BIOGRAPHICAL SKETCH

NAME: Kei M Igarashi, Ph.D

eRA COMMONS USER NAME: KIGARASHI

POSITION TITLE: Associate Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Start Date MM/YYYY	Completion Date MM/YYYY	FIELD OF STUDY
University of Tokyo	BS	04/1996	03/2001	Molecular Biology
University of Tokyo	PhD	04/2001	03/2007	Neurophysiology
University of Tokyo	Postdoc	04/2007	05/2009	Neurophysiology
Norwegian University of Science and Technology	Postdoc	05/2009	01/2016	Systems 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 spike and oscillatory activities in the 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. Lee JY, Jun H, Soma S, Nakazono T, Shiraiwa K, Dasgupta A, Nakagawa T, Xie JL, Chavez J, Romo R, Yungblut Y, Hagihara M, Murata K, and **Igarashi KM*** (2021)
   Dopamine facilitates associative memory encoding in the entorhinal cortex.
   Nature 598: 321-326 PMID: 34552245
2. Jun H, Soma S, Saito T, Saido TC, **Igarashi KM*** (2020)
   Disrupted place cell remapping and impaired grid cells in a knock-in model of Alzheimer's disease
   Neuron 107:1095-1112 PMID: 32697942
3. 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
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, Scientific Appointments, and Honors

Positions and Employment

2022 -	Associate Professor (tenured); 2016- 2022 Assistant Professor, Department of Anatomy & Neurobiology, University of California, Irvine
2016-	Fellow, Center for the Neurobiology of Learning & Memory, UC Irvine
2018-	Faculty Member, Institute for Memory Impairments and Neurological Disorders, UC Irvine
2009-2015	Postdoctoral Fellow/Research Associate with Drs. Edvard Moser and May-Britt Moser, Kavli Institute for Systems Neuroscience, Norwegian University of Science and Technology
2007-2009	Postdoctoral Fellow with Drs. Kensaku Mori and Manabu Tanifuji University of Tokyo School of Medicine/RIKEN Brain Science Institute
2008	Visiting Researcher with Drs. Wei R Chen and Gordon Shepherd, Yale University
2003-2007	PhD student with Dr. Kensaku Mori, University of Tokyo School of Medicine
2001-2003	MS student with Dr. Kensaku Mori, University of Tokyo School of Medicine
2000-2001	Research assistant with Dr. Hitoshi Sakano, University of Tokyo

Scientific Appointments

2022 – 2025	Society for Neuroscience, Program Committee
2022	European Research Council (ERC), Ad-hoc reviewer
2022	NIH Special Emphasis Panel study section ZRG1 IFCN-J 02, Ad-hoc reviewer
2020	NIH Brain Initiative study section ZRG1 IFCN-T(55), Ad-hoc reviewer
2020	Wellcome Trust (UK), Ad-hoc reviewer
2019, 2022	Israel Science Foundation, Ad-hoc reviewer
2019, 2020	NIH Neurobiology of Learning and Memory (LAM) study section, Ad-hoc reviewer
2019	Alzheimer's Research United Kingdom, Ad-hoc reviewer
2017-pres	Alzheimer's Association, standing grant reviewer
2010-	Member, Federation of European Neuroscience Societies
2010-	Member, Norwegian Neuroscience Society
2005-	Member, Society for Neuroscience
2001-	Member, Japan Neuroscience Society

Reviewer for Journals: Nature, Nat Neurosci, Neuron, Sci Adv, Mol Psych, J Neurosci, eLife, Frontier journals, Scientific Reports, PLoS Biology, J Neurophysiol, Curr Opin Neurobiol

Honors

2022	Robert & Sylvia Mapel Research Endowment, UC Irvine School of Medicine
2022	Outstanding Early-Career Faculty Research Award, UC Irvine School of Medicine
2019	Alzheimer's Disease Research Award, BrightFocus Foundation
2019	New Vision Award for Alzheimer's Disease Research, Donors Cure Foundation
2018	Ando Momofuku Award, Ando Foundation
2017	Mishima Kaiun Prize, Mishima Kaiun Memorial Foundation
2016	Fay/Frank Seed Grant, Brain Research Foundation
2016	PRESTO Career Development Award, Japan Science and Technology Agency
2014	Young Investigator Award, Japan Neuroscience Society
2013	Gordon Research Conference Travel Award
2012	Norwegian Research Council Postdoctoral Fellowship
2007 – 2009	Postdoctoral Fellowship, Japan Society for the Promotion of Science
2004 – 2007	Predoctoral Fellowship, Japan Society for the Promotion of Science

C. Contributions to Science

1. In the current learning and memory research, one of the most important and outstanding questions is to understand **circuit mechanisms underlying associative memory**, which is the most common form of memory in our daily life. In the past 30 years, neuronal circuits underlying *spatial* memory and navigation have been identified by O'Keefe, Moser and Moser (2014 Nobel Prize). Despite these findings, mechanisms for episodic memory remain unclear. During my postdoc, I showed that the lateral entorhinal cortex (LEC) plays a major role in associative memory (**Igarashi et al., *Nature* 2014**). For summarizing the function of the

entorhinal cortex, I wrote a review paper (**Igarashi, *Brain Res*, 2016**). These works led to three awards (PRESTO Award from Japanese government, Ando Momofuku Award and Mishima Kaiun Award). However, my previous study was a correlational recording study of LEC spike activities from rats. This type of correlational recording study has been a classical tradition in electrophysiology research over the decades, and subsequent correlational recording studies from other labs further implicated roles of the LEC in various functions. Our views on the function of the LEC have thus been significantly divided in the past ten years, hampering advancement of the field. A major reason for this discordance was that these studies, including ours, were merely correlational without any circuit interventions, and recordings were collected from unknown neuronal populations. Since I started my lab, I investigate the role of the LEC using cell-type-specific intervention and recording to dissolve the status quo of the field. After a long-term effort, we recently obtained compelling results demonstrating that neurons in the LEC play a critical role in associative memory, a fast-type associative learning between newly-learned information and pre-learned memory (**Lee, Jun et al., *Nature*, 2021**). We also found that dopamine input to the LEC plays a critical role in associative memory. Our results provide a breakthrough in the field of learning and memory research that the LEC is the brain area that achieve associative memory. Furthermore, our novel discovery on the control of LEC by dopamine will bring a major conceptual breakthrough in that two previously independent fields of neuroscience, the memory research field and the field of reinforcement learning, can be now unified.

a. Lee JY, Jun H, Soma S, Nakazono T, Shiraiwa K, Dasgupta A, Nakagawa T, Xie JL, Chavez J, Romo R, Yungblut Y, Hagihara M, Murata K, and **Igarashi KM*** (2021) Dopamine facilitates associative memory encoding in the entorhinal cortex. ***Nature*** 598: 321-326 PMID: 34552245
b. **Igarashi KM*** (2015). Plasticity in oscillatory coupling between hippocampus and cortex. ***Curr Opin Neurobiol*** 35:163-168 PMID: 26425996
c. **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)
d. **Igarashi KM***, Ito HT, Moser EI, Moser, M-B (2014) Functional diversity along the transverse axis of hippocampal area CA1. ***FEBS Lett*** 588:2470-2476

2. Alzheimer's disease (AD) currently affects 50 million people worldwide, but no cure exists. Although molecular and cellular mechanisms of AD are becoming clearer from past studies, it remains unclear what type of impairment in neuronal activity causes memory impairment in AD subjects. This is a critical gap in knowledge in current AD research: If we can clearly identify such mechanisms, we may be able to develop a therapeutic treatment to prevent the deterioration of memory circuits in AD patients. To fill this critical gap, I have been striving to elucidate **circuit mechanisms of AD** that cause memory impairment using in vivo circuit analysis and electrophysiological methods applied to a mouse model of AD. My specific focus is the role of the **entorhinal cortex** in the pathogenesis of AD. Although it has been long known that the entorhinal cortex is the primary brain area showing functional and cellular degeneration in the early phase of AD, little has been known for the entorhinal cortex in AD because the AD research field has been primarily focusing on the hippocampus. We first focused on gamma oscillations, a network activity essential for the communication between the entorhinal cortex and hippocampus. We provided the first evidence that in vivo gamma oscillations are impaired in the entorhinal cortex of an AD mouse model (**Nakazono et al., *Front Syst Neurosci*, 2017**). This finding was also summarized in our review (**Nakazono et al., *Neurosci Res*, 2018**). To answer the question as to what circuit activity is causing memory impairment, we recently provided the first evidence that the impairment of place cell remapping, a network activity for distinguishing different environments, is disrupted in an AD mouse model (**Jun et al., *Neuron* 2020**). We showed that the remapping deficit emerges together with memory impairment over the course of pathogenesis, whereas the impairment of grid cells in the entorhinal cortex precedes the remapping/memory impairment. Our results suggest that remapping impairment is a circuit mechanism underlying spatial memory impairment in AD, and grid cell degeneration can be a primary cause of the remapping impairment in the hippocampus. Our finding is expected to lead to future therapeutic methods that slow the rate of spatial memory decline in AD patients. Since the publication of the Neuron paper we have received an increasing number of requests to provide experimental methods. To share the methods with a larger community, we published a protocol paper (**Jun et al., *STAR Protocols*, 2021**).

a. Jun H, Chavez J, Bramian, A, **Igarashi KM*** (2021) Protocol for remapping of place cells in disease mouse models. ***STAR Protocols*** 2:100759 PMID: 34467228

b. Jun H, Soma S, Saito T, Saido TC, **Igarashi KM*** (2020) Disrupted place cell remapping and impaired grid cells in a knock-in model of Alzheimer's disease ***Neuron*** 107:1095-1112 PMID: 32697942

c. Nakazono T, Jun H, Blurton-Jones, M, Green KN, **Igarashi KM*** (2018) Gamma oscillations in the entorhinal-hippocampal circuit underlying memory and dementia ***Neurosci Res*** 129:40-46

d. 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. 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. **Igarashi KM*** (2016). Entorhinal map of space. ***Brain Research*** 1637:177-87 PMID: 26940561

   b. 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. 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. I continue working with my long-term collaborators to understand circuit mechanisms for olfactory sensory processing.

   a. Cavarretta F, Burton SD, **Igarashi KM**, Shepherd GM, Hines ML, Migliore M (2018) Parallel odor processing by mitral and middle tufted cells in the olfactory bulb. ***Scientific Reports*** 8:7625 PMID: 29769664

   b. **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

   c. 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

   d. **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

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

PENDING
None

Completed Research Support

Alzheimer's Association Research Grant (AARG-17-532932) 10/1/17 – 9/30/21
Alzheimer's Association
Role: PI

Research Grant (2016-08-01) 9/1/17 – 8/31/21
Whitehall Foundation
Role: PI

PRESTO Career Development Award (JPMJPR1681) 10/1/16 – 3/31/20
Japan Science and Technology Agency
Role: PI

Fay/Frank Seed Grant (BRFSG-2017-04) 6/1/17 – 5/31/19
Brain Research Foundation
Role: PI