BIOGRAPHICAL SKETCH

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NAME: Kei M Igarashi, Ph.D

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

POSITION TITLE: Assistant 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 Tokyo	BS	03/2001	Molecular Biology
University of Tokyo	PhD	03/2007	Physiology
University of Tokyo	Postdoc	05/2009	Physiology
Norwegian University of Science and Technology	Postdoc	12/2015	Neuroscience

A. Personal Statement

Throughout my career, a central direction of my research has been to understand how interactions between multiple brain regions give rise to behavior and how impairment of these interactions results in disease. To this end, I have been pursuing research using the entorhinal-hippocampal circuit as a model system, and investigating cellular and circuit mechanisms that support memory. I have a broad background in systems neuroscience, with extensive training in high-density electrophysiology from rodents performing memory tasks, spike and local field potential (LFP) analyses, functional optical imaging, and single-cell neuroanatomy. My Ph.D. work in the Kensaku Mori lab at the University of Tokyo and postdoc research in the lab of Edvard Moser and May-Britt Moser at the Norwegian University of Science and Technology revealed fundamental circuit mechanisms and architectures that underlie sensory perception and memory (see selected publication list below). In particular, studies conducted with the Mosers made extensive use of multielectrode recording from behaving animals and gave rise to fundamental discoveries pertaining to learning-dependent changes in coherence in oscillatory activity between hippocampus and entorhinal cortex. In my own lab at the University of California, Irvine (UCI), I am extending these approaches to study (1) cellular and circuit mechanisms of sensory perception and memory in healthy subjects, and (2) how impairment of such mechanisms causes memory deficit in Alzheimer's disease. The work outlined in this proposal constitutes a logical extension of my postdoctoral work and recent work from my own lab and will allow me to make a significant contribution to the field of Alzheimer's research, by using the expertise I have gained in my career.

1. Jun H, Soma S, Saito T, Saido TC, **Igarashi KM***, Disrupted place cell remapping and impaired grid cells in a knock-in model of Alzheimer's disease (2020) *Neuron.* 107:1095-1112 PMID: 32697942
2. Nakazono T, Lam TN, Patel AY, Kitazawa M, Saito T, Saido TC, **Igarashi KM*** (2017). Impaired In Vivo Gamma Oscillations in the Medial Entorhinal Cortex of Knock-in Alzheimer Model. *Front Syst Neurosci*. 11:48 PMID: 28713250
3. Lu L, **Igarashi KM**, Witter MP, Moser EI, Moser MB (2015). Topography of Place Maps along the CA3-to-CA2 Axis of the Hippocampus. *Neuron*. 87:1078-92 PMID: 26298277
4. **Igarashi KM***, Lu L, Colgin LL, Moser MB, Moser EI* (2014). Coordination of entorhinal-hippocampal ensemble activity during associative learning. *Nature*. 510: 143-7 PMID: 24739966 (*Co-corresponding authors)

B. Positions and Honors

Positions and Employment

2016- Assistant Professor, Department of Anatomy & Neurobiology, UCI
2016- Fellow, Center for the Neurobiology of Learning & Memory, UCI
2018- Faculty Member, Institute for Memory Impairments and Neurological Disorders, UCI

Other Experience and Professional Memberships

2001-pres Member, Japan Neuroscience Society
2005-pres Member, Society for Neuroscience
2010-pres Member, Federation of European Neuroscience Societies
2010-pres Member, Norwegian Neuroscience Society
2019, 2020 NIH Neurobiology of Learning and Memory (LAM) study section, Ad-hoc reviewer
2020 NIH Brain Initiative study section ZRG1 IFCN-T(55), Ad-hoc reviewer
2020 Wellcome Trust (UK), Ad-hoc reviewer

Honors

2004 – 2007 Predoctoral Fellowship, Japan Society for the Promotion of Science
2007 – 2009 Postdoctoral Fellowship, Japan Society for the Promotion of Science
2012 Norwegian Research Council Postdoctoral Fellowship
2013 Gordon Research Conference Travel Award
2014 Young Investigator Award, Japan Neuroscience Society
2016 PRESTO Career Development Award, Japan Science and Technology Agency
2016 Fay/Frank Seed Grant, Brain Research Foundation
2017 Mishima Kaiun Prize, Mishima Kaiun Memorial Foundation
2018 Ando Momofuku Award, Ando Foundation
2019 New Vision Award, Donors Cure Foundation
2019 Alzheimer's Disease Research Award, BrightFocus Foundation

C. Contributions to Science

1. In my postdoctoral work in the laboratory of Edvard Moser and May-Britt Moser at the Norwegian University of Science & Technology, I established a novel paradigm to unravel the role of **the entorhinal-hippocampal circuit in memory**. I developed a simultaneous recording method from the entorhinal cortex and hippocampus with high-density electrodes, while rats are performing an association memory task. I discovered that synchronizing gamma oscillations in the entorhinal cortex and hippocampal CA1 triggered increase of memory performance during learning. These results for the first time indicated entorhinal-hippocampal gamma oscillations as a brain mechanism to enhance memory. I proposed that gamma oscillations enhance memory performance though an LTP mechanism in the synapse between the entorhinal cortex and CA1. In my own lab at UCI, I further tested the role of entorhinal gamma oscillations in an Alzheimer's disease model mouse, and found that the entorhinal gamma oscillations are impaired in the medial entorhinal cortex (MEC) of an APP knock-in mouse.

    a. **Igarashi KM***, Lu L, Colgin LL, Moser MB, Moser EI* (2014). Coordination of entorhinal-hippocampal ensemble activity during associative learning. *Nature*. 510: 143-7 PMID: 24739966 (*Co-corresponding authors)
    b. **Igarashi KM*** (2015). Plasticity in oscillatory coupling between hippocampus and cortex. *Curr Opin Neurobiol*. 35:163-168 PMID: 26425996
    c. Nakazono T, Lam TN, Patel AY, Kitazawa M, Saito T, Saido TC, **Igarashi KM*** (2017). Impaired In Vivo Gamma Oscillations in the Medial Entorhinal Cortex of Knock-in Alzheimer Model. *Front Syst Neurosci*, 11:48 PMID: 28713250
    d. Jun H, Soma S, Saito T, Saido TC, **Igarashi KM***, Disrupted place cell remapping and impaired grid cells in a knock-in model of Alzheimer's disease (2020) *Neuron.* 107:1095-1112 PMID: 32697942

2. During my postdoctoral work in the Moser lab, I also investigated **pattern separation of place cells and grid cells** in the hippocampus and medial entorhinal cortex during animals' spatial memory. We found that place cells in the CA2 area of the hippocampus show pattern completion (memory filling-in) compared to those in CA3, which showed pattern separation (memory dissociation). I also investigated the roles of gamma oscillations in the spatial representation of grid cells in the medial entorhinal cortex (paper in preparation).

    a. Lu L, **Igarashi KM**, Witter MP, Moser EI, Moser MB (2015). Topography of Place Maps along the CA3-to-CA2 Axis of the Hippocampus. *Neuron*. 87:1078-92 PMID: 26298277
    b. **Igarashi KM*** (2016). Entorhinal map of space. *Brain Research*, 1637:177-87 PMID: 26940561

3. My Ph.D. and successive short postdoc works identified **olfactory brain circuits** that enable rodents to process a wide variety of odor information. These studies were performed in the laboratory of Kensaku Mori at the University of Tokyo. Basic circuitry in the olfactory brain regions, including the olfactory bulb and olfactory cortex, has been long unexplored, and thus it was unclear how the brain processes odor information. I have investigated rodent olfactory circuits, as they share olfactory brain regions of a similar structure to those in humans. In the publications listed below, I used a variety of imaging, electrophysiology, and anatomical techniques to investigate the circuit architecture of the olfactory bulb and cortex. I found that a small compartmentalized structure in the olfactory bulb (glomeruli) processes information of distinct odor molecules, forming clusters for hydrophilic and hydrophobic odors. I further discovered that individual odor information is decomposed into temporally fast coarse information and slow precise information by two distinct cell types, and conveyed to distinct regions in the olfactory cortex. These results contributed to the foundations of current research on olfactory perception and behaviors, and have been cited as background references in many research papers. Through the collaboration with Dr. Yoshihara and Dr. Mitsui at RIKEN BSI, Japan, I also had experience in generating BAC transgenic mice and macro-scale fluorescence imaging of neural activity from piriform cortex.

    a. **Igarashi KM**, Mori K. (2005). Spatial representation of hydrocarbon odorants in the ventrolateral zones of the rat olfactory bulb. *Journal of Neurophysiology*. 93:1007-1019 PMID: 15385587
    b. Mori K, Takahashi YK, **Igarashi KM**, Yamaguchi M. (2006). Maps of odorant molecular features in the Mammalian olfactory bulb. *Physiol Rev*. 86:409-433 PMID: 16601265
    c. Mitsui S, **Igarashi KM**, Mori K and Yoshihara Y. (2011). Genetic visualization of the secondary olfactory pathway in Tbx21 transgenic mice. *Neural Systems & Circuits*. 1:5 PMCID: PMC3257540
    d. **Igarashi KM***, Ieki N, An M, Yamaguchi Y, Nagayama S, Kobayakawa K, Kobayakawa R, Tanifuji M, Sakano H, Chen WR, Mori K.* (2012). Parallel mitral and tufted cell pathways route distinct odor information to different targets in the olfactory cortex. *Journal of Neuroscience*. 32:7970-85 (*Co-corresponding authors) PMCID: PMC3636718

Complete list of published work can be found on PubMed
https://pubmed.ncbi.nlm.nih.gov/?term=Igarashi+KM%5Bau%5D&sort=date

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

Ongoing Research Support

ACTIVE
R01AG063864 08/01/19 – 05/31/24
NIH/NIA
"Understanding the role of gamma oscillations underlying entorhinal cortex dysfunction in Alzheimer's disease"
Objective: This project will identify the role of gamma oscillations in the dysfunction of entorhinal cortex, and establish if brain stimulation at gamma frequency can be used for deep brain stimulation to rescue memory in AD mouse models.
Role: PI

R01MH121736 09/12/19 – 06/30/24
NIH/NIMH
"Understanding neural circuits for associative memory in the lateral entorhinal cortex"
Objective: This project will investigate the role of the lateral entorhinal cortex in associative memory.
Role: PI

R01AG066806 05/01/20 – 01/31/25
NIH/NIA
"Cell-type-specific vulnerability of the entorhinal cortex in Alzheimer's disease"
Objective: This project will investigate role of individual cell types in the medial entorhinal cortex during the progression of Alzheimer's disease.
Role: PI

Alzheimer's Disease Research Award 07/01/19 – 06/30/22
BrightFocus Foundation
"Rescuing Memory using Cell-type Specific Reactivation of Memory Network Activity"
Objective: This project will investigate role of fan cells in the lateral entorhinal cortex during the progression of Alzheimer's disease.
Role: PI

Alzheimer's Association Research Grant (AARG-17-532932) 10/1/17 – 9/30/21
Alzheimer's Association
"In vivo entorhinal-hippocampal synchronization in APP knock-in mice"
Objective: This project will develop methods for neurophysiological recording from entorhinal cortex and hippocampus of APP knock-in mice.
Role: PI

Research Grant (2016-08-01) 9/1/17 – 8/31/21
Whitehall Foundation
"Mechanisms for entorhinal-hippocampal circuit interactions"
Objective: This project will investigate the causal role of gamma synchronization in associative memory in healthy animals.
Role: PI

<u>PENDING</u>
None

<u>Completed Research Support</u>

PRESTO Career Development Award (JPMJPR1681) 10/1/16 – 3/31/20
Japan Science and Technology Agency
"Reverse Engineering of Brain Circuit Communications"
Objective: The goal of this project is to identify and manipulate the circuit activities underlying brain circuit communications in olfactory cortical regions.
Role: PI

Fay/Frank Seed Grant (BRFSG-2017-04) 6/1/17 – 5/31/19
Brain Research Foundation
"Neural circuit mechanisms in the early stage of Alzheimer's disease"
Objective: The goal of this project is to identify changes in neural circuit activities in the entorhinal cortex and hippocampus in the early phase of Alzheimer's model mice.
Role: PI