Curriculum Vitae

Juliet K. Knowles, M.D, Ph.D.
Palo Alto, CA 94304
jkk1@stanford.edu
(650) 521-2932
Lab website: med.stanford.edu/pedsepilepsy-lab
March 10, 2022

Professional Experience

Assistant Professor, Pediatric Neurology and Epilepsy Stanford Children's Hospital	5/2021 - present
Instructor, Pediatric Neurology and Epilepsy Stanford Children's Hospital	7/2018 – 5/2021
Pediatric Epilepsy Fellow Stanford Children's Hospital	7/2016 - 6/2018
Chief Resident Stanford University Hospital, Department of Neurology	7/2015 - 6/2016
Residency, Pediatrics and Pediatric Neurology Stanford Children's Hospital / Stanford University Hospital	7/2012 - 6/2016
Internship, Pediatrics Stanford Children's Hospital	6/2011 - 6/2012

Board Certification

American Board of Psychiatry and Neurology, Certification in Neurology with Special Qualifications in Child Neurology	9/2016
American Board of Psychiatry and Neurology, Certification in Epilepsy	10/2018

Education

M.D., Stanford University School of Medicine	6/2011
Ph.D., Stanford University Neurosciences Graduate Program	9/2009
MSTP, University of North Carolina – Chapel Hill (transferred to Stanford for remainder of MD/PhD training)	8/2001 - 8/2005
B.A., Microbiology & Philosophy; Minor in French University of Texas at Austin	5/2001
Study abroad, University of Paris (France)	8/1999 - 6/2000

Competitive Research Funding

NIH-NINDS K08 NS119800 — 9/2021-8/2026
Maladaptive Myelination in Pediatric Epilepsy
Role: PI

NIH-NINDS K12 NS098482 (Child Neurologist Career Development Program) — 7/2018 - 6/2021
Impact of Recurrent Seizures Upon Myelin Structure and Function
Role: PI

Child Neurology Foundation/Pediatric Epilepsy Research Foundation Elterman Award. — 1/2021 – 12/2023
Targeting Aberrant Activity-dependent Myelination in Absence Epilepsy
Role: PI

NIH/NHLBI R01 HL 152757 — 3/2021 – 2/2026
Neurometabolic outcomes of Different Cardiopulmonary Bypass Strategies
Role: co-I with PIs Drs. Frank Hanley and Kirk Riemer

Citizens United for Research in Epilepsy (CURE)-Covid Research Continuity Award. Role: PI — 12/2020

Citizens United for Research in Epilepsy (CURE) Taking Flight Award — 10/2018 - 4/2020
Abnormal myelination in absence epilepsy: cause and functional impact
Role: PI

Stanford Maternal and Children's Health Research Institute (MCHRI) Pilot Grant — 7/2018 - 6/2019
Impact of Recurrent Seizures Upon Myelin Structure and Function
Role: PI

Stanford MCHRI K support award. Role: PI — 7/2018 - 6/2020

American Epilepsy Society Clinical Translational Research Fellowship — 7/2016 - 6/2017
Impact of Recurrent Seizures Upon Myelin Structure and Plasticity
Role: PI

NIH-NINDS F30 Pre-doctoral Fellowship — 6/2006 - 6/2009
P75NTR-mediated protection from amyloid neurodegeneration
Role: co-PI (with PhD mentor Dr. Frank Longo)

Honors and Awards

Johns Hopkins University — 2021
Stroup Award for "Rising Star" in Pediatric Epilepsy Research

Stanford University School of Medicine

First place, Stanford Neuroscience Forum (Resident Research Day) — 2015

Stanford Society of Physician Scholars — 2014

First place, Stanford Neuroscience Forum	2013
Northern California Alzheimer's Association Outstanding Young Scientist	2009

University of North Carolina at Chapel Hill School of Medicine

First place, Neuroscience Center Pierre Morrell Research Day	2004
Summer Research Scholarship, American Academy of Neurology	2004
Frank Porter Graham Honor Society	2004
Order of the Grail-Valkyries Honor Society	2004
Social Medicine Paper Prize	2003
Eugene S. Mayer Community Service Honor Society	2003
John B. Graham Student Research Society	2003
Loyalty Fund Scholarship	2001 - 2003

University of Texas at Austin

Phi Beta Kappa	2001
Graduated with Honors	2001
Honors Research Thesis in Neurobiology	2001
College Scholar (Honor Roll for Academic Year)	1997 - 2001
Margaret Jane McKinney Fellowship in Bacteriology	2001
National Leadership Award for Outstanding Collegian, Alpha Xi Delta Sorority, based on service as UT-Austin Chapter President (1998) and Vice President (1997)	2001

Peer Reviewed Publications (Original Research)

1. **Knowles JK***, Xu H, Soane C, Batra A, Saucedo T, Frost E, Tam L, Fraga D, Villareal K, Huguenard J*, Monje M*. Maladaptive Myelination Contributes to Generalized Epilepsy Progression. **Accepted,** *Nature Neuroscience* 2022. *co-corresponding author. (an earlier vision of this manuscript is on BioRxiv at https://www.biorxiv.org/content/10.1101/2020.08.20.260083v1)

2. Pavitt S, Carley A, Porter B, **Knowles JK.** A Standardized Protocol to Improve Management of Acute Seizures in the Pediatric Epilepsy Monitoring Unit. *Hospital Pediatrics,* 2021. PMID: 33685859.

3. Sandoval Karamian AG, Wusthoff CJ, Boothroyd D, Yeom KW, **Knowles JK.** Neonatal genetic epilepsies display convergent white matter microstructural abnormalities. *Epilepsia,* 2020. PMID: 33098118.

4. **Knowles JK**, Santoro JD, Porter BE, Baumer FM. Refractory Focal Epilepsy in a Paediatric Patient with Primary Familial Brain Calcification. *Seizure*, February 2018. PMID: 29448117.

5. Simmons DA, Knowles JK, Belichenko NP, Banerjee G, Finkle C, Massa SM, Longo FM. A small molecule p75NTR ligand, LM11A-31, reverses cholinergic neurite dystrophy in Alzheimer's disease mouse models with mid- to late-stage disease progression. *PLoS One*, August 2014. PMID: 25153701.

6. **Knowles JK,** Simmons DA, Nguyen T-V, Vander Griend L, Xie Y, Zhang H, Yang T, Pollak J, Chang T, Arancio O, Buckwalter M, Wyss-Coray T, Massa SM, Longo FM. A small molecule $p75^{NTR}$ ligand prevents cognitive deficits and neurite degeneration in an Alzheimer's mouse model. *Neurobiology of Aging*, August 2013. PMID 23545424.

7. **Knowles JK,** Rajadas J, Vander Griend L, Ishikawa C, Nguyen T, LeMieux M, Wyss-Coray T, Longo FM. The p75 neurotrophin receptor promotes amyloid-β(1-42) induced neuritic dystrophy *in vitro* and *in vivo*. *The Journal of Neuroscience,* August 2009. PMID 19710315.

8. Yang T*, **Knowles JK***, Lu Q, Zhang H, Arancio O, Moore L, Chang T, Wang Q, Andreasson K, Rajadas J, Fuller G, Xie Y, Massa SM, Longo FM. Small molecule, non-peptide $p75^{NTR}$ ligands inhibit Aβ-induced neurodegeneration and synaptic impairment. *PLoS One*, October 2008. PMID 18978948. *co-first author

9. Prip-Buus C, Thuillier L, Abadi N, Prasad C, Dilling L, **Klasing J**, Demaugre F, Greenberg CR, Haworth JC, Droin V, Kadhom N, Gobin S, Kamoun P, Girard J, Bonnefont JP. Molecular and enzymatic characterization of a unique carnitine palmitoyltransferase 1A mutation in the Hutterite community. *Molecular Genetics and Metabolism*, May 2001. PMID 11350182.

Book Chapters and Reviews

1. **Knowles JK,** Porter BE. Practical Advice on Surviving and Thriving as an Academic Physician-Neuroscientist. *JAMA Neurology*, 2021. PMID: 34694341.

2. **Knowles JK***, Helbig I*, Metcalf C*, Lubbers, LS, Isom LL, Demarest S, Goldberg E, George AL, Lerche H, Weckhuysen S, Whittemore V, Berkovic SF, and Lowenstein DH. Precision medicine for genetic epilepsy on the horizon: recent advances, present challenges and suggestions for continued progress.In revision at *Epilepsia*.

3. Adaptive and maladaptive myelination in health and disease. **Knowles JK,** Batra A, Xu H and Monje M. Under review at *Nature Reviews Neurology*.

4. **Knowles JK**, Wusthoff CJ. Quantitative EEG in Neonatal Seizures. In: Husain A, Sinha S (eds) Continuous EEG Monitoring. Springer, 2017.

5. **Knowles JK,** Penn AA. Perinatal Brain Development, Malformation and Injury. Morgan and Claypool Life Sciences Colloquium Series on the Developing Brain, 2012.

6. Longo FM, Yang T, **Knowles JK**, Xie Y, Moore LA, Massa SM. Small molecule neurotrophin receptor ligands: novel strategies for targeting Alzheimer's disease mechanisms. *Current Alzheimer Research,* 2007. PMID 18220511.

Presentations

1. *"Maladaptive Myelination in Pediatric Epilepsy."* Invited speaker, American Epilepsy Society, December 2021.

2. *"Maladaptive Myelination in Pediatric Epilepsy."* Radiology Science Laboratories seminar, Stanford University, April 2021.

3. *"Maladaptive Myelination in Pediatric Epilepsy."* Johns Hopkins Stroup Award lecture, March 2021.

4. *"Maladaptive Myelination in Pediatric Epilepsy."* Stanford MCHRI joint seminar with Michelle Monje, March 2021.

5. *"Abnormal white matter in neonates with nonstructural epilepsy."* Senior author, poster at American Epilepsy Society meeting 2020.

6. *"Maladaptive myelination contributes to epileptogenesis."* Selected speaker, Cold Spring Harbor meeting, Glia in Health and Disease 2020.

7. *"Aberrant Activity-Dependent Myelination in Epilepsy."* First author, Child Neurology Society meeting 2020.

8. *"A standardized protocol to improve acute seizure management in the Pediatric EMU."* Senior author, poster at the Child Neurology Society meeting 2020.

9. *"Precision Medicine in Pediatric Genetic Epilepsy."* Stanford Children's Health, presentation to families of children with epilepsy 2020.

10. *"Maladative Myelination in Pediatric Epilepsy."* Annual presentation to the national Child Neurologist Career Development Program – K12 (NIH/NINDS) Committee: 2018, 2019, 2020.

11. *"Maladative Myelination in Epilepsy."* Invited speaker, Epilepsy Precision Medicine National Meeting, Washington DC, 2019.

12. *"Maladaptive Myelination in Epilepsy."* Invited speaker, University of Iowa Department of Pediatrics, 2019.

13. *"Improving Acute Seizure Management in the Pediatric Epilepsy Monitoring Unit."* Senior author, Stanford Resident Quality Improvement/Patient Safety Symposium, 2019.

14. *"Impact of Recurrent Seizures on Myelin Structure and Function."* American Epilepsy Society Annual International meeting, 2017.

15. *"Impact of Recurrent Seizures on Myelin Structure and Plasticity."* Stanford University Neurology Grand Rounds, 2016.

16. *"Genetic and Optogenetic Models to Investigate the Impact of Recurrent Seizures on Myelin Plasticity."* Stanford University Neuroscience Research Forum, 2015.

17. "*A Pediatric Case of Acute Flaccid Monoplegia."* Stanford Department of Neurology Grand Rounds, 2014.

18. *"A small molecule p75^{NTR} ligand prevents cognitive deficits and neurite degeneration in vivo."* Stanford University Neuroscience Research Forum, 2013.

19. *"A small molecule p75^{NTR} ligand prevents cognitive deficits and neurite degeneration in an Alzheimer's mouse model."* Society for Neuroscience international annual meeting, New Orleans, 2012.

20. *"The p75 neurotrophin receptor promotes amyloid-β(1-42) induced neuritic dystrophy in vitro and in vivo."* Society for Neuroscience international annual meeting, Chicago 2009.

21. Selected speaker, *"Novel Small Molecule p75^{NTR} Ligands Prevent Aβ-induced Neurodegeneration"* Molecular Mechanisms of Neurodegeneration international meeting organized by Dr. Rudy Tanzi, Antigua, 2007.

22. *"Small Molecule Mimetics of NGF Loop 1 are Candidate Novel Alzheimer's Disease Therapeutics"* UNC Chapel Hill Neuroscience Center, Pierre Morrell Research Day, 2004.

23. *"Aß$_{1-40}$ and Aß$_{1-42}$ Peptides are Partial Agonists of the α7 Nicotinic Acetylcholine Receptor,"* UNC Medical Student Research Day, 2003.

Scholarly Research

2018 - present: *Maladaptive myelination in epilepsy.*

Structural and functional changes in neural networks underlie epileptogenesis and cognitive dysfunction in multiple forms of epilepsy. However, these pathological changes are incompletely understood and, as a result, there are no disease-modifying therapies for epilepsy. Myelin plasticity is a newly recognized dimension of activity-dependent neural network adaptation that occur throughout the lifespan. Numerous studies in humans and animals indicate that neuronal activity influences myelin structure; this activity-regulated myelination in turn, sculpts neuronal network function, and is an adaptive process that is required for multiple forms of learning. The potential role of activity-regulated myelination in disease states characterized by persistent and abnormal patterns of neuronal activity, such as epilepsy, is unknown**. I hypothesized that in epilepsy, pathological patterns of neuronal activity may also influence myelin to alter network function; aberrant increases or decreases in myelination could in turn, contribute to epilepsy pathogenesis**.

Using quantitative histological, electron microscopy and neurophysiological techniques, my research has identified aberrantly increased myelination of seizure network projections in multiple rodent models of generalized epilepsy. Blockade of seizures with the drug ethosuximide prevented the abnormal myelination, indicating that seizures are required for these abnormalities. Conditional genetic blockade of activity-dependent myelin plasticity in a mouse model of generalized epilepsy prevented progression of absence seizures that is characteristic of animal models of generalized epilepsy. Furthermore, pharmacological blockade of myelin plasticity, initiated after seizure onset, also prevented seizure progression. This is the first

demonstration that activity-dependent myelination can become *maladaptive* to promote progression of seizures. These discoveries suggest that maladaptive myelination is a novel pathogenic mechanism which may be applicable in multiple other forms of epilepsy and other neurological and neuropsychiatric diseases. **My first author/corresponding author manuscript describing these findings has been accepted at *Nature Neuroscience*.**

In my independent laboratory, my team and I are developing research directions that build on this work including 1. High-resolution diffusion-based MR imaging of humans and rodent models of epilepsy in collaboration with Stanford Radiology faculty researcher Dr. Jennifer McNab, as well as CLARITY and related methods, for high resolution visualization of whole brain myelination; 2. cellular and molecular mechanisms underlying abnormal myelination in epilepsy models; 3. further functional investigation of abnormal myelination at the circuit and network level using a range of neurophysiological techniques; 4. the role of abnormal myelination in multiple forms of pediatric epilepsy and other diseases characterized by abnormal neuronal activity, and cognitive co-morbidities; 5. therapeutic strategies to target abnormal myelination.

2018 - 2021: *Aberrant white matter in neonatal genetic epilepsy*.
Mentor/senior author.
In parallel to the laboratory efforts detailed above, I mentored resident physician Dr. Amanda Sandoval Karamian (Stanford Child Neurology) on a clinical project investigating white matter in neonates with nonstructural/genetic epilepsy. We found white matter structural abnormalities in association with seizures, which parallel my findings in rodent models. This work was presented at the 2020 American Epilepsy Society meeting and was published in *Epilepsia*.

2003 - 2009: *$p75^{NTR}$-mediated protection from β-amyloid induced neurodegeneration.*
Doctoral thesis, laboratory of Dr. Frank Longo at Stanford.
The p75 neurotrophin receptor ($p75^{NTR}$) is expressed on neuron populations which degenerate in Alzheimer's disease (AD), is upregulated in the disease, and induces neurodegeneration under many circumstances. I tested the hypothesis that $p75^{NTR}$ modulates AD-like amyloid (Aβ)-induced neurodegeneration using $p75^{NTR}$ +/+ and -/- neuron cultures and $p75^{NTR}$ -/-, mutant amyloid precursor protein (APP) transgenic mice modeling AD. Both *in vitro* and *in vivo*, $p75^{NTR}$ signaling contributes significantly to Aβ-induced deleterious effects. In addition to degenerative signaling, $p75^{NTR}$ is also capable of pro-survival signaling via the PI3K/Akt pathway, which is known to inhibit major signaling cascades in Aβ-induced degeneration. A strategy to shift $p75^{NTR}$ signaling toward pro-survival pathways could block Aβ-induced neurodegeneration. We tested this hypothesis using novel small molecule ligands which bind to $p75^{NTR}$ to activate Akt and promote neuron survival. My work demonstrated that, in neuron culture and hippocampal slices, $p75^{NTR}$ ligands were potent neuroprotectives that prevented multiple Aβ-induced deleterious effects. I further demonstrated that treatment of transgenic mouse models of AD with an orally bioavailable lead $p75^{NTR}$ ligand, LM11A-31, significantly reduced hippocampal, cholinergic basal forebrain and cortical neuritic dystrophy relative to vehicle treated mice and improved cognitive performance in the Novel Object Recognition and Y maze behavioral tests. These findings led to a recently completed, successful Phase 2 clinical trial of LM11A-31 for AD, featured on the cover of *TIME* magazine in 2016. The work was supported by a NIH-NINDS F30 grant.

2018 - 2021: *Management of Acute Seizures in the Pediatric Epilepsy Monitoring Unit.*
Mentor/senior author.
Stanford Neurology chief resident Dr. Sara Pavitt and I, in collaboration with the Stanford/LPCH Brain and Behavior Nursing Group and Pediatric Epilepsy Chief Dr. Brenda Porter, led a quality improvement effort to standardize the management of acute seizures in the pediatric Epilepsy Monitoring Unit (EMU) at Lucile Packard Children's Hospital / Stanford Children's Health. Such safety measures are particularly imperative in Phase 1 EMU patients, who are admitted expressly for the purpose of eliciting and recording seizures on video EEG for surgical planning;

provoking measures such as medication cessation are often used, putting these patients at risk for complications including status epilepticus. We implemented a standardized seizure management protocol, including didactic teaching of nursing staff, posting of the protocol in the room of all EMU patients, and other iterative improvements by the physician/nursing team. Following this, in Phase 1 study patients, the number of seizures that are managed in full accordance with national safety and quality standards (including providing rapid seizure first aid and brief neurologic assessment) significantly increased from 40% to 90%, along with an increase in self-reported nursing confidence with seizure management. These data were presented at the 2020 Child Neurology Society meeting, and this work is published in *Hospital Pediatrics*.

Trainees

Currently, I mentor 3 research assistants and 6 undergraduate students in my independent laboratory.

Past trainees:
Dr. Amanda Sandoval Karamian (2018-2020)
Project: *Aberrant White Matter in Neonates with Nonstructural Epilepsy*
Dr. Sandoval Karamian was awarded a **Neurosciences Research Scholars Track** fellowship, entitling her to 6 months protected research time during residency to perform this work. This work resulted in a publication in *Epilepsia.*
Position: Epilepsy fellow at the Children's Hospital of Philadelphia.

Dr. Sara Pavitt (2018-2020)
Project: *Quality Improvement in the Pediatric Epilepsy Monitoring Unit*. Published in *Hospital Pediatrics*.
Current position: Assistant Professor, UT-Austin School of Medicine.

Tristan Saucedo (2019- present)
Project: *Maladaptive Myelination in Epilepsy*. Tristan was awarded a **2020 BioX Summer Undergraduate Fellowship and a 2021 Stanford Undergraduate Major Grant** to continue this work.
Position: Stanford Undergraduate

Eleanor Frost (2016-2020)
Project: *Maladaptive Myelination in Epilepsy.* Eleanor was awarded a **2017 BioX Summer Undergraduate Fellowship** to continue this work.
Position: Graduated from Stanford with a co-terminal master's degree; applying to MD-PhD programs.

Caroline Soane (2018-2019)
Project: *Maladaptive Myelination in Epilepsy.*
Position: Graduated from Stanford; now a medical student at Vanderbilt University.

Lydia Tam (2017-2018)
Project: *Maladaptive Myelination in Epilepsy.*
Position: Graduated from Stanford; now a medical student at Stanford.

Danielle Fraga (2016-2017)
Project: *Maladaptive Myelination in Epilepsy.*

Position: Completed undergraduate and master's degree at Stanford, now a Study Data Manager at Genentech.

Other Teaching / Mentoring

Invited to give Neurology lectures to Stanford medical students, 2019

Preceptor in Pediatric Neurology / Epilepsy resident/fellow clinic, 2019

"Pediatric Epilepsy Syndromes," Neurology residents didactic presentation, 2020

"Management of Pediatric Status Epilepticus," Neurology residents Boot Camp lecture series, 2017, 2018, 2020, 2021

Other Professional Experience

Member, Child Neurology Society Research Committee, 2021 - present

Member, Scientific Program Committee, American Epilepsy Society, 2019 - present

Courses in Optical Fiber Photometry and CLARITY, laboratory of Dr. Karl Deisseroth at Stanford, 2018-2019

Stanford University Intensive Course on Clinical Research, 2018

SCOPE Physician for Stanford Children's Hospital, 2012 - 2013
Served as an advocate for a severely disabled child requiring multiple subspecialty care, including accompanying family to appointments, leading goals of care discussions and making home visits.

Pack the Bag program, Ecumenical Hunger Program, 2011 - 2015
My pediatrics residency class started this program to help school age children with food insecurity in East Palo Alto.

Mentor for high school students interested in careers in medicine (Woodside High School Woodside, CA), 2011-2012

Tutor for medical pharmacology course, UNC-Chapel Hill School of Medicine, 2004

Medical Student Mentoring Workshop, Association of University Professors of Neurology, 2004

Co-President, UNC American Medical Women's Association, 2002 - 2004
Our chapter organized a seminar series addressing issues pertaining to women in medicine and started a mentoring program pairing female medical students and senior female faculty members of UNC School of Medicine.

Co-President, UNC Student Interest Group in Neurology, 2003 - 2004
Organized a seminar series and mentoring program.

Coordinator, UNC Student Health Action Coalition, 2002 - 2003

UNC SHAC is the oldest student-run free health clinic in the US. I regularly led the weekly clinic, and led fundraising and community outreach efforts. Among other accomplishments, the committee I headed raised sufficient funds to establish the first SHAC Endowment Fund.

Professional Affiliations

International Society for Neuroscience	2009 - present
American Academy of Neurology	2016 - present
American Epilepsy Society	2016 - present
American Clinical Neurophysiology Society	2018 - present
Child Neurology Society	2018 - present