nagi bioscience

APPLICATION NOTE

Unlocking New Frontiers in Longevity & Healthspan

Streamlining aging studies with automated high-content screening for 3Rs *in vivo* testing at the *in vitro* scale

Unlocking New Frontiers in Longevity and Healthspan

As aging research remains at the forefront of biomedical science and an increasingly growing social issue, understanding the biological mechanisms behind cellular and organismal decline is crucial to extending healthspan—the period of life spent in good health—and overall lifespan. Despite the need to accelerate the discovery of preventive aging interventions, traditional methods depending on manual work face limitations that hinder scalability, increase costs, and slow progress toward actionable outcomes.

To address these challenges, Nagi Bioscience has developed an innovative platform that integrates the biological relevance of *in vivo* testing with the scalability of *in vitro* systems, offering actionable insights into the effects of various interventions on aging pathways, all while maintaining ethical standards.

By providing a streamlined solution for testing and evaluating a wide range of compounds, Nagi Bioscience accelerates the discovery and de-risking of potential therapeutics that can enhance healthspan, mitigate age-related decline, and ultimately contribute to a longer, healthier life.

C. elegans: A Cornerstone of Aging Research

Caenorhabditis elegans is an established powerful ally in the quest to unravel the complexities of aging and extend human healthspan. Its short lifespan allows researchers to rapidly test interventions and observe outcomes within days, accelerating discoveries in longevity science. Coupled with its genetic tractability and remarkable conservation of aging pathways, *C. elegans* offers an unparalleled platform for studying the biological mechanisms of aging and identifying genetic and pharmacological potential interventions that delay age-related decline.

As a whole organism, *C. elegans* bridges the gap between simplistic *in vitro* models and ethically challenging vertebrate systems. Unlike cell cultures or organoids, it offers a holistic view of aging, integrating systemic interactions among tissues, metabolism, and behavior while also avoiding ethical concerns, high costs, and logistical limitations of vertebrate models.

The translational impact of *C. elegans* research continues to grow, with discoveries in this model often paving the way for clinical trials. By combining scalability, ethical advantages, and mechanistic depth, *C. elegans* not only advances our understanding of aging but also serves as a critical testing ground for interventions aimed at promoting healthier, longer lives.

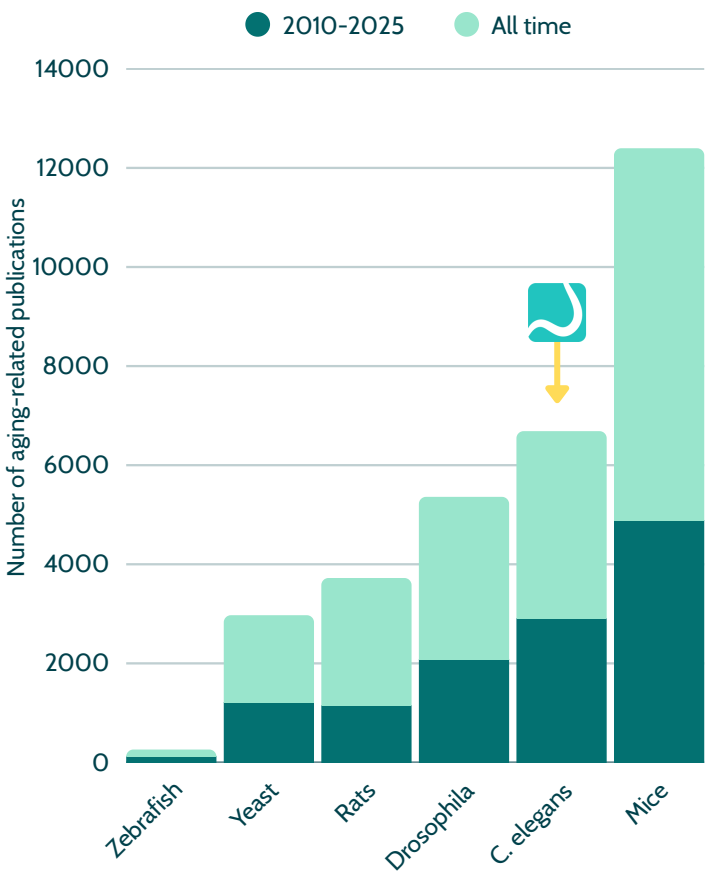

Figure 1. Comparative Analysis of Aging-Related Publications by Model Organism: Data were retrieved from PubMed using search terms combining "longevity" with each organism's name.

From research to results

Explore the technology:
SydLab™ One Technical Note

Our approach

Age synchronized populations of *C. elegans* are injected into the microfluidic chips and controlled by a fully automated protocol. In each channel, *C. elegans* are exposed to a well-defined environment, including the temperature, the feeding, and the compounds to be tested. All experimental measurements and data points are monitored throughout C. *elegans*'s life cycle. In addition to aging-related insights, the high-content imaging enables the visualization and analysis of diverse phenotypes, supporting broader applications.

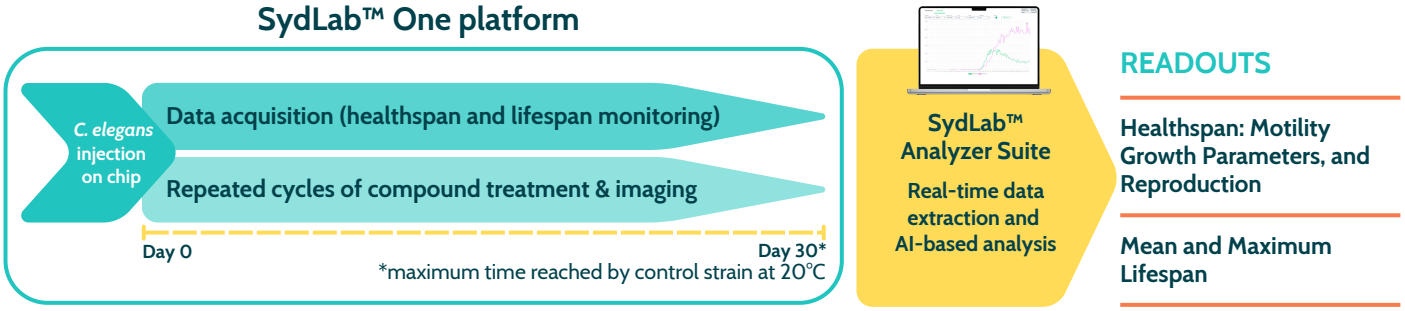

Figure 2. Automated workflow on SydLab™ One.

Case study

This study was focused on evaluating the effects of compounds influencing aging pathways, such as paraquat (PQT), nicotinamide (NAM), metformin, α-ketoglutarate (AKG), and doxycycline. As a positive control, the nematodes were subjected to caloric restriction (CR) (16% & 20%), and as negative controls, they were provided with water. Using Nagi's microfluidic chips, we tested all compounds and conditions in 4 technical replicates (chips A–D).

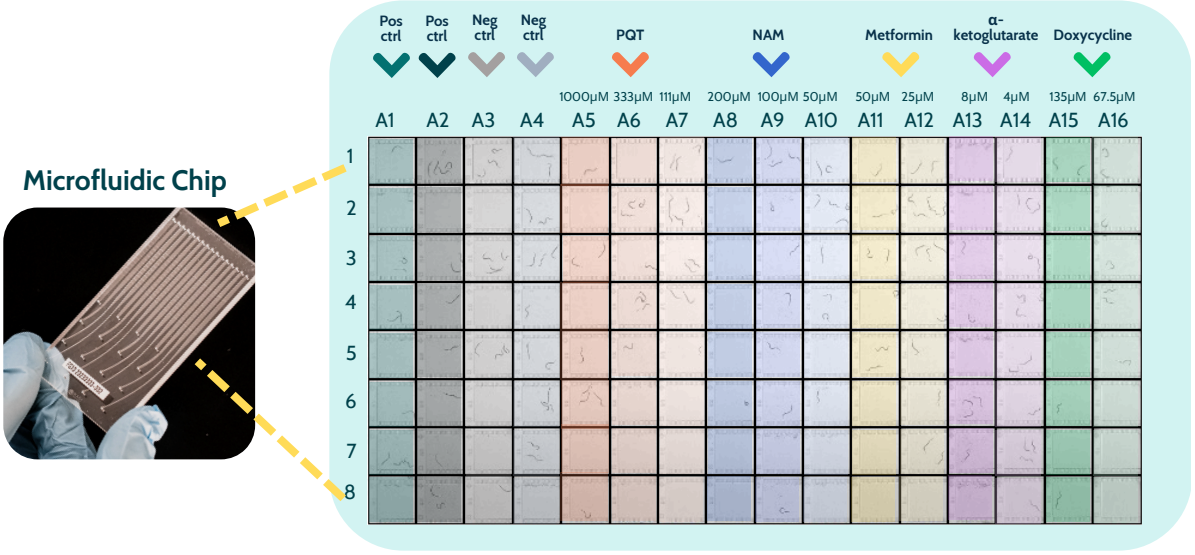

Figure 3. Schematic illustration of the channel layout within the graphical user interface (GUI) of SydLab™ One software for experimental design: Specific conditions were defined for each of the 16 channels of each chip.

CASE STUDY

Validating Aging Interventions with SydLab™ One

Lifespan

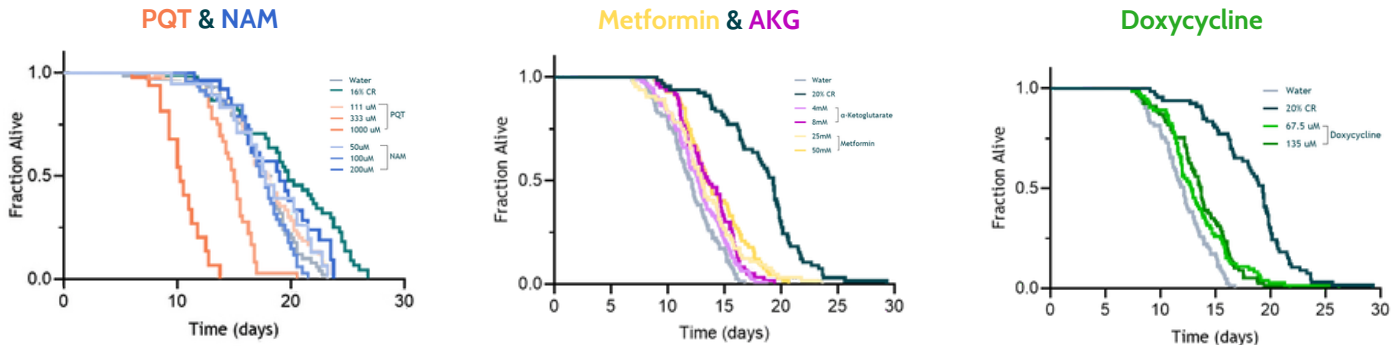

Figure 4. Effects of compounds influencing aging pathways on lifespan in *C. elegans*. Survival curves showing the impact of (A) Nicotinamide (NAM) and Paraquat (PQT), (B) Metformin and α-Ketoglutarate (AKG), and (C) Doxycycline on *C. elegans* lifespan.

This case study reveals dose-dependent effects across compounds. Paraquat (PQT) at increasing concentrations (111-1000 µM) reduced lifespan, consistent with its role as a pro-oxidant. In contrast, nicotinamide (NAM) (50–200 µM) showed a potential lifespan extension, particularly at 200 µM, aligning with its NAD+ boosting properties that enhance mitochondrial resilience. A trend for lifespan extension was also observed with metformin and α-ketoglutarate in a dose-dependent manner. Doxycycline showed a similar trend of lifespan extension, potentially through the induction of a mild stress response—an effect reported in mice.

Healthspan

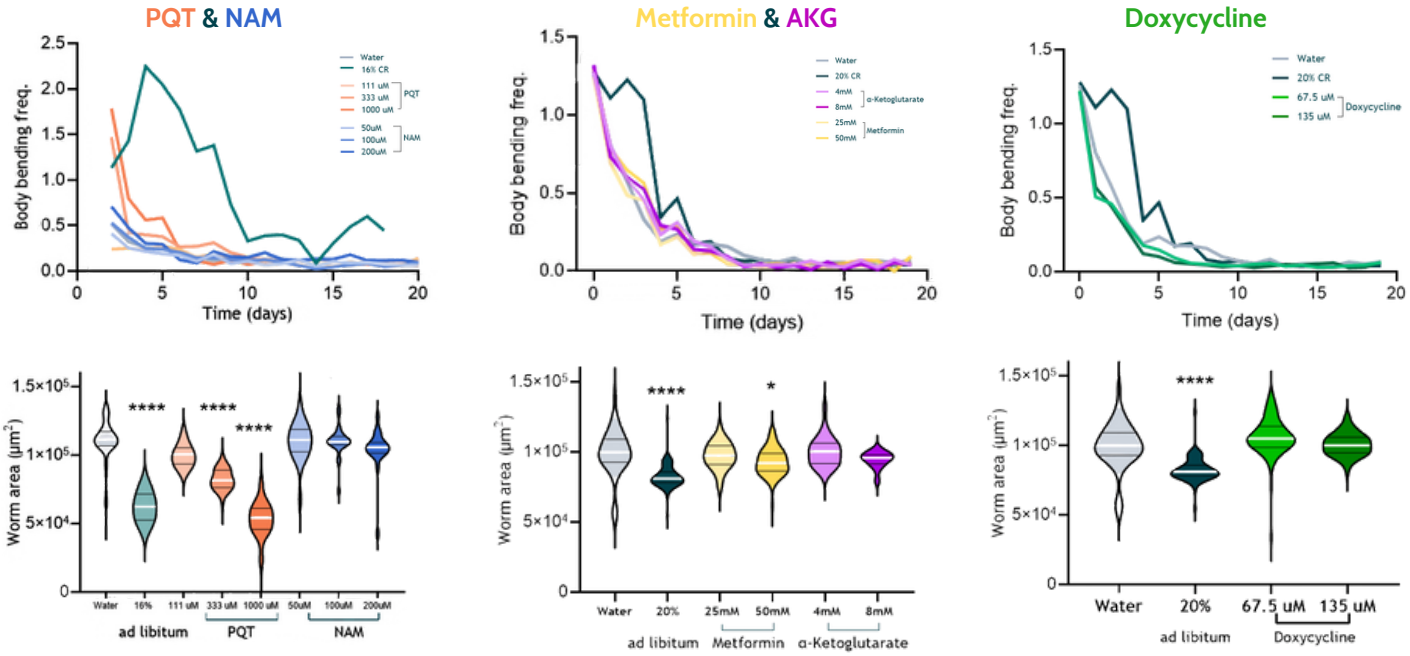

Figure 5. Effects of compounds influencing aging pathways on healthspan parameters in *C. elegans*. Motility (body bending frequency (Hz)) (above) and worm area on day 10 (below) were evaluated upon (A) Nicotinamide (NAM) and Paraquat (PQT), (B) Metformin and α-Ketoglutarate (AKG), and (C) Doxycycline interventions. Non-normally distributed data (worm area) were analyzed with Kruskal-Wallis and Dunn's post-hoc tests (α = 0.05). Significance levels: $p < 0.05$, $p < 0.01$

CASE STUDY

Validating Aging Interventions with SydLab™ One

Our analysis revealed distinctive patterns in healthspan metrics across the tested compounds. PQT treatment exhibited significant toxicity at 1000 µM, as there was a high motility response (body bending frequency) at the onset of the experiment, which rapidly declined at levels below control motility. Also, the worm area decreased substantially at both 333 µM and 1000 µM, indicating dose-dependent growth inhibition. NAM-induced lifespan extension was not accompanied by changes in motility and worm area compared to the control organisms. Metformin treatment maintained body-bending frequency comparable to baseline values but significantly reduced adult growth at 50 mM, indicating a metabolic fitness response. α-Ketoglutarate treatment sustained normal motility patterns and adult growth metrics throughout the experimental period, suggesting preserved developmental homeostasis. Doxycycline treatment demonstrated a trend toward decreased mobility compared to controls while maintaining stable adult body size.

Reproduction

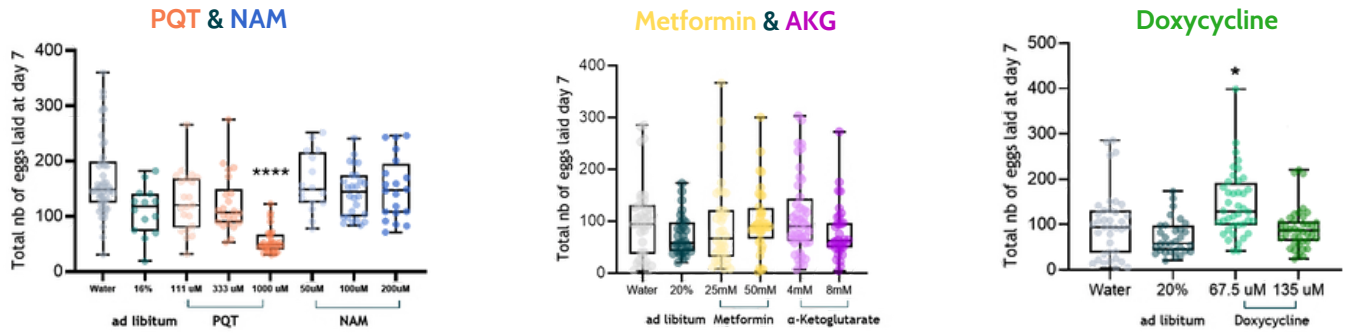

Figure 6. Effects of compounds influencing aging pathways on reproduction in *C. elegans*. Total egg production per worm at day 7 was assessed upon (A) Nicotinamide (NAM) and Paraquat (PQT), (B) Metformin and α-Ketoglutarate (AKG), and (C) Doxycycline interventions Non-normally distributed data were analyzed with Kruskal-Wallis and Dunn's post-hoc tests (α = 0.05). Significance levels: $p < 0.05$, $p < 0.01$

PQT treatment at 1000 µM resulted in a confounding effect, as reproductive function was significantly impaired, likely due to PQT impact on adult growth (worm area) that hinders reproductive capabilities. These findings underscore the toxic effects of PQT in the context of aging. NAM-induced lifespan extension was not accompanied by changes in egg production compared to the control organisms, suggesting that its longevity benefits occur without reproductive trade-offs. Both metformin and α-ketoglutarate treatments preserved normal reproductive capacity, with egg counts remaining consistent with control values throughout the experimental period. Most notably, doxycycline administration at 67.5 µM demonstrated a stimulatory effect on reproduction, with enhanced egg production observed at day 7.

Conclusions

This case study demonstrates SydLab™ One's effectiveness for interventions and mechanistic studies in longevity and healthspan. By combining an automated workflow with real-time data analysis, SydLab™ One evaluates the effects of compounds on lifespan and healthspan with unmatched speed and precision. The platform's ability to monitor multiple phenotypic traits not only accelerates anti-aging research but also deepens our understanding of the fundamental biological mechanisms that drive the aging process.

SUPPLEMENTARY GUIDE

Interpreting your healthspan data

This guide suggests a comprehensive framework that researchers can leverage for a quick assessment and interpretation of experimental results in longevity and healthspan studies generated by SydLab™ One.
The streamlined approach helps translate the data into meaningful insights, accelerating your research outcomes.

Table 1. SydLab™ One Parameter Assessment for Aging Interventions.

Parameters measured by SydLab™One	Baseline	Positive Drug Effect	Negative Drug Effect	Healthspan Interpretation
Motility	Declines ~ Day 10-15	Maintains motility longer	Early motility loss	**High motility = key positive indicator**
Reproductive Span	~6-7 days, ~250-300 eggs	Preserves reproductive function & egg production	Shortened reproductive span & fewer eggs	**Essential indicator when preserved with other positive parameters**
Growth Dynamics	Normal L4→Adult, stable	Maintained size stability once adult	Stunted growth/rapid shrinkage/ abnormal swelling	**Normal growth patterns = healthspan supportive indicator**

Strong healthspan improvement: High motility, preserved reproductive span, and normal growth with no shrinkage.

Possible energy shift, healthspan positive: High motility, but decreased reproductive span and a mild shrinkage of the worms.
Frailty extension: Extended lifespan with normal growth patterns but early motility decline.

Pro-aging/toxic effect: Motility, reproduction, and lifespan decline.

SUPPLEMENTARY GUIDE

Translational Relevance of Key Metabolic Compounds

Aging research focuses on interconnected biological mechanisms known as the hallmarks of aging, including oxidative stress, epigenetic alterations, genomic instability, metabolic dysfunction, impaired proteostasis, and gut microbiome imbalance. These overlapping processes decline with age, influencing disease onset. Both lifestyle modifications and pharmacological interventions show promise in slowing biological aging.

In our case study, we evaluated five compounds known for their potential to modulate longevity in humans using our automated *C. elegans* screening platform. This approach highlights the effectiveness of SydLab™ One in evaluating various healthspan and lifespan parameters for efficient therapeutic discovery.

Nicotinamide (NAM)

Translational value: Vital precursor of NAD^+ that enhances its biosynthesis. NAD^+ is a coenzyme central to cellular metabolism, DNA repair, and longevity pathways.
Mechanism of Action: NAM is involved in the NAD^+ salvage pathway and is a substrate for PARP-1, supporting genomic stability, cellular energy homeostasis, and healthy aging.
Human relevance: Early research in *C. elegans* provided key insights into NAD+ boosters that swiftly advanced from laboratory discovery to human clinical trials (1), highlighting the strong translational power of this model organism.

Paraquat (PQT)

Translational relevance: Neurotoxicant model to study Parkinson's disease and neurodegeneration.
Mechanism of Action: Induces oxidative stress and microglial activation, highlighting critical mechanisms such as NADPH oxidase-mediated inflammation and dopaminergic neuron vulnerability (2).
Therapeutic exploration: Understanding paraquat's mode of action informs preventive strategies and therapeutic interventions targeting environmental neurotoxins and oxidative stress pathways in neurodegenerative diseases.

α-ketoglutarate (AKG)

Translational potential: Significant potential in human healthspan extension as a metabolic intermediate supporting protein synthesis and mitochondrial function.
Therapeutic exploration: Its pleiotropic roles in muscle maintenance, metabolic regulation, and stress resistance position it as a compelling candidate in longevity and age-related therapeutic strategies.
Human relevance: AKG supplementation can reduce biological age by DNA methylation measures (5).

Metformin

Mechanism of Action: Activates AMPK and inhibits mTOR, influencing cellular energy balance, autophagy, and mitochondrial health.
Therapeutic exploration: Metformin can restore autophagic flux and mitochondrial function in myoblasts, potentially preventing age-related muscle loss (3).
Human relevance: RJx-01 combination therapy (metformin with galantamine) synergistically extends lifespan and improves fitness in age-associated sarcopenia. Initially validated in *C. elegans*, this intervention has progressed to ongoing human clinical trials (4).

Doxycycline

Translational significance: Recognized for its antimicrobial activity with translational significance in mitochondrial biology and aging research.
Mechanism of Action: Inhibits mitochondrial protein synthesis via the 28S ribosome, as a result, selectively targets cancer stem cells and modulates oxidative metabolism (6).
Therapeutic exploration as a mitochondrial modulator in aging research, with potential implications in oncology, metabolic health, and lifespan extension.

References:
1. Mouchiroud et al., *Cell,* 2013, **2.** Berry et al., Cell Death and Differentiation (2010) 17, 1115–1125, **3.** Bang et al., Biomedicine & Pharmacotherapy 180 (2024) 116981
4. Tezze et al., *JCI Insight*, 2023, **5.** Demidenko et al., Aging 2021, Vol. 13, No. 22, **6.** Lamb et al., Oncotarget, 2025 Vol. 6, No.7

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APPLICATION NOTE

Explore our technologies and research solutions

Discover the capabilities of SydLab™ One with the Discovery Pack experience

Let's connect

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