NATIONAL TOXICOLOGY PROGRAM
FACT SHEET
Headquartered at the National Institute of Environmental Health Sciences • NIH • DHHS

C. *ELEGANS*: A MEDIUM THROUGHPUT SCREENING TOOL FOR TOXICOLOGY

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One of the NTP's goals is to develop and validate improved testing methods that can provide better information, hopefully faster and cheaper. As part of the NTP's vision for the 21st century, the program is interested in developing rapid, mechanism-based, predictive screens for environmentally induced diseases. New tools in robotics, image acquisition and analysis, and gene knockout, and for measuring the expression of genes and the synthesis of proteins make it possible to study complex biological processes in a medium throughput fashion. The free-living, soil nematode *Caenorhabditis elegans* is being developed as a model to assess the effects of potential developmental and neurological toxicants on multi-cellular organisms.

Why Use *C. elegans*?

Several issues collectively make *C. elegans* a practical species for assessing the potential impacts of environmental agents on development and the nervous system. First, using non-mammalian species such as *C. elegans* contributes to advancement of the 3 Rs: reduction, replacement, and refinement of the use of mammals in laboratory testing. Second, the wealth of knowledge available on *C. elegans* is vast and includes (1) its complete genomic sequence, (2) a detailed database on its cellular and developmental biology, and (3) maps of all of its neuronal pathways. Several studies demonstrate that changes in *C. elegans* following chemical exposure appear to be predictive of developmental shifts and/or neurological damage seen in laboratory studies using rodents. The technology is now available to produce "transgenic" nematodes, that is, *C. elegans* in which the genome has been manipulated by adding or knocking out genes. This will enable the study of specific gene/environment interactions or a gene's role in disease etiology.

What Activities are Ongoing to Develop *C. elegans* as a Testing Tool?

The transition of *C. elegans* from a research tool into a testing tool consists of 5 main tasks. The overall goal of these activities is to determine the possibility of using the nematode as a practical and efficient mode in toxicology studies. These tasks include:

- Development of medium throughput technologies to enable measurement of the toxicity of known developmental and/or neurological toxicants, using computer and image analysis software to monitor phenotypic characteristics including growth, size, reproduction, feeding, and movement.
- Exposure of *C. elegans* to 200 known or suspected developmental and/or neurological toxicants followed by evaluation to determine if changes occur in the phenotypic characteristics noted above.
- Creation and/or attainment of green fluorescent, protein-based, stress-responsive transgenic *C. elegans* to test whether this genetically modified nematode has improved sensitivity and specificity for screening toxicants. Development of multi-dimensional (3-D, 4-D) computer imaging software for use in measuring quantitatively the effects of exposure to toxicant(s) on development of the nervous system in *C. elegans*.
- Development of *C. elegans* microarrays and analysis of a specific subset of chemicals.

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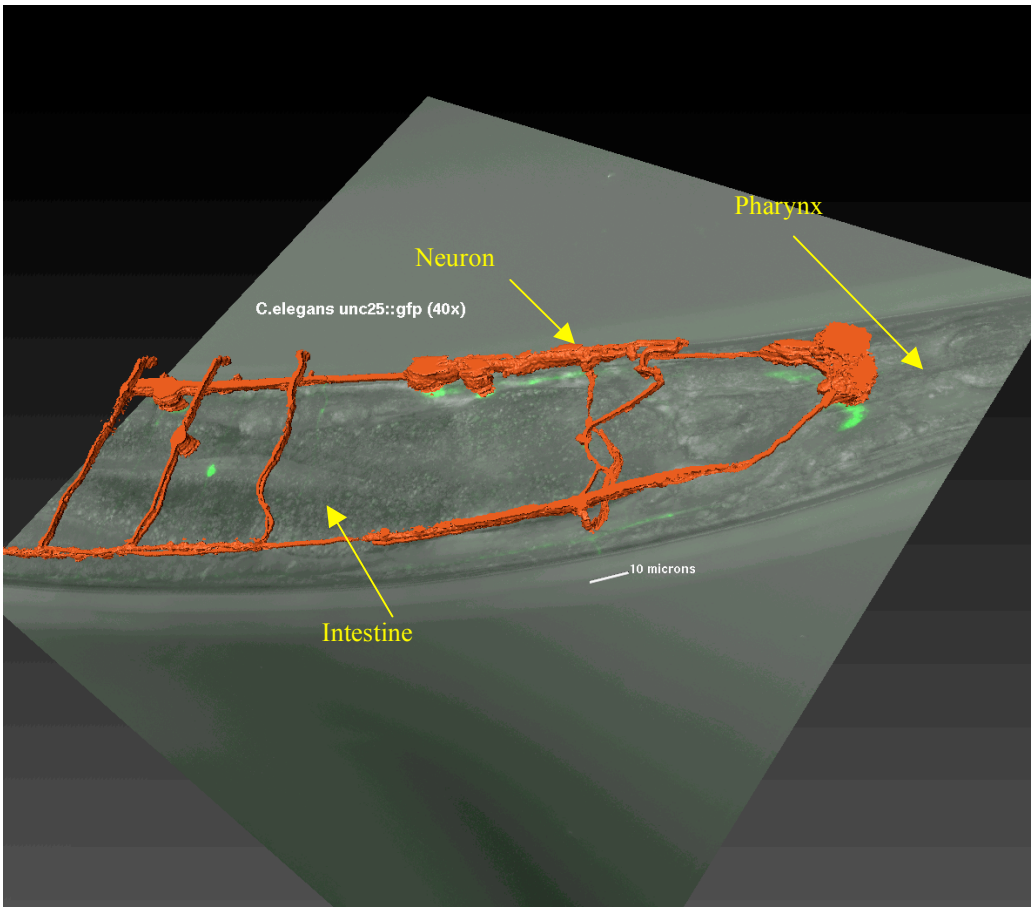
- Adaptation of methods for medium throughput analysis to assess in *C. elegans* the toxicological responses in which each gene has been inactivated using anti-sense RNA technologies (RNA interference).

The NTP has developed several assays for medium throughput screening using a 96-well plate format. These assays are being used to analyze the effects of toxicants on *C. elegans* for effects on feeding, growth, movement, reproduction and viability. The chemicals being tested in this system include transition metals, common laboratory solvents, organophosphate pesticides and, in collaboration with the US EPA, several dozen potential developmental neurotoxicants.

The figure below shows a three-dimensional rendering of a *C. elegans* neuron constructed from a series of confocal images of a green fluorescent protein-labeled neuron acquired and reconstructed into a 3-D image. The neuron is superimposed on a light micrograph image of the same nematode.



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