BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Lee, Wei-Chung Allen

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

POSITION TITLE: Associate Professor of Neurology and Neurobiology

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
California Institute of Technology	S.B.	06/1998	Chemical Engineering
Bowdoin College	A.B.	06/1998	Biochemistry Government
Massachusetts Institute of Technology	Ph.D.	06/2006	Neuroscience
Harvard Medical School	Postdoctoral	07/2012	Neurobiology
Boston Children's Hospital/Harvard Medical School	Instructor	04/2017	Neurobiology

A. Personal Statement

I am an Associate Professor of Neurology and Neurobiology. The long-term mission of my research is to understand the organizational principles of neuronal circuits underlying computations and information processing. I use the rodent [1,3-4] and *Drosophila* nervous systems [1-2] as models for *'functional connectomics'*. Our goal is to discover conserved and distinguishing circuit motifs underlying sensorimotor integration. I have expertise in neuronal anatomy [1-4], large-scale electron microscopy (EM) [2-4], X-ray tomography [1], and combining these structural techniques with functional *in vivo* multi-photon microscopy [4]. We use these approaches to elucidate the logic and mechanisms underlying neuronal circuit wiring and connectivity. While others have collected large connectomic datasets, structural connectomes are most powerful when they are linked to physiological information. My group is at the forefront of this functional connectomics approach.

Citations:

1. Kuan AT*, Phelps JS*, Thomas LA, Nguyen TM, Han J, Chen CL, Azevedo AW, Tuthill JC, Funke J, Cloetens P, Pacureanu A, Lee WCA. Dense neuronal reconstruction through X-ray holographic nano-tomography. ***Nat Neurosci***. 2020 Dec;23(12):1637-1643. PMCID: PMC8354006.
2. Phelps JT*, Hildebrand DGC*, Graham BJ*, Kuan AT, Thomas LA, Nguyen T, Buhmann J, Azevedo AW, Shanny BL, Funke J, Tuthill JC, Lee WCA. Reconstruction of motor control circuits in adult *Drosophila* using automated transmission electron microscopy. ***Cell***. 2021 Feb 4;184(3):759-774.e18. PMCID: PMC8312698.
3. Nguyen T*, Thomas LA*, Rhoades JL, Ricchi I, Yuan XC, Sheridan A, Hildebrand DGC, Funke J, Regehr WG, Lee WCA. Structured connectivity in the cerebellum enables resilient pattern separation. ***Nature*** 2023 Nov 23;613(7944):543-549. PMCID: PMC10324966.
4. Kuan AT*, Bondanelli G*, Driscoll LN, Han J, Kim M, Hildebrand DGC, Graham BJ, Thomas LA, Wilson DE, Panzeri S, Harvey CD, Lee WCA. Synaptic wiring motifs in posterior parietal cortex support decision-making. ***Nature*** 2024 Feb 21. doi: 10.1038/s41586-024-07088-7. Epub ahead of print. PMID: 38383788. PMCID: *in progress*.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2023 - Present	Associate Professor of Neurobiology, Department of Neurobiology, Harvard Medical School
2022 - Present	Associate Professor of Neurology, F.M. Kirby Neurobiology Center, Boston Children's Hospital
2019 - 2021	NIH BRAIN Initiative Study Sections, ad hoc reviewer (ZRG1 IFCN-T, ZEB1 OSR-F)
2017 - 2022	Assistant Professor of Neurology, F.M. Kirby Neurobiology Center, Boston Children's Hospital and Harvard Medical School
2012 - 2017	Instructor in Neurobiology, Harvard Medical School
2007 - 2012	Postdoctoral Fellow, Harvard Medical School
2006 - 2007	Postdoctoral Associate, MIT
2007 - Present	Curriculum Advisory Committee Member, Exploration Summer Programs
1999 - Present	Member, Society for Neuroscience

Honors

2021	Jennifer N. Bourne Prize in Brain Ultrastructure, Society for Neuroscience
2013	Edward R. and Anne G. Lefler Foundation Fellow, Harvard Medical School
2011	Ruth L. Kirschstein National Research Service Award (1F32EY018532-01A1), NIH
2005	Elli Lilly Graduate Student Travel Award, Society for Neuroscience
2004	Poitras Predoctoral Fellow, MIT
1996	James Bowdoin Scholar for Academic Excellence, Bowdoin College

C. Contributions to Science

1. *Sensorimotor Connectomics and Decision-making Circuit Motifs*: My lab develops and uses a combination of high resolution, structural connectomics approaches such as large-scale electron microscopy (EM) and X-ray holographic nanotomography (XNH) to reconstruct the network anatomy of neuronal circuits involved in sensorimotor integration and decision-making. I developed and first applied these techniques to analyze the fly nervous system, mouse cerebellum and association cortex. My aim in our non-mammalian work is to discover general principles that may be conserved in larger brains.

    a. Kuan AT*, Bondanelli G*, Driscoll LN, Han J, Kim M, Hildebrand DGC, Graham BJ, Thomas LA, Wilson DE, Panzeri S, Harvey CD, Lee WCA. Synaptic wiring motifs in posterior parietal cortex support decision-making. ***Nature*** 2024 Feb 21. doi: 10.1038/s41586-024-07088-7. Epub ahead of print. PMID: 38383788. PMCID: *in progress*.

    b. Nguyen T*, Thomas LA*, Rhoades JL, Ricchi I, Yuan XC, Sheridan A, Hildebrand DGC, Funke J, Regehr WG, Lee WCA. Structured connectivity in the cerebellum enables resilient pattern separation. ***Nature*** 2023 Nov 23;613(7944):543-549. PMCID: PMC10324966.

    c. Phelps JT*, Hildebrand DGC*, Graham BJ*, Kuan AT, Thomas LA, Nguyen T, Buhmann J, Azevedo AW, Shanny BL, Funke J, Tuthill JC, Lee WCA. Reconstruction of motor control circuits in adult *Drosophila* using automated transmission electron microscopy. ***Cell***. 2021 Feb 4;184(3):759-774.e18. PMCID: PMC8312698.

    d. Kuan AT*, Phelps JS*, Thomas LA, Nguyen TM, Han J, Chen CL, Azevedo AW, Tuthill JC, Funke J, Cloetens P, Pacureanu A, Lee WCA. Dense neuronal reconstruction through X-ray holographic nano-tomography. ***Nat Neurosci***. 2020 Dec;23(12):1637-1643. PMCID: PMC8354006.

2. *Functional Connectomics*: My connectomics work strives to combine network structure and function. Specifically, we typically integrate structural wiring and connectivity with *in vivo* two-photon calcium imaging. Functional connectomics is a nascent field that allows us to work across multiple levels of analysis – from networks, subcellular domains, to individual synapses – in the same information-rich datasets. Transmission EM is a key component of this approach because of its unsurpassed spatial resolution, signal-to-noise, and speed relative to other serial EM imaging methods. It allows us to identify excitatory and inhibitory neurons

and synapses, examine connectivity motifs (such as convergent input onto common targets), and analyze the spatial distribution of synaptic contacts, all within the same functionally characterized networks.

I first demonstrated that large-scale EM could be applied to uncover circuit motifs in the cortex. Our results argued for functionally specific wiring patterns between pyramidal neurons that are radically different than for inhibitory interneurons. These excitatory functional assemblies are poised to amplify and sharpen incoming signals and selectively bind long-range target regions with local information processing, whereas inhibitory interneurons are best positioned to modulate the local gain of cortical circuits. My lab is now developing and applying novel connectomics approaches to discover differences in circuit architectures in areas beyond primary visual cortex and their role in computations.

a. Kuan AT, Bondanelli G, Driscoll LN, Han J, Kim M, Hildebrand DGC, Graham BJ, Thomas LA, Wilson DE, Panzeri S, Harvey CD, Lee WCA. Synaptic wiring motifs in posterior parietal cortex support decision-making. ***Nature*** 2024 Feb 21. doi: 10.1038/s41586-024-07088-7. Epub ahead of print. PMID: 38383788. PMCID: *in progress*.

b. Lee WCA, Bonin V, Reed M, Graham BJ, Hood G, et al. Anatomy and function of an excitatory network in the visual cortex. ***Nature***. 2016 Apr 21;532(7599):370-4. PMCID: PMC4844839.

c. Hildebrand DGC, Cicconet M, Torres RM, Choi W, Quan TM, Moon J, Wetzel AW, Scott Champion A, Graham BJ, Randlett O, Plummer GS, Portugues R, Bianco IH, Saalfeld S, Baden AD, Lillaney K, Burns R, Vogelstein JT, Schier AF, Lee WCA, Jeong WK, Lichtman JW, Engert F. Whole-brain serial-section electron microscopy in larval zebrafish. ***Nature***. 2017 May 18;545(7654):345-349. PMCID: PMC5594570.

d. Bock DD, Lee WCA, Kerlin AM, Andermann ML, Hood G, Wetzel AW, Yurgenson S, Soucy ER, Kim HS, Reid RC. Network anatomy and *in vivo* physiology from a group of visual cortical neurons. ***Nature***. 2011 Mar. 10; 471(7337): 177-82. PMCID: PMC3095821.

3. *Connectomics Tools*: My lab has developed labeling strategies, imaging platforms, and analysis pipelines for connectomics. Our efforts are aimed at understanding organizational principle of network anatomy and physiology of neuronal circuits using a combination of high resolution, structural connectomics approaches such as large-scale electron microscopy (EM) and X-ray holographic nanotomography (XNH) coupled with machine learning tools for connectomic analysis. We make all of our tools, datasets, and instrumentation designs open-access and publicly accessible to democratize connectomics.

   a. Sheridan A, Nguyen T, Deb D, Lee WCA, Saalfeld S, Turaga S, Funke J. Local Shape Descriptors for Neuron Segmentation. ***Nat Methods***. 2022 Dec 30. PMCID: PMC9911350.

   b. Buhmann J, Sheridan A, Gerhard S, Krause R, Nguyen T, Heinrich L, Schlegel P, Lee WCA, Wilson RI, Saalfeld S, Jefferis G, Bock D, Turaga S, Cook M, Funke J. Automatic Detection of Synaptic Partners in a Whole-Brain *Drosophila* EM Dataset. ***Nat Methods***. 2021 Jul;18(7):771-774. PMCID: PMC7611460.

   c. Zhang Q, Lee WCA, Paul DL, Ginty DD. Multiplexed peroxidase-mediated electron microscopy labeling in the mammalian nervous system. ***Nat Neurosci***. 2019 May; 22(5):828-839. PMCID: PMC6555422.

   d. Yoo I, Hildebrand DGC, Tobin WF, Lee WCA, Jeong WK. ssEMnet: Serial-section Electron Microscopy Image Registration using a Spatial Transformer Network with Learned Features. In Deep Learning in Medical Image Analysis and Multimodal Learning for Clinical Decision Support (Springer), ***MICCAI***. 2017. pp. 249-257. doi: 10.1007/978-3-319-67558-9_29.

4. *Adult Neuronal Plasticity*: My early molecular experiments (below) examined the expression of a candidate plasticity gene, *cpg15*, and led to the hypothesis that neuronal remodeling occurs normally in the superficial layers of the adult neocortex. To directly test this prediction, I used two-photon microscopy and transgenic mice to monitor neuronal remodeling in the intact brain. I discovered that the dendritic arbors of inhibitory interneurons are more structurally dynamic than pyramidal neurons in the mature cortex. This finding was surprising, because structural plasticity at the level of dendritic arbors was assumed not to normally occur in the adult. Moreover, the differences in structural plasticity between interneurons and pyramidal cells suggested that cell type-specific rules govern plasticity in the adult circuit. These findings opened up questions of how interneurons (and their remodeling) impact circuit properties.

a. Lee WCA, Huang H, Feng G, Sanes JR, Brown EN, et al. Dynamic remodeling of dendritic arbors in GABAergic interneurons of adult visual cortex. ***PLoS Biol***. 2006 Feb;4(2):e29. PMCID: PMC1318477.

b. Lee WCA, Chen JL, Huang H, Leslie JH, Amitai Y, et al. A dynamic zone defines interneuron remodeling in the adult neocortex. ***PNAS***. 2008 Dec 16;105(50):19968-73. PMCID: PMC2604980.

c. Holtmaat A, Bonhoeffer T, Chow DK, Chuckowree J, De Paola V, et al. Long-term, high-resolution imaging in the mouse neocortex through a chronic cranial window. ***Nat Protoc***. 2009;4(8):1128-44. PMCID: PMC3072839.

d. Chen JL, Flanders GH, Lee WCA, Lin WC, Nedivi E. Inhibitory dendrite dynamics as a general feature of the adult cortical microcircuit. ***J Neurosci***. 2011 Aug 31;31(35):12437-43. PMCID: PMC3180878.

5. *Molecular Mechanisms of Cortical Plasticity*: My early work examined molecular mechanisms of activity dependent neuronal plasticity. I focused on an effector gene known as candidate plasticity gene 15 (*cpg15*) or neuritin (its human homolog). *cpg15* is an activity-regulated gene encoding a membrane-bound ligand that coordinately regulates growth of apposing dendritic and axonal arbors and the maturation of their synapses. These properties made it an attractive candidate for participating in mammalian visual system plasticity. I discovered that *cpg15* expression in visual cortex correlates with the critical period for development of eye-specific preference in the primary visual cortex and reflects the capacity of the circuit for plasticity in response to visual perturbation. In collaboration with Tadahiro Fujino, we also examined the upstream signaling pathways governing *cpg15* expression and generated a conditional mutant model.

   a. Lee WCA, Nedivi E. Extended plasticity of visual cortex in dark-reared animals may result from prolonged expression of *cpg15*-like genes. ***J Neurosci***. 2002 Mar 1;22(5):1807-15. PMCID: PMC3062906.

   b. Fujino T, Lee WCA, Nedivi E. Regulation of *cpg15* by signaling pathways that mediate synaptic plasticity. ***Mol Cell Neurosci***. 2003 Nov;24(3):538-54. PMCID: PMC3065975.

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/1p36qcyNuh-Aq/bibliography/public/