BIOGRAPHICAL SKETCH

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NAME: Tomita, Susumu

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POSITION TITLE: Professor of Physiology

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
The University of Tokyo	B.S.	03/1995	Biophysics
The University of Tokyo	Ph.D.	03/2000	Neurobiology
The University of Tokyo	Post-doc	05/2000	Neurobiology
University of California, San Francisco	Post-doc	12/2005	Neurobiology

A. Personal Statement

A goal of my laboratory is to understand the principal rules governing synaptic transmission by focusing on ligand-gated ion channels as a mediator of fast chemical transmission. I have a broad background in molecular biology, biochemistry, mouse genetics and electrophysiology, with specific training and expertise in key research areas for this application. As a graduate student (Ph.D.), I studied molecular mechanisms for production of β-amyloid, which causes Alzheimer's disease (AD), and determined the sorting pathway for APP. As a postdoctoral fellow at UCSF, I identified TARPs as auxiliary subunits of AMPA receptors. As a PI at Yale University, and in close collaboration with the Howe lab, we published several additional papers on TARP modulation of AMPAR and identified Neto1/2 as a novel auxiliary subunit of kainate receptors that determines distinct properties of kainate receptors. In addition, we found that phosphorylation of TARP□-2 modulates synaptic AMPA receptor activity through lipid interaction. Importantly we recently identified GARLH family protein as putative auxiliary subunits of GABAARs to play critical roles in their synaptic localization. Identification of three distinct auxiliary subunits for three distinct ligand-gated ion channels puts us very unique position to pursue proposed research. Identification of auxiliary subunits and true interactors in vivo paradigm shifts the field of molecular neuroscience of synaptic transmission and their functional analysis push the field forward in terms of basic understanding of machinery and drug discovery.

B. Positions and Honors

Positions and Employment

2005-2005 Associate Specialist, University of California, San Francisco, CA
2006-2010 Assistant Professor of Physiology, Yale University School of Medicine, CT
2009-current Primary Faculty in Program in Cellular Neuroscience, Neurodegeneration and Repair (CNNR), Yale University School of Medicine, CT
2010-2012 Associate Professor of Physiology (Tenure track), Yale University School of Medicine, CT
2012-2015 Associate Professor of Physiology (Tenured), Yale University School of Medicine, CT
2013-current Member, The Kavli Institute for Neuroscience at Yale University/Neurobiology
2015-current Professor of Physiology (Tenured), Yale University School of Medicine, CT
2015-current Neuroscience (Tenured), Yale University School of Medicine, CT

Other Experience and Professional Memberships

2001-current Member, Society for Neuroscience

2006-current Member, Faculty of 1000
2011 Ad hoc member, LAM Study Section, NIH
2011 Ad hoc member, Board of Scientific Counselors (BSC), NIH/NINDS
2012 Ad hoc member, SYN Study Section, NIH
2013 Ad hoc member, SEP IFCN-B, NIH
2014 Ad hoc member, SEP MDCN-R, NIH
2015 Ad hoc member, SEP MDCN-C, NIH
2015 Ad hoc member, SEP MDCN-R, NIH
2015 Ad hoc member, Board of Scientific Counselors (BSC), NIH/NINDS
2012-2018 Regular member, SYN Study Section, NIH
2018 Ad hoc member, SEP, NIH

Honors and Awards

1997-2000 Research fellowships of the Japan Society for the Promotion of Science for Young Scientists (Predoctoral)
2000-2001 Research fellowships of the Japan Society for the Promotion of Science for Young Scientists (Postdoctoral)
2002-2003 NIH Training Grant from UCSF Neuroscience Program
2003-2005 NIH Postdoctoral NRSA F32 fellowship
2006-2009 Klingenstein Fellowship Awards in the Neurosciences
2007-2009 Alfred P. Sloan Research Fellowship Award
2007-2009 NARSAD Young Investigator Award

C. Contributions to Science

1. Identification of a first example of auxiliary subunits of ligand-gated ion channels.
AMPA-type ionotropic glutamate receptor determines most of synaptic strength. Because AMPA receptors expressed in heterologous cells are functional, AMPA receptors are thought to function by themselves in neurons. However, we found that native AMPA receptors in the brain form a complex with novel transmembrane auxiliary subunits, TARPs. TARP is the first example of auxiliary subunits of ligand-gated ion channels. Since then, several auxiliary subunits for ligand-gated ion channels have been found. These papers are representative papers when I was a post-doc at UCSF.

a. Tomita, S., Chen, L., Kawasaki, Y., Petralia, R. S., Wenthold, R. J., Nicoll, R. A., and Bredt, D. S. (2003). Functional studies and distribution define a family of transmembrane AMPA receptor regulatory proteins. **J Cell Biol** 161, 805-816.
b. Tomita, S., Fukata, M., Nicoll, R. A., and Bredt, D. S. (2004). Dynamic interaction of stargazin-like TARPs with cycling AMPA receptors at synapses. **Science** 303, 1508-1511.
c. Tomita, S., Stein, V., Stocker, T. J., Nicoll, R. A., and Bredt, D. S. (2005) Bi-directional synaptic plasticity regulated by phosphorylation of stargazin-like TARPs. **Neuron** 45, 269-277.
d. Tomita, S, Adesnik, H., Sekiguchi, M., Zhang, W., Wada, K., Howe, J. R., Nicoll, R. A., and Bredt, D. S. (2005) Stargazin modulates AMPA receptor gating and trafficking by distinct domains. **Nature** 435, 1052-1058

2. Identification of novel auxiliary subunit of kainate receptors.
Ionotropic glutamate receptors are classified as three classes, AMPA, NMDA and kainate-types. Compared AMPA and NMDA receptors, kainate receptors show distinct slow decay kinetics and distribution in the brain. However, their mechanisms remain unclear. We identified novel auxiliary subunit for kainate receptors, Neto1/2 by proteomic approach. Furthermore, we showed that Neto1/2 defined distinct decay kinetics and distribution of kainate receptors in the brain. Several attempts to isolate drugs against kainate receptor have been failed, perhaps due to lack of Neto auxiliary subunit in drug screening system. Inclusion of Neto auxiliary subunit in drug discovery system may allow us to identify drugs for kainate receptors, which disruption causes epilepsies, autisms and other neurological disorders. I served as the primary investigator in all of these studies.

a. Zhang W, St-Gelais F, Grabner CP, Trinidad JC, Sumioka A, Morimoto-Tomita M, Kim KS, Straub C, Burlingame AL, Howe JR, Tomita S. (2009) Novel transmembrane accessory subunit modulates kainate-type glutamate receptors. **Neuron**, *61*, 385-96 PMCID: PMC2803770

b. Straub C, Hunt DL, Yamasaki M, Kim KS, Watanabe M, Castillo PE, and Tomita S (2011) Unique functions of kainate receptors in the brain are determined by the auxiliary subunit Neto1. **Nature Neurosci**., *14*, 866-873 PMCID: PMC3125417
c. Yan D, Yamasaki M, Straub C, Watanabe M, and Tomita S. (2013) Homeostatic control of synaptic transmission by distinct glutamate receptors. **Neuron***,78*, 687-399 PMCID: PMC3668311
d. Straub C, Noam Y, Nomura T, Yamasaki M, Yan D, Fernandes HB, Zhang P, Howe JR, Watanabe M, Contractor A, and Tomita S (2016) Distinct subunit domains govern synaptic stability and specificity of the kainate receptor. **Cell Report**, *16*, 531-44 PMCID: PMC4963241

3. Identification of the first example of putative auxiliary subunits of ligand-gated anion channels.
Ionotropic GABA receptors ($GABA_AR$) is a pentameric anion channel, which localize at synapses to function. However, their mechanisms remain unclear. We identified novel auxiliary subunit for $GABA_ARs$, GARLH by novel biochemical purification method combined with Blue-native PAGE. Using this method, we identified that native $GABA_ARs$ in the brain form a tripartite complex with GARLH and neuroligins. And GARLHs are required for synaptic localization and inhibitory transmission in the brain. I served as the primary investigator.

a. Yamasaki T, Hoyos-Ramirez E, Martenson JS, Morimoto-Tomita M, and Tomita S (2017) GARLH family proteins stabilize GABAA receptors at synapses. **Neuron**, *93*, 1138-1152 PMCID: PMC5347473
b. Martenson JS, Yamasaki T, Chaudhury N, Albrecht D, and Tomita S (2017) Assembly rules for GABAA receptor complexes in the brain. **eLife**, 2017;6: e27443. PMID: 28816653
c. Chiu CQ, Martenson JS, Yamazaki M, Natsume R, Sakimura K, Tomita S, Tavalin SJ, and Higley MJ (2018) Input-specific NMDAR-dependent potentiation of dendritic GABAergic inhibition. **Neuron**, *97*, 368-377 PMID:29346754 PMCID:PMC5777295
d. Noam Y, and Tomita S (2018) On the path from proteomics to function: GABAAR trafficking takes a turn. **Neuron**, *97,* 479-481 PMCID:PMC5828027

4. Revealing mechanisms for synaptic plasticity
Synaptic plasticity has been believed to play roles in brain functions and dynamics. As such example, long-term potentiation (LTP) has been studied since late 60'. It has been shown that activation of CaMKII through NMDA receptors increases AMPA receptor activity at synapses, but it mechanism remains unclear. Based on analysis of components of native AMPAR complex, we identified that TARPγ-8 isoform is required for LTP and the AMPAR/TARP complex localizes at synapses in a TARP phosphorylation dependent manner. And TARP phosphorylation dissociates the TARP cytoplasmic domain from negatively charged membranes, and allows the TARP PDZ binding domain to interact with postsynaptic density abundant protein, PSD-95. These studies suggest critical roles of TARP and its phosphorylation in synaptic transmission and plasticity. Furthermore, we found a mechanism of homeostatic regulation of synaptic transmission. In these studies, we first succeeded to reconstitute AMPAR- and kainate receptor-mediate synaptic transmission in heterologous systems. This set of experiments first identified a complete set of receptor components in the brain, which can be applied for drug discovery. I served as the primary investigator in these studies.

a. Park J, Chavez AE, Mineur YS, Morimoto-Tomita M, Lutzu S, Kim KS, Picciotto MR, Castillo PE, and Tomita S (2016) CaMKII phosphorylation of TARPγ-8 is a mediator of LTP and learning and memory. **Neuron**, *92*, 75-83 PMID: 27667007
b. Sumioka A, Brown T, Kato AS, Bredt DS, Kauer JA, and Tomita S. (2011) PDZ binding of TARPγ-8 controls synaptic transmission, but not synaptic plasticity. **Nature Neurosci.**, *14*, 1410-1412 PMCID: PMC3206644
c. Kato AS, Gill MB, Ho MT, Yu H, Tu Y, Siuda ER, Wang H, Qian YW, Nisenbaum ES, Tomita S, and Bredt DS (2010) Hippocampal AMPA receptor gating controlled by both TARP and cornichon proteins. **Neuron**, *68*, 1082-1096 PMCID: PMC3034222
d. Sumioka A, Yan D, Tomita S. (2010) TARP phosphorylation regulates synaptic AMPA receptors through lipid bilayers. **Neuron**, *66*, 755-67 PMCID: PMC2887694

5. *Novel methods to identify and to characterize ion channel complex and its pharmacology*
We developed several new methods to reveal properties of functional AMPA receptor complex. A, We first utilized FLIPR assay to determine functional modulators of AMPA receptors as higher throughput assays. As a result, we identified Porcupine as a novel functional modulator. B, we combined Blue Native PAGE and

molecular biology to reveal stoichiometry of AMPA receptors with TARP auxiliary subunits in reconstituted systems and in the brain. This approach is now widely taken in the field. 3, we applied mathematical modeling to simulate TARPed and TARPless AMPA receptors, which reveals agonist-induced uncoupling of AMPA receptor and TARPs. I served as the primary investigator or co-investigator in all of these studies.

a. Brockie PJ, Jensen M, Mellem JE, Jensen E, Yamasaki T, Wang R, Maxfield D, Thacker C, Hoerndli F, Dunn PJ, Tomita S, Madsen DM, Maricq AV (2013) Cornichons control ER export of AMPA receptors to regulate synaptic excitability. **Neuron**, *80*, 129-142 PMCID: PMC3795439
b. Morimoto-Tomita M, Zhang W, Straub C, Cho CH, Kim KS, Howe JR, Tomita S. (2009) Auto-inactivation of neuronal AMPA receptors via glutamate-regulated TARP interaction. **Neuron**, *61*, 101-12 PMCID: PMC2649795
c. Oprea TI, Bologa CG, Brunak S, Campbell A, Gan GN, Gaulton A, Gomez SM, Guha R, Hersey A, Holmes J, Jadhav A, Jensen LJ, Johnson GL, Karlson A, Leach AR, Ma'ayan A, Malovannaya A, Mani S, Mathias SL, McManus MT, Meehan TF, von Mering C, Muthas D, Nguyen DT, Overington JP, Papadatos G, Qin J, Reich C, Roth BL, Schürer SC, Simeonov A, Sklar LA, Southall N, Tomita S, Tudose I, Ursu O, Vidovic D, Waller A, Westergaard D, Yang JJ, Zahoránszky-Köhalmi G. (2018) Unexplored therapeutic opportunities in the human genome. **Nature Review Drug Discovery,** *5*, 317-332.
PMID: 29472638, PMCID: in process
d. Chen Z, Mori W, Zhang X, Yamasaki T, Dunn PJ, Zhang G, Fu H, Shao T, Zhang Y, Hatori A, Ma L, Fujinaga M, Xie L, Deng X, Li H, Yu Q, Rong J, Josephson L, Ma JA, Shao Y, Tomita S, Zhang MR, Liang SH. (2018) Synthesis, pharmacology and preclinical evaluation of 11C-labeled 1,3-dihydro-2H-benzo[d]imidazole-2-ones for imaging γ8-dependent transmembrane AMPA receptor regulatory protein. **European Journal of Medicinal Chemistry,** *157*, 898-908.
PMID:30145376, PMCID: in process

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/sites/myncbi/susumu.tomita.2/bibliography/40324964/public/?sort=date&direction=ascending

D. Other Supports

TOMITA, SUSUMU

ACTIVE

1RF1MH114078-01 (Tomita) 08/01/2017 - 07/31/2020 3.0 Calendar
NIMH/NIH/DHHS Total $750,000 ($250,000/yr for 3 years)
Develop and validate novel chemogenetic tools to modulate synaptic transmission
The goal of this project is to develop and validate novel molecular tools to modulate excitatory synaptic transmission in the brain

1R01MH115705-01 (Tomita) 12/15/2017 - 11/30/2022 3.0 Calendar
NIMH/NIH/DHHS $250,000
Mechanisms for synaptic localization of ionotropic GABA receptors in the brain
The goal of this project is to reveal mechanisms for synaptic localization of GABAA receptors in the brain.

R01MH077939 (Competitive renewal) (Tomita) 06/12/2019 - 03/31/2024 3.0 Calendar
NIMH/NIH/DHHS $250,000
Regulation of glutamate receptors by calcium-dependent protein kinases
The goal of this project is to understand mechanisms for synaptic plasticity that may underlie aspects of learning and memory, especially for regulation of glutamate receptors by calcium-dependent protein kinases

Completed Research Support

U01 MH104984 Tomita (PI) 5/1/2014 – 4/30/2017

Identify functional modulators of ionotropic neurotransmitter receptors in the brain
The goal of this project is to identify novel modulator for ionotropic neurotransmitter receptors using high-throughput screening

R01 MH085080 Tomita (PI) 12/1/2009 – 11/30/2014
Mechanism for regulating kainate-type glutamate receptor activity
The goal of this project is to understand roles of kainate-type glutamate receptor activity.