BIOGRAPHICAL SKETCH

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NAME: MILLER, DAVID

eRA COMMONS USER NAME: millerdm

POSITION TITLE: Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE (if applicable)	END DATE	FIELD OF STUDY
Univ. of Southern Mississippi, Hattiesburg, MS	BS	06/1973	Biology
Rice University, Houston, TX	PhD	06/1981	Biochemistry
Baylor College of Medicine, Houston, TX	Postdoctoral Fellow	08/1983	Muscle Assembly, HF Epstein, MD
MRC-Laboratory of Molecular Biology, Cambridge	Postdoctoral Fellow	12/1984	Myogenesis, Sydney Brenner, MD

A. Personal Statement

The Miller lab uses the model organism *C. elegans* to investigate synaptic specificity, neuronal remodeling and dendrite morphogenesis The goal of this work is to identify molecular pathways that control these events and to establish the cell biological mechanism of each process. The PI has extensive experience with key approaches used in these studies including *C. elegans* genetics, high-resolution light microscopy, genomic analysis and protein biochemistry. Of particular significance is our leadership in the development of cell-specific expression profiling methods for *C. elegans* (Spencer, 2011, 2014; Taylor, 2021), and their use for the identification of transcription factor targets that regulate synaptic specificity (Von Stetina, 2007), circuit remodeling (Petersen, 2011) and dendrite morphogenesis (Smith, 2013). The PI is actively involved in graduate education in the classroom as well as serving on over 100 PhD and MS committees and mentoring 19 graduate students and 11 postdoctoral fellows in the Miller lab. Graduate students from the Miller lab are postdoctoral fellows (Andrea Cuentas-Condori, Yale; Sierra Palumbos, Penn), in academic positions (Jennifer Wolf, Assoc. Prof., Carlton College; Sarah Petersen, Assoc. Prof., Kenyon College; Laurie Earls, Assist. Prof., Tulane University; Cody Smith, Assoc. Prof., University of Notre Dame; Mallory Hacker, Assist. Prof., Vanderbilt University) or have joined biotech/consulting firms (Kim Lickteig, Takeda Pharmaceuticals; Rebecca Fox, Phosphorous; Rachel Skelton, Leica Biosystems; Siwei He, Boston Consulting Group). The PI has maintained an ongoing role in the Fisk-Vanderbilt Masters-PhD Bridge program by serving on the committees of twelve Fisk University MS students. Five of these students, Erica Tross, Corey Roach, Kai Bracey, Jennifer Quinde and Destane Garrett were accepted into PhD programs at Vanderbilt. In addition, the PI hosted URM student interns for the Vanderbilt Summer Research Program (Amanda Mitchell, 2017) and MSTP Summer Research Program (Isaiah Swan) and mentored a Vanderbilt Academic Pathways postdoctoral fellow (Jamie Stern). The Vanderbilt Academic Pathways program supported postdocs from underrepresented minorities. To enhance my mentoring skills, I attended a workshop at Vanderbilt (April 26, 2019) led by Maura Belliveau, Director of the Center for Diversity and Innovation at the University of Buffalo. I will attend a future presentation of the Culturally Aware Mentoring CIMER workshop at Vanderbilt lead by Drs. Pfund and Byars-Winston from the University of Wisconsin.

Ongoing and recently completed projects:

R01 NS100547 (Hammarlund, Hobert, Miller, Krishnaswamy, Co-PI) 01/01/2023-12/31/2028)
Discovery and analysis of the *C. elegans* neuronal gene expression network (CeNGEN*).*

R01 NS113559 Miller (PI) 05/15/2020 – 04/30/2025
Molecular mechanisms for neuron-specific assembly of electrical synapses

R01 NS106951 Miller (PI) 02/01/2018 – 01/31/2024
Molecular genetics of synaptic plasticity

R01 NS100547 (Hammarlund, Hobert, Miller, Sestan, Co-PI) 09/25/2017 - 07/31/2022
Discovery and analysis of the *C. elegans* neuronal gene expression network (CeNGEN*).*

R21 NS108505 Paschalis, Miller (Co-PI) 04/01/2019 – 03/31/2021
Identification of the transcriptional targets of three conserved regulatory factors necessary for motor neuron subtype function.

R01 NS118078 Paschalis (Univ. Chicago, PI) 06/15/2020 – 03/31/2021
Molecular mechanisms of motor neuron terminal identity

R01 NS079611 (Miller, PI) 06/01/2013 - 05/31/2019
Molecular regulation of dendrite morphogenesis.

1. **Taylor SR**, Santpere G, Weinreb A, Barrett A, Reilly MB, Xu C, Varol E, Oikonomou P, Glenwinkel L, **McWhirter R**, **Poff A**, Basavaraju M, Rafi I, Yemini E, Cook SJ, Abrams A, Vidal B, Cros C, Tavazoie S, Sestan N, Hammarlund M, Hobert O, **Miller DM 3rd**. Molecular topography of an entire nervous system. Cell. 2021 Aug 5;184(16):4329-4347.e23. PubMed Central PMCID: PMC8710130.
2. **Smith CJ, O'Brien T**, Chatzigeorgiou M, **Spencer WC**, **Feingold-Link E**, Husson SJ, Hori S, Mitani S, Gottschalk A, Schafer WR, **Miller DM 3rd**. Sensory neuron fates are distinguished by a transcriptional switch that regulates dendrite branch stabilization. Neuron. 2013 Jul 24;79(2):266-80. PubMed Central PMCID: PMC3795438.
3. **Spencer WC**, Zeller G, **Watson JD,** Henz SR, **Watkins KL**, **McWhirter RD**, **Petersen S**, Sreedharan VT, Widmer C, Jo J, Reinke V, Petrella L, Strome S, **Von Stetina SE**, Katz M, Shaham S, Rätsch G, **Miller DM 3rd**. A spatial and temporal map of *C. elegans* gene expression. Genome Res. 2011 Feb;21(2):325-41. PubMed Central PMCID: PMC3032935.

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2020 - 2020	Reviewer, SYN Study Section, NINDS
2020 - 2020	Reviewer, COVID-19 Study Section, NIAID
2019 - 2019	Reviewer, Special Emphasis Panel, ZNS1 SRB-1(12), NINDS
2015 - 2019	Member, NST-2 Study Section, NINDS
2013 - 2014	Reviewer, NST-2 Study Section, NINDS
2011 - 2013	Reviewer, Special Emphasis Panel, NIH
2007 - 2007	Reviewer, MDCN-K Study Section, NIH
2005 -	Professor, Department of Cell and Developmental Biology, Vanderbilt University, Nashville, TN
2005 -	Editorial Board, genesis: the Journal of Genetics and Development
2004 - 2005	Reviewer, NIF-7 Study Section, NIH
2003 -	Member, Genetics Society of America
1999 -	Member, Society for Neuroscience
1994 - 2005	Associate Professor, Department of Cell and Developmental Biology, Vanderbilt University, Nashville, TN
1990 - 1994	Assistant Research Professor, Department of Cell Biology, Duke University, Durham, NC
1985 - 1985	Visiting Scientist, Laboratory of Molecular Biology, MRC, Cambridge
1984 - 1990	Assistant Professor, Department of Zoology, North Caroline State University, Raleigh, NC
1983 -	Member, American Society for Cell Biology
1983 - 1984	Postdoctoral Fellow, Laboratory of Molecular Biology, MRC, Cambridge
1981 - 1983	Postdoctoral Fellow, Department of Neurology, Baylor College of Medicine, Houston, TX
1978 - 1978	Instructor, Department of Biochemistry, Rice University, Houston, TX

Honors

2015 - 2015	Outstanding Mentor of the Year, Vanderbilt Neuroscience Graduate Program
2013 - 2013	Fellow, AAAS
2012 - 2012	Elaine-Sanders-Bush Award for Excellence in Teaching, Vanderbilt University
1985 - 1985	Travel Grant, Burroughs Wellcome Fund
1983 - 1984	Long Term Fellowship, EMBO
1983 - 1983	Travel Grant, Burroughs Welcome Fund
1980 - 1982	Postdoctoral Fellow, Muscular Dystrophy Association
1973 - 1977	Predoctoral Fellow, Robert Welch Foundation
1973 - 1973	Outstanding Student in Biochemistry, University of Southern Mississippi

C. Contribution to Science

1. **Methods for generating transcriptional profiles of specific *C. elegans* cells.** The Miller laboratory contributed to the first published description of a primary culture system for *C. elegans* embryonic cells (Christensen, 2002). This method has been widely used for a range of applications including cell-specific expression profiling, electrophysiology and biochemical analysis (>230 citations). Beginning with this work, we have sustained a longterm effort to develop innovative approaches to cell-specific profiling and bioinformatic analysis. A series of papers from the Miller lab demonstrated the utility of FACS for isolating embryonic cells for expression profiling and the application of the mRNA tagging method for cataloging expression in specific larval cells (Von Stetina, 2007; Smith, 2010; Smith, 2013). Our paper (Spencer, 2011) demonstrates the value of this strategy for gene discovery and for prediction of gene regulatory mechanisms. The Miller lab generated a large database of cell-specific expression profiles that was critically important for the modENCODE effort to map all *C. elegans* transcripts and for comprehensive descriptions of gene expression mechanisms (Gerstein, 2014). We described the first successful use of FACS to isolate larval *C. elegans* neurons for RNA-Seq analysis (SeqCel) (Spencer, 2014). This work significantly advanced the prospect of a gene expression map to match the unrivaled single cell resolution of the *C. elegans* body plan. On the basis of these results, NINDS funded a multi-investigator project (CeNGEN) involving the Miller lab to accomplish this goal by profiling each of the 118 different neurons classes in the adult *C. elegans* nervous system (Hammarlund, 2018). To achieve this objective, the Miller lab used single cell RNA-Seq to produce gene expression profiles of all known classes of *C. elegans* neurons (Taylor, 2021). Culminating in this work, our decades-long effort has validated powerful techniques that can now be used to profile essentially any specific *C. elegans* cell throughout development. In addition, we have made extensive use of this technology to identify the targets of transcriptional pathways that regulate key developmental processes including synaptic specificity (Von Stetina, 2007; Palumbos, 2021), dendrite morphogenesis (Smith, 2013), synaptic remodeling (Petersen, 2011), axon regeneration (Byrne, 2016), neuronal fate (Lim, 2016) and behavior (Oranth, 2018; Konietzka, 2019). **(Miller lab in bold)**

    a. Hammarlund M, Hobert O, **Miller DM 3rd**, Sestan N. The CeNGEN Project: The Complete Gene Expression Map of an Entire Nervous System. Neuron. 2018 Aug 8;99(3):430-433. PubMed Central PMCID: PMC6576255.
    b. **Spencer WC, McWhirter R, Miller T**, Strasbourger P, Thompson O, Hillier LW, Waterston RH, **Miller DM 3rd**. Isolation of specific neurons from *C. elegans* larvae for gene expression profiling. PLoS One. 2014;9(11):e112102. PubMed Central PMCID: PMC4221280.
    c. Christensen M, Estevez A, Yin X, **Fox R**, Morrison R, **McDonnell M, Gleason C, Miller DM 3rd**, Strange K. A primary culture system for functional analysis of *C. elegans* neurons and muscle cells. Neuron. 2002 Feb 14;33(4):503-14. PubMed PMID: 11856526.

2. **Molecular genetic mechanisms that specify synaptic choice.** Work in the Miller laboratory has advanced understanding of the genetic mechanisms that regulate wiring specificity in the nervous system. A landmark paper (Miller et al, 1992) describes the first report of a transcriptionally-regulated pathway that defines synaptic choice. This work is significant because it demonstrated the explicit role of a genetic program involving the homeodomain transcription factor, UNC-4, in the creation of connections between specific

neuron partners. Notably, UNC-4 controls the specificity of both chemical (neurotransmitter) and electrical (gap junctions). Winnier (1999) reported the first example of a necessary role of the conserved transcriptional co-repressor protein, Groucho, in motor circuit development and presaged the discovery of a similar function in the vertebrate spinal cord. Von Stetina (2007) demonstrated the utility of cell-specific profiling methods for identifying UNC-4-regulated genes and suggested that the homolog of one of these components (CEH-12), the homeodomain transcription factor, HB9, exerts a parallel role in vertebrate motor circuit differentiation. A subsequent paper extended this work to show that unc-4 antagonizes a canonical Wnt signaling pathway to specify the wild-type pattern of connectivity (Schneider, 2012).

a. **Palumbos SD, Skelton R, McWhirter R, Mitchell A, Swann I, Heifner S, Von Stetina S, Miller DM 3rd.** cAMP controls a trafficking mechanism that maintains the neuron specificity and subcellular placement of electrical synapses. Dev Cell. 2021 Dec 6;56(23):3235-3249.e4. PubMed Central PMCID: PMC8665141.
b. **Schneider J, Skelton RL, Von Stetina SE,** Middelkoop TC, van Oudenaarden A, Korswagen HC, **Miller DM 3rd**. UNC-4 antagonizes Wnt signaling to regulate synaptic choice in the *C. elegans* motor circuit. Development. 2012 Jun;139(12):2234-45. PubMed Central PMCID: PMC3357913.
c. **Von Stetina SE, Fox RM, Watkins KL,** Starich TA, Shaw JE, **Miller DM 3rd**. UNC-4 represses CEH-12/HB9 to specify synaptic inputs to VA motor neurons in *C. elegans*. Genes Dev. 2007 Feb 1;21(3):332-46. PubMed Central PMCID: PMC1785118.
d. **Miller DM**, Shen MM, Shamu CE, Bürglin TR, Ruvkun G, **Dubois ML, Ghee M, Wilson L.** *C. elegans unc-4* gene encodes a homeodomain protein that determines the pattern of synaptic input to specific motor neurons. Nature. 1992 Feb 27;355(6363):841-5. PubMed PMID: 1347150.

3. Mechanisms of Synaptic Remodeling: Work from the Miller laboratory offers an unprecedented opportunity to delineate molecular pathways that regulate synaptic plasticity. Neural circuits are actively remodeled during development and in response to injury or disease but the mechanisms that drive these changes are incompletely understood. To address this question, we used a genetic screen to identify at least 19 proteins with conserved vertebrate homologs that direct the remodeling of GABAergic synapses in *C. elegans* (Petersen, 2011). Thus, our approach exploits the ready accessibility of a synaptic plasticity program in *C. elegans* to define a pathway that could also drive circuit remodeling in the brain. Indeed, ongoing work in the Miller lab has shown that one of these proteins, the DEG/ENaC cation channel UNC-8 (Wang, 2013), promotes presynaptic remodeling in a mechanism that depends on neuronal activity (Miller-Fleming, 2016). In recent work, we determined that UNC-8 promotes a Ca^{2+}-dependent endocytic process that recycles presynaptic components for assembly at new connections (Cuentas-Condori et al., 2023). These findings are significant because members of the DEG/ENaC family mediate learning and memory in mammals but the mechanism of this effect is unknown. We have also identified an additional pathway that functions in parallel to UNC-8 to dismantle specific presynaptic components (Miller-Fleming, 2021). Finally, we have shown that a negative regulator of synaptic remodeling, the Immunoglobulin domain (Ig) protein OIG-1, is down-regulated by a transcriptional cascade to unleash the overall synaptic remodeling program (He, 2015).

a. **Andrea Cuentas-Condori, Siqi Chen,** Mia Krout, Kristin Gallik, **John Tipps, Casey Gailey, Leah Flautt,** Janet E. Richmond, **David M. Miller, III** (2023) The Epithelial Na^+ channel UNC-8 promotes an endocytic mechanism that recycles presynaptic components to new boutons in remodeling neurons. Cell Reports 41, 113327. PubMed Central PMCID: PMC10921563
b. **He S, Cuentas-Condori A, Miller DM 3rd.** NATF (Native and Tissue-Specific Fluorescence): A Strategy for Bright, Tissue-Specific GFP Labeling of Native Proteins in *Caenorhabditis elegans*. Genetics. 2019 Jun;212(2):387-395. PubMed Central PMCID: PMC6553825.
c. **Miller-Fleming TW, Petersen SC,** Manning L, Matthewman C, **Gornet M, Beers A**, Hori S, Mitani S, Bianchi L, Richmond J, **Miller DM 3rd**. The DEG/ENaC cation channel protein UNC-8 drives activity-dependent synapse removal in remodeling GABAergic neurons. Elife. 2016 Jul 12;5 PubMed Central PMCID: PMC4980115.
d. **Petersen SC, Watson JD,** Richmond JE, Sarov M, Walthall WW, **Miller DM 3rd**. A transcriptional program promotes remodeling of GABAergic synapses in Caenorhabditis elegans. J Neurosci. 2011 Oct 26;31(43):15362-75. PubMed Central PMCID: PMC3229156.

4. **Nociceptor morphogenesis and dendrite self-avoidance:** Smith (2010) provided the first comprehensive description of the morphogenesis and gene expression signature of the PVD sensory neuron. This work has contributed significantly to the rapid emergence of PVD as a useful model for investigations of dendrite morphogenesis and sensory neuron function (Sundararajan, 2019a). A second paper (Smith, 2012) is important because it provided a new, and unexpected model of dendrite self-avoidance, a widely observed but poorly understood phenomenon. This work showed that a soluble cue, the axon guidance protein, UNC-6/Netrin, mediates self-avoidance in a novel capture and display mechanism involving the canonical axon guidance receptors UNC-40/DCC and UNC-5. We have recently shown that UNC-6/Netrin-mediated self-avoidance depends on a downstream pathway that stimulates actin assembly and depends on myosin motor activity (Sundararajan, 2019b). The strong conservation of these components argues that this mechanism could be employed for self-avoidance in mammals. Thus, our discovery opens the door for the use of *C. elegans* as a model for rapidly advancing our understanding of the basic cell biology of dendrite self-avoidance. An additional paper (Smith, 2013) is significant because it describes an elegant transcriptional mechanism that distinguishes the developmental fates of two different classes of mechanosensory neurons. In addition, this study exploits pioneering cell-specific profiling methods to identify downstream effectors including a member of a conserved class of cell adhesion proteins. This finding is particularly notable because recent work has shown that a surprisingly large number of transcription factors are involved in sensory neuron morphogenesis but few downstream targets are known.

   a. **Sundararajan L, Stern J, Miller DM 3rd.** Mechanisms that regulate morphogenesis of a highly branched neuron in *C. elegans*. Dev Biol. 2019a Jul 1;451(1):53-67. PubMed Central PMCID: PMC7755292.
   b. **Sundararajan L, Smith CJ, Watson JD,** Millis BA, Tyska MJ, **Miller DM 3rd**. Actin assembly and non-muscle myosin activity drive dendrite retraction in an UNC-6/Netrin dependent self-avoidance response. PLoS Genet. 2019b Jun;15(6):e1008228. PubMed Central PMCID: PMC6605669.
   c. **Smith CJ, Watson JD**, VanHoven MK, Colón-Ramos DA, **Miller DM 3rd.** Netrin (UNC-6) mediates dendritic self-avoidance. Nat Neurosci. 2012 Mar 18;15(5):731-7. PubMed Central PMCID: PMC3337961.
   d. **Smith CJ, Watson JD, Spencer WC, O'Brien T,** Cha B, Albeg A, Treinin M, **Miller DM 3rd**. Time-lapse imaging and cell-specific expression profiling reveal dynamic branching and molecular determinants of a multi-dendritic nociceptor in *C. elegans*. Dev Biol. 2010 Sep 1;345(1):18-33. PubMed Central PMCID: PMC2919608.

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