## BIOGRAPHICAL SKETCH

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NAME: David M. Miller

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

POSITION TITLE: Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

| INSTITUTION AND LOCATION | DEGREE *(if applicable)* | Completion Date MM/YYYY | FIELD OF STUDY |
|---|---|---|---|
| University of Southern Mississippi (Hattiesburg MS) | B.S. | 1973 | Biology |
| Rice University (Houston TX) | Ph.D. | 1981 | Biochemistry |
| Baylor College of Medicine (Houston TX) | Postdoc | 1983 | Muscle assembly<br>Mentor: *H.F. Epstein, MD* |
| MRC-Laboratory of Molecular Biology (Cambridge UK) | Postdoc | 1984 | Myogenesis<br>Mentor: *S. Brenner, MD* |

**Please refer to the Biographical Sketch sample in order to complete sections A, B, C, and D of the Biographical Sketch.**

### A. PERSONAL STATEMENT

The Miller lab uses the model organism *C. elegans* to investigate neural development and function. Research topics include mechanisms of synaptic specificity, neuronal plasticity, sensory neuron morphogenesis and neurodegeneration. 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 acquired extensive experience with key approaches used in these studies including *C. elegans* genetics, high-resolution light microscopy, genomic analysis and protein biochemistry.


1. WC Spencer*, G Zeller*, JD Watson, SR Henz, KL Watkins, RD McWhirter, SC Petersen, VT Sreedharan, C Widmer, J Jo, V Reinke, L Petrella, S Strome, S Von Stetina, M Katz, S Shaham, G Raetsch, DM Miller, III (2011). A spatial and temporal map of *C. elegans* gene expression. *Genome Research 21: 325-341.* *Equal contributions. PMID: 21177967.
2. WC Spencer, R McWhirter, T Miller, P Strasbourger, O Thompson, LW Hillier, RH Waterston, DM Miller, III (2014) Isolation of specific neurons from *C. elegans* larvae for gene expression profiling. PLOS ONE 9, e112102. PMCID: PMC4221280.
3. *SE Von Stetina, *RM Fox, KL Watkins, TA Starich, JE Shaw, and DM Miller III (2007) UNC-4 represses CEH-12/HB9 to specify synaptic inputs to VA motor neurons in *C. elegans. Genes Dev* 21: 332-346. *Equal contributions. PMCID: PMC1785118.
4. SC Petersen, JD Watson, JE Richmond, M Sarov, WW Walthall, DM Miller, III (2011). A transcriptional program promotes remodeling of GABAergic synapses in *Caenorhabditis elegans*. *J. Neuroscience 31, 15362–15375*. PMCID: PMC3229156.
5. *CJ Smith, *T O'Brien, M Chatzigeorgiou, WC Spencer, E Feingold-Link, SJ Husson, S Hori, S Mitani, A Gottschalk, WR Schafer, DM Miller, III (2013). Sensory neuron fates are distinguished by a transcriptional switch that regulates dendrite branch stabilization. *Neuron* 79, 266-280. PMID: 23889932. *These authors contributed equally.


### B. POSITIONS AND HONORS

**Positions and Employment**

| | |
|---|---|
| 1978 | Instructor, Department of Biochemistry, Rice University, Houston, TX |
| 1980-1983 | Postdoctoral Fellow, Dept of Neurology, Baylor College of Med., Houston, TX (HF Epstein) |
| 1983-84 & S85 | Visiting Scientist, MRC Laboratory of Molecular Biology, Cambridge, UK (S. Brenner) |
| 1984-1990 | Assistant Professor of Zoology and Genetics, Department of Zoology, North Carolina State University, Raleigh, NC |
| 1990-1994 | Assistant Research Professor, Department of Cell Biology, Duke University, Durham, NC |
| 1994-2005 | Associate Professor, Department of Cell Biology and Developmental Biology, Vanderbilt University, Nashville, TN |
| 2005-present | Professor, Department of Cell Biology and Developmental Biology, Vanderbilt University, Nashville, TN |

**Other Experience and Professional Memberships**

| | |
|---|---|
| 1983 – 2002 | American Society for Cell Biology |
| 1994- | Society for Developmental Biology |
| 1998- | American Association for the Advancement of Science |
| 1999- | Society for Neuroscience |
| 2003- | Genetics Society of America |
| 2005- | Editorial Board: *genesis: the Journal of Genetics and Development* |
| 2004-2005 | Ad Hoc reviewer for NIH NIF-7 Study Section |
| 2007 | Ad Hoc reviewer for MDCN-K Study Section |
| 2011-2013 | NIH Special Emphasis Panel (SEP) reviewer |
| 2015- | Member, NIH NST-2 Study Section |

**Honors**

| | |
|---|---|
| 1973 | Phi Kappa Phi: Outstanding Student in Biochemistry, University of Southern Mississippi |
| 1973-1977 | Robert Welch Foundation Fellow, Rice University |
| 1980-1982 | Muscular Dystrophy Association Postdoctoral Fellow |
| 1983,1985 | Burroughs Wellcome Fund Travel Grant |
| 1984 | EMBO Long Term Fellowship |
| 1985 | Burroughs Wellcome Fund Travel Grant |
| 2012 | Elaine Sanders-Bush Award for Excellence in Teaching (For Mentoring graduate students in a research setting), Vanderbilt University |
| 2013 | AAAS Fellow |

**C. Contributions to Science**

**1. Molecular genetic mechanisms that specify synaptic choice.** Work in the Miler 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 for defining 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. **Winnier et al. (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 et al. (2007)** demonstrated the utility of cell-specific profiling methods (see below) for identifying UNC-4-regulated genes and suggested that the homolog of one of these components, the homeodomain transcription factor, HB9, exercises a parallel role in vertebrate motor circuit differentiation. A recent paper extended this work to show that unc-4 antagonizes a canonical Wnt signaling pathway to specify the wild type pattern of connectivity. Ongoing studies exploit new methods for cell-specific profiling developed in the Miller lab (see below) to identify additional downstream effectors of the UNC-4-regulated pathway. (**Miller lab members shown in bold**)

**DM Miller, III,** MM Shen, CE Shamu, TR Bürglin, G Ruvkun, **ML Dubois, M Ghee**, and **L Wilson**. (1992) *C. elegans unc-4* gene encodes a homeodomain protein that determines the pattern of synaptic input to specific motor neurons. *Nature 355, 841-845.* (142 citations)

*AR Winnier , *JY-J Meir, JM Ross, T Ishihara, I Katsura, N Tavernarakis, M Driscoll, M, and DM Miller, III. (1999) UNC-4/UNC-37-dependent repression of motor neuron-specific genes controls synaptic choice in *Caenorhabditis elegans*. Genes and Dev 13, 2774-2786. *Equal contributions.

*SE Von Stetina, *RM Fox, KL Watkins, TA Starich, JE Shaw, and DM Miller III (2007) UNC-4 represses CEH-12/HB9 to specify synaptic inputs to VA motor neurons in *C. elegans.* Genes Dev 21: 332-346. *Equal contributions. PMCID: PMC1785118.

JD Schneider*, RL Skelton*, SE Von Stetina*, A van Oudenaarden, T Middelkoop, H. Korswagen, DM Miller, III (2012). UNC-4 antagonizes Wnt signaling to regulate synaptic choice in the *C. elegans* motor circuit. Development 139, 2234-2245. PMCID: PM3357913. *These authors contributed equally.

**2. 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 et al., 2002**). This method has been widely utilized for a range of applications including cell-specific expression profiling, electrophysiology and biochemical analysis (>180 citations). Beginning with this work, we have sustained an ongoing effort to develop innovative approaches to cell-specific profiling and bioinformatics analysis. A series of papers published 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 et al., 2007, Smith et al., 2010, Smith et al, 2013**). A recent paper **(Spencer et al., 2012)** 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 were critically important for the modENCODE effort to map all *C. elegans* transcripts and for comprehensive descriptions of gene expression mechanisms (**Gerstein et al., 2014**). Finally, in a paper published last year, we described the first successful use of FACS to isolate larval *C. elegans* neurons for RNA-Seq analysis **(Spencer et al., 2014).** Culminating in this work, our decade-long effort has validated powerful techniques that can now be used to profile essentially any given *C. elegans* cell throughout development. This work significantly advances the prospect of a gene expression map to match the unrivaled single cell resolution of the developmental program that defines the *C. elegans* body plan. In addition, we have made extensive use of this technology to identify the targets of transcription factors that regulate key developmental processes including synaptic specificity, dendrite morphogenesis and synaptic remodeling (see below).

M Christensen, A Estevez, X Yin, R Fox, R Morrison, M McDonnell, C Gleason, DM Miller, III and K Strange. (2002) A primary culture system for functional analysis of *C. elegans* neurons and muscle cells. Neuron 33, 503-514.

WC Spencer*, G Zeller*, JD Watson, SR Henz, KL Watkins, RD McWhirter, SC Petersen, VT Sreedharan, C Widmer, J Jo, V Reinke, L Petrella, S Strome, S Von Stetina, M Katz, S Shaham, G Raetsch, DM Miller, III (2011). A spatial and temporal map of *C. elegans* gene expression. Genome Research 21: 325-341. *Equal contributions. PMID: 21177967.

MB Gerstein + modENCODE Consortium (including DM Miller, III, WC Spencer) (2014) Comparative Analysis of the Transcriptome across Distant Species. Nature 512, 445-448. PMID: 25164755.

WC Spencer, R McWhirter, T Miller, P Strasbourger, O Thompson, LW Hillier, RH Waterston, DM Miller, III (2014) Isolation of specific neurons from *C. elegans* larvae for gene expression profiling. PLOS ONE 9, e112102. PMCID: PMC4221280.

3. Nociceptor morphogenesis and dendrite self-avoidance: Publications from the Miller lab have lead the field in the use of *C. elegans* for studies of nociceptor development and function. CJ Smith et al., (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 the PVD neuron as a useful model for investigations of dendrite morphogenesis and sensory neuron function. A second paper (Smith et al., 2012) is important because it provides a new, and unexpected model of dendrite self-avoidance, a widely observed but poorly understood phenomenon. This work showed that the soluble cue, the axon guidance protein, UNC-6/Netrin, mediates self-avoidance in a novel capture and display mechanism involving the canonical receptors UNC-40/DCC and UNC-5. The strong conservation of these components argues that this mechanism is likely also employed for self-avoidance in mammals. Thus, this discovery opens the door for the use of *C. elegans* as a model for rapidly advancing our understanding of the basic cell biology of the dendrite self-avoidance response. A recent paper, (Smith et al., 2013) is significant because it describes an elegant transcriptional mechanism that distinguishes the developmental fates of two different classes of mechanosensory neurons. This work uncovered parallel roles for a transcription factor (aryl hydrocarbon receptor/spineless) in the specification of dendrite morphology in nematodes and insects and therefore argues that this transcription

factor is similarly employed in mammals. In addition, this study exploits pioneering cell-specific profiling methods from the Miller lab to identify downstream effectors in this pathway 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.


*__CJ Smith,__ *__JD Watson__, __WC Spencer__, T __O'Brien__, B Cha, A Albeg, M Treinin, __DM Miller, III__ (2010) Time-lapse imaging and cell-specific expression profiling reveal dynamic branching and molecular determinants of a multi-dendritic nociceptor in *C. elegans*. *Developmental Biol. 345, 18-33.* PMID: 20537990. *Equal contributions. Cover Art.

__CJ Smith, JD Watson,__ MK Van Hoven, DA Colon-Ramos, __DM Miller, III__. (2012) Netrin (UNC-6) mediates dendritic self-avoidance. *Nature Neuroscience* 15, 731-737. PMID: 22426253. Recommended by Faculty of 1000.

*__CJ Smith, *T O'Brien,__ M Chatzigeorgiou, __WC Spencer, E Feingold-Link__, SJ Husson, S Hori, S Mitani, A Gottschalk, WR Schafer, __DM Miller, III__ (2013). Sensory neuron fates are distinguished by a transcriptional switch that regulates dendrite branch stabilization. *Neuron* 79, 266-280. PMID: 23889932. *These authors contributed equally.


**4. Mechanisms of Synaptic Remodeling:** New work from the Miller laboratory offers an unprecedented opportunity to delineate a complex mechanism of synaptic plasticity. Neural circuits are actively remodeled during development and in response to injury or disease but the molecular mechanisms that drive these changes are poorly defined. A recent paper (**Petersen et al., 2011**) used a novel genetic screen to identify at least 19 proteins with conserved vertebrate homologs that direct the remodeling of GABAergic synapses in *C. elegans*. Thus, this work holds the promise of exploiting the ready accessibility of a synaptic plasticity program in *C. elegans* to define a pathway that could also drive circuit remodeling in the human brain. Indeed, ongoing work in the Miller lab has shown that one of these proteins, the DEG/ENaC cation channel UNC-8, (**Wang et al, 2013**) is required for presynaptic remodeling in a pathway that depends on neuron activity. This finding is significant because members of the DEG/ENaC family are known to mediate learning and memory in mammals but the mechanism of this effect is unknown (**Miller et al, in preparation**). Finally, we have recently discovered that the secreted Immunoglobulin domain (Ig) Protein OIG-1 regulates postsynaptic remodeling in the GABA circuit. This finding is significant because Ig domain proteins are known to be highly expressed in the nervous system but have not been previously shown to control synaptic plasticity (**He et al., in revision**).


SC Petersen, JD Watson, JE Richmond, M Sarov, WW Walthall, DM Miller, III (2011). A transcriptional program promotes remodeling of GABAergic synapses in *Caenorhabditis elegans*. *J. Neuroscience 31, 15362–15375*. PMID: 22031882.

Wang, L Han, C Matthewman, __T Miller__, __DM Miller, III,__ L Bianchi (2013) Neurotoxic *unc-8* mutants encode constitutively active DEG/ENaC channels that are blocked by divalent cations. *J. Gen. Physiology* 142, 157-169. PMCID: PMC3727304.


**Complete List of Published Work in My PubMed Bibliography:**

http://www.ncbi.nlm.nih.gov/pubmed/?term=(Miller+DM+AND+gerstein+AND+agarwal+AND+waterston)+OR+(Miller+DM+3rd)+OR+(Miller+AND+unc-4)+OR+(Miller+DM+AND+vanderbilt+AND+elegans)

## D. RESEARCH SUPPORT

**ACTIVE**

1R01 NS079611-01A1 Miller (PI) 06/01/2013-05/31/2018
*Molecular regulation of dendrite morphogenesis.*
Molecular genetic approaches to identify determinants of dendrite branching and self-avoidance.
Role: PI

1R01 NS081259-01A1 Miller (PI) 06/01/2013-04/30/2017
*Molecular determinants of synaptic plasticity.*
The role of a DEG/ENaC cation channel protein, UNC-8, in an activity-dependent mechanism of synaptic remodeling.
Role: PI

1R21 NS66882 Hammarlund (PI) 09/01/2013 – 08/31/2015

*Identification of transcriptional targets of the DLK-1 axon regeneration pathway.*
Cell-specific profiling and genetic analysis to identify DLK-1-regulated genes that promote neuron regeneration.
Role: Co-PI

**COMPLETED (last 3 years)**

5R01 NS026115-21 Miller (PI) 08/15/2008-06/30/2013
*Molecular Genetics of Neural Specificity*
The main goal of this project is to identify the *unc-4* pathway genes that regulate synaptic specificity.
Role: PI

5 U01 HD004263-04 Waterston (PI) 04/01/2007-03/31/2013
*Global Identification of Transcribed Elements in the C. elegans Genome*
The goal of this project was to identify all transcripts expressed by the *C. elegans* genome.
Role: PI of U01 project

IDEAS Pilot Grant (Vanderbilt) Miller (PI) 07/01/2010 – 06/30/2012
*A genetic screen in C. elegans to identify the in vivo target of the potent Wnt inhibitor, pyrvinium.*
A genetic screen and next generation DNA sequencing to identify the target of a novel drug now in clinical trials for treatment of colon cancer.
Role: Miller (PI), E. Lee (Co-PI)

5R21 NS066882-02 Miller (PI) 05/01/2009 – 04/30/2012
*Identification of transcriptional determinants of dendritic patterning*
This project used cell-specific microarray profiling to identify the targets of transcription factors that control morphogenesis of a nociceptive neuron in *C. elegans*
Role: PI