BIOGRAPHICAL SKETCH

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NAME: Matthew P. Anderson

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POSITION TITLE: Professor, Pathology (Neuropathology), Case Western Reserve University

Co-Director, Oxford-Harrington Rare Disease Centre

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
Cornell College, Iowa City, IA	BS	06/85	Chemistry
University of Iowa College of Medicine	MD, PhD	1993	Medicine, Physiology and Biophysics
University of Iowa Hospitals and Clinics	Resident	1993-1995	Anatomic Pathology
Harvard Medical School/Brigham and Women's Hospital/Children's Hospital, Boston, MA	Clinical Fellow	1995-1997	Neuropathology
Massachusetts Institute of Technology, Cambridge, MA	Research Fellow	1997-2005	Neuroscience

A. Personal Statement

Matthew P. Anderson, M.D., Ph.D. is a Professor, Case Western Reserve University, Department of Pathology; Division of Neuropathology, University Hospitals Cleveland Medical Center; Co-Director, Oxford-Harrington Rare Disease Centre. Following his undergraduate degree in Chemistry (Phi Beta Kappa), Dr. Anderson completed his M.D. (Alpha Omega Alpha) and Ph.D. (Summa cum laude) degrees at the University of Iowa where he won the *International Distinguished Dissertation Award* (top PhD thesis in science in U.S.A. and Canada, awarded once every 5 years) for his seminal work uncovering the ion channel and regulatory functions of the cystic fibrosis gene product that were published in *Cell*, *Science*, *Nature*, and *PNAS*. Foundation for the studies that enable small molecule therapeutics that prolonged the life of individuals with cystic fibrosis. Matthew P. Anderson, M.D., Ph.D. was Director of Neuropathology, Beth Israel Deaconess Medical Center; Neuropathologist of Autism BrainNet; and Faculty, Harvard Medical School Neuroscience PhD Program. He won the International Distinguished Dissertation Award (top PhD thesis in science in U.S.A. and Canada, awarded once every 5 years) for seminal work with HHMI Investigator Michael Welsh by uncovering the ion channel and regulatory functions of the cystic fibrosis gene product (Cell, Science, Nature, and PNAS). His postdoctoral fellowship at Massachusetts Institute of Technology with Nobel Laureate Susumu Tonegawa (somatic recombination to generate immune receptor and antibody diversity) led to training in neuroscience, immunology, Cre-LoxP conditional mouse molecular genetics, brain slice electrophysiology and synaptic physiology, *in vivo* electrophysiology, and behavioral neurosciences. At Harvard, his laboratory leveraged these technologies to investigate the molecular, neuronal circuit, immunologic, and genetic basis of forms of human neurological and psychiatric disease including autism spectrum disorder, intellectual disabilities, obesity, and epilepsy. His laboratory identified the first human genetic epilepsy disorder with defective postnatal developmental pruning and maturation of glutamatergic circuits (Zhou et al. Nature Medicine 2009). They created the first genetic mouse model of a frequent and strongly penetrant genetic autism spectrum disorder [maternal 15q11-13 triplications, idic(15); Smith et al. Science TM 2011]. Increased *Ube3a* gene dosage alone (a 15q11-13 gene expressed exclusively from the maternal allele in neurons) reconstituted the behavioral deficits resembling those in human autism (impaired social interaction and vocalization and increased repetitive behavior). Recently (Krishnan et al. Nature 2017), they applied transcriptional profiling, protein interaction network analysis, Cre-loxP conditional genetics, stereotaxic viral vectors, chemogenetics,

and optogenetics to map the sociability deficits characteristic of autism that they found result from the actions of increased UBE3A in the cell nucleus. They discovered that UBE3A and seizures synergize to repress *Cbln1* gene expression and impair sociability. *Cbln1* encodes a secreted synapse organizing protein that bridges presynaptic neurexin (*Nrxn1*) and postsynaptic glutamate delta receptor (*Grid1*), two genes deleted in autism. Loss of *Cbln1* disrupts synapses of previously enigmatic glutamatergic neuron in the mesolimbic motivation circuits of the ventral tegmental area (VTA) to impair social behavior. Enabled by his expertise in clinical neuropathology and brain banking with Autism BrainNet, his laboratory reported the novel discovery of CD8+ T-cell immune dysregulation in about 65% of postmortem cases of autism spectrum disorder including evidence for the cytotoxic T-cell attack of the astrocyte CSF-brain barrier formed by glia limitans; a novel histopathologic finding where astrocyte membranous blebs (cytotoxic response) correlates to the number of lymphocytes across the autism cases. More recently his lab reported CD8+ T-cell infiltrates in hypothalamus (with neuronal cytotoxicity) in ~45% of postmortem obesity cases and recreated T-cell induced obesity in mice. He has trained 20 MD-PhD physician scientists and 20 PhD scientists who have now gone on to become Professors at Harvard Medical School, Yale, University of Washington, Massachusetts General Hospital, Washington University-St Louis, Zhejiang University, M.D. Anderson, and New York Medical College. He has served on advisory boards of the National Institute of Health, American Epilepsy Society, Rett Syndrome Foundation, and Nancy Lurie Marks Foundation; has serves as editor for multiple journals; and has authored over 90 scientific chapters, reviews, and manuscripts. He served as Clinical Neuropathologist and Boston Node Director for the Autism BrainNET, a brain banking program supported by the Simons Foundation to collect postmortem brains for cases of autism spectrum disorder (ASD) and age and sex matched controls. Dr. Anderson also studies the neuropathology of sudden unexpected death in epilepsy (SUDEP), a frequent comorbidity in ASD, serving as the Clinical Neuropathologist and Brain Bank Director for the Morphometric Core of The Center for SUDEP Research (CSR), a National Institute for Neurological Disorders and Stroke (NINDS) funded Center Without Walls for Collaborative Research in the Epilepsies. In late summer of 2021, he became the Head of the Neuroscience Therapeutic Focus Area and Vice President in Research and Preclinical Development at Regeneron Pharmaceutical to develop new therapeutics for neurodegenerative, neurological, neuropsychiatric, neurodevelopment, and pain disorders. Under his direction, the Neuroscience Therapeutic Focus Area team (45 scientists) collaborated with teams from Alnylam (siRNA), Regeneron Genetic Center (human genetics to identify therapeutic targets), Regeneron Molecular Medicine (CNS- and PNS-retargeted AAV, cDNA, shRNA, and sgRNA/CRISPR), Protein Therapeutics (engineered human antibodies and BBB-crossing and retargeting arms), and Velocigene (humanized genetic mouse models) to develop and test novel therapeutics in mouse models of neurologic, psychiatric, epilepsy, and pain diseases. He worked with Regeneron and Alnylam Clinical Development and Precision Medicine teams to build clinical paths for moving therapeutics into clinic. Therapeutics were under development targeting multiple neurodegenerative proteinopathy disorders (Ab amyloid, ApoE4, tauopathy, synucleinopathy, and prion), genetic neurologic and psychiatric disorders (e.g., epilepsy and schizophrenia), and pain (ion channels). They developed novel strategies for retargeting of siRNA and AAV therapeutic payloads across the blood brain barrier to the CNS and separately into neurons of the peripheral nervous system.

1. Nadler MJ, Chang W, Ozkaynak E, Huo Y, Nong Y, Boillot M, Johnson M, Moreno A, **Anderson MP**. Hominoid SVA-lncRNA AK057321 targets human-specific SVA retrotransposons in SCN8A and CDK5RAP2 to initiate neuronal maturation. ***Commun Biol.*** 2023 Mar 30;6(1):347.

2. DiStasio MM, Nagakura I, Nadler MJ, **Anderson MP**. T lymphocytes and cytotoxic astrocyte blebs correlate across autism brains. ***Ann Neurol.*** 2019 Oct 8. doi: 10.1002/ana.25610.

3. Krishnan V, Stoppel DC, Nong Y, Johnson MA, Nadler MJS, Ozkaynak E, Teng BL, Nagakura I, Mohammad F, Silva MA, Peterson S, Cruz TJ, Kasper EM, Arnaout R, and **Anderson MP**. Autism gene Ube3a and seizures impair sociability by repressing VTA Cbln1. ***Nature.*** 2017 Mar 15. doi: 10.1038/nature21678

4. Smith SEP, Zhou YD, Zhang G, Jin Z, Stoppel DC, **Anderson MP**. Increased gene dosage of Ube3a results in autism traits and decreased glutamate synaptic transmission in mice. ***Science Translational Medicine*** 2011; 3:42-53. PMID: 36909588; PMCID: PMC3356696

Ongoing Research Support

Investigator, Harrington Discovery Institute (Anderson, PI) 05/01/25 - 04/31/30
Goal: Biomedical research of genetic neurologic and psychiatric disease and therapeutics

MAPK8IP3 Axonopathy Therapeutics (Anderson, PI) 06/01/25-05/31/29
Wolverine Foundation
MAPK8IP3 Axonopathy Therapeutics
The major goal of this project is to investigate the cellular and molecular mechanisms, genetic reversibility, and to develop nucleic acid and small molecule therapeutics for autosomal dominant MAPK8IP3 disease.

Completed Research Support (last 3 years)

Nancy Lurie Marks Family/Landreth Family Foundations (Anderson, PI) 01/01/20 - 12/31/22
Autoimmune Attack by Cytotoxic T-Lymphocytes Drives Inflammatory ASD
Goal: The major goal of this project is to perform a series of studies addressing the hypothesis that autoimmune attack by cytotoxic T-lymphocytes drives inflammatory ASD using human postmortem and mouse.

NIH/NIMH 1R01MH114858-01 (Anderson, PI) 09/12/17 - 05/31/22
Neurobiology of Aggression Comorbidity in Autism
Goal: The major goal of this project is to investigate the molecular and neuronal circuit basis of irritability, tantrumming, and self-injurious aggressive behaviors in human genetic forms of autism using engineered mouse models and AAV viral vectors.

NIH/NIMH 1 R01MH112714-01 (Anderson, PI) 04/01/18 - 03/31/23
VTA VGluT2 Sociability Circuit in Genetic Autism
Goal: The major goal of this project is to investigate the molecular and neuronal circuit basis of sociability deficits in human genetic forms of autism using engineered mouse models and AAV viral vectors.

Autism BrainNET (Anderson, PI) 04/01/15-03/31/22
Foundation Associated, LLC (SFARI and Autism Speaks)
Autism BrainNET – Boston Node
Goal: To bank brain tissue samples for cases of autism in the New England region and perform clinical neuropathologic diagnostics for autism cases across the US.

B. Positions, Scientific Appointments, and Honors

2025-	Professor of Pathology, Case Western Reserve University
2025-	Co-Director, Oxford-Harrington Rare Disease Centre
2025-	Investigator, Harrington Discovery Institute
2021-2024	Vice President, Research and Head, Neuroscience Therapeutic Focus Area, Regeneron
2015-2021	Neuropathologist and Investigator, The Center For SUDEP Research Morphometric Core
2013-2021	Neuropathologist and Boston Node Director, Autism BrainNET
2011-2021	Associate Professor of Pathology, Harvard Medical School, Boston, MA
2008-2021	Faculty, PhD Program in Neuroscience, Harvard Medical School, Boston, MA
2008-2010	Assistant Professor of Pathology, Harvard Medical School, Boston, MA
2003-2021	Assistant Professor of Neurology, Harvard Medical School, Boston, MA
2003-2021	Senior Clinical Neuropathologist, Pathology, Beth Israel Deaconess Medical Center, Boston
2003-2008	Visiting Scientist, Picower Center for Learning and Memory, Department of Brain and Cognitive Science, MIT, Cambridge, MA
2000–2003	Burroughs Wellcome Fellow, Picower Center for Learning and Memory, (Principal Investigator: Susumu Tonegawa), Brain and Cognitive Sciences, MIT, Cambridge, MA
1999–2002	Clinical Associate in Pathology, Massachusetts General Hospital, Boston, MA
1998-2021	Consultant in Pathology, Children's Hospital, Boston, MA
1998–2003	Instructor and Clinical Associate in Pathology, Brigham and Women's Hospital, Harvard
1997–2000	Howard Hughes Medical Institute Postdoctoral Fellow, Picower Center for Learning and Memory, (Principal Investigator: Susumu Tonegawa), Brain and Cognitive Sciences, MIT)
1996–2000	Lecturer, Behavioral Sciences Course, Neuroanatomy, Harvard Medical School, Boston, MA
1995–1997	Clinical Fellow, Neuropathology, (Chairman, Ramzi S. Cotran) Brigham & Women's Hospital, Children's Hospital, Massachusetts General Hospital, Boston, MA

1993–1995 Medical Resident, Anatomic Pathology, University of Iowa Hospitals, Iowa City, IA
1986–1993 Medical Scientist Training Program (MD-PhD), University of Iowa Hospitals, Iowa City, IA

C. Contributions to Science

1. Cystic fibrosis (CF) is an early childhood life-threatening, genetic disease that primarily affects the lungs and digestive system. It is found in about 30,000 people in the United States (70,000 worldwide). Our studies determined the function of the gene mutated to cause CF, the cystic fibrosis transmembrane conductance regulator (CFTR) that codes for an ATP-binding cassette (ABC) transporter-class protein. By mutating transmembrane domains of CFTR, we altered it anion selectively to show these contribute directly to the channel pore conducting chloride ions across epithelial cell membranes. We also established that it is regulated by cycles of ATP binding and hydrolysis at its nucleotide binding domains and by an intracellular phosphorylated domain.

1. **Anderson MP**, Gregory RJ, Thompson S, Souza DW, Paul S, Mulligan RC, Smith AE, Welsh MJ. Demonstration that CFTR is a chloride channel by alteration of its anion selectivity. ***Science***. 1991; 253(5016):202-5. PMID: 1712984
2. **Anderson MP**, Rich DP, Gregory RJ, Smith AE, Welsh MJ. Generation of cAMP-activated chloride currents by expression of CFTR. ***Science*** 1991; 251(4994):679-82. PMID: 1704151
3. **Anderson MP**, Berger HA, Rich DP, Gregory RJ, Smith AE, Welsh MJ. Nucleoside triphosphates are required to open the CFTR chloride channel. ***Cell***. 1991; 67(4):775-84. PMID: 1718606
4. **Anderson MP**, Welsh MJ. Regulation by ATP and ADP of CFTR chloride channels that contain mutant nucleotide-binding domains. ***Science***. 1992; 257(5077):1701-4. PMID: 1382316

2. Thalamic and hypothalamic circuit mechanisms. Thalamic neuron burst firing is a unique firing pattern seen in the thalamus during sleep and under a variety of pathologic conditions including chronic pain and epilepsy – a cluster of action potentials occur at a very high frequency (> 250 Hz) followed by a prolonged refractory period. **Transplanted neuronal progenitors to reconstitute hypothalamic neuronal circuits** and rescue obesity and defective glucose homeostasis in leptin receptor deficient mice.

1. **Anderson MP**, Mochizuki T, Xie J, Fischler W, Manger JP, Talley EM, Scammell TE, Tonegawa S. Thalamic Cav3.1 T-type calcium channel plays a crucial role in stabilizing sleep. ***Proc Natl Acad Sci USA***. 2005; 102(5):1743-1748. PMID: 15677322; PMCID: PMC547889
2. Kasten MR, Rudy B, **Anderson MP**. Differential regulation of action potential firing in adult murine thalamocortical neurons by Kv3.2, Kv1, and SK potassium and N-type calcium channels. ***J Physiology***. 2007; 584.2:565-582. PMID: 17761775; PMCID: PMC2277158
3. Kasten MR, **Anderson MP**. Self-regulation of adult thalamocortical neurons. ***J Neurophysiology***. 2015; May 6:jn.00800.2014. PMID: 25948871
4. Czupryn A*, Zhou Y-D*, Chen X*, McNay D, **Anderson MP†**, Flier JS†, Macklis JD†. Transplanted hypothalamic neurons restore leptin signaling and ameliorate obesity in db/db mice. ***Science***. 2011; 334:1133-1137. *co-first authors; **† co-senior authors** PMID: 22116886

3. Established a new pathophysiological mechanism for human genetic temporal lobe epilepsy: arrested neurodevelopmental glutamate synapse pruning and maturation during early childhood.

1. Zhou Y-D, Lee S, Jin Z, Wright M, Smith SEP, **Anderson MP**. Arrested maturation of excitatory synapses in autosomal dominant lateral temporal lobe epilepsy. ***Nature Medicine***. 2009; 15(10):1208-14. PMID: 19701204; PMCID: PMC2759408 (Cited 199; Highlighted in news and views of ***Nature Medicine*** and ***Lancet***)
2. Zhou YD, Zhang D, Wang X, Kasper EM, Leguern E, Baulac S, **Anderson MP**. Epilepsy gene LGI1 regulates postnatal developmental remodeling of retinogeniculate synapses. ***J Neurosci.*** 2012; 32:903-910. PMID: 22262888; PMCID: PMC3342858
3. Smith SE, Xu L, Kasten MR, **Anderson MP**. Mutant LGI1 Inhibits Seizure-Induced Trafficking of Kv4.2 Potassium Channels. ***J Neurochem***. 2012; 120:611-621. PMID: 22122031; PMCID: PMC3261618
4. Boillot M, Huneau C, Marsan E, Lehongre K, Navarro V, Ishida S, Dufresnois B, Ozkaynak E, Garrigue J, Miles R, Martin B, Leguern E, **Anderson MP**, Baulac S. Glutamatergic neuron-targeted loss of LGI1 epilepsy gene results in seizures. ***Brain***. 2014; 137:2984-96. PMCID: PMC4208469

4. Autism spectrum disorder (ASD) is an early childhood disorder defined by reduced social and increased repetitive behaviors and often irritability/aggressive behavioral comorbidities. We looked for the most frequent strongly penetrant genetic form of autism and found the maternally-inherited interstitial 15q11-13 duplication

and maternally-inherited extranumerary isodicentric chromosome 15q, idic(15). Significantly, maternal deletions of the same locus or inactivating mutations of the imprinted gene *UBE3A* cause Angelman syndrome a neurologic disorder that includes behaviors interpreted as hyper-sociability - opposite ASD. *UBE3A* is the only gene in the duplicated region expressed exclusively from the maternal allele in mature neurons. So additional maternally-derived copies of 15q11-13 locus would double (interstitial duplication) or triple [idic(15)] the neuronal-expressed dosage of *UBE3A*. We showed adding increased copies of a non-imprinted full-length *Ube3a* gene to mice cause a dose-dependent defect of social behavior and increased repetitive behavior and defects in glutamatergic, but not GABAergic, synaptic transmission in cortex. We engineered AAV constructs (cell-type-specific promoters and Cre-conditional cDNA rescue, shRNA, and chemogenetics techniques) to define the origins of major behavioral deficits: 1) sociability deficits in glutamatergic neurons in ventral tegmental reward circuitry; and 2) elevated aggression in ventromedial hypothalamus.

Human-specific SVA retrotransposons are enriched in neurodevelopmental disease genes regulate gene expression in hominid brain evolution. Retrotransposons function like retroviruses but rather than generate viral particles, they reinsert elsewhere in the genome. The youngest retrotransposon family in the human genome is the SINE-VNTR-Alu (SVA) that arose and expanded in hominoid primates concurrent with the slowing of brain maturation to expand cerebral and cerebellar cortex in human. We reported our discovery that genes with intronic or promoter SVA transposons are enriched for neurologic (e.g., epilepsy gene *SNC8A* with human-specific SVA) and neurodevelopmental disease (e.g., microcephaly gene *CDK5RAP2* with human-specific SVA) genes and showed these intronic SVAs, through SVA-binding transcription factor ZNF91, act to slow human neuronal maturation. We also identified the function of a novel SVA regulatory gene family: long non-coding RNAs that transcribe SVA sequences. We showed SVA-lncRNA *AK057321*, duplicated in ultrarare ASD, forms RNA:DNA heteroduplexes with genomic intronic SVAs to release ZNF91-mediated repression and initiate neuronal maturation. The diversity of neuronal genes with intronic SVAs suggest this transposon-based gene regulatory mechanism may act at multiple steps to achieve neoteny of the human brain.

1. Nadler MJ, Chang W, Ozkaynak E, Huo Y, Nong Y, Boillot M, Johnson M, Moreno A, **Anderson MP**. Hominoid SVA-lncRNA AK057321 targets human-specific SVA retrotransposons in SCN8A and CDK5RAP2 to initiate neuronal maturation. ***Commun Biol.*** 2023 Mar 30;6(1):347.
2. Nong Y, Stoppel DC, Johnson MA, Boillot M, Todorovic J, Shen J, Zhou X, Nadler MJS, Rodriguez C, Huo Y, Nagakura I, Kasper EM, and **Anderson MP**. UBE3A and transsynaptic complex NRXN1-CBLN1-GluD1 in a hypothalamic VMHvl-arcuate feedback circuit regulates aggression. ***bioRxiv*** 2023. PMID: 21974935; PMCID: PMC10002692
3. Krishnan V, Stoppel DC, Nong Y, Johnson MA, Nadler MJS, Ozkaynak E, Teng BL, Nagakura I, Mohammad F, Silva MA, Peterson S, Cruz TJ, Kasper EM, Arnaout R, and **Anderson MP**. Autism gene Ube3a and seizures impair sociability by repressing VTA Cbln1. ***Nature.*** 2017 Mar 15. doi: 10.1038/nature21678
4. Smith SEP, Zhou YD, Zhang G, Jin Z, Stoppel DC, **Anderson MP**. Increased gene dosage of Ube3a results in autism traits and decreased glutamate synaptic transmission in mice. ***Science Translational Medicine*** 2011; 3:42-53. PMID: 36909588; PMCID: PMC3356696

5. CNS T-cell immune disease: We discovered for the first time that ~65% of ASD postmortem brain cases have pathologic evidence of dysregulated T-cell immunity with damage to astrocytes at the CSF-brain barrier. We also identified hypothalamus T-cell infiltrates and neuron cytotoxicity in ~45% of human postmortem cases of obesity and reconstituted the pathology and obesity in mice. We also reported a case of a T-cell intestinal ganglionitis explaining dilated dysfunctional large intestine leading to death arising in the context of a long-term survival (8 years) with a T-cell rich glioblastoma. Role of T-type Ca^{2+} channel CACNA1G in helper T-cells.

1. DiStasio MM, Nagakura I, Nadler MJ, **Anderson MP**. T lymphocytes and cytotoxic astrocyte blebs correlate across autism brains. ***Ann Neurol.*** 2019 Oct 8. doi: 10.1002/ana.25610.
2. Ahrendsen JT, Nong Y, Huo Y, Steele J, **Anderson MP**. CD8 cytotoxic T-cell infiltrates and cellular damage in the hypothalamus in human obesity. ***Acta Neuropathologica Communications*** 2023 Oct 9;11(1):163. doi: 10.1186/s40478-023-01659-x.
3. Ahrendsen JT, Anderson KR, **Anderson MP**. Lymphocytic ganglionitis leading to megacolon in lymphocyte-rich glioblastoma. ***J Neuroimmunol.*** 2019 Dec 15;337:577075. doi: 10.1016/j.jneuroim.2019.577075. Epub 2019 Oct 19.

4. Wang H, Zhang X, Xue L, Xing J, Jouvin MH, Putney JW, **Anderson MP**, Trebak M, Kinet JP. Low-Voltage-Activated CaV3.1 Calcium Channels Shape T Helper Cell Cytokine Profiles. ***Immunity***. 2016 Apr 19;44(4):782-94.

Full bibliography: https://www.ncbi.nlm.nih.gov/myncbi/matthew.anderson.1/bibliography/public/