Worming into Relevance – How *C. elegans* Can Help us Understand Human Health

Disease Modeling / By Yoanne Clovis, Ph.D.

Animal testing in the research-based pharmaceutical industry has been reduced in recent years both for ethical and cost reasons. However, it is still a staple when it comes to discovering new compounds directed at improving human health.

Recently, I have come across more and more researchers who are looking for the most efficient way to move forward in the discovery of new compounds that will improve human health. Their goal is to rapidly:
i) identify the most promising compounds;
ii) understand their mechanisms of action;
iii) test their efficacy and/or toxicity in a living animal to quickly and more confidently move to commercialization or clinical trial.

Most of them have relied on mice or mammalian cells, but many are concerned about the cost and time of such approaches at an early stage. As one researcher told me, "mammalian cell lines are very difficult to work with and they make everything more expensive. It's a time issue too." Live mammals, even more so. These scientists know that the microscopic soil nematode *C. elegans*, on the other hand, has built a solid reputation as a powerful genetic model organism. Highly tractable, with a 2-week life cycle, *C. elegans* provides an attractive alternative for devising and streamlining efficient pre-clinical testing.

However a question remains on their mind: "How relevant is *C. elegans* for studying human health?" I hope that the following excerpts from peer reviewed publications will help answer this question.

Disease Modeling and Drug Testing

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mammalian model systems is extremely expensive and requires time-consuming experimental designs that can be prohibitive".[1] "Much of the essential genes involved in disease presentation are highly conserved from yeast to humans. For instance, when one restricts the comparison to the 6460 genes known to be associated with genetic disease (1/3rd the human genome), clear similarity (orthology) to *C. elegans* occurs for 79% of the human disease genes (ClinVar database). This high degree of interspecies conservation between worm and human has recently become more recognized and appreciated for use in disease biology understanding".[6,8,9,15]

"A number of practical advantages […] such as short lifespan allowing rapid in-vivo testing, conservation of disease and stress response pathways, availability of mutant and transgenic strains, and wealth of biological information, have led to the increased use of *C. elegans* in toxicological studies." [5]

Learn more about using *C. elegans* for disease modeling.

Toxicity Assessment

"Unlike toxicity testing using cell cultures, *C. elegans* toxicity assays provide data from a whole animal with intact and metabolically active digestive, reproductive, endocrine, sensory and neuromuscular systems. Toxicity ranking screens in *C. elegans* have repeatedly been shown to be as predictive of rat LD50 ranking as mouse LD50 ranking. Additionally, many instances of conservation of mode of toxic action have been noted between *C. elegans* and mammals. These consistent correlations make the case for inclusion of *C. elegans* assays in early safety testing and as one component in tiered or integrated toxicity testing strategies, but do not indicate that nematodes alone can replace data from mammals for hazard evaluation." [10]

"Positive predictive power of *C. elegans* for toxicological research has been shown. For example, one study demonstrated that 89% of compounds compromising egg viability in the worm also have known developmental effects in mammals[12], while a study of 47 compounds associated with mammalian reproductive toxicity showed up to 69% concordance between *C. elegans* data and ToxRefDB mammalian data[13]. In a more extensive study, toxic effects associated with exposure of *C. elegans* to over 900 chemicals were compared with ToxCast data from zebrafish, rats and rabbits.[14]

The authors found concordance of *C. elegans* data with data from rats and rabbits of between 45 and 53% across a range of doses, which is only slightly lower than the concordance between rat and rabbit data (58%)." [11]

Learn more about using *C. elegans* for toxicology studies.

The nematode *C. elegans* is accepted by the scientific and pharmaceutical community as a model system to study the underlying molecular mechanisms involved in neuronal health "because of it's well-characterized and easily accessible nervous system, short generation time (~3 days) and lifespan (~3 weeks), tractability to genetic manipulation, distinctive behavioral and neuropathological defects, coupled with a surprisingly high degree of biochemical conservation compared to humans. Remarkable similarities exist at the molecular and cellular levels between nematode and vertebrate neurons. For example, ion channels, receptors, classic neurotransmitters such as acetylcholine, glutamate, γ-aminobutyric acid (GABA), serotonin, and dopamine (DA), vesicular transporters and the neurotransmitter release machinery are similar in both structure and function between vertebrates and *C. elegans*. Importantly, the impact of different environmental and genetic changes such as exposure to small molecules on the health, survival and function of the nervous system can be readily studied in *C. elegans* in-vivo." [1]

Aging

"C. elegans is well-established as an aging research model and has enabled the identification of pathways influencing aging, such as the insulin/IGF-1 (IIS) and mTOR pathways, which are evolutionary conserved in mammals. […] A number of recent studies have identified microbial pathways affecting aging and longevity in *C. elegans*, introducing this model as a viable way to understand the role of the gut microbiota in health and aging." [3]

Learn more about using *C. elegans* for aging studies.

Microbiome

Studies on *C. elegans* microbiomes demonstrate that bacteria are able to enhance growth of nematode populations, as well as resistance to biotic and abiotic stressors, including high/low temperatures, osmotic stress, and pathogenic bacteria and fungi. The characteristics of these effects, their relevance for *C. elegans* fitness, the presence of specific co-adaptations between microbiome members and the worm, and the molecular underpinnings of microbiome-host interactions represent promising areas of future research, for which the advantages of *C. elegans* as an experimental system is of high value.[3,4]

The high tractability and fast life cycle of *C. elegans* makes it a prime model for early in-vivo testing and drug discovery. As NemaMetrix is working with clinicians and pharmaceutical companies, we have simplified and accelerated their access to rapid, re[illegible]le insight on human health. We do so by providing specific strains made to

to hefty investments into one discovery pipeline or the other. *C. elegans* has already facilitated the identification of potential novel therapeutics, and the combination of genetic models with screening platforms continues to be a very efficient strategy for therapeutic drug discovery for aging and human diseases.

Learn more about using *C. elegans* as an alternate animal model.

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Yoanne Clovis has been with NemaMetrix almost since its inception. She has worn many hats at the company over the years – from lab work to her current sales manager position, she truly understands not just the company, but the *c. elegans* research field as well.

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