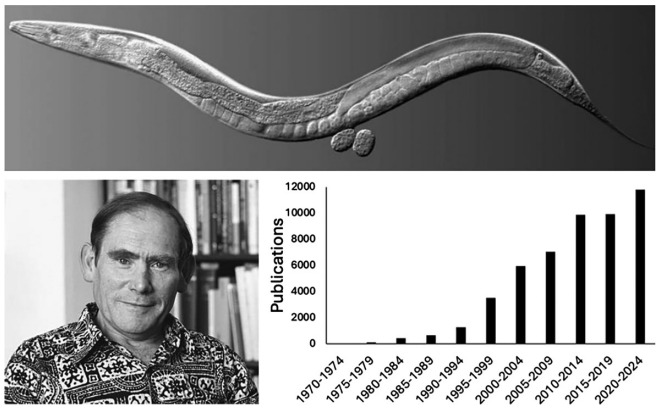

Fig. 1. A *C. elegans* adult next to two developing embryos (*Top*) [(1) reused with permission of Genetics Society of America, courtesy of Maria Gallegos], (*Bottom* Left) Syndey Brenner (with permission of the MRC), and (*Bottom* Right) graph showing striking growth in the number of PubMed-indexed publications with key word "*C. elegans*."

of sharing clones and mapping data that John Sulston, Bob Waterston, and colleagues established not only contributed to *C. elegans* being the first animal with a sequenced genome but also led to the tradition of open data sharing that influenced the human genome project and other large community projects that have moved human biology forward (6).

Three community resources have been critical for the success of *C. elegans* research: the Caenorhabditis Genetics Center which curates and distributes strains, WormBase, the online compendium of *C. elegans* molecular knowledge, and WormAtlas, the online resource for cellular and anatomical data. These resources have connected individual, independent labs to push science forward synergistically, making fundamental and unexpected advances that would otherwise have taken decades, providing a great return on investment.

In this essay, we interweave vignettes describing Nobel Prize research on *C. elegans* with descriptions of key community resource centers that have facilitated research advances throughout the *C. elegans* community.

Nobel Prize, 2002: "For Their Discoveries Concerning Genetic Regulation of Organ Development and Programmed Cell Death"

The first Nobel Prize awarded for studies using *C. elegans* was shared by Sydney Brenner, H. Robert Horvitz, and John Sulston. As described above, Brenner, a towering figure in the history of molecular genetics, sought an experimental organism that would be amenable to "the analytic methods of microbial genetics." Remarkably, at the outset of his efforts in 1963, Brenner articulated a clear and prophetic vision: "identify every cell in the worm and trace lineages … investigate the constancy of development and study the genetic control by looking for mutants" (7).

Taking advantage of the transparency, microscopic size, and small cell number of the worm, Sulston heroically and meticulously traced the pattern of nongonadal cell divisions in living individuals from the single-celled fertilized egg to the mature adult, which in conjunction with the somatic gonadal lineage (8), defined the first and to date only complete cell lineage of an animal (3, 9, 10). Sulston described a largely invariant cell lineage that produced, for the hermaphrodite, 1,090 somatic cells. Remarkably, only 959 of these cells were present in the adult—the other 131 initially looked like typical cells but quickly underwent a series of stereotypical morphological changes that culminated in their disappearance. In short, these 131 cells underwent a naturally occurring or "programmed" cell death.

Programmed cell death, also called "apoptosis," had been known to be a widespread aspect of animal development—e.g., in the regression of a tadpole's tail and the formation of fingers and toes during human embryogenesis. The challenge was to determine the mechanistic basis of this striking phenomenon. The starting point, as for many important studies using model organisms, was a chemical mutagenesis screen for mutants that disrupt a specific biological process. Sulston identified the first cell-death gene, *nuc-1*, which encodes a nuclease that degrades the DNA of the dying cell (9, 11). A few years later, Edward Hedgecock identified mutations in two genes, *ced-1* and *ced-2*, required for the phagocytic engulfment of the dying cells—in mutants that lack *ced-1* or *ced-2* function, the cell corpses persist (12).

Major insights into the mechanism of apoptosis followed from Horvitz's subsequent genetic screens for mutations that cause too few or too many apoptotic deaths. Horvitz and Sulston together demonstrated the feasibility of identifying and characterizing mutants with specific cell-lineage abnormalities (13, 14), which included some of the "discoveries concerning genetic regulation of organ development" and led to novel insights into the EGFR-Ras-ERK (15) and LIN-12/Notch pathways (16). Focusing this approach on apoptosis, Ellis and Horvitz performed a screen for mutations that eliminate the persistent corpses of *ced-1* mutants, reasoning that such mutants might include those in which the cells that normally die instead live (17). This screen and related screens were spectacularly successful, identifying the core molecular genetic components of an apoptotic pathway that is conserved across the animal kingdom, including in humans (reviewed in ref. 18). Three proapoptotic genes—*egl-1, ced-4,* and *ced-3* promote programmed cell death, while a single antiapoptotic gene—*ced-9*—prevents programmed cell death. The discovery that *ced-3* encodes a protease that activates multiple processes that "execute" cell death, including the engulfment of dying cells by their neighbors, defined a mechanistic basis of killing (19). Further studies by Horvitz and others identified additional genes that function in cell-corpse engulfment (Fig. 2).

In addition to its fundamental importance in animal development, apoptosis can eliminate abnormal cells on the path to neoplastic transformation (20). The human counterpart of *ced-9, BCL2*, is a proto-oncogene, the overexpression of which prevents apoptotic death and results in follicular lymphoma (21). The discovery that CED-9 is similar to human BCL2 established that studies of worm programmed cell death were likely to inform an understanding of human biology and disease. BCL2-family inhibitors, such as Venetoclax indeed have proved to be effective treatments for certain blood cancers (22). Apoptosis has also been implicated in the pathogenesis of several neurodegenerative diseases, such as retinitis pigmentosa, and there have been clinical trials exploring antiapoptotic drugs as treatments for such diseases (23). Furthermore, apoptosis is crucial in immune system function, and reduced apoptosis is associated with autoimmune disease, while excess apoptosis is associated with immunodeficiency (24). Studies of human biology and therapeutic applications based on

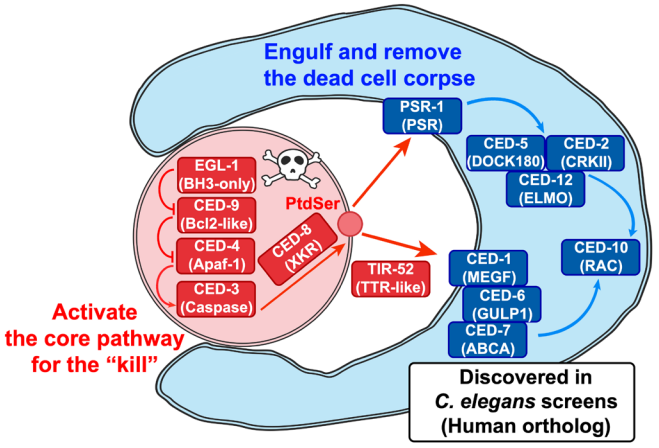

Fig. 2. A conserved pathway for programmed cell death occurs in four steps: identify the victim, make the kill, get rid of the body, and destroy the evidence.

manipulating apoptosis both owe a great debt to the understanding of apoptosis that emerged from analyses of *C. elegans*.

The Caenorhabditis Genetics Center, Established 1979

The Caenorhabditis Genetics Center was the first of the major research resources that emerged from the cooperative spirit of the worm community. By the mid-1970s, leaders in the growing field recognized that a central repository for collecting, cataloging, preserving, and distributing strains was critical for rapid research progress. The National Institute on Aging awarded a contract to initiate stock center operations at the University of Missouri (Director Don Riddle, 1979–1992). In its first year, the CGC fulfilled a mere 15 strain requests. Now in its 47th year of operation and relocated to the University of Minnesota (Director Bob Herman, 1992–2007), the CGC curates a growing cryopreserved collection of >27,000 different strains and has evolved into a premier animal resource.

The CGC plays an essential role in facilitating *C. elegans* research through the fast, reliable, and accurate curation and distribution of strains. The growing strain catalog is continually updated in an online ordering system that provides searchable access to the collection and detailed information about all strains (Fig. 3). The website is also well-integrated with WormBase/Alliance of Genome Resources, described below, providing users with essentially seamless integration with the *C. elegans* genome database.

The CGC greatly accelerates biomedical discovery via its large collection of strains relevant to human biology. CRISPR has opened vast new possibilities for engineering alleles, including those that model human disease. Disease models of neurodegenerative diseases, as well as strains used for studies of aging and lifespan, are among the most requested strains in the collection. Large genome-scale mutation projects have also provided alleles of many genes with human orthologs to distribute (e.g., ref. 25).

The Pursuit of Rigor and Reproducibility and Efficiency of Scale. As a centralized strain distribution center, the CGC enhances the rigor and reproducibility of all research in the field by standardizing genetic strain usage across laboratories and ensuring their continued existence. For example, in disease model research, the CGC helps to ensure uniform strain background, eliminating differences that can confound results for quantitative phenotypes.

The CGC offers major cost-savings to research labs by making new mutants and genetic tool strains readily available. In addition to receiving strains, researchers in all locales supply the CGC, in turn, with important strains that they have generated that could be of use to others. If the CGC were not performing this distribution service, strain acquisition would be extremely inefficient and far more costly; the burden of filling these requests would be placed upon individual labs. The Horvitz lab provides a prime illustration. Of the tens of thousands of strains Horvitz lab members have generated over the years, 917 have been identified as especially useful to others and added to the CGC collection. Remarkably, these strains have generated over 40,830 requests from the community. By assuming the responsibility of maintenance and distribution, the CGC staff frees researchers from individual labs to devote full effort to their science.

The CGC provides one-stop shopping for its entire collection of strains through the efforts of only four full-time and two part-time personnel. Together, this small team efficiently runs an assembly line to complete the core CGC activities: to accurately acquire, maintain, and curate *C. elegans* stocks of high interest to the community and economically distribute

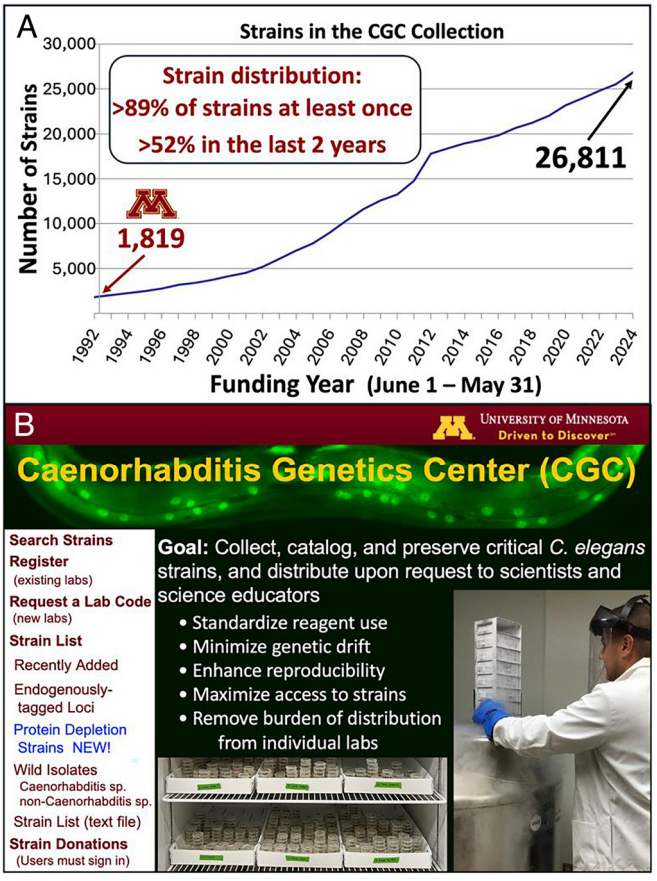

Fig. 3. The Caenorhabditis Genetics Center. (*A*) Growth of the CGC collection since it relocated to the University of Minnesota. (*B*) Montage of CGC operations and goals.

them upon request to scientists and educators with quick turnaround times. Approximately 30,000 strain requests are now fulfilled annually, supporting basic and applied research in thousands of labs and enhancing science education through hands-on experimentation.

Increasing Access for Research and Education. The CGC is a popular resource—over 4,100 individual labs have obtained strains from the CGC within the last 10 y. Of these, more than 1,600 have official "worm lab" designations required for naming strains and alleles. Many of the other labs are primarily focused on other organisms but look to the worm to explore homologs of their favorite genes; often they can find strains premade and ready to order, streamlining the efforts required to test a hypothesis. In this way, a human disease research lab can jumpstart investigation of a relevant worm homolog without spending months or years building research tools from scratch. Educators form another significant user group, using *C. elegans* for hypothesis-based science projects for high school students and undergraduates, training the next generation of scientists.

Safeguarding Scientific Heritage. The CGC functions as a permanent guardian of the intellectual heritage of the field. Its >27,000 strain collection grows nearly every business day. A robust, multitiered cryopreservation strategy provides a critical safeguard against loss of these valuable strains. Stocks frozen in liquid nitrogen for over 40 y remain viable, allowing cryopreserved strains to be maintained essentially in perpetuity. Time and again a new finding will rekindle interest in a mutant strain frozen long ago, and that strain can simply be thawed and revived for study. New stocks received by the CGC are confirmed by established benchmarks, made free of contaminants, and cryopreserved; multiple aliquots are stored locally in two different buildings as a safeguard against sudden equipment failure or localized fire or flood. To safeguard against a catastrophic event in Minnesota, one complete frozen copy of the collection is stored off-site at the National Animal Germplasm Program in Fort Collins, Colorado, providing a literal "ark" for the field. The CGC's efforts ensure that strains—the engines for future discoveries—will remain available for future generations.

Nobel Prize, 2006: "For Their Discovery of RNA Interference—Gene Silencing by Double-Stranded RNA"

RNA interference (RNAi) is a natural biological process by which cells and organisms limit the expression of specific genes and genetic elements. Andrew Fire and Craig Mello led research groups that identified double-stranded RNA as a potent and specific trigger for RNAi and consequent gene silencing in *C. elegans*. This discovery uncovered an ancient guided-search mechanism that cells use to recognize and regulate genetic information (Fig. 4). We now know that RNAi and related small RNA pathways are universal—governing gene expression, protecting genomes, and shaping heredity.

RNAi has become a valuable tool for high-throughput functional screens and individual intervention experiments. While this role has been shared with genome editing

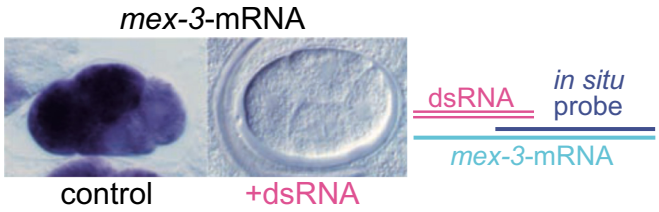

Fig. 4. Introduction of dsRNA results in disappearance of the targeted *mex-3* mRNA (26).

methods such as CRISPR in more recent years, both workflows share the features of combining production of limited or massive libraries of RNA guide sequences that target specific genes with methods for introduction into cells, phenotyping, and assessment of causal relationships. Pioneered in *C. elegans* (27), large scale RNAi-based screens (28–30) became a standard for functional genomic approaches in cell biology, genetics, and biotechnology in myriad organisms, and later served as a paradigm for RNA-guided CRISPR-based functional genomic screens.

There were a series of singular observations and exploratory research programs that came together in enabling these RNAi-based tools. Among these was a key study (published in 1998 and recognized in the 2006 Nobel Prize in Physiology or Medicine) that connected double-stranded RNA structures with a remarkable gene silencing process that had previously been mysterious. It is no accident that teasing out the structural requirements for RNA-based silencing occurred through use of the *C. elegans* model system. For years prior to 1998, different groups had freely shared observations, shared materials (including key strains shared through the CGC), shared genomic information (in what was then the online genome map), and shared insights and discussion in phone calls and at scientific meetings. It was from all of this cross-fertilization that advances in the RNA biology of this organism could synergize groups in Baltimore, Bloomington, Boston, Boulder, Bristol, Cambridge, Dallas, Ithaca, Madison, New York, Seattle, St. Louis, St. Paul, Vancouver, and Worcester, leading to the 1998 transformative study (26). While it was the first and last authors of that study (Fire and Mello) who were credited with the Nobel Prize, the work could not have happened without the community and shared resources that provided the information, the strains, the knowledge, and the connections that enabled thinking-outside-of-the-box experiments. Likewise, it was only with these resources that the initial work enabled further advances to the point where, by the early 2000s, the field could deliver a solid set of experimental parameters and guidelines, enabling the development of RNAi medicines.

The therapeutic potential of RNAi is now realized in approved drugs treating diseases ranging from rare genetic disorders to common conditions. With the 2018 FDA approval of Onpattro for treating a hereditary amyloidosis (31)—the first RNAi-based drug—and subsequent approvals of additional therapies, medicine has acquired a unique and powerful tool for treating diseases once thought intractable. By 2025, thousands of patients are living healthier lives because of these advances. The path to RNAi therapeutics began in *C. elegans*; crucially, the Nobel Prize–winning breakthrough as well as subsequent studies that have provided insights into the process of RNAi relied on strains provided by the

CGC, anatomical context from WormAtlas, genome information in WormBase, and the tradition of shared information in the community. This ecosystem of shared resources allowed ideas and tools to cross-pollinate across institutions, accelerating progress and laying the groundwork for today's RNAi medicines.

WormBase, Established 2000, and the Alliance of Genome Resources, Established 2016

C. elegans was the first animal for which a whole genome sequence was available (5). Remarkably, nearly 40% of *C. elegans* genes have human orthologs based on extensive primary sequence conservation (32, 33). In addition, many additional worm genes are functional orthologs of human genes, recognizable by conserved domain structures and/or AI-assisted structural predictions, exemplified by *lin-14* (34, 35), a direct target of the *lin-4* microRNA (*Nobel Prize, 2024*). The genome sequence is generally the starting point for the creation and study of human disease models and is integral to all studies of aging, neurobiology, development, and physiology with applications to human biology.

Accurate, Comprehensive, and Accessible Genome Data. WormBase is the sole caretaker and annotator of the *C. elegans* genomic sequence. It serves as the source-of-truth for pan-organism resources such as RefSeq, the National Center for Biotechnology Information Reference Sequence Database, and feeds data into a range of downstream resources for particular subsets of the genome, such as the UCSC genome browser, MirGeneDB (microRNAs), and BioCyc (metabolic pathways). WormBase also serves as data broker for large-scale NIH genome-based initiatives, like modENCODE/MODern and the *C. elegans* Neuronal Gene Expression Map & Network (CeNGEN), providing the research community with user-friendly data access, and affording long-term data availability and impact of flagship projects.

Beyond genome sequence information, WormBase models and standardizes >100 different types of data (Fig. 5). Examples include annotation of all available nematode genomic data (such as genome sequence, transcripts, and *cis*-regulatory sites), large-scale functional genomic datasets, the functions and interactions of genes and gene products in development, physiology, and behavior, as well as biological reagents and their source information. WormBase biocurators ensure consistency and integrity of the database and provide detailed attribution of data sources. Furthermore, genes featured in published *C. elegans* papers include links to WormBase for easy entry into genome information, and within WormBase, each gene is linked to both published and unpublished data in any associated papers, worm meeting abstracts, and old Worm Breeder's Gazette articles. Finally, WormBase, the CGC, and WormAtlas all include extensive links to each other to enable access to the additional specialized and in-depth information needed to drive efficient research progress from any starting point.

Even knowledge about a genome sequence is dynamic, and therefore, WormBase requires regular review, curation, and updates to the database. Genome assemblies depend on the state of technology and gradually improve over time.

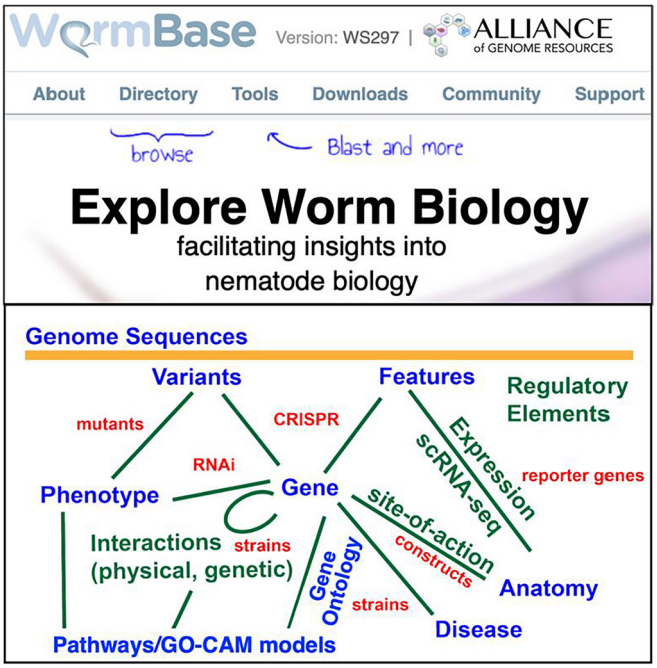

Fig. 5. WormBase in the Alliance. *Top*, Entrees to explore the worm genome. Image credit: Reprinted with permission from WormBase.org. *Bottom*, some of the logical connections among entities in WormBase. Genes and Regulatory elements are genome features. Variants have a physical location on the genome and define genes as well as confer phenotypes. Links to other databases enhance WormBase, including links from "Anatomy" to WormAtlas by expression and genetic site of action experiments, and "Strains" to the CGC.

In addition, the annotation of gene structure models continually improves with more information and often better technology. Indeed, each release of WormBase has seen changes in gene structures and often new genes. Annotation of other features of the genome, notably regulatory elements, are less definitive and must continue to be improved.

Support for an Expanding Research Tool-Kit. WormBase is crucial to all *C. elegans*-related research based on genes and the genome: for molecular identification of genes identified in unbiased chemical genetic screens, for RNAi screens (*Nobel Prize, 2006*), and for efficient CRISPR/Cas9-based genome editing for modifying gene and genome features as well as tagging of endogenous loci. Transcriptional and translational fusions with fluorescent proteins (*Nobel Prize, 2008*) revolutionized real-time in vivo studies of gene expression. WormBase has captured the explosion of these valuable expression constructs and their resulting cellular expression patterns, many of which are linked to strains available in the CGC. Cell/anatomy pages in WormBase are also linked to Cell/anatomy pages in WormBase (*WormBase*) for full descriptions and identification.

WormBase curates a vast amount of genetic and physical interaction data for diverse biological processes, including key signaling pathways involved in cell fate specification, apoptosis by caspases (*Nobel Prize, 2002*), developmental timing by microRNAs (*Nobel Prize, 2024*), and aging by insulin-like growth factor signaling. Interpretation of a list of genes derived from a transcriptomic, proteomic, or cell-specific sequencing experiment requires easily accessible

information about genes and a list of their commonalities. Bioinformatic and genomic research critically depends on WormBase. Any genome-scale analysis (e.g., transcriptomics, proteomics) uses the gene structures curated by WormBase. Also, a single-cell atlas of neuronal cell types [CeNGEN; (36)] relied on curated data from WormBase to identify cell clusters. In addition, mapping of RNAi to genes is crucial to full genome screens (e.g., ref. 37). Any researcher studying any gene or pathway in *C. elegans* uses information from WormBase. The summaries of information provide rapid access to a wide swath of experimental detail.

Innovation and the Alliance of Genome Resources. WormBase has also been an innovator, making improvements in curation, analysis, and display with more general application; e.g., WormBase developed and spun-off GBrowse (38), the predecessor to JBrowse. The automated summaries of gene function based on structured information were generalized to human and other organisms in the Alliance of Genome Resources (hereafter, "the Alliance") and also embraced by other resources such as RefSeq. Similarly, WormBase Textpresso (39) and microPublication projects (40) were subsequently adopted more widely.

The Alliance was created as an umbrella organization to make more reliable software infrastructure for six extensively used biomedical model organism communities (yeast, *C. elegans*, Drosophila, mouse, zebrafish, and rat) and the Gene Ontology Consortium. This consortium of knowledgebases will also facilitate comparative genome approaches in the study of human health and disease. Going forward, the Alliance will jointly develop infrastructure for better service and cost-effectiveness (33). The Alliance has economies of scale that allow deployment of improvements in processes, software, tools, displays, data modeling and integration immediately across all included organisms. Within the Alliance, WormBase will still exist for the curation and community interaction. The current plan is for each community-focused resource to continue its individual work and identity, curating their relevant information, interacting with their communities, and defining needs for tools and data analyses. As an example, the Alliance hosts a multifaceted forum that allows both community-specific and cross-community access to information posts.

Nobel Prize, 2008: for "the Discovery and Development of the Green Fluorescent Protein, GFP"

Martin Chalfie credits *C. elegans* for his interest in green fluorescent protein (GFP) and his consequent Nobel Prize for introducing it as a biological marker. When he first heard about GFP, he was using genetics to study nerve cell development and function in *C. elegans*. He had just begun cloning the genes they were studying and wanted to learn where those genes were expressed. He realized that if GFP could be expressed in living cells, it would be a very useful marker for studies of gene expression in living *C. elegans*, given the worm's transparency. Chalfie's subsequent experiments using *Escherichia coli* and *C. elegans* showed that GFP was an outstanding biological marker that could be used in living cells and organisms (41). Even before publication, he began distributing GFP to others who validated the general utility of GFP as a marker in a variety of organisms (see footnote 23 in ref. 41).

The introduction of GFP as a transcriptional (41) and translational (42) marker led to a wealth of studies in genetics, cell biology, and developmental biology and to consequences well beyond those initial uses. One indirect measure of these consequences is the increase in citations for the phrase "fluorescent protein" in PubMed. Before Chalfie et al. (41), about 100 papers used the phrase; as of September 2025, over 54,800 had done so. These studies have greatly amplified our knowledge of fundamental and conserved functions of biology, including human biology. They have also enabled the discovery of new biological phenomena such as phase-separated particles, first identified in the worm (43).

GFP was the gateway to development of variant proteins with a plethora of altered activities, beginning with the generation of GFP mutants with altered spectra (44), and the discovery of new fluorescent proteins from other organisms, starting with the first red fluorescent protein from coral (45). The fluorescent protein database (fpbase.org) currently lists over 1,000 of these proteins. Using fluorescent proteins, researchers have developed biosensors for biological activity (e.g., ref. 46)- and monitors of protein–protein interactions (e.g., refs. 47 and 48), as well as gene-expression markers for thousands of proteins in many different organisms. The use of GFP and other fluorescent proteins has revolutionized studies in the worm in myriad ways [(49); see also Figs. 6 and 7 and *WormAtlas*). All worm community resources have been essential for applying fluorescent protein technology: WormBase for interrogating gene structures and finding mutant strains, WormAtlas for aiding in cell identification when a new gene expression pattern is examined, and the CGC for rapid strain acquisition. One exciting aspect of doing genetics is that often when you molecularly identify the gene whose mutation produced an abnormal phenotype, you find that you need to learn an entirely new area of biology. Suddenly, mutants defective in other genes must be

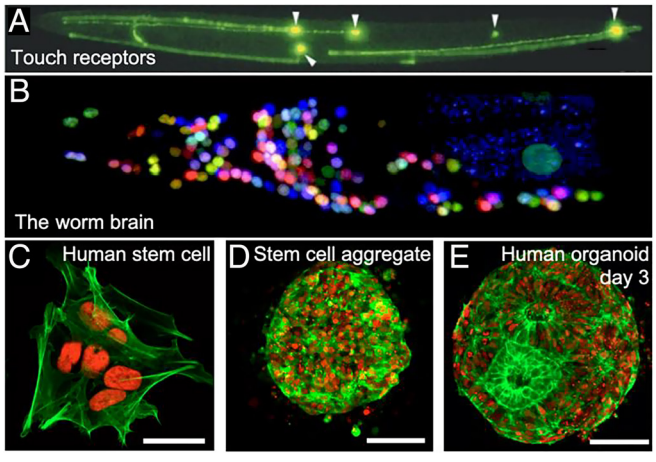

Fig. 6. Broad applications of GFP. (*A*) *mec-17::gfp* identifies touch neurons (50). (*B*) NeuroPAL uses multiple fluorescent proteins for neuron identification (51) (Reprinted from ref. 51, with permission from Elsevier). (*C–E*) Histone H2B-mcherry and lifeact-GFP illustrate embryonic stem cells and early steps in human brain organoid development (Adapted from ref. 52, which is licensed under CC BY 4.0).

examined. The CGC with its extensive genetic collection of mutants and more that 10,000 strains carrying fluorescent reporters available makes exploring these new areas of biology straightforward, cost-effective, rapid, and efficient.

The impacts of GFP on human health have been far-reaching. In addition to gaining a general understanding of diverse aspects of human biology, unforeseen aspects of disease processes have been studied using fluorescent proteins in mice and human cells. For example, the spread of HIV was studied in mouse cells in culture using a virus encoding GFP (53). A review of work using mice (54) said, "Fluorescent proteins have revolutionized in vivo biology [...This] report reviews applications of fluorescent proteins for imaging cancer progression, gene expression, angiogenesis, stem cells, bacterial infection, Leishmania infection, and asthma, at the cellular and subcellular level in live mice [...]. Such imaging possibilities can provide new visual targets for novel drug therapy." Fig. 6 *C–E* shows examples of how fluorescent proteins enhance the power of human stem cell and organoid biology.

WormAtlas, Established 1998

The Center for *C. elegans* Anatomy began with the goal of creating an anatomical atlas for *C. elegans* similar to Netter's Atlas of Human Anatomy (55). By 1998, sufficient anatomical information of the worm had been determined at the single-cell and organ levels that creation of a compendium was considered a valuable undertaking. Like Netter's atlas, a *C. elegans* version would combine scientific understanding of anatomy with detailed illustrations and art to create a comprehensive guide to worm anatomy. In the past year, 67,000 users have visited WormAtlas 317,000 times to use the resulting resource.

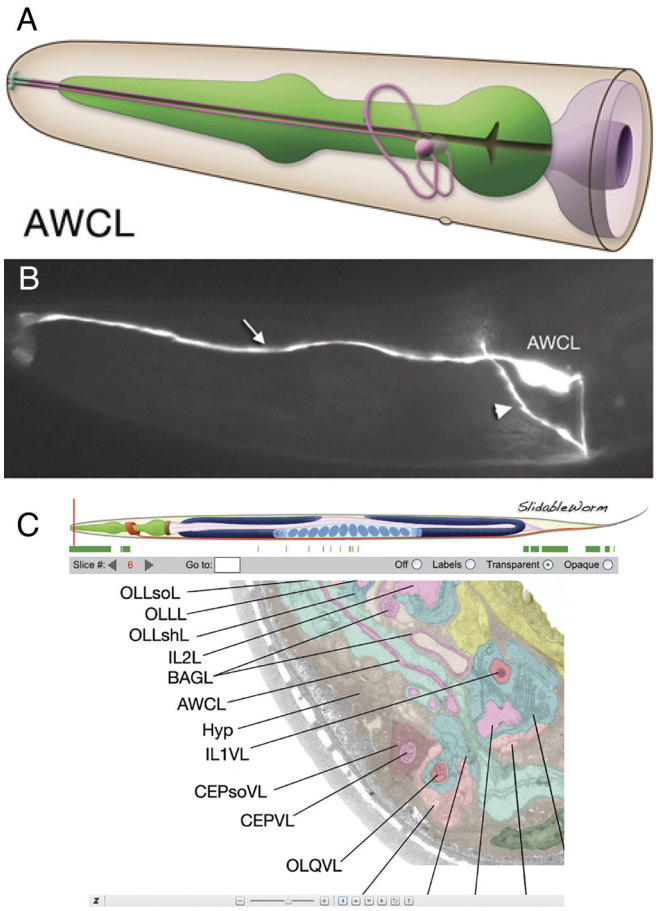

Fig. 7. WormAtlas provides users with numerous anatomical resources including (*A*) illustrations of individual cells (*B*) corresponding fluorescent micrographs and (*C*) tools to view EM slices of the same cell. Image credit: Reprinted with permission from WormAtlas.org.

A Dynamic Anatomical Reference to Support Free-Living and Parasitic Nematode Research. Today WormAtlas is an online platform comprising hundreds of individual web pages that provide a comprehensive view of *C. elegans* anatomy, including the two sexes, the anatomy of which differs substantially. Each handbook chapter includes large numbers of illustrations, annotated EM micrographs, and images of individual cells lit up with fluorescent reporters (Fig. 7). WormAtlas also hosts a full catalog description of each neuron in both the hermaphrodite and male and includes links to both gene expression data in WormBase and suggested reporter strains available from the CGC. In addition to the tissue descriptions for the hermaphrodite, handbooks have been added for the male, dauer larva (a specialized alternative third larval stage entered in response to harsh environments), and changes that occur during aging. WormAtlas also hosts a section about anatomical methods and html versions of important anatomical publications and theses. Most recently, a comparative approach has been pioneered by providing coverage of the satellite model nematode *Pristionchus pacificus* and the human-parasitic nematode *Strongyloides stercoralis.* Cell numbers and fates are remarkably similar across the evolution of nematodes, so that cell identities and functions among species are highly conserved and relatively simple to infer (56). The addition of more nematode species should further expand the breadth of WormAtlas users and foster new connections among diverse research groups.

Archived Electron Microscopy Data Continue to Generate Discovery and New Hypotheses. An essential function of WormAtlas is to archive and interpret EM data. One key factor in Brenner's original selection of *C. elegans* was its suitability for EM, and throughout the 70s and 80s, hundreds of thousands of EM negatives and prints were obtained, leading to seminal publications, including the first nervous-system connectomics paper by White et al. (4).

The MRC data were collected before digital microscopy and the internet. John White realized that there were likely numerous untold stories within these images and graciously shipped this large collection to WormAtlas (57). This collection required eleven shipping crates filled with thousands of prints and glass-plate negatives, along with hundreds of pages of notes, grids containing the original sections and even blocks with unsectioned nematodes. Individual micrographs have since been digitized and evaluated to provide tissue-specific metadata tags. These data served as the foundation of WormImage, a database of over 80,000 micrographs from about 100 specimens. Recently, tens of thousands of micrographs for other nematode species have been acquired and scanned, which will drive work in both parasitology and comparative biology.

The archived data in WormImage are a vital source for generation and testing of hypotheses. The original micrographs were directly annotated using a color code system (Fig. 7*C*), allowing individual cell assignments for many specimens, reanalyses of which have provided substantial new insights into nervous system structure and function (58–60). These data also make important contributions to cell biology, extracellular matrix structure, and evolution (61–63). As new EM data are generated, these archival data also serve as an important comparison, ensuring scientific rigor and reproducibility. These high-quality images can also serve to train machine learning models to help facilitate new EM projects.

When WormAtlas was founded, few researchers had the specialized skills to produce high-quality nematode-specific EM data. Over the past three decades, WormAtlas staff have provided hands-on experience in EM to scores of scientists at all levels. As EM techniques have evolved, WormAtlas has helped the community to adopt new tools, hosting workshops and recording them for YouTube.

One of the unique powers of *C. elegans* as a model is the ability to track expression and signaling down to individual cells, and throughout development. This ability remains an important task for *C. elegans* researchers, especially as spatial transcriptomics becomes more important for understanding expression patterns. WormAtlas provides the most up-to-date information to propel rigorous anatomical research within the *C. elegans* community and beyond.

Nobel Prize, 2024: For Their "Discovery of MicroRNA and Its Role in Posttranscriptional Gene Regulation"

microRNAs are small, noncoding RNAs that play important roles in posttranscriptional regulation of gene expression in plants and animals. The discovery of microRNAs emerged as an unexpected outcome of the Ambros and Ruvkun labs' studies, during the 1980s and 1990s, of the *lin-4* and *let-7* genes of *C. elegans* and their roles in controlling the timing of larval developmental events (64–67). For a half-dozen years after publication of the 1993 paper reporting the discovery of the first microRNA, lin-4 (64), it was not clear whether this little noncoding regulatory RNA was merely a specialty of *C. elegans* or alternatively, a representative of a broadly conserved class of RNA regulators (68).

The 1999 discovery that a second *C. elegans* microRNA, let-7, is conserved (perfectly!) in sequence across all the bilaterian animals, put all doubts to rest (66, 67). In short order, hundreds of miRNAs were discovered across the eukaryotes, including humans (69–71). Strikingly, let-7 is not the only microRNA to be deeply conserved across animals, and in some cases, even the specific target genes of conserved microRNAs are conserved over vast evolutionary distances (Fig. 8), emphasizing the fundamental importance of microRNA-mediated gene regulatory mechanisms.

Why was *C. elegans* the first organism to yield up the secret of microRNAs? For one thing, the worm mutants that led to the discovery of microRNAs were unique: Worms carrying mutations in *lin-4* or *let-7* exhibited developmental timing phenotypes—temporally disjointed expression of juvenile and adult somatic features in the same animal (77)—readily apparent thanks to the simple, accessible,

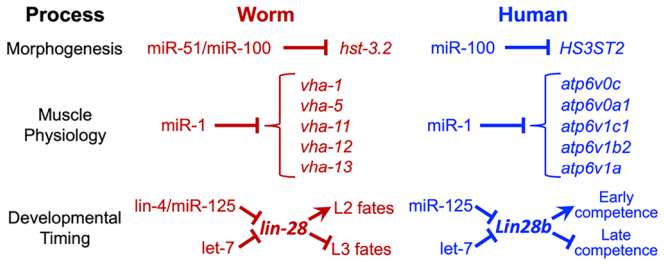

Fig. 8. Evolutionarily conserved microRNA-target regulatory motifs. Compiled from refs. 72–76. Regulation of Lin28b in humans is inferred from experiments on transitions in neural progenitor competence in the mouse retina (and by inference, humans) (76).

and invariant cell lineage. Furthermore, internal self-fertilization can occur even in hermaphrodites with severe body-wide morphological abnormalities: The *lin-4* and *let-7* mutants lack a vulva (78), but still propagate as homozygotes through self-fertilization (and subsequent matricide by the hatched larvae). So, the stage was set for the discovery of microRNAs by fortunate convergences—unique and intriguing developmental timing phenotypes displayed by mutants that valiantly reproduced (and hence offered themselves up for study) despite their strikingly abnormal body morphology.

Also vital to the discovery of microRNAs and the work that followed was the existence of community-shared resources. Scientific progress has a geometric growth component, so that when last year's discovery becomes the reagent for this year's discoveries, the field can move by jumps rather than steps. The initial work as well as follow-up studies of microRNA gene regulatory networks in the 2000s and beyond were greatly accelerated by the synergistic intersection of the CGC strain holdings, the genetic and molecular data stored, processed, and presented by WormBase, and the encyclopedic knowledge of anatomy and development in WormAtlas. The easy access to worm strains and data from these sources not only enhances the work in all worm labs, but it also allows non–*C. elegans* labs to begin to do *C. elegans* experiments to complement, extend, and accelerate their discoveries other systems, including human models such as tissue culture and organoids.

It is now clear that microRNAs and the tiny RNAs associated with RNAi represent different adaptations of the same fundamental phenomenon—sequence-specific posttranscriptional gene silencing by small RNA guided Argonaute proteins. Both have impacts on medicine: Small-RNA based therapies for human diseases were outlined above (*Nobel Prize, 2006*), and miRNAs have emerged as useful markers for diagnostics and prognostics, owing to robust differential microRNA expression profiles that can distinguish normal and pathological cellular states (79).

The Future: Layer Upon Layer of Discovery

One of the clearest lessons from *C. elegans* research is that each breakthrough opens unexpected new directions. The genetics of apoptosis revealed mechanistic roots of cancer and neurodegeneration. GFP transformed live-cell imaging. RNAi revealed a universal system of genome defense now harnessed as medicine. microRNAs reshaped our understanding of gene regulation. Each discovery was amplified

by shared resources and community practices that remain models for modern science.

With powerful genetic screens, CRISPR, and deep annotation, *C. elegans* continues to connect genotype to phenotype with increasing power and precision. The worm demonstrates that curiosity-driven science using a simple animal can not only illuminate biology but also help deliver medicines that change human lives, as discussed in each of the Nobel sections above. Discoveries from *C. elegans* research have impacted society beyond biomedical outcomes. Several agricultural companies are developing RNAi technology to combat important agricultural pests. For example, RNAi technology has been used throughout the United States to control pests of maize that have developed resistance to Bt-based products (80).

The past half-century of *C. elegans* research compellingly demonstrates how fundamental investigations using an experimental model organism can reveal conserved biological mechanisms and greatly impact our understanding of human biology, disease, and the ways to develop novel therapeutics. It is fair to say that all studies in *C. elegans* have been greatly enhanced—and indeed would not be possible without—the NIH-funded shared research resources of the CGC, WormBase/Alliance, and WormAtlas. And if history is any guide, the next half-century will bring insights we cannot even imagine today—insights that will again transform our understanding of biology and our ability to treat disease.

Data, Materials, and Software Availability. There are no data underlying this work.

ACKNOWLEDGMENTS. We are indebted to Iva Greenwald, Jeff Simon, David Fay, Tim Schedl, and an anonymous reviewer for helpful comments on the manuscript and Eugene Lee and Dongyeop Lee for help in preparing Fig. 2 and Oliver Hobert for Fig. 6*B*. We gratefully acknowledge NIH support for the CGC (P40OD010440 to A.E.R. and A.L.D.), WormBase (U24HG002223, U24HG010859 to P.W.S.), and WormAtlas (R24OD010943 to D.H.H. and N.E.S.).

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