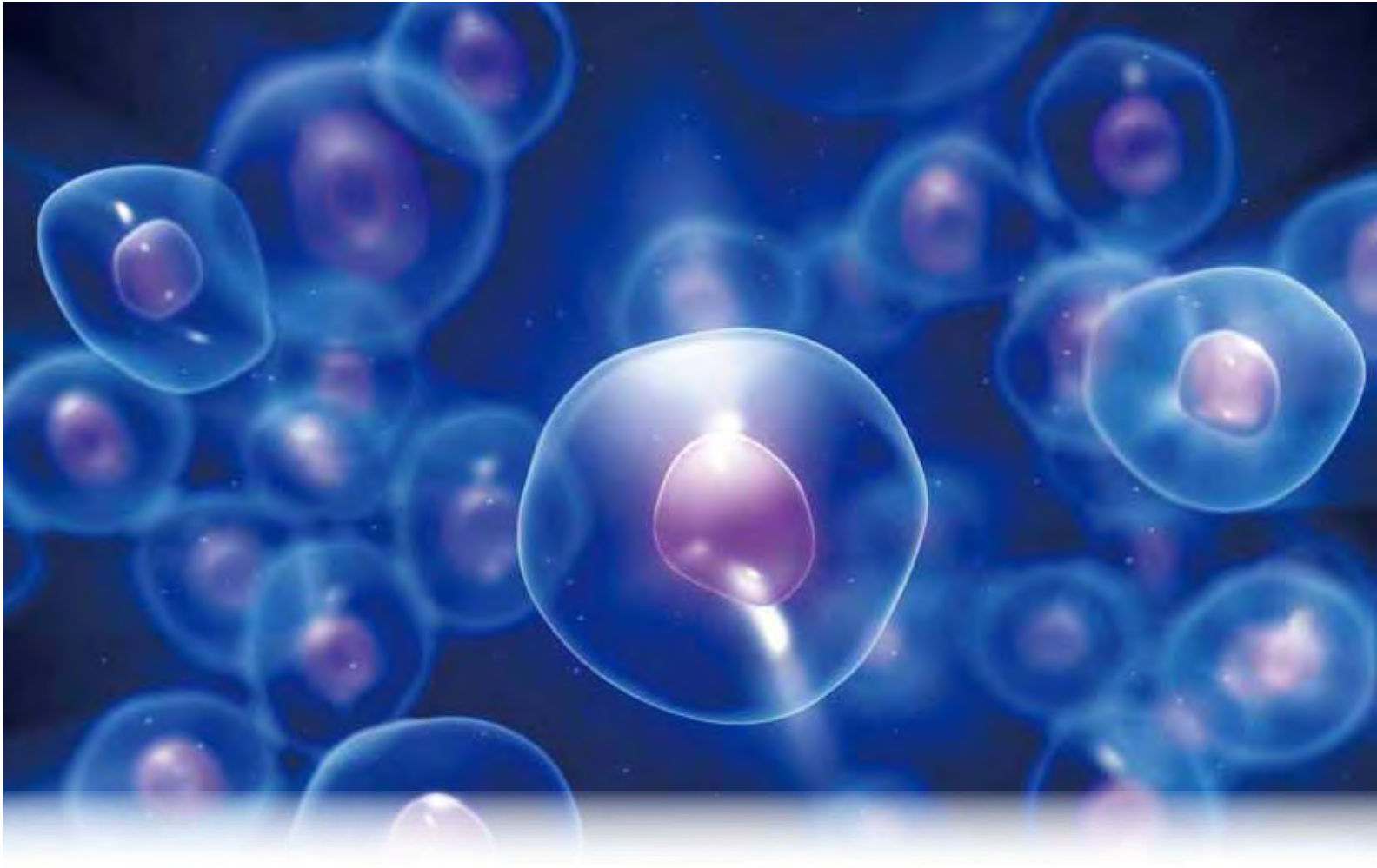


最先端研究開発支援プログラム（FIRST）
「心を生み出す神経基盤の遺伝学的解析の戦略的展開」国際シンポジウム

「幹細胞から見た神経発生」

Neural Development: Stem Cell Perspective

2012年1月17日(火) 9:30～17:40 (開場 9:00)
1月18日(水) 9:00～15:00 (開場 8:30)

慶應義塾大学 三田キャンパス 北館ホール

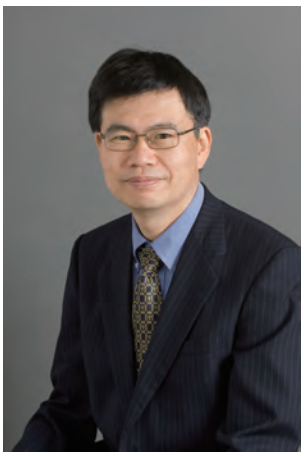
主　　催：理化学研究所　駐日英国大使館
共　　催：慶應義塾大学　実験動物中央研究所
後　　援：内閣府　文部科学省　慶應義塾大学－理化学研究所 人間知性研究センター
　　慶應義塾大学グローバルCOEプログラム「幹細胞医学のための教育研究拠点」
オーガナイザー：岡野 栄之（慶應義塾大学医学部）　佐々木 えりか（実験動物中央研究所）

Greetings

This project, ” Strategic Exploitation of Neuro-Genetics for Emergence of the Mind” (Core researcher:Hideyuki Okano, Keio University School of Medicine) was launched in 2009, with funding from the Japanese government and support from Keio University, the Central Institute for Experimental Animals and the RIKEN Brain Science Institute. This funding is a part of large-scale undertaking by Japanese government to keep Japan at the forefront of global scientific research through encouraging milestone projects that will benefit the world.

We aim to identify the mechanisms of neuro-genetics for mind and high-level functioning in this project utilizing various new research methods such as genetic engineering technology on common marmosets. The entire symposium focuses on the technical aspects of creating model animals and investigates neural development from a stem cell perspective. We consider this a significant opportunity to discuss the technical methods with active leading-edge participants in the field.

We would like to thank the British Embassy Tokyo for supporting the organization of this symposium, and we hope to further develop and reinforce our global research links with our peers in the world, in particular with the U.K.



Core Researcher: Hideyuki Okano

Chair of Keio University Graduate School of Medicine
Professor, Keio University School of Medicine
Team Leader, RIKEN-Keio Univ. Joint Research Laboratory

International Symposium

Neural Development: Stem Cell Perspective

Date：Tuesday-Thursday, 17～18January 2012

Venue: Kita-kan Hall, Keio University Mita Campus

<Program>

Day 1:　Tuesday, 17 January

Opening Remarks

09:30　Dr. Tasuku Honjo, Professor, Kyoto University
　　Former Executive Member, Council for Science and Technology Policy (CSTP), Cabinet Office

09:35　British Embassy Tokyo

09:40　Hideyuki Okano, Core Researcher, FIRST

I. Stem cells and their Pluripotency

Chair: Jennifer Nichols & Hitoshi Niwa

10:00　Jennifer Nichols (University of Cambridge)

10:30　Hitoshi Niwa (RIKEN CDB)

11:00　＜Break＞

11:20　Toru Nakano (Osaka University)

11:50　Toshiaki Noce (Keio Advanced Research Centers)

12:20　＜Lunch＞

II. Germline Stem Cells and their Differential Regulation: towards Production of Recombinant Model Animals

Chair: Penato Liu & Erika Sasaki

13:30　Pentao Liu (Wellcome Trust Sanger Institute)

14:00　Shoukhrat Mitalipov (Oregon Health and Science University, USA)

14:30　Erika Sasaki (Central Institute for Experimental Animals, Keio University)

15:00　＜Coffee Break＞

III. Stem Cells and Their Asymmetric Cell Divisions

Chair: Andrea Brand & Fumio Matsuzaki

15:30 Andrea Brand (University of Cambridge)
16:00 Fumio Matsuzaki (RIKEN CDB)

16:30 ＜Break＞

16:40 Panel Discussion
Coordinator: Hirotaka James Okano (Jikei University School of Medicine)
17:40 close

Day 2: Wednesday, 18 January

IV. Neural Induction and Neural Circuit Formation

Chair: Shigeyoshi Itohara & John Parnavelas

09:00 Shigeyoshi Itohara(RIKEN BSI)
09:30 John Parnavelas (University College London)

10:00 ＜Break＞

V. Cortical Development and Neural Disorder

Chair: William Richardson & Hideyuki Okano

10:20 William Richardson (University College London)
10:50 Tomomi Shimogori (RIKEN BSI)
11:20 Takaki Miyata (Nagoya University)

11:50 ＜Lunch＞

13:00 Byoung-Il Bae (Children's Hospital Boston, Harvard Medical School)
13:30 Hideyuki Okano (Keio University & RIKEN BSI)
14:15 Panel Discussion
Coordinator: Hirotaka James Okano (Jikei University School of Medicine)
15:00 Closing Remarks
Atsushi Seike, President, Keio University

Capturing and characterising naïve pluripotency in early mammalian embryos

Jennifer Nichols

Wellcome Trust Centre for Stem Cell Research, University of Cambridge, UK

Embryonic stem (ES) cells derived from blastocysts of mice and humans differ in their morphology, culture requirements and molecular profile. However, pluripotent cell lines produced from post-implantation mouse epiblasts resemble human ES cells (Tesar et al., 2007). Therefore, it is postulated that during the derivation process explanted human embryos progress to a post-implantation-like state that is primed for differentiation, whereas explanted mouse blastocysts can be captured in a naïve, pre-implantation-like state (Nichols and Smith, 2009). The efficiency of capturing this state can be significantly improved by inhibiting the Erk and GSK3 pathways during culture of mouse embryos (Ying et al., 2008), but so far no naïve human ES cells have been derived directly from blastocysts using this regime, suggesting that the control of developmental progression differs between these species. We have previously shown that multiple ES cell clones can be derived from peri-implantation mouse epiblasts by plating single cells into medium supplemented with Erk and GSK3 inhibitors (Nichols et al., 2009). We are currently applying this system to establish the timing of acquisition and loss of ES cell forming ability from single cells from the blastocyst to early post-implantation stages in order to define the mechanism by which naïve pluripotency is established. In parallel, we are using single cell molecular profiling to create a blueprint for naïve pluripotency in the mouse which we will use to probe for an equivalent state in primate embryos. We hope to use the results to devise more informed protocols for the derivation of naïve ES cells from other mammals, including humans.

References

Nichols, J., Silva, J., Roode, M. and Smith, A. (2009). Suppression of Erk signalling promotes ground state pluripotency in the mouse embryo. *Development* **136**, 3215-22.

Nichols, J. and Smith, A. (2009). Naive and primed pluripotent states. *Cell Stem Cell* **4**, 487-92.

Tesar, P. J., Chenoweth, J. G., Brook, F. A., Davies, T. J., Evans, E. P., Mack, D. L., Gardner, R. L. and McKay, R. D. (2007). New cell lines from mouse epiblast share defining features with human embryonic stem cells. *Nature* **448**, 196-9.

Ying, Q. L., Wray, J., Nichols, J., Batlle-Morera, L., Doble, B., Woodgett, J., Cohen, P. and Smith, A. (2008). The ground state of embryonic stem cell self-renewal. *Nature* **453**, 519-23.

JENNIFER NICHOLS, CURRICULUM VITAE

Career history

2006-present: Group Leader, Wellcome Trust Centre for Stem Cell Research, University of Cambridge.

1995-2006: Post-Doctoral Research Fellow with Professor Austin Smith, University of Edinburgh.

1990-1995: Research Assistant/Graduate Student with Dr. Austin Smith, University of Edinburgh.

1981-1990: Research Assistant to Professor Richard Gardner, Oxford University.

Qualification

PhD (1995, University of Edinburgh)
'A Study of the Expression and Function of Differentiation Inhibiting Activity and its Receptor in the Early Mouse Embryo'

Research Interests

Mechanisms that establish and maintain pluripotency in the early embryo and during the formation of embryonic stem cells in mammals

Additional Responsibilities

Academic coordinator of transgenics facility for the Cambridge Stem Cell Intitiative
Member of ethics review committee, University of Cambridge
Committee member of British Society for Developmental Biology
Co-organiser of 'ES cells as a model for mammalian development' workshops in Latin America since 2006
Organiser of ES cell derivation course and workshop, July 2010
Teaching on various international courses
Undergraduate and graduate student teaching and supervision in Cambridge and abroad

Awards

NC3Rs '3Rs' prize 2009 for research to reduce, refine or replace the use of animals in biomedical research, £10,000
Elected Fellow of the Society of Biology, 2010

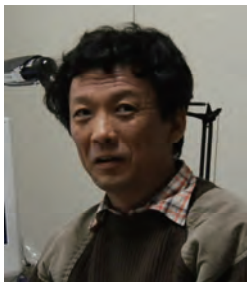
Pluripotency-associated transcription factor network

Hitoshi Niwa
Laboratory for Pluripotent Stem Cell Studies,
RIKEN Center for Developmental Biology

The generation of induced pluripotent stem (iPS) cells by introduction of 4 transcription factors into somatic cells revealed that the transcription factors have primary role to determine pluripotency. Moreover, since the introduced transgenes are silenced in the resulting iPS cells, it is suggested that the exogenous transcription factors act as switches to turn on the endogenous transcription factor genes, which form the autonomous network to maintain their expressions in the exogenous signal-dependent manner. We have analyzed the character of the pluripotency-associated transcription factor network in mouse embryonic stem (ES) cells. Mouse ES cells continue self-renewal in the presence of the cytokine leukemia inhibitory factor (LIF). We previously confirmed the function of the canonical pathway composed by Jak kinases and Stat3, but recently found that the LIF signal integrates into the transcription factor network via three intracellular signal transduction pathways including PI3K-Akt and MAPK pathways. Why is the network so complex? One possible answer is that the complex structure of the network contributes to make binary decisions of pluripotent stem cells to self-renew or differentiate with canceling the noise of signal integration. Now we are trying to dissect the network structure more precisely by analyzing the functions of each components as well as monitoring the dynamics in the time course of differentiation after withdrawal of LIF or perturbation of particular component. I will introduce our recent progress in this field.

CURRICULUM VITAE

Hitoshi Niwa
Laboratory for Pluripotent Stem Cell Studies, RIKEN Center for Developmental Biology



1983-1989	Nara Medical University (MD)
1989-1993	Kumamoto University Graduate School of Medicine (PhD)
1993-1994	Research Associate, Department of Developmental Genetics, Institute of Molecular Embryology and Genetics, Kumamoto University School of Medicine
1994-1996	Postdoctoral Fellow, Centre for Genome Research, University of Edinburgh
1996-2001	Research Assiociate, Department of Nutrition and Physiological Chemistry, Osaka University Graduate School of Medicine
2001-	Laboratory Head, Laboratory for Pluripotent Cell Studies, RIKEN Center for Developmental Biology
2002-	A guest professor, Laboratory for Developmental and Regenerative Medicine, Kobe University Graduate School of Medicine
2009-	Project Leader, Laboratory for Pluripotent Stem Cell Studies, RIKEN CDB

DNA Methylation and Hydroxymethylation in Development

Toru Nakano, M.D.
Osaka University

Epigenetic regulation, which plays pivotal roles in development and cell differentiation, consists of DNA and histone modifications. In contrast to various histone modifications, methylation of 57 position of cytosine (5MC) had been known as only one kind of DNA modification for long time. Drastic change of DNA methylation, namely global DNA demethylation, takes place for capturing totipotency soon after fertilization. During this process, demethylation of maternal genome is delayed by the phenomenon of “epigenetic asymmetry” and some genes such as IAP retrotransposons and imprinted genes are escaped from the so called “active demethylation” process. We revealed that methylation of maternal genome and these genes was protected by PGC7/Stella, a maternal factor essential for early embryogenesis, from active demethylation. For the protection, PGC7/Stella recognizes chromatin containing di-methylated lysine 9 of histone H3 (H3K9me2).
Recently, another DNA modification, hydroxymethylation of 5’ position of cytonsine, has emerged as a major issue of active DNA demethylation. Several reports strongly suggest that Tet enzymes catalyze hydroxylation of methylated cytosine and the resultant 5-hydroxymethyl cytosine (5HmC) is an intermediate of active demethylation. Among three Tet’s (Tet1 ~ Tet3), early embryos mainly express Tet3 and the enzyme is essential for the active demethylation. Nuclear localization of Tet3 is also regulated by PGC7/Stella via binding of PGC7/Stella to H3K9me2 and is required for the appropriate DNA demethylation in early embryogenesis. In addition to the zygotes, the data of function of Tet in fetal glia cell differentiation will be presented and discussed (in collaboration with Prof. Tetsuya Taga of Tokyo Medical and Dental University)

<References>

Nakamura T, Arai Y, Umehara H, Masuhara M, Kimura T, Taniguchi H, Sekimoto T, Ikawa M, Yoneda Y, Okabe M, Tanaka S, Shiota K, Nakano T
PGC7/Stella protects against DNA demethylation in early embryogenesis
Nature Cell Biol, 9: 64-71, 2007

Wossidlo M, Nakamura T, Lepikhov K, Marques J, Zakhartchenko V, Boiani M, Arand J, Nakano T, Reik W, Walter J
5-hydroxymethylcytosine in the mammalian zygote is linked with epigenetic reprogramming *Nature Commun,* 2:241, 2011

Curriculum Vitae

Toru Nakano, M.D.
Professor
Department of Pathology,
Osaka University Medical School

Toru Nakano is a Professor of the Department of Pathology, Osaka University Medical School, Osaka Japan. He received his M.D. from Osaka University Medical School in 1981. After working as a physician for three years, he worked from 1984 to 1988 at the Medical School where he was engaged in the transplantation experiments of mast cells and hematopoietic stem cells. From 1989, he joined to European Molecular Biology Laboratory (EMBL) as a visiting scientist and was involved in the viral leukemogenesis of chicken. As a staff scientist, he next went on to work, first as an assistant professor (1990) and then as a lecturer (1991) at the Faculty of Medicine, Kyoto University, on a project studying the molecular mechanisms of hematopoesis using his unique *in vitro* differentiation induction method from mouse ES cells. He took a professor position at the Research Institute for Microbial Diseases, Osaka University in 1995 and started his study of germ cell development. In 2004, he was appointed as a professor at the Graduate School of Frontier Biosciences and Medical School, Osaka University. His major interest is “How various kinds of cells are produced from single totipotent cells, zygotes?” Based on the interest, he has been studying epigenetic modification, especially DNA methylation, in early embryogenesis and in spermatogenesis. To be more precisely, his recent and major scientific theme s are the regulation of DNA methylation in early embryogenesis and *de novo* DNA methylation of male germ cells by germ cell specific small RNA, pi-RNA (piwi interacting RNA).

Trend of pluripotent stem cell-derived gamete research

Toshiaki Noce

Keio Advanced Research Centers,
Keio University School of Medicine, Tokyo Japan

Pluripotent stem cell (PSC)-derived gamete research has potential both for understanding basic mechanisms of differentiation and maintenance of gamete-producing (germline) cells and overcoming clinical problems related to infertility. For example, PSC-derived germ cells purified from various culture stages enable us to explore molecular mechanisms such as developmental network and epigenetic regulation of lineage-specific genes, which are essential for understanding germline-specificity. Culture system of functional maturation of PSC-derived gametes (eggs and sperm) *in vitro* will provide valuable techniques for overcoming various difficulties in researches for reproduction of human as well as experimental animals.

Another advantage of this line of research is possibility to realize the alternation of generations without growth and sexual maturation of individual bodies. Thus technical revolution is required for the reproductive engineering to generate genetically modified animals using non-human primate species, which must serve as much more valuable models for human diseases or biomedical researches than those of mouse. Similarly, further studies using monkey iPS-derived cells will play a crucial role for preclinical assessment of their safety and efficacy prior to application of iPS cell-based therapies.

Based on those scientific and social meanings, PSC-derived gamete research becomes the object of public attention, and the extensive approaches in some years ahead have accelerated the progress. Nevertheless, there are several differences found in the reproductive system between mouse and primate animals, which will be a current problem awaiting solution to be solved.

Curriculum Vitae

Toshiaki NOCE, Ph.D

Project Professor,

Dept. of Physiology, Keio University School of Medicine

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EDUCATION & EXPERIENCE:

Faculty of Science, Kyoto University, Kyoto, Japan 1979 - 1984
M.D. & Ph.D. degree (Major in Developmental Biology)

Post-doctoral Fellow 1985 - 1986
Department of Biology, McGill University, Montreal, Canada

Department of Developmental Biology, National Institute of 1986 - 1987
Basic Biology, Aichi, Japan.
(granted by fund for Promoting Science and Technonogy, Japan)

Senior Researcher 1987 - 2009
Mitsubishi Kasei Institute of Life Sciences, Tokyo, Japan
Group of Reproductive & Regenerative Development

Project Professor 2009 - 2011
Molecular Neuroscience Research Center,
Shiga University of Medical Science, Shiga, Japan

Project Professor 2011-present
Keio Advanced Research Centers,
Keio University School of Medicine, Tokyo, Japan

Sanger Human iPS Cells, a Distinct Type of Human Pluripotent Stem cells

Wei Wang, Jian Yang and Pentao Liu
Wellcome Trust Sanger Institute, Cambridge, U. K.

Abstract:

Human pluripotent stem cells include human ES cells and iPS cells. I will present our work on producing, maintaining and differentiating a new type of human pluripotent stem cells, Sanger Human iPS Cells or SH-iPSCs. We produce SH-iPSCs by using a six-factor reprogramming cocktail including OCT4, SOX2, KLF4, MYC, RARG and NR5A2 (LRH1). SH-iPSCs grow in 2i plus LIF medium, have similar culture behavior as mouse ES cells and are receptive to genetic manipulation. They depend on JAK/STAT signaling pathway but are independent of FGF signaling to keep pluripotent. Female SH-iPSCs have two active X chromosomes. SH-iPSCs can be converted to human ES cell-like cells by culturing in FGF-containing medium. Therefore, SH-iPSCs are highly similar to mouse ES cells. We are able to efficiently differentiate SH-iPSCs to neural stem cells using a mouse ES cell differentiation protocol.

1. Wang, W., Yang, J., Liu, H., Lu, D., Chen, X., Zenonos, Z., Campos, L. S., Rad, R., Guo, G., Zhang, Z., Bradley, A., and Liu, P. (2011). Rapid and efficient reprogramming of somatic cells to induced pluripotent stem cells by retinoic acid receptor gamma and liver receptor homolog 1 Proc Natl Acad Sci USA. 108(45):18283-18288.

2. Wang, W., Lin, C., Lu, D., Ning, Z., Cox, T., Melvin, D., Wang, X., Bradley, A., and Liu, P. (2008). Chromosomal Transposition of PiggyBac in Mouse Embryonic Stem Cells. Proc Natl Acad Sci USA *105*, 9290-9295.

CURRICULUM VITAE

Pentao Liu, Ph.D.

Senior Investigator
Wellcome Trust Sanger Institute
Wellcome Trust Genome Campus
Hinxton, Cambridge CB10 1HH
United Kingdom

Phone 44-(0)1223496850
Fax 44-(0)1223496802
E-mail pl2@sanger.ac.uk

Education:

1992-1998 Baylor College of Medicine, Houston, Texas. USA. Ph.D.

1985-1988 Institute of Genetics, Chinese Academy of Sciences. China. M.Sc.

Research:

2010- Senior Investigator. Wellcome Trust Sanger Institute, Cambridge, United Kingdom. My lab is studying mouse genetics and stem cells. We are particularly interested in how stem cells are produced and maintained in the mouse, and how these multi-potent cells are differentiated to specific cell types. We are able to convert T lymphocytes to a new type of killer cells. In the last few years, we have developed a new reprogramming technology to rapidly and efficiently reprogramme mouse somatic cells to naïve iPS cells.

This technology also enables us to produce human iPS cells that are highly similar to naïve or ground state mouse ES cells. The new human pluripotent stem cells are therefore useful for many applications.

2003-2010 Investigator. Wellcome Trust Sanger Institute, Cambridge, United Kingdom.

1998-2003 Research Fellow. Mouse Cancer Genetics Program, National Cancer Institute at Frederick, Maryland. USA.

Primate totipotent and pluripotent cells

Shoukhrat Mitalipov,
Oregon National Primate Research Center, Oregon Health & Science University

Mammalian development commences with the totipotent zygote, which is capable of developing into all the specialized cells that make up a whole organism, as well as into the extraembryonic support structures necessary for fetal development. Early embryonic blastomeres, up to at least the 4-cell stage embryo, also retain totipotency. Pluripotent cells in the inner cell mass (ICM) of blastocysts are the descendants of totipotent cells and can differentiate into any cell type of a body except extraembryonic tissues.

Pluripotent cells can be isolated, adapted and propagated indefinitely in vitro in an undifferentiated state as embryonic stem cells (ESCs). ESCs retain their ability to differentiate into cells representing the three major germ layers: endoderm, mesoderm or ectoderm or any of the 200+ cell types present in the adult body. Since many human diseases result from defects in a single cell type, pluripotent human ESCs represent an unlimited source of any cell or tissue type for replacement therapy thus providing a possible cure for many devastating conditions.

Pluripotent cells resembling ESCs can also be derived experimentally by the reprogramming of somatic cells (Byrne et al., Nature, 2007). Reprogrammed somatic cells may have an even more important role in cell replacement therapies since the patient's own somatic cells can be used to make stem cells thereby eliminating immune based rejection of transplanted cells.

The ability to contribute to chimeras upon reintroduction into host embryos is the key feature of murine totipotent and pluripotent cells. We recently demonstrated that rhesus monkey ESCs and isolated ICMs failed to incorporate into host embryos and develop into chimeras (Tachibana et al., Cell, In press). However, ICMs transplanted into blastocysts formed separate viable fetuses while sharing the placental compartment of the host embryo. Monkey chimeras were produced by aggregation of totipotent cells of the 4-cell embryos.

Currently, there is little known about human and nonhuman primate embryo development and lineage specification and how closely the mouse development reflects primates. Our study presents a first glimpse at the similarities and differences between mouse and primate preimplantation embryo development and offers an important experimental model to investigate lineage commitment and interactions.

Producing primate embryonic stem cells by somatic cell nuclear transfer. Byrne JA, Pedersen DA, Clepper LL, Nelson M, Sanger WG, Gokhale S, Wolf DP, Mitalipov SM. Nature. 2007 Nov 22;450(7169):497-502

Totipotent but not pluripotent primate embryonic cells contribute to chimeras
Tachibana M, Sparman M, Ramsey C, Ma H, Lee HS, Penedo MC , Mitalipov S. Cell. In press

CURRICULUM VITAE

Shoukhrat Mitalipov, Ph.D.

Oregon Health & Science University
505 NW 185th Ave
Beaverton, OR 97006
E-mail: mitalipo@ohsu.edu
Website:
http://www.ohsu.edu/xd/research/centers-institutes/stem-cell-center/labs/mitalipov-lab/index.cfm

Biography

Shoukhrat Mitalipov is an Associate Scientist in the Division of Reproductive & Developmental Sciences, Oregon National Primate Research Center, Oregon Health & Science University. He is also an Associate Professor at the Oregon Stem Cell Center and Departments of Obstetrics & Gynecology and Molecular & Medical Genetics. Dr. Mitalipov earned his Ph.D. degree in Developmental & Stem Cell Biology at the Research Center for Medical Genetics, Moscow, Russia. He came to Utah State University in 1995 to conduct a postdoctoral research training before joining the faculty at OHSU in 1998. Dr. Mitalipov is a recipient of the 2010 Discovery Award from the Medical Research Foundation of Oregon.

Research Overview

Our overall research goal is to use molecular and cellular approaches to answer scientifically and clinically pertinent questions regarding gamete, embryo and stem cell biology. The main focus of several ongoing projects is to understand the mechanisms of genetic and epigenetic reprogramming of aged somatic cells to the totipotent and pluripotent states following somatic cell nuclear transfer (SCNT). Specifically, we are interested in the role of mitochondria and mitochondrial (mt)DNA in reprogramming and re-setting the developmental program in experimental pluripotent stem cells derived from aged somatic cells. Another objective is to develop efficient protocols for deriving human pluripotent stem cells via SCNT for patients carrying mtDNA mutations.

Several other projects in the lab are focused on the assessment of the safety and efficacy of stem cell based therapies by transplantation studies in a clinically relevant nonhuman primate model. The overall goal of these studies is to take advantage of recent developments in our lab that allowed for the first time derivation of immuno-matched pluripotent cells by SCNT or iPS approaches, suitable for autologous transplantation into existing monkeys.

Our lab is also investigating novel germ line gene therapy approaches for the treatment of inherited human diseases. Particularly, mutations in mtDNA contribute to a diverse range of still incurable human diseases and disorders including neurodegenerative diseases, myopathies, diabetes, blindness, cancer and infertility. Our team recently demonstrated that the mitochondrial genome could be efficiently replaced in mature nonhuman primate oocytes by chromosome transfer from one egg to an enucleated, mitochondrial-replete egg. The reconstructed oocytes with the mitochondrial replacement were capable of supporting normal fertilization, embryo development and produced healthy offspring. This discovery suggest that the nuclear genetic material from a patient's egg containing mtDNA mutations could be removed, and transplanted into an enucleated egg containing normal mtDNA donated by a healthy female. A child born following fertilization with the husband's sperm would be free of risk from maternal mtDNA mutations as well as the authentic biological child of the patients.

Genetically modified non-human primate models in life science

Erika Sasaki

Central Institute for Experimental Animals

Transgenic mice have contributed immensely to biomedical science. However, the genetic and physiological differences between primates and mice including their physiologic functions hamper the extrapolation of results from mouse disease models to direct clinical applications in humans. Thus, the development of non-human primate models that mimic various human physiologic function including neuronal system would accelerate the advance of biomedical research. In particular, genetically modified primates would be a powerful human disease model for basic neuroscience, preclinical study for newly developed therapies or drugs.

The common marmoset (*Callithrix jacchus*), a new world primate has a number of advantages as an experimental animal, including small body size (300–450 g), high fertility, and early sexual maturity. The common marmoset has attracted considerable attention as a potentially useful biomedical research animal in fields such as neuroscience, stem cell research and regenerative medicine.

Recently, we have established techniques to produce transgenic marmosets using self-inactivating lenti-viral vector containing the EGFP transgene into marmoset embryos[1)]. With this success of the first transgenic primate, research into human disease, physiology, and the development of drug therapies and their validation is expected to increase. In addition, we also have established two kinds of pluripotent stem cells; embryonic stem (ES) cells and developed iPS cells from the marmoset[2, 3)]. Both of these pluripotent stem cell lines offered much hope to the numbers of patients who could benefit from tissue transplants. Furthermore these pluripotent stem cells also show interesting characteristics to study reproductive biology because pluripotent stem cells can produce genetically modified animals in several ways.

These marmoset transgenic technologies, the pluripotent stem cells of the common marmoset brain will provide an excellent model to study in the field of neuroscience.

1. Sasaki, E., et al.: Nature, 459: 523-7, 2009
2. Sasaki, E., et al.: Stem Cells, 23: 1304-13, 2005
3. Tomioka, I., et al.: Genes Cells, 15: 959-69, 2010

Curriculum Vitae

Erika Sasaki, Ph.D.

Academic Appointments

2010-	Department Head, Department of Applied Developmental Biology, Central Institute for Experimental Animals
2007-	Associate Professor, Keio Advanced Research Centers (KARC), Keio University, Tokyo, Japan
2007-2010	Laboratory head, Laboratory of Applied Developmental Biology, Department of Marmoset research
2004-2007	Assistant professor, Department of Anatomy, School of Medicine, Keio University, Tokyo, Japan
2003-2007	Project leader, Research Group of non-human primate reproduction and development, Laboratory of non-human primate research, Division of Biomedical Science, Central Institute for Experimental Animals
2002-2003	Research Associate, Medical Institute of Bio Regulation, Kyusyu University
2001-2002	Research Associate, Institute of Medical Science, University of Tokyo
1996-2000	Postdoctoral fellow, Department of Animal Science, University of Guelph, Canada
1995-1996	Research fellow, Japan Science and Technology Agency (JST)
1994-1995	Young Scientist Research fellow, Japan Society for the Promotion Science

Education

1995	Ph.D.	Department of agricultural and forestry science University of Tsukuba, Tsukuba, Japan
1992	M.S.	Department of agricultural and forestry science University of Tsukuba, Tsukuba, Japan
1989	B.S.	Department of agricultural and forestry science University of Tsukuba, Tsukuba, Japan

Stem cells to synapses: regulation of self-renewal and differentiation in the nervous system

Andrea H. Brand FRS FMedSci
Herchel Smith Professor of Molecular Biology
The Gurdon Institute, University of Cambridge, Tennis Court Road, Cambridge UK CB2 1QN

Discovering how stem cells are maintained in a multipotent state and how their progeny differentiate into distinct cellular fates is a key step in the therapeutic use of stem cells to repair tissues after damage or disease. We are investigating the genetic networks that regulate neural stem cells in *Drosophila*.

Stem cells can divide symmetrically to expand the stem cell pool, or asymmetrically to self-renew and generate a daughter cell destined for differentiation. The balance between symmetric and asymmetric division is critical for the generation and repair of tissues, as unregulated stem cell division results in tumourous overgrowth. Symmetrically dividing stem cells exist in the optic lobe of the brain, where they convert to asymmetrically dividing neuroblasts. By comparing the transcriptional profiles of symmetrically and asymmetrically dividing stem cells, we identified Notch as a key regulator of the switch from symmetric to asymmetric division. During asymmetric division cell fate determinants, such as the homeodomain transcription factor Prospero, are partitioned from the neural stem cell to its daughter. By identifying Prospero's targets throughout the genome we showed that Prospero represses genes for self-renewal and activates differentiation genes. In *prospero* mutants, differentiating daughters revert to a stem cell-like fate: they express markers of self-renewal, continue to proliferate, fail to differentiate and generate tumours.

The systemic regulation of stem cells ensures they meet the needs of the organism during growth, and in response to injury. A key point of regulation is the decision between quiescence and proliferation.

During development, Drosophila neural stem cells transit through a period of quiescence separating distinct embryonic and post-embryonic phases of proliferation. Neuroblasts exit quiescence in response to a nutrition-dependent signal from the fat body. We identified a population of glial cells that produce Insulin/IGF-like peptides in response to nutrition, and show that the Insulin/IGF Receptor pathway is necessary for neuroblasts to exit quiescence.

Chell JM and Brand AH (2010) Nutrition-responsive glia control exit of neural stem cells from quiescence. **Cell** 143, 1161-1173

Egger B, Gold KS and Brand AH (2010) Notch regulates the switch between symmetric and asymmetric neural stem cell division in the Drosophila optic lobe. **Development** 137, 2981-2987

Southall TD and Brand AH (2009) Multiple transcription factor binding identifies neural stem cell gene regulatory networks. **EMBO J.** 28, 3799-807

Choksi, S.P. et al. (2006). Prospero acts as a binary switch between self-renewal and differentiation in Drosophila neural stem cells. **Dev. Cell** 11, 775-789.

Brand, A.H. and Perrimon, N. (1993). Targeted gene expression as a means of altering cell fate and generating dominant phenotypes. **Development** 118, 401-415.

ANDREA H. BRAND FRS FMedSci

Professor Andrea H Brand is the Herchel Smith Professor of Molecular Biology at the Wellcome Trust/Cancer Research UK Gurdon Institute, University of Cambridge. Professor Brand's lab studies the genetic networks that regulate the transition from a multipotent neural stem cell to a specialised neuronal or glial cell type. With sufficient knowledge of these networks, it should be possible to manipulate stem cells to proliferate, to remain quiescent, or to differentiate into specialised, predefined, cell types. Professor Brand was awarded the Royal Society Rosalind Franklin Award in 2006, the William Bate Hardy Prize in 2004, the Hooke Medal of the British Society of Cell Biology in 2002 and Special Award of Excellence at the Wellcome Biomedical Imaging Awards, 2001. She was elected a Fellow of the Royal Society in 2010, a Fellow of the Academy of Medical Sciences in 2003, and a member of the European Molecular Biology Organization in 2000.

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1986-1988:	**Helen Hay Whitney Fellow, Harvard University** Department of Biochemistry, Cambridge, MA, U.S.A. Laboratory of Dr. Mark Ptashne
1981-1986:	**Ph.D., MRC Laboratory of Molecular Biology,** **University of Cambridge**, Cambridge, UK Adviser: Dr. Kim Nasmyth
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Transitions in division mode of neural stem cells during cortical development

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In the developing mammalian brain, elongated neuroepithelial cells function as neural stem cells. These cells initially undergo symmetric divisions to proliferate, and subsequently initiate asymmetric divisions that continuously generate a self-renewing daughter (radial glia or apical progenitors) and a differentiating daughter cell (neurons and intermediate progenitors). This transition from a proliferative to a neurogenic mode plays a critical role in determining brain size. In the neurogenic mode, the self-renewing daughters of radial glial divisions inherit the complete epithelial structure including both apical and basal processes, therefore maintaining the pseudo-stratified brain organization. Our recent live imaging studies, however, have revealed that, on occasion, these radial glia also undergo oblique cleavages that separate the dividing radial glia into the apical and basal part. The basal daughters, which inherit only the basal process, generate a different type of self-renewing progenitor cells; they migrate out from the ventricular zone (VZ), undergoing asymmetric neurogenic divisions. These progenitors are very similar to the outer subventricular zone (OSVZ) progenitors, a major type of progenitors in gyrencephalic animals, revealing the presence of OSVZ progenitors in rodents. Thus, the self-renewing progenitors in the developing mammalian cortex undergo two transitions in the division mode, first from symmetric to asymmetric divisions of radial glia, and then subsequently from radial glia to OSVZ progenitors. We have proposed that this second transition is initiated by oblique cleavages that split the apical and basal part of the dividing radial glia. Mutant mice defective in cleavage plane orientations generate a number of the OSVZ progenitors as seen in the LGN-mutant strain, and using these mice as a model makes it possible to analyze properties and genetic defects of the OSVZ progenitors, which may affect human cortical development.

References:
Konno et al. Nat Cell Biol.100, 93-101 (2008).
Shitamukai et al. J Neurosci. 31, 3683–3695 (2011).

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PROFESSIONAL EXPERIENCE

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12 1988- 03 1998	Section chief, Department of Molecular Genetics, National Institute of Neuroscience, Japan
04 1987- 12 1988	Postdoctoral fellow, Laboratory of Cell Biology, Rockefeller University, Professor: Dr. Gerald Edelman
04 1984- 03 1987:	Postdoctoral fellow, Department of Cell Biology, Tokyo Metropolitan Institute of Medical Science

EDUCATION

04 1979- 03 1984	Ph.D. University of Tokyo
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SHORT BIOGRAPHICAL SKETCH

Fumio Matsuzaki received his doctorate at the University of Tokyo in 1984, and carried out postdoctoral research, first at the Tokyo Metropolitan Institute of Medical Science, then in the laboratory of Gerald Edelman at the Rockefeller University. He was a section chief in the National Institute of Neuroscience in Japan from 1989 to 1998. In 1998, he was appointed professor in the Institute for Development, Aging and Cancer at Tohoku University and remained there until taking his current position as group director at the RIKEN CDB in 2002.
He has been interested in genetic programs and plastic mechanisms underlying neural development. He began genetic research of neurogenesis using *Drosophila*, and discovered asymmetric segregation of Prospero during neural stem cell divisions. Since then, his lab studies how neural stem cells divide asymmetrically. His lab is currently using both *Drosophila* and mouse as model systems to understand how brain development is controlled by neural stem cell function.

Netrin-G/NGL interaction in elaborated neuronal circuits

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Higher brain functions such as cognition, learning, language, attention, and emotion are attributed to the formation of highly complex and organized neural circuits associated with an increase in cerebral volume. The laminar structures of the cortex provide a fundamental basis for integrating information. Two pairs of a synaptic trans-neuronal ligand and receptor, namely netrin-G1/-G2 and netrin-G ligand (NGL) 1/2, have likely evolved by genomic duplication as vertebrate-specific genes, and have specific roles associated with the cortical laminar structures. Remarkably, the netrin-G1 and netrin-G2 genes are expressed in distinct neuronal circuits in a complementary manner. Loss-of-function studies of these genes in mice demonstrate that presynaptic netrin-G1 and netrin-G2, which are expressed in distinct neuronal pathways, constrain specific ligands NGL1 and NGL2 to a specific sub-domain of the dendrites of their target neurons, and thus contribute to determine circuit specificity within a single neuron. The lack of either netrin-G1 or netrin-G2 results in abnormal synaptic plasticity in a circuit-specific manner, and thus causes differential abnormalities in various behavioral domains. The retina also has highly elaborated laminar structures and serves as a mini-brain model. We revealed complementary expression patterns of netrin-G1/-G2 and NGL1/2 in the retina, similar to other brain areas. A lack of presynaptic netrin-G1 or netrin-G2 results in abnormal postsynaptic properties in a layer-specific manner. These findings indicate that netrin-G/NGL interactions contribute to laminar structure-dependent information processing.

1. Nakashiba T. et al., Netrin-G1: a novel GPI-linked mammalian netrin that is functionally divergent from classical netrins. *J Neurosci.,* 20: 6540-6550, 2000.
2. Nakashiba T. et al., Complementary expression and neurite outgrowth activity of netrin-G subfamily members. *Mech Dev.,* 111: 47-60, 2002.
3. Nishimura-Akiyoshi S. et al., Axonal netrin-Gs transneuronally determine lamina-specific subdendritic segments. *PNAS* 104: 14801-14806, 2007.

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1972-1976 Yamaguchi University, BSc in Veterinary Medicine
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Research and Professional experience:

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1991-1993 Senior Researcher and then Laboratory Head, NIAH
1993-1997 Associate Professor, Institute for Virus Research, Kyoto University
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Publications

1. Gomi H, Sassa T, Thomson RF, and Itohara S. Involvement of cyclin-dependent kinase-like 2 in cognitive function required for contextual and spatial learning in mice. *Front. Behav. Neurosci.,* doi: 10.3389, 2010.
2. Sano Y, Ornthanalai VG, Yamada K, Homma C, Suzuki H, Suzuki T, Murphy NP and Itohara S. X11-like protein deficiency is associated with impaired conflict resolution in mice. *J. Neurosci.,* 29, 5884-96, 2009.
3. Imayoshi I, Sakamoto M, Ohtsuka T, Takao K, Miyakawa T, Yamaguchi M, Mori K, Ikeda T, Itohara S, and Kageyama R. Roles of continuous neurogenesis in the structural and functional integrity of the adult forebrain. *Nat. Neurosci.,* 11: 1153-61, 2008.
4. Iwasato, T., Inan, M., Kanki, H., Erzurumlu, R., *Itohara, S., and *Crair M.C. Cortical adenylyl cyclase 1 is required for thalamocortical synapse maturation and proper layer IV neuronal morphology during barrel map development. *J. Neurosci.,* 28: 5931-43, 2008. (co-correspondence)
5. Kobayakawa K, Kobayakawa R, Matsumoto H, Oka Y, Imai T, Ikawa M, Okabe M, Ikeda T, Itohara S, Kikusui T, Mori K, and Sakano H. Innate versus learned odour processing in the mouse olfactory bulb. *Nature* 450: 503-8, 2007.
6. Nishimura-Akiyoshi S, Niimi K, Nakashiba T, and Itohara S. Axonal netrin-Gs transneuronally determine lamina-specific subdendritic segments. *PNAS* 104: 14801-6, 2007.
7. Iwasato T, Katoh H, Nishimaru H, Ishikawa Y, Inoue H, Saito YM, Ando R, Iwama M, Takahashi R, Negishi M, and Itohara S. Rac-GAP α-Chimerin Regulates Motor-Circuit Formation as a Key Mediator of EphrinB3/EphA4 Forward Signaling. *Cell* 130: 742-53, 2007.
8. Park J-S, Onodera T, Nishimura S, Thompson RF, and Itohara S. Molecular evidence for two-stage learning and partial laterality in eyeblink conditioning of mice. *PNAS* 103: 5549-54, 2006.
9. Nishiyama H, Knöpfel T, Endo S, and Itohara S. Glial protein S100B modulates long term neuronal synaptic plasticity. *PNAS* 99: 4037-42, 2002.
10. Nakashiba T, Nishimura S, Ikeda T, and Itohara S. Complementary expression and neurite outgrowth activity of netrin-G subfamily members. *Mech. Dev.,* 111: 47-60, 2002.
11. Nakashiba T, Ikeda T, Nishimura S, Tashiro K, Honjo T, Culotti JG, and Itohara S. Netrin-G1: a novel GPI-linked mammalian netrin that is functionally divergent from classical netrins. *J. Neurosci.,* 20: 6540-50, 2000.
12. Iwasato T, Datwani A, Wolf AM, Nishiyama H, Taguchi Y, Tonegawa S, Knöpfel T, Erzurumlu RS, and Itohara S. Cortex-restricted disruption of NMDAR1 impairs neuronal patterns in the barrel cortex. *Nature* 406: 726-31, 2000.

THE ROLE OF ROBO RECEPTORS IN CORTICAL INTERNEURON MIGRATION

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We have been investigating the molecular mechanisms that guide the migration of cortical interneurons from their origin in the subpallial ganglionic eminences (GE) to the neocortex. Numerous molecules such as transcription, motogenic and neurotrophic factors have already been demonstrated to play important roles in their migration. Earlier studies have suggested that cortical interneurons express neuropilin (Nrp) receptors, which enable them to respond to the chemorepulsion produced by class 3 semaphorins (Sema3A and Sema3F) expressed in the striatum. This repulsive activity in the developing stratum creates an exclusion zone for migrating interneurons and channels them into adjacent paths, leading to the formation of their migratory routes into the cortex. However, we have discovered that interneurons in Robo1 null mice ($Robo1^{-/-}$) migrate through the striatum *en route* to the cortex. Our recent studies have indicated that Robo1 controls the migration of cortical interneurons by modulating their responsiveness to semaphorins. Specifically, we have found, using *in vitro* assays, that GE cells taken from $Robo1^{-/-}$ mice are markedly less responsive to Sema3A and Sema3F and this effect is not due to direct interaction between semaphorins and Robo1. Moreover, expression studies illustrated specific downregulation of semaphorin receptors (Nrp and plexin) in GE-derived cells of $Robo1^{-/-}$ mice. Biochemical studies also demonstrated that Nrp1 is able to directly bind to Robo1. Our data demonstrate that Robo1 modulates semaphorin-neuropilin/plexin signalling to steer interneurons around the stratum and into the cortex. We are currently trying to identify downstream molecules that may be involved in this interaction.

Metin, C., Baudoin, J.-P., Rakic, S. and Parnavelas, J.G. (2006) Cell and molecular mechanisms involved in the migration of cortical interneurons. Eur J Neurosci 23, 894-900.

Hernández-Miranda, L.R., Cariboni, A., Faux, C., Ruhrberg, C., Cho, J.H., Cloutier, J.F., Eickholt, B.J., Parnavelas, J.G. and Andrews, W.D. (2011) Robo1 regulates semaphorin signaling to guide the migration of cortical interneurons through the ventral forebrain. J Neurosci 31: 6174-6187.

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POSITIONS HELD:

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1983-1988	Lecturer in Anatomy, Department of Anatomy and Embryology, University College London
1978-1983	Assistant Professor, Department of Cell Biology, The University of Texas Health Science Center, Dallas
1975-1978	Postdoctoral Fellow, Department of Anatomy and Embryology, University College London

Fates and functions of NG2 cells in the postnatal CNS

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Abstract:

Oligodendrocyte precursors (OLPs, also known as NG2 cells) are generated in the ventricular zones (VZ) of the embryonic central nervous system (CNS), from the same set of neuroepithelial stem cells that generated neurons at earlier developmental times. NG2 cells subsequently proliferate and migrate widely throughout the CNS before associating with and ensheathing axons. Many NG2 cells persist in the adult CNS, where they comprise ~5% of all neural cells, raising questions about their function during adulthood. Since they can be induced to generate neurons as well as oligodendrocytes and astrocytes in culture, the idea developed that NG2 cells might behave as multipotent stem cells during normal adulthood or following CNS disease or injury. Many labs have now examined the fates of NG2 cells in the normal mouse brain or following disease or injury, using Cre-lox recombination in transgenic mice. The conclusion so far seems to be that NG2 cells overwhelmingly generate new myelinating oligodendrocytes during adulthood. Early reports that NG2 cells might generate astrocytes or neurons have not been upheld. This draws attention to the role of new myelinating cells in the healthy adult CNS. Do these myelinate previously unmyelinated axons, or do they remodel existing myelin? Are new oligodendrocytes and myelin involved in neural plasticity – for example, motor skills learning and memory? These ideas and experiments to test them will be discussed.

References:

Richardson, W.D., Young, K.M., Tripathi, R.B., and McKenzie, I. (2011). NG2-glia as multipotent neural stem cells: fact or fantasy? *Neuron* 70, 661-673.

Tripathi, R.B., Rivers, L.E., Jamen, F. Young, K.M. and Richardson, W.D. (2010). NG2 glia generate new oligodendrocytes but few astrocytes in a murine experimental autoimmune encephalomyelitis model of demyelinating disease. *J. Neurosci.* 30, 16383-16390.

Rivers, L.E., Young, K.M., Rizzi, M., Jamen, F., Psachoulia, K., Wade, A., Kessaris, N. and Richardson, W.D. (2008). PDGFRA/NG2-positive glia generate myelinating oligodendrocytes and piriform projection neurons in adult mice. *Nat. Neurosci.* 11, 1392-1401.

Curriculum Vitae

William D Richardson PhD
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Prof William (Bill) Richardson obtained his BSc (Physics) from Manchester University in 1973 and PhD (Biophysics; 1978) from King's College London, where he examined chromatin structure in the electron microscope. His first postdoctoral position was at the National Institutes of Health USA (Child Health and Human Development), investigating adenovirus gene structure and expression, followed by a second postdoc at the National Institute for Medical Research, London, where he was involved in ground-breaking research into the mechanism of nuclear targeting of proteins (1982-1985). He continued this work for a time after moving (in 1985) to the Dept of Zoology at UCL as a new Lecturer. Soon after, he switched to work in the emerging field of neural development, a path he has followed most of his professional life. Recently, he has become intrigued by the continuing production of neurons and glia (notably myelinating oligodendrocytes) during adulthood and the potential role of this "adult development" in learning and memory. He is now Professor of Biology in the Wolfson Institute for Biomedical Research at UCL. He has published more than 100 original papers.

Molecular Mechanisms of Barrel Cortex Development

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In the mouse primary somatosensory cortex (barrel cortex), thalamocortical axons (TCAs) from individual thalamic barrelloids are almost entirely confined to single barrel clusters, followed by arrangement of cortical layer IV neurons into barrel hollows and septa during early postnatal stage. Furthermore, spiny stellate neurons in barrel hollows form unidirectional dendrite toward barrel TCAs during first postnatal week for efficient synapse formation. To elucidate the molecular mechanism of unique dendrite development, we searched for genes expressed in the barrel cortex using Allen Brain Atlas. As a consequence, we identified Btbd3, BTB/POZ domain containing 3, is expressed exclusively in barrel hollow. BTB/POZ domain mediates homomeric/heteromeric dimerisation and its family member, Abrupt, controls dendrite formation in *Drosophila* (ref 1 and 2). Therefore, we tested Btbd3 function in spiny stellate dendrite formation and revealed that suppression of Btbd3 is efficient to generate more numbers of primary dendrite. We also revealed that initial expression of Btbd3 is induced by TCA innervation that suggests correct synapse formation control gene expression in postsynaptic neuron. We further tested whether this induction of Btbd3 expression is controlled by neuronal activity. However, no difference of Btbd3 expression was observed in neuronal activity suppressed somatosensory cortex. We next performed microarray analysis from neuronal activity suppressed barrel cortex and isolated molecule, which has BTB/POZ domain in its internal sequence. These results suggest that dendrite formation of spiny stellate cells is controlled by dimerization of both molecules induced by neuronal activity independent Btbd3 expression and neuronal activity dependent gene expression. Taken together, our results provide molecular framework of activity dependent/independent circuit development.

Reference

1. Li W, Wang F, Menut L, Gao FB. BTB/POZ-zinc finger protein abrupt suppresses dendritic branching in a neuronal subtype-specific and dosage-dependent manner. Neuron. 2004 43:823-34.

2. Sugimura K, Satoh D, Estes P, Crews S, Uemura T. Development of morphological diversity of dendrites in Drosophila by the BTB-zinc finger protein abrupt. Neuron. 2004 43:809-22.

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SERVICE TO PROFESSIONAL PUBLICATIONS:

2008-now Review Editor, Frontiers in Neural Circuits

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1. **Shimogori T***, Lee DA, Miranda-Angulo A, Yang Y, Jiang L, Yoshida AC, Kataoka A, Mashiko H, Avetisyan M, Qi L, Qian J, and Blackshaw S*. (2010) A genomic atlas of mouse hypothalamic development. *Nat Neurosci.* 13:767-75. *corresponding authors.
2. Suzuki-Hirano A, Ogawa M, Kataoka A, Yoshida AC, Itoh D, Ueno M, Blackshaw S, **Shimogori T**. (2011) Dynamic spatiotemporal gene expression in embryonic mouse thalamus. J Comp Neurol. 519; 528-43.
3. Yuge K, Kataoka A, Yoshida AC, Itoh D, Aggarwal M, Mori S, Blackshaw S, **Shimogori T**. (2011) Region-specific expression in early postnatal mouse thalamus. J Comp Neurol. 519; 544-61.
4. Matsui A, Yoshida AC, Kubota M, Ogawa M and **Shimogori T**. (2011) Mouse in utero electroporation: Controlled spatio-temporal gene transefection. J Vis Exp. 54 pii: 3024. doi: 10.3791/3024.
5. Hama H, Kurokawa H, Kawano H, Ando R, **Shimogori T**, Noda H, Fukami K, Sakaue-Sawano A, Miyawaki A. (2011) Scale: a chemical approach for fluorescence imaging and reconstruction of transparent mouse brain. doi: 10.1038/nn.2928.

Neural stem cells and early-born neurons collaborate three-dimensionally for neocortical histogenesis

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We are asking how neural stem cells' morphology is regulated three-dimensionally and how this regulation contributes to continuous cell production and the overall brain formation. Stem cells in the mammalian brain primordia originally take a neuroepithelial structure in which their nuclei diffusely occupy the entire wall (about ten nuclei thick) of the neural tube or brain vesicle. This diffuse nuclear distribution is due to the cell cycle-dependent, to-and-fro nuclear movement (called interkinetic nuclear migration) exhibited by each neuroepithelial cell (80 μm long), which spans from the apical (inner) surface to the basal (outer) surface of the wall. When the first neuronal group comes out as a result of divisions within the initial neuroepithelium, neurons accumulate in an outer zone (1-2 cell thick) just beneath the basal lamina and stem cells become longer (90-100 μm). The elongated stem cells keep their apicobasal attachment as well as nuclear migration trajectory in a range of 80 μm (ten nuclei thick) with a basal process (~20 μm) extended. Stem cells' elongation coupled with maintenance/renewal of basal processes further continues as the wall thickens. How this elongation occurs is unknown and it is important to understand whether and if so how this phenomenon might affect stem cells' cytogenetic behavior. Through in vivo RNAi experiments and live imaging in slice culture, we found that the earliest cohort of neurons in the developing mouse neocortex may play an important role in extrinsically shaping the neural stem cells.

Miyata, T., and Ogawa, M.: Twisting of neocortical progenitor cells underlies a spring-like mechanism for daughter-cell migration. *Curr. Biol.* 17, 146-151 (2007)

Miyata, T., Kawaguchi, A., Saito, K., Kawano, M., Muto, T., and Ogawa, M.: Asymmetric production of surface-dividing and non-surface-dividing cortical progenitor cells. *Development* 131, 3133-3145 (2004)

Miyata, T., Kawaguchi, A., Okano, H., and Ogawa, M.: Asymmetric inheritance of radial glial fibers by cortical neurons. *Neuron* 31, 724-741 (2001)

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Developmental and Evolutionary Roles of a Noncoding DNA Element in Perisylvian Cerebral Cortex

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The Sylvian fissure (SF), dividing frontal and parietal lobes from the temporal lobe, is remarkably enlarged in humans, but is indistinct in non-primates. Despite the signal importance of perisylvian cortex, which mediates crucial human cognitive functions including language, it is completely unknown how development and evolution of these regions is regulated. Here, we identify a conserved noncoding DNA element (CNE) critical for perisylvian cortex development. Mutation of the CNE selectively and symmetrically disrupts perisylvian cortex, including "Broca's area," the primary language area. The CNE is present only in placental mammals, with its associated exon showing the signature of an ancient L4 retrotransposon insertion after divergence of placental and non-placental mammals. The CNE represents one of ~17 promoters for the *GPR56* gene, and the CNE mutation disrupts interaction with RFX transcription factors, ablating the promoter activity. GPR56, a G protein-coupled receptor essential for cortical development, mediates adhesion between cortical progenitors and the basal lamina. When fused to the beta-galactosidase gene (β-gal), the human CNE drives gene expression in mice in a sharply delineated lateral cerebral cortical zone, representing a potential orthologue of human perisylvian cortex, whereas the corresponding mouse CNE drives expression diffusely in cerebral cortex. Evolutionary differences between the mouse and human CNE also shift gene expression from apical progenitors, common to all vertebrates, to $SOX2^{+}TBR2^{-}$ outer subventricular zone (OSVZ) progenitors that are absent from non-placental vertebrates, rare in mice, and most abundant in humans. Our data show that perisylvian development requires an evolutionarily dynamic CNE, and suggest that modulation of *GPR56* expression in OSVZ progenitors by this CNE may play important roles in development and evolution of perisylvian cortex. Our study also represents a potential starting point to identify transcriptional programs regulating development of OSVZ progenitors in distinct cortical regions.

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- Children's Hospital Boston/NIH Developmental Neurology Training Grant (T32 NS007473), 2008-2009.
- Korea Foundation for Advanced Studies Predoctoral Fellowship, 1999-2004.
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- Howard Hughes Medical Institute Predoctoral Fellowship, 2000 (honorable mention).
- Korea Foundation for Advanced Studies Undergraduate Fellowship, 1996-1998.
- Seoul National University Scholarship, 1994-1995.

SELECTED PUBLICATIONS

1. **Bae, B.-I.**, Tietjen, I., Evrony, G.D., Chang, B.S., Barkovich, A.J., Murayama, A., Shimada, H., Asare, E., Atabay, K.D., Im, K., Grant, P.E., Crosier, M., Lisgo, S.N., Lindsay, S., Johnson, M.B., Šestan, N., Topçu, M., Politsky, J., Okano, H., Piao, X., and Christopher A. Walsh. Developmental and Evolutionary Roles of a Noncoding DNA Element in Perisylvian Cerebral Cortex. (in preparation)
2. Sen, N., Hara, M.R., Kornberg, M.D., Cascio, M.B., **Bae, B.-I.**, Shahani, N., Thomas, B., Dawson, T.M., Dawson, V.L., Snyder, S.H., and Sawa, A. (2008) Nitric oxide-induced nuclear GAPDH activates p300/CBP and mediates apoptosis. *Nat. Cell Biol.* 10: 866-873.
3. **Bae, B.-I.**, Hara, M.R., Cascio, M.B., Wellington, C.L., Hayden, M.R., Ross, C.A., Ha, H.C., Li, X.-J., Snyder, S.H., and Sawa, A. (2006) Mutant Huntingtin: Nuclear Translocation and Cytotoxicity Mediated by GAPDH. *Proc. Natl. Acad. Sci. U S A* **103**(9):3405-3409.
4. **Bae, B.-I.**, Xu, H., Igarashi, S., Fujimuro, M., Agrawal, N., Taya, Y., Hayward, S.D., Moran, T.H., Ross, C.A., Montell, C., Snyder, S.H., and Sawa, A. (2005) p53 Mediates Cellular Dysfunction and Behavioral Abnormalities in Huntington's Disease.
   Neuron **47**(1):29-41. This work was previewed in *Neuron* (2005) **47**(1):1-3, and highlighted in *Nature* (2005) **436**(7048):154-155, *Chemical & Engineering News* (2005) **53**(29):9, *The Lancet Neurology* (2005) **4**(9):528-529 and *Science* (2005) **310**(5745):43-45.
5. Baranano, D.E., Wolosker, H., **Bae, B.-I.**, Barrow, R.K., Snyder, S.H., and Ferris, C.D. (2000) A Mammalian Iron ATPase Induced by Iron. *J. Biol. Chem.* **275**(20):15166-73.

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Neural Development and Disorder from a viewpoint of stem cells

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In the human brain, there are structures that have been conserved through evolution, as well as structures that are unique to only primates, acquired through the enlargement of the cerebral cortex. The clarification of these types of structure and their fundamental brain functions is required to properly understand the normal brain functioning of humans, as well as mental health, and illnesses caused by abnormal brain functioning. Existing research on the operating principles of the brain, however, has suffered from the biases and limitations of information derived from animal experiments. Many were optimistic that the complementary nature of genetic engineering techniques, which focus on rodents and fish, and cognitive neuroscience techniques, which focus on primates, would lead to progress in this area. However, results have been disappointing, with few practical or theoretical connections between these techniques having developed.

Recently, however, a connection has finally been made with the success of our team in creating the world's first transgenic primate using marmosets. This technological breakthrough promises to trigger a huge paradigm shift by enabling researchers to analyze both brain structures that are conserved through evolution as well as brain structures, acquired through the enlargement of the cerebral cortex, that are unique to non-human primates and humans.

In this talk, I will present not only marmoset research, but also patient-derived iPS cell results, discussing neural development and regeneration from a viewpoint of stem cells.

Reference

1. Sasaki E, Suemizu H, Shimada A, Hanazawa K, Oiwa R, Kamioka M, Tomioka I, Sotomaru Y, Hirakawa R, Eto T, Shiozawa S, Maeda T, Ito M, Ito R, Kito C, Yagihashi C, Kawai K, Miyoshi H, Tanioka Y, Tamaoki N, Habu S, Okano H, Nomura T. Generation of transgenic non-human primates with germline transmission. Nature. 2009;459:523-7.
2. Okano H, Temple S. Cell types to order: temporal specification of CNS stem cells. Curr Opin Neurobiol. 2009;19:112-9

CURRICULUM VITAE

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Profile

Hideyuki Okano was born in 1959 and started his research carrier in 1983 with the molecular genetic studies of myelination and hereditary dysmyelinating disease model mice at Department of Physiology, Keio University School of Medicine, after graduating from the same school. In 1988, he received Ph.D. from Keio University with this theme. He performed pioneering work on the molecular genetic study of mammalian neural development, which led to subsequent extensive studies of neural development and regeneration as follows. From 1989 to 1991, he began the investigation of molecular neurobiology of *Drosophila* as a Post-Doctoral fellow in Department of Biological Chemistry in Johns Hopkins University School of Medicine in U.S.A. From 1992 to 1994, he worked in Institute of Medical Science, University of Tokyo, where he started molecular biology of mammalian neural development and stem cells. He was promoted to Professor at University of Tsukuba in 1994 and became Head of the laboratory of Molecular Neurobiology at Institute of Basic Medical Science. He moved to Department of Neuroanatomy, Osaka University Medical School in 1997, where he started the investigation on the regeneration of adult mammalian central nervous system. He moved to Department of Physiology, Keio University School of Medicine in 2001, where he educated many students in the field of neuroscience and regenerative medicine. He was awarded Naka-akira Tsukahara Award in 2001, Distinguished Scientific Award from University of Catania School of Pharmacy in 2004, Minister Award of Ministry of Education, Culture, Sports, Science and Technology in 2006, and Medal with Purple Ribbon in 2009 for his pioneering studies on the neural development and regeneration. 2007 ~ present, he acts as a Chair of Keio University Graduate School of Medicine. From 2011, he added the role of the Team Leader, RIKEN-Keio Univ. Joint Research Laboratory, RIKEN Brain Science Institute.