IBI* SERIES WINNER

A Mutant Search—*Caenorhabditis elegans* and Gene Discovery

Worm Mutants, an IBI Prize–winning module, offers Biology majors the opportunity to identify mutants and learn about genes that regulate biological functions.

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With ~36,000 students enrolled, the University of North Texas is the fourth largest state university in Texas. To provide each of the >1800 undergraduate Biology majors the opportunity to participate in a discovery-based project, we developed "Worm Mutants," a worm mutant screen module for the required genetics laboratory, where students apply approaches used by geneticists to identify genes that regulate biological processes.

The genetics lab meets once a week for 4 hours; however, the worm mutant module requires additional time. Graduate student teaching assistants instruct the seven genetics lab sections offered each semester; each has a maximum of 24 students per lab section. Thus, as part of the required coursework for Biology majors, >300 students per year take part in the worm mutant screen project.

The module emphasizes scientific discovery while teaching the challenging concept of how mutant animals are used to identify genes that regulate biological processes [see Supplementary Materials (SM)]. Through an experimental approach, students learn the relations among gene, allele, and phenotype in wild-type and mutant organisms, by studying the nematode *Caenorhabditis elegans,* which is a well-researched model organism with considerable background information on its genetics and development. Students conduct a "forward" genetic screen, by starting with a predicted phenotype resulting from disruption of specific biological processes, and seek to identify, from a mutagenized population, a mutant with that phenotype. As a team of four, students devise a plan to identify a mutant worm with a phenotype potentially owing to a mutation in a gene involved with the biological process of interest to them. For example, students interested in how neurons regulate muscle movement look for a worm mutant that does not move normally.

Lab team. Undergraduate research team and graduate student teaching assistant working on a *C. elegans* project.

Recognizing the power of conducting a genetic screen to identify mechanisms for biological processes can be a challenge for undergraduate students, because they need to understand that model systems can be used to understand conserved genes, that analysis of a mutant with a specific phenotype can lead to a greater understanding of normal gene function, and that mutations in different genes involved with different cellular processes can result in a similar phenotype. For example, mutations affecting neurological function could also identify mutants that have muscle dysfunction or have motility issues for reasons not pertaining to neurological function. In addition to these conceptual challenges, student teams do not know if they will identify the mutant of interest and, therefore, there are no "right" answers to the lesson (see the first figure). Instead, the worm mutant screen challenges students to think about observable mutant phenotypes and biological processes.

The worm mutant screen is modeled after the pioneering work by the "Father of *C. elegans* genetics," Sydney Brenner, who demonstrated that induced mutations in *C. elegans* could be used to gain a molecular understanding of animal development (*1*). His work, along with that of John Sulston and Robert Horvitz, led to the elucidation of genetic pathways that regulate complex processes, such as organ development and function. Students are introduced to *C. elegans,* affectionately referred to as worms, by examining their anatomy, life cycle, and husbandry methods. Students also become familiar with the *C. elegans* genetic database, WormBase; relevant scientific papers; and *C. elegans* nomenclature. In a prior lab lesson, students are familiarized with wild-type and common mutant phenotypes (table S1) (*2*, *3*).

Students discuss the range of biological processes that intrigue them and which processes can be studied using *C. elegans* as a

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*IBI, *Science* Prize for Inquiry-Based Instruction; www.sciencemag.org/site/feature/data/prizes/inquiry/.

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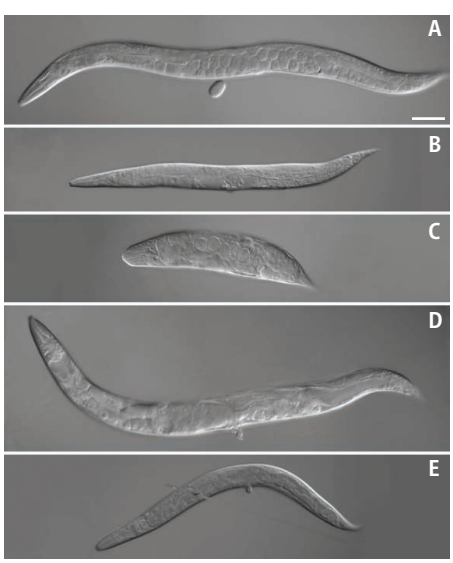
Published by AAAS

model. Discussion points include known worm phenotypes (e.g., uncoordinated, sterility, egg-laying defects, and high incidence of males) and a predicted phenotype of interest to them (*4*). Students screen for a range of phenotypes: from the common (e.g., uncoordinated and dumpy) to the more challenging to isolate (abnormal pharynx pumping and sterility) to the unattainable owing to limited resources (e.g., altered responses to a particular molecule).

Students are encouraged to think critically and creatively as they develop a hypothesis and lay out an experimental plan. Students are required to read peer-reviewed publications (*1*, *4*) relevant to their topic of interest and to incorporate the information into their research proposal, which will be presented with their findings to the class.

Students are provided animals (P_0 generation) in which the germ line was mutagenized with the chemical EMS (see the second figure and SM). The mutagenized animals are grown for two generations to obtain offspring (F_2 generation) to visually screen, using stereomicroscopes, for a phenotype of interest (*4*). If the mutant is not identified, students are then encouraged to think about why the phenotype was not observed within their mutagenized population and to describe the mutants observed during the screening process. After students isolate a mutant animal, they observe the F_3 generation and determine whether the mode of inheritance is recessive or dominant. If the mode of inheritance is more complex, they describe their observations regarding inheritance pattern. Although isolation of a genetic mutant provides a path to many levels of further investigation, student experiments are limited to a general phenotype analysis because of resource constraints. To date, our undergraduate students have isolated many mutants with various phenotypes (see the second figure).



***C. elegans* mutants with observable phenotypes.** These were isolated by undergraduate students. (**A**) Wild-type; (**B**) small mutant (adults are small); (**C**) Dumpy mutant (adult animals are short and thick); (**D**) egg laying–defective mutant (adult animals rarely lay eggs, so embryos mature and hatch inside the hermaphrodite); (**E**) protruding vulva mutant. Scale bar, 50 μm.

Aside from the isolation of *C. elegans* mutants, student-learning experiences include teamwork, time management, recording of results, problem-solving, data collection, and scientific communication. Furthermore, students have shown innovation and creativity by using smart phones and video to capture images of lab tools, techniques, and experimental animals; have gained a sense of independence and ownership of discovery ("my mutant" is often heard); and have achieved experimental accomplishments not often observed with "cookbook" laboratory lessons. To demonstrate their communication skills, students' research proposals describe background, hypotheses, methods, preliminary data collection (their mutant identified), data interpretations, and future work proposed. We opted to have students write a research proposal, instead of a report, so that they understand the importance of preliminary data and gain practice proposing future experiments. The final research proposals reveal an understanding of the concept of a genetic screen and the nature of scientific inquiry. Team PowerPoint presentations describe their experimental approach, phenotype they screened for, results, and potential significance. Students are assessed on participation, proposal content, and team presentation (see SM).

Formal assessments of the student's ability to answer questions regarding genetic screens indicate a statistically significant increase in understanding key genetic concepts. We have found that this worm mutant screen is sustainable even with the challenge of implementation into a high-enrollment course with fixed and shared resources (e.g., stereomicroscopes and worm picks). Given the success of this module we intend to collect, freeze, and store some mutant strains isolated by the students so that we can expand the inquiry-based lesson to analyze the mutants. In conclusion, we found that the majority of students were more enthusiastic about this module, in comparison with past traditional lessons; that for some students it sparked an interest in joining a research lab; and that students became more aware of scientific research and the skill sets necessary for scientists, including communication, teamwork, and the development of scientific ideas.

About the authors

Pamela A. Padilla, Ph.D., an Associate Professor in the Department of Biological Sciences at the University of North Texas, studies the genetic and environmental factors that influence oxygen deprivation response and survival in developing, adult, and aging animals using the *C. elegans* genetic model system. Aside from her research, she teaches genetics at the undergraduate and graduate level. Notably, she was awarded an NSF CAREER grant, which has a teaching component, to develop inquiry-based lessons for the genetics undergraduate laboratory course. **Candace C. LaRue** is a Ph.D. candidate in Padilla's lab at the University of North Texas. She has a Master of Science degree in Biology as well as a Life Science teaching certification. Evaluating how changes in teaching methods can improve student understanding of conceptually difficult concepts is central to her research. In addition, she is interested in assessing programs that include students of various levels into primary research.

References and Notes

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Acknowledgments: This work has been supported in part by an NSF CAREER grant to P.A.P. We thank L. Finn for graphic art assistance for fig. S2. We thank the Department of Biological Sciences, Genetics teaching assistants, and the Lab Coordinator for support of this project and A. Colon-Carmona for comments.

Supplementary Materials

www.sciencemag.org/cgi/content/full/338/6106/487/DC1

10.1126/science.1215229