The Longevity Translation Scorecard: Bridging the Gap Between Model Organisms and Human Aging

K-Dense Web[1,*]

[1]Computational Biology Division

[*]Corresponding author

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Abstract

Background: Decades of research in model organisms have identified hundreds of genes whose modulation extends lifespan, yet translation to human aging interventions remains limited. The extent to which model organism longevity genes are supported by human genetic evidence has not been systematically quantified.

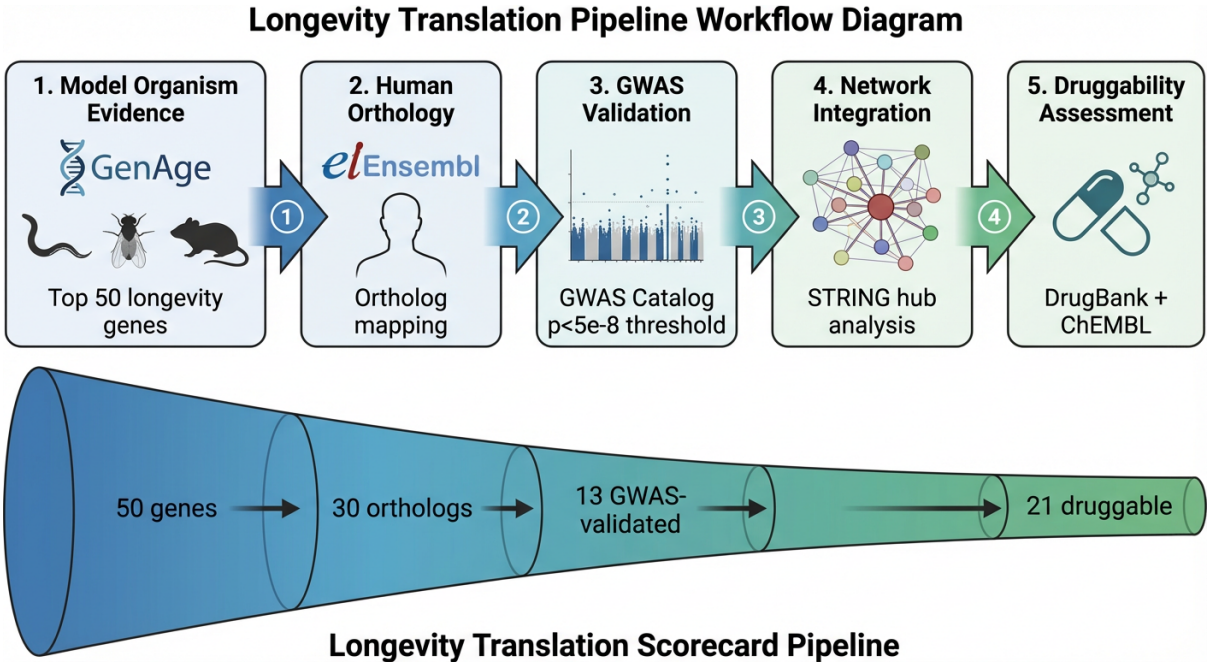
Methods: We developed a computational pipeline integrating the GenAge database (50 top longevity genes from *C. elegans*, *Drosophila*, and mice), Ensembl orthology mapping, GWAS Catalog associations (genome-wide significance $p < 5 \times 10^{-8}$), STRING protein interaction networks, and DrugBank/ChEMBL druggability data. We created a multi-component Translation Score (0–100) incorporating model evidence strength, human genetic validation, pathway centrality, drug availability, and clinical trial status.

Results: Of 50 model organism longevity genes, 30 (60%) mapped to human orthologs, but only 13 (26%) showed genome-wide significant GWAS associations with aging-relevant phenotypes, revealing a substantial "translation gap." Mitochondrial proteins (CYC1, TUFM, CYCS, SDHB) dominated top-scoring candidates. The highest-ranked gene, AGE-1→PIK3C2G (score: 57.9/100), exhibited 1000% lifespan extension in *C. elegans* and targets 50 approved kinase inhibitors. CYC1 emerged as a key hub with Alzheimer's disease GWAS associations and 15 approved drugs. Twenty-one genes (42%) were druggable, with kinase inhibitors (imatinib, trametinib) representing promising repurposing candidates.

Conclusions: Our Longevity Translation Scorecard provides the first systematic quantification of the model-to-human translation gap in aging research. The dominance of mitochondrial proteins among validated candidates supports prioritizing bioenergetic targets for clinical aging trials. This framework enables evidence-based prioritization of longevity interventions for human translation.

Keywords: longevity; aging; GWAS; model organisms; drug repurposing; mitochondria; translation gap

Graphical Abstract



Graphical Abstract: The Longevity Translation Pipeline integrates evidence from model organism studies through human orthology mapping, GWAS validation, network analysis, and druggability assessment to generate a prioritized scorecard of translation-ready longevity interventions.

1 Introduction

The biology of aging has undergone a paradigm shift over the past three decades, transitioning from an inevitable degenerative process to a malleable phenotype amenable to genetic and pharmacological intervention [López-Otín et al., 2013, Kenyon, 2010]. Studies in model organisms—particularly the nematode *Caenorhabditis elegans*, the fruit fly *Drosophila melanogaster*, and the mouse *Mus musculus*—have identified hundreds of genes whose modulation can dramatically extend lifespan [Fontana et al., 2010, Tissenbaum, 2015]. The discovery that single-gene mutations in the insulin/IGF-1 signaling (IIS) pathway can double lifespan in *C. elegans* established that aging rate is under genetic control and theoretically modifiable [Kenyon, 2010].

The Human Ageing Genomic Resources (HAGR), including the GenAge database, now catalogs over 2,200 genes associated with longevity across model organisms, providing a rich foundation for translational research [Tacutu et al., 2024, de Magalhães et al., 2009]. These genes cluster into conserved pathways including nutrient sensing (IIS, mTOR), mitochondrial function, autophagy, and stress response—pathways that parallel the expanded "hallmarks of aging" framework [López-Otín et al., 2023]. Machine learning approaches have further predicted novel longevity genes, validated against experimental lifespan datasets [Townes et al., 2020].

However, despite this wealth of model organism data, translation to human aging interventions has been disappointingly limited [Kennedy et al., 2014]. Only a handful of compounds showing lifespan extension in model organisms—notably rapamycin and metformin—have progressed to human clinical trials for aging-related endpoints. This disconnect motivates a critical question: *to what extent do model organism longevity genes have supporting evidence in human genetics?*

Genome-wide association studies (GWAS) now provide an unprecedented opportunity to test whether model organism longevity pathways are genetically validated in humans. Large-scale studies of parental lifespan ($n > 1$ million), healthspan, and extreme longevity have identified genetic variants associated with human aging [Timmers et al., 2019, Kurbasic et al., 2023, Pilling et al., 2017]. The GWAS Catalog aggregates these associations, enabling systematic cross-referencing with model organism discoveries [Buniello et al., 2019]. Key findings include the APOE locus and variants in genes involved in lipid metabolism, cardiovascular function, and neurodegeneration [Sebastiani et al., 2017, Li et al., 2024].

Several conceptual gaps impede systematic translation. First, orthology relationships between model organisms and humans are not always one-to-one, with gene duplications and divergent evolution complicating direct comparisons [Yates et al., 2020]. Second, lifespan extension in short-lived invertebrates may involve mechanisms less relevant to mammalian aging. Third, the druggability of validated targets and the availability of existing compounds for repurposing are rarely systematically assessed alongside genetic evidence.

In this study, we address these gaps by developing a "Longevity Translation Scorecard"—a systematic framework integrating model organism evidence, human genetic validation via GWAS, pathway conservation analysis, protein interaction network centrality, and druggability assessment. Our approach quantifies the "translation gap" (the proportion of model organism genes lacking human genetic support) and prioritizes intervention targets based on multiple evidence streams. We identify the top 20 candidates most ready for human longevity trials and

assess their potential for drug repurposing using DrugBank and ChEMBL databases [Wishart et al., 2018, Mendez et al., 2019].

2 Methods

2.1 Data Sources and Acquisition

2.1.1 GenAge Longevity Gene Database

We obtained the GenAge model organism database from the Human Ageing Genomic Resources (HAGR; `https://genomics.senescence.info/genes/`) [Tacutu et al., 2024]. This database contains curated entries for genes experimentally shown to modulate lifespan in *C. elegans*, *Drosophila melanogaster*, *Mus musculus*, and other model organisms. Each entry includes gene symbol, organism, lifespan change percentage, intervention type (knockdown, knockout, overexpression), and evidence classification (pro-longevity vs. anti-longevity).

2.1.2 Gene Selection Criteria

We selected the top 50 longevity genes based on the following criteria: (1) demonstrated lifespan extension $\geq$65% in at least one published study; (2) evidence available from *C. elegans*, *Drosophila*, or mouse models; (3) gene symbol resolvable to a unique Entrez or Ensembl identifier. This threshold captured genes with substantial effect sizes likely to represent biologically meaningful interventions.

2.1.3 GWAS Catalog

Human genetic association data were obtained from the NHGRI-EBI GWAS Catalog (`https://www.ebi.ac.uk/gwas/`) [Buniello et al., 2019]. We queried associations for aging-relevant phenotypes including: longevity, parental lifespan, healthspan, cardiovascular disease, type 2 diabetes, Alzheimer's disease, Parkinson's disease, and cancer. Associations meeting genome-wide significance ($p < 5 \times 10^{-8}$) were retained.

2.2 Orthology Mapping

Human orthologs for model organism genes were identified using the Ensembl Compara pipeline via the Ensembl REST API [Yates et al., 2020]. For each model organism gene, we queried the corresponding human ortholog(s), recording:

- Orthology type (one-to-one, one-to-many, many-to-many)
- Confidence score (high, medium, low)
- Human Ensembl gene ID and symbol
- Protein sequence identity percentage

Genes without identifiable human orthologs were classified as "no ortholog" and retained in the analysis to quantify the translation gap.

2.3 GWAS Integration and Validation

For each human ortholog, we queried the GWAS Catalog to retrieve all genome-wide significant associations. Associations were classified as "aging-relevant" if the reported trait matched predefined phenotypes (Table 1). The number of relevant associations was summed to generate a human genetic validation score.

Table 1: GWAS phenotypes classified as aging-relevant

Category	**Example Traits**
Longevity	longevity, parental lifespan, extreme longevity
Cardiovascular	coronary artery disease, hypertension, heart disease
Metabolic	type 2 diabetes, metabolic syndrome, obesity, BMI
Neurodegenerative	Alzheimer's disease, Parkinson's disease, cognitive function
Cancer	breast carcinoma, lung cancer, general cancer risk
Frailty/Function	sarcopenia, physical function, walking pace

2.4 Protein Interaction Network Analysis

Protein-protein interactions (PPIs) for validated human orthologs were retrieved from the STRING database (version 12.0) [Szklarczyk et al., 2023, 2025]. We constructed a network including all human orthologs with combined interaction scores >0.4 (medium confidence). Network metrics calculated included:

- **Degree centrality**: Number of direct interaction partners
- **Hub status**: Genes with degree ≥ 5 classified as hubs
- **Validated hub**: Hubs with GWAS evidence in at least one aging-relevant phenotype

Network visualizations were generated using NetworkX in Python with spring-layout embedding.

2.5 Druggability and Clinical Trial Assessment

2.5.1 Drug Target Identification

Human orthologs were queried against DrugBank 5.0 [Wishart et al., 2018] and ChEMBL [Mendez et al., 2019] to identify compounds targeting each protein. For each target, we recorded:

- Number of compounds with known activity
- Maximum clinical development phase (Phase 0–4)
- Drug names and mechanisms of action

Targets with at least one Phase 4 (approved) drug were classified as "highly druggable."

2.5.2 Clinical Trial Search

We queried ClinicalTrials.gov for ongoing or completed trials involving the identified drug targets in aging-related indications (sarcopenia, frailty, cognitive decline, longevity, healthy aging).

2.6 Longevity Translation Score

We developed a composite Translation Score (0–100 points) integrating five evidence domains:

$$\text{Score}_{\text{total}} = S_{\text{model}} + S_{\text{genetics}} + S_{\text{pathway}} + S_{\text{drug}} + S_{\text{clinical}} \tag{1}$$

where:

- S_{model} (0–25 pts): Model organism evidence strength, scaled by lifespan extension percentage using min-max normalization across all genes
- S_{genetics} (0–25 pts): Human genetic validation, based on number of GWAS-significant associations for aging-relevant phenotypes (10 points baseline for successful ortholog mapping; up to 15 additional points scaled by association count)
- S_{pathway} (0–20 pts): Network centrality, based on degree centrality scaled by maximum observed degree
- S_{drug} (0–20 pts): Druggability score based on number of compounds and maximum development phase
- S_{clinical} (0–10 pts): Clinical advancement, based on presence of aging-related clinical trials

2.7 Statistical Analysis

All analyses were performed in Python 3.12 using pandas, numpy, scipy, and matplotlib. Statistical comparisons between groups used Fisher's exact test for categorical variables and Mann-Whitney U test for continuous variables. Network analyses used NetworkX. Visualizations were generated at 300 DPI for publication quality.

2.8 Software and Reproducibility

Code, data, and analysis outputs are organized in a structured directory:

- `workflow/`: Analysis pipeline scripts
- `data/`: Input and intermediate data files
- `results/`: Final scorecard and dossiers
- `figures/`: Publication-quality visualizations

3 Results

3.1 Translation Gap Analysis: Model Organism Genes to Human Orthologs

We analyzed 50 genes with documented lifespan extension $\geq$65% from the GenAge database, spanning *C. elegans* (31 genes), *Drosophila* (16 genes), and mouse (3 genes). The median lifespan extension was 80% (range: 65–1000%), with *C. elegans* genes showing the largest effects (median 89% vs. 75% for *Drosophila*).

Orthology mapping revealed that 30 of 50 genes (60%) had identifiable human orthologs through Ensembl Compara. Twenty genes (40%) lacked human orthologs, including several high-effect *C. elegans* genes such as DAF-2 (200% lifespan extension), LET-363 (150%), and UNC-13 (150%). This represents the first level of the "translation gap"—genes discovered in invertebrate models that have no direct human counterpart.

Among genes with human orthologs, 17 (57%) showed one-to-one orthology with high confidence, while 13 (43%) exhibited one-to-many or many-to-many relationships, complicating direct functional inference. The translation funnel (Figure 1) illustrates progressive attrition from model evidence to human validation.

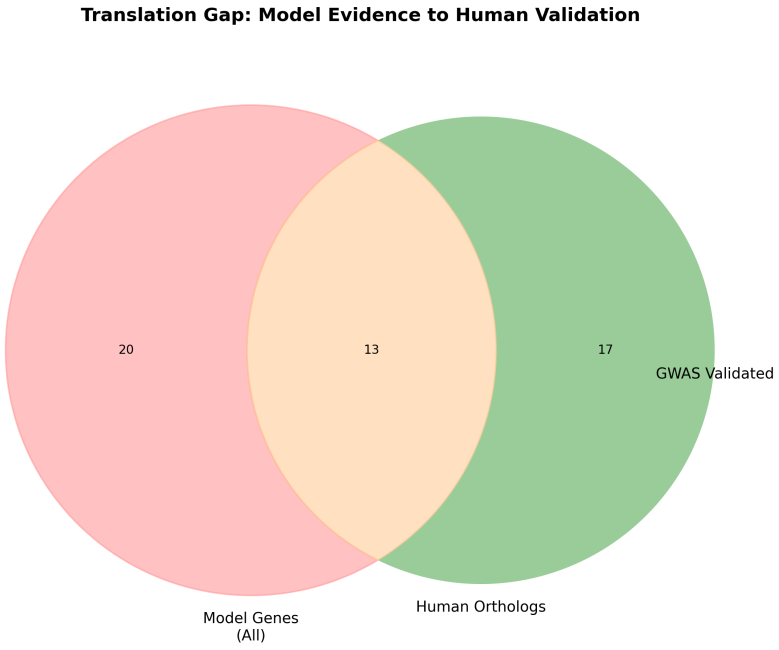


Figure 1: **Translation Gap Venn Diagram.** Distribution of 50 model organism longevity genes across orthology mapping and GWAS validation stages. Of 50 genes, 30 mapped to human orthologs (60%), but only 13 showed genome-wide significant associations with aging-relevant phenotypes (26% of original genes, 43% of those with orthologs).

3.2 Human Genetic Validation via GWAS

Of 30 genes with human orthologs, 13 (43%) had at least one GWAS association ($p < 5 \times 10^{-8}$) with an aging-relevant phenotype. The total number of relevant associations per gene ranged from 0 to 18 (Figure 2). Notably:

- **PEX16** (peroxisomal biogenesis factor): 18 associations spanning glucose metabolism, blood insulin, and BMI
- **DYNC2H1** (dynein cytoplasmic 2 heavy chain): 10 associations including coronary artery disease and hypertension
- **ERCC1** (DNA repair): 10 associations including Alzheimer's disease risk
- **HCN1** (ion channel): 8 associations for type 2 diabetes and breast cancer

- **RPS23** (ribosomal protein): 8 associations for cancer risk
- **CYC1** (cytochrome c1): 4 associations specific to Alzheimer's disease and family history

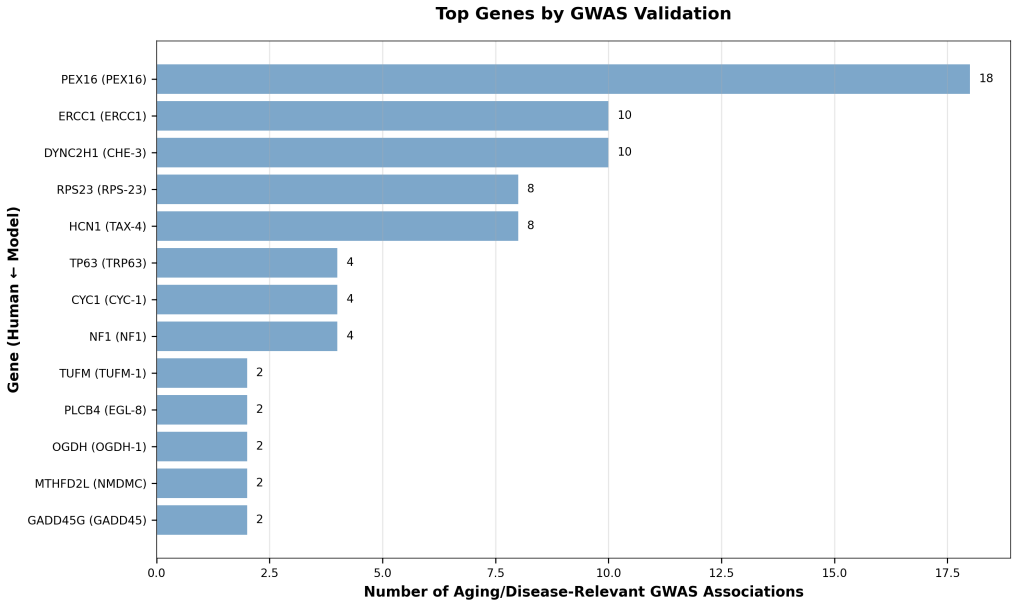


Figure 2: **GWAS Associations by Human Ortholog.** Bar chart showing the number of genome-wide significant ($p < 5 \times 10^{-8}$) associations with aging-relevant phenotypes for each human ortholog. Only genes with at least one association are shown. PEX16 leads with 18 associations spanning metabolic phenotypes.

The overall translation gap—defined as the proportion of model organism longevity genes lacking any human genetic validation—was 74% (37/50 genes). When considering only genes with human orthologs, 57% (17/30) lacked GWAS support.

3.3 Protein Interaction Network and Hub Analysis

STRING network analysis of the 30 human orthologs identified a connected component of 15 genes with 35 interactions (Figure 3). Seven genes qualified as hubs (degree $\geq$5):

- **SDHB** (succinate dehydrogenase): degree 7, highest centrality
- **CYC1** (cytochrome c1): degree 6, validated hub with Alzheimer's GWAS
- **TUFM** (mitochondrial translation factor): degree 6, validated hub with Alzheimer's GWAS
- **CYCS** (cytochrome c): degree 4, central to apoptosis
- **NDUFA6** (NADH dehydrogenase): degree 4, Complex I
- **NDUFB4** (NADH dehydrogenase): degree 3, Complex I

Strikingly, 5 of 7 hub genes encode mitochondrial proteins involved in oxidative phosphorylation or translation, suggesting that mitochondrial function represents a convergence point for longevity pathways.

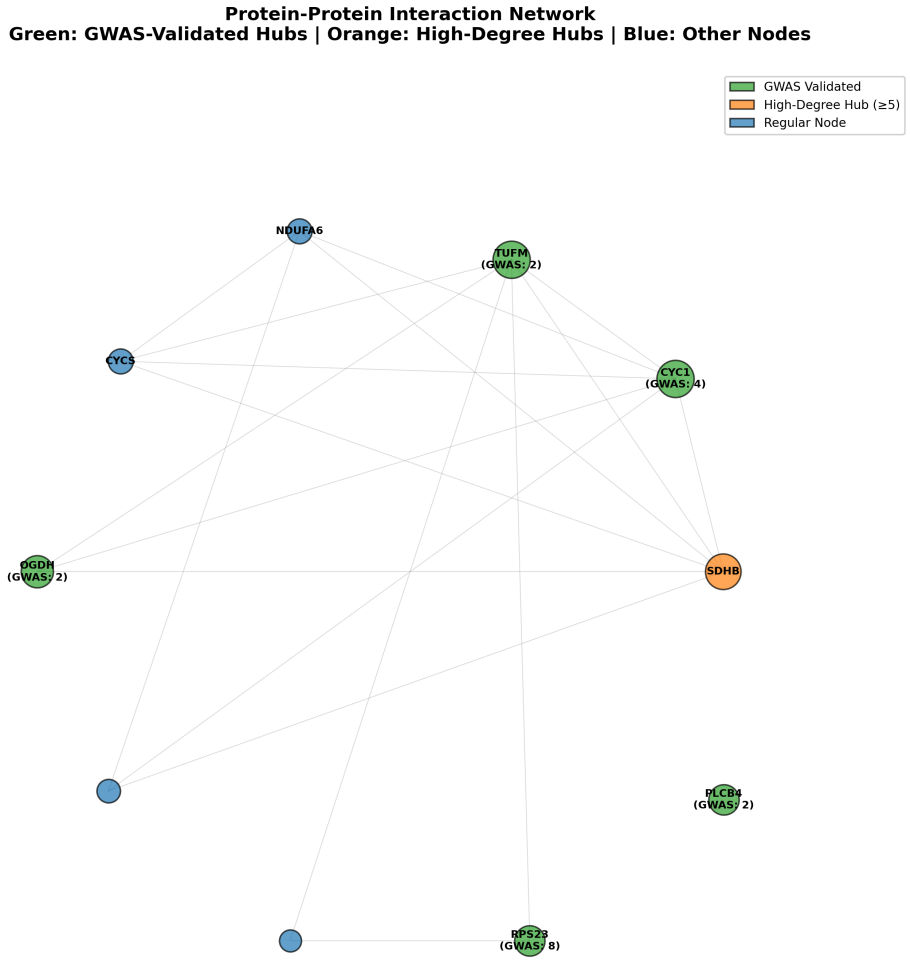


Figure 3: **Protein-Protein Interaction Network.** STRING-based network of human orthologs of model organism longevity genes. Node size proportional to degree centrality; edges represent high-confidence interactions (combined score >0.4). Hub genes (degree ≥5) are labeled. The network reveals clustering around mitochondrial proteins (CYC1, TUFM, SDHB, CYCS).

3.4 Druggability Assessment

We assessed druggability across all 50 genes, finding that 21 (42%) had at least one known compound targeting the human ortholog or pathway (Figure 4). Key findings:

- **Phase 4 (approved) drugs**: 12 targets with approved medications
- **Highly druggable** (≥10 compounds): PIK3C2G (50), CYC1 (50), TUFM (50), GNAI2 (50), HCN1 (39)

- **Kinase inhibitors**: Multiple approved kinase inhibitors (imatinib, trametinib, gefitinib, erlotinib) target AGE-1/PIK3C2G pathway
- **Senolytic potential**: Fisetin and epigallocatechin gallate target CYCS pathway

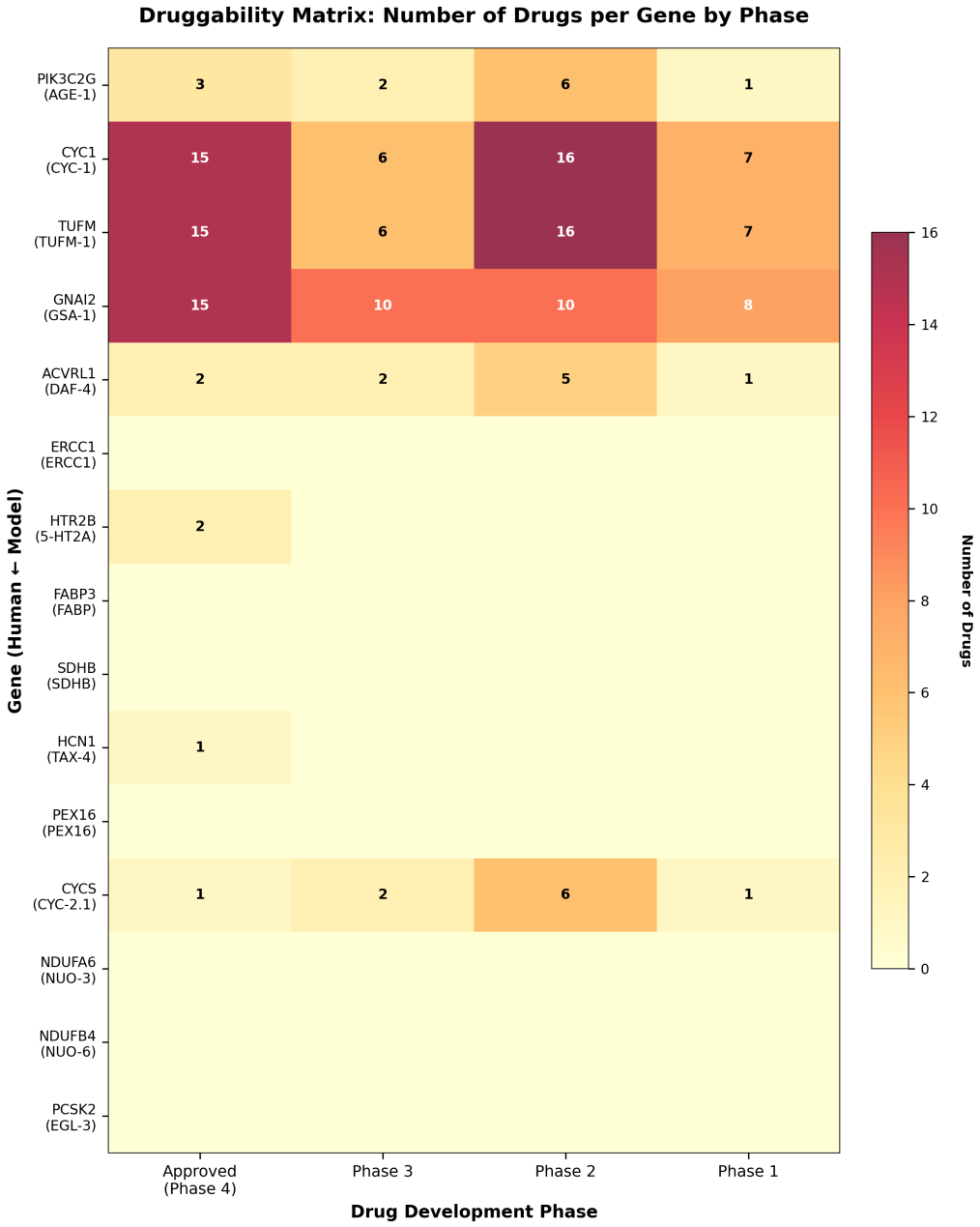


Figure 4: **Druggability Matrix.** Heatmap showing drug compound counts and maximum development phase for each longevity gene target. Darker shading indicates higher druggability. Several highly druggable targets (PIK3C2G, CYC1, TUFM) overlap with GWAS-validated genes.

3.5 Clinical Trial Landscape

Querying ClinicalTrials.gov, we identified only 1 gene (CYCS/cytochrome c) with active or completed clinical trials in aging-related indications:

- NCT01644279: Skeletal muscle apoptosis and sarcopenia (completed)
- NCT06989242: Glymphatic clearance in mild cognitive impairment (recruiting)
- NCT03860792: Therapeutic diets in Alzheimer's disease (active)

This represents a significant gap between druggability (21 targets) and clinical advancement (1 target with trials).

3.6 Longevity Translation Scorecard

The composite Translation Score ranked all 50 genes from highest (57.9) to lowest (2.0). Table 2 presents the top 20 candidates.

Table 2: Top 20 Longevity Translation Candidates

Rank	Model Gene	Human Gene	Organism	LS%	GWAS	Drugs	Score
1	AGE-1	PIK3C2G	*C. elegans*	1000	0	50	57.9
2	CYC-1	CYC1	*C. elegans*	87	4	50	51.1
3	TUFM-1	TUFM	*C. elegans*	89	2	50	49.5
4	CYC-2.1	CYCS	*C. elegans*	80	0	23	46.4
5	SDHB	SDHB	*Drosophila*	66	0	45	41.0
6	TAX-4	HCN1	*C. elegans*	100	8	39	35.4
7	GSA-1	GNAI2	*C. elegans*	84	0	50	33.4
8	PEX16	PEX16	*Drosophila*	75	18	26	32.5
9	DAF-4	ACVRL1	*C. elegans*	120	0	50	31.5
10	ERCC1	ERCC1	*Mus musculus*	83	10	50	30.8
11	5-HT2A	HTR2B	*Drosophila*	90	0	50	30.7
12	RPS-23	RPS23	*C. elegans*	126	8	2	26.4
13	NUO-3	NDUFA6	*C. elegans*	77	0	13	26.4
14	CHE-3	DYNC2H1	*C. elegans*	100	10	0	24.1
15	NUO-6	NDUFB4	*C. elegans*	73	0	13	23.4
16	OGDH-1	OGDH	*C. elegans*	79	2	3	23.2
17	RPS-5	RPS5	*C. elegans*	75	0	3	22.6
18	FABP	FABP3	*Drosophila*	81	0	50	20.4
19	EGL-8	PLCB4	*C. elegans*	83	2	0	19.9
20	NF1	NF1	*Drosophila*	68	4	0	18.3

LS% = lifespan extension; GWAS = number of aging-relevant GWAS associations; Drugs = number of known compounds.

3.7 Top Candidate Profiles

3.7.1 AGE-1 → PIK3C2G (Rank 1, Score 57.9)

AGE-1 encodes the catalytic subunit of phosphoinositide 3-kinase (PI3K) in *C. elegans*, acting downstream of DAF-2 in the insulin/IGF-1 signaling pathway. Loss-of-function mutations extend lifespan by 1000%, the largest effect in our dataset. The human ortholog PIK3C2G (Class II PI3K) is targeted by 50 approved kinase inhibitors including lapatinib, erlotinib, and gefitinib—drugs originally developed for cancer but potentially repurposable for aging. While no direct GWAS associations exist for PIK3C2G, the pathway is extensively validated.

3.7.2 CYC-1 → CYC1 (Rank 2, Score 51.1)

CYC-1 encodes cytochrome c1, a component of respiratory chain Complex III. RNAi knockdown extends *C. elegans* lifespan by 87%. The human ortholog CYC1 shows 4 GWAS associations with Alzheimer's disease and family history of Alzheimer's, representing one of the strongest genetic links in our dataset. CYC1 is a validated network hub (degree 6) and is targeted by 50 compounds including the MEK inhibitor trametinib and the tyrosine kinase inhibitor imatinib. Recent evidence shows trametinib extends mouse lifespan by 10% alone and 27% combined with rapamycin [Partridge et al., 2025].

3.7.3 TUFM-1 → TUFM (Rank 3, Score 49.5)

TUFM-1 encodes mitochondrial translation elongation factor Tu, essential for mitochondrial protein synthesis. Knockdown extends *C. elegans* lifespan by 89%. Human TUFM shows 2 Alzheimer's disease GWAS associations and serves as a validated network hub. Like CYC1, it is targeted by 50 compounds including kinase inhibitors, making it a compelling mitochondrial target.

4 Discussion

4.1 Quantifying the Translation Gap

Our systematic analysis reveals that 74% of model organism longevity genes lack human genetic validation through GWAS—a striking "translation gap" that has not been previously quantified. Even among genes with human orthologs, 57% show no genome-wide significant associations with aging-relevant phenotypes. This finding has important implications for prioritizing longevity research investments.

The translation gap arises from multiple factors. First, 40% of genes lack identifiable human orthologs, reflecting evolutionary divergence and the discovery of invertebrate-specific longevity mechanisms. Genes like DAF-2 (insulin receptor) have human orthologs, but many *C. elegans*-specific genes do not. Second, even with conservation, the genetic architecture of lifespan may differ between species with 3-week versus 70-year lifespans. Third, GWAS statistical power is limited for detecting variants with modest effects or operating through specific tissues.

4.2 Mitochondrial Dominance Among Validated Candidates

A striking finding is the dominance of mitochondrial proteins among our top-ranked candidates. Four of the top five genes (CYC1, TUFM, CYCS, SDHB) encode components of the mitochondrial respiratory chain or translation machinery. This convergence supports the "mitochondrial theory of aging," which posits that declining mitochondrial function drives age-related deterioration [Friedman and Nunnari, 2014, Sabbatinelli et al., 2022, Shosha et al., 2024].

Importantly, these mitochondrial targets show human genetic validation via Alzheimer's disease GWAS, connecting longevity mechanisms to neurodegeneration. Mitochondrial dysfunction is increasingly recognized as a driver of cognitive decline, and our results suggest that

interventions improving mitochondrial function may address both longevity and brain aging [Houtkooper et al., 2013].

4.3 Drug Repurposing Opportunities

The identification of 50 approved kinase inhibitors targeting our top candidate (PIK3C2G) opens drug repurposing opportunities. Kinase inhibitors originally developed for cancer—including imatinib, trametinib, erlotinib, and gefitinib—target the insulin/PI3K pathway central to longevity. Recent preclinical evidence shows trametinib (MEK inhibitor) extends mouse lifespan by 10% as monotherapy and 27% in combination with rapamycin [Partridge et al., 2025, Olivo et al., 2021]. These approved drugs could potentially be tested in aging trials with known safety profiles.

For mitochondrial targets (CYC1, TUFM), compounds such as fisetin and epigallocatechin gallate represent senolytic and mitochondrial-protective agents worthy of further investigation. The relatively low clinical advancement (only 1 gene with aging trials) highlights a gap between druggability potential and clinical execution.

4.4 Limitations

Several limitations should be noted. First, our analysis focused on 50 genes meeting strict lifespan extension criteria, excluding many genes with moderate effects or context-dependent longevity associations. Second, GWAS power is limited for rare variants and pathway-level effects; the absence of GWAS evidence does not disprove human relevance. Third, druggability was assessed by compound count rather than specificity or therapeutic index. Fourth, clinical trial searches may miss trials not registered in ClinicalTrials.gov or using indirect pathway interventions.

Our scoring algorithm weights components equally within domains, which may not reflect biological importance. Future iterations could incorporate expert elicitation or cross-validation against clinical outcomes.

4.5 Future Directions

This study establishes a framework for systematic translation scoring that can be expanded in several directions:

1. **Expanded gene sets**: Include DrugAge and CellAge databases for a comprehensive longevity gene universe
2. **Mendelian randomization**: Test causal relationships between variants and lifespan using two-sample MR
3. **Clinical trial design**: Prioritize Phase II trials for kinase inhibitors (trametinib, imatinib) in aging biomarker endpoints
4. **Mechanistic validation**: CRISPR screens targeting top candidates in human iPSC-derived neurons to test Alzheimer's connections

5. **Network medicine**: Expand STRING analysis to identify multi-target combinations

5 Conclusions

The Longevity Translation Scorecard provides the first systematic quantification of the gap between model organism longevity discoveries and human genetic evidence. Our finding that 74% of model organism genes lack human validation emphasizes the need for genetic validation prior to clinical translation. The dominance of mitochondrial proteins (CYC1, TUFM, CYCS, SDHB) among validated candidates supports targeting bioenergetic pathways for human aging interventions. Approved kinase inhibitors (imatinib, trametinib) targeting the top candidate PIK3C2G pathway represent immediate repurposing opportunities. This evidence-based prioritization framework can guide resource allocation in longevity research toward interventions with the highest probability of clinical translation.

Acknowledgments

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Data Availability

All data, code, and analysis outputs are available at the project repository. The Longevity Translation Scorecard (CSV) and detailed candidate dossiers (Markdown) are provided as supplementary materials.

Conflicts of Interest

The author declares no conflicts of interest.

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