BIOGRAPHICAL SKETCH

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NAME: McConnell, Michael

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

POSITION TITLE: Investigator

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)	END DATE MM/YYYY	FIELD OF STUDY
North Carolina State University, Raleigh, NC	B.S.	05/1992	Zoology, Genetics minor
Virginia Tech, Blacksburg, VA	M.S.	09/1999	Cancer Immunology
University of California San Diego, La Jolla, CA	Ph.D.	09/2004	Developmental Neuroscience
Harvard Medical School, Boston, MA	Postdoctoral Fellow	09/2007	Systems Neuroscience
Stanford University, Stanford, CA	Postdoctoral Fellow	12/2008	Systems Neuroscience (cont'd)
Salk Institute for Biological Studies, La Jolla, CA	Junior Fellow	07/2012	Brain Somatic Mosaicism

A. Personal Statement

The long-term goal of my research program is to determine how brain somatic mosaicism contributes to neuronal diversity and neural circuit function, in both health and disease. My laboratory pioneered single cell genome analysis of primary human neurons, human induced pluripotent stem cell (hiPSC)-derived neurons, and, recently, mouse models to study the cause and consequence of brain somatic mosaicism. We found that mosaic megabase-scale copy number variants (CNVs) are a major mediator of neuron-to-neuron genomic variation in human brains and that mosaicism is also brought about during hiPSC-based neurogenesis (1). This work was named the #4 Neuroscience Discovery of 2013 by NIMH. NIMH formed the Brain Somatic Mosaicism Network (BSMN), and we were awarded a U01 in the first round of BSMN funding (2). We have developed improved methods for single cell whole genome amplification and neuronal CNV detection (3). Moreover, we recently discovered that CNVs mark some neurons for selective vulnerability to aging-related atrophy (4).

Alongside single cell genome analysis of primary tissue in schizophrenic, aged, and Alzheimer's individuals, my laboratory develops hiPSC-based models of neurological disease. One of these is a rare childhood epilepsy and movement disorder resulting from mutations in *GNAO1*. Now at LIBD, we are studying rare donors with Alzheimer's disease pathology but without clinical dementia. The overarching aim of current work is to identify neuronal resilience mechanisms using single cell analysis of neuronal genomes.

1. McConnell MJ, Lindberg MR, Brennand KJ, Piper JC, Voet T, Cowing-Zitron C, Shumilina S, Lasken RS, Vermeesch JR, Hall IM, Gage FH. (2013). Mosaic copy number variation in human neurons. *Science*. Nov 1;342(6158):632-7. PMID: 24179226; PMCID: PMC3975283.

2. McConnell MJ, Moran JV, Abyzov A, Akbarian S, Bae T, Cortes-Ciriano I, Erwin JA, Fasching L, Flasch DA, Freed D, Ganz J, Jaffe AE, Kwan KY, Kwon M, Lodato MA, Mills RE, Paquola ACM, Rodin RE, Rosenbluh C, Sestan N, Sherman MA, Shin JH, Song S, Straub RE, Thorpe J, Weinberger DR, Urban AE, Zhou B, Gage FH, Lehner T, Senthil G, Walsh CA, Chess A, Courchesne E, Gleeson JG, Kidd JM, Park PJ, Pevsner J, Vaccarino FM. (2017). Intersection of diverse neuronal genomes and neuropsychiatric disease: The Brain Somatic Mosaicism Network. *Science* Apr 28;356(6336). PMID: 28450582; PMCID: PMC5558435.

3. Burbulis IE, Wierman MB, Wolpert MJ, Haakenson MF, Lopes MB, Schiff D, Hicks J, Loe J, Ratan A, McConnell MJ. (2018). Improved molecular karyotyping in glioblastoma. *Mutation Research*. Jul 8;811:16-26. doi: 10.1016/j.mrfmmm.2018.06.002. [Epub ahead of print] PubMed PMID: 30055482.

4. Chronister WD, Burbulis IE, Wierman MB, Wolpert MJ, Haakenson MF, Smith ACB, Kleinman JE, Hyde TM, Weinberger DR, Bekiranov S, McConnell, MJ. Neurons with Complex Karyotypes Are Rare in Aged Human Neocortex. *Cell Reports* (2019) Jan 22;26(4):825-835.e7. doi: 10.1016/j.celrep.2018.12.107. PubMed PMID: 30673605.

B. Positions and Honors

Positions and Employment

1991 - 1992	Co-op Student / Summer Intern, Glaxo, Inc., Research Triangle Park, NC
1993 - 1995	Assistant Scientist, Macronex, Inc., Morrisville, NC
1995 - 1995	Associate Biochemist, Sphinx Pharmaceuticals, (Eli Lilly), Durham, NC
1995 - 1996	Research Associate, IDUN Pharmaceuticals, La Jolla, CA
1997 - 1999	Graduate Teaching Assistant / PhD Candidate, Virginia Tech, Blacksburg, VA
1998 - 1999	Biology Instructor, Southwest Virginia Upward Bound Program, Blacksburg, VA
1999 - 2000	Research Assistant, University of California San Diego, La Jolla, CA
2000 - 2004	PhD Student / Candidate, University of California San Diego, La Jolla, CA
2001 - 2003	UCSD PhD Student / Candidate, Salk Institute for Biological Studies, La Jolla, CA
2003 - 2004	UCSD PhD Candidate, The Scripps Research Institute, La Jolla, CA
2004 - 2007	Postdoctoral Fellow, Harvard Medical School, Boston, MA
2007 - 2008	Postdoctoral Fellow, Stanford University, Stanford, CA
2009 - 2012	Crick-Jacobs Junior Fellow, Salk Institute for Biological Studies, La Jolla, CA
2012 - 2020	Assistant Professor, University of Virginia School of Medicine, Charlottesville, VA
2015 - 2020	Faculty Co-Director, University of Virginia School of Medicine, Stem Cell Core Facility, Charlottesville, VA
2015 –	Faculty Co-Director, Single Cell Analysis Course, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY
2019 –	Investigator, Lieber Institute for Brain Development, Baltimore, MD

Other Experience and Professional Memberships

2000 -	Member, Society for Neuroscience
2003	Selected Participant, Santa Fe Institute, Complex Systems Summer School
2006	Selected Participant, Weizmann Institute, Kahn-Minerva Winter School on Design Principles of Biological Systems
2008 -	Member, International Society for Stem Cell Research
2012 -	Ad hoc Grant Review: INSERM (4), Wellcome Trust UK (202903/Z/16/Z), Israel Science Foundation, NWO Netherlands, Helmholtz Young Investigators Germany.
2013 -	Ad hoc Reviewer:, *Nature Methods, Nature Biotechnology, Nature Communications, Nature Neuroscience, Genome Research, Genome Biology, eLife, Nature Protocols, PLoS One, PLos Biology, Cerebellum, Cell and Tissue Research, BMC Genomics, BMC Medical Genomics, Acta Neuropathalogica, Nucleic Acids Research, Epilepsy Research, Schizophrenia Bulletin*
2013 - 2015	Co-organizer, Stem Cells and Regeneration Seminar Series, UVa School of Medicine
2013 - 2014	Faculty Advisor, UVa Biotechnology Training Grant, Student Seminar Series
2014 -	NIH/NIMH study sections: ZMH1-ERB-M(06), ZRG1-MDCN-P(57), ZMH1-ERB-C(03)1, MH1-ERB-M(04)S, ZRG1 MDCN-P(57), ZMH1-ERB-C(02), ZRG1 MDCN-P(57)
2014	Invited Participant, Gliobastoma Think Tank II
2015 -	Editorial Board Member, *Mutation Research*
2015 - 2017	Councilor, Central Virginia Chapter, Society for Neuroscience
2015	Invited Participant, Cold Spring Harbor Banbury Meeting, "Creating Patient-specific Neural

Cells for the In Vitro Study of Brain Disorders"
2015 – 2017 Faculty Advisor, MINDS student seminar series, UVa Neuroscience Graduate Program
2017 - Editorial Board Member, *Molecular Cytogenetics*
2018 – 2019 President, Central Virginia Chapter, Society for Neuroscience

Honors

1986 Eagle Scout, Boy Scouts of America
1992 Outstanding Undergraduate Achievement, Microbiology Dept., North Carolina State University
1993 Outstanding Performance, Macronex, Inc.
1994 Outstanding Performance, Macronex, Inc.
2007 Crick-Jacobs Junior Fellowship, Salk Institute for Biological Studies
2010 NIH Loan Repayment Program, NIMH
2014 Top 10 Discoveries in Neuroscience for 2013, NIMH

C. Contribution to Science

Publication History:
https://www.ncbi.nlm.nih.gov/sites/myncbi/michael.mcconnell.1/bibliography/43182060/public/?sort=date&direction=descending

1. **Discovery of Brain Somatic Mosaicism:** The hypothesis that somatic gene rearrangement may diversify neuronal genomes had persisted for decades despite only indirect support. My PhD dissertation provided the first direct evidence of neuron-to-neuron genomic diversity in the cerebral cortex; we found that ~33% of neural progenitor cells (NPCs) were aneuploid, and that some of these aneuploid NPCs survived development (a) and were functionally integrated into mature neural circuits (c). I also showed that genetic deficits in DNA damage signaling and repair proteins (Atm, p53, Ku80) can elevate levels of aneuploidy and chromosome translocations in NPCs and in the mature cerebral cortex (b). Later, as a Crick-Jacobs Junior Fellow, I discovered that somatic duplications and deletions (i.e. CNVs) are prevalent (~10-40%) in the human cerebral cortex (d). This study, ranked the #4 Neuroscience Discovery of 2013 by NIMH, also showed that hiPSC-based neurogenesis is a tractable model system for the study of brain somatic mosaicism.

a. Rehen SK[1], McConnell MJ[1], Kaushal D[1], Kingsbury MA, Yang AH, Chun J. Chromosomal variation in neurons of the developing and adult mammalian nervous system. (2001) *Proc Natl Acad Sci U S A.* Nov 6;98(23):13361-6. PMID: 11698687; PMCID: PMC60876.

b. McConnell MJ, Kaushal D, Yang AH, Kingsbury MA, Rehen SK, Treuner K, Helton R, Annas EG, Chun J, Barlow C. Failed clearance of aneuploid embryonic neural progenitor cells leads to excess aneuploidy in the Atm-deficient but not the Trp53-deficient adult cerebral cortex. (2004). *J Neurosci*. Sep 15;24(37):8090-6. PMID: 15371510.

c. Kingsbury MA, Friedman B, McConnell MJ, Rehen SK, Yang AH, Kaushal D, Chun J. Aneuploid neurons are functionally active and integrated into brain circuitry. (2005). *Proc Natl Acad Sci U S A.* Apr 26;102(17):6143-7. PMID: 15837924; PMCID: PMC1087909.

d. McConnell MJ, Lindberg MR, Brennand KJ, Piper JC, Voet T, Cowing-Zitron C, Shumilina S, Lasken RS, Vermeesch JR, Hall IM, Gage FH. (2013). Mosaic copy number variation in human neurons. *Science*. Nov 1;342(6158):632-7. PMID: 24179226; PMCID: PMC3975283.

2. **Single Cell Analysis of Neurons:** Single cell genome analysis was named "Method of the Year" by Nature Methods in 2014, my paper (citation d, contribution 1) was featured in this article. We were the first to show that relevant transcriptome information can also be obtained from single neuronal nuclei (b, c). We extended this work to show that nuclei provide a more robust representation of cell state than intact cells (a). I have been a selected talk, invited speaker, or session chair at Cold Spring Harbor meetings on Single Cell Analysis, and now Co-Direct the Cold Spring Harbor Summer Course on Single Cell Analysis.

a. Lacar B, Linker SB, Jaeger BN, Krishnaswami S, Barron J, Kelder M, Parylak S, Paquola A, Venepally P, Novotny M, O'Connor C, Fitzpatrick C, Erwin J, Hsu JY, Husband D, McConnell MJ, Lasken R, Gage FH. Nuclear RNA-seq of single neurons reveals molecular signatures of activation. (2016). *Nat Commun.* Apr 19;7:11022. PMID: 27090946; PMCID: PMC4838832.

b. Krishnaswami SR, Grindberg RV, Novotny M, Venepally P, Lacar B, Bhutani K, Linker SB, Pham S, Erwin JA, Miller JA, Hodge R, McCarthy JK, Kelder M, McCorrison J, Aevermann BD, Fuertes FD,

Scheuermann RH, Lee J, Lein ES, Schork N, McConnell MJ, Gage FH, Lasken RS. Using single nuclei for RNA-seq to capture the transcriptome of postmortem neurons. (2016). *Nat Protoc*. Mar;11(3):499-524. PMID: 26890679; PMCID: PMC4941947.

c. Grindberg RV, Yee-Greenbaum JL[2], McConnell MJ[2], Novotny M, O'Shaughnessy AL, Lambert GM, Araúzo-Bravo MJ, Lee J, Fishman M, Robbins GE, Lin X, Venepally P, Badger JH, Galbraith DW, Gage FH, Lasken RS. (2013). RNA-sequencing from single nuclei. *Proc Natl Acad Sci U S A*. Dec 3;110(49):19802-7. PMID: 24248345; PMCID: PMC3856806.

3. **Class I Major Histocompatibility Complex (MHCI) in the Brain:** Contrary to the dogma that MHCI is not expressed by neurons, Carla Shatz's lab showed that MHCI expression is regulated by neuronal activity and mediates restrictive aspects of synaptic plasticity. I showed that genetic deficits in classical MHCI genes, H2-Kb and H2-Db (KbDb-/-), lead to altered synaptic transmission at climbing fibre to Purkinje cell synapses and IMPROVED motor learning in KbDb-/- mice (c). We also showed exuberant ocular dominance plasticity in KbDb-/- mice (b), and found roles for MHCI proteins in ALS (a). I continue to be interested in testing the hypothesis that MHCI complexes convey neuron-to-neuron genomic differences via differential peptide presentation in a subset of neurons.

a. Song S, Miranda CJ, Braun L, Meyer K, Frakes AE, Ferraiuolo L, Likhite S, Bevan AK, Foust KD, McConnell MJ, Walker CM, Kaspar BK. Major histocompatibility complex class I molecules protect motor neurons from astrocyte-induced toxicity in amyotrophic lateral sclerosis. Nat Med. 2016 Apr;22(4):397-403. PubMed PMID: 26928464; PubMed Central PMCID: PMC4823173.

b. Datwani A, McConnell MJ, Kanold PO, Micheva KD, Busse B, Shamloo M, Smith SJ, Shatz CJ. Classical MHCI molecules regulate retinogeniculate refinement and limit ocular dominance plasticity. Neuron. 2009 Nov 25;64(4):463-70. PubMed PMID: 19945389; PubMed Central PMCID: PMC2787480.

c. McConnell MJ, Huang YH, Datwani A, Shatz CJ. H2-K(b) and H2-D(b) regulate cerebellar long-term depression and limit motor learning. Proc Natl Acad Sci U S A. 2009 Apr 21;106(16):6784-9. PubMed PMID: 19346486; PubMed Central PMCID: PMC2672503.

4. **NPC Death during Cerebral Cortical Development:** Brain somatic mosaicism is the net result of at least two processes: 1) the generation and 2) the survival of NPCs with variant genomes. Although high levels (~50%) of neuronal cell death are known to occur before or during the critical period, existing mathematical models of cerebral cortical development disregarded NPC death despite existing data. I developed quantitative mathematical models which showed that high levels of NPC death (~30 - 50%) were required for normal cerebral cortical development (a). We went on from this work to develop branching process models of NPC fate decisions that establish a quantitative framework for the development of brain somatic mosaicism (b).

a. McConnell MJ, MacMillan HR, Chun J. Mathematical modeling supports substantial mouse neural progenitor cell death. Neural Dev. 2009 Jul 14;4:28. PubMed PMID: 19602274; PubMed Central PMCID: PMC2729736.

b. MacMillan HR, McConnell MJ. Seeing beyond the average cell: branching process models of cell proliferation, differentiation, and death during mouse brain development. Theory Biosci. 2011 Mar;130(1):31-43. PubMed PMID: 20824512.

D. Additional Information: Research Support

Active Research Support

Catalyst Award, Human Longevity Global Grand Challenge
NAM McConnell, Michael J. (PI) 11/01/20-10/30/21
Resilient Brains: New insights for healthy brain aging. This award enables genomic and transcriptomic analysis of 30 asymptomatic Alzheimer's disease brains from the LIBD brain repository toward establishing an hiPSC-based platform for

Completed Research Support

U01 MH106882 NIH/NIMH Gage, Fred H. (PI) 07/01/15 – 01/31/21
Schizophrenia Genetics and Brain Mosaicism. The overarching goal of this project is to determine if brain somatic mosaicism contributes to the genetic risk architecture of schizophrenia. My laboratories role in this

project is to identify and interpret single cell CNVs (in frontal cortex and in hippocampus) in 20 schizophrenic individuals and 20 neurotypic individuals.
Role: Co-Investigator

R444HG009467-02 SBIR/NHGRI Gebhart, Stephen (PI) 04/01/19 – 06/01/20
High throughput CRISPR/Cas9 cell line generation using the CellRaft Array. This phase II SBIR aims, in part, to demonstrate utility of the CellRaft AIR Technology (Cell Microsystems) for rapid identification and isolation of genome-edited hiPSC lines. The McConnell lab, with the UVA Stem Cell Core Facility, will perform these experiments.
Role: Collaborator

1R56AG058663-01 NIH/NIA McConnell, Michael J. (Co-PI) 09/30/18 – 08/31/19
Transcription-associated DNA damage and neurodegeneration. This multi-PI R56 (with Mark Zylka (UNC)) was awarded to our initial R01 submission. We presented preliminary data that *Top1* cKO neurons have large megabase-scale somatic mutations (deletions, duplications and chromosome loss/gain), which provides a mouse model to test our hypothesis that neurons with complex karyotypes may be selectively vulnerable to aging-related atrophy (Chronister, *et al.* 2018. bioRxiv). This finding will be extended to additional ages and treatments here.

U01 MH106882-04S1 NIH/NIMH Gage, Fred H. (PI) 07/23/18 – 06/30/19
*Schizophrenia Genetics and Brain Somatic Mosaicism (*Computational Supplement). This is a supplemental award made to the UVA Consortium Site on 5U01MH106882-04. The goal of the supplement is to compare classical machine learning models developed in 03S1 to their application on the IBM quantum computer.
Role: Co-Investigator

W81XWH-12-1-0531 DOD/CDMRP/ERP/IDA Dulla, Chris (PI) 09/30/17 – 09/29/21
Preventing PTE Using Inhibitors of Glycolysis: Cell-type Specific Approaches to Maintaining Inhibitory Cortical Networks This projects examines how glycolytic systems are affected by TBI and whether they may be therapeutic targets of interest. My role is to assist and advise with single nuclei transcriptome analysis.
Role: Collaborator

R21 NS098009-01A1 NIH/NINDS Dulla, Chris (PI) 02/01/17 – 1/31/19
Preserving Inhibitory Cortical Networks Following TBI: Attenuating Excitation Using Inhibitors of Glycolysis
We propose to manipulate glycolysis, a source of neuronal energy supply, in order to attenuate behavioral and cognitive losses, as well as post-traumatic epilepsy, after TBI. We will specifically determine if inhibiting glycolysis can restore normal synaptic communication following TBI in order to reduce associated pathology. My role is to assist and advise with single nuclei transcriptome analysis.
Role: Collaborator

Owens Philanthropic Fund McConnell, Michael J. (PI) 08/01/17 – 07/30/19
Brain Somatic Mosaicism in Mouse Models of Alzheimer's Disease. The goal of this project is to establish mouse models of brain somatic mosaicism, including a Tau transgenic mouse line.

Bow Foundation McConnell, Michael J. (PI) 10/01/17 – 09/30/19
Pluripotent stem cell-based models of GNAO1 mutations. GNAO1 mutations occur in a rare disease that presents as either a movement disorder or epilepsy. We are reprogramming two cohorts (patient and both parents), one with movement disorder and one with epilepsy to determine the phenotype of hiPSC-derived neurons with GNAO1 mutations.

U01 MH106882-03S1 NIH/NIMH Gage, Fred H. (PI) 07/10/17 – 07/09/18
*Schizophrenia Genetics and Brain Somatic Mosaicism (*Computational Supplement). This is a supplemental award made to the UVA Consortium Site on 5U01MH106882-03. The goal of the supplement is to train and test machine learning models that cluster as well as predict SZD and control samples from CNV and phenotype data, and to determine CNV gene enrichments.
Role: Co-Investigator