BIOGRAPHICAL SKETCH

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NAME: Murphy, Coleen T.

eRA COMMONS USER NAME (credential, e.g., agency login): CTMURPHY

POSITION TITLE: Professor of Molecular Biology and Genomics

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Houston, Houston, TX	B.S.	1992	Biochemical & Biophysics
University of Texas Southwestern Medical Center, Dallas, TX	Post-baccalaureate	1993	Structural Biology
Stanford University, Stanford, CA	Ph.D.	1999	Biochemistry
University of California, San Francisco, CA	Postdoctoral training	2005	Biology of Aging

A. Personal Statement

My group studies aging and the quantitation of quality of life with age, including the decline of cognitive and reproductive capacities with age, primarily using C. elegans a model system. We develop genomic, genetic, biochemical, robotic, microfluidic, and computational approaches to address these questions, using the nematode *C. elegans* as our model system. We have a strong track record for developing new approaches to address important questions in the field of aging research, combining genomic approaches with genetics and novel behavioral assays, including the full-genome identification of insulin signaling/FOXO transcriptional targets (Murphy, et al. ***Nature*** 2003) and the identification of PQM-1 as an antagonist of FOXO transcription (Tepper, et al. ***Cell*** 2013); the identification of TGF-β signaling as a primary regulator of reproductive aging (Luo, et al. ***Cell*** 2010) and insulin signaling as a regulator of cognitive aging and CREB-regulated long-term memory (Kauffman, et al. ***PLoS Biology*** 2010; Lakhina, et al. ***Neuron*** 2015), and the discovery that signaling from males drives pro-aging pathways that kill mothers after reproduction (Shi & Murphy, ***Science*** 2014). Recently my lab developed a method to isolate adult *C. elegans* cells that allows us to carry out transcriptional studies with unprecedented refinement (Kaletsky, et al., ***Nature*** 2015). We have used this method to isolate specific tissues, single cells, and subcellular compartments, for RNA-seq analysis (Kaletsky & Yao, ***PLoS Gen*** 2019). Most recently, we discovered that *C. elegans* can "read" bacterial species and pass on learned avoidance of pathogens transgenerationally (Moore, et al. ***Cell*** 2019; Kalestky et al. ***BioRxiv*** 2019) through an RNA interference and piRNA-dependent pathway. **This is one of the first examples of trans-kingdom communication in which the host utilizes small RNAs to identify a pathogen**. This exciting result suggests that bacterial small RNAs can be "read" by metazoans to influence their biology. Our newest work focuses on the role of mitochondrial function and morphology in reproductive aging and neurodegeneration.

B. Positions and Honors

Positions and Employment

2005-2012 Assistant Professor of Molecular Biology and Genomics, Princeton University
2012-2014 Associate Professor of Molecular Biology and Genomics, Princeton University
2012-Present Director, Glenn Center for Quantitative Aging Research at Princeton University
2015-Present Professor of Molecular Biology and Genomics, Princeton University
2016-2018 Faculty director, Summer Undergraduate Research Program

Honors

1987 National Merit Scholar; Valedictorian, Spring Hill HS, Spring Hill, KS; *Kansas City Star* Scholar Athlete
1992 Rhodes Scholarship Semi-Finalist

1994 Howard Hughes Medical Institute Pre-Doctoral Fellowship
1994 NSF Pre-doctoral Fellowship (declined)
2000 Life Sciences Research Foundation Postdoctoral Fellowship
2000 American Cancer Society Fellowship (declined)
2003 Ellison Medical Foundation/American Federation for Aging Research, Senior Postdoct.Fellowship
2003 Burroughs-Wellcome Career Awards in the Biomedical Sciences Finalist
2006 Sloan Research Fellowship
2006 Ellison Medical Foundation New Scholar in Aging (declined)
2006 Pew Biomedical Scholar
2008 Basil O'Connor March of Dimes Starter Scholar Research Award
2008 American Society for Cell Biology Women in Cell Biology Jr. Award
2008 McKnight Scholars Award
2008 Keck Distinguished Young Scholars in Medical Research Award
2009 National Institute on Aging Lab. of Neurosciences Disting. Lect. in Neuroscience and Aging
2008 NIH Director's *New Innovators* (DP2) Award
2009 NIH Research Partnership in Cognitive Aging Award
2010 Glenn Award for Research in Biological Mechanisms of Aging
2014 Princeton Molecular Biology Innovation Award
2015 NIH Director's *Pioneer* (DP1) Award
2016 HHMI-Simons Faculty Scholar Award
2017 SAB, Max Planck Partner Institute for Computational Biology in Shanghai
2017 SAB, Buck Institute for Aging Research, Chair
2018 *Nansen Neuroscience Lecture*, Norwegian Academy of Science and Letters, Oslo, Norway
2019 American Society for Cell Biology *Women in Cell Biology Mid-Career Award*

C. Contributions to Science

My lab focuses on understanding how aging, longevity, and health span are regulated. "Longevity pathways" couple the timing of reproduction, based on information the organism perceives about its environment and nutrient status, with somatic health; selection for any longevity pathway must act at the level of reproduction, not late in life. Because I am interested in reproductive and cognitive decline with age, and how they are regulated both cell autonomously and non-autonomously, the work in my lab incorporates several lines of research that are unified by this reasoning.

1. *Regulation of Longevity*: I first became interested in the question of aging as a postdoc, when it was known that insulin signaling mutants, such as the *daf*-2 insulin receptor mutant, were long-lived and required the activity of the FOXO transcription factor DAF-16, but the downstream targets were unknown. I built my own *C. elegans* microarrays and performed transcriptional analyses of *daf-2* and *daf-16;daf-2* mutants in early aging (Murphy, et al. ***Nature*** 2003). These results not only answered the original question, showing that DAF-16 activates a large suite of genes that keep proteins and cells functional, but also identified a motif, the "DAF-16 Associated Element" that is associated with the opposing activity, growth, which we later found is regulated by the PQM-1 transcription factor (Tepper, et al., ***Cell*** 2013). Our 2003 results enabled us and other researchers to study particular targets, co-factors, and mechanisms in greater detail, and is still a source of aging research, including our new findings regarding collagen upregulation (Ewald, et al. ***Nature*** 2014). The genomic analysis also revealed that other factors and pathways, such as TGF-β signaling and HSF-1, are closely connected with IIS/DAF-16 activity (Shaw, et al. 2007; Hsu, et al. ***Science*** 2003), and all of the pathways we have studied are conserved through mammals, thus our work will have a lasting impact.

a. Shaw W.M., Luo S., Landis J, Ashraf J, **Murphy C.T.,** "The *C. elegans* TGF-β Dauer pathway regulates longevity via insulin signaling." ***Current Biology.*** (2007) Oct 9;17(19):1635-45.
b. Ewald, C, Landis, J, Abate, J, and **Murphy*, CT** & Blackwell*, TK. "Dauer-independent insulin/IGF-1 signalling implicates extracellular matrix remodelling in longevity." ***Nature***, 2014 ***co-corr. authors** PMCID: PMC4352135
c. Tepper, R., Ashraf, J.A., **Murphy*, C.T.,** and Bussemaker*, H., "PQM-1 complements DAF-16 as a Key Transcriptional Regulator of DAF-2-mediated development and longevity." ***Cell,*** 2013 Aug 1; ***co-corresponding authors** PMCID:PMC3763726
d. Kaletsky*, R., Lahkina*, V., Arey, RA, Williams, A, Landis, J, Ashraf, J, & **Murphy, CT**, "The *C. elegans* adult neuronal IIS/FOXO transcriptome reveals adult phenotype regulators," 2016 ***Nature***, Jan

7;529(7584):92-6 PMCID: PMC4708089

2. Regulation of Reproductive Aging: One of the earliest age-related declines humans experience is the loss of female reproductive ability. When I started my lab, I realized that the causes of reproductive decline were not known, no treatments that can slow this decline are available, and the aging field in general has not yet focused on this issue, despite the fact that reproductive status and longevity are intimately linked (Luo, et al. 2009). To address the question of reproductive aging, my lab has carried out unbiased genetic screens (Kaletsky, et al. in preparation), and genetic and genomic analyses (Luo, et al. 2009; Luo et al 2010). We discovered that mutants of the conserved TGF-β pathway slow reproductive decline, and do so by maintaining oocyte quality with age (Luo, et al. ***Cell*** 2010). Despite differences in time scales, *C. elegans* and mammalian oocyte quality decline is due to the loss of transcription of the same set of genes; this suggests that mechanisms and compounds that slow worm reproductive decline could also extend women's reproductive period. I am now interested in discovering biomarkers of reproductive decline that are present in oocytes, blood, and other tissues that would allow me to develop a diagnostic of reproductive age (provisional patent).

a. Templeman, NM, Luo, S, Kaletsky, R, Shi, C, Ashraf, J, Keyes, W, and **Murphy, CT**. "Oocyte-specific insulin/IGF-1 signaling transcriptomics reveal a role for Cathepsin Bs in regulating reproductive aging and oocyte quality maintenance," ***Current Biology*** (2018) Mar 5;28(5):753-760.e4. PMCID:PMC5893159
b. Luo, S, Shaw, W, Ashraf, J, **Murphy, CT** (2009). "TGF-b Sma/Mab signaling mutations uncouple reproductive aging from somatic aging." ***PLoS Genet.*** 2009 Dec. 5 (12) PMCID: PMC2791159
c. Luo, S., Kleemann, G.A., Ashraf, J.M., Shaw, W.M., and **Murphy, C.T**., "TGF-β and Insulin Signaling Regulate Reproductive Aging via Oocyte and Germline Quality Maintenance." ***Cell*** 2010 Oct 15;143(2):299-312. PMCID: PMC2955983
    - *Feat. in **Cell**'s PaperClip, Oct. 15, 2010*
    - *Feat. in **New York Times**, Oct. 15, 2010*
    - *Feat. in **News & Views**, Nature* **468**: 386-387
d. **Murphy, C.T**., US Provisional Patent # 62/089,604: *Biomarkers of Oocyte Quality* (2015)

3. Regulation of Cognitive Aging: The loss of cognitive abilities is one of the most devastating effects of aging. While *C. elegans* has been used to study regulation of longevity, it had not been well-studied as a model for cognitive aging. My lab developed new assays to study *C. elegans'* learning, short-term, and long-term associative memory (Kauffman, et al. 2010; Kauffman, et al. 2011), and found that long-lived IIS *daf-2* mutants have extended learning and short-term memory, and increase long-term memory through increased levels of CREB. We went on to identify the genetic components of short-term memory (Stein & Murphy, 2014), and to identify the set of genes that CREB activates upon long-term memory training (Lakhina, et al. ***Neuron*** 2015). Together, these studies show that worms use and lose their cognitive abilities via similar mechanisms as humans, and that their abilities can be maintained under specific longevity conditions. Worms will therefore be a good system to explore additional conditions and treatments that may slow cognitive decline with age.

a. Arey, RN, Stein, GM, Kaletsky, R, Kauffman, A, and **Murphy, CT**. "Activation of G_{aq} signaling enhances memory consolidation and slows cognitive decline," ***Neuron***, 2018 May 2;98(3):562-574.e5. PMCID:PMC5934306
b. Stein, GM and **Murphy, CT**. "*C. elegans* Positive Olfactory Associative Memory is a Molecularly Conserved Behavioral Paradigm." ***Neurobiol Learn Mem***, 2014 Aug 7; DOI: 10.1016/j.nlm.2014.07.011; PMID: 25108196 PMCID: PMC4250358
c. Lakhina, V., Arey, R.A., Kaletsky, R., Kauffman, A., Stein, G. Keyes, W., Xu, D., and **Murphy, C.T. "**Genome-wide Functional Analysis of CREB/Long-Term Memory-Dependent Transcription Reveals Distinct Basal and Memory Gene Expression Programs." ***Neuron*** 2015 Jan 21;85(2):330-45. PMCID:PMC4340687
d. Kaletsky*, R., Lahkina*, V., Arey, RA, Williams, A, Landis, J, Ashraf, J, & **Murphy, CT**, "The *C. elegans* adult neuronal IIS/FOXO transcriptome reveals adult phenotype regulators," 2016 ***Nature***, Jan 7;529(7584):92-6 PMCID: PMC4708089
e. Crocker A, Guan XJ, **Murphy CT**, Murthy M. "Cell-Type-Specific Transcriptome Analysis in the Drosophila Mushroom Body Reveals Memory-Related Changes in Gene Expression." ***Cell Rep.*** 2016 May 17;15(7):1580-1596. PMCID:PMC5047377

4. Post-mating Changes in Physiology and Behavior: We discovered serendipitously that mating kills C. *elegans* mothers just after having produced the male's progeny, possibly due to sperm competition (death prevents any later matings). Remarkably, the mechanisms that males use to kill the mothers is by reversing

pathways that we normally think of as pro-longevity: insulin signaling is turned up "high," removing DAF-16 from the nucleus, and NHR/DAF-12 signaling is also shut off. Together these result in the worms losing all stress protection, causing shrinking and rapid death. Thus, the males have hijacked the same pathways that females normally use slow reproduction and extend somatic lifespan in times of low nutrients, driving them in the opposite direction. The effect is also conserved in true female/male species, such as *C. remanei*, meaning that females must always have a shortened lifespan if they reproduce. Moreover, we observe major shifts in behavior after mating, suggesting that neuronal signals are also changed. Our current studies focus on identifying the sperm and seminal fluid components that induce these effects, the signals between the germline and soma, the signal to the neurons, and the gene expression changes in neurons that mediate the behavioral shifts we observe.

a. Shi C, **Murphy CT**. "Mating induces shrinking and death in *Caenorhabditis* mothers." ***Science***. 2014 Jan 31; 343(6170):536-40. DOI: 10.1126/science.1242958. PMCID:PMC6719292
   - *Feat. in* ***Current Biology*** **2014** Mar 3;24(5):R196-8.
   - *Feat. in* ***Science.*** 2014 Jan 31;343(6170):491-2.
   - *Feat. in* ***Jezebel***, http://jezebel.com/sex-is-kiss-of-death-for-female-worms-because-patriar-1488279886

b. Shi, C., Runnels, AM, and **Murphy, CT**, "Mating-induced Male Death and Pheromone Toxin-related Androstasis," ***BioRXiv***, December 15, 2015; doi**:** http://dx.doi.org/10.1101/034181. NIHMSID:1016120

c. Shi, C., Runnels, A. and Murphy, CT, "Mating and Male pheromone kill *Caenorhabditis* males through distinct mechanisms," *eLife* (2017) Mar 14;6.pii:323493. PMCID:PMC5378475

d. Shi, C., Booth, LN, and **Murphy, CT**. "Insulin-like peptides and the mTOR-TFEB pathway protect *Caenorhabditis elegans* hermaphrodites from mating-induced death," ***eLife*** 8, e46413 (2019) PMCID:PMC6697448

5. Tissue Specificity and adult C. elegans tissue profiling: Although lifespan is a whole-organism phenotype, different tissues can age at different rates, tissue-specific phenotypes develop at different ages, and cell non-autonomous effects are important in the regulation of longevity. Therefore, my lab is interested in being able to determine where all genes are expressed. However, this is not a simple problem; adult worms have a tough outer cuticle that prevents easy dissociation of cells. To explore localized gene expression, we first used known gene expression profiles (10% of the genome) to predict where the remaining genes are likely to be expressed (Chikina, et al. 2009). More recently, we developed a chemo-mechanical method to dissociate adult worm cells (Kaletsky, et al. ***Nature*** 2016). We are using this technique to study gene expression changes in adults with age and in longevity mutants, isolating tissues (muscles, neurons, intestine, hypodermis), neuron types, individual neurons, and pre- and post-synaptic compartments.

a. Kaletsky*, R., Lahkina*, V., Arey, RA, Williams, A, Landis, J, Ashraf, J, & **Murphy, CT**, "The *C. elegans* adult neuronal IIS/FOXO transcriptome reveals adult phenotype regulators," 2016 ***Nature***, Jan 7;529(7584):92-6 PMCID: PMC4708089

b. Yao† V, Kaletsky† R, Keyes W, Mor DE, Wong AK, Sohrabi S, **Murphy* CT**, Troyanskaya* OG. An integrative tissue-network approach to identify and test human disease genes. ***Nature Biotech.*** 2018 Oct 22. doi: 10.1038/nbt.4246. NIHMSID:1016160

c. Tabuchi TM, Rechtsteiner A, Jeffers TE, Egelhofer TA, **Murphy CT**, Strome S. C. elegans sperm carry a histone-based epigenetic memory of both spermatogenesis and oogenesis. ***Nature Commun***. 2018 Oct 17;9(1):4310. doi: 10.1038/s41467-018-06236-8. PMCID:PMC6193031

d. Kaletsky R, Yao V, Williams A, Runnels AM, Tadych A, Zhou S, Troyanskaya OG, **Murphy CT**. "Transcriptome analysis of adult Caenorhabditis elegans cells reveals tissue-specific gene and isoform expression." ***PLoS Genet.*** 2018 Aug 10;14(8):e1007559. doi: 10.1371/journal.pgen.1007559. eCollection 2018 Aug. PMCID:PMC6105014

e. Chikina, M.D., Huttenhower, C., **Murphy, C.T**.* and Troyanskaya, O.G., "Global Prediction of Tissue Specific Gene Expression and Context-Dependent Gene Networks in *C. elegans.*" ***PLoS Comput Biol.*** 2009 Jun;5(6). ***co-corresponding authors.** PMCID: PMC2692103

6. ***Transgenerational inheritance of pathogenic avoidance:*** Recently, we discovered that worms can pass on a learned avoidance of pathogenic bacteria (*Pseudomonas aeruginosa*) to their progeny for four generations before returning to their natural state of attraction to Pseudomonas. This effect is pathogen-specific and requires the Piwi/Argonaute PRG-1 and DAF-7 TGF-beta in the ASI sensory neuron. Our data suggest that worms can "read" individual bacterial small RNAs and use this information to influence behavior.

a. Moore, R.S., Kaletsky, R., and **C.T. Murphy**, "Piwi/PRG-1 Argonaute and TGF-β mediate Transgenerational Learned Pathogenic Avoidance," ***Cell,*** 177(7):1827-41(2019) PMC Journal – In Process

b. Kaletsky*, R, Moore*, RS, Parsons, LR, and **Murphy, CT**. “Cross-kingdom recognition of bacterial small RNAs induces transgenerational pathogenic avoidance,” ***bioRxiv***, 697888 (2019)

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