BIOGRAPHICAL SKETCH

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NAME: Niswander, Lee Ann

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

POSITION TITLE: Distinguished Professor, Dept of Molecular, Cellular and Developmental Biology

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 Colorado Boulder, CO	B.A.	05/1980	Chemistry
Univ. of Colorado, Health Sciences Center, Denver	M.S.	05/1985	Biochem. & Genetics
Case Western Reserve University, Cleveland, OH	Ph.D.	05/1990	Genetics
Univ. of California, San Francisco	Postdoctoral	12/1993	Developmental Biology

A. Personal Statement

The Niswander lab investigates novel mouse models of embryonic development with the overarching goal of providing insights into fundamental developmental processes, major human birth defects and potential clinical therapies. Our multi-disciplinary studies investigate the interplay among genes, environment, and epigenetic mechanisms. Studies through my research career have provided a unique perspective on the molecular mechanisms that control gastrulation and the formation of the central and peripheral nervous system, as well as lung, limb, craniofacial and neuromuscular development. We developed time-lapse imaging methods to visualize and quantify the cell and tissue behaviors during embryonic morphogenesis. Our particular focus is on the common and severe birth defect wherein the neural tube (NT) fails to close, resulting in neural tube defects (NTDs, such as spina bifida) and early neural developmental defects such as microcephaly and MeCP2 neurological disorders. Using our mouse models, we explore gene-environment interactions that influence NTD risk, including zinc and iron homeostasis and folic acid fortification. More recently we have transitioned our knowledge to inform genomic data arising from human NTD cases, to model human specific mutations and to test functional relevance using cell and in vivo assays.

Through studies originally supported by the International Rett Syndrome Foundation (Innovation Award), we found a long non-coding RNA *Rncr3*, deletion of which results in Rett syndrome-like phenotypes in mice. This led to our discovery that MeCP2, the predominant risk gene for Rett syndrome, directly interacts with *lncRncr3* RNA. Moreover, MeCP2-*Rncr3* interaction occurs through the unexplored intervening domain and this serves to regulate the expression of the embedded miRNA miR124a (Nature Communications, 2024). These studies lay the framework for new studies using biochemical and molecular approaches and human organoid models to understand the role of the intervening domain of MeCP2 in RNA interactions and the functional significance of MeCP2 intervening domain in Rett pathology.

I have extensive experience and success in administering research projects, in mentoring and training, leading collaborative and multi-disciplinary projects, and an excellent track record in significant scientific achievements. Collaborative grants include U01, P01, three multi-PI R01s (including with clinicians and geneticists), and as mentor/co-mentor on numerous F31 and F32 awards. I have served on numerous external Advisory Boards and as full member and ad hoc member of NIH study sections (>35) and NIH NIDCR Science Council. In terms of faculty mentorship, I recruited 3 junior faculty when Section Head in Pediatrics at Univ of Colorado Anschutz Medical Campus, all have vibrant labs and have been promoted. At CU Boulder, I recruited 6 junior faculty and all Assistant Professors have obtained numerous NIH and other prestigious awards, built strong lab environments, and are successfullly proceeding through promotion and tenure.

I am firmly committed to mentoring and to education. I am very proud that 100% of my former graduate students (26), postdoctoral trainees (23) and clinical fellows (2) have remained in scientific careers. I believe this and our record of >120 publications is an excellent reflection of our rigorous approach to experimental design, analysis and interpretation. Of my >55 former and current trainees, >65% of them are women and >10 underserved, and 3 with physical disabilities. Since coming to CU Boulder in 2017, my lab has trained 24 undergraduates (18 of whom have graduated, 5 with honors thesis, 11 underserved/underrepresented). My lab works together to provide a welcoming and supportive environment and we have a keen interest in increasing research opportunities for undergraduates and enhancing their capabilities to pursue higher education and research-based careers. As a former transfer student myself, I am acutely aware of how the opportunity to be immersed in a meaningful research experience can open unrealized doors and transform career goals. It is my passion to open doors for others and to be a female role model. I lead efforts to help smooth the transfer of students from a two-year to four-year institution through summer research opportunities for Front Range Community College students. As chair of the Molecular, Cellular and Developmental Biology Department at CU Boulder (from 2017-2025), I have used these skills to advance the research, training, and mentoring efforts of my lab members, all MCDB undergraduate and graduate students, postdoctoral scholars and faculty.

Ongoing projects that I would like to highlight:

Active

NIH/NINDS 1R01 NS110887-01A1 Niswander (PI) 11/1/2019 – 10/31/2024 (NCE 10/25)
Non-coding RNA regulation of early neural development

International Rett Syndrome Foundation (Innovation Award, PI) 12/2022-11/2024 (NCE 11/25)
Advancing an understanding of MeCP2 function by identification of methylated RNA targets

PO1 NIH/NICHD 1P01HD104436-01 12/1/2020 – 11/30/2025
Developmental Mechanisms of Human Meningomyelocele
University of Colorado (Niswander project III), University of California San Diego (Gleeson, Admin Core and Project I), Salk Institute (Ecker Core B, Kintner Project II)

Pending:

R01NS142290: MeCP2 neurological diseases: interplay between RNA binding and MeCP2 genomic occupancy (PI)

R21HD123148-01: Investigating lipid droplet regulation and function in the developing neural tube (PI)

B. Positions, Scientific Appointments, and Honors

2026 –	Distinguished Professor, Molecular, Cellular and Developmental Biology, Univ. of Colorado Boulder
2017–2025	Professor and Chair, Molecular, Cellular and Developmental Biology, Univ. of Colorado Boulder
2004 – 2017	Professor, Pediatrics Dept, Section Head of Developmental Biology, Univ. of Colorado Denver
2003 – 2004	Member, Developmental Biology Program, Sloan-Kettering Institute
1998 – 2003	Associate Member, Molecular Biology and Developmental Biology Program, Sloan-Kettering
1997 – 2014	Howard Hughes Medical Institute Investigator
1993 – 1998	Assistant Member, Molecular Biology Program, Sloan-Kettering Institute
1990 – 1993	Postdoctoral Fellow, Program in Developmental Biology, Univ. of California at San Francisco
1980 – 1984	Research Assistant, Univ. of Colorado Health Sciences Center, Denver, CO

Scientific Appointments and Professional Activities

2023-2026	Wellcome Trust Career Development Award Interview Panel, London, UK
2022-2023	Organizer, Understanding Developmental Disorders in the Genomic Age. Keystone Symposium
2018-2030	Pew Biomedical Scholars National Advisory Committee; Chair 2024-2030
2019-2025	Keystone Symposia Scientific Advisory Board
2019-2023	NIH National Advisory Dental and Craniofacial Research Council member
2016–2020	Board of Directors, FASEB (Federation of American Societies for Experimental Biology),
2013 – 2016	Scientific Advisory Board, Deciphering the Mechanisms of Developmental Disorders, International consortium

2013 – 2017 Scientific Advisory Board, Knock-Out Mouse Project, Jackson Laboratories, Bar Harbor, ME
2013 – 2017 Science Council (Education) for Marine Biological Laboratory, Woods Hole, MA
2013 – 2016 President and Board of Directors, Society for Developmental Biology
2013 – 2016 Scientific Advisory Board, Whitney Laboratory for Marine Bioscience, Univ of Florida
2011 – 2017 Leader, Developmental Origins of Health & Disease Research Program, Children's Hospital CO
2010 – 2017 Editorial panel reviewer for the NIH Director's New Innovator Award Program
2010 – 2015 Editorial Committee for Annual Review of Cell and Developmental Biology
2009 – 2012 Scientific Review Committee, Cancer Prevention and Research Institute of Texas (CPRIT)
2007 – 2012 Associate Director, Graduate Program in Biomedical Sciences Program, UCD
2006 – 2011 Co-Director Embryology Course, Marine Biological Laboratory, Woods Hole, MA
2006 – 2009 Damon Runyon Scientific Advisory Committee
2006 NIH Developmental Biology, Genetics, and Teratology (DBGT) Branch Report to Council Advisory Panel
2004 Co-organizer, Santa Cruz Conference on Developmental Biology
2001 – 2004 Director, Molecular Biology Program, Cornell Univ. Medical College Graduate School
2000 – 2005 Member, NIH CDF5 & Developmental 2 Study Section; Chair 2004-2005
1999 – 2005 Northeast Representative and Board of Directors, Society for Developmental Biology
1997 – 2018 Faculty, Embryology Course, Marine Biological Laboratory, Woods Hole, MA

Awards: Institutes of Health (NRSA) Predoctoral Traineeship (1984-89), American Cancer Society Postdoctoral Fellowship (1991-93), American Cancer Society Junior Faculty Award (1995-97), Pew Scholars in the Biomedical Sciences Award (1995-99), Frederick R. Adler Chair for Junior Faculty (1996-97), Presidential Early Career Award for Scientists and Engineers (1996), Irma T. Hirschl-Monique Weill-Caulier Trusts Career Scientist Award (1997-2001), Harland Winfield Mossman Developmental Biologist Award (2002), Harvey Society Lecture (2008), President, Society for Developmental Biology (2013-2016), Howard Hughes Medical Institute Investigator (1997-2014), Univ of Colorado Distinguished Professor (2025).

C. Contribution to Science

123 peer-reviewed manuscripts and 31 review articles; Total citations = 21340; H-index = 67; i10-index = 134

1. *Unbiased discoveries of novel genes involved in embryonic development and birth defects:* In four sets of forward genetic screens in mice, we identified mouse mutants that disrupt development of the central and peripheral nervous system, limb, lung, craniofacial, pancreas, placenta development, and we provided many of these to our colleagues and made them publicly available through Jackson Laboratories. In >40 publications we defined the function of these genes, with a particular focus on novel genes that control central and peripheral nervous system development. We have partnered with KOMP/IMPC gene knock-out projects to discover the functions of additional novel mutant lines (currently studying 5 new lines).

The mouse models that the Niswander lab has created and studied provide accurate representations of human congenital diseases including Rett syndrome, Meckel-Gruber syndromes 1 and 2, Joubert syndrome 2, primary ciliary dyskinesia, holoprosencephaly, microcephaly, Hirschsprung Disease, scoliosis, and neuromuscular diseases, as well as neural tube defects. Our efforts have led to identification of causative mutations in patients (Blood 2007, Nature Genetics 2011, G3 2018, Human Mutation 2018, Human Mutation 2018, Human Mutation 2020; Development 2020; Neural Dev. 2020; submitted). Our studies have also provided animal models that reveal new potential therapies (Development 2010, Developmental Biology 2015, eLife 2015, Development 2020).

a) Zohn, I.E., Li, Y., Skolnik, E.Y., Anderson, K.V., Han, J. and NISWANDER, L. (2006). p38 and a p38-interacting protein are critical regulators of E-cadherin downregulation during mouse gastrulation. Cell 125, 957-969. PMID: 16751104
b) Zhang, Y., Kim, T-H. and NISWANDER, L. (2012). Phactr4 coordinates directional migration of Enteric Neural Crest Cells through β1 integrin signaling. Genes & Development 1, 69-81. PMCID3258968
c) Li, H., Zhang, J., Chen, S., Wang, F., Zhang, T., NISWANDER, L. (2018). Genetic contribution of retinoid related genes to neural tube defects. Human Mutation 39, 550-562. doi:10.1002/humu.23397
d) Brown, H.M., Murray, S.A., Northrup, H., Au, K.S. and NISWANDER, L.A. (2020). Snx3 is important for mammalian neural tube closure via its role in canonical and non-canonical WNT signaling. Development 147(22):dev192518. doi: 10.1242/dev.192518. PMID: 33214242 PMCID: PMC7687862

2. *Neural progenitor proliferation and differentiation:* How self-renewal versus differentiation of neural progenitor cells is temporally controlled during neural development remains an important question. Disruption of this tightly coordinated process can result in severe neurological defects including microcephaly. The Niswander lab has explored neural progenitor regulation through key RNA binding proteins Lin28a and Lin28b, by modeling human microcephaly mutations to understand mechanisms of action, and through novel genes identified by our forward genetic screens. These studies have revealed new insights into neural biology including 1) control of neural progenitor cell proliferation through physical and functional interactions of the Lin28 RNA binding proteins with mRNA targets encoding Igf1R and Hmga2; 2) that Lin41 acts as a temporal regulator to promote neural progenitor cell maintenance through FGF signaling, and not through the expected regulation of Argonaute 2 (AGO2), a key effector of the miRNA pathway (Development 2015); 3) control of mitotic progression of neural progenitors through interaction of Wdr62 with Aurora A, loss of which leads to spindle assembly checkpoint activation and cell death; 4) control of neuroectoderm progenitor proliferation through TGFb and WNT signaling (Dev Bio 2004); 5) neural progenitor control via Gcn5 acetyltransferase epigenetic regulation of retinoic acid signaling as a mechanistic link in the restriction of WNT and SHH signaling; and 6) a long non-coding RNA and embedded miRNA (Nat Comm 2024); 7) and interaction between this lncRNA and an unexplored domain of MeCP2, the most commonly mutated gene in Rett syndrome. Deletion of small intervening domain of MeCP2 in iPSC-derived neurons and cortical organoids results in neural differentiation defects and loss of astrocytes.

a) Chen, J., Lai, F. and NISWANDER, L. (2012). The ubiquitin ligase mLin41 temporally promotes neural progenitor cell maintenance through FGF signaling. Genes & Development 26, 803-815. PMCID3337455
b) Chen, J., Zhang, Y., Wilde, J., Hansen, K., Lai, F., and NISWANDER, L. (2014). Microcephaly gene Wdr62 interacts with Aurora A/Tpx2 to regulate spindle stability and mitotic progression of neural stem cells. Nature Communications 5:3885. doi: 10.1038/ncomms4885 PMID: 24875059, PMCID: PMC4216695
c) Wilde, J.J., Siegenthaler, J.A., Dent, S.Y.R., and NISWANDER, L.A. (2017). Diencephalic Size is Restricted by a Novel Interplay Between GCN5 Acetyltransferase Activity and Retinoic Acid Signaling. J Neurosci. 2017 Feb 2. pii: 2121-16. doi: 10.1523/JNEUROSCI.2121-16.2017. PMID: 28154153
d) Zhang, J, Li, H. and NISWANDER LA. (2024). m^5C methylated lncRncr3-MeCP2 interaction restricts miR124a-initiated neurogenesis. Nature Communications 15(1):5136. PMID: 38879605

3. *Dynamic imaging of neural development:* Historically, neural tube formation has been studied in fixed and sectioned tissues. Understanding the dynamic cell behaviors that drive mammalian neural tube closure has presented a particular challenge as a consequence of inaccessibility due to mammalian in utero development. The Niswander lab pioneered an innovative and robust approach of whole-mouse embryo culture method in combination with live imaging of genetically-encoded reporters to visualize the entire process of neural tube closure from the face through the brain and along the spinal cord. This cutting-edge technology has provided a unique viewpoint, which we capitalized on with our genetic mutants to uncover the molecular mechanisms that drive the cell behaviors necessary for this critical embryonic closure event (pubs below and Development 2016; Dev Bio 2016). We have also used in utero electroporation and live imaging of brain cultures to reveal centrosomal deficits underlying microcephaly and tumor invasion (Nature Comm 2014; Neuro Oncol. 2013; Development 2015) and live imaging of lung and enteric nervous system development (Genes & Development 2012; PLoS One. 2012; Dev Dynamics 2013; Neurogastroenterol Motil. 2013).

a) Pyrgaki, C., Liu, A., and NISWANDER, L. (2011). *Grainyhead-like 2* regulates neural tube closure and adhesion molecule expression during neural fold fusion. Developmental Biology 353, 38-49. PMCID3114429
b) Massarwa, R. and NISWANDER, L. (2013). In Toto Live Imaging of Mouse Morphogenesis and New Insights into Neural Tube Closure. Development Jan;140(1):226-36. PMCID3514000
c) Zhang, Y., Kim, T-H. and NISWANDER, L. (2012). Phactr4 coordinates directional migration of Enteric Neural Crest Cells through β1 integrin signaling. Genes & Development 1, 69-81. PMCID3258968
d) Li, H., Zhang, J. and NISWANDER, L. (2018). Zinc deficiency causes neural tube defects through attenuation of p53 ubiquitination. Development, 2018 Dec 13;145(24). pii: dev169797. doi: 10.1242/dev.169797

4. *Genetics of neural tube defects*: Through both forward and reverse genetic screens, the Niswander lab has contributed to the identification of ~1/6 of the known mouse mutants that affect neural tube closure, and the great majority of these genes had not been previously implicated in neural tube closure (>30 publications). This includes co-discovery of the link between genes required for ciliogenesis and Sonic Hedgehog (SHH) signaling and numerous other molecular and cellular processes that are required for neural tube closure and that act in the neural ectoderm, the non-neural ectoderm and the mesoderm.

a) Huangfu, D., Liu, A., Rakeman, A. S., Murcia, N. S., NISWANDER, L. and Anderson, K. V. (2003). Hedgehog Signaling in the Mouse Requires Intraflagellar Transport Proteins. Nature 426, 83-87. PMID: 14603322
b) Ray, H.J. and NISWANDER, L.A. (2016). Grainyhead-like 2 downstream targets act to suppress EMT during neural tube closure. Development. 143(7):1192-204. doi: 10.1242/dev.129825. PMID:26903501
c) Li, H., Wang, X., Zhao, H., Wang, F., Bao, Y., Guo, J., Chang, S., Wu, L., Cheng, H., Chen, S., Zou, J., Cui, X., NISWANDER, L., Finnell, R.H., Wang, H., Zhang, T. (2020). Low folate concentration impacts mismatch repair deficiency in neural tube defects. Epigenomics. 2020 Jan;12(1):5-18. doi: 10.2217/epi-2019-0279. Epub 2019 Nov 26. PMID: 31769301
d) Li, B., Bruzman, L., Dahlka, J. and NISWANDER LA. (2022). TMEM132A ensures mouse caudal neural tube closure and regulates integrin-based mesodermal migration. Development 2022 Sep 1;149(17): dev200442. doi: 10.1242/dev.200442 PMID: 35950911

4. *Gene-Environment Interactions:* Focusing on environmental risks for NTDs, we identified a role for iron transport across the early extraembryonic membranes as being required for neural patterning (Development 2010). We showed that zinc levels need to be in an appropriate range for NT closure and identified key molecular targets and shifts in their molecular interactions by zinc levels: zinc finger proteins are predominantly expressed at this stage of development and rare predicted deleterious mutations in zinc finger proteins are enriched in human NTD samples (Development 2018). For more than 25 years, doctors have recommended that women of childbearing age take folic acid (FA), with the express purpose of reducing the risk for neural tube defects (NTDs). However, at a mechanistic level it is not clear how FA acts to prevent NTDs or whether particular gene mutations are more or less sensitive to FA supplementation. Our current experiments employ transcriptome and epigenome profiling to determine the mechanisms by which FA impacts NTD incidence. Current studies tie together folic acid levels with reactive oxygen species (ROS) levels and the impact on GTPase proteins that drive ciliogenesis (Dev Bio 2025). For folate non-responsive mutations, we utilize insights gained from our molecular analysis to identify other pathways to target such as WNT signaling (Development 2020; Front. Cell Dev. Biol 2020). We are also comparing the effect of folic acid versus multi-vitamin/multi-mineral supplementation using metabolomics (submitted). Alterations in retinoid signaling are known to cause birth defects. We identified a new regulator of retinoid signaling required for NT closure and early brain patterning in mice (Dev Neurobio 2014, J. Neuroscience 2017) and discovered mutations that functionally impair retinoid metabolism associated with human NTD (Human Mutation 2018). We have identified a set of lipid-related genes required for neural tube closure that respond positively to vitamin A administration (in prep). In a model of human muscle myopathy, we discovered increasing potassium by diet or FDA-approved drugs can reverse muscle weakness, fatigue-like physiology, and pathology (eLife 2015).

a) Marean, A., Graf, A., Zhang, Y. and NISWANDER, L. (2011). Folic acid supplementation can adversely affect murine neural tube closure and embryonic survival. Human Molecular Genetics 20, 3678-83. PMCID3159553
b) Hanson, M. G., Wilde, J. J., Moreno, R. L., Minic, A. D., & NISWANDER, L. (2015). Potassium dependent rescue of a myopathy with core-like structures in mouse. eLife, 4. doi:10.7554/eLife.02923
c) Li, H., Zhang, J. and NISWANDER, L. (2018). Zinc deficiency causes neural tube defects through attenuation of p53 ubiquitination. Development, 2018 Dec 13;145(24). pii: dev169797. doi: 10.1242/dev.169797
d) Engelhardt D, Petersen J, Martyr C, Kuhn-Gale H, Niswander LA. Moderate levels of folic acid benefit outcomes for cilia based neural tube defects. Dev Biol. 2025 Jan 2:S0012-1606(24)00291-4. doi: 10.1016/j.ydbio.2024.12.019.

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