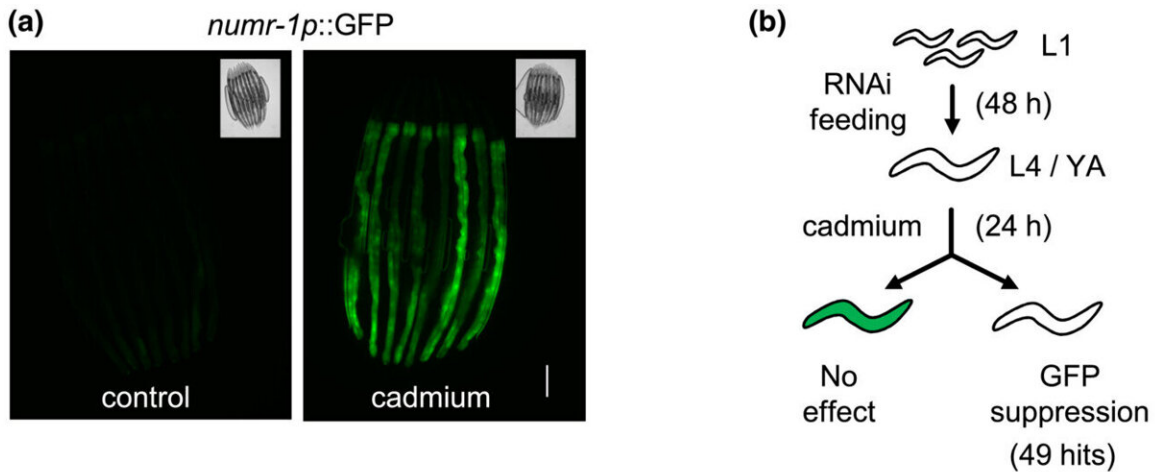


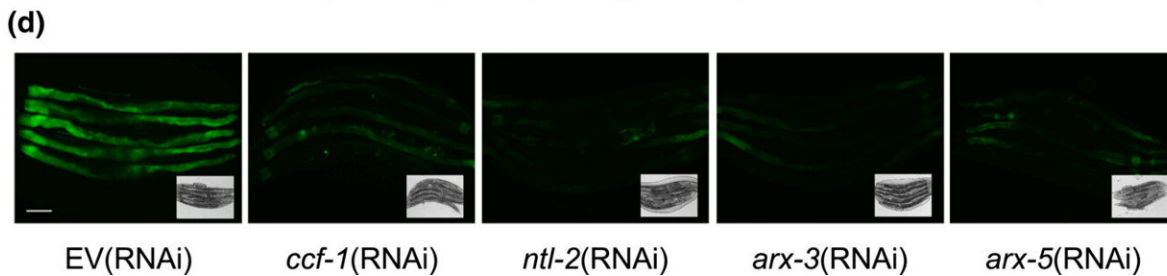
Protein from a round worm may unlock a cellular 'fountain of youth'

May 2 2023



(c)

Enriched Gene	Functional annotation	Fold Enrichment	FDR
<i>ccf-1</i> <i>ntl-2</i> <i>ntl-3</i> <i>let-711</i>	CCR4-NOT complex (Cellular component) RNA degradation (KEGG pathway)	89.6 16.2	7.90E-4 2.8E-2
<i>arx-3</i> <i>arx-5</i> <i>arx-7</i>	Arp2/3 protein complex (Cellular component) Endocytosis (KEGG pathway)	67.2 5.3	2.10E-2 9.8E-1



Genome-wide RNAi screen reveals a requirement for genes encoding the

CCR4-NOT complex for cadmium-induced activation of numr-1p::GFP. (a) Representative fluorescence and brightfield micrographs of worms expressing numr-1p::GFP under control and cadmium conditions. (b) Workflow of genome-wide RNAi screen. (c) DAVID enrichment of dsRNA clones that inhibited cadmium-induced numr-1p::GFP expression. (d) Representative fluorescent and brightfield micrographs of worms fed dsRNA resulting in the inhibition of cadmium-induced expression of numr-1p::GFP. The scale bar is 100 μ m. Credit: *Aging Cell* (2023). DOI: 10.1111/ace1.13795

Working with tiny, nematode worms called *C. elegans*, a USask research team has identified a pair of genes responsible for clearing cells of the toxins which accumulate in the body and are responsible for aging. By inactivating genes called CCF-1 and PAL-1, the researchers found nematodes die 50% faster than normal.

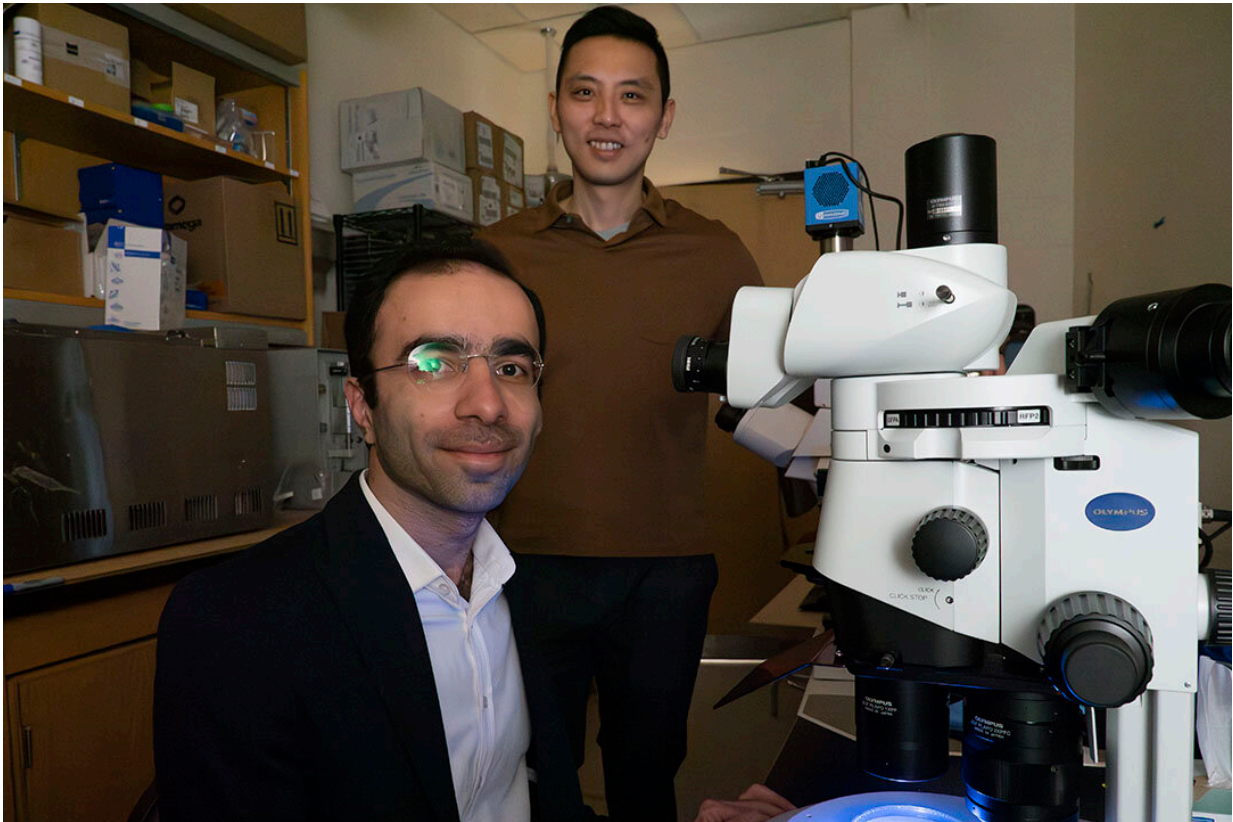
"If you remove CCF-1 gene from the worms, they become super sensitive to even the mildest amount of stressors, such as those which can cause neurodegeneration," said Dr. Michael Wu (Ph.D.), researcher in veterinary biomedical sciences at USask's Western College of Veterinary Medicine (WCVN) and senior author of the paper published in *Aging Cell*. "These [genes](#) may be a key regulator in what causes premature aging in individuals."

While the research was conducted in nematodes, approximately 40% of [nematode](#) genes—including CCF-1 and PAL-1—have the same function in humans. In humans, CCF-1's equivalent is named CNOT7 and PAL-1 is called Cdx2.

"These genes can be traced back to an individual human's ability to fight off chemical stressors at the [cellular level](#), which then is directly linked to the rate at which they age," said Wu. "Our goal is, at the basic, fundamental level, to define what drives aging—age is the primary

driving factor of basically every chronic human disease."

"When you age, you increase susceptibility to getting cancer. When you age, you're more prone to neurodegeneration. When you age, your metabolism slows down, and you're more susceptible to the development of diabetes or cardiovascular failure," he said.



Left to right: USask master's student Hadi Tabarraei with his supervisor, Dr. Michael Wu (PhD), analyses nematodes with a fluorescent microscope. Credit: Daniel Hallen/USask

Much of the research which involved screening all 20,000 nematode genes—a process that took over six months to complete—was conducted

by USask master's student Hadi Tabarraei and doctoral student Brandon Waddell, aided by undergraduate students Kelly Raymond and Sydney Murray. The team also included University of Florida researchers Dr. Ying Wang (Ph.D.) and Dr. Keith Choe (Ph.D.).

Nematodes were exposed to cadmium, a [heavy metal](#) which can accumulate in the body, and the neurotoxin acrylamide, mimicking the cellular stress conditions an organism experiences as part of the aging process. Using a technique called RNA interference, the researchers inactivated one gene at a time, finding nematodes with CCF-1 inactivated were more vulnerable to the chemicals and died at a much faster rate.

"We were following hundreds of worms at different conditions, and tracking how long these worms go from birth to death," said Wu. "Nematodes only live about two to three weeks on average, so we can correlate our [genetic data](#) to a phenotype at the whole-organism level."

After realizing the importance of the CCF-1 gene, the research team discovered that inactivating the PAL-1 gene created an almost identical response—the two genes work in concert to regulate the expression of multiple genes in responding to chemical stressors in the body.

The next steps in the research involve further investigation into the [cellular processes](#) in the nematode model to identify pharmacological compounds that can effectively turn on and off the genes in a controlled manner. Wu expects to pinpoint those compounds in the next five years and, in tandem, he intends to replicate the research with human cell lines and humanized mouse models, working with collaborators.

"If you want to measure whether [a pharmacological] compound has an impact on lifespan or disease development, that can take three to five years because mice can live for two years and more, normally," said Wu.

"With an extended lifespan, it's probably four to five years down the road."

More information: Hadi Tabarraei et al, CCR4-NOT subunit CCF -1/CNOT7 promotes transcriptional activation to multiple stress responses in *Caenorhabditis elegans*, *Aging Cell* (2023). [DOI: 10.1111/accel.13795](https://doi.org/10.1111/accel.13795)

Provided by University of Saskatchewan

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