BIOGRAPHICAL SKETCH

NAME: Matthew P. Anderson

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

POSITION: Associate Professor, Pathology (Neuropathology) and Neuroscience, Harvard Medical School

Chief Neuropathology, Department of Pathology, Beth Israel Deaconess Medical Center

Head and VP, Neuroscience Therapeutic Focus Area, Regeneron

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	06/1985	Chemistry
University of Iowa College of Medicine	MD, PhD	07/1993	Medicine, Physiology and Biophysics
University of Iowa Hospitals and Clinics	Resident	07/1995	Anatomic Pathology
Harvard Medical School/Brigham and Women's Hospital/Children's Hospital, Boston, MA	Clinical Fellow	07/1997	Neuropathology
Massachusetts Institute of Technology, Cambridge, MA	Research Fellow	07/2005	Neuroscience and Immunology
Harvard Medical School/Beth Israel Deaconess Medical Center/Children's Hospital, Boston, MA	Chief of Neuropathology	07/2007	Neuroscience and Immunology

A. Personal Statement

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 (Aβ 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.

B. Positions and Employment

1986–1993	Medical Scientist Training Program (MD-PhD), University of Iowa Hospitals, Iowa City, IA
1993–1995	Medical Resident, Anatomic Pathology, University of Iowa Hospitals, Iowa City, IA
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
1997–2000	Howard Hughes Medical Institute Postdoctoral Fellow, Picower Center for Learning and Memory, (Principal Investigator: Susumu Tonegawa), Brain and Cognitive Sciences, MIT)
1998–2003	Instructor and Clinical Associate in Pathology, Brigham and Women's Hospital, Harvard
1998-	Consultant in Pathology, Children's Hospital, Boston, MA
1999–2002	Clinical Associate in Pathology, Massachusetts General Hospital, Boston, MA
2000–2003	Burroughs Wellcome Fellow, Picower Center for Learning and Memory, (Principal Investigator: Susumu Tonegawa), Brain and Cognitive Sciences, MIT, Cambridge, MA
2003-2008	Visiting Scientist, Picower Center for Learning and Memory, Department of Brain and Cognitive Science, MIT, Cambridge, MA
2003-2021	Associate Neuropathologist, Pathology, Beth Israel Deaconess Medical Center, Boston, MA
2003-	Assistant Professor of Neurology, Harvard Medical School, Boston, MA
2008-2010	Assistant Professor of Pathology, Harvard Medical School, Boston, MA
2008-	Faculty, PhD Program in Neuroscience, Harvard Medical School, Boston, MA

2011-	Associate Professor of Pathology, Harvard Medical School, Boston, MA
2013-2021	Neuropathologist and Boston Node Director, Autism BrainNET
2015-2021	Neuropathologist and Investigator, The Center For SUDEP Research Morphometric Core
2021-2024	Vice President, Research and Head, Neuroscience Therapeutic Focus Area, Regeneron

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 (Cited 1394)
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 (Cited 712)
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 (Cited 695)
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 (Cited 298)

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 (Cited 247)
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 (Cited 65)
3. Kasten MR, **Anderson MP**. Self-regulation of adult thalamocortical neurons. ***J Neurophysiology***. 2015; May 6:jn.00800.2014. PMID: 25948871 (Cited 4)
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 (Cited 65; Altmetric 71)

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 (Cited 22)
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 (Cited 18 times)

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 (Cited 62)

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 that 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 the major behavioral deficits: 1) mapped sociability deficits to glutamatergic neurons in ventral tegmental reward circuitry; and 2) mapped elevated aggression to glutamatergic neurons in ventromedial hypothalamus that project to arcuate nucleus which feedback to inhibit aggression behaviors.

1. 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
2. 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 (Cited 139; Altmetric 151)
3. Stoppel DC, **Anderson MP**. Hypersociability in the Angelman syndrome mouse model. ***Exp Neurol.*** 2017 Apr 11;293:137-143. (Cited 28)
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 (Cited 292; Altmetric 48)

5. CNS adaptive immune disease (T-cell:circuit interactions): 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. In collaboration with our colleagues, we also defined the role of T-type calcium channel CACNA1G in the function of 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. (Cited 72; Altmetric 169.
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. Amato AA, Sanelli PC, **Anderson MP**. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 38-2001. A 51-year-old woman with lung cancer and neuropsychiatric abnormalities. ***N Engl J Med.*** 2001 Dec 13;345(24):1758-65

5. 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. (Cited 50)

6. Human-specific SVA retrotransposons in neuronal gene regulation and hominid 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 uniquely in hominoid primates concurrent with the slowing of brain maturation that contributed to the expanded cerebral and cerebellar cortex in the human species. We recently 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) 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* forms RNA:DNA heteroduplexes with genomic intronic SVAs to release ZNF91-mediated repression and initiate neuronal maturation. SVA-lncRNA *AK057321* also promotes species-specific cortex and cerebellum-enriched expression of human genes with intronic SVAs (e.g., HTT, CHAF1B and KCNJ6) but not mouse orthologs. The diversity of neuronal genes with intronic SVAs suggest this hominoid-specific SVA transposon-based gene regulatory mechanism may act at multiple steps to specialize and 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. doi: 10.1038/s42003-023-04683-8 (Cited 2)

Full bibliography: http://www.ncbi.nlm.nih.gov/myncbi/collections/bibliography/40537686/

D. Research Support

Research Support

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 address the hypothesis that autoimmune attack by cytotoxic T-lymphocytes drives inflammatory ASD using human postmortem tissues and mouse models.

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.