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Omipalisib increases median lifespan by 41% in *Caenorhabditis elegans* but does not consistently delay Aβ-associated paralysis in GMC101 mutant

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Abstract

Gerotherapeutics target conserved pathways of aging and may offer a strategy for age-associated diseases such as Alzheimer's disease. We found that Omipalisib (GSK2126458), a PI3K/mTOR inhibitor, extended lifespan in wild-type N2 *Caenorhabditis elegans*, increasing median lifespan by 41.1%, while rapamycin doses increased median lifespan by 0–10.2% and were not significant relative to matched DMSO controls. We then tested whether this longevity effect translated to the GMC101 amyloid-β model. Across 23°C, 24°C, and 25°C, 10 µM omipalisib did not consistently delay paralysis relative to DMSO controls. These findings show that lifespan extension does not necessarily confer protection against Aβ-associated proteotoxicity.

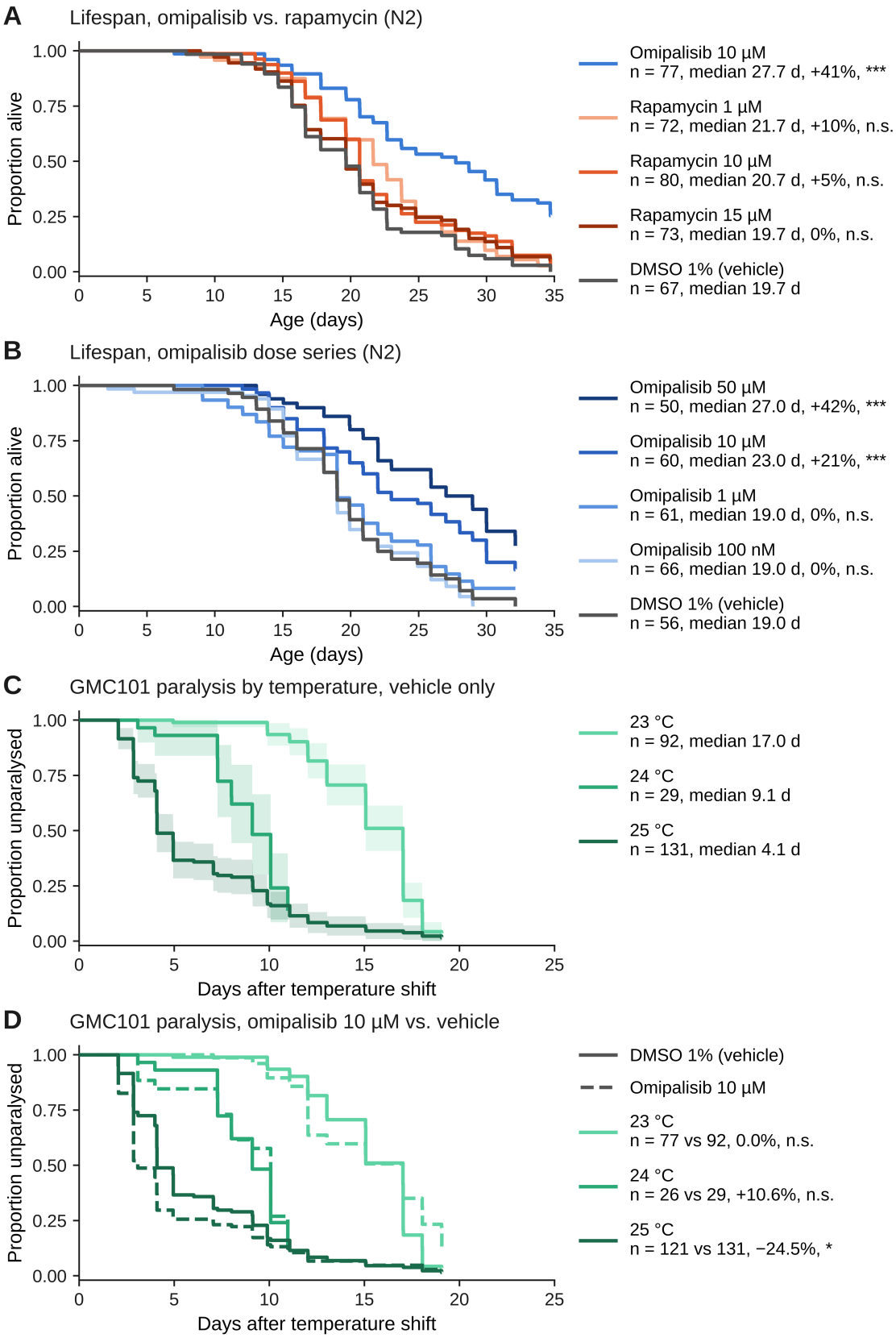


Figure 1. Omipalisib increases median lifespan in wild-type N2 C. elegans but does not consistently delay Aβ-associated paralysis in GMC101. Kaplan–Meier time-to-event curves show lifespan in wild-type N2 animals and time to paralysis in GMC101 animals:

(A) N2 animals treated with 10 µM omipalisib (n = 77; median lifespan = 27.7 days) were compared with a matched 1% DMSO control (n = 67; median = 19.7 days) and rapamycin at 1 µM (n = 72; median = 21.7 days), 10 µM (n = 80; median = 20.7 days), and 15 µM (n = 73; median = 19.7 days). Omipalisib differed significantly from DMSO (log-rank $p = 1.4 \times 10^{-9}$) and 1 µM rapamycin ($p = 7.4 \times 10^{-7}$); none of the rapamycin conditions differed significantly from DMSO.

(B) N2 animals were treated with 100 nM (n = 66), 1 µM (n = 61), 10 µM (n = 60), or 50 µM (n = 50) omipalisib and compared with matched 1% DMSO controls (n = 56). Median lifespan was 19.0 days for DMSO, 100 nM, and 1 µM omipalisib, 23.0 days for 10 µM omipalisib ($p < 0.001$), and 27.0 days for 50 µM omipalisib ($p < 0.001$).

(C) Vehicle-treated GMC101 animals were assessed at 23°C (n = 92), 24°C (n = 29), and 25°C (n = 131). Median time to paralysis decreased from 17.03 days at 23°C to 9.10 days at 24°C and 4.09 days at 25°C.

(D) GMC101 animals treated with 10 µM omipalisib were compared with matched vehicle controls at 23°C, 24°C, and 25°C. Median time to paralysis was 17.03 days for both vehicle (n = 92) and omipalisib (n = 77) at 23°C ($p = 0.062$), 9.10 versus 10.07 days at 24°C (n = 29 and 26; $p = 0.994$), and 4.09 versus 3.09 days at 25°C (n = 131 and 121; nominal $p = 0.0288$). The 25°C comparison was not significant after false-discovery-rate correction ($q = 0.055$). Solid lines indicate vehicle and dashed lines indicate 10 µM omipalisib.

Description

Aging is a major risk factor for Alzheimer's disease, motivating geroscience-based approaches that target conserved biological processes of aging rather than a single disease-associated pathway (Kawas et al., 2000). Gerotherapeutics are interventions intended to modify pathways involved in aging and longevity with the goal of extending healthy lifespan and increasing resistance to age-associated disease. Conserved nutrient-sensing pathways are particularly relevant to this approach: inhibition of TOR signaling extends lifespan in C. elegans, and pharmacological inhibition of mTOR with rapamycin extends lifespan in mice (Vellai et al., 2003; Harrison et al., 2009). A gerotherapeutic approach therefore asks whether an intervention that improves organismal longevity might also increase resilience to disease-associated stress. This question is relevant to Alzheimer's disease, where therapeutic development has historically been difficult and multiple amyloid-targeting therapies have failed to meet primary clinical endpoints (Doody et al., 2014; Salloway et al., 2014).

Omipalisib (GSK2126458) inhibits phosphoinositide 3-kinase (PI3K) and mammalian target of rapamycin (mTOR) signaling (Knight et al., 2010). PI3K/mTOR signaling regulates nutrient sensing, protein synthesis, stress responses, autophagy, and other processes involved in aging and cellular homeostasis (Blackwell et al., 2019). Because autophagy and related proteostasis mechanisms contribute to the removal of damaged or aggregated proteins, modulation of these pathways provides a potential mechanistic connection between lifespan extension and resistance to proteotoxic stress. Omipalisib was evaluated as a gerotherapeutic candidate through Ora Biomedical's Million Molecule Challenge (Lee et al., 2023). We therefore hypothesized that if mechanisms associated with omipalisib-mediated lifespan extension also improved cellular stress resistance or protein homeostasis, the same intervention might reduce toxicity associated with Aβ expression.

This hypothesis was motivated by repeated lifespan extension in wild-type N2 animals. In one experiment, 10 µM omipalisib increased median lifespan from 19.7 to 27.7 days, a 41.1% increase relative to the matched DMSO control (Fig. 1A). Rapamycin increased median lifespan by 0–10.2% across the concentrations tested and did not significantly extend lifespan relative to control, whereas 10 µM omipalisib significantly increased survival relative to the best-performing rapamycin condition ($p = 7.4 \times 10^{-7}$; Fig. 1A). In a separate dose-response experiment, 10 µM omipalisib again increased median lifespan, from 19.0 to 23.0 days (21%), while 50 µM increased median lifespan by 42% (Fig. 1B). Thus, the same 10 µM concentration increased median lifespan by 21–41.1% across two experiments, providing the experimental basis for testing whether this gerotherapeutic effect would also modify an Aβ-associated proteotoxic phenotype.

The GMC101 strain provided a whole-animal model for testing this question. GMC101 animals express full-length human Aβ1–42 in body-wall muscle and develop progressive, temperature-dependent paralysis associated with Aβ proteotoxicity (McColl et al., 2012). Although GMC101 does not reproduce the neuronal complexity or cognitive symptoms of human Alzheimer's disease, its measurable paralysis phenotype provides an accessible first-pass system for evaluating candidate interventions. We tested 10 µM omipalisib at 23°C, 24°C, and 25°C to determine whether any protective effect persisted under conditions in which paralysis progressed at different rates. In vehicle-treated animals, median time to paralysis decreased from 17.03 days at 23°C to 9.10 days at 24°C and 4.09 days at 25°C (Fig. 1C). Because temperature also influences general C. elegans physiology, these conditions should not be interpreted as altering Aβ-associated toxicity alone (Horikawa et al., 2015).

Despite increasing N2 median lifespan by 21–41.1% at 10 µM across two experiments, the same omipalisib concentration did not consistently delay GMC101 paralysis (Fig. 1D). Median time to paralysis was unchanged at 23°C (17.03 versus

17.03 days; p = 0.062) and was not significantly altered at 24°C (9.10 versus 10.07 days; p = 0.994). At 25°C, median time to paralysis decreased from 4.09 to 3.09 days (−24.5%; p = 0.0288), although this comparison did not remain significant after FDR correction across the broader GMC101 arm set (q = 0.055; Fig. 1D). Thus, repeated lifespan extension in wild-type animals did not translate into protection against Aβ-associated paralysis. One possibility is that pathways sufficient to extend lifespan during normal aging are not sufficient to overcome Aβ-associated proteotoxic stress. Alternatively, effects on stress responses or proteostasis may depend on dose, treatment timing, or experimental context. Because Aβ abundance, aggregation, autophagic activity, and protein misfolding were not directly measured, these mechanisms remain speculative. Future experiments measuring these outcomes or testing additional omipalisib doses and treatment schedules could help determine why the gerotherapeutic lifespan effect did not translate to the GMC101 phenotype.

Methods

Worm maintenance and synchronization

N2 lifespan experiments were conducted at 20°C. GMC101 animals were initially maintained at 18°C and were transferred to 23°C, 24°C, or 25°C following placement on experimental plates. These temperatures were selected to examine the effect of increasing temperature on the paralysis phenotype associated with Aβ expression in GMC101 animals and to determine whether 10 µM omipalisib delayed paralysis relative to the matched vehicle control at each temperature. Temperature-dependent paralysis following temperature upshift has previously been established for GMC101 animals (McColl et al., 2012). All animals were maintained on nematode growth medium (NGM) agar seeded with E. coli OP50. Animals were age-synchronized by hypochlorite treatment according to standard C. elegans synchronization procedures (Stiernagle, 2006). Following synchronization, isolated eggs were suspended in S-basal solution overnight to obtain synchronized L1 larvae. Experimental 12-well plates were prepared following previously described protocols (Pitt et al., 2019). Each well contained 3 mL NGM agar supplemented with 50 µM 5-fluoro-2′-deoxyuridine (FUdR) to prevent progeny development and 100 U/mL nystatin to reduce fungal contamination.

Drug preparation and treatment-plate dosing

Omipalisib was stored at −20°C and thawed before experimental use. Drug solutions were prepared as 100× stocks in DMSO and added to experimental wells at a volume of 30 µL per 3 mL NGM agar. Vehicle-control wells received volume-matched DMSO, resulting in a final DMSO concentration of 1%. Compounds were added to the 12-well plates approximately 24 h before animal transfer and stored at 4°C in the interim.

For the N2 head-to-head experiment shown in Figure 1A, animals were exposed to 10 µM omipalisib, 1 µM rapamycin, 10 µM rapamycin, 15 µM rapamycin, or 1% DMSO vehicle control. For the omipalisib dose-response experiment shown in Figure 1B, animals were exposed to 100 nM, 1 µM, 10 µM, or 50 µM omipalisib or the matched 1% DMSO control.

For the GMC101 experiments shown in Figure 1C–D, animals were treated with either 10 µM omipalisib or matched vehicle control and maintained at the experimental temperatures indicated in the figure.

Experimental timeline and animal transfer

Following overnight synchronization, L1 animals were transferred to 100mM NGM agar growth plates seeded with E. coli OP50, with approximately 700 animals placed on each growth plate. To allow for differences in developmental timing, GMC101 growth plates were maintained for approximately 72 h before transfer, whereas N2 growth plates were maintained for approximately 50 h. Growth plates containing L4 larvae were rinsed with M9 solution into a 15 mL conical tube and allowed to concentrate to approximately 25 animals per 15 µL. Under a microscope, approximately 25 animals were transferred by micropipette into each experimental well. Plates were then transferred to incubators maintained at the assigned experimental temperature. Approximately 24 h following transfer, when animals had reached adulthood, experimental plates were placed on the imaging platform for longitudinal lifespan or paralysis assessment.

Image acquisition and paralysis analysis

Animal lifespan and paralysis were assessed using the WormBot-AI platform (Pitt et al., 2019; Lee et al., 2023). Images were collected using either continuous image capture or periodic capture of multiple frames in short succession from racks of 12-well plates, which were returned to precision-temperature incubators following image acquisition. Images were post-processed for alignment and analyzed with Worm-YOLO, a custom-trained neural network that identifies and longitudinally tracks individual animals. Once animals were identified and tracked, movement-based features were used to identify slow-moving animals, paralyzed animals, and animal deaths. Quality control was performed computationally to identify common sources of error, including contamination and well fogging, and experiments were additionally inspected manually every five days with annotations made for observed abnormalities (Pitt et al., 2019; Lee et al., 2023).

For N2 analyses, lifespan was the primary outcome. For GMC101 analyses, time to paralysis was the primary outcome. Paralysis was defined as sustained loss of body movement detected through longitudinal WormBot-AI tracking. The

resulting time-to-paralysis event was used to construct Kaplan–Meier curves. Animals that did not experience the relevant endpoint before assay termination were treated as right-censored observations.

Statistical Analysis

Lifespan and paralysis time-to-event distributions were visualized using Kaplan–Meier curves. For the N2 experiments, treatment groups were compared with matched 1% DMSO controls using log-rank tests of lifespan distributions. Median lifespan was calculated for each treatment condition, and percentage change in median lifespan was calculated relative to the corresponding vehicle control. In the N2 head-to-head experiment, 10 µM omipalisib was additionally compared with the best-performing rapamycin condition using a log-rank test. For the GMC101 experiments, paralysis time-to-event distributions for 10 µM omipalisib were compared with matched vehicle controls at each experimental temperature using log-rank tests. Animals that had not experienced the relevant endpoint by assay termination were treated as right-censored observations.

Reagents

Strain	Genotype	Available from
N2	*Caenorhabditis elegans* wild type	Caenorhabditis Genetics Center (CGC)
GMC101	*dvIs100 [unc-54p::Aβ1–42::unc-54 3′ UTR + mtl-2p::GFP]*	Caenorhabditis Genetics Center (CGC)

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References

Doody RS, Thomas RG, Farlow M, Iwatsubo T, Vellas B, Joffe S, et al., Solanezumab Study Group. 2014. Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. N Engl J Med 370(4): 311-21. PubMed ID: 24450890

Harrison DE, Strong R, Sharp ZD, Nelson JF, Astle CM, Flurkey K, et al., Miller RA. 2009. Rapamycin fed late in life extends lifespan in genetically heterogeneous mice. Nature 460(7253): 392-5. PubMed ID: 19587680

Kawas C, Gray S, Brookmeyer R, Fozard J, Zonderman A. 2000. Age-specific incidence rates of Alzheimer's disease: the Baltimore Longitudinal Study of Aging. Neurology 54(11): 2072-7. PubMed ID: 10851365

Knight SD, Adams ND, Burgess JL, Chaudhari AM, Darcy MG, Donatelli CA, et al., Dhanak D. 2010. Discovery of GSK2126458, a Highly Potent Inhibitor of PI3K and the Mammalian Target of Rapamycin. ACS Med Chem Lett 1(1): 39-43. PubMed ID: 24900173

Lee MB, Blue B, Muir M, Kaeberlein M. 2023. The million-molecule challenge: a moonshot project to rapidly advance longevity intervention discovery. Geroscience 45(6): 3103-3113. PubMed ID: 37432607

McColl G, Roberts BR, Pukala TL, Kenche VB, Roberts CM, Link CD, et al., Cherny RA. 2012. Utility of an improved model of amyloid-beta ($A\beta_{1-42}$) toxicity in Caenorhabditis elegans for drug screening for Alzheimer's disease. Mol Neurodegener 7: 57. PubMed ID: 23171715

Pitt JN, Strait NL, Vayndorf EM, Blue BW, Tran CH, Davis BEM, et al., Kaeberlein M. 2019. WormBot, an open-source robotics platform for survival and behavior analysis in C. elegans. Geroscience 41(6): 961-973. PubMed ID: 31728898

Salloway S, Sperling R, Fox NC, Blennow K, Klunk W, Raskind M, et al., Bapineuzumab 301 and 302 Clinical Trial Investigators. 2014. Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease. N Engl J Med 370(4): 322-33. PubMed ID: 24450891

Stiernagle T. 2006. Maintenance of C. elegans. WormBook: 1-11. PubMed ID: 18050451

Vellai T, Takacs-Vellai K, Zhang Y, Kovacs AL, Orosz L, Müller F. 2003. Genetics: influence of TOR kinase on lifespan in C. elegans. Nature 426(6967): 620. PubMed ID: 14668850

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