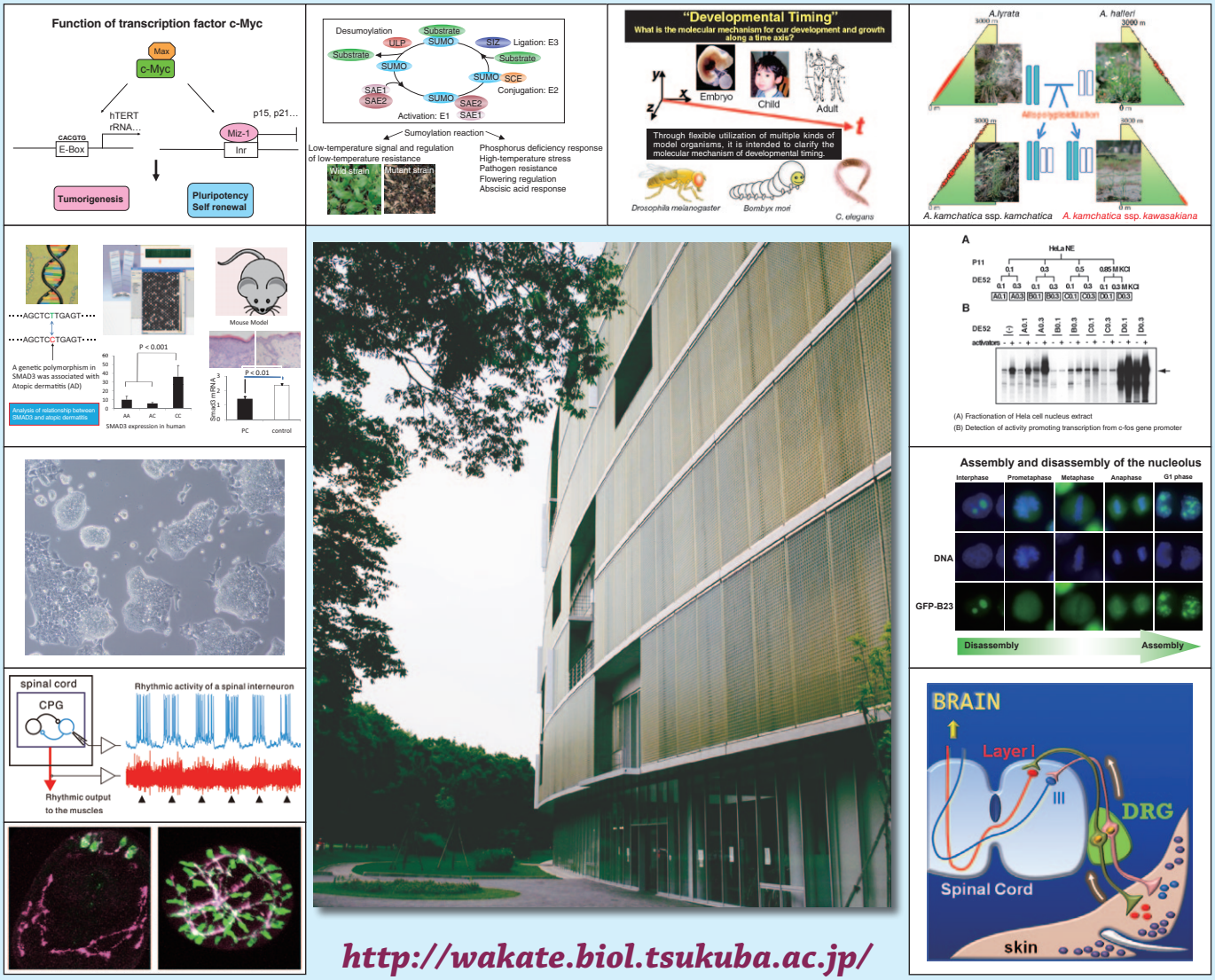
Special Coordination Funds for Promoting Science and Technology

Program for the Promotion to Improve Independent Research Environments for Young Scientists

Initiative to Train Young Researchers Who Will Lead the Next Generation

Ver. 2

"Initiative for the Promotion of Young Scientists' Independent Research-developing the next generation of leaders at the University of Tsukuba"



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University of Tsukuba

Expectations for "Young Researchers Who Will Lead the Next Generation"

Representative of the program
Yoshihiro Shiraiwa

To promote improvement in the environment ensuring independent researches by young scientists, the special coordination funds for promoting science and technology "Program for the Promotion to Improve Independent Research Environments for Young Scientists" was started based on the tenure track system to give opportunities for young scientists to independently conduct their researches under competitive conditions in research institutes aspiring toward world-class achievements. This program aims at reforming staff training systems (introducing the "Japanese style tenure track system"). After the completion of the 5-year program, the university should continue the system as its own effort.

In the University of Tsukuba, the "Initiative to Train Young Researchers Who Will Lead the Next Generation", which was adopted in FY 2007, has been carried out. Concerning the reformation of staff training systems in the University of Tsukuba, the TARA (Tsukuba Advanced Research Alliance) Center introduced a fixed-term employment system in 1994 for the first time in Japan. Initiative to the application of this program, the Institute of Basic Medical Sciences having the fixed-term employment system since FY 2002 and the Institute of Biological Sciences having the tenure track system since FY 2005 early in Japan started to set up a cooperative program for the application. Subsequently, the Institute of Physics and the Institute of Applied Biochemistry joined the program to collaborate with the present program. In response to the trials by these pioneering institutes, the University of Tsukuba determined in January 2007 to introduce either the tenure track system or the fixed-term employment system into every department throughout the university during the first intermediate trial and intermediate planning phase.

On the other hand, the University of Tsukuba launched its "Organization for the Support and Development of Strategic Initiatives" under the leadership of the president as "a new framework for improving the educational and research level of the entire university including the existing organizations by energetically developing activities whereby the university can carry out world-class achievements in research and then give back those achievements to institutions such as graduate schools and centers for education or research" in FY 2007. The present "Initiative to Train Young Researchers Who Will Lead the Next Generation" is ranked at the top level S and has been carried out with the university's support concerning research space, funds and personnel. According to this program, young teachers, three associate professors and 12 assistant professors, were employed and one or two mentors who give scientific, educational and administration advice are provided for each of the young teachers. To ensure the independence of the young teachers, an independent-style core facility (General Research Building D), where one research assistant for each of the young teachers and five technical and clerical staff are provided, was set up.

This program is characterized by being voluntarily managed routinely by an "Administration and Coordination Committee" organized by the young teachers themselves. Young teachers with proven research achievements were employed and allowed to conduct their researches in a well-established environment with sufficient assistance for improving their "scientific", "educational" and "research administration" capabilities. Under these circumstances, it is really expected that these young teachers will become not mere scientists or teachers but "leaders of the university in the next generation".

The present program is now in its third year and has been smoothly conducted. In FY 2009, the intermediate evaluation of the overall program as well as the intermediate evaluation of the individual young teachers will be conducted and it is planned to give an incentive award to those showing outstanding achievement. Furthermore, a follow-up program has just been started using the post of a member of staff who moved on to another national institute. Based on the results of the program, we look forward to continuous support from all persons concerned in order to construct a tenure track system appropriate for the University of Tsukuba.

Target of the Project

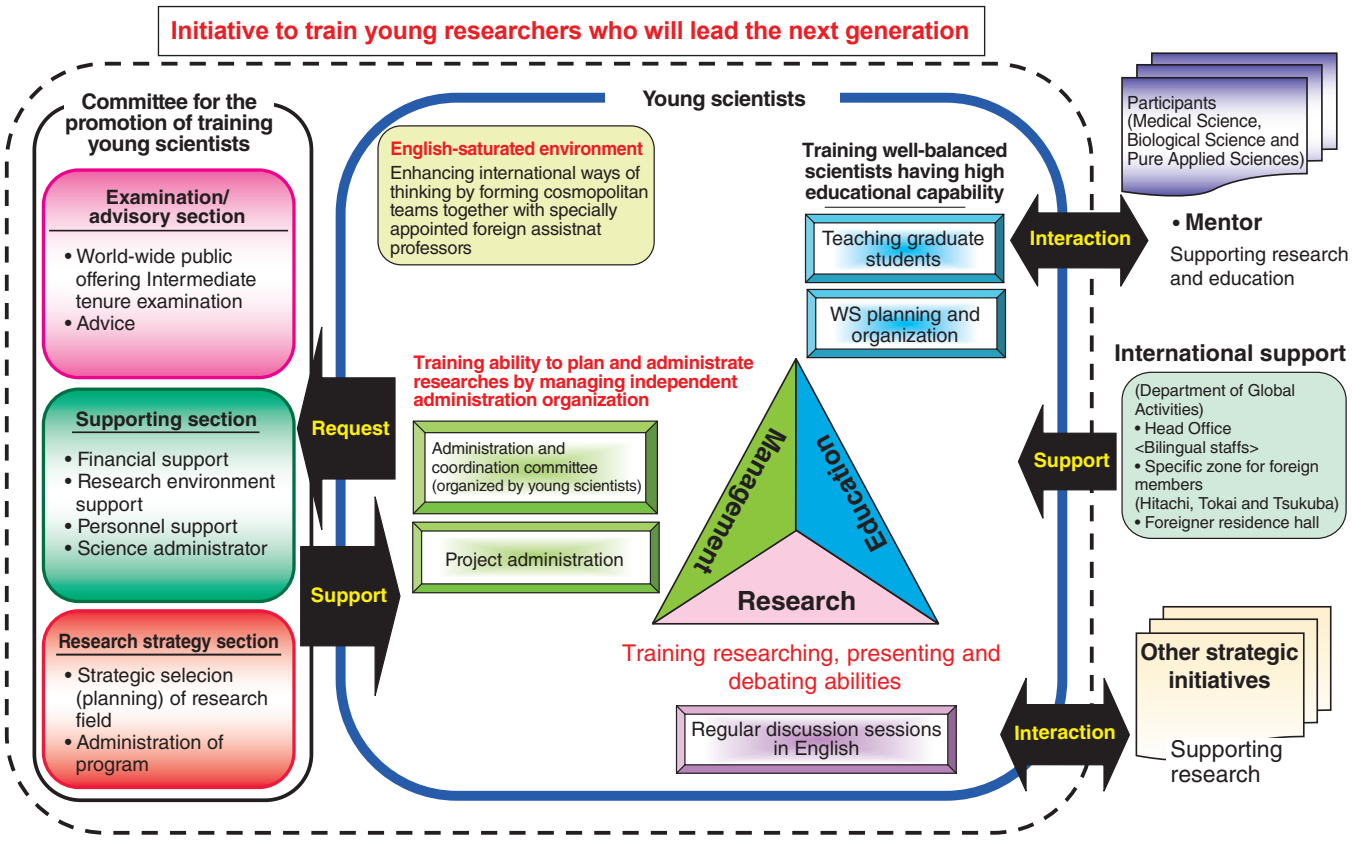
Background Based on the trials by pioneering institutes (for example, the introduction of the fixed-term employment system by the TARA (Tsukuba Advanced Research Alliance) Center in 1994 for the first time in Japan, the introduction of the fixed-term employment system by the Institute of Basic Medical Sciences in 2002, and the introduction of the tenure track system for lecturers and assistant professors by the Institute of Biological Sciences in 2005 for the first time in Japan, the University of Tsukuba determined in January 2007 to introduce either the tenure track system or the fixed-term employment system into every department throughout the university during the first intermediate planning phase.

Purpose To fix the personnel system based on the tenure track system as a common staff training system throughout the university for training researchers who will play a major role in future researches at the University of Tsukuba.

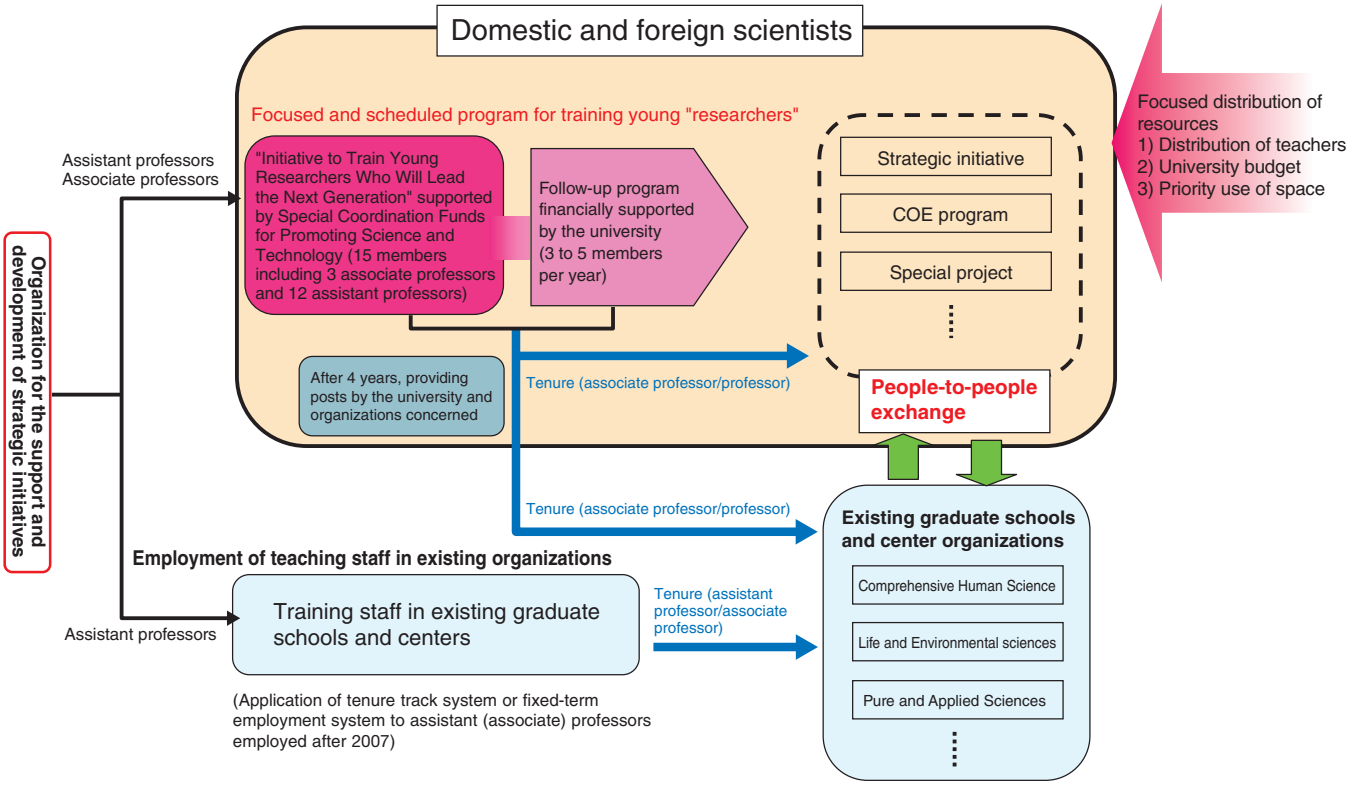
To achieve this goal, the tenure track system will be broadened and fixed first in the life and natural science fields. Next, the tenure track system will be introduced into all organizations in the university within the first intermediate planning phase.

Goal By combining the abilities of young scientists trained in different fields, it is intended to create novel research fields based on interdisciplinary studies beyond the boundaries of organizations and international research cores for carrying out world-class achievements in research.

Execution — Methodology for training "researchers"



Summary of follow-up after the completion of the program and summary of all-university system for training young scientists



Introduction of Young teachers

Name	Research field	Diploma and graduating university
Shunsuke Yaguchi	Marine biology	Ph.D.(life science), School of Life Science, Tohoku University
Kenji Miura	Phytophysiology	Ph.D.(agriculture), School of Agriculture, Kyoto University
Tomoyasu Sugiyama	Molecular cell biology	Ph.D.(medicine), School of Medicine, Osaka University
Ryusuke Niwa	Developmental biology	Ph.D.(science), School of Science, Kyoto University
Kenta Tanaka	Biodiversity	Ph.D.(science), School of Science, Kyoto University
Hiroshi Masumoto	Applied biochemistry	Ph.D.(medicine), School of Medicine, Osaka University
Yoshitaka Hatta	Nuclear/particle physics	Ph.D.(science), School of Science, Kyoto University
Hiroshi Hasegawa	Neurophysiology	Ph.D.(pharmacy), School of pharmacy, Kyoto University
Hiroyuki Suzuki	Molecular pathology	Ph.D.(pharmacy), School of pharmacy, University of Tokyo
Mami Matsuo-Takasaki	Regenerative medicine	Ph.D.(science), School of biology, University of Tsukuba
Mitsuru Okuwaki	Infection biology	Ph.D.(engineering), School of Bioscience and Biotechnology, Tokyo Institute of Technology
Hall Damien Richard	Bioinformatics, Science communication	Ph.D.(bioscience), School of Science, University of Queensland
Hiroshi Nishimaru	Physiology	Ph.D.(medicine), School of Medicine, University of Tsukuba
Aya Fukuda	Pharmacology	Ph.D.(medicine), School of Medicine, Saitama Medical University
*Emiko Noguchi	Genome science	Ph.D.(medicine), School of Medicine, University of Tsukuba

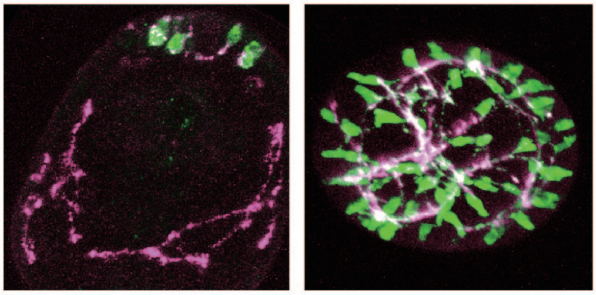
*: Recipient of follow-up program (2009/07/01 to 2014/03/31).

Searching for the mechanisms of axis formation and nerve cell differentiation with the use of marine invertebrates

Shunsuke Taniguchi Graduate School of Life and Environmental Sciences

Analysis of axis formation mechanism: For the construction of a three-dimensional body, accurate differentiation and placement of cells, tissues and organs along individual body axes, i.e., dorsal-ventral and right-left are required for all existing multicellular organisms including humans. Moreover, since these tissues are constantly constructed at accurate timing, it seems that signaling between the axes is essentially necessary. Based on studies hitherto, there has been suggested a possibility that a transcription factor FoxQ2 acts as a coordinator linking the formation of two axes (Yaguchi et al., 2008 Dev Cell). Under these circumstances, we are attempting to clarify the detailed mechanism of how the transcription factor FoxQ2 mediates the signaling of the primary axis (animal-vegetable axis) formation to the secondary axis (oral-aboral axis) formation using embryos of the urchin which is a marine invertebrate.

Analysis of nerve cell differentiation mechanism: A nerve cell has a specific signaling function from the cell itself to the next cell or tissue. In the growth process of the urchin, only several cells can acquire this specific property among about 1,000 cells formed by the repeated cell division of a fertilized egg (Yaguchi et al., 2006 Development; Yaguchi et al., 2007 Dev Biol). In the course of the division of a single cell into two cells and the two cells into four cells, how can such cells that are candidates for nerve cells be formed and differentiated into nerve cells? The other research theme of our laboratory is to pay attention to nerve cells capable of producing serotonin, which is a neurotransmitter playing an important role in the human brain too, and analyze the molecular mechanism of the differentiation of these cells. Moreover, we are conducting research on the function of the nerve system in an individual by using urchin larva and nematocysts.



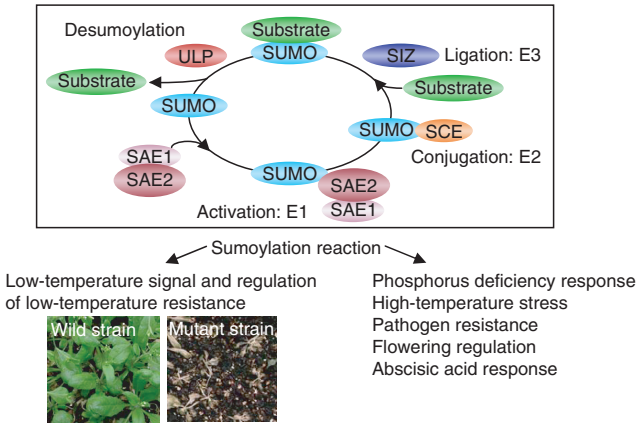
Left: Nerve cell of urchin embryo. Right: Embryo consisting of neural ectoderm alone by blocking the nuclear transport of β-catenin. In both photos, green parts show serotonin nerves.

Environmental stress response mechanism of plant by sumoylation

Kenji Miura Graduate School of Life and Environmental Sciences

SUMO (Small Ubiquitin-like Modifier) is a 14 kDa protein which regulates various proteins by post-translational modification. SUMO attaches to a substrate protein via E1, E2 and E3 proteins. Owing to studies hitherto, it has been clarified that sumoylation contributes to the regulation of functions in various proteins in eukaryotes, for example, regulation of the activity of a transcription factor, reconstruction of chromatin and regulation of nuclear location. Similar mechanisms are observed in plants. Using *Arabidopsis thaliana* as a model plant, we fixed one SUMO E3-ligase SIZ1. It has been clarified that SIZ1 plays an important role in several stress responses caused by environmental factors such as low-temperature resistance, phosphorus deficiency, high-temperature stress response, pathogen tolerance, flowering regulation and abscisic acid response. It has been clarified that, in particular, the function of low-temperature resistance is regulated by sumoylating a transcription factor ICE1 playing an important role in signaling. Although sumoylation is required for environmental stress responses in plants as discussed above, its regulatory mechanism has been little known so far. The object of the present study is to analyze biochemically and genetically the roles and regulatory mechanism of sumoylation in plants.

Although sumoylation regulates ICE1 relating to a low-temperature signal, the ICE1 activatory mechanism is still unknown. Therefore, we are attempting to clarify the ICE1 regulatory mechanism by searching for a protein interacting with ICE1 and transferring site-specific mutation to disclose the ICE1 activatory mechanism, thereby constructing a plant that is more resistant to low-temperature stress.



Analysis of chromosome function-regulatory mechanism by RNA molecule and RNA-binding protein

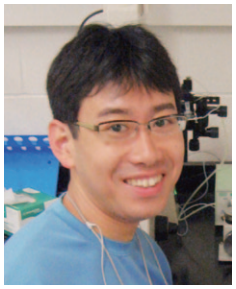
Tomoyasu Sugiyama Graduate School of Life and Environmental Sciences

Concerning the participation of functional RNA in gene expression regulation, X chromosome inactivation (Xis/Tsix) in mammals and X chromosome activation (rox1/2) in *Drosophila melanogaster* are very well known. It is also known that inference (RNAi), which was discovered recently, evokes degradation or gene expression regulation of mRNA at the post-translational level (silencing). It has been recently disclosed that RNAi acts not only at the post-translational level but also at the chromosomal level, namely, an epigenetic change typified by heterochromatin formation or DNA methylation as well as a genetic change such as removing partial genomic DNA. We have been analyzing the heterochromatin formation mechanism by RNAi using a fission yeast *Schizosaccharomyces pombe* as a model. Further, we have conducted purification of a complex RITS (RNA-induced transcriptional gene silencing) which plays a major role in heterochromatin formation by RNAi (Verdel et al., Science, 2004); analysis of the heterochromatin formation mechanism by RITS (Noma et al., Nat. Genet., 2004); identification of RITS target sequence by cloning small interfering RNA (siRNA) contained in RITS; comprehensive mapping of RNAi and heterochromatin factors on the fission yeast genome by CHIP-chip comprising the chromatin immunoprecipitation method (ChIP) combined with microarray (Cam et al., Nat. Genet., 2005); and analysis of RNA-dependent RNA polymerase (RdRP) (Sugiyama et al., Proc. Natl. Acad. Sci., 2005). Furthermore, we have biochemically identified a novel complex SHREC (SNF2 and HDAC-containing repressor complex) which is essentially required in transcriptional level suppression in the heterochromatin region and clarified the gene expression suppression mechanism at the transcriptional level by histone deacetylase (HDAC) and a chromatin modeling factor (Sugiyama et al., Cell, 2007).

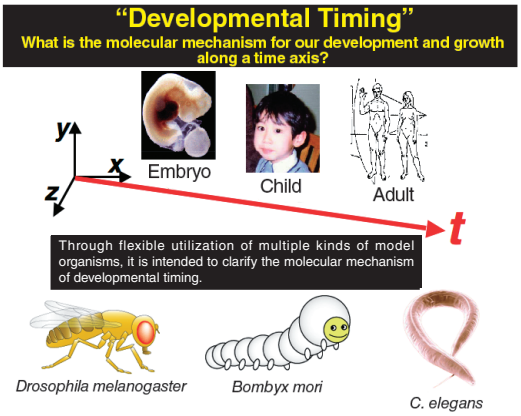
Now, we are carrying out not only the construction of heterochromatin but also the analysis of various chromosome regulatory mechanisms including recombination, repair and distribution. Among all, we are focusing our attention on the role of non-coding RNA in these chromosome regulatory mechanisms.

Study on regulatory mechanism of developmental timing in insect and nematode

Ryusuke Niwa Graduate School of Life and Environmental Sciences



The developmental process of an organism consists of development stages along a time axis. Namely, the developmental process proceeds stepwise from an immature stage to maturation at an appropriate timing. For example, a holometabolous insect hatches from an egg and then repeatedly casts the skin at predetermined points at a definite frequency during the larva stage. Next, the larva spins a cocoon and becomes an adult insect. So, what is the mechanism that determines the shift timing from one stage to the next stage? Also, what is the mechanism that specifies the development stage where the developmental program characteristic of larva, cocoon, or the like can run? It has been proposed for a long time that the control of developmental timing largely affects the evolution of organisms (heterochrony) and human diseases (developmental impairments and aging-associated diseases). Thus, it is highly meaningful to understand the mechanism at molecular level. Compared with the clarification of the development regulatory mechanism in a three-dimensional space that made a great advance in the second half of the 20th century, however, understanding of developmental timing largely falls behind. We aim at clarifying the molecular mechanism of developmental timing by using insects (fruit fly (*Drosophila melanogaster*) and silk worm (*Bombyx mori*)) and a nematode (*C. elegans*) as model organisms. At present, studies with two major themes are undertaken, namely, a study on the biosynthesis of a steroid hormone (ecdysone) controlling insect ecdysis and metamorphosis and a study on micro RNA relating to the switching from nematode larva to adult and downstream transcription factors. In future, we will employ a research style with the interactive combination of insects and nematodes, which are organisms having different life styles, to disclose the molecular mechanisms of developmental timing having been conserved in the faunal realm.

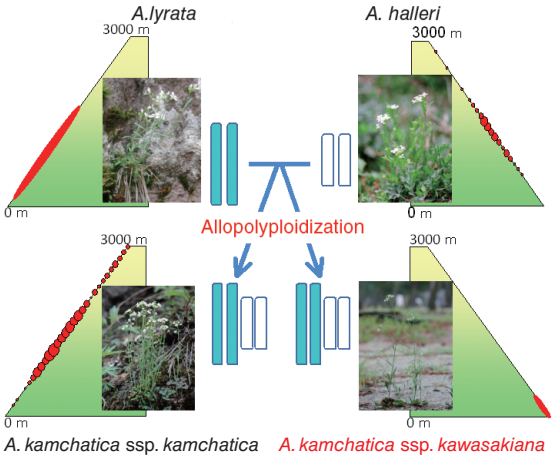


Ecological and population-genetic responses of plants to temporal-spatial environmental changes

Kenta Tanaka Graduate School of Life and Environmental Sciences

With the progress of genetics, it has been clarified that about half of genes show no abnormality after breakage in laboratories. These genes possibly have some function in outdoor ecosystem too. In the field of outdoor ecology, on the other hand, phenotypic studies have been mainly carried out. Under these circumstances, we are trying to clarify the environmental adaptation and temporal-spatial dynamics in an outdoor ecosystem of a wild species belonging to *Arabidopsis*, which are ecologically interesting and genetically advantageous, at gene level.

Arabidopsis kamchatica ssp. *kamchatica* and *A. kamchatica* ssp. *kawasakiana* are known as allopolyploids independently obtained by species crossing of *A. lyrata* with *A. halleri.* Thus, these two daughter subspecies take over the complete genome sets of the parent species. However, *A. kamchatica* ssp. *kamchatica* is perennial and distributed over a wide altitudinal range of from 30 m to 3,000 m at roughly the same latitude, while *A. kamchatica* ssp. *kawasakiana* is annual and grows exclusively in lakeside and seaside in low altitudinal areas. Why do these subspecies have such different properties? Why can *A. kamchatica* ssp. *kamchatica* adapt to widely different environments? Is there a new natural selection of *A. kamchatica* ssp. *kamchatica* concerning global warming in low altitudinal areas? To answer these questions, we are searching for genes efficacious for studies of life history and altitudinal adaptation and studying temporal-spatial changes in allele frequency, local adaptation level, the meaning of life history in adaptation and so on by taking an integrated approach from the standpoints of ecology and genetics.



Clarification of the regulatory mechanism of time-course ageing in eukaryotic cells using budding yeast

Hiroshi Masumoto Graduate School of Life and Environmental Sciences

Organisms age with the passage of time and finally meet an end. Ageing accelerators include excessive nutrition intake, cumulative DNA mutations likely caused by UV light or chromosome reduplication and protein inactivation due to oxidation caused by active oxygen accumulated in cells. Cells have a specific molecular mechanism for regulating ageing by which the aforesaid factors are detoxified to retard the progress of ageing. However, this molecular mechanism for regulating ageing has not been completely clarified.

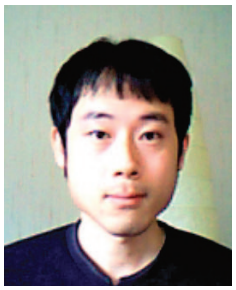
Various post-translational chemical modifications of histone (histone modifications) constituting chromatin in chromosome participate in various intracellular functions via structural changes in chromatin. Interestingly it is has been found that histone modifications also participate in the progress of cellular ageing.

We have given our attention to the histone modifications. This is because various cellular functions mediated by histone modifications are possibly regulated indirectly by regulating enzymes relating to the histone modifications with the use of inhibitors or the like. In its turn, it is expected that artificial regulation of the modification, addition or removal of histone participating in cellular ageing could contribute to the retarding of the progress of cellular ageing or the establishment of therapies for various ageing-associated diseases.

Using a budding yeast for which a number of genetic and biochemical techniques have been established as an organic model, we are attempting to analyze histone acetylase and deacetylase participating in the repair of DNA damage and cellular ageing, clarify the mechanism for regulating ageing mainly relating to histone modifications, and clarify an upper regulatory mechanism of the mechanism for regulating ageing by histone-modifying enzymes. Further, we are planning to examine whether or not the mechanism for regulating ageing mainly relating to histone modifications is conserved not only in the budding yeast but also commonly in other species. Furthermore, we are planning to indirectly control the function of the mechanism for regulating ageing with the use of a chemical capable of regulating the activity of histone-modifying enzymes, thereby searching for a possibility of the application in the medical field for retarding the onset of ageing-associated diseases.

Study on high-energy reaction of QCD by gauge/string duality

Yoshitaka Hatta Graduate School of Pure Applied Sciences



It is known that protons, neutrons and atomic nuclei ultimately consist of quarks and gluons and interaction between them are controlled by quantum chromodynamics (QCD). My major is QCD-based theoretical analysis on high-energy collision experiments which are undertaken by using accelerators such as RHIC in Brookhaven in USA, HERA in DESY in Germany and LHC in CERN in Switzerland. My research aims at, for example, clarifying interactions and inner structure of protons by computing the cross-sectional area (scattering probability) in the collision between electrons and protons in HERA and the distribution of detected particles. Among all, I am strongly interested in the so-called Regge limit at which collision energy becomes much higher than on any other scale such as mass. In this area, particles having vacuum quantum numbers that are called pomerons determine the cross-sectional area behavior. Studies for theoretically understanding the structure of pomerons have been carried out over a long time. I have been attempting to solve this problem by taking two approaches. First, in the perturbation theory based on the first principle derived from QCD, certain higher terms amplified by the logarithm of energy should be preferentially added up. Under this approximation, however, the cross-sectional area becomes too large compared with discovered data. Thus, gluon saturation originating in intragluon interaction should be taken into consideration. So, I attempted to establish a self-consistent formula therefor. Concerning certain phenomena in the Regge region, on the other hand, it is sometimes observed that the perturbation theory cannot be employed at all since the coupling constant becomes too large. Therefore, I propose high-energy scattering in the supersymmetric Yang-Mills theory which allows analytic handling even in the case of strong coupling. This theory is attractive since it achieves a duality together with the string theory in a certain background field. This duality makes it possible to compute various physical amounts in the strong coupling region in the Yang-Mills theory using the perturbation theory of the string theory which cannot be carried out in usual. Owing to these characteristics, the duality has strongly attracted public attention in recent years. I'm trying to understand phenomena in the strong coupling region of high-energy QCD by using this duality.

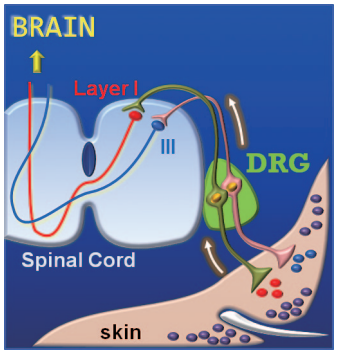
Molecular biological basis for the diversity of neural circuit controlling pain/itching transmission

Hiroshi Hasegawa Graduate School of Comprehensive Human Science

Among the five human sensations, "tactile sensation" comprises a neutral system which receives various stimuli on the skin caused by, for example, pains, temperature or chemicals and mechanical stimuli and transmits the same to the brain. It is known that primary sensory nerve cells directly receiving these stimuli are roughly classified into algetic nerve cells perceiving pains and mechanical stimulus-sensing nerve cells perceiving pressure and these cells are further classified into subtypes depending on their molecular biological and electrophysiological properties. Such diversity of these primary sensory nerve cells seemingly plays an important role in the accurate cognition by the brain of the various stimuli on the skin. However, there still remain unsolved problems concerning molecular systems. Namely, what stimuli do the individual primary sensory nerve cells receive? What signaling systems do the primary sensory nerve cells use? How are neural circuits specific for the individual sensations formed?

An object of the present study is to clarify the diversity of primary sensory nerve cells occurring in dorsal root ganglions (DRG) depending on differences in gene expression patterns and thus disclose molecular mechanisms by which signaling systems and neural circuit networks carried by individual nerve cell subtypes are constructed. Based on screening techniques with the use of DNA microarrays and the like, we have identified novel genes specifically expressed in nerve cell subtypes. Moreover, we have conducted biochemical and molecular biological analyses on the functions of these genes in sensation signaling and neural circuit network construction using cultured nerve cells. Also, we have discussed these functions at the individual level through the construction of knockout mice.

Although pain and itching have been main concern in the field of medicine over a long time, the signaling mechanisms thereof have never been completely clarified so far. As a result, no sufficient technique for treating or ameliorating pain and itching has been established hitherto. Through the aforesaid studies, we are trying to clarify the biological basis for the construction of the sensation cell circuit and search for a new drug design target that is useful in treating pain and itching.

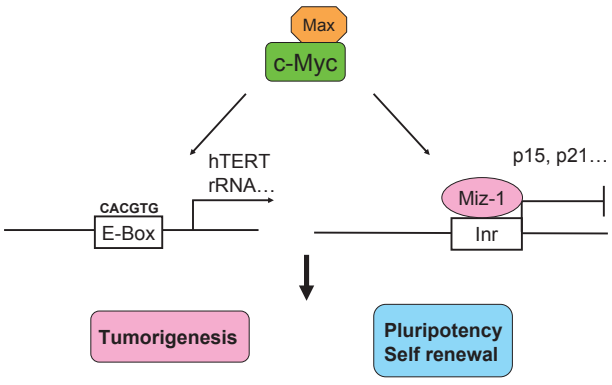


Cell proliferation regulatory mechanism by Tsc-22 family protein

Hiroyuki Suzuki Graduate School of Comprehensive Human Science

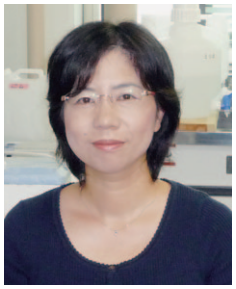
Stem cells play important roles in homeostatic tissue construction and regeneration from injury. Tissue stem cells are known as being capable of producing differentiated cells of multiple systems and having self-replicating ability. Induction of the differentiation from embryonic stem cells (ES cells), which are established from the blastocyst of a fertilized egg and have high capacity of proliferation and undifferentiation, into ectodermal, mesodermal and endodermal cells seemingly plays the major role in regenerative medicine. In recent years, there has been proposed a concept "cancer stem cells" which means a cancer tissue has a hierarchical structure similar to normal stem cell systems. Cancer stem cells, which are formed due to the accumulation of mutagens in cancer genes or tumor suppressor genes in tissue stem cells, are considered as the target in definitively treating cancer. However, there still remain a number of unknown points concerning the onset mechanism, location sites and maintenance mechanism of cancer stem cells. An object of the present study is to clarify the regulatory mechanism of stem cells and cancer stem cells by analyzing c-Myc, which is a transcription factor playing an important role in regulating stem cells, and its novel control protein Tsc-22 and also analyzing the signaling pathway (TGF-β, Wnt signal path and low-molecular weight G protein).

Function of transcription factor c-Myc



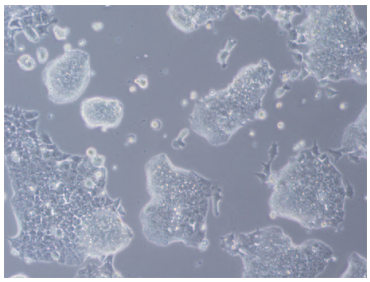
Molecular mechanism controlling the developmental destiny of ectoderm

Mami Matsuo-Takasaki Graduate School of Comprehensive Human Science



All body-constituting cells generate from three regions defined in an early embryo, namely, ectoderm, mesoderm and endoderm. We have paid attention to the early development of ectoderm capable of producing nerve cells, sensory cells, epitheliums and so on and therefore conducted studies thereon. Ectoderm is classified into neurogenic ectoderm and non-neurogenic ectoderm depending on differentiated cells. Cranial sensory organs playing an important role in receiving signals from outside are differentiated from a specialized non-neurogenic ectodermal region adjacent to the cranial neurogenic plate that is called specified sensory placodes. In the early developmental stage, it is considered that the following phenomena are controlled stepwise: (1) destination of cranial non-neurogenic entoderm; (2) formation of consecutive specified sensory placodes outside the cranial neurogenic plate; (3) determination of the differentiation as sensory placodes; and (4) final specialization into individual sensory epitheliums (olfactory epithelium, crystalline lens and inner ear). Concerning the question "What positional information determines sensory placodes in the development?", we have conducted analyses using *Xenopus* as a model animal and clarified that a transcription factor Xfoxi1a is essentially required in specific sensory placode formation and that combination of BMP with anti-Wnt signal is a positional information that controls Xfoxi1a expression.

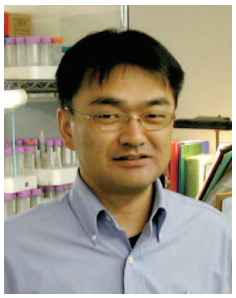
On the other hand, the differentiation mechanism of non-neurogenic ectoderm in the early developmental stage of mammals has been scarcely known. One of the reasons therefore is that, relating to mammals such as mice, there is no such *in vitro* experimental system as observed in the animal cap assay using *Xenopus*. In recent years, *in vitro* differentiation techniques using embryonic stem (ES) cells have been developed and studies have been energetically made both in Japan and abroad on the differentiation of ectoderm especially into nerve cells. We are now trying to apply the findings obtained in amphibian to *in vitro* differentiation systems of mouse and primate ES cells to thereby disclose the development mechanism of mammalian non-neurogenic ectoderm (in particular, sensory placode formation) that still remains unknown. Moreover, we are going to make fundamental researches aiming at stem cell therapy for diseases associated with sensory organ disorders such as cataract, olfactory disturbance and sudden deafness.



Mouse ES cells

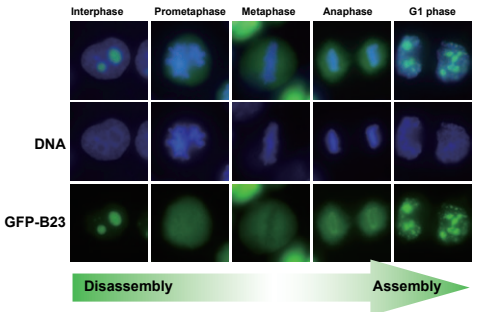
Function of cell nucleus relating to DNA virus proliferation

Mitsuru Okuwaki Graduate School of Comprehensive Human Science



When enclosed in a particle, a virus genome, regardless of either DNA or RNA, forms a complex together with basic proteins that originate in the host or are encoded by the virus *per se*. The formation of such nucleic acid-protein complexes enables the enclosure of a great number of DNAs or RNAs in small particles. Also, DNAs or RNAs of the host cells are enclosed in the cells in the same manner. In human cells, DNA of 3×10^8 base pairs is enclosed in a cell nucleus having a small diameter of 10 μm. Therefore, the DNA forms a complex with basic proteins including histone to construct a chromatin structure. The nucleic acid-DNA complex formation restricts the access of a transcription factor to the DNA and thus represses transcription or duplication. For these reactions, therefore, nucleic acid-protein complexes should be remodeled both in viruses and humans. Using an adenovirus as a model material, studies are now undertaken in our laboratory to identify a host factor relating to the remodeling of a nucleic acid-protein complex, clarify the proliferation process of the adenovirus and disclose the function of the host factor in non-infected cells to thereby clarify the nucleic acid-protein complex remodeling mechanism in cells. Moreover, we are interested in the formation of cell nucleus structure in which chromosome is enclosed and now conducting further studies on, in particular, the function and structure of nucleolus. It is suggested that the host factor handled in the present study might relate to canceration such as leukemia. Thus, the clarification of the function of the host factor possibly results in the clarification of cell canceration mechanism. Furthermore, it has been found out that nucleolus, in which ribosome is biosynthesized, has various functions concerning cell cycles and cellular response to stress. It is also known that a mutation in nucleolus induces not only cancer but also various inherited diseases. Accordingly, to clarify the structure and function of nucleolus is a very meaningful task for disclosing the causes of these diseases too.

Assembly and disassembly of the nucleolus



Prevention of viral infection by improving surface adsorptivity, directional diffusion in lipid membrane and mechanism of amyloid fibril dissolution

Hall Damien Richard Graduate School of Comprehensive Human Science

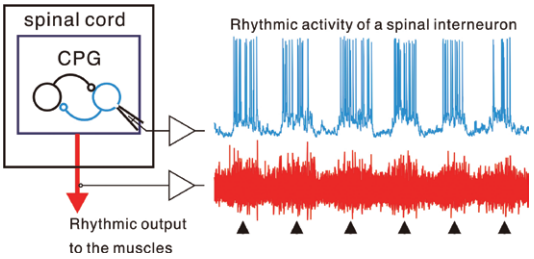
My research is concerned with the biophysical study of important biochemical processes related to disease states. The three topics studied in my laboratory are (i.) amyloid formation and its molecular relationship to disease, (ii.) novel mechanisms for preventing viral adsorption/entry to/through the epithelial cell membrane, and (iii.) protein diffusion in the cell cytosol and cell membrane and its relationship to cell/cell signaling. We use a combination of theoretical and experimental methods ranging from high level computing to basic molecular biology, cell biology and biochemical techniques. The advantage of this combined approach is that it allows the research questions to be tackled in greater depth and the experimental results generated to be subjected to greater rigor prior to publication. In this first six months (January 2008 – present) the research focus has been spread equally on all three topics with a book chapter on adsorption measurement and theory published by the Royal Society of Chemistry (1), a paper concerned with measurement of diffusion in the cell membrane (2) and a review (3) and paper (4) respectively concerned with the measurement and simulation of protein aggregation.

(1) Hall, D. (2008) 'Kinetic Models Describing Biomolecular Interactions at Surfaces.' Chapter 4: Handbook of Surface Plasmon Resonance Eds. R. Schasfoort and A. Tudos. Royal Society of Chemistry. London, U.K.
(2) Hall, D. (2008) 'Analysis and interpretation of two-dimensional single-particle tracking microscopy measurements: effect of local surface roughness.' Analytical Biochemistry 377, 24-32.
(3) Hall, D. (2008) 'Protein Aggregation: Theory and Measurement' (manuscript in preparation).
(4) Hall, D., and Hirota, N. (2008) 'Multi-scale modeling of amyloid growth from unfolded proteins using a set of 'theory derived' rate constants.' (manuscript in preparation).

Disclosure of the activation mechanism of mammalian spinal motor center

Hiroshi Nishimaru Graduate School of Comprehensive Human Science

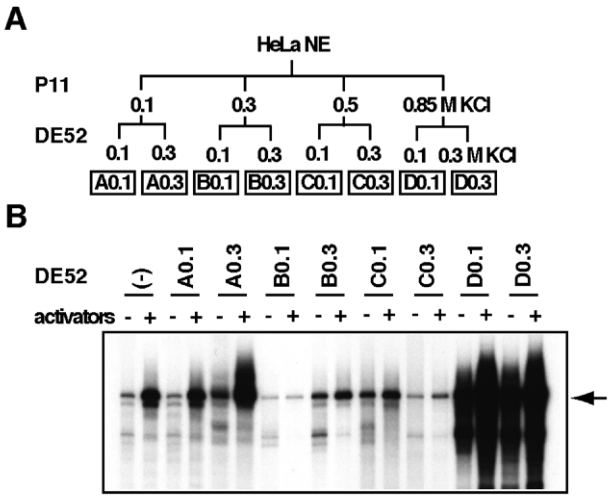
It is considered that our body and mental movements are evoked by neuronal circuits consisting of nerve cells in the central nerve system that are bonded to each other. Concerning these neuronal circuits, however, there have been scarcely disclosed even the fundamental facts, for example, how electrochemical actions of nerve cells with what properties are combined together to generate output patterns from individual circuits. To solve these problems, our research targets neuronal circuits that evoke walking. Walking movements are achieved by rhythmic bursts of motor nerve cells controlling the respective muscles each at an appropriate timing. At this stage, the rhythmic input to the motor nerve cells is realized by the walking motor neuronal circuit network localized in the spinal cord. This circuit network can form rhythmic output patterns without having rhythmic input from outside. A circuit having the aforesaid properties is generally called a central pattern generator (CPG). Such rhythmic nerve actions are common phenomena that are observed not only in the walking CPG but also in many sites in the central nerve system including brain cortex, hippocampus and brain stem. Therefore, we think that the clarification of the activation mechanism of the walking CPG directly relating to movements can provide an important cue for understanding the activation principles of not only the spinal cord but also other neuronal circuits in the central nerve system. We are going to identify nerve cells constituting CPG by using physiological research techniques by which nerve cell actions can be understood on real time, morphological research techniques by which axons and dendrites can be clarified in detail, and techniques for visualizing specific cells using gene modification techniques combined with knockout mice. Thus, detailed discussion can be made on how a single nerve cell's behavior contributes to the output from neuronal circuits. Using factors that are important in neural transmission and axon guidance, we are attempting to examine what roles these factors play in the function and developmental differentiation of CPG with the use of knockout mice of these factors.



Novel coactivator of c-fos gene and analysis of gene regulatory mechanism

Aya Fukuda Graduate School of Comprehensive Human Science

It is estimated that we each have more than 20,000 genes. Expression of these genes is delicately regulated and varies over a wide scope depending on development, differentiation, external stimulation and so on. In many cases, gene expression is regulated in the transcription stage. Owing to prior studies, there have been identified a number of cis factors (enhancers and promoters) and trans actors (transcription factors and conjugation factors). However, it still remains unknown at many points how these factors regulate RNA polymerase functions and regulate transcription. We are conducting studies to clarify gene regulatory mechanism by RNA polymerase II at the molecular level. For analysis, a transcription system that has been reconstituted *in vitro* using recombinant proteins and proteins purified from cells is mainly employed. Thus, we have so far identified novel coactivator-like molecules capable of promoting transcription from c-fos gene promoter. At present, the functions of the identified coactivator-like molecules are analyzed and transcription-activating mechanism is examined. Moreover, the relationship between histone modifications (acetylation, methylation, phosphorylation and so on), which become the focus in recent years, and gene expression is also analyzed by constructing a transcription system using chromatin reconstituted *in vitro* as a template.



(A) Fractionation of Hela cell nucleus extract
(B) Detection of activity promoting transcription from c-fos gene promoter

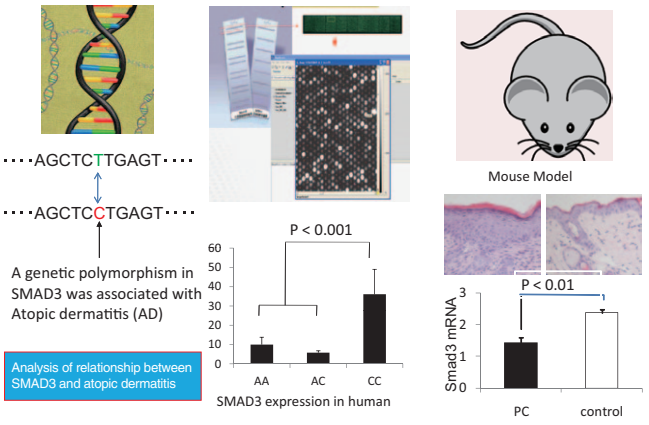
Clarification of clinical conditions of allergic diseases based on genetic approach

Emiko Noguchi Graduate School of Comprehensive Human Science

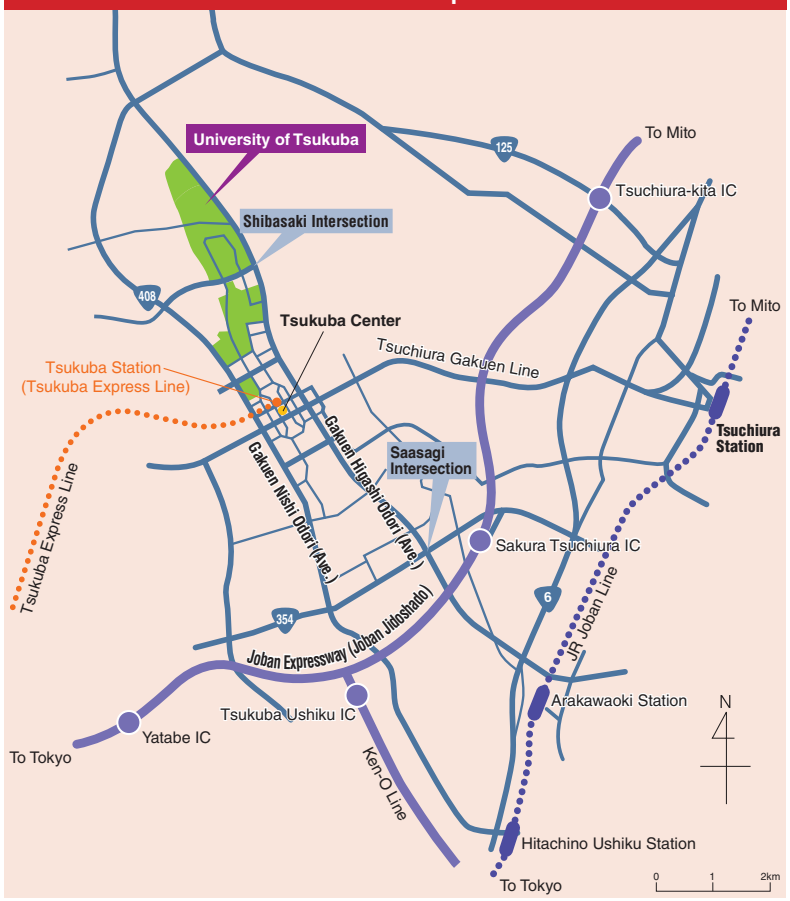
We humans differ from person to person both in appearance and nature. Also, susceptibility to disease varies from individual to individual and the susceptibility is determined by "genetic information" carried by the human body and its "environment".

The subject of my study is the transmission of allergy. I selected this research theme because we have a family history of allergies. That is, I myself have suffered from severe asthma, my brother is an asthmatic too and my sister suffers from atopic dermatitis. Allergy (atopy) is defined as a hypersensitivity to an antigen (dust, animal hair, pollen, etc.) to form IgE antibody. Typical examples of atopic diseases include bronchial asthma, atopic dermatitis, allergic rhinitis and conjunctivitis. Atopy is a concept originally proposed because of its hereditary tendency which has been proved by studying families and twins. However, it is assumed that the hereditary pattern of atopy is not a mere Mendelian heredity. Namely, these diseases are seemingly multifactorial disorders in which multiple genes and factors caused by environmental exposure participate together.

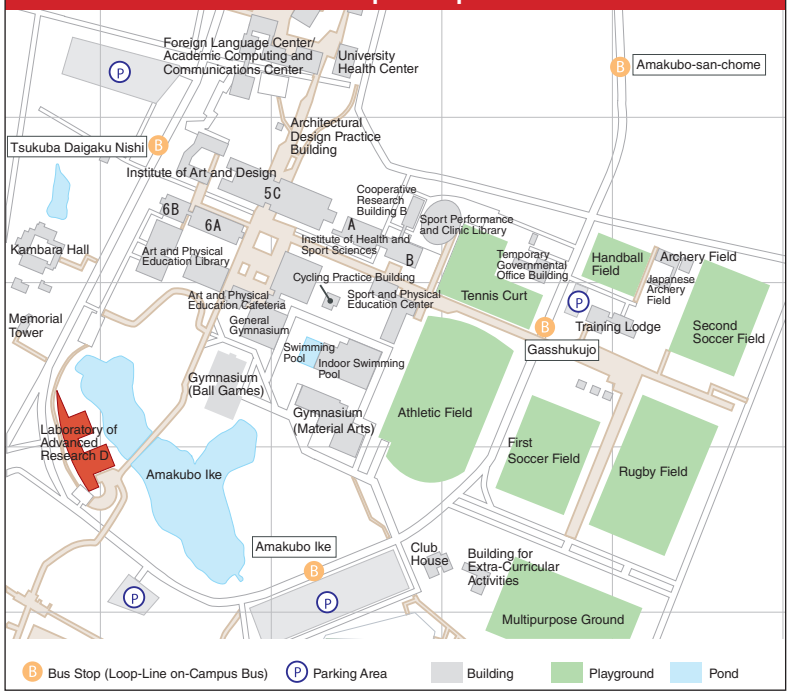
I am attempting to clarify such complicated disease mechanisms using various techniques including genome-wide associated studies examining several hundred-thousand kinds of gene polymorphisms, gene expression analysis, proteome analysis, construction of allergic disease model animals and so on. My research goal is to clarify complicated disease networks and, in its turn, give something back to patients. So, I am studying hard everyday to achieve this object.



Access map



Campus map



University of Tsukuba
Promotion Committee for the "Initiative to Train Young Researchers Who Will Lead the Next Generation"
Division for Supporting Young Scientists [edited by Furugen]
Laboratory of Advanced Research D, 1-1-1 Tennodai, Tsukuba, 305-8577 Ibaraki, Japan
TEL: 029-853-6939　029-853-7929
FAX: 029-853-5983

Access to University

Tsukuba Express Line

- From Akihabara Station to Tsukuba Station (45 minutes at the minimum)
  At Tsukuba center, transfer to bus bound for "Tsukuba Daigaku Chuo" (10 minutes)
  Loop-line on-campus bus (clockwise, anticlockwise) (10-15 minutes)

JR Joban line

- From Hitachino-Ushiku Station Bus Terminal (East Exit)
  By bus bound for "Tsukuba Center" (40-50 minutes)
  By taxi from East Exit (20-25 minutes)
- From Arakawaoki Station Bus Terminal (West Exit)
  By bus bound for "Tsukuba Daigaku Chuo" (30-40 minutes)
  By taxi from West Exist (20-25 minutes)
- From Tsuchiura Station Bus Terminal (West Exit)
  By bus bound for "Tsukuba Daigaku Chuo" (25-35 minutes)
  By taxi from West Exist (15-20 minutes)

Highway bus

- From Tokyo Station Yaesu South Ticket Gate
  By highway bus bound for "Tsukuba Center" (65 minutes)
  (runs every 20 minutes)
  At Tsukuba center, transfer to bus bound for "Tsukuba Daigaku Chuo" (10 minutes)
  Loop-line on-campus bus (clockwise, anticlockwise) (10-15 minutes)

Car

- From Joban Expressway (Joban Jidoshado)
  Turn left at Sakura-Tsuchiura Interchange towards Tsukuba
  Turn right at Sasagi intersection
  → Drive along Ibaraki Prefectural Route 55 (Higashi Odori) heading north
  → Turn left at the main gate of the University of Tsukuba
  (8 km from the exit of Joban Expressway)
- From National Highway Route 6
  Turn into Ibaraki Prefectural Route 55 (Higashi Odori) at Gakuen Higashi Odori Iriguchi intersection (Arakawaoki) and head north
  → Go straight through Sasagi intersection
  → Turn left at the main gate of the University of Tsukuba
  (in front of the Administration Center building)

Flight

- From Narita International Airport
  By highway bus bound for "Tsukuba Center" (100 minutes)
  At Tsukuba center, transfer to bus bound for "Tsukuba Daigaku Chuo" (10 minutes)
  Loop-line on-campus bus (clockwise, anticlockwise) (10-15 minutes)
- From Tokyo International Airport (Haneda)
  By highway bus bound for "Tsukuba Center" (100 minutes)
  At Tsukuba center, transfer to bus bound for "Tsukuba Daigaku Chuo" (10 minutes)
  Loop-line on-campus bus (clockwise, anticlockwise) (10-15 minutes)

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