

BIOGRAPHICAL SKETCH

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NAME Okuno, Hiroyuki	POSITION TITLE Professor		
eRA COMMONS USER NAME N/A			
EDUCATION/TRAINING (<i>Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.</i>)			
INSTITUTION AND LOCATION	DEGREE (if applicable)	YEAR(s)	FIELD OF STUDY
University of Tokyo, Tokyo, Japan	B.S.	1986-1990	Biophysics and Biochemistry
University of Tokyo, Tokyo, Japan	M.Sc.	1990-1992	Biophysics and Biochemistry
University of Tokyo, Tokyo, Japan	Ph.D.	1992-2000	Neuroscience/Physiology
Johns Hopkins University, Baltimore, MD	Post Doc	2000-2003	Neurobiology

A. Personal Statement.

Dr. Okuno has been interested in molecular and cellular mechanisms underlying synaptic and cortical plasticity for more two decades. His Ph.D. work, which was conducted in the laboratory of Dr. Yasushi Miyashita (Dept. of Physiology, University of Tokyo), investigated expression of immediate early genes (IEGs) during declarative memory formation in non-human primates (**Okuno** and Miyashita, 1996; **Okuno** et al., 1995, 1997, 1999). As a postdoctoral fellow in the laboratory of Dr. Paul Worley at Johns Hopkins University, and later as an assistant professor in the University of Tokyo, Dr. **Okuno** focused mainly on one neuronal immediate-early gene, named *Arc* (also called *arg3.1*). His major achievements during these periods are 1) identification of a critical activity-dependent enhancer in the *Arc* promoter region (Kawashima, **Okuno** et al., PNAS, 2009) and 2) the discovery of selective *Arc* accumulation at inactive synapses to remove AMPA receptors (**Okuno** et al., Cell, 2012). Dr. Okuno is now a full professor at Kagoshima University Graduate School of Medical and Dental Sciences since April, 2018. His laboratory at Kagoshima is fully equipped with lab instruments and tools to carry out modern biochemistry and molecular biology as well as cell biology.

B. Positions and Honors.

Positions and Employment

04/95-05/00 **Research Associate**, University of Tokyo Graduate School of Medicine, Tokyo, Japan
06/00-10/03 **Postdoctoral fellow**, Johns Hopkins University School of Medicine, Baltimore, Maryland
06/03-06/13 **Assistant Professor**, University of Tokyo Graduate School of Medicine, Tokyo, Japan
07/13-03/18 **Associate Professor**, Kyoto University Graduate School of Medicine, Kyoto, Japan
03/18-present **Professor**, Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima, Japan

Honors

1994 Fellowships for Japanese Junior Scientists of Japan Society for Promotion of Science
2000-2003 Long-term Fellowship of Human Frontier Science Program (HFSP)
2004-2006 Career Development Award of HFSP
2009 Young Investigator Award of Japan Neuroscience Society
2011 Teacher's Award of Medical Scientist Program of Faculty of Medicine, University of Tokyo

C. Selected peer-reviewed publications

- Okuno H**, Minatohara K, Bito H. Inverse synaptic tagging: An inactive synapse-specific mechanism to capture activity-induced *Arc/arg3.1* and to locally regulate spatial distribution of synaptic weights. *Semin Cell Dev Biol*, 77: 43-50, 2017.
- Minatohara K, Akiyoshi M, **Okuno H**. Role of immediate-early genes in synaptic plasticity and neuronal ensembles underlying the memory trace. *Front Mol Neurosci*, 8: Article 78, 2016

3. Kawashima T, Kitamura K, Suzuki K, Nonaka M, Kamijyo S, Takemoto-Kimura S, Kano M, **Okuno H**, Ohki K, Bito H. Functional labeling of neurons and their projections using the synthetic activity–dependent promoter E-SARE. *Nat Methods*, 10, 889-895. (2013).
4. Mikuni T, Uesaka N, **Okuno H**, Hirai H, Deisseroth K, Bito H Kano K. Arc/Arg3.1 is a postsynaptic mediator of activity-dependent synapse elimination in the developing cerebellum. *Neuron*, 78, 1024-1035, (2013).
5. **Okuno H**, Akashi K, Ishii Y, Yagishita-Kyo N, Suzuki K, Nonaka M, Kawashima T, Fujii H, Takemoto-Kimura S, Abe M, Natsume R, Chowdhury S, Sakimura K, Worley PF, Bito H. Inverse synaptic tagging of inactive synapses via dynamic interaction of Arc/Arg3.1 with CaMKII β . *Cell*, 149, 886-898,(2012)..
6. **Okuno H**. Regulation and function of immediate-early genes in the brain: beyond neuronal activity markers. *Neuroscience Res.*, 69, 175-186. (2011).
7. Tse D, Takeuchi T, Takeyama M, Kajii Y, **Okuno H**, Tohyama C, Bito, H, Morris, RGM. Schema-dependent gene activation and memory encoding in neocortex. *Science*, 333, 891-895. (2011).
8. Redondo RL, **Okuno H**, Spooner PA, Frenguelli BG, Bito H, Morris, R.G.M. Synaptic tagging and capture: differential role of distinct calcium-calmodulin kinases in protein synthesis-dependent long-term potentiation. *J. Neurosci.*, 30, 4981-4989, (2010).
9. Kawashima* T, **Okuno* H**, Nonaka M, Adachi-Morishima A, Kyo N, Okamura M, Takemoto-Kimura S, Worley P, Bito H. A synaptic activity-responsive element in the Arc/Arg3.1 promoter essential for synapse-to-nucleus signaling in activated neurons, *Proc. Natl. Acad. Sci. USA*, 106, 316-321, (2009).
10. Chowdhury S, Shepherd JD, **Okuno H**, Lyford G, Petralia RS, Plath N, Kuhl D, Huganir RL, Worley, PF. Arc interacts with the endocytic machinery to regulate AMPA receptor trafficking. *Neuron*, 52, 445-459, (2006).
11. Tokuyama* W, **Okuno* H**, Hashimoto T, Li Y-X, Miyashita Y. BDNF upregulation during declarative memory formation in the monkey inferotemporal cortex. *Nature Neurosci.*, 3, 1134-1142, (2000).
12. Okuno H, Miyashita Y. Expression of the transcription factor Zif268 in the temporal cortex of monkeys during visual paired associate learning. *Eur. J. Neurosci.*, 8, 2118-2128, (1996).

D. List of full publications.

1. Okuno H, Minatohara K, Bito H: Inverse synaptic tagging: An inactive synapse-specific mechanism to capture activity-induced Arc/arg3.1 and to locally regulate spatial distribution of synaptic weights. *Semin Cell Dev Biol*, 77: 43-50, 2018.
2. Steward O, Matsudaira-Yee K, Rarris S, Salgado-Pirbhoy P, Worely P, Okamura K, Okuno H, Bito H: Delayed degradation and impaired dendritic delivery of intron-lacking EGFP-Arc/Arg3.1 mRNA in EGFP-Arc transgenic mice. *Front Mol Neurosci*, 10:435, 2018.
3. Honjoh S, de Vivo L, Bito H, Okuno H, Tononi G, Cirelli C: Higher Arc nucleus-to-cytoplasm ratio during sleep in the superficial layers of the mouse cortex. *Front Neural Circuits*, 11:Article 60, 2017.
4. Jenks KR, Kim T, Pastuzyn ED, Okuno H, Taibia AV, Bito H, Bear MF, Jason SD: Arc restores juvenile plasticity in adult mouse visual cortex. *Proc Natl Acad Sci USA*, 114:9182-9187, 2017.
5. Inokuchi K, Imamura F, Takeuchi H, Kim R, Okuno H, Nishizumi H, Bito H, Kikusui T, Sakano H: Nrp2 is sufficient to instruct circuit formation of mitral-cells to mediate odor-induced attractive social responses. *Nat Commun*, 8:15977, 2017.
6. Minatohara K, Akiyoshi M, Okuno H: Role of immediate-early genes in synaptic plasticity and neuronal ensembles underlying the memory trace. *Front Mol Neurosci*, 8:Article 78, 2016.
7. Hirano Y, Ihara K, Masuda T, Yamamoto T, Iwata I, Takahashi A, Awata H, Nakamura N, Takakura M, Suzuki Y, Horiuchi J, Okuno H, Saitoe M: Shifting transcriptional machinery is required for long-term memory maintenance and modification in Drosophila mushroom bodies. *Nat Commun*, 7:13471, 2016.
8. Okuno H, Araki A, Minatohara K: Inverse synaptic tagging by Arc. In: *Novel Mechanisms of Memory* (eds. K.P. Giese & K. Radwanska), pp. 99-118, Springer, 2016.

9. Yamamoto K, Tanei Z, Hashimoto T, Wakabayashi T, Okuno H, Naka Y, Yizhar O, Fenno LE, Fukayama M, Bito H, Cirrito JR, Holtzman DM, Deisseroth K, Iwatsubo T: Chronic optogenetic activation augments Abeta pathology in a mouse model of Alzheimer disease. *Cell Rep*, 11:859-865, 2015.
10. Fukuchi M, Tabuchi A, Kuwana Y, Watanabe S, Inoue M, Takasaki I, Izumi H, Tanaka A, Inoue R, Mori H, Komatsu H, Takamori H, Okuno H, Bito H, Tsuda M: Neuromodulatory effect of Gαs- or Gαq-coupled GPCR on NMDAR selectively activates the NMDAR/Ca²⁺/calcineurin/CREB-regulated transcriptional coactivator 1 (CRTC1) pathway to effectively induce Bdnf expression in neurons. *J Neurosci*, 35:5606-5624, 2015.
11. Fukuchi M, Nakashima F, Tabuchi A, Shimotori M, Tatsumi S, Okuno H, Bito H, Tsuda M: Class I Histone deacetylase-mediated repression of the proximal promoter of the activity-regulated cytoskeleton-associated protein gene regulates its response to brain-derived neurotrophic factor. *J Biol Chem*, 290:6825-6836, 2015.
12. Vousden DA, Epp J, Okuno H, Nieman BJ, van Eede M, Dazai J, Ragan T, Bito H, Frankland PW, Lerch JP, Henkelman RM: Whole-brain mapping of behaviourally induced neural activation in mice. *Brain Struct Funct*, 220:2043-2057, 2015.
13. Okuno H: Neuroplasticity. In: Homeostatic control of brain function (eds. S.A. Masino & D. Boison), pp. 174-186, Oxford University Press, 2015.
14. Kawashima T, Okuno H, Bito H: A new era for functional labeling of neurons: activity-dependent promoters have come of age. *Front Neural Circuits*, 8:Article 37, 2014.
15. Nonaka M, Fujii H, Kim R, Kawashima T, Okuno H, Bito H: Untangling the two-way signalling route from synapses to the nucleus, and from the nucleus back to the synapses. *Philos Trans R Soc Lond B Biol Sci*, 369:20130150, 2014.
16. Nonaka M, Kim R, Fukushima H, Sasaki K, Suzuki K, Okamura M, Ishii Y, Kawashima T, Kamijo S, Takemoto-Kimura S, Okuno H, Kida S, Bito H: Region-specific activation of CRTC1-CREB signaling mediates long-term fear memory. *Neuron*, 84:92-106, 2014.
17. Okuno H: Smythies J, Edelstein L: Selected key areas for future research on the claustrum. In: The Claustrum (eds. J. Smythies, L. Edelstein & V.S. Ramachandran), pp. 363-376, Elsevier, 2014.
18. Kawashima T, Kitamura K, Suzuki K, Nonaka M, Kamijyo S, Takemoto-Kimura S, Kano M, Okuno H, Ohki K, Bito H: Functional labeling of neurons and their projections using the synthetic activity-dependent promoter E-SARE. *Nat Methods*, 10:889-895, 2013.
19. Mikuni T, Uesaka N, Okuno H, Hirai H, Deisseroth K, Bito H, Kano K: Arc/Arg3.1 is a postsynaptic mediator of activity-dependent synapse elimination in the developing cerebellum. *Neuron*, 78:1024-1035, 2013.
20. Fujii H, Inoue M, Okuno H, Sano Y, Takemoto-Kimura S, Kitamura K, Kano M, Bito H: Nonlinear decoding and asymmetric representation of neuronal input information by CaMKIIα and Calcineurin. *Cell Rep*, 3:978-987, 2013.
21. Okuno H, Akashi K, Ishii Y, Yagishita-Kyo N, Suzuki K, Nonaka M, Kawashima T, Fujii H, Takemoto-Kimura S, Abe M, Natsume R, Chowdhury S, Sakimura K, Worley PF, Bito H: Inverse synaptic tagging of inactive synapses via dynamic interaction of Arc/Arg3.1 with CaMKIIβ. *Cell*, 149:886-898, 2012.
22. Kim[#] R, Okuno[#] H, Bito H: Deciphering the molecular rules governing synaptic targeting of the memory related protein Arc. *Commun Integr Biol* 5:493-495, 2012.
23. Endo T, Takeyama M, Uemura Y, Haijima A, Okuno H, Bito H, Tohyama C: Executive Function deficits and low social dominance in mice exposed to a low dose of dioxin in utero and via lactation. *PLoS One*, 7:e50741, 2012.
24. Watakabe A, Kato S, Kobayashi K, Takaji M, Nakagami Y, Sadakane O, Ohtsuka M, Hioki H, Kaneko T, Okuno H, Kawashima T, Bito H, Kitamura Y, Yamamori T: Visualization of the cortical projection neurons by retrograde TET-OFF lentiviral vector. *PLoS One*, 7:e46157, 2012.
25. Yagishita-Kyo N, Inoue M, Nonaka M, Okuno H, Bito H: CREB. In: Encyclopedia of Signaling Molecules (ed. S. Choi), pp. 454-458, Springer, 2012.
26. Okuno H: Regulation and function of immediate-early genes in the brain: beyond neuronal activity markers. *Neuroscience Res*, 69:175-186, 2011.
27. Tse D, Takeuchi T, Takeyama M, Kajii Y, Okuno H, Tohyama C, Bito H, Morris RGM: Schema-dependent

gene activation and memory encoding in neocortex. *Science*, 333:891-895, 2011.

28. Komatsu T, Johnsson K, Okuno H, Bito H, Inoue T, Nagano T, Urano Y: Real-time measurements of protein dynamics using fluorescence activation-coupled protein labeling (FAPL) method. *J Am Chem Soc*, 133:6745-6751, 2011.
29. Inoue M, Yagishita-Kyo N., Nonaka M., Kawashima T., Okuno H, Bito H: Synaptic activity-responsive element (SARE): A unique genomic structure with an unusual sensitivity to neuronal activity. *Commun Integr Biol*, 3:443-446, 2010.
30. Takemoto-Kimura S, Suzuki K, Kamijo S, Ageta-Ishihara N, Fujii H, Okuno H, Bito H: Differential roles for CaM kinases in mediating excitation-morphogenesis coupling during formation and maturation of neuronal circuits. *Eur J Neurosci*, 32:224-230, 2010.
31. Redondo RL, Okuno H, Spooner PA, Frenguelli BG, Bito H, Morris RGM: Synaptic tagging and capture: differential role of distinct calcium-calmodulin kinases in protein synthesis-dependent long-term potentiation. *J. Neurosci*, 30:4981-4989, 2010.
32. Kawashima[#] T., Okuno[#] H, Nonaka M, Adachi-Morishima A, Kyo N, Okamura M, Takemoto-Kimura S, Worley P, Bito^{*} H: A synaptic activity-responsive element in the Arc/Arg3.1 promoter essential for synapse-to-nucleus signaling in activated neurons. *Proc Natl Acad Sci USA*, 106:316-321, 2009.
33. Ageta-Ishihara N, Takemoto-Kimura S, Nonaka M, Adachi-Morishima A, Kamijo S, Suzuki S, Fujii H, Mano M, Blaeser F, Chatila TA, Mizuno H, Hirano T, Tagawa Y, Okuno H, Bito H: Control of cortical axon elongation by a GABA-driven Ca²⁺/calmodulin-dependent protein kinase cascade. *J. Neurosci*, 29:13720-13729, 2009.
34. Bito H, Takemoto-Kimura S, Okuno H: Activity-dependent gene regulation: How do synapses talk to the nucleus and fine-tune neuronal outputs? In: *Molecular Pain* (ed. M. Zhuo), pp. 207-217, Springer, 2008.
35. Takemoto-Kimura S, Ageta-Ishihara N, Nonaka M, Adachi-Morishima A, Mano T, Okamura M, Fujii H, Fuse T, Hoshino M, Suzuki S, Kojima M, Mishina M, Okuno H, Bito H: Regulation of dendritogenesis via a lipid raft-associated Ca²⁺/calmodulin-dependent protein kinase CLICK-III/CaMKI γ . *Neuron*, 54:755-770, 2007.
36. Chowdhury S, Shepherd JD, Okuno H, Lyford G, Petralia RS, Plath N, Kuhl D, Huganir RL, Worley PF: Arc interacts with the endocytic machinery to regulate AMPA receptor trafficking. *Neuron*, 52:445-459, 2006.
37. Ohmae S, Takemoto-Kimura S, Okamura M, Adachi-Morishima A, Nonaka M, Fuse T, Kida S, Tanji M, Furuyashiki T, Arakawa Y, Narumiya S, Okuno H, Bito H: Molecular identification and characterization of a family of kinases with homology to CaMKI/CaMKIV. *J. Biol. Chem*, 281:20427-20439, 2006.
38. Tokuyama[#] W, Okuno[#] H, Hashimoto T, Li Y-X, Miyashita Y: Selective zif 268 mRNA induction in the perirhinal cortex of macaque monkeys during formation of visual pair-association memory. *J. Neurochem*, 81:60-70, 2002.
39. Li Y-X, Hashimoto T, Tokuyama W, Miyashita Y, Okuno H: Spatiotemporal dynamics of brain-derived neurotrophic factor mRNA induction in the vestibulo-olivary network during vestibular compensation. *J. Neurosci*, 21:2738-2748, 2001.
40. Li Y-X, Tokuyama W, Okuno H, Miyashita Y, Hashimoto T: Differential induction of brain-derived neurotrophic factor mRNA in rat inferior olive subregions following unilateral labyrinthectomy. *Neuroscience*, 106:385-394, 2001.
41. Tokuyama[#] W, Okuno[#] H, Hashimoto T, Li Y-X, Miyashita Y: BDNF upregulation during declarative memory formation in the monkey inferotemporal cortex. *Nat Neurosci*, 3:1134-1142, 2000.
42. Hashimoto T, Okuno H, Tokuyama W, Li Y-X, Miyashita Y: Expression of brain-derived neurotrophic factor, neurotrophin-3 and their receptor messenger RNAs in monkey rhinal cortex. *Neuroscience*, 95:1003-1010, 2000.
43. Okuno H., Tokuyama W, Li Y-X, Hashimoto T, Miyashita Y: Quantitative evaluation of neurotrophin and trk mRNA expression in visual and limbic areas along the occipito-temporo-hippocampal pathway in adult macaque monkeys. *J Comp Neurol*, 408:378-398, 1999.
44. Tokuyama W, Hashimoto T, Li Y-X, Okuno H, Miyashita Y: Quantification of neurotrophin-3 mRNA in the rat hippocampal subregions using the RT-PCR-based coamplification method. *Brain Res Protocols*, 4:407-414, 1999.
45. Tokuyama W, Hashimoto T, Li Y-X, Okuno H, Miyashita Y: Highest trkB mRNA expression in the

entorhinal cortex among hippocampal subregions in the adult rat: contrasting pattern with BDNF mRNA expression. *Mol Brain Res*, 62:206-215, 1998.

46. Okuno H, Kanou S, Tokuyama W, Li Y-X, Miyashita Y: Layer-specific differential regulation of transcription factors Zif268 and JunD in visual cortex V1 and V2 of macaque monkeys. *Neuroscience*, 81:653-666, 1997.
47. Sato T, Tokuyama W, Miyashita Y, Okuno H: Temporal and spatial dissociation of expression patterns between Zif268 and c-Fos in rat inferior olive during vestibular compensation. *NeuroReport*, 8:1891-1895, 1997.
48. Okuno H, Miyashita Y: Expression of the transcription factor Zif268 in the temporal cortex of monkeys during visual paired associate learning. *Eur J Neurosci*, 8:2118-2128, 1996.
49. Okuno H, Saffen DW, Miyashita Y: Subdivision-specific expression of Zif268 in hippocampal formation of the macaque monkey. *Neuroscience*, 66:829-845, 1995.
50. Miyashita Y, Date A, Okuno H: Configurational encoding of complex visual forms by single neurons of monkey temporal cortex. *Neuropsychologia*, 31:1119-1131, 1993.
51. Okuno H, Akahori A, Sato H, Xanthoudakis S, Curran T, Iba H: Escape from redox regulation enhances the transforming activity of Fos. *Oncogene*, 8:695-701, 1993.
52. Miyashita Y, Sakai K, Okuno H, Tanatsugu Y, Ninomiya Y: Neural mechanisms of the pictorial long-term memory in the primate temporal cortex. In: *Brain Mechanisms of Perception and Memory* (eds, T. Ono, LR. Squire, et al.), pp. 397-404, Oxford University Press, London, 1993.
53. Okuno H, Suzuki T, Hashimoto Y, Curran, T, Iba H: Inhibition of jun transformation by a mutated fos gene: design of an anti-oncogene. *Oncogene*, 6:1491-1497, 1991.
54. Suzuki T, Hashimoto H, Okuno H, Sato H, Nishina H, Iba H: High-level expression of human c-jun gene causes cellular transformation of chicken embryo fibroblasts. *Jpn J Cancer Res*, 82:58-64, 1991.
55. Suzuki T, Okuno H, Yoshida T, Endo T, Nishina H, Iba H: Difference in transcriptional regulatory function between c-Fos and Fra-2. *Nucleic Acids Res* 19:5537-5542, 1991.

E. Research Support.

Ongoing

FY2012-FY2014 Grant-in-Aids for Scientific Research Kiban (B) from Japan Society for Promotion of Science (JSPS) (15H04258).

"Role of synaptic plasticity-related gene Arc on regulating cognitive function in the brain"

Role: Principle Investigator

FY2013-FY2014 Grant-in-Aid for Scientific Research on Innovative Areas from JSPS (18H05127).

"Evaluation of Standard Consolidation Theory and Multiple Trace Theory using multi-color functional labeling and single-cell transcriptome"

Role: Principle Investigator

Completed

FY2013-FY2018 SK project at Kyoto University.

"Identification of novel activity-dependent mechanisms underlying cognitive functions"

Role: Principle Investigator

FY2014-FY2018 EUREKA grant from the National Institutes of Health / National Institutes of Aging (R01 AG048907).

"CATT: Development and Application of a Neuronal Cell Activity-Tagging Toolbox"

Role: Co-Investigator

FY2012-FY2014 Grant-in-Aids for Scientific Research Kiban (B) from JSPS (24300117).

"Roles of activity-dependent gene Arc on regulating synaptic plasticity"

Role: Principle Investigator

FY2013-FY2014 Grant-in-Aid for Scientific Research on Innovative Areas from JSPS (25116507).
"Single-cell transcriptome analysis of activated hippocampal neurons "
Role: Principle Investigator

FY2009-FY2011, Grant-in-Aids for Scientific Research, Kiban (C) from JSPS (21500301).
"Molecular mechanisms of neuronal and activity-dependent expression of Arc"
Role: Principle Investigator

FY2007-FY2008, Grant-in-Aids for Scientific Research, Kiban (C) from JSPS(19500263).
"Regulation of dendritic spines by immediate-early gene product Arc"
Role: Principle Investigator

FY2007-FY2008, Grant-in-Aids for Scientific Research on Priority Areas from JSPS (19021009).
"Development of the monitoring system for new protein synthesis in neuronal circuits"
Role: Principle Investigator

FY2006-FY2007, Grant-in-Aids for Scientific Research on Priority Areas from JSPS (18019008).
"Visualization of neuronal circuits by activity-dependent gene expression reporters"
Role: Principle Investigator

FY2005-FY2006, Grant-in-Aids for Scientific Research, Kiban (C) from JSPS (17500201).
"Expression and synaptic targeting of the neuronal immediate-early gene Arc"
Role: Principle Investigator

FY2004-FY2006, Career Development Award from HFSP (CDA-0024/2004-C).
"Imaging of activity-dependent nucleus-to-synapse signaling in living neurons"
Role: Principle Investigator