BIOGRAPHICAL SKETCH

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NAME: **Monica Driscoll**

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POSITION TITLE: Distinguished Professor of Molecular Biology and Biochemistry

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Douglass College, Rutgers University	A.B.	05/79	Chemistry
Harvard University	Ph.D.	05/85	Biochemistry and Molecular Biology
Columbia University	Postdoctoral	85-91	Molecular Genetics

A. Personal Statement

Aging is by far the most potent risk factor for cancer and other late-onset diseases such as diabetes and Alzheimer's disease. Because aging has such a potent impact on cancer incidence, it has been suggested that addressing the nature of aging itself, and slowing its progression might be the most efficacious intervention against cancer. Our lab has a long-term dedication to understanding the basic biology of adult healthy maintenance, exploiting powerful experimental advantages in *C. elegans* to address questions relevant to major problems in human health.

I studied yeast genetics for my doctoral thesis, developing a strong appreciation for the discipline. I then trained in *C. elegans* doing postdoctoral studies in the lab of now Nobel Prize winner Dr. Martin Chalfie, where I initiated long-term work on *C. elegans* touch receptor function and neuronal degeneration associated with necrosis. My interests in necrosis led me to wonder whether necrotic death (associated with physiological insult) might contribute to the aging of the animal. Coming into the aging field, I was struck by the fact that despite an enormous amount of work that had been devoted to longevity genetics, very little had been done to examine how *C. elegans* actually ages. We published a major paper on this question (Herndon, *Nature* 2002) and we have been working on the problem of tissue-specific aging and the biology of healthspan (the period of healthy maintenance prior to functional decline) ever since. Overall, our *C. elegans* work established a powerful foundation for our evaluation of how drugs, exercise and metabolism impact adult health and maintenance, enabling us to approach the problem from a unique angle with *in vivo* single cell and individual tissue focus, over the entire life of the animal.

Determining how to promote resilience in older age is a significant world health challenge. We know of two interventions that can promote healthy aging and protect against age-associated diseases such as cancer and diabetes; these are dietary restriction and exercise. Dietary restriction is unpleasant. Exercise can be pleasant (when finished), but many choose not to exercise and some cannot. Still, one can expect that detailed understanding of molecular, cellular, and system-wide circuits that promote and maintain long-term benefits of exercise can inform on the biology of resilience mechanisms. Insights from such studies might well influence design of novel health-promoting interventions—but for now, the critical first steps are to define the molecules of enhanced maintenance and determine how they work system-wide. With an appreciation of the power of exercise to promote health and resilience and an expectation that invertebrate genetic models can generate unique insights into the associated molecular physiology, we developed a *C. elegans* adult exercise model (Laranjeiro, 2017; Hartman 2018; Laranjeiro 2019).

Another cancer-relevant project focuses on proteostasis—the balance protein folding and degradation critical for cell function. Proteostasis is also critical to the tumor biology. For example, autophagy is a major component of proteostasis that impacts the tumor microenvironment. We discovered a previously unknown capacity of young adult *C. elegans* neurons to exude substantial packets of cellular contents, which can include aggregated human neurodegenerative disease proteins, lysosomes, and/or mitochondria (Melentejevic 2017). We call the extrusions exophers. We propose that the exopher extrusion phenomenon constitutes a significant but currently unknown pathway by which healthy cells maintain their functions by ridding themselves of toxic contents. Our continued study of the basic biology of exophers in aging and compromised *C. elegans*

cells should provide considerable novel insight into a process relevant to tumors biology. Indeed, *C. elegans* neurons are very similar to tumor cell oncosomes—learning about how these influence cell health and viability might suggest novel chemotherapy approaches.

Currently funded research projects to highlight include:

R01AG047101 (Driscoll, PI Grant co-PI) 09/30/2013 -11/30/2022 NCE
Understanding the Exopher: A Novel Mechanism for Extrusion of Neurotoxic Contents

R37AG56510 (Driscoll, PI) 08/01/2017 - 03/31/2027
Defining Roles of Genetics and Age in Extracellular Elimination of Neurotoxic Aggregates

U01AG045864 (Driscoll, PI) 05/01/2017 - 7/31/2027
C. elegans Intervention Testing Program: Interventions That Modulate Health, Longevity and Aging Hallmarks

R21AG074536 (Driscoll, PI) 01/15/2022-11/30/2023
Molecular Underpinnings of Enduring Exercise Benefits

B. Positions, Scientific Appointments, and Honors

June, 2015 – present	Distinguished Professor, Rutgers University, Dept. of Molec. Biol. and Biochem.
July, 2003 - June, 2015	Professor, Rutgers University, Department of Molecular Biology and Biochemistry
Sept., 1997 - June, 2003	Associate Professor, Rutgers University, Department of Molec. Biology & Biochem.
Sept., 1991 - Aug., 1997	Assistant Professor, Rutgers University, Department Molec. Biology & Biochem.
Sept., 1985 - Aug., 1991	Postdoctoral Research Fellow, Department of Biological Sciences, Columbia University, laboratory of Dr. M. Chalfie; *Area: C. elegans neurogenetics*
June, 1985 - Aug., 1985	Preliminary postdoctoral work on *C. elegans*, Harvard University, in laboratories of Dr. Dan Stinchomb and Dr. Victor Ambros. *Area: C. elegans genetics*
Sept., 1975 - May, 1985	Doctoral research, Department of Biochemistry and Molecular Biology, Harvard University in laboratory of Dr. Helen Greer. Thesis: Regulation of Amino Acid Biosynthesis in *S. cerevisiae. Area: molecular genetics of gene regulation*

Other Experience and Professional Memberships

2024	Co-Chair elect Gordon Conference on Cell Biology of the Neuron, Vice Chair '22
2019-2023	NIA National Advisory Council on Aging, appointed member, Chair of Working Group on Program
2009-present	American Federation for Aging Research Scientific Advisory Board
2009-present	Regional Member, Institute for Aging Research, Albert Einstein Coll. of Medicine
2006	Co-Chair, Gordon Conference on the Biology of Aging
2004-2008	Ellison Medical Foundation Senior Scholar In Aging
2004-2005	AFAR National Scientific Advisory Council
2005	Co-Chair International *C. elegans* Meeting (2,500 participants)
NIH study section service:	NIH CMAD (ad hoc 6/16), CMND (member, 2009-2013; **Chair 2011-2013**; ad hoc 6/08; 10/08); ZAG1 ZIJ-2 (9/10) ZAG1 ZIJ-5 (10/09); ZNS1 SRB-E (8/09); ZRG BDA-C (12/08); CMAD (2/08); SEP GGG-E 02 S (2007); NIH NCRR Special Emphasis Panel, Chair (ZRR1 CM-6(01) (2006); NIH Special Emphasis Panel 01 ZRG1 NOMD-A (2006); NIH Special Emphasis Panel, Chair ZRG1 MDCN-F (02).

Honors

2017	National Institute on Aging MERIT Award
2012	Election as Fellow of the American Association for the Advancement of Science
2011-2013	Chair, NIH Study Section, Cellular and Molecular Biology of Neurodegeneration
2009-2013	Member, NIH Study Section CMND
2007-2009	Glenn Foundation Award for Research on Biological Mechanisms of Aging
2004-2008	Ellison Medical Foundation Senior Scholar In Aging
1993-1995	Alfred P. Sloan Research Fellow
1985-1990	National Institutes of Health Postdoctoral Fellowship; American Cancer Society Postdoctoral Fellowship; Muscular Dystrophy Association Postdoctoral Fellowship
1979	A.B. Chemistry, *summa cum laude*; 1978 Phi Beta Kappa

C. Contributions to Science

1) Molecular Mechanisms of Mechanotransduction—Touch and Feeling at the Molecular Level. The process by which mechanical signals, such as pressure or force, are interpreted to direct biological responses is not well understood. In brief, I contributed to the identification of a new family of ion channels (the *C. elegans* degenerin channels, some of which (MEC-4 and MEC-10) (Driscoll and Chalfie 1991) normally function as the core mediators of touch transduction in specialized mechanosensory neurons, and proprioception in *C. elegans* (UNC-8; Tavernarakis 1997). We contributed some of the first genetic structure/function studies that defined the MEC channel pore (Hong 1994; Lai 1996, Hong 2000), used *in vivo* calcium measurements to show that the MEC channel is the likely primary sensor of force in touch sensation (Suzuki 2003), identified an unexpected Ca^{2+} current associated with the MEC channel (Bianchi 2004), and defined factors that regulate DEG/ENaC trafficking (Royal 2005). Overall, our work pioneered understanding of a novel ion channel class with members that can recognize and respond to force to initiate neuronal responses.

Driscoll, M. and Chalfie, M. 1991. The *mec-4* gene is a member of a family of *Caenorhabditis elegans* genes that can mutate to induce neuronal degeneration. ***Nature*** 349: 558-593. PMID: 1672038

Hong, K. and Driscoll, M. 1994. A transmembrane domain of the putative channel subunit MEC-4 influences mechanotransduction and neurodegeneration in *C. elegans.* ***Nature*** 367: 470-473. PMID: 8107806

Hong, K., Mano, I. and Driscoll, M. 2000. *In vivo* structure/function analysis of *C. elegans mec-4*, a candidate mechanosensory ion channel subunit. ***J. Neurosci.*** 20: 2575-2588. PMID: 10729338

Bianchi, L., Gerstbrein, B., Royal, D., Xue, J. and Driscoll, M. 2004. The neurotoxic MEC-4(d) Na^{+} channel conducts calcium: implications for normal and aberrant activities of DEG/ENaC channels. ***Nature Neurosci.*** 7: 1337-1344. PMID: 15543143

2) Mechanisms of Necrotic Cell Death in Injury and Disease. Brain injury and neurodegenerative conditions are often associated with exacerbated ion channel activity, inducing necrotic cell death. We pioneered study of neuronal necrosis in *C. elegans*. Novel mutant forms of the channel encoded by *mec-4(d)* mutants specify hyper-activated ion channels that conduct excess ions, resulting in neuronal swelling and cell death (Driscoll and Chalfie, 1991). We developed this genetic necrosis model to show that elevated ion conductance is a critical component of necrosis initiation, and, unexpectedly, that Ca^{+2} influx is essential for neurotoxicity (originally this channel family was thought to be Na^{+}-selective) (Bianchi 2004). We conducted powerful genetic interaction screens to identify molecules critical for the progression through necrosis (Zhang 2008), and we developed a second model of *C. elegans* excitotoxicity in which we disrupted glutamate transporters to elevate endogenous glutamate levels to mimic the neurotoxic condition of glutamate excitotoxicity in humans (Mano 2009). Our genetic enhancer and suppressor screens defined a downstream necrosis pathway that requires channel hyperactivation, calcium influx (Bianchi 2004; Royal 2005; Zhang 2008), catastrophic release of stored calcium in the ER compartment of the cell (Xu 2001), and the later activation of lysosomal cathepsin enzymes that degrade cellular proteins (Syntichaki 2002). Overall, our work in this area provided the earliest evidence that necrosis is not merely a run-away breakdown of the neurons, but rather can be modulated by specific regulated steps, which are logical targets for therapeutic intervention against stroke.

Driscoll, M. and Chalfie, M. 1991. The *mec-4* gene is a member of a family of *Caenorhabditis elegans* genes that can mutate to induce neuronal degeneration. ***Nature*** 349: 558-593. PMID: 1672038

Xu, K., Tavernarakis, N. and Driscoll, M. 2001. Necrotic cell death in *C. elegans* requires the function of calreticulin and regulators of Ca^{2+} release from the endoplasmic reticulum. ***Neuron*** 31: 957-971.

Bianchi, L., Gerstbrein, B., Royal, D., Xue, J. and Driscoll, M. 2004. The neurotoxic MEC-4(d) Na^{+} channel conducts calcium: implications for normal and aberrant activities of DEG/ENaC channels. ***Nature Neurosci.*** 7: 1337-1344. PMID: 15543143

Mano, I., Straud, S. and Driscoll, M. 2007. Glutamate clearance strategies impact behavior and learning in the *C. elegans* nervous system. ***J. Biol. Chem*** 282: 34412-34419. PMID: 17681948

3) Healthspan Genetics and Pharmacology: Molecular Promotion of Healthy Aging. I have a long term interesting in the understanding of how *C. elegans* actually ages, the topic of my first paper in the aging field (Herndon 2002). In brief, we showed that basic age-associated tissue degeneration is strikingly reminiscent of that which transpires in humans, including mid-life onset sarcopenia. Given my interest in quantitating age-associated mobility decline in *C. elegans,* I collaborated with computer vision experts to develop CeleST (C. elegans Swim Test), a sophisticated algorithm that analyses swimming vigor decline using 8 self-referential movement parameters (Restif 2014). In 2013, I was fortunate to be selected as one of the collaborative partners in the *Caenorhabditis* Intervention Testing Program, which is charged with the identification of efficacious longevity interventions in lifespan across a genetically diverse group of *Caenorhabditis* strains spanning three species. A cornerstone of this project was to demonstrate reproducibility of outcomes across the three partner sites. This proved to be a fairly daunting task, but with meticulously designed and

documented protocols, and near constant communication, our CITP teams were able to generate data for which there was essentially no variance attributed to a particular site or group (Lucanic 2017; Lithgow 2017). More than 450,000 scored animals later, the CITP has identified compounds that promote longevity in nematodes (Lucanic, 2017) that share genetic differences on the order of mouse-human difference, some of which also promote longevity in mouse ITP tests. We contributed technology improvements (Abbott, 2019; Banse, 2020) and opened the portal for public nomination of candidate test compounds, some of which look promising in the preliminary pipeline.

Herndon, L.A., Schmeissner, P., Dudaronek, J, Listner, K.M., Brown, P.A., Sakano, Y., Paupard, M., Hall, D. and Driscoll, M. Stochastic and genetic factors influence tissue-specific decline in ageing *C. elegans.* 2002. ***Nature*** 419: 808-14. PMID: 12397350

Restif, C., Ibanez-Ventoso, C., Vora, M., Guo, S., Metaxas, D. and Driscoll, M. 2014. CeleST: Computer vision software for quantitative analysis of *C. elegans* swim behavior reveals novel features of locomotion. ***PLoS Computational Biology***, 0(7):e1003702 PMID:25033081

Lucanic, M., et. Al. 2017. Impact of genetic background and experimental reproducibility on identifying chemical compounds with robust longevity effects ***Nature Comm.***, 8:14256.

Lithgow, G., Driscoll, M., and Phillips, P. 2017. A long walk toward reproducibility: Lessons from tiny worms. ***Nature***, 548:387-388. *Invited commentary*. PMID: 28836615

4) Single Neuron Aging and Neuronal Proteostasis Management in Physiological Context. Subtle changes in neuronal morphology are hypothesized to contribute to age-associated functional decline in human brain and may be exacerbated in neurodegenerative disease. Defining the mechanisms by which adult nervous systems maintain their structural integrity is thus of considerable importance to both normal aging and neurodegenerative disease. Our interests in neuronal healthspan led us to show that morphological features of synapses deteriorate with age and that aberrant dendrite restricting is a dramatic feature of some aging neurons (Toth, 2012). We found that specific *C. elegans* neurons exhibit striking aberrant structural morphologies as they age, with two distinct abnormality types, dendrite branching and novel soma outgrowths, differentially controlled at the genetic level. Insulin signaling pathways that modulate aging and healthspan on other fronts also influence dendritic restructuring (Scerbek, 2014). Our work suggests that proteostasis crises can modulate older age morphological restructuring in single neurons in the living animal (Vayndorf et al., 2016). We also collaborated to document touch neuron mitochondrial change over adult life to show phases of increase, maintenance, and decrease in mitochondrial volume and in oxidative stress response capacity (Morsci, 2016). Collaborative work also developed the mitoTimer regent for study of mitochondria in worm neurons and other models (Laker, *J. Biol. Chem.* 289, 12005-12015, 2104).

A novel neuronal trash disposal mechanism. While observing aging and stress neurons in physiological context, we discovered a previously unknown capacity of young adult *C. elegans* neurons to extrude noxious material—neurons can release large soma-sized packets of cellular contents, which can include aggregated human neurodegenerative disease proteins, mitochondria and ER (Meletijevic 2017). The ability to throw out cell contents changes with age and is markedly enhanced if proteostasis is disrupted, suggesting the extrusion of “exophers” may be a previously undescribed last-resort effort to restore proteostasis. Physiological stresses such as oxidative, osmotic, and fasting stress can enhance exopher production via EGF, FGF and lipid biosynthesis dependent mechanisms (Cooper 2021). We propose that the neuronal extrusion phenomenon constitutes a significant and conserved, but currently uncharacterized pathway in which stressed neurons maintain their functions by ridding themselves of toxic contents. Study of the basic biology of exopher formation in *C. elegans* neurons (markedly distinct from exosome formation) should provide novel insight into the aggregate spreading process relevant to human neurodegeneration. Papers co-authored by Dr. Grant and me on an intermediate filament-dependent aggresome mechanism that modulates exophergenesis, and on the fate of the extruded exopher vesicle as recognized and phagocytosed by the surrounding hypodermal glial-like cell, are posted on the BioRxiv preprint server, with revisions submitted or underway in response to previous review.

Toth, M. Melentijevic, I. Shah, L., Bhatia, A., Lu, K., Talwar, A., Naji, H., Ibanez-Ventoso, C., Ghose, P., Jevince, A., Herndon L., Bhanot, G., Rongo, C., Hall, D.H., and Driscoll, M. 2012. Neurite sprouting and synapse deterioration in the aging *C. elegans* nervous system. ***J. Neurosci.*** 32: 8778-90.

Vayndorf, E.M., Scerbak, C., Hunter, S., Neuswanger, JR., Toth, M., Parker, JA, Neri, C., Driscoll, M. and Taylor, B. 2016. Morphological remodeling of *C. elegans* neurons during aging is modified by compromised protein homeostasis. ***NPJ Aging and Mech. Disease***, 16001 1-10.

Melentijevic, I., Toth, M.L., Arnold, M.L., Guasp, R., Harinath, G. Nguyen, K.C., Taub, D., Parker, A., Neri, C., Gabel, C.V., Hall, D.H., and Driscoll, M. 2017. *C. elegans* neurons jettison protein aggregates and mitochondria under neurotoxic stress. ***Nature,*** 542:367-371. ***F1000 selected for special significance***.

Cooper, J., Guasp, R., Arnold, M.,Grant, B, and Driscoll, M. 2021. Stress-induced increases in neuronal exopher extrusion requires lipid biosynthesis, FGF and EGF RAS/ERK signaling, ***PNAS***, 18:e2101410118 PMID: 34475208

5) Exercise Promotion of Healthy Aging and Proteostasis Resilience. Exercise exerts remarkably powerful effects on metabolism and health, with anti-disease and anti-aging outcomes. We have had a long term interest in exploiting the powerful genetic model *C. elegans* to gain novel insight into conserved molecular mechanisms for exercise benefit. This work included a productive collaboration with Dr. Zhen Yan, in which we co-developed the use of the MitoTimer reagent for assessment of mitochondrial health in exercised animals (Laker 2014). To anchor a new field in molecular genetics of exercise and aging in *C. elegans*, we showed that a single swim exercise confers physiological changes that increase robustness (Laranjeiro 2017), and we showed that extended swim training can both confer molecular muscle adaptation similar to mammalian exercise and induce long-lasting benefit to muscle, neurons, intestine and pharynx (Hartman 2018, Laranjeiro 2019). *C. elegans* swim training is also protective in four different neurodegenerative disease models and in a simple memory paradigm. The development of a basic exercise model in which we can reproducibly generate systemic long-term health benefits that can be quantitatively measured in multiple tissue types, and can be readily perturbed using molecular genetics, approaches opens exciting new avenues in deciphering resilience outcomes of exercise, an issue of high relevance in cancer prophylaxis.

Laker, R.C., Xu, P., Ryall, K., Sujkowski, A., Kenwood, B.K., Chain, K.H., Zhang, M., Hoehn, K.L., Adler, P.N., Royal, M., Driscoll, M., Wessells, RJ, Saucerman, J.J, and Yan, Z. 2014. A novel MitoTimer reporter gene for mitochondrial content, structure, stress, and damage *in vivo*. ***J. Biol. Chem*.** 289:12005-15. PMID: 24644293

Laranjeiro, R., Harinath, G., Burke, D., Braeckman, B.P., and Driscoll, M. 2017. Single swim sessions in *C. elegans* induce key features of mammalian exercise. ***BMC Biol.*** 15:30.

Hartman, J., Smith, L., Gordon, K., Laranjeiro, R., Driscoll, M., Sherwood D., and Meyer J. 2018. Swimming Exercise and Transient Food Deprivation in *Caenorhabditis elegans* Promote Mitochondrial Maintenance and Protect Against Chemical-Induced Mitotoxicity. ***Sci Rep.*** 8(1):8359.

Laranjeiro, R., Harinath. G., Hewitt, J.E., Hartman, J.H., Royal, M.A., Meyer, J.N., Vanapalli. S.A., Driscoll. M. (2019) Swim exercise in *Caenorhabditis elegans* extends neuromuscular and gut healthspan, enhances learning ability and protects against neurodegeneration. ***Proc Natl Acad Sci USA***. 116:23829-23839. ***F1000 recommended.***

Complete List of Published Work in MyBibliography:

https://www.ncbi.nlm.nih.gov/myncbi/1joK71dg7NS5d/bibliography/public/