PPROPOSAL FOR BARRY GOLDWATER SCHOLARSHIP

Altering and Understanding Lifespan in Model Animal Caenorhabditis elegans

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Introduction and Specific Aims

With the passage of time, animals grow old, become susceptible to disease, and eventually die.[1] Aging was previously thought to be an unavoidable biological process. Recently, researchers identified specific genes that play a significant role in regulating lifespan, driven by pioneering studies in the nematode *C. elegans*. Remarkably, many of these genes also regulate lifespan in other organisms such as flies, mice, and possibly humans.[2,3,4,5] While dozens of aging-related genes have been identified, the interactions between such genes generally remain poorly understood.[6,7] A complete understanding of the role of genetic interactions is crucial to understanding how lifespan is regulated.

My lab's *long-term goal* is to understand the interactions between aging-associated genes and the extent to which lifespan can be scaled up and down by genetic manipulation. My *overall objective* in this proposal is to understand the role of interactions between transcription factors in the regulation of lifespan, resilience, and health. My *hypothesis* is that stress-responsive transcription factors interact to determine lifespan, resilience to stressors, and health. This hypothesis was formulated based on the following findings: (i) many transcription factors have been demonstrated to play a role in lifespan;[8,9,10,11] (ii) my preliminary studies demonstrate that two transcription factors jointly determine lifespan and resilience to thermal stress (Figures 2,3); (iii) I have shown that health is affected by *skn*-1, but not by *daf-16* or *daf*-12 (Figure 4). The *rationale* of this proposed research is that by studying interactions between transcription factors we will better understand the relationship between lifespan, resilience, and health. My specific aims are:

Aim 1: To systematically determine the genetic interactions between transcription factors in the control of lifespan. I will (a) construct double, triple, and higher null mutant combinations, (b) measure mutant survival relative to controls, and (c) use statistical tools to model survival analysis and genetic interactions. The pattern(s) of genetic interactions will provide new classifications for the mechanisms that regulate lifespan.

Aim 2: To systematically determine the genetic interactions between transcription factors in the control of resilience to a variety of stressors. I will follow the scheme for Aim 1 but measure resilience under specific stressors: heat, oxidants, and pathogens. These studies will provide new classifications for the mechanisms that regulate resilience.

Aim 3: To systematically determine the genetic interactions between transcription factors in the control of different facets of an organism's health. I will follow a similar scheme to the previous aims but measure health: brood size, movement, and developmental time. These studies will provide new classifications for the mechanisms that regulate health.

Overview of research strategy

Finally, I will use clustering techniques[12] to compare my findings from Aims 1, 2, and 3. This will reveal the complex relationships between lifespan, resilience, and health.

Research Strategy

Overall methods will include: (i) identifying genes of interest, (ii) obtaining a null allele of the identified genes, (iii) eliminating unwanted background mutations (outcrossing), and (iv) creating mutant combinations via classical genetic techniques (crossing).

Lifespan will be recorded by checking for survival at set time points. Data acquisition can be accomplished by hand or by using a system that utilizes a series of flatbed scanners to automatically record lifespan.[13] *Preliminary data* includes the lifespan of the *daf-16; daf-12* double mutant (Figure 2). I will also measure resilience and health using the same methods as those outlined for lifespan. Additional *preliminary data* includes resilience of *daf-16; daf-12* (Figure 3) and movement of *skn-1* and *daf-16; daf-12* (Figure 4).

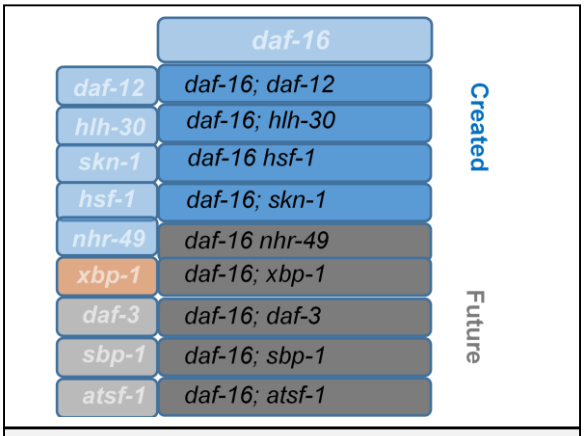

Figure 1: Project progress. Out-crossed single mutants shown in blue, partially outcrossed single mutants shown in orange, and un-outcrossed single mutants shown in grey.

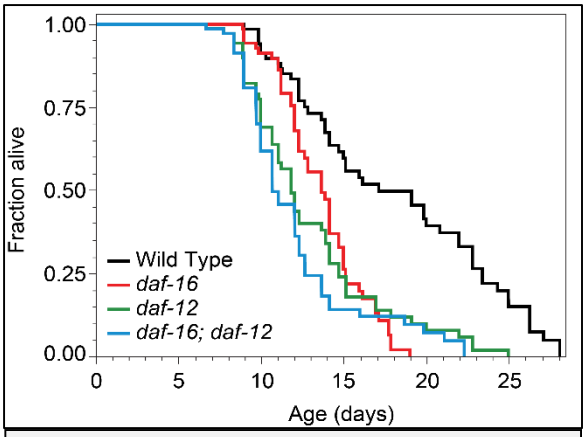

Figure 2: Survival of *daf-16; daf-12* and controls at 20°C. There are no significant differences between the single and double mutants.

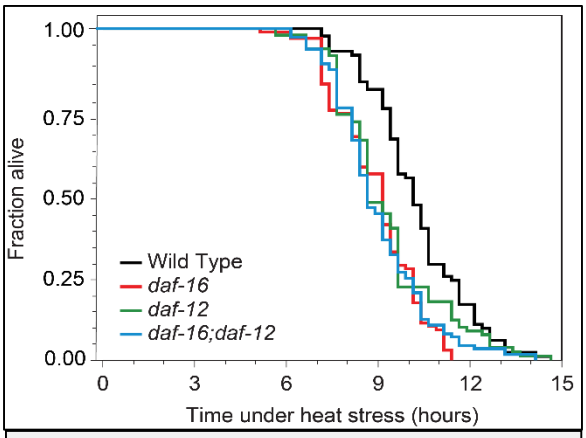

Figure 3: Survival of *daf-16; daf-12* and controls at 20°C. There are no significant differences between the single and double mutants.

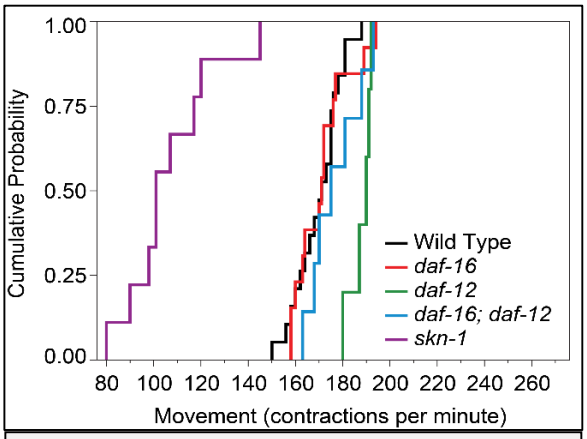

Figure 4: Thrashing of multiple mutants at 20°C. *Skn-1* single mutants thrash significantly more slowly than other mutants (p<.0001).

References

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