BIOGRAPHICAL SKETCH

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NAME: Andrew Tadashi Kodani

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

POSITION TITLE: Assistant Member (Professor)

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 California, Berkeley	BA	05/2005	Molecular and Cell Biology
University of California, Irvine	Ph.D.	03/2010	Development and Cell Biology
University of California, San Francisco	Post Doc	06/2016	Biochemistry and Biophysics

A. Personal Statement

I am an Assistant Member (Professor) of Cell and Molecular Biology at St. Jude Children's Research Hospital. My research program aims to elucidate how human mutations in centrosome proteins cause the neurodevelopmental diseases, microcephaly (small head and brain) and lissencephaly (smooth brain). We have been recognized by several prestigious awards including: the NIH Exploratory/Developmental Research Grant Award, the Charles Hood Foundation Award, and the William Randoph Hearst Foundation, to study brain development.

We have long-standing interest in the function and mechanism of the centrosome in neurodevelopmental diseases. We discovered that MCPH-associated proteins assemble at the base of the mother centriole to promote centriole duplication (Kodani et al. *Elife*. 2015) in neural progenitor cells to prevent mitotic delays and premature differentiation (Jayarman and Kodani et al. *Neuron.* 2016). We have also uncovered a novel regulatory pathway controlled by a deubiquitylase and microcephaly-associated protein, USP9X, which controls the stability of a centriole duplication initiating factor at the centrosome (Kodani et al. *JCB*. 2019). We recently discovered a novel LIS-associated protein, *CEP85L*, which promotes centrosome organization and neuronal migration. Disruption to *CEP85L* causes posterior specific pachygyria (small brain folds) (Kodani et al. *Neuron*. 2020). I have demonstrated a record of successful and productive research projects related to elucidating how mutations in centrosome proteins underly the etiological cause of MCPH and LIS by disrupting neural progenitor expansion, differentiation and neuronal migration.

B. Positions and Honors

Academic Positions:

2020-present Assistant Member (Professor), Department of Cell and Molecular Biology and The Center for Pediatric Neurological Disease Research, St. Jude Children's Research Hospital
2016-2020 Instructor, Department of Genetics and Genomics, Boston Children's Hospital and the Department of Pediatrics, Harvard Medical School

Professional Memberships:

2000-present American Society for Cell Biologists

2020-present Society for Neuroscience

Ad hod Journal Reviewer:
Journal of Cell Biology, EMBO, EMBO reports, Life Science Alliance, Developmental Cell, Cells, Science

Honors:

2018–present	NIH R21NS104633
2018	ASCB Meeting Travel Grant
2018	Hearst Foundation Award FY18
2017–2020	Charles Hood Foundation Award
2016	ASCB Meeting Travel Award
2014-2016	Sandler Family Supporting Foundation Program for Breakthrough Biomedical Research Fellowship
2013	The EMBO Meeting Travel Grant
2013	The EMBO Meeting Poster of the Day
2013	The EMBO Meeting Poster Prize Awarded for Outstanding Poster Presentation
2010-2013	NIH Institutional Research Service Award in Molecular and Cellular Basis of Cardiovascular Disease
2009	William Redfield Graduate Fellowship
2006-2007	Howard Hughes Medical Institute Teaching Fellows Program

Invited Seminars (2016-2020):

2016	ASCB Meeting 2016 Talks San Francisco, CA
2017	Seminar, Rowland Institute Cambridge, MA
2018	ASCB Meeting 2018 Talks San Diego, CA
2019	Seminar, UC Davis, Davis, CA
2019	Cold Spring Harbor Centrosome and Cilia Meeting, Suzhou, China
2020	Seminar, Rutgers University, New Brunswick, NJ
2020	Seminar, University of Chicago, Chicago, IL
2020	Seminar, Kennedy Krieger Institute and Johns Hopkins, Baltimore, MD
2020	Seminar, New York University, Manhattan, NY
2021	Seminar, University of Tennessee Health Science Center, Memphis, TN
2021	Seminar, Kabuki Syndrome Foundation Annual Meeting

C. Contribution to Science
Total publications: 15 **Total citations:** 1174
h-index: 14
Complete list (My Bibliography): https://tinyurl.com/2bj7sy86

1. Centrosomes promote neuronal migration.

Using clinical sequencing of cohorts with neural migrational disorders, we identified a new syndrome with marked regional-specific pachygyria (small brain folds) in the posterior cortex, caused by de novo mutations in CEP85L. We demonstrated that CEP85L is a centrosomal protein required for neuronal migration in the developing mouse cortex, a phenotype associated with human pachygyria [1]. Loss of CEP85L disrupted the organization of the centrosome and microtubule cytoskeletal stability. This led us to conclude that CEP85L controls centrosomal architecture and microtubule dynamics, a novel paradigm in understanding the mechanisms governing neuronal migration and brain disease.

1. **Kodani A** et al., Walsh C.A**.** *Posterior Neocortex-Specific Regulation of Neuronal Migration by CEP85L Identifies Maternal Centriole-Dependent Activation of CDK5.* Neuron, 2020. 106(2): 246-255. PMID: 32097629.

2. Centrosome biogenesis controls neurogenesis

Mutations that cause Primary Microcephaly (MCPH), a neurodevelopmental disorder characterized by a reduction in brain size, affect genes encoding centrosomal proteins. It had been proposed that MCPH mutations

disrupt centrosome biogenesis, but it was unclear whether MCPH proteins function together to promote centriole duplication. While in Jeremy Reiter's lab at UCSF, I discovered that a subset of four MCPH proteins form a biochemical complex and are recruited to the centrosome in a hierarchical manner to promote centriole duplication [2]. This was the first indication that MCPH proteins function together to control a specific cellular function critical for neurogenesis.

These findings led us to investigate the role of proteins downstream of these four MCPH proteins and expanded the centriole duplication pathway to include the MCPH proteins, ASPM and CPAP/CENPJ [3, 4]. To study the developmental function of two components in this pathway, we created mutations in the genes encoding mouse *Wdr62* and *Aspm*. Consistent with patient phenotypes, *Wdr62* and *Aspm* mutant mice were microcephalic and neural progenitors exhibited centriole duplication defects [3]. Strikingly, there was an increase in intermediate progenitors at the expense of NPC in the embryonic mutant brains. The premature differentiation defect resulted from the inability of NPC to form apical attachments to the ventriclular membrane. This was the first demonstration that centrioles have a function beyond mitotic spindle formation in NPC during neurodevelopment. Consistent with the premature differentiation in the mouse brain, ferrets with *ASPM* mutations exhibited a similar phenotype, suggesting that centriole biogenesis is required for progenitor maintenance in mammals [4].

To expand on the role of centrioles during neurodevelopment we investigated the role of the evolutionarily conserved role of the centrosomal protein SFI1 in centriole duplication. We found that SFI1 recruits the deubiquitylating enzyme USP9X to the centrosome where it removes ubiquitin from the microcephaly protein, *STIL*, a protein required for centriole duplication [5]. As *USP9X* is mutated in female restricted mental retardation with microcephaly, we examined patient derived fibroblasts and found STIL to be largely degraded. Moreover, we concluded that enzymatic regulation of centrosome protein stability is critical for normal neurodevelopment.

2. **Kodani A**, et al., and Reiter J.F. *Centriolar satellites assemble centrosomal microcephaly proteins to recruit CDK2 and promote centriole duplication* **. Elife**, 2015. 22(4). PMID: 26297806.

3. Jayaraman D and **Kodani A** et al., Walsh C.A**.** *Microcephaly Proteins Wdr62 and Aspm Define a Mother Centriole Complex Regulating Centriole Biogenesis, Apical Complex, and Cell Fate*. **Neuron**, 2016. 92(4): 813-828. PMID: 2794163.

4. Johnson M, Sun Z, **Kodani A** et al., Walsh C.A. *Aspm knockout ferret reveals an evolutionary mechanism governing cerebral cortical size.* **Nature,** 2018. 556(7701):370-375. PMID: 29643508

5. **Kodani A,** et al., Walsh C.A., Reiter J.F. *SFI1 promotes centriole duplication by recruiting USP9X to stabilize the microcephaly protein STIL.* **Journal of Cell Biology,** 2019. 10.1083/jcb. 201803041. PMID: 31197030

3. Zika virus disrupts centrosome organization to suppress innate immunity.

Zika virus (ZIKV) is transmitted in over 45 countries including the United States, and ZIKV infection during pregnancy is a cause of microcephaly. Despite extensive work showing that ZIKV can infect neural progenitor cells in both mice and humans, the cellular mechanisms by which ZIKV disrupt neural progenitor expansion and maintenance remains unclear. We have elucidated a molecular mechanism by which ZIKV disrupts centrosome organization in neural stem cells and made the surprising discovery that ZIKV coopts the same pathway that is disrupted in inherited microcephaly. We also found that ZIKV disorganizes the centrosome to degrade TBK1, a major regulator of the innate immune response. ZIKV infection led to the Ubiquitin-mediated degradation of TBK1 and suppression of IFNβ production [6,7]. These was the first indication that ZIKV disrupts centrosome integrity to evade host immunity.

6. **Kodani A,** *Knopp K,* et al., and Reiter J.F. *Zika virus alters centrosome organization to suppress the innate immune response.* **EMBO Reports, 2022.** 10.15252/embr.202052211. PMID: 35793002

7. Guise A, et al., **Kodani A,** Mochida G, Steen J. *Integrative systems biology characterizes immunopathogenesis of murine Zika Virus microcephaly. In review at* **Immunity, 2021.**

4. Centrioles control signaling in NPCs.

Centrioles are microtubule-based structures that nucleate the primary cilia, which are cellular projections required to transduce Hedgehog signaling, a developmental pathway required for neurogenesis. In collaboration with Dr. Christopher A. Walsh we discovered that a MCPH mutation in the microtubule-severing enzyme, Katanin B1 led to the formation of supernumerary centrioles in patient cells and *Katanin* mutant mice [8]. Consequently, these extra centrioles nucleated primary cilia that were defective in transducing Hedgehog signaling leading to

neurogenesis defects in the mouse mutants. This was the first demonstration that a microcephaly gene disrupts Hedgehog signaling during neurodevelopment.

8. Hu W.F., Pomp O, Ben-Omran T, **Kodani A.** et al., and Walsh, C.A, *Katanin p80 Regulates Human Cortical Development by Limiting Centriole and Cilia Number.* **Neuron**, 2014. 84(6):1240-57. PMID: 25521379.

5. Alternative splicing of centrosomal genes controls NPC identity

The centrosomal protein, *Ninein* is mutated in microcephalic primordial dwarfism, a rare genetic disorder that causes growth retardation, microcephaly and mental retardation. I discovered that Ninein is recruited to the subdistal appendage by the intraflagellar transport component KIF3A [9]. This was the first demonstration that ciliary transport components have a role in anchoring microtubules at the centrosome during interphase.

In a collaboration with Drs Xiaochang Zhang and Christopher A. Walsh, we found that Ninein was alternatively spliced in neurons [10]. In NPCs Ninein localizes to the subdistal appendage but in neurons a cryptic truncating exon precludes Ninein from the centrosome. Strikingly, expression of the neuronal Ninein isoform in NPCs causes premature differentiation. This was the first indication that splicing of a centrosomal protein altering its localization is sufficient to drive neural progenitor differentiation.

9. **Kodani A.**, et al., and J.F. Reiter, *Kif3a interacts with Dynactin subunit p150^{Glued} to organize centriole subdistal appendages*. **EMBO J.**, 2013 32(4):597-607. PMID: 23386061. PMC3579144.
10. Zhang X, Chen MH, Wu X, **Kodani A,** *et* al., and Walsh C.A., *Cell-Type-Specific Alternative Splicing Governs Cell Fate in the Developing Cerebral Cortex.* **Cell**, 2016. 166(5):1147-1162. PMID: 2756344.

D. Additional Information: Research Support and/or Scholastic Performance

Completed Research Support

NIH R21NS104633 (co-PI Andrew Kodani and Jeremy Reiter) 7/01/18-6/30/21
Charles Hood Foundation Award Kodani (PI) 1/1/18-12/31/20
William Randolph Hearst Foundation Award Kodani (PI) 6/01/18-12/31/19
NIH T32HL007731 Kodani (PI) 8/01/10-7/31/12 and 8/01/12-7/31/13