IIAS Research Conference 2011

Organized by : Hitoshi Sakano (U Tokyo)
Tetsuo Yamamori (NIBB)
Yoshiro Shimura (IIAS)

Sponsored by : Ministry of Education, Culture, Sports, Science and Technology
Japan Society for the Promotion of Science

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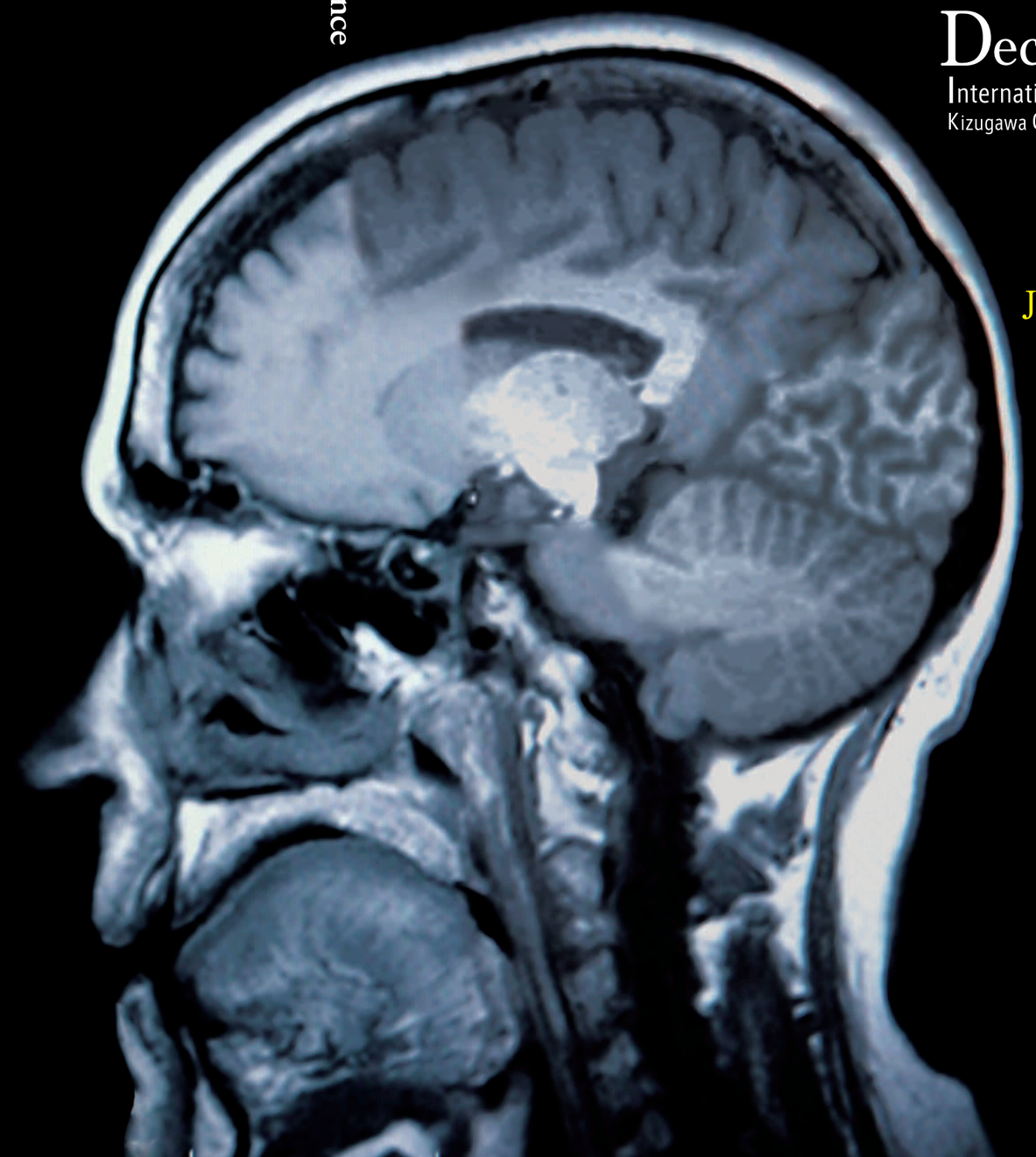
Frontiers in Neuroscience

From Brain to Mind

Frontiers in Neuroscience

December 6-9, 2011

International Institute for Advanced Studies
Kizugawa City, Kyoto, Japan



David Anderson Caltech
Linda Buck Fred Hutch
Jean-Pierre Changeux Pasteur
Barry Dickson IMP
Michael Greenberg Harvard
Nobutaka Hirokawa U Tokyo
Haruo Kasai U Tokyo
Sigrun Korsching U Cologne
Hiroaki Matsunami Duke U
Tetsuro Matsuzawa Kyoto U
Kensaku Mori U Tokyo
Kenichi Ohki Kyushu U
Svante Pääbo Max Planck
Mu-ming Poo UC Berkeley
Ivan Rodriguez U Geneva
Hitoshi Sakano U Tokyo
Noam Sobel Weizmann
Nicholas Spitzer UCSD
Lisa Stowers Scripps
Michael Stryker UCSF
Keiji Tanaka RIKEN
Kazushige Touhara U Tokyo
Naoshige Uchida Harvard
Tetsuo Yamamori NIBB
Yoshihiro Yoshihara RIKEN

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Program

Schedule for IIAS Research Conference 2011 on "Frontiers in Neuroscience: From Brain to Mind"

2011	Tuesday, Dec. 06	Wednesday, Dec. 07	Thursday, Dec. 08	Friday, Dec. 09	
9:00					9:00
10:00		**Axons and Wiring** 9:30 - 12:30 Chair: Sigrun Korsching David Anderson (Caltech) Barry Dickson (IMP, Vienna) *Coffee Break* Nobutaka Hirokawa (Univ. Tokyo) *Short Talks*	**Neural Circuit** 9:30 - 12:30 Chair: Ivan Rodriguez Michael Stryker (UCSF) Hitoshi Sakano (Univ. Tokyo) *Coffee Break* Nicholas Spitzer (UCSD) *Short Talks*	**Sensory Perception** 9:30 - 12:30 Chair: Hiroaki Matsunami Tetsuo Yamamori (NIBB) Noam Sobel (Weizmann Inst.) *Coffee Break* Naoshige Uchida (Harvard Univ.) Kensaku Mori (Univ. Tokyo)	10:00
11:00					11:00
12:00					12:00
13:00		**Lunch** 12:30 - 13:30	**Lunch** 12:30 - 13:30	**Lunch** 12:30 - 13:30	13:00
14:00	**Registration** 14:00 - 15:00	**Synapse** 13:30 - 17:00 Chair: Nicholas Spitzer	**Pheromone-induced Behavior** 13:30 - 17:00 Chair: Yoshihiro Yoshihara	**Cognition and Behavior** 13:30 - 16:30 Chair: Tetsuo Yamamori	14:00
15:00	**Opening Remarks** 15:00 - 15:10 Kazuo Oike (IIAS)	Michael Greenberg (Harvard Univ.) Haruo Kasai (Univ. Tokyo) *Coffee Break* Mu-ming Poo (UC Berkeley) Short Talks	Lisa Stowers (Scripps Inst.) Kazushige Touhara (Univ. Tokyo) *Coffee Break* Ivan Rodriguez (Univ. Geneva) Hiroaki Matsunami (Duke Univ.)	Svante Pääbo (Max Planck) Kenichi Ohki (Kyushu Univ.) *Coffee Break* Keiji Tanaka (RIKEN) Tetsuro Matsuzawa (Kyoto Univ.)	15:00
16:00	**Opening Lecture** 15:10 - 16:10 Chair: Hitoshi Sakano Linda Buck (Fred Hutchinson) *Coffee Break*			**Closing Lecture** 16:30 - 17:30 Chair: Sigrun Korsching Jean-Pierre Changeux (Collège de France)	16:00
17:00	**Olfactory System** 16:30 - 18:30 Chair: Lisa Stowers Yoshihiro Yoshihara (RIKEN) Sigrun Korsching (Univ. Cologne)		**Poster Presentation** 17:00 - 18:30	**Concluding Remarks 17:30-17:35** Yoshiro Shimura (IIAS)	17:00
18:00					18:00
19:00	**Welcome Dinner** 18:30 - 20:30		**Dinner** 18:30 - 20:30		19:00
20:00					20:00

IIAS Research Conference 2011 on "Frontiers in Neuroscience: From Brain to Mind" PROGRAM

- Tuesday, December 6 -

14:00-15:00 Registration

15:00-15:10 **Opening Remarks**
Kazuo Oike (IIAS)

15:10-16:10 **Opening Lecture**
Chair Person:
Hitoshi Sakano (Univ. Tokyo)

1. Deconstructing smell
Linda Buck (Fred Hutchinson)

< Coffee Break >

16:30-18:30 **Olfactory System**
Chair Person:
Lisa Stowers (Scripps)

1. Molecular genetic dissection of olfactory neural circuitry in zebrafish
Yoshihiro Yoshihara (RIKEN)
2. Evolution of olfactory receptor gene repertoires and function
Sigrun Korsching (Univ. Cologne)

18:30-20:30 Welcome Dinner

- Wednesday, December 7 -

9:30-12:30 **Axons and Wiring**
Chair Person:
Sigrun Korsching (Univ. Cologne)

1. The neural circuitry of emotion in flies and mice
David Anderson (Caltech)
2. Wired for sex: the neurobiology of drosophila courtship behaviour
Barry Dickson (IMP, Vienna)

< Coffee Break >

3. Kinesin superfamily molecular motors (KIFs) as key regulators for intracellular transport and higher brain function
Nobutaka Hirokawa (Univ. Tokyo)

Short Talks

12:30-13:30 Lunch

13:30-17:00 **Synapse**
Chair Person:
Nicholas Spitzer (UCSD)

1. Signaling networks that regulate synapse development and cognitive function
Michael Greenberg (Harvard Univ.)
2. Synaptic competition in the dendritic spines of CA1 pyramidal neurons
Haruo Kasai (Univ. Tokyo)

< Coffee Break >

3. Circuit mechanisms for perceptual memory of the temporal sequence and time intervals of sensory events
Mu-ming Poo (UC Berkeley)

Short Talks

- Thursday, December 8 -

9:30-12:30 **Neural Circuit**
Chair Person:
Ivan Rodriguez (Univ. Geneva)

1. Enhancement of activity and plasticity in visual cortex
Michael Stryker (UCSF)
2. Neuronal identity and circuit formation in the mouse olfactory system
Hitoshi Sakano (Univ. Tokyo)

< Coffee Break >

3. Activity-dependent neurotransmitter respecification: novel plasticity
Nicholas Spitzer (UCSD)

Short Talks

12:30-13:30 Lunch

13:30-17:00 **Pheromone-induced Behavior**
Chair Person:
Yoshihiro Yoshihara (RIKEN)

1. Diverse coding logic to encode olfactory-mediated behavior
Lisa Stowers (Scripps Inst.)
2. Narrowly-tuned chemosensory reception for food and pheromone signals
Kazushige Touhara (Univ. Tokyo)

< Coffee Break >

3. Emergence of novel chemosensors: from the immune to the olfactory system
Ivan Rodriguez (Univ. Geneva)
4. Calreticulin chaperones regulate functional expression of V2R pheromone receptors
Hiroaki Matsunami (Duke Univ.)

17:00-18:30 **Poster Presentation**

18:30-20:30 Dinner

- Friday, December 9 -

9:30-12:30 **Sensory Perception**
Chair Person:
Hiroaki Matsunami (Duke Univ.)

1. Genes that are selectively expressed in regions of primate neocortex: the functions and implication for cortical specialization
   Tetsuo Yamamori (NIBB)
2. Olfactory white: odorant mixtures containing many components converge towards a common percept
   Noam Sobel (Weizmann Inst.)

< Coffee Break >

3. Toward the circuit physiology of midbrain dopamine neurons: beyond stamp collecting
   Naoshige Uchida (Harvard Univ.)
4. Sensory experience-dependent reorganization of neuronal circuits in the olfactory cortex and olfactory bulb during postprandial sleep
   Kensaku Mori (Univ. Tokyo)

12:30-13:30 Lunch

13:30-16:30 **Cognition and Behavior**
Chair Person:
Tetsuo Yamamori (NIBB)

1. A neandertal perspective on human origins
   Svante Pääbo (Max Planck)
2. Functional architecture of cerebral cortex
   Kenichi Ohki (Kyushu Univ.)

< Coffee Break >

3. Functional division among prefrontal areas in macaque monkeys
   Keiji Tanaka (RIKEN)
4. Cognitive development in humans and chimpanzees
   Tetsuro Matsuzawa (Kyoto Univ.)

16:30-17:30 **Closing Lecture**
Chair Person:
Sigrun Korsching (Univ. Cologne)

1. Experimental and theoretical approaches to conscious processing
   Jean-Pierre Changeux (Collège de France)

17:30-17:35 **Concluding Remarks**
Yoshiro Shimura (IIAS)

Invited Speakers

The neural circuitry of emotion in flies and mice

David Anderson
California Institute of Technology

Research interests in my laboratory focuses on understanding how emotional behavior is encoded in the brain, at the level of specific neuronal circuits, and the specific neuronal subtypes that comprise them. We want to understand the structure and dynamic properties of these circuits and how they give rise to the outward behavioral expressions of emotions such as fear, anxiety or anger. This information will provide a framework for understanding how and where in the brain emotions are influenced by genetic variation and environmental influence ("nature" and "nurture"), and the mechanism of action of drugs used to treat psychiatric disorders such as depression. We are using both mice and the vinegar fly *Drosophila melanogaster* as model systems. A central focus of the laboratory is on the neural circuits underlying aggression and fear. We are using molecular genetic tools, as well as functional imaging and electrophysiology, to establish cause-and-effect relationships between the activity of specific neuronal circuits and behavior. We hope that this research will lead to new insights into the organization of emotion circuits, and their dysregulation in psychiatric disorders.

NAME: DAVID JEFFREY ANDERSON, PH.D.

BUSINESS ADDRESS: California Institute of Technology
1200 E. California Blvd.
Division of Biology, 216-76
Pasadena, CA 91125

EDUCATION

1978	A.B. Biochemical Sciences; Harvard College (advisor: D. ranton)
1983	Ph.D. Cell Biology; Rockefeller University (advisor: G. Blobel)
1986	Postdoctoral Molecular Biology; Columbia University, College of Physicians and Surgeons (advisor: R. Axel)

ACADEMIC APPOINTMENTS

2009	Seymour Benzer Professor of Biology, California Institute of Technology
2004- 2009	Roger W. Sperry Professor of Biology, California Institute of Technology
1996- 2004	Professor of Biology, California Institute of Technology
1996- present	Investigator, Howard Hughes Medical Institute
1992- 1996	Associate Professor of Biology (tenured), California Institute of Technology

1992-1996	Associate Investigator, Howard Hughes Medical Institute
1989- present	Adjunct Assistant Professor of Cell and Neurobiology, USC School of Medicine
1989-1992	Assistant Investigator, Howard Hughes Medical Institute
1986-1992	Assistant Professor of Biology, California Institute of Technology

AWARDS AND HONORS

2011	Harvey Lecture, Rockefeller
2011	Seymour Benzer Lecture, Oberlin College
2011	Kuffler Lecture, Harvard Medical School
2010	Allen Distinguished Investigator
2010	Max Birnstiel Lecture, IMP, Vienna
2009	Honors Lecture, NYU School of Medicine
2008	Picower Lecture, MIT
2007	Elected Member, National Academy of Sciences
2005	Alexander von Humboldt Award
2004	Named Roger W. Sperry Professor of Biology, California Institute of Technology
2004	NYU School of Medicine Honors Lecture, Speaker
2004	Learning and Memory Picower Lecture, MIT
2004	The Joseph L. Melnick distinguished Guest Lecturer, Baylor College of Medicine
2003	Keynote Speaker, Gordon Conference on Angiogenesis
2003	Keynote Speaker, Gordon Conference on Neurotrophins
2002	American Association for the Advancement of Science Fellow
2002	American Academy of Arts and Sciences Fellow
2001	Swirling Lecture, Harvard University
2001	Elected Associate, The Neurosciences Institute
2001	Mager Lecture, Hebrew University, Jerusalem
2000	Visiting Professor, College de France
1999	Alden Spencer Award in Neurobiology, Columbia University
1998	Ferguson Award for Graduate Teaching
1996	Ferguson Award for Biology Education
2001	Ferguson Award for Graduate Teaching
1993	Donald D. Matson Lecture, Harvard University
1990	Charles Judson Herrick Award in Comparative Neurology
1989	Javits Investigator in Neuroscience (NIH)
1988	Pew Faculty Fellowship for Neuroscience Research
1988	Alfred P. Sloan Research Fellowship in Neuroscience
1987	Searle Scholars Award
1986	NSF Presidential Young Investigator Award
1983-86	Helen Hay Whitney Foundation Fellow
1978	NSF Predoctoral Fellow
1978	A.B. Summa Cum Laude, Harvard College, Phi Beta Kappa

AWARD SELECTION COMMITTEES

2004 -2008	McKnight Neuroscience of Brain Disorders Awards Selection Committee
2002-2007	Alfred P. Sloan Research Fellowships in Neuroscience Program Committee

2001-present Wiley Prize Selection Committee
1996 Sloan General Motors Cancer Research Award, Vice-Chair, Selection Committee
1995 Sloan Prize, General Motors Cancer Research Foundation Selection Committee

PROFESSIONAL ACTIVITIES

2011 Neural Coding Advisory Council, Allen Institute for Brain Science
2010- present Neural Systems & Circuits Editorial Board
2010- present Connectional Atlas Advisory Council, Allen Institute for Brain Science
2009- present SAB Chair, Allen Institute for Brain Science SAB
2009- present Scientific Advisory Committee, Helen Hay Whitney Foundation
2007- 2009 Scientific Center Advisory Council, Allen Institute for Brain Science
2006- 2009 SAB Member, Autism Consortium
2007- 2009 SAB Member, Allen Institute for Brain Science
2002- 2008 SAB Member, Allen Institute Brain Atlas
2002- present The International Behavioural and Neural Genetics Society
2002- 2006 Gene Expression International Journal of Cellular and Molecular Science Editorial Board
2001- present SAB Member, Vascular Biology Institute Board
2001- 2006 Board of Directors, International Society for Stem Cell Research
2001 Hereditary Disease Foundation Scientific Advisory Board
1999- present Journal of Regenerative Medicine Editorial Board
1998- 2002 Annual Reviews Editorial Board
1997- present SAB Member, Stem Cells, Inc.
1995- present Development Editorial Board
1995- present Molecular and Cellular Neuroscience Editorial Board
1991- present American Association for the Advancement of Science
1990- present Society for Developmental Biology
1990- present Society for Neuroscience
1989- present Neuron Editorial Board
1989- 2000 Cambridge Neuroscience Scientific Advisory Board
1991-1997 J. Neuroscience Editorial Board
1995-1997 Developmental Biology Editorial Board
1995-1997 American Society for Cell Biology
1996-1997 CIT Presidential Search Committee Member

SCIENCE COMMUNITY SERVICE

2010 Panel Member on PBS Charlie Rose program "The Anxious Brain"
2010 Natural History Museum of Los Angeles, *"First Fridays"* presentation series
2004 California Science Center National Fear Exhibit Technical Advisory Board
2004 The California Stem Cell Research & Cures Act Speakers' Bureau
2003 Californians for Stem Cell Research & Cures Scientific Advisory Council Co-Chair
2002 CuresNow Scientific Advisory Board

RECENT PUBLICATIONS

Hochstim, C.J. Deneen, B., Lukaszewicz, A., Zhou, Q., and Anderson, D.J. (2008) Identification of positionally distinct astrocyte subtypes whose identities are specified by a homeodomain code. *Cell* **133(3**):510-22. PMCID: PMC2394859

Wang, L. and Anderson, D. J. (2008) A common genetic target for environmental and heritable influences on aggressiveness in *Drosophila*. *PNAS* **15;105(15):**5657-63. PMCID: PMC2311352

Cell. 2009 Dec 24;139(7):1353-65. Epub 2009 Dec 10.
Sensory neuron-specific GPCR Mrgprs are itch receptors mediating chloroquine-induced pruritus.
Liu Q, Tang Z, Surdenikova L, Kim S, Patel KN, Kim A, Ru F, Guan Y, Weng HJ, Geng Y, Undem BJ, Kollarik M, Chen ZF, Anderson DJ, Dong X.

Lebestky, T., Chang, J., Dankert, H., Zelnik, L., Kim, Y., Han, K., Perona, P., and Anderson, D.J. (2009) Genetically Separable Circuits Mediating Distinct Forms of Arousal are Oppositely Regulated by the D1 Receptor Ortholog DopR in Drosophila. *Neuron* **64**(4)522-36. PMCID: PMC2908595

Yorozu, S., Wong, A., Fischer, B.J., Dankert, H., Kernan, M.J., Kamikouchi, A., Ito, K., and Anderson, D.J. (2009) Distinct sensory representations of wind and near-field sound in the *Drosophila* Brain. *Nature* **458:**201-5 PMCID:PMC2755041

Dankert, H., Wang, L., Hoopfer, E.D., Anderson, D.J., and Perona, P. (2009) Automated Monitoring and Analysis of Social Behavior in *Drosophila. Nature Methods* EPub March 8 2009**: 4:**297-303 PMCID:PMC2678418

Wang, L., and Anderson, D.J. (2010) Identification of an agression-promoting pheromone and its receptor neurons in drosophila. *Nature* **463**(7278):227-31. PMID: 19966787. PMC2999963

Haubensak, W., Kunwar, P.S., Cai, H., Ciocchi, S., Wall, N.R., Ponnusamy, R., Biag, J., Dong, H-W., Deisseroth, K., Callaway, E.M., Fanselow, M.S., L▪hi, A., and Anderson, D.J. (2010) Genetic Dissection of an Amygdala Microcircuit that Gates Conditioned Fear. *Nature* **468**(7321):270-76 NIHMS243118. [PubMed - in process]

Lin, D., Boyle, M.P., Dollar, P., Lee, H., R., Perona, P., Lien, E.S., and Anderson, D.J. (2011) Functional identification of an aggression locus in the mouse hypothalamus. *Nature* **470**(7333):179-81 [PubMed - in process]

Wang, L., Han, X., Mehren, J., Hiroi, M., Billeter, J-C., Miyamoto, T., Amrein, H., Levine, J.D., and Anderson, D.J. (2011) Hierarchical chemosensory regulation of male-male social interactions in *Drosophila* . *Nature Neuroscience* June;14(6):757-62. Epub 2011 Apr 24. PMID: 21516101 [PubMed - in process]

Deconstructing smell

Linda B. Buck
Howard Hughes Medical Institute
Fred Hutchinson Cancer Research Center

The sense of smell allows humans and other mammals to detect a multitude of environmental chemicals. Most are perceived as odors, but some, such as pheromones and predator odors, elicit hormonal changes or instinctive behaviors. In early work, we discovered the odorant receptor (OR) family, which mediates odor detection in the nasal olfactory epithelium (OE). Our studies showed that ORs are used in a combinatorial fashion to detect odorants and encode their unique identities, a scheme explaining how nearly identical chemicals can be distinguished. We found that each OE neuron expresses a single OR gene and that while thousands of neurons with the same OR are scattered in one OE zone, they all synapse in a few specific glomeruli at semi-stereotyped locations in the olfactory bulb. The spatial code for an odorant in the nose is thus a dispersed ensemble of neurons expressing different OR components of the chemical's receptor code whereas in the olfactory bulb it is a specific combination of glomeruli whose arrangement is similar among individuals. In other studies, we and others uncovered three different families of chemosensory receptors in the vomeronasal organ (VNO), which is involved in pheromone detection. To study neural circuits underlying odor and pheromone sensing, we are employing genetic transneuronal tracers. By examining the connections of hypothalamic neurons that control reproduction, we obtained evidence that those neurons are likely to obtain pheromone signals from the OE as well as the VNO. In a subsequent search for potential pheromone receptors in the OE, we discovered a second small family of OE receptors, called TAARs. At least two TAARs detect compounds elevated in male versus female mouse urine, suggesting that TAARs may be involved in the detection of social cues.

NAME: **Linda B. Buck**

ADDRESS: Fred Hutchinson Cancer Research Center
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1100 Fairview Avenue North
Seattle, WA 98109-1024
http://labs.fhcrc.org/buck/index.html

PLACE OF BIRTH: Seattle, Washington

EDUCATION AND TRAINING:

1975 B.S.	Microbiology, University of Washington, Seattle, Washington
1975 B.S.	Psychology, University of Washington, Seattle, Washington
1980 Ph.D.	Immunology, Microbiology Department, University of Texas Southwestern Medical Center, Dallas, Texas, Advisor: Ellen Vitetta
1980-82	Postdoctoral Fellow, Microbiology Department, Columbia University College of Physicians and Surgeons, New York, New York, Laboratory of Benvenuto Pernis
1982-84	Postdoctoral Fellow, Institute of Cancer Research, Columbia University College of Physicians and Surgeons, New York, New York, Laboratory of Richard Axel
1984-91	Associate, Howard Hughes Medical Institute, Columbia University College of Physicians and Surgeons, New York, New York, Laboratory of Richard Axel

ACADEMIC APPOINTMENTS:

1991-1996	Assistant Professor, Department of Neurobiology, Harvard Medical School, Boston, Massachusetts
1994-1997	Assistant Investigator, Howard Hughes Medical Institute
1996-2001	Associate Professor, Department of Neurobiology, Harvard Medical School, Boston, Massachusetts
1997-2001	Associate Investigator, Howard Hughes Medical Institute
2001-2002	Professor, Department of Neurobiology, Harvard Medical School, Boston, Massachusetts
2001-	Investigator, Howard Hughes Medical Institute
2002-	Full Member, Division of Basic Sciences, Fred Hutchinson Cancer Research Center, Seattle, Washington

2003- Affiliate Professor, Department of Physiology and Biophysics, University of Washington, Seattle, Washington

2004-2007 Associate Director, Division of Basic Sciences, Fred Hutchinson Cancer Research Center, Seattle, Washington

OTHER APPOINTMENTS:

1997- Editorial Board, Current Opinion in Neurobiology

2000-2003 Scientific Advisor, Primal, Inc., Seattle, WA

2002- Editorial Board, Molecular and Cellular Neuroscience

2003- Editorial Board, Developmental Neurobiology

2003-2006 Scientific Advisory Board, Nura Inc., Seattle, WA

2004- Scientific Advisory Board, Center for Molecular Medicine, Karolinska Hospital, Stockholm, Sweden

2005- Medical Advisory Board, The Gairdner Foundation, Toronto, Canada

2005- Advisory Committee, March of Dimes Prize in Developmental Biology

2005- President's Council, New York Academy of Sciences

2005- Editorial Advisory Council, HFSP Journal

2005-2009 Advisory Board, Peter Gruber Foundation Neuroscience Prize

2006- Founding Board, Rosalind Franklin Society

2007- Consultant, Omeros Corp., Seattle, WA

2007- Board of Directors, International Flavors & Fragrances, Inc., New York

2007 Member, Kavli Prize Committee in Neuroscience

2007 Committee Member, Unilever Science Prize

2008 Committee Member, Kavli Prize in Neuroscience

2009 Committee Member, The Royal Swedish Academy of Sciences Göran Gustafsson Prize

2010- Committee Member, Shaw Prize in Life Science and Medicine

2011 Committee Member, Eric Kandel Young Neuroscientists Prize, The Hertie Foundation

SELECTED HONORS AND AWARDS:

1992 The Takasago Award for Research in Olfaction

1992 The LVMH Moet Hennessy Louis Vuitton Science for Art Prize

1992 The Sense of Smell Award, The Fragrance Foundation

1992 McKnight Scholar Award from The McKnight Endowment Fund for Neuroscience

1992 Alfred P. Sloan Research Fellowship Award

1993 John Merck Scholarship in the Biology of Developmental Disabilities in Children

1995 The 1995 Distinguished Alumnus, Graduate School, University of Texas Southwestern Medical Center

1996 The Unilever Science Award

1996 The R.H. Wright Award in Olfactory Research

1997 The Lewis S. Rosenstiel Award for Distinguished Work in Basic Medical Research

2000 Senior Scholar Award in Aging, The Ellison Medical Foundation

2002 Fellow, the American Association for the Advancement of Science

2003 Member, the National Academy of Sciences

2003 Perl/UNC Neuroscience Prize

2003 The Gairdner Foundation International Award

2004 The Nobel Prize in Physiology or Medicine

2005 Golden Plate Award, The Academy of Achievement

2005 Distinguished Alumnus Award, University of Washington

2005 Brava Award, Women's University Club

2006 The International Hall of Fame, International Women's Forum

2006 Alumna Summa Laude Dignata, University of Washington

2006 Member, the Institute of Medicine of the National Academies

2007 The Medal of Merit, State of Washington

2008 Member, the American Academy of Arts & Sciences

2009 Member, the European Academy of Sciences

BIBLIOGRAPHY (selected):

Buck L and Axel R (1991) A novel multigene family may encode odorant receptors: a molecular basis for odor recognition. Cell 65:175-187.

Ressler KJ, Sullivan SL and Buck LB (1993) A zonal organization of odorant receptor gene expression in the olfactory epithelium. Cell 73:597-609.

Ressler KJ, Sullivan SL, and Buck LB (1994) Information coding in the olfactory system: evidence for a stereotyped and highly organized epitope map in the olfactory bulb. Cell 79:1245-1255.

Sullivan SL, Bohm S, Ressler KJ, Horowitz LF and Buck LB (1995) Target-independent pattern specification in the olfactory epithelium. Neuron 15:779-789.

Sullivan SL, Adamson MA, Ressler KJ, Kozak CA and Buck LB (1996) The chromosomal distribution of mouse odorant receptor genes. Proc. Natl. Acad. Sci. USA 93:884-888.

Berghard A, Buck LB, and Liman ER (1996) Evidence for distinct signaling mechanisms in two mammalian olfactory sense organs. Proc. Natl. Acad. Sci. USA 93:2365-2369.

Berghard A and Buck LB (1996) Sensory transduction in vomeronasal neurons: evidence for G_{ao}, G_{ai2}, and adenylyl cyclase II as major components of a pheromone signaling cascade. J. Neurosci. 16:909-918.

Matsunami H and Buck LB (1997) A multigene family encoding a diverse array of putative pheromone receptors in mammals. Cell 90: 775-784.

Malnic B, Hirono J, Sato T and Buck LB (1999) Combinatorial receptor codes for odors. Cell 96: 713-723.

Horowitz LF, Montmayeur J, Echelard Y and Buck LB (1999) A genetic approach to trace neural circuits. Proc. Natl. Acad. Sci. USA 96:3194-3199.

Matsunami H, Montmayeur J-P and Buck LB (2000) A family of candidate taste receptors in human and mouse. Nature 404: 601-604.

Montmayeur J-P, Liberles SD, Matsunami H and Buck LB (2001) A candidate taste receptor gene near a sweet taste locus. Nature Neurosci. 4:492-498.

Sam M, Vora S, Malnic B, Ma W, Novotny MV and Buck LB (2001) Odorants may arouse instinctive behaviours. Nature 412: 142.

Godfrey PA, Malnic B, and Buck, LB (2004) The mouse olfactory receptor gene family. Proc. Natl. Acad. Sci. USA. 101:2156-2161.

Malnic B, Godfrey PA, and Buck LB (2004) The human olfactory receptor gene family. Proc. Natl. Acad. Sci. USA. 101:2584-2589.

Boehm U, Zou Z, Buck LB (2005) Feedback loops link odor and pheromone signaling with reproduction. Cell 123(4):683-95.

Liberles SD, Buck LB (2006) A second class of chemosensory receptors in the olfactory epithelium. Nature 442:645-650.

Petrascheck M, Ye X, and Buck LB (2007) An antidepressant that extends lifespan in adult *Caenorhabditis elegans*. Nature 450-553-556.

Liberles SD, Horowitz LF, Kuang D, Contos JJ, Wilson KL, Siltberg-Liberles J, Liberles DA, Buck LB (2009) Formyl peptide receptors are candidate chemosensory receptors in the vomeronasal organ. Proc. Natl. Acad. Sci. USA. 106:9842-9847.

Nara K, Saraiva LR, Ye X, Buck LB (2011) A large-scale analysis of odor coding in the olfactory epithelium. J. Neurosci. 31:9179-9191.

Experimental and theoretical approaches to conscious processing

Jean Pierre Changeux
Collège de France

The presentation focuses on the well-delimited issue of how an external or internal piece of information gains access to conscious processing, as characterized by a reportable subjective experience. Converging neuroimaging and neurophysiological data, acquired during conscious and nonconscious processing, point to objective neural measures of conscious access: late amplification of relevant sensory activity, long-distance cortico-cortical synchronization at beta and gamma frequencies, and "ignition" of a large-scale prefronto-parietal network. These findings are compared to current theoretical models of conscious processing, including the Global Neuronal Workspace (GNW) model according to which conscious access occurs when incoming information is made globally available to multiple brain systems through a network of neurons with long-range axons densely distributed in prefrontal, parieto-temporal, and cingulate cortices. The clinical implications of these results for general anesthesia, coma, vegetative state, and schizophrenia are discussed.

1) Academic training

Ecole Normale Supérieure (rue d'Ulm, Paris) (1955) and Licence de Sciences Naturelles (1956, 1957) at Paris University.
Diplôme d'Etudes Supérieures (Mention Très Bien et Félicitations duJury) (1958). Agrégé des Sciences Naturelles (received first) (1958). Doctorat d'Etat de Sciences Naturelles, Paris (Mention Très Honorable et Félicitations du Jury), under the supervision of Pr. Jacques Monod, Institut Pasteur (1964).

2) Academic positions

Agrégé-préparateur of Zoology, Ecole Normale Supérieure, 1958 ; Postdoctoranl fellow, Universiy of California, Berkeley, 1965-1966 ; visiting Assistant Professor Columbia University College of Physicians & Surgeons, New-York, 1966-1967 ; Sous-Directeur, Collège de France, Paris (Chaire de Biologie Moléculaire), 1967 ; Director of the Unit of Molecular Neurobiology, Institut Pasteur, Paris, 1972-2006 ; Professor Collège de France, 1975-2006 ; Professor Institut Pasteur, 1975-2006, emeritus since 2007 ; Skaggs distinguished visiting professor in Pharmacology, University of California San Diego 2008-2011.

3) Scientific prizes and awards

Prix Alexandre Joannidès, Académie des Sciences, Paris, 1977 ; Gairdner Foundation Award, Toronto, Canada, 1978 ; Richard Lounsbery Prize, National Academy of Sciences, Washington (USA) and Académie des Sciences, Paris, 1983 ; Wolf Foundation Prize in Medicine, Jerusalem, Israel, 1983 ; Prix Broquette-Gonin, Académie Française, for l'"Homme Neuronal", 1983 ; Ciba Geigy Drew Award in Biomedical Research, Madison, 1985 ; F.O. Schmitt medal and prize, Neuroscience Research Program, Rockefeller University, New York, 1986 ; Rita Levi-Montalcini Award, Fidia Research Foundation, Washington, 1988 ; Bristol-Myers-Squibb Award in Neuroscience, New York, 1990 ; Carl-Gustaf Bernhard medal, Swedish Royal Academy of Sciences, Stockholm, 1991 ; Science for Art, Prix d'Honneur LVMH, Paris, 1992 ; International Prize Amedeo e Frances Herlitzka for Physiological Sciences, Torino, 1992 ; Médaille d'Or, Centre National de la Recherche Scientifique, Paris, 1992 ; Louis Jeantet Prize for Medicine, Geneva, 1993 ; Thudichum medal, Biochemical Society, London 1993 ; Goodman and Gilman Award in drug receptor pharmacology, American Society for Pharmacology and Experimental Therapeutics, Anaheim, California, 1994 ; Camillo Golgi medal, Accademia Nazionale dei Lincei, Rome 1994 ; Sir Hans Krebs medal, FEBS, Helsinki, 1994 ; Max-Delbrück medal, in Molecular Medicine, Berlin, 1996; Grand Prix de la Fondation pour la Recherche Médicale, Paris, 1997 ; Jean-Louis Signoret prize in Neuropsychology, Paris, 1997 ; Emanuel Merck prize in Chemistry, Darmstadt, 1998 ; Linus Pauling medal, 1998/1999, Stanford, USA ; Eli Lilly award in preclinical Neuroscience, European College of Neuropsychopharmacology, London, 1999 ; Langley Award for basic research on nicotine and tobacco, Washington, 2000 ; Balzan Prize for Cognitive Neuroscience, Berne, 2001 ; American Philosophical Society's Karl Spencer Lashley Award in neuroscience, Philadelphia, 2002 ; Lewis Thomas Prize for Writing about Science, Rockefeller University, New-York, 2005 ; Dart/NYU Biotechnology Award in Basic Biotechnology, New- York, 2006 ; Golden Eurydice Award from International Forum of Biophilosophy, Bruxelles, 2006 ; National Academy of Sciences Award in the Neurosciences, Washington, 2007 ; Neuronal plasticity prize, IPSEN Foundation, Geneva, 2008 ; International College of NeuroPsychopharmacology Pioneer Award, for the fundamental discoveries concerning « The structure and function of the nicotinic acetylcholine receptor», Munchen, 2008 ; Passarow award for «extraordinary achievements in neuropsychiatric research», Los Angeles, 2010.

4) Academies & Honorary degrees

Deutsche Akademie der Naturforscher Leopoldina zu Halle (Pharmacology), 1974 ; Académie deMédecine de Turin, 1976 ; National Academy of Sciences, Washington (USA) (foreign associate), 1983 ; Royal Academy of Sciences, Stockholm, (Sweden) (foreign member), 1985 ; Académie des Sciences, Paris, 1988 ; Académie Royale de Médecine de Belgique (Bruxelles) (foreign honorary member), 1988 ; Academia Europaea (founding member), 1988 ; American Academy of Arts and Sciences, Boston, (USA) (foreign member), 1994 ; Romanian Academy of Medical Sciences, Bucarest (foreign member), 1996 ; Institute of Medicine of the National Academies, Washington, (USA) (foreign associate), 2000 ; Istituto Veneto di Scienze, Lettere Ed Arti, Venezia (Italy), 2001 ; Hungarian Academy of Sciences, Budapest (foreign member associate), 2004 ; European Academy of Sciences, Bruxelles (member), 2004 ; International Academy of Humanism ; Académie Royale des Sciences, des Lettres & des Beaux-Arts de Belgique (foreign member), 2010; Accademia Nazionale dei Lincei, Rome, (Italy) (foreign member) , 2010. Doctor honoris causa : Universities of Torino, Italy, 1989 ; Dundee, Scotland, 1992 ; Geneva, Switzerland, 1994 ; Stockholm, Sweden, 1994 ; Liège, Belgium, 1996 ; Ecole Polytechnique Fédérale of Lausanne, Switzerland, 1996 ; University of Southern California, Los Angeles, USA, 1997 ; Bath, UK, 1997 ; Montréal University, Canada, 2000 ; The Hebrew University of Jerusalem, Israel, 2004 ; Ohio State University, Columbus, USA, 2007 ; University of Buenos Aires, Argentina, 2010.

5) Honorary conferences (selection)

Smith, Kline and French Lectures in Pharmacology, Vanderbilt University, School of Medicine (USA), 1974; Third Louis B. Flexner Lecture, University of Pennsylvania, Philadelphia (USA), 1974 ; Fourth FEBS Ferdinand Springer Lecture, 1975 ; William Draper Harkins Memorial Lecture, Department of Chemistry, University of Chicago (USA), 1977 ; Windsor C. Cutting Memorial Lecture, Department of Pharmacology, Stanford University (USA), 1978 ; John Krantz Memorial Lecture, Department of Pharmacology, Baltimore (USA), 1978 ; *Harvey Lecture*, Rockfeller University, New York (USA), 1980 ; *Wolfgang Pauli Vorlesungen Lecture*, E.T.H. Zurich (Switzerland), 1980 ; Otto Loewi Memorial Lecture, Department of Pharmacology, New York University (USA), 1982 ; Conférence Pfizer, Institut de Recherches Cliniques de Montréal (Canada), 1985; *Woodward Lecture*, Yale University, 1985 ; *Wittaker Distinguished Lecture in Brain Science*, Massachusetts Institute of Technology, Cambridge, MA. (USA), 1986 ; First Walter Dandy lecture, Baltimore (USA), 1986 ; *Warner-Lambert Lecture*, 17th Annual Meeting of the Society for Neuroscience, New Orleans (USA), 1987 ; First Trends in Pharmacological Sciences Lecture, FASEB meeting, Washington (USA), 1990 ; *Aharon Katzir-Katchalsky Lectures*, Rehovot (Israel) 1990 ; Third Jean Brachet Memorial Lecture, Bruxelles (Belgium), 1991 ; Opening lecture European Neuroscience Association meeting, Cambridge (U.K.), 1991 ; Inaugural lecture EUROMEDECINE 92, Montpellier, 1992 ; Special lecture *dedicated to the memory of Prof. Shosaku Numa,* New York Academy of Sciences, Waseda University, Tokyo (Japan), 1993 ; Special lecture 11th European Workshop on Cognitive Neuropsychology, Accademia Cusano, Bressanone (Italy), 1993 ; Giuseppe Moruzzi lectures, Accademia Nazionale dei Lincei, Scuola Normale Superiore of Pisa, Italy, 1993 ; First *Jus lecture* on Ethics and Neurosciences, Toronto, 1995 ; *Berlin Lecture* in Molecular Medicine, Berlin (RFA), 1995 ; Sterling drug Lecture, Boston University School of medicine (USA), 1996 ; Flynn Lecture, Yale University, 1996 ; Cass Memorial Lecture, Dundee University, Scotland, 1996 ; *Bruno Ceccarelli Lecture*, Milan (Italy), 1996 ; First Cavalieri-Ottolenghi Lecture, Turin (Italy), 1996 ; EMBO Lecture : British Brain Research Association meeting, Liverpool (UK), 1997 ; Seventh annual *Edmond Fischer Lecture*, *Seattle* (USA), 1997 ; Ralph I. Dorfman Memorial Lecture, Stanford Univ. School of Medicine (USA), 1998; *Ferrier Lecture*, The Royal Society, London (UK), 1998 ; *Emanuel Merck-Vorlesung*, Technische Universität, Darmstadt (RFA), 1998; *Linus Pauling* lecture, Stanford (USA), 1998/1999 ; F.C. Donders Lectures on cognitive neuroscience, Nijmegen (NL), 1999 ; Burroughs-Wellcome lecture in Pharmacology, Washington, (USA), 1999 ; *First Mind Brain and Behavior lectures*, Harvard University, (USA), 1999 ; Carl Friedrich Von Siemens Foundation lecture, Munich (RFA), 1999 ; Friday evening lecture, Woods Hole (USA), 2000 ; Annual Sterling lecture, Albany Medical College, New York, 2001 ; Schueler distinguished lecture in pharmacology, New Orleans, (USA), 2002 ; *Wenner-Gren distinguished lecture*, Stockholm (Sweden), 2002 ; *The Kenneth Myer Lecture,* Melbourne (Australia), 2003 ; *The Heller Lecture Series* in Computational Neuroscience, Institute of Life Sciences, Jerusalem (Israel), 2004 ; *Jerry A. Weisbach memorial lecture*, Rockefeller University, 2005 ; *Benjamin W. Zwelfach Memorial Lecture*, University of California San Diego (USA), 2007 ; *ASPET's Centennial meeting*, San Diego (USA) 2008 ; *Nobel symposium* « Genes, Brain and Behavior », Stockholm, (Sweden) 2008 ; Keynote lecture *CARTA Symposium* « Evolutionary origins of Art and Aesthetics », San Diego, (USA) 2009 ; Keynote lecture *Keystone Symposium* « Protein, dynamics, allostery and function », Keystone (USA) 2009 ; Inaugural Elaine Sanders-Bush lecture Vanderbilt University (USA) 2010 ; *Open lecture* Swedish Royal Academy of Sciences, Stockholm (Sweden) 2010 ; *Nobel symposium* « The Enlightened Brain», Stockholm, (Sweden) 2010 ; Edwin G. Krebs Lecture on Molecular Pharmacology, Seattle (USA) 2011.

6) Distinguished honors

Grand Croix dans l'Ordre National de la Légion d'Honneur, 2011; Grand-Croix dans l'Ordre National du Mérite 1995 ; Commandeur dans l'Ordre des Arts et des Lettres, 1994 ; Commandeur des Palmes Académiques.

7) Scientific societies

Honorary member of Neurosciences Research Program, MIT and Rockefeller University (USA), since 1984; Honorary member of the Japanese Biochemical Society, Sendai, Japan, 1985 ; Honorary member of the American Neurology Association, 1988 ; Honorary member of University College London, 1990 ; Membre d'honneur à titre étranger de la Société Belge de Neurologie, Bruxelles, 1991 ; Member of European Molecular Biology Organization.

8) Administrative and scientific responsibilities

Membre du Conseil Scientifique de l'Action Concertée Membranes Biologiques de la Délégation générale à la Recherche Scientifique et Technique (DGRST), 1969-1977 ; Membre de la Commission 6 de l'Institut National de la Santé et de la Recherche Médicale (INSERM), 1974- 1979 ; Membre du Conseil d'Administration de l'Association des Pharmacologistes, 1978-1983 ; *Président de l'Action Concertée "Dynamique du Neurone" (DGRST), 1977-1983* ; Membre de la Commission 22 du Centre National de la Recherche Scientifique (CNRS), "Interactions Cellulaires", 1980-1982 ; Membre du Comité Sectoriel Sciences de la Vie (CNRS), 1981-1982 ; *Vice-Président du Conseil Scientifique de la Fondation Fyssen, 1979-2000* ; *Président du Conseil Scientifique de l'INSERM, 1983-1987* ; Membre du Conseil Supérieur de la Recherche et de la Technologie, 1987-1989 ; Membre du Conseil Scientifique de l'Institut Pasteur, 1989-1992 ; Président de la Société des Neurosciences, 1989-1992 ; *Président de la Commission Interministérielle pour la Conservation du Patrimoine Artistique National, since 1989* ; Président de l'Action Concertée "Sciences de la Cognition" du Ministère de la Recherche Scientifique et Technique et du Ministère de l'Education Nationale, 1988-1992 ; Membre du Conseil Scientifique de "Human Frontiers Science Program", 1990-1992 ; Membre du Comité Scientifique "Life Sciences" de l'European Science Foundation (ESF), 1990-1992 ; Membre du Conseil du Développement Européen de la Science et de la Technologie (CODEST), 1991-1992 ; *Président du Comité Consultatif National d'Ethique pour les Sciences de la Vie et de la Santé, 1992-1998* ; Membre du Comité de l'Energie Atomique *1998-2003* ; Membre du Conseil d'Administration de l'Institut Pasteur, 2000-2005 ; Directeur du Département de Neuroscience Institut Pasteur, 2002- 2006 ; *Président du Comité de Vigilance Ethique de l'Institut Pasteur, since 2007* ; Membre du Conseil Scientifique de l'Agence Internationale des Musées, France Muséums, since 2007 ; Membre du Comité de programmation du Musée du Luxembourg since 2010 ; Président du Conseil d'Orientation de l'Institut du Cerveau et de la Moëlle épinière, La Salpétrière, 2010.

9) Training and teaching

Jean-Pierre Changeux mentored more than 85 students and postdoctoral fellows, many of whomare now distinguished leaders in the fields of biological sciences, neuroscience in particular : Stanislas Dehaene (Prof Collège de France), Thierry Heidmann (médaille argent CNRS), Jérome Giraudat (médaille argent CNRS), Jacques Mallet, Nicolas LeNovère, Pierre-Jean Corringer, Uwe Maskos... in France, Jim Patrick (Prof Baylor college), Jonathan Cohen (Prof Harvard U), Henry Lester (Prof CalTech), Richard Olsen (Prof UCLA), Christopher Henderson (Prof Columbia U), Marina Picciotto (Prof Yale U)… in the USA. Naguib Mechawar (Prof McGill U) in Canada Katsuhiko Mikoshiba (Prof Tokyo U & Riken I) ; Vivian Teichberg (Prof Weizman I); Heinrich Betz (Prof Francfurt U)...

10) Books and publications

J.-P. CHANGEUX
L'Homme neuronal, Fayard Paris (1983) ; Neuronal Man (Laurence Garey translator) 1985 Pantheon Books;
J.-P. CHANGEUX
Molécule et Mémoire, Bedou Gourdon (1988)
J.-P. CHANGEUX (dir.)
Fondements naturels de l'Ethique, Odile Jacob Paris (1993)
J.-P. CHANGEUX (dir.)
Une même éthique pour tous? Odile Jacob Paris (1997)
J.-P. CHANGEUX, A. CONNES
Matière à pensée, Odile Jacob Paris (1989, 2000, 2008) ; Conversations on Mind, Matter and Mathematics (M.B. De Bevoise 1995 Princeton University Press;
J.-P. CHANGEUX
Raison et Plaisir, Odile Jacob Paris (1994, 2002)
J.-P. CHANGEUX, P. RICOEUR
Ce qui nous fait penser: La Nature et la Règle, Odile Jacob Paris (1998, 2008) ; What makes us think ? a neuroscientist philosopher argue about ethics, human nature and the brain (M.B. De Bevoise translator) (2000) Princeton University Press;
J.-P. CHANGEUX
L'homme de vérité, Odile Jacob Paris (2002, 2004, 2008) ; The Physiology of Truth : neuroscience & human knowledge De Bevoise translator) Harvard University Press;
J.-P. CHANGEUX (dir.) Gènes et Culture, Odile Jacob Paris (2003)
J.-P. CHANGEUX (dir.) La Vérité dans les sciences, Odile Jacob (2003)
J.-P. Changeux & S. Edelstein Nicotinic acetylcholine receptors : from molecular biology to cognition (2005) Odile Jacob J.-P. CHANGEUX catalogue d'exposition La lumière au siècle des Lumières et aujourd'hui, Odile Jacob Paris (2005)
J.-P. CHANGEUX catalogue d'exposition
Les passions de l'âme, Odile Jacob Paris (2006)
J.-P. CHANGEUX (dir.)
L'Homme artificiel, Odile Jacob Paris, Colloque annuel du Collège de France (2007)
J.-P. CHANGEUX
Du vrai, du beau, du bien, Odile Jacob Paris (2008)
More than 600 publications in international journals

Wired for sex: the neurobiology of drosophila courtship behaviour

Barry Dickson
Research Institute of Molecular Pathology

How are innate behavioural repertoires pre-programmed into the nervous system? And how does trial-and-error learning allow each individual to fine tune this innate templates to adapt to the conditions of the local environment? The courtship behaviour of *Drosophila melanogaster* males offers a tractable genetic model system to address these questions. I will present our efforts to define the anatomy and function of neural circuity that generates male courtship behaviour, with a specific focus on the sexual dimorphisms sculpted into these circuits by the *fruitless* gene, and how these sex differences may lead to male-specific generation of the courtship song. I will also discuss elements of these circuits that mediate learning in the adult fly, so that his courtship activity is preferentially directed at the most appropriate target – the receptive virgin female.

Biosketch

Barry Dickson studied at the Universities of Melbourne and Queensland, graduating with a B.Sc. in computer science and a B.Sc.Hons. in genetics. After a brief period at the Salk Institute in San Diego, he then moved for his PhD studies to the University of Zurich, Switzerland, where he worked with Ernst Hafen on receptor tyrosine kinase signalling during *Drosophila* eye development. His postdoctoral work on axon pathfinding was performed with Corey Goodman at the University of California, Berkeley. In 1996 he set up his own group in Zurich, and in 1998 moved to Vienna, Austria, as a group leader at the Research Institute of Molecular Pathology (IMP), where he is now the Scientific Director.
Barry's research group has made key contributions to understanding the molecular and cellular mechanisms of axon pathfinding, in particular in the choices axonal growth cones as they navigate the midline of the *Drosophila* central nervous system. Recently, their research focus has shifted to investigating how dedicated neural circuits mediate complex behaviours, and how genes direct the assembly and function of these circuits. As a model system, his group focuses on the innate reproductive behaviours of *Drosophila*.

Selected recent publications

1. Demir, E. and Dickson, B.J. (2005). *fruitless* splicing specifies male courtship behavior in *Drosophila*. **Cell** 121: 785-794
2. Stockinger, P., Kvitsiani, D., Rotkopf, S., Tirian, L. and Dickson, B.J. (2005). Neural circuitry that governs *Drosophila* male courtship behavior. **Cell** 121: 795-807
3. Kurtovic, A., Widmer, A., and Dickson, B.J. (2007). A single class of olfactory neurons mediates behavioural responses to a *Drosophila* sex pheromone. **Nature**,446: 542-546.
4. Dietzl, G., Chen, D., Schnorrer, F., Su, K.-C., Barinova, Y., Fellner, M., Gasser, B., Kinsey, K., Oppel, S., Scheiblauer, S., Couto, A., Marra, V., Keleman, K., and Dickson, B.J. (2007). A genome-wide transgenic RNAi library for conditional gene inactivation in *Drosophila*. **Nature** 448: 151-156.
5. Keleman, K., Krüttner, S., Alenius, M., and Dickson, B.J. (2007). Function of the *Drosophila* CPEB protein Orb2 in long-term courtship memory. **Nature Neuroscience** 10: 1587-1593..
6. Yapici, N., Kim, Y.-J., Ribeiro, C., and Dickson, B.J. (2008). A receptor that mediates the post-mating switch in *Drosophila* reproductive behaviour. **Nature** 451: 33-37.
7. Häsemeyer, M., Yapici, N., Heberlein, U., and Dickson, B.J. (2009). Sensory neurons in the Drosophila genital tract regulate female reproductive behavior. **Neuron** 61: 511-518
8. Spitzweck, B., Brankatschk, M., Dickson, B.J. (2010). Distinct protein domains and expression patterns confer divergent axon guidance functions for *Drosophila* Robo receptors. **Cell** 140: 409-420.
9. Yu, Y.J., Kanai, M.I., Demir, E., Jefferis, G.S.X.E., and Dickson, B.J. (2010). Cellular organization of the neural circuit that drives *Drosophila* courtship behavior. **Curr Biol.** 20: 1602-1614.
10. von Philipsborn, A.C., Liu, T., Yu, J. Y., Masser, C., Bidaye, S.S. and Dickson, B.J. (2011). Neuronal control of *Drosophila* courtship song. Neuron 69: 509-522.

Signaling networks that regulate synapse development and cognitive function

Michael E. Greenberg
Harvard Medical School

Our interactions with the outside world trigger changes at neuronal synapses that are critical for proper brain development and higher cognitive function. Research in the Greenberg laboratory has focused on the identification of a genetic program that is activated by neuronal activity, the mechanisms of signal transduction that carry the neuronal activity-dependent signal from the membrane to the nucleus, and the identification of regulators of this experience-dependent process that affect synapse development and plasticity. Our recent studies using global screening techniques have identified a number of activity-dependent genes that control various processes such as 1) the complexity of the dendritic arbor, 2) the formation, maturation, and maintenance of spines, the post-synaptic sites of excitatory synapses, 3) the composition of protein complexes at the pre- and post-synaptic sites, 4) the relative number of excitatory and inhibitory synapses, and 5) the production and secretion of neuropeptides that control synaptic inhibition. These activity-regulated processes are critical for normal brain development and function, and defects in the activity-dependent gene program contribute to disorders of human cognition such as Rett Syndrome (RTT) and Angelman Syndrome (AS), two neurological disorders associated with syndromic autism. Understanding how the neuronal activity-dependent gene program functions may provide insight into how the dysregulation of this process leads to neurological diseases and, ultimately, may suggest therapies for treatment of disorders of cognitive function.

Michael E. Greenberg, Ph.D.
Nathan Marsh Pusey Professor of Neurobiology
Chair, Department of Neurobiology
Harvard Medical School

Michael E. Greenberg, PhD was named Chair of the Department of Neurobiology and Nathan Marsh Pusey Professor in September, 2008. He came to Harvard Medical School from Children's Hospital Boston, where he directed the F.M. Kirby Neurobiology Center.

Dr. Greenberg's selection as chair reflects his unique qualification to lead the department at a pivotal moment in the field of neuroscience, when understanding of the nervous system at a molecular, cellular and physiological level is increasingly translating to direct influence on the treatment of neurologic and psychiatric disease.

Dr. Greenberg's own research has expanded understanding of the molecular basis of the major events in neural development, the neural responses to injury and disease, and the potential for intervention, treatment, or cure. His research has also explored the molecular biology and genetics of autism spectrum disorders. More specifically, Dr. Greenberg and his research group focus on identifying mechanisms that trigger proliferation, differentiation and survival of neurons during development, and adaptive responses in the mature nervous system. Their work has uncovered the existence and function of a genetic program that is activated by neuronal activity, the mechanisms of signal transduction that carry the neuronal activity-dependent signal from the membrane to the nucleus, and the identification of regulators of this experience-dependent process that affect synapse development and plasticity. Professor Greenberg is particularly interested in those activity-dependent processes whose dysfunction can lead to the development of diseases of cognitive function.

Dr. Greenberg currently serves on the editorial boards of *Neuron*, *Journal of Neuroscience*, *Learning & Memory*, and *Molecular & Cellular Neuroscience*. He is the recipient of numerous honors and awards, including membership in both the American Academy of Arts and Sciences and the National Academy of Science. He is also the recipient of the McKnight Innovation in Neuroscience Award, the Edward M. Scolnick Prize in Neuroscience, and the A. Clifford Barger Award for Excellence in Mentoring, a prize given annually by Harvard Medical School to faculty members who have established a long-term commitment to fostering strong mentoring relationships with students, trainees, and junior faculty.

Professor Greenberg graduated Magna Cum Laude from Wesleyan University, and received his Ph.D. from Rockefeller University.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
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NAME	POSITION TITLE
Michael E. Greenberg	Professor of Neurobiology Head of the Department of Neurobiology, Harvard Medical School
eRA COMMONS USER NAME (credential, e.g., agency login) MiGreenberg	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Wesleyan University, Middletown, CT	B.A.	05/76	Chemistry
The Rockefeller University, New York, NY	Ph.D.	06/82	Biochemistry

A. Personal Statement

Over the last two decades Dr. Greenberg has served as a leader in the field of molecular neurobiology. His research has revealed a complex activity-regulated gene expression program relevant to synapse development and neural circuitry. His research contributes greatly to our understanding of diseases of cognition in which these processes of synapse development and neural circuit formation have gone awry.

B. Positions and Honors.

Positions and Employment

1983-1986 Postdoctoral Fellow with Dr. Edward B. Ziff, Department of Biochemistry, New York University Medical Center (New York, NY)
1986-1991 Assistant Professor, Department of Microbiology and Molecular Genetics, Harvard Medical School (Boston, MA)
1991-1993 Associate Professor, Department of Microbiology and Molecular Genetics, Harvard Medical School (Boston, MA)
1993-1994 Professor, Department of Microbiology and Molecular Genetics, Harvard Medical School (Boston, MA)
1994-2008 Professor, Department of Neurology and Neurobiology, Harvard Medical School and Director, Neurobiology Program, Children's Hospital (Boston, MA)
2008- Nathan Marsh Pusey Professor of Neurobiology, Chair of the Department of Neurobiology, Harvard Medical School (Boston, MA)

Other Experience and Professional Memberships

1990- Editorial Boards: Neuron; J. Neuroscience, Learning & Memory; Mol. & Cell Neuroscience; Molecular & Cellular Biology
1992-1996 Member/Chair, National Institutes of Health Neurology C Study Section
1993-2006 Member/Chair, Medical Foundation/Charles A. King Trust Study Section
1996-2006 Scientific Advisory Board, Upstate Biotechnology Inc.
1991-2001 Scientific Advisory Board, Helicon Inc.
1998-2002 Scientific Advisory Board, Cogent Neuroscience, Inc.
2008- Scientific Advisory Board, Constellation
2008- International Science Advisory Council
2008- Harvard University Science and Engineering Committee (HUSEC)

Honors

1976 Phi Beta Kappa, Sigma Xi, B.A. Magna Cum Laude, Honors in Chemistry
1983-1984 Damon Runyon-Walter Winchell Postdoctoral Fellowship
1987-1990 Searle Scholars Program Award--Chicago Community Trust
1990-1993 McKnight Scholars Award in Neuroscience
1991-1996 American Cancer Society Faculty Research Award
1999-2001 McKnight Innovation in Neuroscience Award
1999-2006 Jacob Javits Neuroscience Award
2001-2003 Ellison Medical Foundation Senior Scholar's Award
2003 Election to the American Academy of Arts and Sciences
2006 A. Clifford Barger Award for Excellence in Mentoring—Harvard Medical School
2006 3rd Annual Edward M. Scolnick Prize in Neuroscience (McGovern Institute)
2007 Harvey Lecture (Rockefeller University)
2008 J. Allyn Taylor International Prize in Medicine
2008 Elected to the National Academy of Sciences

2009 Perl-UNC Neuroscience Prize
2009 Julius Axelrod Prize
2010 Vernon B. Mountcastle Lecture (Johns Hopkins University)
2010 Walter Massey Family Lecture (Marine Biological Laboratory, Woods Hole, MA)

C. Selected peer-reviewed publications (selected from >170 total)

1. Dolmetsch RE, Urvi P, Fife K, Spotts JM, **Greenberg ME**. Signaling to the nucleus by an L-type calcium channel-calmodulin complex through the MAP Kinase Pathway (Research Article). *Science* 2001; 294: 333-339.
2. Tran H, Brunet A, Grenier JM, Data SR, Fornace AJ Jr, DeStefano PS, Chiang LW, **Greenberg ME**. DNA repair pathway stimulated by the forkhead transcription factor FOXO3a (FKHRL1) through the Gadd45 protein. *Science* 2002; 296(5567): 530-540.
3. Kornhauser JM, Cowan CW, Shaywitz AJ, Dolmetsch RE, Griffith EC, Hu LS, Haddad C, Xia Z, **Greenberg ME**. CREB transcriptional activity in neurons is regulated by multiple, calcium-specific phosphorylation events. *Neuron* 2002; 34(2): 221-233.
4. Datta SR, Ranger AM, Lin MZ, Sturgill JF, Ma YC, Cowan CW, Dikkes P, Korsmeyer SJ, **Greenberg ME**. Survival factor-mediated BAD phosphorylation raises the mitochondrial threshold for apoptosis. *Developmental Cell* 2002; 3(5): 631-643.
5. Chen WG, Chang Q, Lin Y, Meissner A, West AE, Griffith EC, Jaenisch R, **Greenberg ME**. Derepression of BDNF transcription involves calcium-dependent phosphorylation of MeCP2. *Science* 2003; 302(5646): 885-889.
6. Brunet A, Sweeney LB, Sturgill JF, Chua KF, Greer PL, Lin Y, Tran H, Ross SE, Mostoslavsky R, Cohen HY, Hu LS, Cheng HL, Jedrychowski MP, Gygi SP, Sinclair DA, Alt FW, **Greenberg ME**. Stress-dependent regulation of FOXO transcription factors by the SIRT1 deacetylase. *Science* 2004; 303(5666): 2011-2015.
7. Tolias KF, Bikoff JB, Burette A, Paradis S, Harrar D, Tavazoie S, Weinberg RJ, **Greenberg ME**. The Rac1-GEF Tiam1 couples the NMDA receptor to the activity-dependent development of dendritic arbors and spines. *Neuron* 2005; 45(4): 525-538.
8. Cowan CW, Shao YR, Sahin M, Shamah SM, Lin MZ, Greer PL, Gao S, Griffith EC, Brugge JS, **Greenberg ME**. Vav family GEFs link activated Ephs to endocytosis and axon guidance. *Neuron* 2005; 46(2): 205-217
9. Schratt GM, Tuebing F, Nigh EA, Kane C, Sabatini ME, Kiebler M, **Greenberg ME**. A brain-specific microRNA regulates dendritic spine development. (Article) *Nature* 2006; 439(7074): 283-289.
10. Ma YC, Song MR, Park JP, Henry Ho HY, Hu L, Kurtev MV, Zieg J, Ma Q, Pfaff SL, **Greenberg ME**. Regulation of motor neuron specification by phosphorylation of neurogenin 2. *Neuron*. 2008; 58(1): 65-77.
11. Lin Y, Bloodgood, BL, Hauser JL, Lapan, AD, Koon, AC, Kim T-K, Hu LS, Malik AN, **Greenberg ME**. Activity-dependent regulation of inhibitory synapse development by Npas4. (Article) *Nature*, 2008; 455(7217): 1198-1204. PMCID: PMC2637532
12. Flavell SW, Kim TK, Gray JM, Harmin DA, Hemberg M, Hong EJ, Markenscoff-Papadimitriou E, Bear DM, **Greenberg ME**. Genome-wide analysis of MEF2 transcriptional program reveals synaptic target genes and neuronal activity-dependent polyadenylation site selection. *Neuron* 2008; 60(6): 1022-1038. PMCID: PMC2630178
13. Greer PL, Hanayama R, Bloodgood BL, Mardinly AR, Lipton DM, Flavell SW, Kim TK, Griffith EC, Waldon Z, Maehr R, Ploegh HL, Chowdhury S, Worley PF, Steen J, **Greenberg ME**. The Angelman Syndrome protein Ube3A regulates synapse development by ubiquitinating Arc. *Cell* 2010; 140(5): 704-716. PMCID: PMC2843143
14. Ross SE, Mardinly AR, McCord AE, Zurawski J, Cohen S, Jung C, Hu L, Mok SI, Shah A, Savner EM, Tolias C, Corfas R, Chen S, Inquimbert P, Xu Y, McInnes RR, Rice FL, Corfas G, Ma Q, Woolf CJ, **Greenberg ME**. Loss of inhibitory interneurons in the dorsal spinal cord and elevated itch in Bhlhb5 mutant mice. *Neuron* 2010; 65(6): 886-898. PMCID: PMC2856621
15. Kim TK, Hemberg M, Gray JM, Costa AM, Bear DM, Wu J, Harmin DA, Laptewicz M, Barbara-Haley K, Kuersten S, Markenscoff-Papadimitriou E, Kuhl D, Bito H, Worley PF, Kreiman G, **Greenberg ME**. Widespread transcription at neuronal activity-regulated enhancers. (Article) *Nature* 2010; 465(7295): 182-187. NIHMSS 233355

Kinesin superfamily molecular motors (KIFs) as key regulators for intracellular transport and higher brain function

Nobutaka Hirokawa
Department of Cell Biology and Anatomy, Graduate School of Medicine, University of Tokyo

Abstract: Kinesin superfamily motor proteins, KIFs play fundamental roles on the neuronal functions and survival by transporting various cargos, such as synaptic vesicle precursor, mitochondria, plasma membrane protein vesicles, protein complexes, vesicles containing receptors, and mRNAs with large protein complex in the axon and dendrites. KIF 1A and KIF1B beta transport synaptic vesicle precursors in the axon and KIF 17 transports vesicles containing NMDA type glutamate receptors in dendrites. In this symposium first I will focus on the mechanisms how KIF1A/1B beta and KIF 17 recognize the cargoes and unload them. KIF1A/1B beta bind DENN/MADD through their stalk region and DENN/MADD recognizes and binds Rab3 in the synaptic vesicle precursor. The binding to Rab3 is controlled by GTP-hydrolysis. GTP-Rab3 can bind DENN/MADD, while GDP-Rab3 cannot. In the case of KIF 17 KIF 17 binds Mint-1(mLin10) and recognizes and binds NR2B in the cargo vesicle through interaction with scaffold protein complex containing Mint-1. The interaction between KIF 17 and Mint- 1 is controlled by phosphorylation of KIF17 tail by CaMKIIalpha. CaMKIIalpha binds KIF17 tail domain and phosphorylates S1029. Then Mint-1 is released from KIF 17. Thus the mechanisms coupled with hydrolysis of small G-protein in the cargos and phosphorylation of KIF have been identified as the mechanisms to unload cargos. Second, I will introduce in vivo function of KIF 17. Disruption of kif17 gene inhibits NR2B transport, accompanied by decreased transcription of nr2b, resulting in a loss of synaptic NR2B. In kif17-/- hippocampal neurons, the NR2A level is also decreased because of accelerated ubiquitin proteasome system-dependent degradation. Accordingly, NMDA receptor-mediated synaptic currents, early and late long-term potentiation, long-term depression, and CREB responses are attenuated in kif17-/- neurons, concomitant with a hippocampus-dependent memory impairment in knockout mice. In wild-type neurons, CREB is activated by synaptic inputs, which increase the levels of KIF17 and NR2B. Thus, KIF17 differentially maintains the levels of NR2A and NR2B, and, when synapses are stimulated, the NR2B/KIF17 complex is upregulated on demand through CREB activity. These KIF17-based mechanisms for maintaining NR2A/2B levels could underlie multiple phases of memory processes in vivo. Further, as the last subject I will introduce significant unexpected functions of KIFs revealed by molecular genetics. KIF2A is fundamental for neuronal migration and brain wiring by depolymerizing microtubules in growth cones and suppressing unnecessary elongation of axon collaterals. KIF4 controls the activity-dependent survival of neurons by regulating PARP-1 activity during brain development. KIF26A controls development of enteric nervous system as a key suppressor of GDNF/Ret signaling cascade. Thus, KIFs play a number of significant roles not only on various neuronal functions by transporting important cargos, but also on fundamental physiological processes such as higher brain function, brain wiring, and CNS/PNS development.

Biography: Nobutaka Hirokawa graduated from the School of Medicine at the University of Tokyo in 1971. He received Ph D degree from the University's Faculty of Medicine in 1978. He did postdoctoral work at the University of California at San Francisco and Washington University School of Medicine in St. Louise and became a Research Assistant Professor of Physiology and Biophysics there (1981-83), and then an Associate Professor of Anatomy and Neurobiology (1983). From 1983 until 2009 he has served at the Graduate School of Medicine at the University of Tokyo as a Professor and Chairman of the Department of Cell Biology and Anatomy. From 2003 April to 2007 March he was also appointed as the dean of Graduate School of Medicine, University of Tokyo. He is now a project professor in University of Tokyo, Graduate School of Medicine. He is a member of Japan Academy and an elected associate member of EMBO. Widely respected in international circles, Hirokawa has been on the editorial boards of many international top journals including Cell, Science, Neuron, Dev Cell, J Cell Biol, EMBO J, Curr Opi Cell Biol, and Trends in Cell Biol. (http://cb.m.u-tokyo.ac.jp)

Recent Publication:

1. Tanaka, Y., Y. Okada, and **N. Hirokawa**. ***Nature***, 435: 172-177, 2005.
2. Okada, Y., S. Takeda, Y. Tanaka and **N. Hirokawa**. ***Cell***, 121 : 633-644, 2005
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9. **Hirokawa, N.**, S. Niwa and Y. Tanaka. ***Neuron*** 18; 610-638, 2010.
10. Yin, X,. Y. Takei, M. Kido and **N. Hirokawa.** ***Neuron*** 70: 310-325, 2011

Synaptic competition in the dendritic spines of CA1 pyramidal neurons

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Competitive stabilization and elimination of synaptic connections play key role in the refinement of neuronal networks during development, learning and memory_ENREF_2. Biological processes underlying the synaptic competition, however, have been poorly understood. In the cerebral cortex, excitatory synapses are formed on small protrusions of dendrites, dendritic spines, in the pyramidal neurons. Selection of dendritic spines is achieved by structural plasticity of dendritic spines, their enlargement, shrinkage, which are associated with long-term potentiation (LTP) and depression (LTD), respectively_ENREF_4. Two-photon uncaging of glutamate revealed that long-lasting plasticity of excitatory synapses, i.e. long-term potentiation, can be induced at the level of single spines and is associated with spine enlargement (1,4-9). In contrast, although spine shrinkage can be induced with electrical stimulation of presynaptic fibers, no one has succeeded in induction of spine shrinkage by stimulation of identified spines, which has hampered understanding of synaptic competition. Here we report that spine shrinkage could be robustly induced when GABA inhibition (2) was applied to a dendrite during the spike-timing protocol for induction of LTD. Such spine shrinkage spread to the neighboring spines readily over 10 μm, and competed with the spine enlargement. In contrast, the spine enlargement never spread to the neighboring spines, and did neither induce nor suppress shrinkage of surrounding spines. Thus, the spine synapses tightly interacted each other for competitive selection of synapses owing to the spread of spine shrinkage, while individual modifiability of synapse was preserved because spine enlargement is confined. Such spine shrinkage was dependent on $GABA_A$ receptors, which likely suppress dendritic Ca^{2+} influx following action potential. We will introduce the molecular mechanisms underlying both the spread of shrinkage and the confinement of enlargement of dendritic spines in CA1 pyramidal neurons.

1981	Graduated from the University of Tokyo, Faculty of Medicine.
1988-1990	Humboldt Fellow in the Max-Planck Institute.
1993-1999	Associate Professor in the University of Tokyo.
1999-2005	Professor, National Institute for Physiological Sciences.
2005-Present	Professor in the University of Tokyo

References:

1. Noguchi, J., Nagaoka, A., Watanabe, S., Ellis-Davies, G.C.R., Kitamura, K., Kano, M., Matsuzaki, M. & Kasai H. *In vivo* two-photon uncaging of glutamate revealing the structure-function relationships of dendritic spines in the neocortex of adult mice. *J.Physiol.* 589: 2320-2329, 2011.
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Evolution of olfactory receptor gene repertoires and function

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Most olfactory receptor gene families evolve rapidly, following a birth-and-death mode of evolution. It is widely assumed that the purpose of such dynamic evolution is adaptation to species-specific ecological niches and communication signals. We have phylogenetically characterized the fish *taar* gene family and find this family to be an extreme example of evolutionary dynamics, with several instances of positive selection. At the other extreme lies the V1R-related *ora* gene family, which we found to be highly conserved, with orthologues of individual genes detectable in species as far apart as shark, zebrafish and frog. We have begun to deorphanize receptors from both families. Preliminary observations are consistent with the hypothesis that the evolutionary dynamic of receptor genes does not correspond to a similar dynamic in biological function.

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Dr. Korsching obtained her Ph.D. (*summa cum laude*) 1984 from the *Ludwigs-Maximilians-Universität* Munich in the research field of neurotrophic factors, with Prof. Hans Thoenen as scientific advisor. For this work she received the *Otto-Hahn-Medal* of the Max-Planck-Society. She extended her studies in this field during a postdoc period at the *California Institute of Technology*, USA. While a junior group leader at the *Max-Planck-Institut für Entwicklungsbiologie*, Tübingen, Dr. Korsching began to investigate the sense of smell. 1995 she became professor at the *Institute of Genetics, University of Cologne*, and 1996 she habilitated in "Biochemistry and Molecular Biology" at the *Faculty of Chemistry and Pharmacy, University of Tübingen*. She has been board member of the *German Neuroscience Society* (NWG) for several years and has served as President of this society 2009-2011.

Dr. Korschings current research interests center on the question of how odors are recognized, represented and perceived within the nervous system, and in particular on the evolution of these mechanisms in vertebrates. She has made several contributions to the field of olfactory coding, demonstrating individually identifiable glomeruli in the vertebrate olfactory bulb (1), showing fuzzy spatial segregation in teleost odorant receptor expression domains (2), and showing both combinatorial and labeled line coding in vertebrates (3, 4). In depth studies of the molecular properties guiding odor representation in the olfactory bulb followed (5, 6). Recently, she discovered an unexpectedly conserved fish olfactory receptor gene family (7), which despite its small size of just 6 genes comprises the large family of mammalian V1R receptors as a single subclade. Further phylogenetic studies have led to a reappraisal of the origin and evolutionary dynamics of another olfactory receptor family (8) and to the discovery of a whole new class of G{alpha} proteins (9). Recently she reported a novel type of olfactory receptor gene expression, a 'one cell type – one receptor' mode of expression (10).

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4. Friedrich, R. W. & Korsching, S. I. (1998) Chemotopic, Combinatorial, and Noncombinatorial Odorant Representations in the Olfactory Bulb Revealed Using a Voltage-Sensitive Axon Tracer. J Neurosci. 18, 9977-88.
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Calreticulin chaperones regulate functional expression of V2R pheromone receptors

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Abstract:

Intraspecific communication in animals is often mediated by pheromones, partly detected by the accessory olfactory organ, the Vomeronasal Organ (VNO) in mammals. Previous studies have uncovered molecules that are specifically expressed in the VNO, including three independent groups of putative pheromone receptors, the V1Rs, the V2Rs and the Fprs.

The V2Rs are thought to detect peptide cues from other animals. However, no specific ligand-receptor pairs have been demonstrated heterologously, partly because V2Rs are difficult to study since they fail to traffic to the surface of heterologous cells.

The VNO appears to be vestigialized in humans and the vast majority of the V1Rs and all of the V2Rs as well as the VNO-specific ion channel, Trpc2, are pseudogenes in the human genome. We hypothesized that genes that have specific functions in the VNO are pseudogenized in humans. We used a published list of human pseudogenes to identify intact orthologues in mouse and asked if any of them might be specifically expressed in the VNO. We performed RT-PCR and *in situ* hybridization to assay transcription of these genes in different mouse tissues and found calreticulin 4, a homologue of calreticulin, with highly enriched expression in the mouse VNO. In contrast, the ubiquitously expressed calreticulin expression is diminished in the VNO.

Reducing calreticulin expression causes the unfolded protein response that is suppressed by calreticulin4 in HEK293T cells. Depleting calreticulin expression in HEK293T cells enhances the trafficking of V2Rs to the cell surface, while overexpression of calreticulin4 has no effects. Using this knowledge, we have established a system to monitor the ligand interaction with V2Rs and demonstrate that ESP family members can activate V2Rs. Our results provide a platform to characterize the cognate ligands of V2Rs in the heterologous system.

BIOGRAPHICAL SKETCH

NAME	POSITION TITLE
Hiroaki Matsunami	Associate Professor of Molecular Genetics and Microbiology Associate Professor of Neurobiology

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Kyoto University, Kyoto, Japan	BS	1991	Biology
Kyoto University, Kyoto, Japan	MS	1993	Biophysics
Kyoto University, Kyoto, Japan	PhD	1996	Biophysics
Harvard Medical School	Postdoctoral	2001	Neurobiology

Positions and Employment

1990-1991	Undergraduate Student, Department of Biophysics, Faculty of Science, Kyoto University
1991-1996	Graduate Degree Researcher, Dept. of Biophysics, Faculty of Science, Kyoto University
1996-2000	Postdoctoral fellow, Department of Neurobiology, Harvard Medical School
2001-2008	Assistant Professor, Department of Molecular Genetics and Microbiology, Duke University Medical Center
2008-present	Associate Professor (with Tenure), Department of Molecular Genetics and Microbiology, Duke University Medical Center

Recent publications

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*equal contribution

Cognitive development in humans and chimpanzees

Tetsuro Matsuzawa
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The human mind is a product of evolution, much like the human body. The evolutionary history of the body can be reconstructed from the fossil record – from ancient skulls, bones, and teeth. However, the mind does not fossilize. Therefore, to explore the evolution of the human mind, comparative work is needed that uses the cognitive world of closely-related species – such as chimpanzees – as a reference point, or an "out-group" for comparison. I have been studying chimpanzees both in Japan and in Africa. The research project, known as the "Ai-project", began in 1978. In parallel to the laboratory work, I have visited Africa each year since 1986 to study wild chimpanzees in their natural habitat. Just like us, chimpanzees acquire many new skills as they mature. In this context, the key issue concerns the mechanisms behind the accumulation of knowledge and technology independent of genetic channels. What is acquired? When? How? Fieldwork at Bossou provides an excellent setting in which chimpanzees' cognitive development can be observed across three generations. We have individual longitudinal records for 13 chimpanzees in a community that has been monitored continuously since 1976. The laboratory at the PRI, Kyoto University, can in turn provide complementary data on the development and detailed features of chimpanzee cognition examined under strictly controlled conditions. In addition to the study of chimpanzees (*Pan troglodytes*), we have just started the new research on bonobos (*Pan paniscus*) both in the laboratory and in the wild. This represents the first ever attempt to compare chimpanzees and bonobos across the two different research settings, and will provide us with a novel and comprehensive picture of the common ancestor of the genus *Pan*. Systematic comparisons of the three hominid species (humans, chimpanzees, and bonobos) will shed new light on the evolutionary origins of the human mind, technology, education, culture, mother-infant bond, and society.

Name: Tetsuro Matsuzawa
Affilliation: Primate Research Institute, Kyoto University
Brief Biography
2006(Apr)-: Director, Primate Research Institute, Kyoto University.
1993(Sep)-: Professor, Primate Research Institute, Kyoto University.
1989(Mar): Ph.D. Science, Kyoto University.
1987(Sep)-1993(Aug): Associate Professor, Primate Research Institute, Kyoto University.
1985(Jun)-1987(Apr): Visiting Researcher, University of Pennsylvania, PA, USA
1976(Dec)-1987(Aug): Assistant Professor, Primate Research Institute, Kyoto University.
1974(Apr)-1976(Nov): Graduate School of Letters, Kyoto University
I have been studying captive chimpanzees from comparative cognitive perspectives. The "Ai project" continues since 1978. Other activities include observations of wild chimpanzees at Bossou and Nimba, Guinea, West Africa since 1986. The more recent focus is wild orangutans in Borneo, wild bonobos in Congo, and wild gorillas in Rwanda. The key question is what is uniquely human. The answer is expected to come from the comparison of humans and nonhuman primates.

List of recent publications
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2. Martin, C., Biro, D. & Matsuzawa T. (2011). Chimpanzees' use of conspecific cues in matching-to-sample tasks: public information use in a fully automated testing environment. *Animal Cognition*, DOI 10.1007/s10071-011-0424-3.
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Sensory experience-dependent reorganization of neuronal circuits in the olfactory cortex and olfactory bulb during postprandial sleep

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Abstract: Learning and recognition of odor cues that predict the availability of nutritious foods are essential for the daily life of humans and animals. During food-exploration behavior, olfactory cortex (OC) is engaged in the processing of external odor information. In contrast, the OC is functionally isolated from the external odor world during slow-wave sleep. However, the neuronal activity pattern in the OC and its functional roles during slow-wave sleep are not well understood yet. In the present study, we demonstrate in freely behaving rats that the OC repeatedly generates sharp waves (SPWs) that are accompanied by synchronized discharges of numerous cortical neurons. The frequency of OC-SPWs increased about 2 times during postprandial sleep compared with the sleep without preceding eating. During slow-wave sleep, the olfactory bulb (OB) showed SPWs that were in synchrony with OC-SPWs, indicating that OC-SPWs drove synchronized top-down inputs to the OB.

Granule cells (GCs) in the rodent OB continue to be generated in adulthood, with nearly half incorporated and the remainder eliminated. Here, we show that elimination of adult-born GCs is promoted during postprandial sleep. Deprivation of olfactory sensory experience in the local OB area potentiated the extent of GC elimination in that area during postprandial sleep. These results suggest that extensive structural reorganization of OB circuitry occurs under the instruction of top-down inputs from OC during the postprandial sleep, reflecting sensory experience during preceding waking period.

Biography:
-Dept. of Physiology, School of Medicine, Gunma University,
Assistant Professor (1974-1978), Lecturer (1980-1987)
-Dept. of Physiology and Section of Neuroanatomy, Yale Univ. Sch. of Medicine. USA
Research Associate (1978-1980)
-Dept. of Neuroscience, Osaka Bioscience Institute, Vice-Head (1987-1995)
-Lab. for Neuronal Recognition Molecules, Neuronal Function Research Group,
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Group Director and Lab. Head (1995-2000)
-Dept. of Physiology, Graduate School of Medicine, University of Tokyo
Professor (1999-present)

Publications:
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4, Murata, M., Imai, M., Nakanishi S., Watanabe, D., Pastan I., Kobayashi, K., Nihira T., Mochizuki, H., Yamada, S., Mori, K. and Yamaguchi, M. (2011) Compensation of depleted neuronal subsets by new neurons in a local area of the adult olfactory bulb *J. Neurosci.* 31(29): 10540-10557.
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9. Mori, K., Takahashi, Y.K., Igarashi, K.M. and Yamaguchi, Y. (2006) Maps of odorant molecular features in the mammalian olfactory bulb *Physiological Reviews*. 86(2): 409-433.
10. Murakami, M., Kashiwadani, H., Kirino, Y. and Mori, K (2005) State-dependent sensory gating in olfactory cortex *Neuron* 46:285-296.

Functional architecture of cerebral cortex

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It has been suggested that local cortical circuits are composed of arrays of anatomical units that run perpendicular to the cortical surface. There are two such anatomical units, called a minicolumn and a microcolumn. A minicolumn is a one-cell-wide vertical array of cell bodies of neurons. A microcolumn is a group of neurons, located roughly vertically, and their apical dendrites make a bundle in upper layers. It has been suggested that neurons in a microcolumn send axons to specific targets, and a microcolumn may serve as a cortical output unit (Innocenti et al., 2010), but it is still under debate whether these anatomical structure have any functional correlate.

We examined whether neurons that belong to either of these anatomical units share the same function in visual processing. We obtained 3-dimensional functional maps of mouse visual cortex with in vivo 2-photon volume imaging of calcium signal, in which a volume (340x170x200 micron) was scanned every 0.6 seconds, using a combination of a resonant scanner and a piezo drive. We successfully reconstructed three-dimensional functional maps in layer II/III of mouse visual cortex. We tested whether neurons in a minicolumn share the same selectivity for orientation, direction, spatial frequency, or receptive field position. Surprisingly, none of these features were shared by neurons in a minicolumn. We also tested whether neurons in a microcolumn share the same selectivity, by imaging from a bundle of apical dendrites. Again, apical dendrites of a bundle had diverse selectivity. We propose that a microcolumn receives diverse information to send a set of information to a specific target.

This newly found motif of functional architecture suggested that individual neurons in a minicolumn or microcolumn receive highly specific and differential inputs. Indeed, the existence of networks of specifically connected subpopulation of excitatory neurons - subnetworks - were found in rodent visual cortex, and they were related to orientation selectivity (Ho et al., 2011). We are now addressing whether there exists any developmental basis of such subnetworks. I would like to discuss a possibility that response selectivity of pyramidal neurons may be affected by their cell lineage.

Biography
1996 M.D. from University of Tokyo, Medical School
2000 Ph.D. from University of Tokyo
2000-2002 Instructor, University of Tokyo
2002-2010 Research Fellow and Instructor, Harvard Medical School
2010- Professor, Kyushu University

Publications
K. Ohki, S. Chung, Y. H.Ch'ng, P. Kara, R. C. Reid. Functional imaging with cellular resolution reveals precise micro-architecture in visual cortex. *Nature*: Vol. 433: 597-603 (2005).
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A neandertal perspective on human origins

Svante Pääbo
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Over the past 25 years, our laboratory has developed of techniques for extracting and analyzing DNA from Pleistocene fossil remains. We recently produced a genome sequence of 1.3-fold genomic coverage from Neandertals, who lived in western Eurasia until becoming extinct around 30,000 years ago. We find that about 2.5% of the genomes of people living outside Africa derive from Neandertals, implying that interbreeding occurred between Neandertals and the ancestors of all present-day people living outside Africa.

We have also sequenced the genome of an ancient finger bone from Denisova Cave in southern Siberia to 1.9-fold coverage. The analysis of the sequence reveals that it drives from a hitherto unknown group of hominins, which we call Denisovans. This group shared a common DNA ancestor with Neandertals about 650,000 years ago and with present-day humans around 800,000 years ago. Approximately 4.8% of the genomes of people now living in Papua New Guinea and other parts of Melanesia derive from Denisovans, suggesting interbreeding in eastern Eurasia between Denisovans and ancestors of some present-day human groups.

Together, these finding suggest a ‘leaky replacement’ scenario of human origins in which anatomically modern humans emerged out of Africa beginning around 1000,000 years ago and received some degree of gene flow from the anatomically archaic human populations in Eurasia that they ultimately replaced. The Neandertal and Denisova genomes also allow novel genomic features that appeared and became fixed in present-day humans since their divergence from common ancestors with these archaic humans to be identified, and regions likely to have been affected by positive selection in modern humans since their divergence from a common ancestor shared with Neandertals and Denisovans to be identified. I will describe our analysis of some such candidates, as well as our work that focuses on the evolution *FOXP2* in humans, a gene involved in the development of speech and language.

Svante Pääbo has developed technical approaches that allow DNA sequences from extinct creatures such as mammoths, ground sloths and Neandertals to be determined. He also works on the comparative genomics of humans, extinct hominins and apes, particularly the evolution of gene activity and genetic changes that may underlie aspects of traits specific to humans such as speech and language. In 2010, his group determined the first Neandertal genome sequence and described Denisovans, a sister group of Neandertals, based on a genome sequence determined from a small bone found in Siberia.

Svante Pääbo holds several honorary degrees, has received several scientific prizes and is a member of numerous academies. He is currently a Director at the Max-Planck Institute for Evolutionary Anthropology in Leipzig, Germany.

Svante Pääbo
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Circuit mechanisms for perceptual memory of the temporal sequence and time intervals of sensory events

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Six decades after the publication of "The Organization of Behavior" by Donald Hebb, the neural circuit basis of perceptual memory remain an unsolved mystery. Hebb postulated that the first step in perceptual memory in the brain is the formation of an experience-specific assembly of neurons, and experience-induced persistent "reverberatory" correlated activity facilitates the formation of the cell assembly by selectively strengthening synaptic connections among these neurons. I will review our recent efforts in search of the circuit mechanism for perceptual memory of temporal sequence and time intervals of sensory events. In the rodent primary visual cortex, we have obtained evidence that spike timing-dependent plasticity (STDP) of intracortical connections may provide a mechanism for short-term storage of sequence information associated with a directional moving object. In the optic tectum of zebrafish larvae, we found that an ensemble of tectal neurons could store the information of the time interval (on the order of seconds) via rhythmic correlated spiking activities among the specific ensemble. Furthermore, unlike long-term potentiation/depression (LTP/LTD) found in slice preparations, synaptic modification induced by a single episode of repetitive correlated pre- and postsynaptic spiking is quickly erased by the high-level spontaneous activity *in vivo*, but repeated episodes of the same total number of spikes resulted in stable LTP/LTD. This suggests that long-term perceptual memory of sensory experience requires spaced pattern of sensory activities.

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Biographic Sketch

Mu-ming Poo received his B.S. in physics from Tsinghua University in Taiwan in 1970, and Ph. D in biophysics from Johns Hopkins University in 1974. He had served on the faculty of University of California at Irvine, Yale University, Columbia University, and University of California at San Diego, before joining University of California, Berkeley in 2000, where he is currently Paul Licht Distinguished Professor in the Department of Molecular and Cell Biology. Since 1999, he also served as the Director of Institute of Neuroscience, Chinese Academy of Sciences in Shanghai. Poo's research interests cover axon guidance, neuronal polarity formation, synaptic plasticity, and neural circuit functions. He received Javitz Neuroscience Investigator Award of NIH (1998), Ameritec Prize (2001), Docteur Honoris Causa from Ecole Normale Supérieure, Paris (2003), P. R. China International Science & Technology Cooperation Award (2005), and Qiushi Distinguished Scientist ward (2010). He is a fellow of AAAS, and a member of Academia Sinica (Taiwan) and National Academy of Sciences (US).

Emergence of novel chemosensors: from the immune to the olfactory system

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Formyl peptide receptor (FPR) genes are found in all mammals. They are expressed in immune cells and recognize disease and pathogen-related molecules. Recently, in some rodent species, gene duplication events followed by gene cluster invasion led to the intermingling of vomeronasal receptor and FPR genes. This accident correlates with a drastically different expression pattern of most FPRs in these species: their transcription is absent from immune cells, and is restricted to sensory neurons of the vomeronasal organ. The peculiar agonist profile of these vomeronasal FPR receptors, and their maintenance in multiple rodent species, suggest that this acquisition may be of selective advantage. Taken together, this rodent-specific chemosensory tool may represent a clean example of evolutionary novelty, resulting from genomic landscape alterations that led to the hijacking by FPR genes of cis regulatory sequences from neighbouring genes.

Neuronal identity and circuit formation in the mouse olfactory system

Hitoshi Sakano
University of Tokyo

Abstract
In the mouse olfactory system, much of axon wiring in neural map formation occurs autonomously by olfactory sensory neurons (OSNs). Axonal projection along the dorsal-ventral (D-V) axis is regulated by positional information of OSNs within the olfactory epithelium (OE). Axon guidance molecules, such as Neuropilin-2 (Nrp2) and Semaphorin-3F (Sema3F) that are expressed by OSNs in a complementary manner, determine D-V positioning of glomeruli. Sema3F secreted by early^arriving dorsal-zone axons repel Nrp2-positive late-arriving axons.

Unlike the projection along the D-V axis, anterior-posterior (A-P) positioning of glomeruli is independent of positional information of OSNs in the OE. Instead, OR molecules regulate the expression levels of axon guidance molecules, e.g., Nrp1 and Sema3A, using OR-derived cAMP signals. How is it, then, that cAMP signal levels are uniquely determined by each OR species? Many G-protein coupled receptors (GPCRs) are known to have two different conformations, active and inactive, and spontaneously transit between the two, generating the basal activity in the absence of agonists. We assume that the OR-derived basal activity participates in the olfactory map formation.

Due to the difficulty of expressing membrane ORs *in vitro,* it has not been easy to study the possible role of OR basal activity in the axonal projection of OSNs. β2-adrenergic receptor (β2-AR) is known to share many functional similarities with OR molecules and substitute ORs for OR-instructed OSN projection. Taking advantage of these observations, we have analyzed axonal projection of OSNs that express the mutant-type β2-AR with the altered levels of basal activity. We have found that the basal activity mutants of β2-AR alter expression levels of axon guidance molecules, e.g., Nrp1 and Sema3A, and change glomerular locations along the A-P axis in the OB.

In rodents, axon-derived guidance molecules alone could organize an olfactory map by axon-axon interactions of OSNs even in the absence of the target OB. However, the map needs to be properly connected with second-order neurons, mitral/tufted (M/T) cells, to make the olfactory circuit functional. Here we report that Sema3F, a repulsive ligand to Nrp2, which is secreted by dorsal OSN axons, guides both $Nrp2^+$ OSN axons and their partner $Nrp2^+$ M/T cells to the ventral region of the OB. This coordinated guidance is an important process for proper alignment and synapse formation of OSN axons with M/T cells during olfactory development.

Hitoshi Sakano
Department of Biophysics and Biochemistry, Graduate School of Science, University of Tokyo

Biography

Dr. Sakano received his Ph.D. degree in 1976 from Kyoto University under the supervision of Prof. Yoshiro Shimura. For his theses work, Dr. Sakano investigated tRNA processing/splicing by isolating and characterizing the temperature-sensitive mutants of E coli, which were mapped at two different genetic loci. It was later found that one locus codes for RNaseP protein and the other for the RNA component of RNaseP, a ribozyme. This discovery served as a genetic proof for Dr. Altman's biochemical studies on RNaseP that won him the Nobel Prize in 1989.

Dr. Sakano, then, spent one year and a half as a postdoc with Prof. John Abelson at UCSD studying yeast tRNA splicing. From 1978 to 1981, Dr. Sakano worked with Prof. Susumu Tonegawa on immunoglobulin (Ig) genes to solve the problem of antibody diversity. He published five Nature article papers, providing the evidence for combinatorial and junctional diversification of antibody genes.

Once independent at UC Berkeley as Assistant Professor of Immunology in 1982, Dr. Sakano continued to work on Ig gene rearrangement and was promoted to Full Professor in 1992. Dr. Sakano relocated to the University of Tokyo in 1996, changing his research field to Neuroscience. Since then, he has been studying axon wiring and neural map formation in the mouse olfactory system.

Selected Publications (last 5 yeas)

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Olfactory white: odorant mixtures containing many components converge towards a common percept

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Olfactory white: odorant mixtures containing many components converge towards a common percept

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Abstract:
In vision, mixtures that combine all visible wavelengths, each at equal intensity, are perceived as white. In audition, sounds that combine all heard frequencies, each at equal amplitude, are perceived as a hum termed white noise. Here we found a similar perceptual phenomenon in olfaction. As we added equal-intensity components that spanned olfactory space to each of two mixtures, the mixtures became more similar to each other, despite not sharing a single component in common. Remarkably, from ~30 components, all mixtures began to smell similar, obtaining a quality we called olfactory white. Such early perceptual morphing poses computational boundaries for the olfactory system, and like auditory white noise, may find its way into everyday life applications.

Brief Biography:
Noam completed a PhD in Neuroscience at Stanford University in 1999. Following a brief postdoctoral stint as a Hellen Hay Whitney Fellow at CalTech division of Biology, he joined the faculty of the Wills Neuroscience Center at UC Berkeley, as an Assistant Professor (2001), and later Associate Professor (2005). In 2006 he joined the Department of Neurobiology at the Weizmann Institute in Rehovot, Israel, where he is Professor of Neurobiology. Noam's lab studies human olfaction.

10 Selected Recent publications:

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Activity-dependent neurotransmitter respecification: novel plasticity

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Ever since the discovery of chemical synaptic transmission we have commonly understood that the identity of neurotransmitter molecules that neurons use to signal to other neurons and target cells is fixed and invariant throughout life. However our recent studies have demonstrated that sensory stimuli such as light or odorants respecify transmitter expression during development of the amphibian brain. We now report that adult rats subjected to different photoperiods show increases or decreases in the number of neurons expressing dopamine in hypothalamic nuclei involved in response to stress, challenging the concept of neurotransmitter stability in the mature brain..

We hypothesized that changes in photoperiod observed seasonally at high latitudes promote changes in the number of dopaminergic neurons in the adult mammalian hypothalamus via activation of the retino-hypothalamic projection. We further hypothesized that such changes in the number of dopaminergic neurons produce changes in behavior.

We find that one-week exposure to long day-short night or short day-long night stimulation produces 20-100% decreases and increases, respectively, in the number of dopaminergic local interneurons in the lateral preoptic area (LPO), the paraventricular nucleus (PaVN) and the periventricular nucleus (PeVN), assessed by stereological scoring of tyrosine hydroxylase and dopamine immunoreactivity. BrdU labeling indicates that adult neurogenesis is absent in these nuclei. Fluorescent false neurotransmitter 511 is taken up by and released from brain slices in response to depolarization, in proportion to the number of dopaminergic neurons, indicating that the changes in numbers of dopaminergic neurons are functional. Strikingly, photoperiod-dependent increases and decreases in numbers of dopaminergic neurons are accompanied by reciprocal decreases and increases in numbers of local interneurons expressing somatostatin in the PaVN and PeVN.

Animals' stress-response behavior was analyzed with the elevated plus maze and the forced swim test. Rats exposed to short day-long night stimulation spend more time in the open arm of the maze and more time swimming than their counterparts exposed to long day-short night stimulation. Stereotactic injection of 6-OHDA ablating PaVN and LPO neurons suppresses this behavioral confidence. Subsequent short-day-long night stimulation leads to the appearance of newly dopaminergic neurons, with recovery of confident behavior in response to stress. This behavior is lost following local introduction of dopamine receptor antagonists, indicating the physiological contribution of the newly dopaminergic neurons. Demonstration of activity-dependent transmitter switching in the adult mammalian brain identifies a novel form of plasticity.

Supported by a grant from the Ellison Medical Foundation.

Nicholas C. Spitzer is Distinguished Professor of Neurobiology and Co-Director of the Kavli Institute for Brain and Mind (KIBM) at the University of California, San Diego. He received his B.A. and Ph.D. at Harvard University. After postdoctoral work at Harvard and University College London he joined the UC San Diego faculty in 1972. He has served on several NIH study sections, as a member of the NIH NINDS Council and as a Trustee of the Grass Foundation. He is Editor-in-Chief of BrainFacts.org, a Fellow of the American Association for the Advancement of Science and a Member of the American Academy of Arts and Sciences.

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Diverse coding logic to encode olfactory-mediated behavior

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The coding logic of sensory information detected by the vomeronasal organ has not been identified. Sensory information can be encoded either by 1) labeled lines in which a sensory input generates a precise outcome or 2) across neuron patterns by which the ensemble of detected sensory cues code variable information. We have generated recombinant variants of the large family of major urinary protein (MUP) ligands and used them each to stimulate VNO neurons and determine their corresponding behavioral output. We find that, Mups are sufficient to generate two different behaviors when detected by males; innate territorial aggression and countermarking. Interestingly, the VNO appears to utilize a different coding strategy in response to Mups for each of these behavioral outputs. Of the tested repertoire of Mups, only two are each sufficient to activate a program of aggressive behavior. The response to these precise Mups appears to be genetically determined since mice that have not previously experienced these ligands generate aggression upon detection. In contrast, we find that all tested Mups are each individually sufficient to initiate countermarking. However, the behavior is dependent upon the entire repertoire of Mups in the environment as well as the history of Mups that have previously been detected. This behavior shows hallmarks of neuron pattern coding. These experiments reveal that the VNO can generate both dedicated and variable behavior from the same ligand, creating a system to detect and respond to an immense amount of chemosensory cues.

Dr. Stowers received her PhD in Molecular and Cellular Biology from Harvard University in 1997. She did post-doctoral training with Catherine Dulac at Harvard University where she studied the role of olfaction to guide stereotyped behavior. In 2002 she established her own group at The Scripps Research Institute where she is now an associate professor in the department of cell biology studying the sensory logic of innate behavior.

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Enhancement of activity and plasticity in visual cortex

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Activity-dependent plasticity of binocular responses in mouse visual cortex during a critical period in early life takes place in several stages that are temporally and mechanistically distinct. Occlusion of one eye initially causes a loss of response to the deprived eye dependent on calcium signaling, which is followed by a homeostatic synaptic scaling up of the responses to the open eye that depends on signaling through tumor necrosis factor alpha (Kaneko et al, *Neuron* 2008a). These processes require adequate levels of inhibitory signaling. Neither of these stages of plasticity, however, requires neurotrophin signaling, but the subsequent recovery of normal responses after re-opening the deprived eye does (Kaneko et al, *Nature Neurosci* 2008b). Responses of neurons in the visual cortex become larger by nearly a factor of 3 during locomotion (Niell & Stryker, *Neuron* 2010), suggesting a possible mechanism for the many earlier reports of effects of enriched environments on brain development and plasticity.

We have explored several means for enhancing plasticity in developing and adult visual cortex, including the enhancement of activity by locomotion (Kaneko poster, this meeting), the enhancement of presynaptic function through expression of a constitutively active H-ras transgene (Kaneko et al, *PNAS* 2010), and the augmentation of inhibitory circuitry by the transplantation of embryonic inhibitory neurons (Southwell et al, *Science* 2010). The findings suggest that at least two pathways that can affect all of these plasticity mechanisms.

Functional division among prefrontal areas in macaque monkeys

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The neural circuitries in the prefrontal cortex are thought to be critical for the flexible control of behavior in primates, but the mechanisms remain largely unknown. Because the prefrontal cortex is composed of multiple areas each with unique anatomical connections with other brain sites, we expect that the comparison of functional roles among the prefrontal subareas would help disentangle the processes of flexible behavioral control.

Application of previously learned behavioral rules beyond simple stimulus-action or action-outcome associations is often necessary in goal-directed behavior, and the currently relevant rule is often not directly indicated by sensory cues. The Wisconsin Card Sorting Test (WCST) mimics such a situation. We have developed an animal version of WCST and trained monkeys with the task. The monkey selected one of the three test stimuli by matching it with the sample stimulus in color or in shape. The matching rule was constant within a block of trials, but changed between blocks without giving any notice to the monkey. There was no cue to indicate the currently relevant rule: the monkey had to find the currently relevant rule only based on rewards given after correct responses and error signals given after erroneous responses. Lesion of the principal sulcus region (PS), the orbitofrontal region (OFC) and the anterior cingulated sulcus region (ACS) resulted in significant degradation of the overall performance of the monkeys. Further analyses of the monkeys' performance in the task and in other probe tests showed that the reasons of the degradation were different. Only the PS lesion impaired maintenance of abstract rules in working memory; only the OFC lesion impaired rapid reward-based updating of rule value; and the ACS lesion impaired active reference to the content of the rule working memory.

These results show that the prefrontal subareas contribute to the flexible control of behavior by playing individually specific functional roles.

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Appointments

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1989-1996	Head, Laboratory for Neural Information Processing, Frontier Research Program, RIKEN
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List of recent publications

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Narrowly-tuned chemosensory reception for food and pheromone signals

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Abstract:

Pheromones elicit an instinctive behavior or neuroendocrine change in different individuals within the same species, and thus, are important chemosignals for maintaining the species. In mice, we discovered a male-specific peptide, named exocrine gland-secreting peptide 1 (ESP1), that was released into tear fluids from the extraorbital lacrimal gland. ESP1 turned out to be a sex pheromone that enhanced female sexual receptive behavior upon male mounting, leading to the successful copulation. Although ESP1 secretion was observed in only a small subset of inbred strains and closed colony, a large amount of ESP1 was detected in male tears of almost all wild-derived mouse strains, suggesting that ESP1 plays an important role in sexual behavior in nature. Moreover, we revealed the molecular mechanisms and the neural pathway involved in decoding the ESP1 signal in the vomeronasal system. ESP1 is recognized by a specific vomeronasal receptor V2Rp5 expressed in vomeronasal sensory neurons, resulting in signal transmission to the amygdaloid and hypothalamic nuclei via the accessory olfactory bulb in a sexually dimorphic fashion. Furthermore, we found that ESP1-induced neural activation and behavior were diminished in the V2Rp5 knock-out mice. The ESP1-signal processing in the vomeronasal system appears to be mediated by the selective neural pathway via the V2Rp5. This study provides the functional link between a sex peptide pheromone and a behavioral output via a selective neural pathway activated by a specific receptor in the vomeronasal system. In this talk, I will also describe other examples of neural circuitries that are designed to send the specific information, leading to the attractive behavior in insect. A pheromone or food odorant that is crucial for survival or mating is often detected by a specific chemosensory receptor expressed by peripheral olfactory sensory neurons.

Biography:

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A list of recent publications:

1. Sato, K., Tanaka, K., *Touhara K. Sugar-regulated cation channel formed by an insect gustatory receptor. **Proc. Natl. Acad. Sci. U.S.A.** 108, 11680-11685 (2011)
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Toward the circuit physiology of midbrain dopamine neurons: beyond stamp collecting

Naoshige Uchida
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Midbrain dopamine neurons play pivotal roles in such brain functions as reward-based learning, motivation and movement. These neurons are located in the ventral tegmental area (VTA) and substantia nigra pars compacta (SNc). It has been postulated that dopamine neurons broadcast reward prediction error signals, i.e., the discrepancy between actual reward and expected reward. While these observations have generated great interest, the underlying mechanisms that regulate the firing patterns of dopamine neurons remain largely unknown. Recently, we have developed a mouse model to study neural circuits that regulate the activity of dopamine neurons. In a first experiment, mice are trained to associate different odors with different outcomes (big reward, small reward, nothing and airpuff). We have recorded the activity of VTA neurons while identifying their types optogenetically. In a second experiment, we have comprehensively identified monosynaptic inputs to midbrain dopamine neurons using the rabies virus-based transsynaptic, retrograde tracing. I will discuss these strategies for studying neural circuits and implications into the mechanisms that regulate the activity of dopamine neurons.

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Naoshige Uchida is an associate professor at the Center for Brain Science and Department of Molecular and Cellular Biology at Harvard University, Massachusetts, USA. He did his graduate studies on molecular mechanisms of synaptic adhesions in Masatoshi Takeichi's laboratory at Kyoto University, Japan. He started studies on olfactory coding in Kensaku Mori's laboratory at the Brain Science Institute, RIKEN, Japan. He then joined Zachary Mainen's laboratory at Cold Spring Harbor Laboratory, New York, USA, where he started psychophysical experiments using rodent olfactory decision tasks. He studies neural mechanisms of sensory coding, decision making, and reward-based learning and memory using rodent psychophysics and multi-electrode recordings.

Publications:

Szuts, T., Fadeyev, V., Kachiguine, S., Sher, A., Grivich, M.V., Agrochao, M., Hottowy, P., Dabrowski, W., Lubenov, E.V., Siapas, A.G., Uchida, N., Litke, A.M., Meister, M. (2011) The brain unplugged: A wireless multi-channel neural amplifier for freely moving animals. *Nature Neurosci.* 14: 263-269.

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Genes that are selectively expressed in regions of primate neocortex: the functions and implication for cortical specialization

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The neocortex, which is characteristic of mammals, has evolved to play important roles in cognitive and perceptual functions. The localization of different functions in different regions of the neocortex was well established within the last century. Studies on the formation of the neocortex have advanced at the molecular level, thus successfully clarifying the mechanisms that control neural or glial cell differentiation and sensory projections. However, mechanisms that underlie cortical area specialization remain unsolved. To address this problem, our approach has been to isolate and characterize the genes that are selectively expressed in particular subsets of neocortical areas in primates; these areas are most distinctive among mammals. By differential display and restriction landmark cDNA scanning (RLCS) methods, we have identified two major classes of genes that are specifically expressed in the adult macaque monkey neocortical areas: One is expressed in the primary sensory areas, particularly, in the primary visual cortex (V1) and the other is expressed in the association areas. The genes that show these specific expression patterns are limited to only several gene families among our large-scale screening. The genes selectively expressed in primate V1 are serotonin receptors of 5-HT1B and 5-HT2A and OCC1. In primate V1, 5-HT1B enhances the signal to noise (S/N) ratio and 5-HT2A works as a gain controller. Recently, Li et al, have shown that the product of the mouse homologue of OCC1 (fstl1) directly binds Na^+, K^+-ATPase and suppresses sensory afferent synaptic transmission (Neuron, 69, 974-987, 2011). Therefore, the three genes that are selectively enriched in primate V1 control visual input-output relations so that the visual homeostasis is retained under a dynamic range of visual inputs. The important feature in these primate V1 enriched genes is that their expressions are controlled in an activity-dependent manner, some of which mechanisms may be different from those of rodents. The genes selectively expressed in primate association areas, are RBP, PNMA5, SAPRC and SLIT1. Although the role of these genes in primate association areas are largely unknown, we speculate that they enhance dendritic branching and spine formation based on the morphological studies in primates by Elston et al., (e.g., Proc. R.Soc. Lond. B., 266, 1367-1374, 1999) and molecular biological studies of Slit1 in the rodent neocortex (Whitford et al., Annu. Rev. Neurosci., 25, 127-149, 2009). Finally, I would like to talk our recent approaches toward proving this hypothesis using genetic manipulations in primates.

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Molecular Genetic Dissection of Olfactory Neural Circuitry in Zebrafish

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Zebrafish has become one of the most useful model organisms in neurobiology. In addition to its general advantageous properties (external fertilization, rapid development, transparency of embryos, etc.), zebrafish is amenable to various genetic engineering technologies such as transgenesis, mutagenesis, gene knockdown/knockout, and transposon-mediated gene transfer. Our transgenic approach unraveled two segregated neural pathways originating from ciliated and microvillous sensory neurons in the olfactory epithelium to distinct regions of the olfactory bulb, which likely convey different types of olfactory information (e.g. pheromones and odorants). Furthermore, the two basic principles (one neuron - one receptor rule and axon convergence to target glomeruli) are essentially preserved also in zebrafish, rendering this organism a suitable model vertebrate for the olfactory research. In this talk, I will summarize recent advances in our knowledge on the functional architecture of the olfactory neural circuits in zebrafish, which mediate specific odor-induced behaviors. In particular, I will focus on molecular genetic dissection of the neural elements involved in the attraction to food odorants, the aversion from alarm pheromone, and the social response to sex pheromones.

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Recent publications

Yoshihara Y. Molecular genetic dissection of the zebrafish olfactory system. In ***Chemosensory Systems in Mammals, Fishes and Insects*** (eds. W. Meyerhof and S. Korsching) pp.97-120 (2009)

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List of publication Kohei Hatta

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Hashimoto M, Shinohara K, Wang J, Ikeuchi S, Yoshiba S, Meno C, Nonaka S, Takada S, Hatta K, Wynshaw-Boris A, Hamada H. Planar polarization of node cells determines the rotational axis of node cilia. **Nature Cell Biology 12**:170-6 (2010)

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Awards and Scholarship

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Paper Award of Japanese Neural Network Society, 2009

Research Award of Japanese Neural Network Society, 2006

Scientific American 50 (named “Research Reader in Neural Imaging”), 2005

Postdoctoral Fellowship of the Japan Society for the Promotion of Science for Young Scientists (SPD), 2003-2006

Uehara Memorial Foundation Postdoctoral Fellowship, 2001-2002

Research Fellowship of the Japan Society for the Promotion of Science for Young Scientists (DC), 1996-1998

Scholarship of the Japan Scholarship Foundation, 1993-1994

Selected Publications

Yanagisawa, T., Hirata, M., Saitoh, Y., Kishima, H., Matsushita, K., Goto, T., Fukuma, R., Yokoi, H., Kamitani, Y., and Yoshimine, T. (2011 in press). Electrocorticographic control of a prosthetic arm in paralyzed patients. Ann Neurol

Toda, H., Suzuki, T., Sawahata, H., Majima, K., Kamitani, Y., and Hasegawa, I. (2011). Simultaneous recording of ECoG and intracortical neuronal activity using a flexible multichannel electrode-mesh in visual cortex. Neuroimage *54*, 203-212.

Kamitani, Y., and Sawahata, Y. (2010). Spatial smoothing hurts localization but not information: Pitfalls for brain mappers. Neuroimage *49*, 1949-1952.

Yamashita, O., Sato, M., Yoshioka, T., Tong, F., and Kamitani, Y. (2008). Sparse estimation automatically selects voxels relevant for the decoding of fMRI activity patterns. Neuroimage *42*, 1414-1429.

Miyawaki, Y., Uchida, H., Yamashita, O., Sato, M. A., Morito, Y., Tanabe, H. C., Sadato, N., and Kamitani, Y. (2008). Visual image reconstruction from human brain activity using a combination of multiscale local image decoders. Neuron *60*, 915-929.

Kamitani, Y. and Tong, F. (2006). Decoding seen and attended motion directions from activity in the human visual cortex. Curr Biol *16*, 1096-1102.

Kamitani, Y. and Tong, F. (2005). Decoding the visual and subjective contents of the human brain. Nat Neurosci *8*, 679-685.

Shimojo, S., Kamitani, Y., and Nishida, S. (2001). Afterimage of perceptually filled-in surface. Science *293*, 1677-1680.

Kamitani, Y., Bhalodia, V. M., Kubota, Y., and Shimojo, Y. (2001). A model of magnetic stimulation of neocortical neurons. Neurocomput. *38-40*, 697-703.

Shams, L., Kamitani, Y., and Shimojo, S. (2000). Illusions. What you see is what you hear. Nature *408*, 788.

Kamitani, Y. and Shimojo, S. (1999). Manifestation of scotomas created by transcranial magnetic stimulation of human visual cortex. Nat Neurosci *2*, 767-771.

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Osumi Publication List (short ver)

Selected Research Articles:

1) Matsuo, T. *, Osumi-Yamashita, N. *, et al.: A mutation in the Pax-6 gene in rat small eye is associated with migration defect of midbrain crest cells. Nat Genet. 3(4), 299-304, 1993. (*equally contributed)

2) Osumi-Yamashita, N., et al.: The contribution of both forebrain and midbrain crest cells to the mesenchyme in the frontonasal mass of mouse embryos. Dev Biol. 164(2), 409-419, 1994.

3) Osumi, N., et al.: Pax-6 is involved in specification of the hindbrain motor neuron subtype. Development. 124(15), 2961-2972, 1997.

4) Akamatsu, W., et al.: Mammalian ELAV-like neuronal RNA-binding proteins HuB and HuC promote neuronal development in both the central and the peripheral nervous systems. Proc Natl Acad Sci U S A. 96(17), 9885-9890, 1999.

5) Inoue, T., et al.: Role of cadherins in maintaining the compartment boundary between the cortex and striatum during development. Development. 128(4), 561-569, 2001.

6) Takahashi, M. and Osumi, N.: Pax6 regulates specification of ventral neuron subtypes in the hindbrain by establishing progenitor domains. Development. 129(6), 1327-1338, 2002.

7) Nomura, T. and Osumi, N.: Misrouting of mitral cell progenitors in the Pax6/Small eye rat telencephalon. Development. 131(4), 787-796, 2004.

8) Tomita, Y., et al.: Cardiac neural crest cells contribute to dormant multipotent stem cells in the mammalian heart. J Cell Biol. 170(7), 1135-1146, 2005.

9) Watanabe, A., et al.: Fabp7 maps to a quantitative trait locus for a schizophrenia endophenotype. PLoS Biol. 5(11), e297, 2007.

10) Sakurai, K. and Osumi, N.: The neurogenesis-controlling factor, Pax6, inhibits proliferation and promotes maturation in murine astrocytes. J Neurosci. 28(18), 4604-4612, 2008.

11) Maekawa, M., et al.: Arachidonic acid drives postnatal neurogenesis and elicits a beneficial effect on prepulse inhibition, a biological trait of psychiatric illnesses. PLoS ONE. 4(4), e5085, 2009.

12) Maekawa, M., et al.: A novel missense mutation (Leu46Val) of PAX6 found in an autistic patient. Neurosci Lett. 462(3), 267-271, 2009.

13) Hara, Y., et al.: Impaired hippocampal neurogenesis and vascular formation in ephrin-A5-deficient mice. Stem Cells. 28(5), 974-983, 2010.

14) Maekawa, M., et al.: Giant Subependymoma Developed in a Patient with Aniridia: Analyses of PAX6 and Tumor-relevant Genes. Brain Pathol. 20(6), 1033-1041, 2010.

15) Umeda, T., et al.: Evaluation of Pax6 mutant rat as a model for autism. PloS One. 5(12), e15500, 2010.

16) Takahashi, M. and Osumi, N.: Pax6 regulates boundary-cell specification in the rat hindbrain. Mech. Dev. 128(5-6), 289-302, 2011.

Curriculum Vitae

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Present position: Professor
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Academic and Professional Career

1979-1985	School of Dentistry, Tokyo Medical & Dental University
1985-1989	Graduate School of Dentistry, Tokyo Medical & Dental University
1989-1996	Research Associate, Department of Craniofacial Morphogenesis and Anomalies, Tokyo Medical & Dental University
1996-1998	Associate Professor, National Institute of Neuroscience, National Center of Neurology & Psychiatry
1998-	Present position
2007-	Special Advisor for Gender Equality (Tohoku University)
2008-2010	Distinguished Professor (Tohoku University)

Award

1985	Nagao Award from School of Dentistry, Tokyo Medical & Dental University (for the top student on graduation)
1992	Hatton Travel Award from International Association for Dental Research for the 70th General Session of the IADR

2006	NISTEP Award from MEXT

Committees (only selected):

Organizing member, Japanese Society of Developmental Biologists
Organizing member, Japanese Society for Cell Biology
Organizing member, Japanese Neuroscience Society
Editorial Board, Development Growth & Differentiation
Editorial Board, Genes to Cells
Editorial Board, J Anatomy
Member, Peer Review Committee for Governmental Grants (MEXT)
Member, Advisory Committee for Life Science (MEXT)
Member, Committee for Ethical Problems in Human ES Cells
Program Officer, Special Grants for Priority Research (JST)
Member, Committee for National Institute of Genetics
Member, Science Council of Japan

Biosketch

Prof. Osumi has graduated Tokyo Medical and Dental University, been given PhD thesis from the same university, and now is a professor of Tohoku University School of Medicine since 1998. She has recently been chosen as one of 25 Distinguished Professors in Tohoku University. She is appointed in various governmental committees such as ethical issues, grant system development, and career paths for young scientists, and also chosen as a youngest member of Japanese Council Japan since 2005. Her research interest covers broad areas such as pre- and postnatal development of the brain and craniofacial region, and behavior of animals as models of psychiatric diseases. More specifically, she is recently eager to understand regulatory mechanisms of neurogenesis and maintenance of neural stem cells at cellular and molecular levels both in embryonic and postnatal stages. Manipulating embryos and imaging brain cells are expertise of her lab. She has translated two books into Japanese: *Essential Developmental Biology* by Jonathan Slack and *The Birth of the Mind* by Gary Marcus. She is a representative of CREST project (2005-2010) supported by JST and Global COE project (2007-2012) supported by MEXT.

Takeshi Sakurai
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Takeshi Sakurai, M.D., Ph.D.

EDUCATION, RESEARCH, AND PROFESSIONAL EXPERIENCE

1988	M.D., Nagoya University School of Medicine, Nagoya, Japan
1988-1989	Internship (Resident of Internal Medicine), St. Luke's International Hospital, Tokyo, Japan
1993	Ph.D., Nagoya University Graduate School of Medicine, Nagoya, Japan
1993-1997	Postdoctoral Associate, New York University Medical Center, New York, Dept. Pharmacology
1997-1999	Research Associate, New York University Medical Center, New York, Dept. Pharmacology
2000-2001	Research Assistant Professor, Rutgers, State University of New Jersey, Piscataway, New Jersey, Keck Center for Collaborative Neuroscience
2001-2002	Research Assistant Professor, Mount Sinai School of Medicine, New York, New York, Dept. Neurology and Neuroscience
2002-2011	Assistant Professor, Mount Sinai School of Medicine, New York, New York Dept. Psychiatry and Pharmacology and Systems Therapeutics and Neurology
2011-present	Associate Professor, Kyoto University Graduate School of Medicine, Kyoto, Kyoto, Japan, Medical Innovation Center

PUBLICATIONS (selected from total 53 originals, reviews, and book chapter)

1 Elior Peles, Moshe Nativ, Phillip L. Campbell, **Takeshi Sakurai**, Ricardo Martinez, Sima Lev, Douglas O. Clary, James Schilling, Gilad Barnea, Gregory D. Plowman, Martin Grumet and Joseph Schlessinger. The carbonic anhydrase domain of receptor tyrosine phosphatase β is a functional ligand for the axonal cell recognition molecule contactin. Cell, 82, 251-260, 1995.

2 **Takeshi Sakurai**, Marc Lustig, Moshe Nativ, John J. Hemperly, Joseph Schlessinger, Elior Peles and Martin Grumet. Induction of neurite outgrowth through contactin and Nr-CAM by extracellular regions of glial receptor tyrosine phosphatase β. Journal of Cell Biology, 136, 907-918, 1997

3 Marc Lustig, Lynda Erskine, Carol A. Mason, Martin Grumet, and **Takeshi Sakurai**. Nr-CAM expression in the developing mouse nervous system: Ventral midline structures, specific fiber tracts, and neuropilar regions. Journal of Comparative Neurology, 434, 13-28, 2001

4 **Takeshi Sakurai**, Marc Lustig, Joanne Babiarz, Andrew J.W. Furley, Steven Tait, Peter J. Brophy. Stephen A. Brown, Lucia Y. Brown, Carol A. Mason and Martin Grumet. Overlapping functions of the cell adhesion molecules Nr-CAM and L1 in cerebellar granule cell development. Journal of Cell Biology, 154, 1259-1273, 2001

5 Scott E. Williams, Fanny Mann, Lynda Erskine, **Takeshi Sakurai**, Shiniu Wei, Derrick J. Rossi, Nicholas W. Gale, Christine E. Holt, Carol A. Mason and Mark Henkemeyer. Ephrin-B2 and EphB1 mediate retinal axon divergence at the optic chiasm. Neuron, 39, 919-935, 2003

6 Scott E. Williams, Martin Grumet, David R. Colman, Mark Henkemeyer, Carol A. Mason, and **Takeshi Sakurai**. A role for Nr-CAM in the patterning of binocular visual pathways. Neuron, 50, 535-547, 2006

7 Shin Yasuda, Hidekazu Tanaka, Hiroko Sugiura, Ko Okamura, Taiki Sakaguchi, Uyen Tran, Takako Takemiya, Akira Mizoguchi, Yoshiki Yagita, **Takeshi Sakurai**, Edward M. De Robertis, and Kanato Yamagata. Activity-induced protocadherin arcadlin regulates dendritic spine number by triggering N-cadherin endocytosis via TAO2β and p38 MAP kinases. Neuron, 56, 456-471, 2007

8 Joseph D. Buxbaum, Lyudmila Georgieva, James J. Young, Christopher Plescia, Yuji Kajiwara, Yuhui Jiang, Valentina Moskvina, Nadine Norton, Tim Peirce, Hywel J. Williams, Nick J. Craddock, Liam Carroll, Gabriel Corfas, Kenneth L. Davis, Michael Owen, Sheila Harroch, **Takeshi Sakurai**, and Michael C. O'Donovan. Molecular dissection of NRG1-ERBB4 signaling implicates PTPRZ1 as a potential schizophrenia susceptibility gene. Molecular Psychiatry, 13, 162-172, 2008

9 Kai Wang, Haitao Zhang, Deqiong Ma, Maja Bucan, Joseph T. Glessner, Brett S. Abrahams, Daria Salyakina, Marcin Imielinski, Jonathan P. Bradfield, Patrick M.A. Sleiman, Cecilia E. Kim, Cuiping Hou, Edward Frackelton, Rosetta Chiavacci, Nagahide Takahashi, **Takeshi Sakurai,** Eric Rappaport, Clara M. Lajonchere, Jeffrey Munson, Annette Estes, Olena Korvatska, Joseph Piven, Lisa I. Sonnenblick, Ana I. Alvarez Retuerto, Edward I. Herman, Hongmei Dong, Ted Hutman, Marian Sigman, Sally Ozonoff, Ami Klin, Thomas Owley, John A. Sweeney, Camille W. Brune, Rita M. Cantor, Raphael Bernier, John R. Gilbert, Michael L. Cuccaro, William M. McMahon, Judith Miller, Matthew W. State, Thomas H. Wassink, Hilary Coon, Susan E. Levy, Robert T. Schultz, John I. Nurnberger Jr., Jonathan L. Haines, James S. Sutcliffe, Edwin H. Cook Jr., Nancy J. Minshew, Joseph D. Buxbaum, Geraldine Dawson, Struan F.A. Grant, Daniel H. Geschwind, Margaret A. Pericak-Vance, Gerard D. Schellenberg, and Hakon Hakonarson. Common genetic variants on 5p14.1 associate with autism spectrum disorders. Nature, 459, 528-533, 2009

10 Joseph T. Glessner, Kai Wang, Guiqing Cai, Olena Korvatska, Cecilia E. Kim, Shawn Wood, Haitao Zhang, Annette Estes, Camille W. Brune, Jonathan P. Bradfield, Marcin Imielinski, Edward C. Frackelton, Jennifer Reichert, Emily L. Crawford, Jeffrey Munson, Patrick M.A. Sleiman, Rosetta Chiavacci, Kiran Annaiah, Kelly Thomas, Cuiping Hou, Wendy Glaberson, James Flory, Frederick Otieno, Maria Garris, Latha Soorya, Lambertus Klei, Joseph Piven, Kacie J. Meyer, Evdokia Anagnostou, **Takeshi Sakurai**, Rachel M. Game, Danielle S. Rudd, Danielle Zurawiecki, Christopher J. McDougle, Lea K. Davis, Judith Miller, David J. Posey, Shana Michaels, Alexander Kolevzon, Jeremy M. Silverman, Raphael Bernier, Susan E. Levy, Robert T. Schultz, Geraldine Dawson, Thomas Owley, William M. McMahon, Thomas H. Wassink, John A. Sweeney, John I. Nurnberger Jr., Hilary Coon, James S. Sutcliffe, Nancy J. Minshew, Struan F.A. Grant, Maja Bucan, Edwin H. Cook Jr., Joseph D. Buxbaum, Bernie Devlin, Gerard Schellenberg, and Hakon Hakonarson. Autism genome-wide copy number variation reveals ubiquitin and neuronal genes. Nature, 459, 569-573, 2009

11 Catalina Betancur, **Takeshi Sakurai**, and Joseph D. Buxbaum. The emerging role of synaptic cell-adhesion pathways in the pathogenesis of autism spectrum disorders. Trends in Neurosciences, 32, 402-412, 2009

12 **Takeshi Sakurai**, Nicolas Romoz, Marta Barreto, Mihaela Gazdoiu, Nagahide Takahashi, Michael Gertner, Nathan Dorr, Miguel A. Gama Sosa, Rita De Gasperi, Gissel Perez, James Schmeidler, Vivian Mitropoulou, H. Carl Le, Mihaela Lupu, Patrick R. Hof, Gregory A. Elder, and Joseph D. Buxbaum. Slc25a12 disruption alters myelination and neurofilaments: a model for a hypomyelination syndrome and childhood neurodevelopmental disorders. Biological Psychiatry, 67, 887-894, 2010

13 Nagahide Takahashi, **Takeshi Sakurai**, Kenneth Davis, and Joseph D. Buxbaum. Linking oligodendrocyte and myelin dysfunction to neurocircuitry abnormalities in schizophrenia. Progress in Neurobiology, 93, 13-22, 2010

14 **Takeshi Sakurai**, Guiqing Cai, Dorothy E. Grice, and Joseph D. Buxbaum. The genomic architecture of autism spectrum disorders. Chapter in Textbook of Autism spectrum disorders**.** Eric Hollander, Alexander Kolevzon, Joseph Coyle, editors. American Psychiatric Publishing Inc., 281-298, 2010

15 Dia Xenaki, Indira Martin, Lynn Yoshida, Kyoji Ohyama, Gianfranco Gennarini, Martin Grumet, **Takeshi Sakurai** and Andrew J.W. Furley. F3/contactin and TAG1 play antagonistic roles in the regulation of sonic hedgehog-induced cerebellar granule neuron progenitor proliferation. Development, 138, 519-529, 2011

16 Galina P. Demyanenko, Thorfinn T. Riday, Tracy S. Tran, Jasbir Dalal, Eli P. Darnell, Leann H. Brennaman, **Takeshi Sakurai**, Martin Grumet, Benjamin D. Philpot, and Patricia F. Maness. NrCAM deletion causes topographic mistargeting of thalamocortical axons to the visual cortex and disrupts visual acuity. Journal of Neuroscience, 31, 1545-1558, 2011

17 **Takeshi Sakurai**, Nathan P. Dorr, Nagahide Takahashi, L. Alison McInnes, Gregory A. Elder, and Joseph Buxbaum. Haploinsufficiency of Gtf2i, a gene deleted in Williams syndrome, leads to increase in social interactions. Autism Research, 4, 28-39, 2011

18 Nagahide Takahashi, **Takeshi Sakurai**, Ozlem Bozdagi-Gunal, Nathan P. Dorr, Joanne Moy, Lisa Krug, Miguel Gama-Sosa, Gregory A. Elder, Rick J. Koch, Ruth H. Walker, Patrick, R. Hof, Kenneth L. Davis, and Joseph D. Buxbaum. Increased expression of receptor phosphotyrosine phosphatase-β/ξ, is associated with molecular, cellular, behavioral and cognitive schizophrenic phenotypes. Translational Psychiatry, 1, e8, 1-10, 2011

Poster Presenters

Neural mechanisms for stereoscopic depth perception in macaque V4: Responses to graded anti-correlation

Mohammad Abdolrahmani
Graduate School of Frontier Biosciences, Osaka University

Abstract

Humans perceive the three dimensional world by solving the stereo correspondence problem, which refers to the problem of matching the visual features in one eye's image to those in the other eye's image. Perception of stereoscopic depth diminishes when the solution for the correspondence problem does not exist. This happens for anti-correlated random-dot stereograms (aRDS), in which all elements of one eye's image is contrast reversed with respect to those of the other eye's image. The ventral visual pathway implements the neural solution for the correspondence problem. The false information about the depth (i.e., inverted disparity energy values) of aRDS is first encoded in the primary visual cortex but later discarded gradually by a mid-level area, V4, and a higher-level area, inferior temporal cortex.

To better understand the neural implementation of the stereo correspondence solution, we examined responses of V4 neurons to graded anti-correlation of RDSs by decreasing the percentage of binocularly contrast-matched dots (match level) gradually. By performing single-unit recordings from area V4 in a macaque using this set of stimuli, we investigated a further correlation between the neuronal and perceptual performances.

We found that the neuronal disparity selectivity decreased sharply as the binocular match level decreased from 100% to 50%, but did not decrease largely for the match levels from 50% to 0%. This neuronal behavior is in sharp contrast to human stereo perception: a recent psychophysical study shows that (fine) depth perception is intact down to 50% match level but deteriorates for the match levels from 50% to 0% (Doi et al., 2011, J Vision).

Our preliminary results suggest that the neural responses in V4 are not consistent with stereoscopic depth if we consider responses not only at zero and full anti-correlation but also at graded levels of anti-correlation.

References:
Takahiro Doi, Seiji Tanabe, and Ichiro Fujita, Matching and correlation computations in stereoscopic depth perception, J Vis March 2, 2011 11(3): 1

Curriculum Vita

Mohammad Abdolrahmani

PhD student, Laboratory for Cognitive Neuroscience (Fujita lab), Scholl of frontier Biosciences (FBS), Osaka University

Courses

1. Research student at Laboratory for cognitive Neuroscience, FBS, Osaka University, May-October 2009
2. Osaka University Global COE and IBRO-APRC Summer School of Neuroscience 2008, Graduate School of Frontier Biosciences, Osaka University, Osaka, Japan
3. Australian National University, research school of biological sciences, Summer School of Neuro-ethology, Feb 2009, Canberra, Australia

International Conferences

1. Abdolrahmani M., Jameie SB. The effects of light deprivation on posterior parietal cortex in rats. Australian Neuroscience Society Conference, Jan 2009, Canberra
2. Abdolrahmani M., Jameie SB., Nobakht M., Effects of light deprivation on lateral geniculate nucleus in rat neonates, Fifth Asian Pacific International Congress of Anatomy, Tehran, Iran, 2008
3. Jameie SB., Abdolrahmani M., Nobakht M., Roozdar B., Tabatabaei P., Retinal mechanisms induce synaptic plasticity in SCN and dLGN in light deprived rat neonates: Electron and light microscopic studies, Fifth Asian Pacific International Congress of Anatomy, Iran, 2008
4. Jameie SB., Abdolrahmani M., Nobakht M., Roozdar B., Tabatabaei P., Retinal mechanisms induce synaptic plasticity in SCN and dLGN in light deprived rat neonates: Electron and light microscopic studies, European Retina Meeting, Frankfort, Germany, 2007

Publications:

1. Seyed Behnam E-Din Jameie, Mohammad Abdolrahmani, Maliheh Nobakht. Effects of Total Light Deprivation on Dorsal Lateral Geniculate Nucleus of Male Neonate Rats, Oman medical journal, 2010. 53, p: 179-183
2. Abdolrahmani M., Jameie SB. Gradual increases in neuronal density of rats' LGN from anterior to posterior. Neurosciences Journal, 2009. 14(2), p: 7-10

Direct comparison between humans and chimpanzees for their pitch-liminance mapping

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Abstract:
In synaesthesia, input to one sensory modality leads to automatic and vivid secondary experiences. For example, sound-colour synaesthetes see colours when they hear sounds. All humans experience such (or similar) cross-modal correspondences to some extent, which has been termed weak synaesthesia. Most prominently, already human toddlers associate high pitch sounds with lighter colours than low pitch sounds, and sound-colour synaesthetes map in this same direction. It has been argued that the tendency to systematically match visual and auditory dimensions was a driving factor in the evolution of language, which might also explain the evolution of synaesthesia. However, none has yet addressed the crucial issue if non-human animals experience cross-modal correspondences as well. Here we provide the first direct comparison between humans and chimpanzees on their pitch-luminance mapping. Participants from both species were required to classify squares as black or white, while hearing irrelevant background sounds that were either high-pitched or low-pitched. Chimpanzees made more mistakes when the background sound was synaesthetically incongruent (low-pitched for white, high-pitched for black) than when it was synaesthetically congruent (high-pitched for white, low-pitched for black). In humans, the effect was evident through increased latencies in incongruent trials in line with previous research. These results suggest that such cross-modal correspondence are shared in these two species tested here and synaesthesia and cross-modal associations in non-synaesthetes partly reflect evolutionary old mechanisms in the primate brain.

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EDUCATION AND TRAINING

2010(Apr)-:Assistant Professor: Center for International Collaboration and Advanced Studies in Primatology, Primate Research Institute, Kyoto University, Aichi, Japan.

2009(Jan)-:Program-Specific Assistant Professor: Primate Research Institute, Kyoto University, Aichi, Japan.

2008(Apr)-2008(Dec): Postdoc fellow: Primate Research Institute, Kyoto University, Aichi, Japan.

2006(Apr)-2008(Mar): Postdoc fellow: Yerkes Primate Research Center, Emory University, GA, USA.

2006(Mar): Ph.D. Psychology, Graduate School of Letters, Kyoto University, Kyoto, Japan

2003(Mar): M. A. Psychology, Graduate School of Letters, Kyoto University, Kyoto, Japan

2001(Mar): B. S. Psychology, Faculty of Letters, Kyoto University, Kyoto, Japan

SELECTED RECENT PUBLICATONS (PEER REVIEWED PAPERS)

1. Ludwig V.*, **Adachi, I.***, Matsuzawa, T. (*under revision*). Can you see sounds? Chimpanzees associate high auditory pitch with visual lightness. *Proceedings of the National Academy of Sciences*
   * These authors contributed equally to this work.

2. **Adachi, I.**, Hampton, RR. (2011). Rhesus monkeys see who they hear: Spontaneous cross-modal memory for familiar conspecifics. *PLoSONE*, 6(8): e23345. doi:10.1371/journal.pone.0023345.

3. **Adachi, I.**, Anderson, JR., Fujita, K. (2011). Reverse-Reward Learning in squirrel monkeys (Saimiri sciureus): Five-Year Assessment, and Tests for Qualitative Transfer. *Journal of Comparative Psychology*, 125, pp. 84-90.

4. Paxton, R., Basile, BM., **Adachi, I.**, Suzuki, WA., Wilson, ME., Hampton, RR. (2010) Rhesus monkeys (Macaca mulatta) rapidly learn to select dominant individuals in videos of artificial social interactions between unfamiliar conspecifics. *Journal of Comparative Psychology*, 124, pp. 395-401.

5. **Adachi, I.**, Chou, DP., Hampton, RR. (2009)
   Thatcher effect in monkeys demonstrates conservation of face perception across primates. *Current Biology*, Volume 19, Issue 15, pp. 1270-1273.

6. **Adachi, I.** (2009). Cross-modal representations in primates and dogs: A new framework of recognition of social objects. *Intraction Studies*, Volume 10, Issue 2, pp. 225-251.

7. **Adachi, I.**, Kuwahata H., Fujita, K., Tomonaga M., Matsuzawa T. (2009). Plasticity of ability to form cross-modal representations in infant Japanese macaques. *Developmental Science*, Volume 12, Issue 3, pp.446-452.

8. **Adachi, I.** Fujita, K. (2007). Cross-modal representation of human caretakers in squirrel monkeys. *Behavioural Processes*, Volume 74, Issue 1, pp. 27-32.

9. **Adachi, I.**, Kuwahata, H., Fujita, K. (2007). Dogs recall owner's face upon hearing owner's voice. *Animal Cognition*, Volume 10, Issue 1, pp. 17-21.

Title of poster presentation Monoallelic genes in single olfactory neurons

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Abstract

Though typical autosomal genes are thought to be transcribed from both alleles, recent evidence suggests that many genes may be only active on one allele, either by imprinting or random monoallelic choice. Identification of such monoallelic genes is fundamental to understand not only how epigenetic regulation works in each gene but also the possible mechanisms of diseases with dominant or semi dominant traits. In neurons, however, it was challenging to study genes that show random monoallelic expression or imprinting in only a subset of neurons, because of the inability to expand the clonal population of mature neurons and the immense heterogeneity of neurons. Here we use single mouse olfactory sensory neurons as a model to analyze genome-wide allelic expression.

We amplified cDNA from single dissociated olfactory neurons derived from F1 of C57BL/6J and SPRET/EiJ. We sequenced seven samples by Illumina single-end sequencing for 36 bases per read. The reads were aligned to both C57BL/6J and SPRET/EiJ genome sequence by bowtie short read aligner that allows 1-2 mismatches per read. The single nucleotide polymorphisms (SNPs) were detected by samtools (mpileup) and further filtered by the known SNPs. 7222-172064 SNPs were detected from the sequenced samples. Among them, we focused on the SNPs with 20 or more reads. The olfactory receptor genes, known to be monoallelically expressed, were confirmed to be monoallelic in our samples. Some genes contained mix of monoallelic and biallelic SNPs in different exons, suggesting that specific exons are monoallelically expressed. More monoallelic SNPs were found in samples with higher sequencing coverage than those with lower coverage, suggesting that monoallelic genes tend to be expressed at lower levels when compared to biallelic genes.

Our data indicates widespread monoallelic genes in the olfactory neurons. We hypothesize that complex epigenetic regulation at the allele level is operated in the nervous system.

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Curriculum Vitae

Education

Duke University (Aug. 2008 -- Present) – Graduate student

- Developmental biology and stem cell program (Aug. 2008 – Present)
- University Program in Genetics and Genomics(Aug. 2009 – Present)
- 1st rotation project– Functional analysis of OR7D4s in different primates (Hiroaki Matsunami's lab)
- 2nd rotation project– Wnt signaling in epidermal patterning of Drosophila embryos (Amy Bejsovec's lab)
- 3rd rotation project– Specific marker genes exploration for different cell-type cortex neurons (Fan Wang's lab)

National Taiwan University (Feb. 2004 – Jan. 2006) – M.S., Institute of Zoology

- Overall GPA : 4.00/4.00
- Thesis: Molecular cloning, expression and functional analyses of citron kinase in zebrafish embryos.
- Poster: 45th Annual Meeting of the American Society for Cell Biology, San Francisco, United State, 2005
- The Memory of Hsieh, Te-Kui and Feng, Sung-Yen Scholarship
- The Scholarship of the Neurobiology and Cognitive Science Center

National Taiwan University (Sep. 1999 – Jan. 2004) – B.S., Department of Horticulture Science
– B.S., Department of Life Science (formerly Zoology)

- Summer Student Project (Jun. 2002 – Sep. 2002) – The effects of carbohydrate on the growth and regeneration efficiency from embryogenic callus cultures of *Oncidium* 'Gower Ramsey' (Peng-Lin Huang's lab)
- Undergraduate Research Program (Jul. 2003 – Jan. 2004) – The effects of Microcystin-LR, a cyanobacterial toxin, on zebrafish embryonic development. (Shyh-Jye Lee's lab)

Work Experience

- **Part-time Amanuensis for Journal of the Taiwan Society for Horticultural Science (Sep. 2000 – Jun. 2002)**
  - Department of Horticulture Science, National Taiwan University. (Iou-Zen, Chen's lab)
- **Research Assistant at (Mar. 2006 – May. 2008)**
  - Institute of Biomedical Science, Academia Sinica, Taipei, Taiwan. (Tang K, Tang's lab)
  - Projects – The checkpoint regulation of kinetochore molecules during meiosis.
    – The effects of centrosomal proteins on the development of neuron.

Publication

1. Zh uang, H, **M.S. Chien**, H. Matsunami. 2009. Dynamic functional evolution of an odorant receptor for sex-steroid-derived odors in primates. Proc Natl Acad Sci. 106(50):21247-51
2. **Chien, Ming-Shan.** 2006. Molecular cloning, expression and functional analyses of citron kinase in zebrafish embryos. (Master Thesis, poster in the 45th Annual Meeting of the American Society for Cell Biology, 2005)
3. Lee, S.J., C.C. Ju, S.L. Chu, **M.S. Chien**, T.H.Chan, and W.L. Liao. 2007. Molecular cloning, expression and phylogenetic analyses of parvalbumin in tilapia, *Oreochromis mossambicus*. J Exp Zool Part A Ecol Genet Physiol. 307:51-61.
4. Wang, P.J., **M.S. Chien**, F. J. Wu, H. N. Chou, and S.J. Lee. 2005. Inhibition of embryonic development by microcystin-LR in zebrafish, *Danio rerio*. Toxicon. 45:303-8.

Dynamic correlations of local inhibition shape late visual responses

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Abstract

The visual cortex responds to spatiotemporally patterned visual stimuli with specifically stereotyped activities; however, less is known about its responses to more featureless, non-patterned stimuli. By patch-clamping layer 2/3 neurons in the mouse primary visual cortex in vivo, we examined visual responses to simple light flashes. A flash stimulus elicited a biphasic response consisting of a rapid, transient depolarization with a latency of approximately 80 ms (the early response); thereafter, we observed a prolonged, larger depolarization that persisted for a few seconds (the late response). Late responses were characterized by a balanced increase in excitatory and inhibitory conductances and were accompanied by occasional action potentials. The timing of action potentials was predominantly determined by intermittent inhibitory barrages, which emerged through a transient coupling of locally correlated inhibitory circuits. Our data suggest that, under basal conditions, nearby inhibitory interneurons are synchronized, forming patches of locally correlated inhibition that synchronize more globally in response to a visual stimulus and shape the cortical spike output pattern.

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Education and professional training

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The Angelman Syndrome protein Ube3A regulates synapse development and function by ubiquitinating Arc

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Angelman Syndrome is a debilitating neurodevelopmental disorder, which is characterized by ataxia, frequent seizures, and severe mental retardation. At the time that we initiated these studies, although it was known that Angelman Syndrome resulted from mutation of the E3 ubiquitin ligase Ube3a, little was known of the role that Ube3a plays during normal nervous system development, or why mutation of Ube3a results in the cognitive impairment underlying Angelman Syndrome. To begin to address these questions, we undertook a mass spectrometry-based screen to identify substrates of Ube3A in the hope that uncovering Ube3A substrates might provide insight into Ube3A's role in nervous system development and function. By this approach we identified the protein Arc, whose principal function appears to be regulating the cell surface expression of AMPA receptors, as a neuronal substrate of Ube3a. The identification of Arc as a Ube3A substrate led us to hypothesize that AMPA receptor expression might be impaired in the absence of Ube3A. Consistent with this hypothesis, when compared to wildtype mice, Ube3A mutant mice have significantly reduced AMPA receptor expression and function. We further found that this defective AMPA receptor function resulted from an excessive accumulation of Arc in Ube3A mutant mice. These results suggest that restoring the level of Arc expression to that which is found in wildtype mice might ameliorate some of the behavioral deficits that are observed in Ube3A deficient mice, and we have recently begun mouse genetic experiments aimed at investigating this possibility. Our preliminary results suggest that restoring Arc levels to those observed in wildtype mice is sufficient to improve cognitive and motor function in Ube3A knockout mice, thus suggesting potential therapeutic approaches in humans for this previously untreatable disorder.

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Publications

Greer PL, Hanayama R, Bikoff JB, Hong EJ, Greenberg ME. Ube3A restricts synapse number by ubiquitinating and degrading Arc. Manuscript in preparation.

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Transformation from relative timing to firing rate in the central olfactory pathway

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Abstract

Sensory stimuli elicit neural spiking which carries information from the periphery to the brain. Traditionally, the overall rate of these spikes has been used to characterize neuronal responses but accumulating evidence suggests that timing of spikes also carries information. However, whether and how downstream neurons decode these temporal patterns remains unclear. We addressed this question by optogenetically stimulating two foci of olfactory nerve inputs or mitral/tufted cells with varying relative timing, while measuring the spiking activity of downstream neurons. We found that the overall spike rates of piriform cortex neurons were exquisitely sensitive to relative timing of input activation. Posterior piriform neurons showed higher sensitivity to relative input times than neurons in the anterior piriform cortex. In contrast, neurons in the olfactory bulb barely showed such sensitivity. Thus, the brain can transform a relative time code in the periphery into a firing rate-based representation in deeper brain areas.

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Education

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2006-2009 The Weizmann Institute of Science, combined PhD in applied mathematics, computer science and neurobiology. (Advisors: Prof. David Harel and Prof. Noam Sobel)

2004-2005 The Weizmann Institute of Science, M.Sc in applied mathematics and computer science. (Advisors: Prof. David Harel)

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Papers

1. R. Haddad, R. Khan, B. Nadler, N. Mandairon, M. Bensafi, E. Schneidman and N. Sobel; "An Axis-Based Olfactory Neural Code that Predicts Behavior and Perception"; J. Neuroscience, 2010.

2. R. Haddad, D. Harel, N. Sobel; "Predicting Odor Pleasantness with an Electronic Nose"; PLoS Computational Biology, 2010.

3. R. Haddad, D. Harel, N. Sobel; "Measuring smell"; Current Opinion in Neurobiology, 2008.

4. R. Haddad, R. Khan, Y.K. Takahashi, K. Mori, D. Harel and N. Sobel; "A metric for odorant comparison"; Nature Methods, 2008.

5. R. Haddad, L. Carmel, N. Sobel and D. Harel; "Predicting the Receptive Range of Olfactory Receptors"; PLoS Computational Biology, 2008.

6. R. Khan, C. Luk, A. Flinker, A. Aggarwal, H. Lapid, R. Haddad and N. Sobel; "Predicting Odor Pleasantness from Odorant Structure: Pleasantness as a Reflection of the Physical World"; J Neuroscience, 2007.

7. R. Haddad, L. Carmel, and D. Harel; "A Feature Extraction Algorithm for Multi-peak Signals in Electronic Noses"; Sensors and Actuators B: Chemical, 2007.

Distinct roles of the direct and indirect pathways in the basal ganglia to reward and aversive behavior

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Abstract: The basal ganglia are the key neural substrates that control motor balance, reward-based and aversive learning. Dysfunction of the basal ganglia leads to neuropsychiatric disorders such as Parkinson's disease, Huntington's disease, depression, schizophrenia, and drug addiction. The striatal projection neurons are GABA-containing medium-sized spiny neurons (MSNs), which are divided into two subpopulations, i.e., striatonigral neurons in the direct pathway and striatopallidal neurons in the indirect pathway. The inputs of these two pathways converge at the substantia nigra pars reticulata and control the dynamic balance of the basal ganglia-thalamocortical circuitry. Because the two types of MSNs exist in a similar number and are indistinguishable in size, shape, and basic physiological properties, the different regulatory roles of the two subpopulations are little understood. We developed a reversible neurotransmission blocking (RNB) technique, in which transmission-blocking tetanus toxin was specifically expressed in the direct striatonigral or the indirect striatopallidal pathway and, in turn, blocked each pathway in a doxycycline-dependent manner. The results indicated that the coordination of these two pathways was necessary for acute psychostimulant actions elicited by dopamine stimulation. This coordinated modulation, however, shifted to the predominant role of each pathway in reward-directed and aversive behavior. Blockade of the direct pathway selectively impaired rewarding learning and cocaine sensitization. By contrast, blockade of the indirect pathway specifically abrogated aversive behavior. These two pathways thus have distinct roles: the direct pathway critical for distinguishing associative rewarding stimuli from non-associative ones and the indirect pathway for rapid memory formation to avoid aversive stimuli.

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AWARDS

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PUBLICATION LIST:

1. Kimura K, Hikida T, Yawata S, Yamaguchi T, Nakanishi S. (2011) Pathway-specific engagement of ephrinA5-EphA4/EphA5 system of the substantia nigra pars reticulata in cocaine-induced responses. Proc Natl Acad Sci U S A, 108 (24): 9981-9986.

2. Hikida T, Kimura K, Wada N, Funabiki K, Nakanishi S. (2010) Distinct roles of synaptic transmission in direct and indirect striatal pathways to reward and aversive behavior. *Neuron,* **66:** 896-907.

3. Schretlen DJ., Vannorsdll TD, Winicki JM, Mushtaq Y, Hikida T, Sawa A, Yolken RH, Dickerson FB,

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11. Hikida T, Kaneko S, Isobe T, Kitabatake Y, Watanabe D, Pastan I, Nakanishi S. (2001) Increased sensitivity to cocaine by cholinergic cell ablation in nucleus accumbens. *Proc. Natl. Acad. Sci. U.S.A.* **98**: 13351-13354.

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Mapping the chemical circuitry of the brain: New neuromodulator sensor revealed dopaminergic gain-control of feeding behavior by starvation in *Drosophila*

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Behavior cannot be predicted from a neuronal "wiring diagram," because the brain contains a chemical "map" of neuromodulation superimposed upon its synaptic connectivity map. Neuromodulation changes how neural circuits process information in different states, such as hunger or arousal. . In order to understand how neuromodulators participate in controlling behavior, it is critical to identify the neuronal populations that are modulated under different behavior states. Here we describe a novel, genetically based method to map, in an unbiased and brain-wide manner, sites of neuromodulation under different conditions in the Drosophila brain. This method reveal that dopamine modulate gustatory sensory neurons under the state of hunger. With genetic perturbations, and calcium imaging we found that the well-known effect of hunger to enhance behavioral sensitivity to sugar is mediated indeed, at least in part, by the release of dopamine onto primary gustatory sensory neurons, which enhances sugar-evoked calcium influx. These data reinforce the concept that sensory neurons constitute an important locus for state-dependent gain-control of behavior, and introduce a new methodology that can be extended to other neuromodulators and model organisms, as well as to the in vivo mapping of GPCR activation in non-neuronal tissues.

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AWARDS & SELECTED ABSTRACTS

Inagaki HK, Ben-Tabou S, Wong A, Jagadish S, Ishimoto H, Barnea G, Kitamoto T, Axel R, Anderson DJ, in prep, Mapping the chemical circuitry of the brain: dopaminergic gain-control of feeding behavior by starvation in *Drosophila*.

Inagaki HK, Kamikouchi A, Ito K. (2010) Protocol for quantifying sound-sensing ability of *Drosophila melanpgaster*. *Nat Protoc*. 5:26-30.

Inagaki HK, Kamikouchi A, Ito K. (2010) Methods for quantifying simple gravity sensing in *Drosophila melanpgaster*. *Nat Protoc*. 5:20-25.

Kamikouchi A, **Inagaki HK**, Yorozu S, Ito K. (2009) Application of Drosophila as an integrative neural model to understand how sound, gravity, an wind information are processed in the brain. *Tanpakushitsu Kakusan Koso*. 54:1817-26.

Kamikouchi A*, **Inagaki HK***, Effertz T, Hendrich O, Fiala A, Göpfert MC, Ito K. (2009) The Neural Basis of *Drosophila* Gravity Sensing and Hearing. *Nature*. 458:165-71.
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2004 –3rd prize in Project Show for Future Engineers, World Engineer's Convention 2004 , Shanghai, China
2006 –A representative of School of Science, University of Tokyo for "Overseas Visit Program (U.C Berkeley & Stanford University)"
2007 –Dean prize, School of Science, University of Tokyo
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Dual roles of OSN-derived Semaphorin-3F in the olfactory circuit formation

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In the mouse olfactory system, olfactory sensory neurons (OSNs) project their axons to specific glomeruli in the olfactory bulb (OB), and creating an olfactory map. Second-order neurons, mitral/tufted (M/T) cells, innervate their dendrites to specific glomeruli and send their axons to the olfactory cortex, transferring the olfactory map information from the OB to higher brain centers. Surgical and genetic studies have demonstrated that axon-derived guidance molecules alone could organize a coarse olfactory map by axon-axon interactions of OSNs. Although the map topography is established independently from the target cues, the map needs to be properly connected with second-order neuron, M/T cells, to make the olfactory circuit functional. How are the primary neuron axons and secondary neurons properly aligned for specific synapse formation between them? Here, we report that OSN-specific knockout of Semaphorin-3F (Sema3F) disrupts both axonal projection of OSNs and migration of mitral cells to the ventral region of the OB. It was found that Nrp2-positive M/T cells are guided to the Sema3F-negative ventral region in the OB, while Nrp2-negative M/T cells stay in the embryonic OB, a prospective dorsal region in the adult OB. These results suggest a novel strategy for axon wiring and synapse formation in the mouse olfactory system: a common guidance molecule (Sema3F) secreted by early-arriving dorsal OSN axons, guides both late-arriving primary neuron (OSN) axons and their partner secondary neurons (M/T cells) to the ventral region of the OB for their proper alignment and synapse formation. Loss of function experiments of Nrp2 revealed that Nrp2-Sema3F signaling also regulates axonal projection of Nrp2-positive mitral cells that target to the medial amygdala. Repeated use of the same pair of guidance molecules may be a general mechanism for the neural circuit formation in the brain.

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Publication List

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Functional spike synchrony has significantly larger onset latency than anatomical spike synchrony in the cat lateral geniculate nucleus

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Precisely synchronized neuronal activity has been commonly observed in the mammalian visual pathway (retina, thalamus and cortex) under a wide range of stimulus conditions. Analysis of this neural behavior has often assumed that synchronous firing is stationary and maintained throughout the period of visual stimulation. We tested this assumption by applying the method of Unitary Events Analysis to pairs of simultaneously recorded spike trains in the cat lateral geniculate nucleus (LGN) that were stimulated with stationary spots of light. To evaluate the significance of synchronous spike events, we developed and applied a non-parametric bootstrap test. The analysis showed that about half of the single unit pairs (96/195, 49%) displayed significant synchronous activity (unitary events). Some unit pairs displaying highly transient unitary events failed to show significant synchrony when analyzed with conventional cross-correlation analysis. In many unit pairs, the unitary events were optimally characterized at a bin width of 1 ms, indicating that neural synchrony has a high degree of temporal precision. Synchronous firings in some unit pairs changed their characteristics under different stimulus context (ON/OFF or stationary spots/moving bar). We also examined the temporal modulation of synchronous firing by another novel bootstrap test and found that half of the unit pairs (46/96, 48%) displayed non-stationary changes in synchrony that could not be predicted by the modulation of firing rates. Those dynamics suggest that synchronous firings in the LGN are functional and are not originated from the anatomical transmission time difference between the retinal inputs to the two relay cells. This conclusion is supported also by another observation: the anatomical synchronies between the retinal afferent (S-potential) and the relay cell had significantly smaller onset latency than the adjacent (intra-tetrode) relay cell pairs. Furthermore, onset latencies were significantly longer in the distant (inter-tetrode, separated by 0.5mm) relay cell pairs than the adjacent relay cell pairs. Irrespective of short onset latency of the firing rates, synchrony in some of distant unit pairs showed a transient increase with a very long latency (300-500ms) after the stimulus presentation. These findings demonstrate that stimulus-evoked synchronous activity within the LGN is highly non-stationary and modulated by endogenous processes that are not tightly correlated with firing rate.

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H.Ito, PE. Maldonado and CM. Gray
Dynamics of stimulus-evoked spike timing correlations in the cat lateral geniculate nucleus. J. Neurophysiol., 104, 3276-3292 (2010).

H. Ito, PE. Maldonado and CM. Gray
Dynamics of stimulus-evoked spike timing correlations in the cat lateral geniculate nucleus. Neurosci. Research, O1-8-3-4, Supplement, (2010). (oral presentation)

Y. Maruyama and H. Ito
Correlated trial variabilities between single units in the cat visual cortex –stimulus dependence and its relation with the firing rate tuning–.
Neuroscience Research, P3-h25, Supplement, (2010). (poster presentation)

H. Ito, PE. Maldonado and CM. Gray
Functional spike synchrony has significantly larger onset latency than anatomical spike synchrony in the cat lateral geniculate nucleus.
Soc. Neurosci. Abstr., 532.10 (2010) (oral presentation)

Y. Maruyama and H. Ito
Stimulus dependence of correlated trial variabilities and its relation with the rate tuning in the cat visual cortex.
Soc. Neurosci. Abstr., 73. 19/003 (2010) (poster presentation)

H. Ito
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Y. Maruyama and H.Ito
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H.Ito
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H.Ito
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H.Ito
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Visual experience during locomotion and TrkB signaling promote recovery of adult visual cortex from prolonged deprivation

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Depriving one eye of normal patterned vision during early life causes neurons in the visual cortex to lose responsiveness and visual acuity through the deprived eye (amblyopia). If such abnormal vision is left uncorrected, recovery of normal visual function is difficult in the adult, both in humans and in higher mammals, because of limited plasticity in mature cortex. However, recent studies using rodents have shown that recovery of the adult visual cortex after prolonged deprivation can be promoted by visual experience in enriched environment or by various pharmacological manipulations. The recent discovery that neurons in mouse visual cortex respond with more than 2 times the number of action potentials during active locomotion than when still (Niell and Stryker, *Neuron*, 2010) led us to test whether this enhanced response might facilitate recovery from early-onset, long-term monocular deprivation (MD). In addition, we examined whether TrkB plays a role in such recovery during adulthood, as we have shown it does for recovery during critical period (Kaneko et al, *Nature Neuroscience*, 2008).

C57BL/6 wild type or TrkB-F616A mutant mice were monocularly deprived by eyelid suture from the beginning of the critical period at P22-24 until ~4 months of age, when we began chronic optical imaging of the intrinsic signal of cortical activity to measure changes in visual responses. After reinstating binocular vision (BV) by opening the deprived eye, cortical responses to that eye gradually increased over 3 weeks but did not reach the level of normally-reared animals. This partial recovery was almost completely inhibited in TrkB-F616A mice treated with 1NM-PP1 to inactivate TrkB kinase. In mice that were exposed to visual stimuli (VS), either contrast-modulated Gaussian noise (noise) or a square bar drifting in several different directions, while running freely on a foam ball suspended in air for 3-4 hours each day, intrinsic signal responses increased much faster and to a greater extent: recovery was already significant by 7 days and reached the normal level within 14 days. The degree of this enhancement depended on the match between VS presented during locomotion and those used for testing. Either VS alone or locomotion alone caused little enhancement of recovery. Locomotion + VS at least partially compensated for blockade of TrkB signaling.

We then used extracellular electrophysiological recording in layers 2, 3, and 4 to examine whether and how response properties of individual neurons improve by reinstated BV following prolonged MD. Consistent with the global changes in the visual cortex as a whole revealed by intrinsic signal imaging, putative excitatory neurons in mice that experienced running + VS either noise or drifting gratings during 7d-BV showed restored spike rates in response to noise or grating stimuli, respectively. These cells in mice that experienced running + grating VS, but not running + noise, also showed improvement in orientation selectivity, the binocular matching of preferred orientation, and acuity. Changes in several physiological characteristics of putative inhibitory neurons after prolonged MD and after 7d-BV demonstrated differences from those in excitatory neurons.

These results indicate that recovery of responsiveness from prolonged MD in adult visual cortex requires TrkB kinase activity and is facilitated by exposure to visual stimulation while the animal is engaged in active locomotion. This facilitation by visual experience accompanies improvement of receptive field properties such as orientation tuning and acuity of individual neurons. These findings suggest that enhanced visual responses during locomotion may also account for other treatments that promote recovery in the adult cortex.

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SELECTED PUBLICATIONS

Kaneko, M.*, Xie, Y.*, Stryker, M.P., Xu, B. A role for dendritic targeting of BNDF mRNA in development and plasticity in visual cortex. *Manuscript submitted* (* co-first authors)

Kaneko, M.*, Cheetham, C.*, Lee, Y-S., Silva, A.J., Stryker, M.P., Fox, K.D. (2010) Constitutively active H-ras accelerates multiple forms of plasticity in developing visual cortex. *Proc. Nat. Acad. Sci. USA 107,* 19026-19031. (* co-first authors)

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Olfactory pathways involved in innate fear responses

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The mouse olfactory system detects odorants and pheromones as well as predator odors that stimulate innate fear responses. This suggests that there are genetically defined neural circuits within the olfactory system that are involved in innate fear responses to specific olfactory stimuli. The anatomical and molecular characteristics of these circuits are presently unknown. Odorants are initially detected in the olfactory epithelium (OE) of the nose. In contrast, the vomeronasal organ (VNO) is thought to be specialized for detecting pheromones and other substances that elicit innate responses, including fear. OE signals travel through the main olfactory bulb to the olfactory cortex, which consists of a number of distinct areas, including the piriform cortex and olfactory cortical amygdala. The piriform cortex is thought to be critical for odor perception, but the functions of the other areas are a mystery. VNO signals travel through the accessory olfactory bulb to two specific parts of the amygdala ('vomeronasal amygdala') that transmit information to the hypothalamus. To investigate the mechanisms and neural circuits that mediate innate fear responses to olfactory stimuli, we have focused on CRH (corticotropin releasing hormone) neurons in the hypothalamus. These neurons serve as key regulators of physiological responses to fear. To identify neurons that transmit olfactory signals to CRH neurons, we have infected CRH neurons with a conditional 'tracer/reporter' virus that travels retrogradely through chains of connected neurons. We have observed virus-infected neurons upstream of CRH neurons in both the OE and VNO pathways, suggesting that both pathways can transmit signals to CRH neurons. Our results further suggest that CRH neurons are directly connected to the vomeronasal amygdala, but indirectly connected to the olfactory cortex. Within the OE pathway, we have observed infected cells in both the piriform cortex and olfactory amygdala, suggesting the potential involvement of both areas in innate fear responses. Interestingly, while responses to common odorants are reportedly seen throughout the piriform cortex, virus-infected neurons were observed predominantly in the posterior part of this structure, raising the possibility that there is a biased organization of neurons involved in innate fear responses within the piriform cortex.

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Publications

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Sunadome K, Yamamoto T, Ebisuya M, Kondoh K, Sehara-Fujisawa A, Nishida E. (2011) ERK5 regulates muscle cell fusion through Klf transcription factors. *Developmental Cell* 20(2):192-205.

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Visualizing Neural Circuits with Activity-Dependent Nuclear Import of a Transcription Factor

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abstract

Marking active neuron in behaving animals is important for understanding of complex behaviors. However methods which label active neurons during behavior are limited. Here we present an activity reporter system dubbed CaLexA (calcium dependent nuclear import of LexA) based on the mechanism of activity-dependent nuclear import of a transcription factor. Nuclear factor of activated T-Cell (NFAT) is a calcium responsive transcription factor. The transport of NFAT between the nucleus and cytoplasm is regulated by the calcium-dependent protein phosphatase calcineurin. The basic strategy of the CaLexA system is to express an exogenous transcription factor in specific neural populations and its import into the nucleus upon sustained depolarization induces the expression of a reporter gene. We employed two binary expression systems: the Gal4/UAS system for expressing the chimeric transcription factor LexA-VP16-NFAT, and the LexA/LexAop system for expressing the GFP reporter.

We tested this strategy on odorant receptor neurons (ORNs) and projection neurons (PNs) in the *Drosophila* olfactory system. Our results showed that fly pheromones excite specific neurons in the antennal lobe. In this proof-of-concept, we expressed the transcription factor to only ORNs or PNs and asked which neurons respond to the pheromones. Furthermore, we applied this system to visualize neural circuits underlying complex behaviors. Courtship of male flies exhibits a complex sequence of behaviors that require multiple sensory inputs. We found a small subset of neurons in the ventral nerve cord was labeled upon courtship experience. This system using activity-dependent expression could be applied to visualize active neurons in different model organism after appropriate modifications.

Curriculum vitae

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Publication List
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Fast, efficient population codes in olfactory cortex through decorrelation and synchronization to theta-frequency sniffing

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In the mammalian olfactory system, stimulus qualities are encoded combinatorially across hundreds of channels and stimulus dynamics are dominated by rhythmic active sampling at theta frequency. It is, however, not known what advantages these properties render in neural representation of odors in the central brain areas. Here, we hypothesized that these confer efficient and rapid population coding in the olfactory cortex that can facilitate rapid and accurate odor-guided behavior. We recorded from ensembles of neurons in the anterior piriform cortex of rats performing an odor mixture categorization task. Odor stimulation evoked rapid and transient burst spiking tightly locked to inhalation onset, and thus phase-locked to the theta cycle. Population decoding analysis showed that the information conveyed by the spikes in the first theta cycle was sufficient to account for behavioral accuracy. The efficacy of odor representations was facilitated by the fact that olfactory cortex neurons showed not only independent stimulus tuning but essentially zero noise correlations, regardless of proximity, allowing for more efficient encoding over large neuronal ensembles. While these properties can be partly attributed to the distributed connectivity of the olfactory system, noise correlations and trial-to-trial variability were also dependent on active sampling, being minimal during theta-frequency sniffing. Thus, distributed, decorrelated and respiration-locked coding in the olfactory cortex yields an efficient and fast odor code, allowing animals to perform accurate odor discrimination using the information contained in a single theta cycle.

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EDUCATION

2006, Ph. D, Physics, Kyoto University, Kyoto, Japan

AWARDS

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2005, Young Researcher Award, Japanese Neural Network Society

2005, Outstanding Student Paper Award (NIPS 2005)

SELECTED PUBLICATION LIST

1. K. Miura, An introduction to maximum likelihood estimation and information geometry, Interdisciplinary Information Sciences, 2011, in press.

2. M. Oizumi, K. Miura, M. Okada, Analytical investigation of the effects of lateral connections on the accuracy of population coding, Physical Review E. 2010;81:051905

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4. K. Miura, N. Uchida, A Rate-Independent Measure of Irregularity for Event Series and Its Application to Neural Spiking Activity, 47th IEEE Conference on Decision and Control, 2008:2006-11

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Light induction causes dynamic alteration in the expression of activity-dependent genes in the marmoset primary visual cortex

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The visual cortex (V1) is one of the best characterize neocortical areas, yet there would be still many unrevealed features particularly in primates. We have reported that three genes, *OCC1, 5-HT1B* and *5-HT2A* serotonin receptor genes, are selectively express in V1 among the neocortex in macaque monkeys (Tochitani et al., 2001; Watakabe et al., 2009). In V1 of many species of primates, including marmosets, the retino-geniculo-cortical pathways from right and left eyes terminate in distinct alternating ocular dominance columns (ODC). By monocular retinal activity deprivation by TTX injection, we observed decrease of the signals for these three genes in the deprived ODC.

In the marmoset (*Callithrix jacchus*), ODC had been reported to be present in young animals, but absent in adults (Spatz, 1989). However, several groups have recently reported that in adult marmosets, the primary visual cortex organized with ODC in layer IVc, being detected by activity-dependent immediate early gene (IEG) expression, and may act under physiological conditions (Markstahler, 1998; Chappert-Piquemal C, 2001). In order to establish a mode system to analyze the activity-dependent gene expression in marmoset V1, we monocularly injected TTX, kept them in darkness for 24-48 hours, and then exposed to light for 0, 0.5, 2, and 4 hours, to examine the time course of the transcription. By this method, we were able to compare the induced and non-induced genes by comparing the neighboring ODC in one tissue from the same animal. We examined the expression patterns of immediate early genes (IEGs) such as *c-FOS, ARC, ZIF28,* and *SIK1* in addition to *5-HT1B* and *5-HT2A* receptor genes.

Under in situ hybridization, IEG expressions were little detected without light induction. Upon light induction, however, the expression of each IEG rapidly changed the signal intensity and laminar pattern in layers IVa, IVc, V, and VI. For example, *c-FOS* was strongly expressed in layers II/III, IVa, IVc, and VI, within 30 minutes of stimulus onset, and then disappeared rapidly. *ARC* was also expressed in layers II/III, IVa, V and VI, at 30 minutes but not in layer IVc. Two hours later, *ARC* in layer IVc increased dramatically and decreased again at four hours of induction.

In contrast to IEG, the expression of *5-HT1B* and *5-HT2A* receptor genes were mostly confined to layer IVc and increased in direct proportion to the length of visual stimuli.

We also examined the phosphorylation state of CREB at ser133 by immunohistochemical staining, which is well known to be a key regulator of activity-dependent gene transcription *in vitro and in vivo* in many species. To our surprise, after visual stimulation, pCREB signal decreased in layer IVc of the input-receiving columns (i.e., in a complementary fashion to IEG expressions). In conclusion, our monocular induction experiments revealed dynamic regulations of activity-dependent genes in marmoset V1, which mechanisms may be somewhat different from those previously studied in other species.

Curriculum Vitae

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Odorant receptor-derived basal activity regulates olfactory map formation in mouse

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In the mouse olfactory system, olfactory sensory neurons (OSNs) expressing the same odorant receptor (OR) species converge their axons into a specific set of glomeruli in the olfactory bulb (OB). A remarkable feature of mammalian olfactory system is that OR molecules instruct axonal projection of OSNs by regulating the expression levels of axon guidance molecules with OR-derived cAMP. However, it is poorly understood how the cAMP signals are generated in an OR-specific manner during development.

Many G protein coupled receptors (GPCRs) are known to possess two different conformations, active and inactive. Sponteneous conversion between them generates a unique level of basal activity even in the absence of agonists. We assumed that the basal activity of ORs is responsible for generating cAMP signals that regulate axonal projection of OSNs. To examine this possibility, we tried to analyze the basal activity mutants of ORs. However, due to the difficulty of functional analyses of ORs *in vitro*, it has not been easy to study a possible role of the basal activity with OR mutants. β2 adrenergic receptor (β2AR) is known to share many functional similarities with ORs, and has extensively been studied for various functions using mutants. It has been reported that β2AR can replace the function of ORs for receptor-instructed axonal projection. Based on these previous studies, we have generated transgenic mice that express the β2AR mutants in OSNs with altered levels of basal activity. Here we report that activity-high mutations cause the posterior shift of glomeruli, whereas activity-low mutations cause the anterior shift. The basal activity mutants affected the expression levels of Neuropilin-1 and Plexin-A1. These results demonstrate that it is the OR-derived basal activity that regulates axonal projection of OSNs, whose level is uniquely determined by OR species.

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Bibliography:

1. Nishizumi H, Kumasaka K, Inoue N, Nakashima A, Sakano H (2007)
Deletion of the core-H region in mice abolishes the expression of three proximal odorant receptor genes in cis. *Proc. Natl. Acad. Sci. U.S.A.,* 104, 20067-20072 .

HCN channels boost spontaneous firing activity of olfactory receptor neurons through basal activation of β2 adrenoceptor

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Olfactory receptor neurons (ORNs) undergo continuous turnover throughout life and maintain an axonal projection map from ORNs to the olfactory bulb. Cyclic AMP-signaling is known to affect the olfactory map formation, but the underlying mechanism is yet unknown. On the other hand, electrical activities affect the synapse connectivity and axonal projections in many neural networks such as visual, auditory and also olfactory systems. We here investigated the possible regulation of spontaneous firing activity of ORNs through hyperpolarization-activated cyclic nucleotide-gated (HCN) channels and endogenous cAMP.
We applied extracellular recordings onto slice preparations of the mouse olfactory epithelium. Inhibition of HCN channels by ZD7288 suppressed the spontaneous activity dose-dependently. The spontaneous activity suppressed by ZD7288 was recovered by field stimulation that depolarized the membrane. Transgenic mice over-expressing HCN4, one of the predominant subtype in mouse ORNs, showed a higher level of spontaneous firing than their littermates, while knockdown of HCN4 resulted in the decrease of the spontaneous firing activity. Then how are HCN channels gated open at rest? Phosphodiesterase inhibitor (rolipram) increased while adenylate cyclase inhibitor (SQ22536) and selective blockers for Gs-coupled beta-2 adrenoceptor (Butaxamine and ICI 118,551) markedly decreased the spontaneous activity, indicating that beta-2 adrenoceptor (ADRB2) constitutively elevates the basal cAMP levels and maintains the spontaneous activity.
These results indicate that HCN channels depolarize the membrane potential of the ORNs and boost the spontaneous firing activity under the standing activation of ADRB2. Thus HCN channels in ORNs would show cell-specific gating under the control of the endogenous cAMP levels that may set the spontaneous firing rate as a dynamic guidance cue for olfactory map formation.

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Education
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Publications
1) Takahiro M. Ishii, Noriyuki Nakashima, Harunori Ohmori,
Tryptophan-scanning mutagenesis in the S1 domain of mammalian HCN channel reveals residues critical for voltage-gated activation. The Journal of Physiology 579; 291-30; 2007 Mar 1

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Peripheral N- and C-terminal domains determine deactivation kinetics of HCN channels. Biochem. Biophys. Res. Commun. 359(3); 592-8; 2007 May 29

Interests and research techniques
I wonder what realizes an entity called the *mind*. The brain might be the fundamental core unit for the mind. I am currently studying how the neural networks are regulated at the basal state by applying **electrophysiological technique** in combination with **molecular biological, histo-anatomical** and **behavioral analyses**.

FKBP52 is a key regulator of microtubule dynamics and modulates TAU activities in zebrafish

Hiroko Nakatani
Fondation Nationale de Gérontologie / Inserm UMR788

Hiroko Nakatani, Christopher I. Javis, Béatrice Chambraud, Marcel Tawk and Etienne-Emile Baulieu

FKBP52 is a member of FK506 binding protein (FKBP) familly that comprises intracellular receptors for immunossuppressing drugs such as FK506 and rapamycin. It was originally discovered in our laboratory in 1992 as a component of a steroid hormone receptor – HSP90 chaperone complex [1]. Interestingly, recent biochemical analysis showed a direct and functional interaction between FKBP52, tubulin and the Microtubule Associated Protein, TAU, which leads to tubulin depolymerisation in vitro [2,3]. Here, we study the function of the FKBP52 ortholog FKBP4 in neural development in zebrafish and will investigate its interaction with physiological and pathological TAU in vivo. A knockdown of FKBP52 leads to axonal outgrowth defects in both primary motoneurons and Posterior Lateral Line nerve (PLLn). Transmitted Electron Microscopy analysis showed a reduction in the number of myelinated axons and mitochondria within axons. Collectively, our results reveal an essential role for FKBP52 in microtubule organization, axonal outgrowth and localization of axonal cargos. Moreover, we shall study a functional interaction between FKBP52 and pathological forms of TAU in vivo. Effects of several FKBP ligands on neuronal cell biology related to several TAU forms will be analysed. The use of an automated fluorescent microscope enabling phenotypic assays on zebrafish whole embryos in high throughput screening is now being tested.

[1] Lebeau MC *et al.* (1992) *J Biol Chem.* **267**, 4281-4.
[2] Chambraud B *et al.* (2007) *FASEB J.* **21**, 2787-97.
[3] Chambraud B *et al.* (2010) *Proc Natl Acad Sci USA.* **107**, 2658-63.

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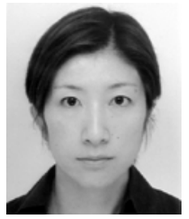

INTERESTS
Developmental neurobiology in mouse & zebrafish.

CARRIERS
2011- Postdoctoral fellow, Etienne-Emile Baulieu Lab, FNG / INSERM U788, France.
2006-2011 Postdoctoral fellow, Carlos Parras Lab, CRICM / INSERM U975, France.
2003-2006 Postdoctoral fellow, Jean-Pierre Changeux Lab, Institut Pasteur, France.
2003 Ph.D. Hitoshi Sakano Lab, The University of Tokyo, Japan.
2000 B.S. Hitoshi Sakano Lab, The University of Tokyo, Japan.

PUBLICATIONS

Binder E, Rukavina M, Hassani H, Weber M, Nakatani H, Reiff T, Parras C, Taylor V, Rohrer H. (2011). Peripheral nervous system progenitors can be reprogrammed to produce myelinating oligodendrocytes and repair brain lesions. *J. Neurosci.* **31**(17), 6379-6391.

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Serizawa S, Miyamichi K, Nakatani H, Suzuki M, Saito M, Yoshihara Y, Sakano H. (2003). Negative feedback regulation ensures the one receptor-one olfactory neuron rule in mouse. *Science* **302**, 2088-2094.

Sengoku S, Ishii T, Serizawa S, Nakatani H, Nagawa F, Tsuboi A, Sakano H. (2001). Axonal projection of olfactory sensory neurons during the developmental and regeneration processes. *Neuroreport* **17**, 1061-1066.

Ishii T, Serizawa S, Kohda A, Nakatani H, Shiroishi T, Okumura K, Iwakura Y, Nagawa F, Tsuboi A, Sakano H. (2001). Monoallelic expression of the odourant receptor gene and axonal projection of olfactory sensory neurones. *Genes Cells.* **6**, 71-78.

Serizawa S, Ishii T, Nakatani H, Tsuboi A, Nagawa F, Asano M, Sudo K, Sakagami J, Sakano H, Ijiri T, Matsuda Y, Suzuki M, Yamamori T, Iwakura Y, Sakano H. (2000). Mutually exclusive expression of odorant receptor transgenes. *Nat. Neurosci.* **3**, 687-693.

Cross-modal interaction in learning stimulus-discrimination tasks in a mouse model

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Andrei T. Popescu, Angie Kang, Jenkang Tao, Michael R Zhou, Arleen Grewal, Hwei Ee, Mu-ming Poo

Learning generalization can be observed when stimuli different than the ones used during training produce the same behavioral response as the original ones (immediate transfer), or lead to the faster learning of a new association (far transfer). In an extreme case, training to discriminate stimuli in one modality allows a faster acquisition of similar discrimination in a different modality (Kehoe & Holt, 1984, Campolattaro et al., 2011). Although the phenomenon of learning transfer has been described and characterized in different forms, the neural circuit basis remains largely unknown. Here, we attempt to uncover the neural mechanisms by using a mouse model of stimulus discrimination learning. Following habituation to head fixation, water-deprived mice were trained to discriminate two sounds, one second in duration, and learned that licking right after one of the sounds (conditioned stimulus - CS+, white noise) resulted in water delivery while the other sound had no effect (non-conditioned stimulus - CS-, 5-kHz pure tone). Performance on this task was measured as percent of CS+ presentations followed by successful reward delivery. A discrimination score was also calculated based on anticipatory licking during the sound presentations, normalizing the difference in anticipatory licking during CS+ and CS- to the total number of anticipatory licks. Both performance and stimulus discrimination increased consistently over the ten days of training, reaching high, stable values (≥ 75% and ≥ 0.55, respectively) after the first five sessions. At the end of the auditory training animals started a similar discrimination task, this time using visual stimuli (4-Hz white flashing light, paired with lick-dependent water delivery,- CS+, vs. continuous white light, no reward - CS-, both one second duration). Performance on the new auditory task improved at a rate similar to the visual task, reaching values of 78.5 ± 0.1 % on the fifth session. Surprisingly, however, mice were impaired at discriminating the new visual stimuli, and reached a discrimination score of 0.6 ± 0.07 only on the tenth day of training. This phenomenon was not specific to the auditory-visual sequence, and occurred when visual-training was performed first as well. Interestingly, animals that had low discrimination scores at the end of training on the first task, either being slow learners, receiving less training – 5 days, or subjected to bilateral injections of dopamine D1 antagonist SCH-23390 in the medial prefrontal cortex (mPFC) were much better at discriminating the second set of stimuli than the mice with high discrimination scores at the end of training on the first task. This indicates that learning stimulus discrimination in one sensory modality hinders learning a similar stimulus discrimination in a different modality, and that dopamine signaling in mPFC plays a crucial part in this process. Future work will focus on elucidating the modification of dopamine-dependent reward circuit and its role in cross-modal interaction in learning.

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Education

2003 – 2010 graduate student in the Integrative Neuroscience Program at Rutgers University, Newark NJ, **Ph.D.** degree

2002 – 2003 graduate student in the Neuroscience and Behavior Program at University of Massachusetts, Amherst MA

1995 – 2001 "Carol Davila" University of Medicine and Pharmacy, Bucharest RO, **Medical Doctor** degree

2000 graduated the Specialized First Aid Medical Course at the Emergency Hospital, Bucharest RO

1991 – 1995 Computer Science High School, Bucharest RO Analyst-Programmer; Computer Operator diploma

Professional experience

2010 – **Postdoctoral Fellow**, Molecular and Cell Biology Dept., University of California, Berkeley

2005 – 2007 **Teaching Assistant** for "Neurobiology" at Rutgers University, Newark NJ

2004 **Teaching Assistant** for "Foundations of Neuroscience" at Rutgers University, Newark NJ

2003 – 2010 **Research**: *in vitro* and *in vivo* characterization of amygdala-facilitated learning

2002 – 2003 **Teaching Assistant** for "Method Inquiry in Psychology" at University of Massachusetts, Amherst MA: lecturing and student evaluation responsibilities

2002 – 2003 **Research:** molecular techniques and confocal imaging; role of adhesion molecules in synaptic plasticity

2001 – 2002 **Lecturer** for Cellular and Molecular Biology at "Carol Davila" University of Medicine, Bucharest RO: lecturing and student evaluation responsibilities

2000 – 2002 **Research:** the anti-apoptotic and neuro-protective role of phosphatidic acid (molecular techniques)

2001 – 2002 **Doctor Practitioner** in Clinical Neurology at "Colentina" Hospital Bucharest, RO

Publications

Shelly M, Cancedda L, Lim BK, **Popescu AT**, Cheng PL, Gao H, Poo MM. Semaphorin3A regulates neuronal polarization by suppressing axon formation and promoting dendrite growth. *Neuron*. Aug 11;71(3):433-46 **2011**

Popescu AT, Paré D. Synaptic interactions underlying synchronized inhibition in the basal amygdala: evidence for existence of two types of projection cells. *J Neurophysiol*. Feb;105(2):687-96 **2011**

Popescu AT, Saghyan AA, Nagy FZ, Paré D. Facilitation of corticostriatal plasticity by the amygdala requires Ca2+-induced Ca2+ release in the ventral striatum. *J Neurophysiol*. Sep;104(3):1673-80 **2010**

Popa D, Duvarci S, **Popescu AT**, Léna C, Paré D. Coherent amygdalocortical theta promotes fear memory consolidation during paradoxical sleep. *Proc Natl Acad Sci U S A*. Apr 6;107(14):6516-9 **2010**

Popescu AT., Popa D., Pare D. Coherent gamma oscillations couple the amygdala and striatum during learning. *Nat Neurosci.* May 10;12(6):801:807 **2009**

Popa D., **Popescu AT**, Pare D. Contrasting activity profile of two distributed cortical networks as a function of attentional demands. *J Neurosci.* Jan 28;29(4):1191-201 **2009**

Popescu AT, Saghyan AA, Pare D. NMDA-dependent facilitation of corticostriatal plasticity by the amygdala. *Proc Natl Acad Sci U S A*. Jan 2;104(1):341-6 **2007**

Likhtik E, Pelletier JG, **Popescu AT**, Pare D. Identification of basolateral amygdala projection cells and interneurons using extracellular recordings. *J Neurophysiol*. Dec;96(6):3257-65 **2006**

Mathew D, **Popescu A**, Budnik V. Drosophila amphiphysin functions during synaptic Fasciclin II membrane cycling. *J Neurosci*. Nov 19;23(33): 10710-6 **2003**

Vidulescu C, **Popescu AT.** Membrane blebbing and apoptotic bodies in cerebellar cells. *J Cell Mol Med*. Jul-Sep;7(3):330-1 **2003**

Popescu AT, Vidulescu C, Stanciu CL, Popescu BO, Popescu LM. Selective protection by phosphatidic acid against staurosporine-induced neuronal apoptosis. *J Cell Mol Med*. Jul-Sep;6(3):433-8, **2002**

Odor Coding by a Mammalian Receptor Repertoire

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Graduate School of Science The University of Tokyo

Odor sensing is closely linked to emotion and memory, which enables animals to find food, identify mates and offspring, and avoid danger). Since the odorant receptor (OR) was identified in 1991, the logics of odor sensing has been intensively studied. In the present study, we attempted to elucidate the fundamental principles of odor coding by OR repertoires. We performed high-throughput screening using our own heterologous system (1) and the results provided a basis for translating odorants into receptor neuron responses (2). Currently, we are focusing on ORs involved in the innate fear response / freezing behavior which are specifically activated by the stimulation of fox odor "2,4,5-trimethylthiazoline (TMT)". We plan to use this information as a platform for studying the neural network in the brain.

Curriculum Vitae

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Education

July 1998 **Ph.D in Life Science**
Babraham Institute, Dept of Neurobiology, Babraham Cambridge UK
March 1993 **Bachelor in Veterinary Medicine**
Iwate University, Ueda, Morioka, Japan

Research Training

5/2009-present **Postdoctoral fellow**
Dept. of Biophys. and Biochem.,
The University of Tokyo, Graduate School of Science
Bunkyo-ku Tokyo 113-0032 Tokyo Japan
Mentor Dr. Hitoshi Sakano
(Major; Cell Biology, Physiology, Molecular biology)
Research involved in the neural network in olfaction

9/2006-4/2009 **Research Scientist**
Dept of Cell Biology
Duke University, Medical Center
Durham North Carolina 27710 U.S.A.
Mentor Dr. Marc G Caron
(Major; Cell Biology) Research involved in the signaling of Chimokine Receptor, CCR5 related HIV infection.

10/2001-8/2006 **Postdoctoral fellow**
Dept of Molecular Genetics and Microbiology,
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Mentor:Dr Hiroaki Matsunami

(Major; Cellular and Molecular Biology) Research involved in trafficking and functional study of mammalian odorant receptors)

4/2000-9/2001 **Postdoctoral fellow**
Department of Anatomy and Neurobiology,
Washington University School of Medicine,
St. Louis, Missouri, 63308 U.S.A.
Mentor:Drs Yi Rao and Jane Y. Wu
(Major; Cell Biology) Research involved in the axon guidance and neuronal migration in the olfactory system.

11/1998-3/2000 **Postdoctoral fellow**
Lab. for Neuronal Recognition molecules
Brain Science Institute, RIKEN,
Wako, Saitama, Japan. Metor:Dr Kensaku Mori
(Major: Anatomy and Molecular Biology): Research involved in the neurogenesis of olfactory and vomeronasal sensory neurons.

4/1998-11/1998 **Research Assistant**
Lab. for Neural Architecture,
Brain Science Institute, RIKEN,
Wako, Saitama, Japan.Mentor:Dr. Tsutomu Hashikawa.
(Major: Anatomy and Cell biology): Research involved in the mouse motor nervous system.

4/1994-3/1998 **Graduate student**
Lab. of Molecular and Cognitive Neuroscience,
Dept. of Neurobiology, The Babraham Institute,
Cambridge, U.K
Mentor:Drs. Barry E..Keverne and Piers.C.Emson
(Major: Anatomy and molecular biology): Research involved in the isolation and characterization of the odorant and pheromone receptors and their transduction cascade.

Publications

Saito H, Mainland JD, Chi Q, Zhuang H , Matsunami H Large-scale Deorphaning of a Mammalian Receptor Repertoire **Science signaling** 2009 Mar 3;2(60):ra9.

Saito H, Kubota M., Roberts RW, Chi Q and Matsunami H. RTP Family Members Induce Functional Expression of Mammalian Odorant Receptors ***Cell*** 2004 vol119: 679-91

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Saito H., Mimmack M.L., Keverne E.B., Kishimoto J., and Emson P.C.Gene expression of olfactory receptors and maturation of olfactory neurons shown by G-protein and N-CAM during development. ***Dev. Brain Res*** Vol 110:69-81. 1998

Saito H., Mimmack M.L., Keverne E.B., Kishimoto J., and Emson P.C.Isolation of vomeronasal receptors and their co-localization with specific G-protein***Mol. Brain Res.*** Vol 60 pp215-227..1998.

Mimmack M.L., **Saito H**., Evans G., Bresler M., Keverne E.B., and Emson P.C.A novel splice veriant of the cell adhesion molecule BIG-2 is expressed in the olfactory and vomeronasal neuroepithelia. ***Mol. Brain Res.*** 1997 47:345-350

Taniguchi K., **Saito H**., Okamura M., Ogawa, K.
Immunohistochemical demonstration of protein gene product 9.5 (PGP 9.5) in the primary olfactory system of the rat. ***Neurosci. Lett***., 1993 156:24-26

Proteomic analysis of odorant receptor-associated proteins in sensory axons

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The axons of olfactory sensory neurons (OSNs) expressing the same odorant receptor (OR) converge in a few glomeruli at specific locations in the olfactory bulb (OB), forming a topographic glomerular map of OR inputs. The OR expressed by the OSN determines its glomerular target. cAMP signaling downstream of ORs appears to play an important role in glomerular target choice, but it is unclear whether the relevant signaling occurs in OSN cilia, where ORs detect odorants, or elsewhere in the neuron. ORs are also present in OSN axons, raising the possibility that axonal ORs are involved in axon guidance. To investigate the role of axonal ORs, we used a combination of immunoprecipitation with anti-OR antibodies and mass spectrometry to identify OR-associated proteins in the olfactory epithelium versus OB of neonatal or adult mice. Surprisingly, we found that Gαi2, an inhibitory G-protein, co-immunoprecipitates with ORs present in neonatal OSN axons during the time of their peak synapse formation in the OB. We also identified additional proteins implicated in axon pathfinding in other systems. Furthermore, analysis of Gαi2 knockout mice showed that the absence of Gαi2 causes a change in the positions of some OR-specific glomeruli, but not others, consistent with the idea that OR interactions with Gαi2 might influence glomerular target choice.

(Funding: Howard Hughes Medical Institute, National Institutes of Health, ARCS Foundation, Poncin Scholarship Fund)

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OBJECTIVE CLINICALLY APPLICABLE RESEARCH IN NEUROSCIENCE

EDUCATION

- M.D., Ph.D., Neurobiology & Behavior, MSTP University of Washington, 2001-2010
- B.A., Molecular & Cell Biology, emphasis in Immunology, UC Berkeley, 1995-1999.

RESEARCH EXPERIENCE

Graduate Training

2003-2008, Dr. L. Buck, Fred Hutchinson Cancer Research Center
I studied how odorant receptors (OR) guide olfactory sensory neuron axons to precise locations in the olfactory bulb. We are the first to successfully isolate OR protein complexes using anti-OR antibodies and to sequence them by mass spectrometry. We discovered that an inhibitory G-protein interacts with the OR. Using knock-out and transgenic mice, we determined that the loss of function of this G-protein alters the axonal targeting in the bulb.

Lab Rotationswith

Dr. L. Buck, Fred Hutchinson Cancer Research Center, 2003, Studied the connectivity of GnRH neurons in the suprachiasmatic nucleus and possible implications on puberty onset.
Dr. R Palmiter, University of Washington, 2002, Studied the behavioral and histological effects of stimulants on Parkin knock-out mice, a genetic model for early-onset Parkinson's disease.
Dr. D. Storm, University of Washington, 2001, Studied the signaling mechanisms of odorant-stimulated plasticity of olfactory neurons when postsynaptic trophic signals are withdrawn.
1997, 1998, Dr. H. Sakano, Tokyo University, Studied the mutually exclusive expression of odorant receptor genes.

Staff Research Assistant Position

1999–2001, Dr. A. Theologis, UC Berkeley, First full genome sequencing of a plant species, A. Thaliana.

TEACHING ASSISTANCE EXPERIENCE

- **Neuropathophysiology:** undergraduate course, 2006
- **Physiology:** medical student course, 2005

AWARDS

ARCS fellowship, 2005-2008 and **Poncin Scholarship**, 2004,2005
Individual predoctoral NRSA (1 F30 NS053055-01), 2005-2009

CONFERENCES

Keystone Symposia on Molecular and Cellular Biology 2009, Poster and Abstract
Keystone Symposia on Molecular and Cellular Biology 2007, Abstract
Western Student Medical Research Forum 2002, Oral Presentation and Abstract

PUBLICATIONS

Sakano H, MacCoss MJ, Berry T, Deo M, Inokuch K, Wu C, Plummer N, Birnbaumer L, Buck LB. "An unexpected role for Gi2 in odorant receptor-directed formation of the olfactory map." *In preparation.*

Sakano H. *Odorant Receptor-Associated Proteins and Axon Pathfinding in the Mouse.* Doctoral Dissertation, 2008.

Watt WC, Sakano H, Lee ZY, Reusch JE, Trinh K, Storm DR. "Odorant stimulation enhances survival of olfactory sensory neurons via MAPK and CREB." *Neuron*, 2004 Mar; 41(6): 955-967. PMID: 15046727.

Yamada K et al., "Empirical analysis of transcriptional activity in the Arabidopsis genome." *Science*, 2003 Oct; 302(5646): 842-846. PMID: 14593172.

Arabidopsis Genome Initiative. "Analysis of the genome sequence of the flowering plant Arabidopsis thaliana." *Nature*, 2000 Dec; 408(6814): 796-815. PMID: 11130711.

Theologis A et al., "Sequence and analysis of chromosome 1 of the plant Arabidopsis thaliana." *Nature*, 2000 Dec; 408(6814): 816-820. PMID: 11130712.

Serizawa S, Ishii T, Nakatani H, Tsuboi A, Nagawa F, Asano M, Sudo K, Sakagami J, Sakano H, Ijiri T, Matsuda Y, Suzuki M, Yamamori T, Iwakura Y, Sakano H. "Mutually exclusive expression of odorant receptor transgenes." *Nature Neuroscience*, 2000 Jul; 3(7): 687-693. PMID: 10862701.

Phenotypic and molecular heterogeneity of zebrafish lateral line neurons during circuit formation

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Authors
Akira Sato, Katsushi Yamaguchi, Sumito Koshida, Shuji Shigenobu, Hiroyuki Takeda

Abstract
A common feature in biological systems is cell-to-cell variability in clonal populations arising from stochastic biochemical reactions and/or differences in microenvironments. From recent studies using unicellular organisms, stem cells and cancer cells, it is suggested that such non-genetic heterogeneity can play an essential role in development and evolution. However, experimental analyses of developing multicellular organisms often face difficulties because of their structural and numerical complexity. In this study, we adopted the zebrafish posterior lateral line (PLL), a simple sensory system comprising a small number of neurons, to analyze cell phenotypes and gene expression at single-cell resolution.

Live imaging of single PLL neurons demonstrated that the individual neurons exhibit extensively diverse behavior and morphologies during circuit formation, and they can be divided into two groups, leaders and followers. These groups not only exhibited distinct behaviors but also established different patterns of neural circuit. Furthermore, inhibiting cell-cell interaction through Notch signaling with DAPT treatment altered the proportion of leaders within the PLL ganglion. These results suggest that such phenotypic heterogeneity regulated by cell-cell interaction is important to develop a functional neural circuit.

To elucidate molecular mechanisms regulating the phenotypic heterogeneity, and to understand a process of the diversification from a homogeneous population, we are performing the single-cell gene expression profiling in this system. This analysis revealed that leaders highly express *β-actin* and *neurod* as compared to followers, and the variety in *neurod* expression level pre-exists to the differentiation into leaders and followers. This suggests that highly expression of *neurod* in part of PLL neurons activates neurogenesis, and these neurons extend their axon early, then, become leaders. Our findings may provide novel insights into the mechanisms of neural circuit formation at the single-cell level.

CURRICULUM VITAE

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Research:
My principle research interests lie in the diversification of neurons in their phenotype and gene expression at the single-cell level. I am currently investigating how cell-to-cell variation in gene expression is generated, regulated and utilized during neural circuit formation, using zebrafish lateral line system as a simple model.

Education:

April 2009 – present	Ph.D student, University of Tokyo
March 2009	M.S. in Bloloty, University of Tokyo
March 2007	B.S. in Biology, University of Tokyo

Experience:

April 2009 – present	JSPS Research Fellow

‘Analysis of Neural Circuit Formation in the Zebrafish Lateral Line System (ゼブラフィッシュ側線神経系をモデルとした神経回路形成機構の解析)’

Publication:
Single-cell analysis of somatotopic map formation in the zebrafish lateral line system, Developmental Dynamics, 2010, 2058-2065

Presentations (selected):

August 2011	International Conference on Systems Biology, ‘Phenotypic and molecular heterogeneity of zebrafish lateral line neurons during circuit formation’
May 2011	Annual Meeting of the Japanese Society for Developmental Biologists, ‘Phenotypic and molecular heterogeneity of zebrafish lateral line neurons during circuit formation’
November 2010	Annual Meeting of the Japanese Society for Quantitative Biology, ‘Fluctuation in cellular phenotypes and gene expression among zebrafish lateral line neurons’
May 2010	Joint Meeting of the French and Japanese Societies for Developmental Biology, ‘Single-Cell Analysis of Somatotopic Map Formation in the Zebrafish Lateral Line System’

Hunting for Genes that Regulate Remodeling and Life-long Maintenance of Dendritic Arbors

Kohei Shimono
Kyoto University

Kohei Shimono, Takafumi Nomura, Tadao Usui, and Tadashi Uemura

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Neurons develop distinctive dendritic morphologies to receive and process sensory or synaptic inputs. Dendritic arbors that are formed in early development are often reorganized and such arbors of many neuronal types are possibly maintained throughout animal life. To genetically investigate underlying mechanisms of this remodeling and maintenance in vivo, we have employed dendritic arborization (da) neurons, which exhibit dramatic dendritic pruning and subsequent growth during metamorphosis, as a model system. We first identified da neurons in the adult *Drosophila* abdomen and then clarified developmental basis of these adult neurons by tracing origins of those cells back to the larval stage. We and others also showed that the dendritic arbor of one da neuron, v'ada, exhibited prominent radial-to-lattice transformation in one day after eclosion, and the resultant lattice-shaped arbor persisted throughout adult life.

To conduct a MARCM screening efficiently, we expressed FLP recombinase in sensory organ precursors (SOPs). By using this 'SOP-FLP' system, we isolated several mutants that displayed defects in the remodeling and/or the life-long maintenance of dendritic arbors. To identify causative genes for these mutants, we have started employing a next-generation sequencing technique to directly compare whole-genomic sequences of several mutants with each other, in addition to conventional mapping methods. In this poster, we will discuss our on-going screening and mapping.

Kohei Shimono (下野耕平)

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Education:

2009 Apr. - Present	Doctoral course, Graduate School of Biostudies, Kyoto University
2007 Apr. - 2009 Mar	Master's course, Graduate School of Biostudies, Kyoto University
2003 Apr. - 2007 Mar	Faculty of Science, Kyoto University

Research experience:

2009 Apr. - Present	The Research Fellow of the Japan Society for the Promotion of Science for Young Scientists

Awards:

1. The Best Poster Presentation Award
The 9th International Student Seminar, Kyoto, Japan, March 8, 2011

Publication:

1. The seven-pass transmembrane cadherin Flamingo controls dendritic self-avoidance via its binding to a LIM domain protein, Espinas, in Drosophila sensory neurons.
Matsubara D, Horiuchi SY, Shimono K, Usui T, Uemura T.
Genes Dev. 2011 Sep 15;25(18):1982-96.

2. Computational modeling of dendritic tiling by diffusible extracellular suppressor.
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Neural activity in cortical area V4 underlies fine stereoscopic depth perception

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Primates are capable of discriminating depth with remarkable precision using binocular disparity. Neurons in area V4 are selective for relative disparity, which is the crucial visual cue for discrimination of fine disparity. Here, we investigated the contribution of V4 neurons to fine disparity discrimination. Monkeys discriminated whether the center disk of a dynamic random-dot stereogram was in front of or behind its surrounding annulus. We first recorded single-unit responses from V4 while the monkeys were performing the task. Neuronal thresholds were higher than the behavioral thresholds on average. The most sensitive neurons reached thresholds as low as the psychophysical thresholds. For subthreshold disparities, the monkeys made frequent errors. The variable decisions were predictable from the fluctuation in the neuronal responses. The predictions were based on a decision model in which each V4 neuron transmits the evidence for the disparity it prefers. We then altered the disparity representation artificially by means of microstimulation to V4. The decisions were systematically biased when microstimulation boosted the V4 responses. The bias was toward the direction predicted from the decision model. Taken together, we suggest that disparity signals carried by V4 neurons underlie precise discrimination of fine stereoscopic depth.

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Shiozaki H, Motonaga T, Tamura H, Fujita I “Pairwise maximum entropy models explain correlated activity of neural populations in the inferior temporal cortex of macaque monkeys” The Society for Neuroscience 40th Annual Meeting, 372.12, San Diego, USA, November, 2010

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An Auditory Field in the Mouse Insular Cortex

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Previous research has identified five auditory fields in mouse auditory cortex, including the primary field (AI) and the anterior auditory field (AAF). Using a voltage‐sensitive‐dye‐based imaging technique, here we confirmed the existence of AI and AAF by examining the tonotopy in each field. Further, we identified a previously unreported insular auditory field (IAF) located rostral to known auditory fields. Pure tone evoked responses in IAF exhibited the shortest latency among all auditory fields at lower frequencies. A rostroventral to dorsocaudal frequency gradient was consistently observed in the IAF in all animals examined. Neither response amplitude nor response duration changed with frequency in the IAF, but the area of activation exhibited a significant increase with decreasing tone frequency. Taken together, the current results indicate the existence of an IAF in mice, with characteristics suggesting a role in

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Regulation of cellular excitability is critical for neuronal migration

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Regulation of excitability is crucial for both mature and developing neural circuit. Excitability of neurons in the developing cerebral cortex is tightly regulated. Previous studies have shown that immature cortical neurons such as those during migration are less excitable, mainly due to low-level expression of sodium channels. It is proposed that hyperexcitability during development has adverse effects on the formation of cortical circuits; however, how increased cellular excitability affects developmental processes such as migration remains unknown.

Here, we examined the effect of hyperexcitability on the development of layer 2/3 cortical neurons in vivo. Prokaryotic voltage-gated sodium channel NaChBac, a genetic tool for increasing excitability, was ectopically expressed with a fluorescent marker (GFP or RFP) in mouse layer 2/3 cortical neurons, and their morphology and electrophysiological properties were examined. Patch clamp recordings from fluorescently labeled migrating neurons showed little or no voltage-dependent inward current in control neurons (expressing only GFP), but large current in NaChBac expressing neurons. This result suggests that ectopically expressed NaChBac is functional in layer 2/3 cortical neurons. NaChBac expressing neurons showed severe migration defects: many neurons were located in the intermediate zone/lower cortical layers at postnatal day 3 (P3) when almost all control neurons already reached the upper cortical layers. Interestingly, migrating neurons expressing NaChBac had dendritic branches. This result implies that NaChBac expressing neurons start dendrite formation before migration is completed. Migration defects were not observed by expression of a channel pore-dead mutant and mutants whose voltage-dependency is positively shifted, suggesting that migration defects were caused by ion channel function of NaChBac. These results together suggest that regulation of cellular excitability is critical for neuronal migration; for proper migration, it may be important to keep cellular excitability at a low level.

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2. Hayashi Y, **Tagawa Y**, Yawata S, Nakanishi S, Funabiki K. Spatio-temporal control of neural activity *in vivo* using fluorescence microendoscopy. (submitted)
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Pheromone Processing in Fly Brain

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Animals need to make a proper decision to find right mates. Drosophila serves as a great model to study this question because of its rich genetic tools and innate sets of robust and well-described mating behavior.

The female-specific pheromone 7, 11-heptacosadiene (7, 11-HD) is a potent stimulator of male courtship, but little is known about the neurons that detect and process this signal. Here, we identify a set of gustatory neurons that co-express *pickpocket 23* (*ppk23*) and *fruitless* (*fru*) as candidate sensory neurons for the detection of 7,11-HD. Silencing these neurons with tetanus toxin (TNT) or K+ channel rectifier protein (Kir2.1) reduces male courtship to females, as well as to males that have been perfumed with 7,11-HD. Conversely, artificial activation of these neurons with TrpA1, a heat sensitive cation channel, or NaChBaCh, a Na+ channel of bacteria, induces male to court other male, mimicking the effect of perfuming them with 7, 11-HD. Moreover, extracellular bristle recordings show that these neurons fire upon 7, 11-HD application.

These *fru*+/ *ppk23*+ neurons send sexually dimorphic projections to the prothoracic ganglion in ventral nerve cord. We used the GRASP method to identify three classes of *fru*+ candidate second-order neurons: vAB3, vAB3_2 and dAB2. Activation of vAB3/ vAB3_2 induces courtship toward male, mimicking both activation of *ppk23+/ fru*+ neurons and 7, 11-HD exposure. In the future, we will silence these neurons to see if they are also required for behavioral responses to 7, 11-HD, and perform physiological assays to test their response to this pheromone.

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PUBLICATIONS

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Sensory input regulates differentiation of a specific subtype of newborn interneurons via 5T4 glycoprotein in the mouse olfactory bulb

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Sensory input has been shown to regulate development in a variety of species and in various structures, including the retina, cortex and olfactory bulb (OB). Within the mammalian OB specifically, the development of dendrites in mitral/tufted cells is well known to be odor-evoked activity-dependent. However, little is known about the developmental role of sensory input in the other major OB population of the GABAgenic interneurons, such as granule cells and periglomerular cells. Here, we identified, with DNA microarray and in situ hybridization screenings, a trophoblast glycoprotein gene, 5T4, whose expression in the OB interneurons is dependent on sensory input. 5T4 is a type I membrane protein, whose extracellular domain contains seven leucine-rich repeats (LRR) flanked by characteristic LRR-N- and C-flanking regions, and a cytoplasmic domain. 5T4 overexpression in the newborn OB interneurons facilitated their dendritic arborization even under the sensory input-deprived condition. By contrast, both 5T4 knockdown with RNAi and 5T4 knockout with mice resulted in a significant reduction in the dendritic arborization of OB interneurons. Further, we identified the amino-acid sequence in the 5T4 cytoplasmic domain that is necessary and sufficient for the sensory input-dependent dendritic shaping of specific neuronal subtypes in the OB. Thus, these results demonstrate that 5T4 glycoprotein is one of molecules that regulate the activity-dependent dendritic differentiation of interneurons and the formation of functional neural circuitry in the OB.

Keywords: dendritic arborization, granule cells, olfactory bulb, activity dependent, 5T4 glycoprotein

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PUBLICATIONS

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2. Takeuchi H, Inokuchi K, Aoki M, Suto F, **Tsuboi A**, Matsuda I, Suzuki M, Aiba A, Serizawa S, Yoshihara Y, Fujisawa H and Sakano H: Sequential arrival and graded secretion of Sema3F by olfactory neuron axons specify map topography at the bulb. **Cell** 141**:** 1056-1067 (2010).

3. Takahashi H, Yoshihara S, Nishizumi H and **Tsuboi A**: Neuropilin-2 is required for the proper targeting of ventral glomeruli in the mouse olfactory bulb. **Molecular and Cellular Neuroscience** 44**:** 233-245 (2010).

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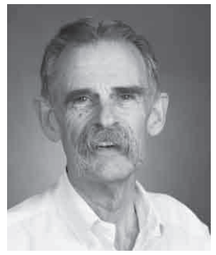

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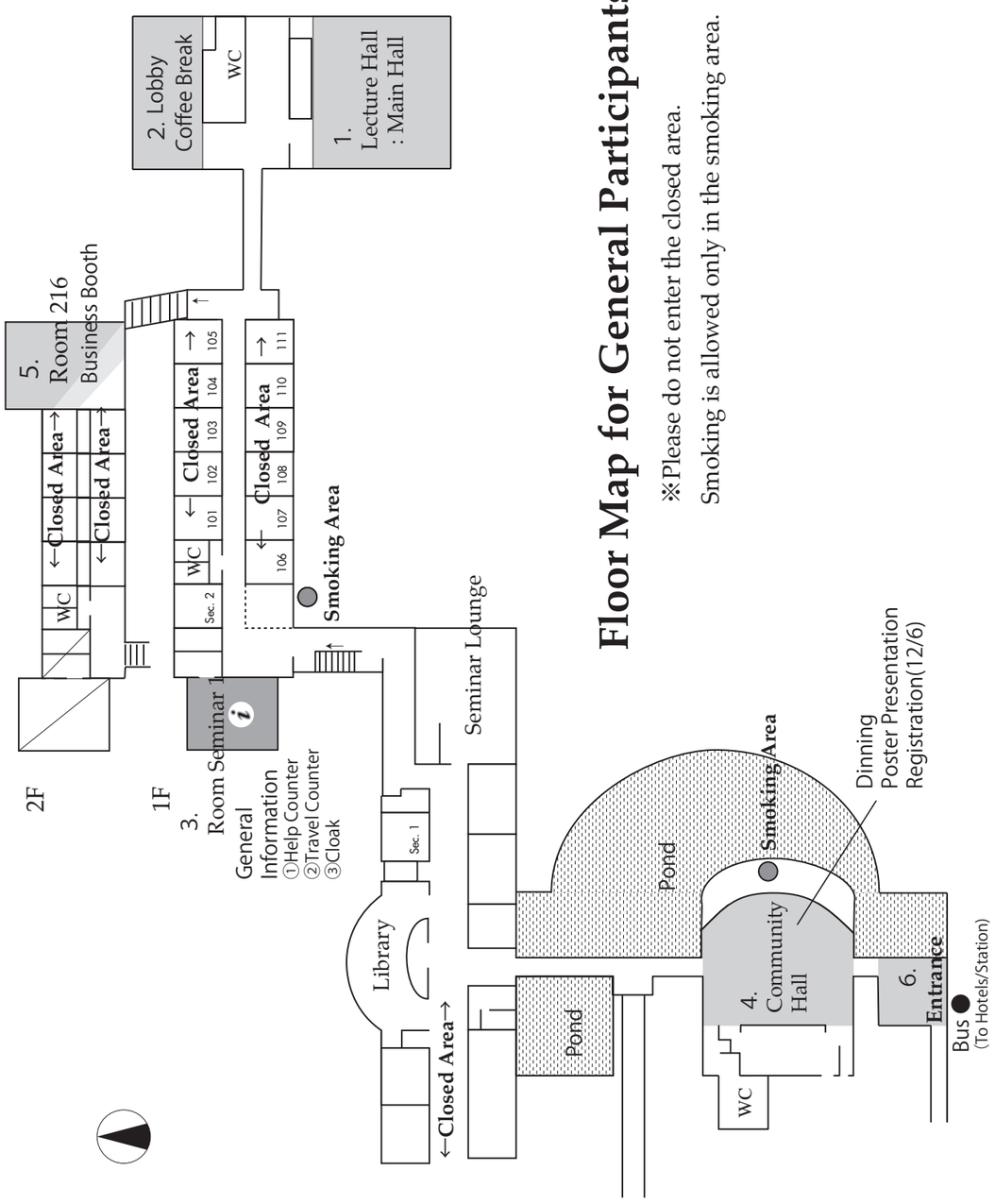
Site Information

Floor Map for General Participants

※Please do not enter the closed area.
Smoking is allowed only in the smoking area.



Site Information

1. Lecture Hall : Main Hall

Oral presentations and discussions will take place in the Lecture Hall.
The Hall will be closed after the meeting.

Capacity	About 100 seats
Equipment	Screen/Projector /PC(Mac/Window)/Cable Microphone Wireless Microphone/Pointer/White Board/ * Equipped with neither Cable nor Wireless LAN

* During the Presentations, no audio or visual recording and no photography is allowed.
* Please leave your oversized luggage at the cloak desk in Room Seminar 1.
* To all speakers, please contact our staff well enough before the start of your presentation using the lunch or other break time to let them know the equipment you will require.
  Staff will assist with any compatibility issues.

2. Lobby : Coffee Break

A beverage counter is available; please help yourself to the free drinks.

Time available	AM9:00~ end of the lecture
Beverage	Mineral water, Tea, Coffee, Green tea

3. Room Seminar 1 : General Information / Late Registration(Dec 7th(Wed)-9th(Fri))

Secretariat is open throughout the conference according to the Date and Time shown below.

Outline

① Help counter: General information about the Conference.
Photocopying, FAX transmissions
Equipment rental
Taxi call
Medical emergencies
Lost and found

② Travel counter: Staff from Kinki Nippon Tourist will assist you with your travel arrangement.

Office hour ① ②	Dec 6th(Tue) PM2:00 ~ PM7:00 Dec 7th(Wed) AM9:00 ~ PM5:30 Dec 8th(Thu) AM9:00 ~ PM7:00 Dec 9th(Fri) AM9:00 ~ PM6:00

③ Cloak : You can check in your luggage and coats.

Office hour ③	Dec 6th(Tue) PM2:00 ~ PM8:40 Dec 7th(Wed) AM9:00 ~ PM5:30 Dec 8th(Thu) AM9:00 ~ PM8:40 Dec 9th(Fri) AM9:00 ~ PM6:00
Note	We recommend that you check in your luggage and coats as aisles are narrow and space is limited.

4. Community Hall : Registration(Dec 6th) / Poster Presentation / Dinning

All participants are required to register on Dec 6th.
Posters are displayed throughout the conference.
Meals will be served in the Community Hall. Details are shown below.

Registration

Date and Time	Dec 6th(Tue) PM2:00 ~ PM3:00
Note	You can register at Room Seminar 1 after PM 3:30 on Dec 6th(Tue).

Poster Presentation

Displaying Period	Dec 6th(Tue) PM3:00 ~ Dec 9th(Fri)PM5:30
Poster Presentation	Dec 8th(Thu) PM5:00 ~ PM6:30

Lunch

Date and Time	Dec 7th(Wed) - 9th(Fr)) AM12:00 ~ PM2:00
	Buffet style/Beverage

Dinner

Date and Time	Dec 6th(Tue) & 8th(Thu) PM6:30 ~ PM8:30
	Buffet style/Beverage

Breakfast

Date and Time	Dec 7th(Wed) - 9th(Fri) AM9:00 ~ AM11:00
	Limited number of sandwich packs and beverage available

5. Room 216 : Business Booth

Please feel free to use Room 216 for Internet connections, e-mailing, and so on. You can also use this room as your own work space.
Free beverage is available.

Time available	AM9:00 ~ end of the lecture
Capacity	About 30 seats
Equipment	Cable LAN/ Beverage

6. Entrance

Time schedules of the bus service to leave the IIAS for related hotels and stations are shown below.

To Hotel Granvia Kyoto

Departure-time	PM 8:40 on Dec 6th(Tue) PM 5:30 on Dec 7th(Wed) PM 8:40 on Dec 8th(Thu) PM 5:50 on Dec 9th(Fri)
Capacity	About 40 ~ 50 seats

To Kintetsu Shin-Hosono Station/JR Hosono Station

Departure-time	PM 8:45 on Dec 6th(Tue) PM 5:35 on Dec 7th(Wed) PM 8:45 on Dec 8th(Thu) PM 5:55 on Dec 9th(Fri)
Capacity	About 30 seats

To Keihanna Plaza Hotel

Departure-time	PM 8:45 on Dec 6th(Tue) PM 5:35 on Dec 7th(Wed) PM 8:45 on Dec 8th(Thu) PM 5:55 on Dec 9th(Fri)
Capacity	About 30 seats

財団法人
国際高等研究所 International Institute for Advanced Studies

Incorporation

- August 22, 1984
Authorized incorporation of the Foundation
- October 1, 1993
Opening of the Institute

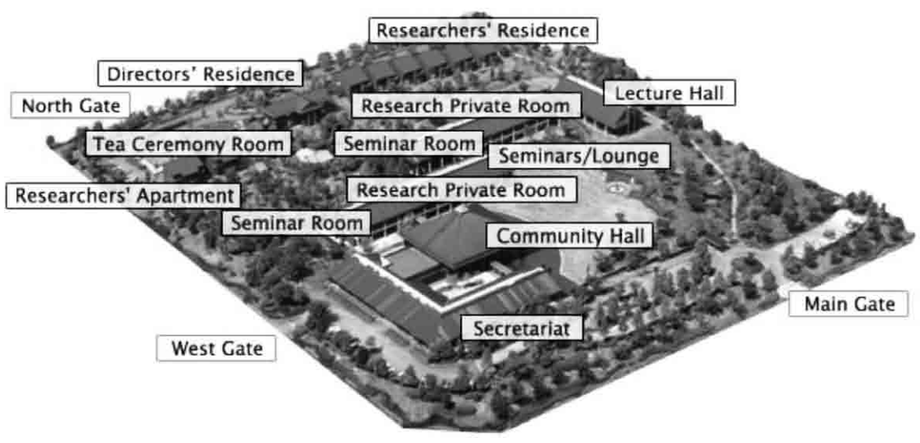
The International Institute for Advanced Studies (IIAS) was established as a foundation in 1984 with the strong support of national and local governments, industrial sectors, and the academic community in Japan.

Overview of Facilities

- Total area:
4ha, Total Floor Space : 6,000㎡

- Major Facilities:
Administration building, community hall, research buildings A and B (library, seminar lounge, 2 seminar rooms, 26 research rooms, large research room, Japanese-style room, etc.), lecture hall (hall with about 120 seats, and lounge)

- Annexed Facilities:
Director's residence, 6 family type houses, 1 single person apartment building consisting of 8 rooms, tea ceremony room



The land is loaned by Kyoto Prefecture free of charge. Construction funds for the facilities (including the garden) were privately donated by the founder of OMRON Corporation, Mr. Kazuma Tateishi and his son Mr. Takao Tateishi, and assistance from Kintetsu Corporation was received. The tea ceremony room was donated by Sen Genshitsu, Grand Master and the former head of Urasenke.

Basic Philosophy and Objectives

Basic Philosophy (Summary)
We study "what we should study for the future and happiness of human beings."

The philosophy and objectives of the IIAS are "to gather global wisdom, create and propose firm ideas as guidelines for the future of human beings" generated and proposed by the "Okuda Round Table" in 1982, and this spirit has been inherited continuously until now.

How should we cope with the various issues that arise from the historical and social background in which we live? What should the proper posture be for culture, science and technology in the 21st century?

The philosophy of the IIAS administration is that we should create new perspectives in academic world, aim to create new concepts, combine global wisdom, and contribute widely to the development of world culture by pursuing research on basic sciences and the humanities.

Objectives

The objectives of the IIAS activity are to contribute to the development of novel advanced research fields and topics, based on the close collaboration and exchange of first-class scientists and scholars from worldwide academia.

Research

Policy for Research Projects

The International Institute for Advanced Studies offers the greatest features for providing forums for mutual understanding and close contacts among researchers in different academic disciplines. Based on this feature, the IIAS has the principal research objectives of excavating and developing new realms of sciences and the humanities for the next generation by accumulation of knowledge in many academic fields through interaction of outstanding researchers.

After reorganization of national universities and national research institutes as corporations, a significantly larger ratio of research expenses is provided by competitive funding. Under the justification of promotion of science and technology, large research funding is granted to particular tasks and fields of national policies, and as a result, there is a growing tendency that researchers are concentrated in such particular tasks and fields. Considering the situation in which Japan is now placed, it is undoubtedly necessary to promote such "problem solving type" research, but if too much focus continues to be placed on "problem solving type" research as we are witnessing now, while detailed knowledge can be accumulated in particular fields, such knowledge will eventually be depleted. This is because under such conditions, we cannot expect breakthroughs that create new concepts and large scale developments in the sciences.

In contrast, research based on the idea of individual researchers is "problem excavation-type" research, which is basic academic study. In many cases, new tasks (new realms of sciences) of "problem solving type" research emerges from the results and knowledge of "problem excavation-type" research. Therefore, it is necessary to maintain a balance between "problem solving type" research and "problem excavation-type" research.

Under such circumstances in Japan, our research projects have a great significance in that they could explore, discover and develop new realms of sciences for the next generation beyond even the boundaries of natural science and the humanities or social sciences. By providing a forum for discussion among outstanding researchers both in Japan and overseas through our research projects and/or conferences, we want to transmit not only research results and novel information to Japan and overseas but also to present to researchers and academic societies, the possibility of development of sciences and important issues for the future of sciences.

Research Planning Committee

The Research Planning Committee is comprised of the Director, Vice Directors and Academic Councilors (limited to 10 persons), which clarifies the basic idea and contents of the core research projects of the International Institute for Advanced Studies and promotes research projects under strong leadership.

Main functions of the Committee are as follows.
- Development of research projects and appointment of their principal investigators
- Theme setting and appointment of organizers for IIAS Conferences
- Investigation of trends in sciences and what research subjects should be taken into account and their prospects
- Selection of members of Research Promotion Committee and Fellows, etc.
- In addition, review of various tasks related to research activities of the IIAS according to referrals of the Director or proposals to the Director

Research Promotion Committee

Research Promotion Committee is comprised of Vice Directors and outside prestigious experts in a variety of fields (within 15 persons), which will put into practice the action plans of the matters determined by the Research Planning Committee.
Main functions of the Committee are as follows.
- Assistance to Director and Vice Directors in relation to promotion of research projects and comprehension and evaluation of the progress of research projects
- Development of implementation plan of IIAS Conference
- In addition, responses to various tasks related to research activities of the IIAS

Working groups will be established from time to time whenever necessary for carrying out individual tasks.

Contact

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FAX: +81-774-73-4005
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E-mail: www_admin@iias.or.jp