





Members of the Unit for Molecular Neurobiology of Learning and Memory

Unit for Molecular Neurobiology of Learning and Memory  
Principal Investigator: Dr. Shogo Endo (center)

The Unit for Molecular Neurobiology of Learning and Memory, headed by Dr. Shogo Endo, was launched in September 2004 in Uruma City. Although Dr. Endo experienced difficulty recruiting staff at the beginning, the unit has now grown into a team of 12. Originally from Japan's northernmost island of Hokkaido, Dr. Endo is also interested in teaching and has given a number of public lectures. In the most recent one that took place last November at Okinawa Prefectural Miyako High School on Miyako Island, he spoke about the secrets of memory to the entire school of about 1,000 students. Now with about 18 months remaining until the end of his five-year research project, Dr. Endo spoke about his unit and its research goals.

***What makes each of us different?***

As a youth, I wanted to study a medicine-related subject because I was a weak child. After studying about the brain at Hokkaido University, however, I became interested in learning what makes us human. Although almost all genes are identical in any one individual, we each have a personality formed by experience. The experiences stored as memory shape our personality and control our daily behaviors. Memory is also the basis for the higher brain function including thought, language, and emotion. I was keen to explore the molecular mechanisms underlying learning and memory.

***Understanding the underlying processes of memory and learning***

**1. Neuronal plasticity**

Neurons communicate each other through a specialized

structure called the synapse. Each neuron's functions and signaling process are mediated by molecules including DNA, RNA and proteins. It is amazing to imagine these biochemical reactions take place in our neurons, which



Dr. Endo at his office in Uruma City



further lead to the increase or decrease of synaptic transmission efficiency. Integration of these biochemical reactions in neurons supports our daily behaviors. If the signaling patterns were fixed based on our gene, our behaviors would always be the same. But we have a flexibility of the brain, called neuronal plasticity. Neuronal plasticity makes it possible to adapt to the ever-changing environment by compensating for the limited information available from our genes. In this unit, we are studying neuronal plasticity and memory.

## 2. Roles of the amygdala, cerebellum and hippocampus in memory

A neuron contains tens of thousands of varieties of proteins. One of our goals is to examine the effect of one-protein manipulation on memory using genetically modified mice. We are studying three parts of the brain, amygdala, cerebellum and hippocampus.

One of the memory classifications is based on contents of information. Declarative memory, which can be stated, requires conscious recall. This type of memory, involving the hippocampus, can be tested by asking "What is the prefectural capital of Okinawa?" In contrast, non-declarative memory cannot be described by words and includes skills such as riding a bicycle. The cerebellum plays a role in non-declarative memory. The amygdala plays an important role in emotional memories, such as likes and dislikes, happiness and sadness, as well as fear and anxiety.

Another memory classification is based on the duration of memory retention. Short-term memory lasts for minutes and long-term memory often lasts for the lifetime of the animal. One of the two physiologically different processes assumed for the formation of long-term memory is the conversion of short-term memory to long-term memory, while the other notion is the consolidation of long-term memory independent of short-term memory. Long-term memory formation requires new protein synthesis via gene expression. In gene expression, mRNA is transcribed from template DNA in our gene and mRNA is translated into proteins, functional units in neurons. The first step, called



Dr. Tomoko Arasaki prepares for protein analysis

transcription, is a complicated and accurately-controlled process by transcription factors that respond to extracellular stimuli. One of our targets, MAP kinase is involved in the transcriptional regulation.

## 3. Cerebellum - the small but amazing brain

Although the size of the cerebellum is just 10% of the cerebral cortex, both have an almost equal number of neurons. Our research has found that G-substrate, a protein expressed exclusively in large neurons called cerebellar Purkinje cells, plays an important role in eye movement called optokinetic response (OKR). OKR can be observed by monitoring synchronization of the eye movements to the screen movement shuttling left-to-right around a mouse. When the head of the mouse turns while the screen remains steady, the eyes move the same amount in opposite direction. This is called vestibulo-ocular reflex (VOR). The OKR and VOR are also observed in humans, and they are critical for seeing the outside environment clearly. These two types of compensatory reflex eye movement rely heavily on the cerebellum, which regulates smooth, accurate and rapid extension and contraction of paired muscles. Thus, patients with cerebellar dysfunction often experience abnormalities in their eye and body movement.

We have discovered the genetically modified mice for G-substrate, MAP kinase and transcription factor ICER have impaired long-term memory with intact short-term memory. With these findings, we hope to identify a cascade of gene expression events

during long-term memory formation. Moreover, we plan to look into the functions of the hippocampus and the amygdala, as our research has discovered the involvement of MAP kinases and ICER in fear memory as well as in spatial memory tasks.

### *The Brain: The last frontier*

Neuroscience research in Japan has made remarkable progress in the past decade. During my post-doctoral research in the United States, I worked on *Aplysia californica*, a 20-30 cm marine mollusk for studies of memory. The George H.W. Bush administration proclaimed



Looking at a human brain model from below. The two parts in brown are the cerebellum. Underneath the cerebellum is the cerebral cortex

the 1990s as the Decade of the Brain to highlight the exciting work in this emerging field. Inspired by the Decade, I shifted my own research target to the mammal hippocampus. I began studying the cerebellum after returning to Japan in 1997 at the RIKEN Brain Research Institute.

Currently, there are 12 members in our unit, including four post-doctoral researchers from Russia, France, the UK and Japan. We have five technicians who have special skills for the generation of genetically modified mice. I feel fortunate to work with such excellent staff, and I am always particularly impressed with the perseverance of the women in our research group. One of the benefits of being at OIST is its research environment. While our research requires good facilities and funding, OIST has allowed us to use state-of-the-art equipment, including what we need for genetically modified mice.

In addition to the research, I would like to continue promoting science to the next generation. Unlike clinical scientists, we, basic researchers, are invisible in the society. I feel it is our responsibility to advocate science to all ages. Okinawa is a compact island, so I hope we can raise local interest in OIST and science through our modest efforts.

The brain, often referred to as the last frontier in biology, has such complex structure and function that we cannot achieve understanding of its performance overnight. Recent medical advances can extend our life span significantly and treat the sick and the victims of accidents. However, aging and brain damage often cause memory problems. Memory works like a glue to adhere an individual to oneself, family and society. Loss of memory has a great impact not only on the individuals but on their family and society. Therefore, basic researchers are working hard to slow down or delay memory loss by the discovery of proteins crucial for memory. Knowledge of these proteins will determine a way to develop treatments or drugs for memory impairment. Understanding the mechanism underlying memory is essential to understanding cognitive impairment in adults.



Dr. Endo gives a lecture at Okinawa Prefectural Miyako High School

## A Promising Star

### Dr. Gilyana Borlikova



Dr. Borlikova is one of the four post-doctoral researchers in the Unit for Molecular Neurobiology of Learning and Memory. Originally from Kalmikiya, a republic in the Russian Federation, Dr. Borlikova studied behavioral psychology and neuroscience at Moscow State University and conducted post-doctoral research on rat behavior at the Russian Academy of Medical Sciences in Moscow. She was also a research fellow at the University of Sussex in the UK for four years. Dr. Borlikova spoke about her research background, ongoing projects and goals, and the culture shock she experienced when she first came to Japan.

I heard about OIST from my friends, who showed me a position announcement while I was still working in the UK. Until then, I only knew about Okinawa as the site of the 2000 G8 summit meeting. After learning about the objectives of OIST and actually visiting it for an interview, I knew I wanted to join this institution. In addition to the research emphasis of the unit and the facilities available in the lab, I was excited by the possibility of working on a project which combined complicated behavior with molecular analysis using mutant mice. I arrived in Okinawa in March 2006. Although I was aware of the potential difficulties awaiting me in a country whose language I did not speak, the reality was far more frustrating. I felt myself suddenly illiterate, and unable to conduct the simplest of tasks by myself, like finding directions on a map. However, thanks to the support of my colleagues and the administrative staff, I became used to the new life quite quickly.

I am currently studying the role of transcription factor ICER in operant-conditioned learning. In the course of operant conditioning, an animal learns to perform certain actions in order to receive a reward, such as food treat, or avoid punishment. We have already found out that ICER plays an important role in the formation of long-term fear memory and now I want to look into its role in reward learning. I am interested in studying reward learning because I personally believe that humans learn the majority of things through positive factors, including satisfaction from discoveries, acknowledgment, or actual rewards like a favorite food.

## OIST Update Dr. Robert Baughman

The past several months have seen great progress at OIST, and we are approaching the end of fiscal year 2007. We now have 17 Principal Investigators (PIs) installed and working, at the site in Uruma City and at the Seaside House in Onna Village. In addition, we have two new PIs, Dr. Noriyuki Satoh from Kyoto University and Dr. Jonathan Miller from Baylor College of Medicine, starting on April 1. Nine of the 17 current PIs are international, and of the 120 members of OIST working in the research laboratories, 32 are international, representing 18 different countries.

The 5th Board of Governors meeting was held on January 25 in Tokyo. Mr. Fumio Kishida, the State Minister for Okinawa and Northern Territories Affairs, Science and Technology Policy, delivered an address reporting that the Japanese



Minister Kishida delivers an address

government has proposed a substantial budget increase for OIST in fiscal year 2008. Several important resolutions were passed. The Board encouraged the consideration of environmental sciences as the next area of scientific focus for OIST. This is a scientific field well suited to the multidisciplinary approach at OIST. The Board also strongly reaffirmed the importance of constructing the new campus as an integrated facility with some housing completed with the initial phase of laboratory construction, in order to provide the kind of community that will make the new campus a vital center of research and training. The Board endorsed the creation of two new academic positions at OIST: Independent New Investigator appointments and Graduate Studentships.

Construction of the new campus in Onna Village is moving forward steadily. Essentially all of the site preparation work is now complete, and the construction of Laboratory 1 and the Center Building will be the next stage. Extensive planning is underway to coordinate the move of the research laboratories and the researchers and their families to Onna Village. Plans are under discussion for building housing in the Village Zone.

The first science and technology ministerial-level meeting, which has ever been held as part of the Group of Eight (G8) summit meeting, will be held in Okinawa in June, 2008. OIST is coordinating with the Cabinet Office (CAO) Bureau of Science and Technology Policy and Innovation, as well as the Okinawa Prefecture, to support satellite activities associated with the ministerial meeting. This meeting is an expansion of the sphere of G8 interactions at



Participants of the 5th BOG meeting

a time when the impact of science and technology is becoming increasingly significant, and it is important for OIST to support this effort. The Board fully endorsed our participation in the Science and Technology ministerial. The G8 summit itself will be held in Hokkaido in July.

As the research program grows, we have made changes in the administrative structure of OIST. The Officers of OIST are the President, Dr. Sydney Brenner, and the Executive Director, myself. We have established two divisions that reflect the mission of OIST to establish a world-class research program in science and technology and to prepare for the establishment of the graduate university. These are the Research Operations Division, with Mr. Ferry Toya as Director, and the University Planning Division, with Mr. Katsuhisa Sagisaka as Director. In addition, Mr. Toya is Executive Assistant to the President for operations issues, and Mr. Kensuke Katsuno has been appointed as Executive Assistant to the President for compliance issues. Mr. Katsuno, who has extensive experience in the CAO, is independent of the line management and advises the President and Executive Director on contract compliance and regulations. To handle the increasing scale of our international scientific effort, we have added new personnel in high performance computing and IT and in several other areas. As we look forward to the coming fiscal year, an especially important activity now is planning for the exciting challenge of moving to the new campus in Onna Village.



**Executive Director**  
**Dr. Robert Baughman**

Born in Pennsylvania, U.S.A. in 1947. After receiving his Ph.D. in chemistry from Harvard University in 1974, Dr. Baughman was a faculty member in neurobiology at Harvard Medical School from 1979 to 1995. He was the director of the graduate program in neurosciences at the university 1991-1993. He moved to the National Institute of Neurological Disorders and Stroke (NINDS) as the director of the Division of Fundamental Neuroscience 1996-1999. From 1999 to 2007, Dr. Baughman served as Associate Director for Technology Development, the Office of the Director at NINDS, while concurrently serving as a special adviser at OIST 2005-2007. He was appointed Vice President and Executive Director of OIST in September 2007.



## ADHD Lecture

Dr. Joseph Sergeant, Professor in the Department of Clinical Neuropsychology at the Free University (Vrije Universiteit) in Amsterdam, presented a lecture on February 7 at the Okinawa Prefectural Nanbu Medical Center and Children's Medical Center in Haebaru Town. Dr. Sergeant is a leading authority on Attention Deficit Hyperactivity Disorder (ADHD), the primary research focus of the Human Developmental Neurobiology Unit at OIST, led by Dr. Gail Tripp. The lecture, focusing on the validity and treatment of ADHD, was jointly hosted by the Nanbu Medical Centers and OIST.

Attention Deficit Hyperactivity Disorder (ADHD) is a disorder characterized by symptoms of inattention, overactivity, and impulsivity. Many researchers now believe that ADHD has a neurobiological basis. Some professionals question the existence of this highly-researched disorder, arguing that children display some degree of inattentiveness, overactivity, and impulsiveness. Offering an accessible and thorough overview of the existing research into the nature and treatment of ADHD, Dr. Sergeant stressed that ADHD is a developmental disorder that is not simply outgrown, and the symptoms of this disorder continue to negatively impact those diagnosed into adolescence and beyond. Dr. Sergeant presented strong empirical evidence for the validity of this disorder. He also presented an overview of available research on the contribution of genes to the development of ADHD, noting that the interplay of several genes and environmental factors is likely to lead to the expression of the disorder symptoms. Dr. Sergeant and colleagues have recently



About 200 people including hospital staff filled the lecture hall



Dr. Gail Tripp of the Human Developmental Neurobiology Unit (left) asks a question

completed data collection from 1,500 children and their families in Europe. These researchers believe much about the genetics of ADHD will be revealed by this study. At the end of the lecture, Dr. Sergeant emphasized the importance of the study of the cerebellum, the basal ganglia and prefrontal cortex to understanding of ADHD. He concluded that specifying gene loci, associated with ADHD, may enable us to clarify diagnostic criteria for ADHD and treat those who have ADHD more effectively in the near future.

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Dr. Joseph Sergeant

Born in Scotland in 1945. After receiving his Ph.D. at the University of Groningen in the Netherlands in 1981, Dr. Sergeant held academic positions at the University of Groningen as well as at the University of Amsterdam. Since joining in 1999, Dr. Sergeant has headed the Free University's Department of Clinical Neuropsychology. He has chaired and coordinated the European Network on Hyperkinetic Disorders (Eunethydis) since its foundation in 1990. Dr. Sergeant has also served on the editorial board of *The Journal of Abnormal Child Psychology* since 1988 and was a member of the editorial board of *The Journal of Child Psychology and Psychiatry* for 10 years. His research career has concentrated on identifying the specific information-processing deficits of hyperactive children. A current focus of this research is on psychopharmacology and its effects on executive processing in children with ADHD.

## International Workshops and Seminars

OIST has been hosting international workshops and seminars to enhance cooperation with research institutions at home and abroad. These workshops and seminars also help introduce the vision of establishing a graduate university in Okinawa to the worldwide scientific community. Below is a list of workshops and seminars that took place between December 2007 and February 2008.

### 2007

#### December 3 Seminar at the Research Laboratory

"An Information Theoretic Framework for Eukaryotic Gradient Sensing "

Speaker: Dr. Peter Thomas, Case Western Reserve University  
Organizer: Dr. Klaus Stiefel, OIST

#### December 6 Seminar at the Research Laboratory

"Reactions to mirror reflection in oval squid "

Speaker: Professor Yuzuru Ikeda, The University of the Ryukyus  
Organizer: Dr. Klaus Stiefel, OIST

#### December 12 Seminar at the Research Laboratory

"Simple neural network model of cue-action-reward tasks based on salience gated working memory and dopamine modulated 3-way balanced Hebbian learning"

Speaker: Dr. Adam Ponzi, RIKEN Brain Science Institute  
Organizer: Dr. Jeff Wickens, OIST

#### December 20 Seminar at the Research Laboratory

"A comparative study of families of children with and without developmental disability - Japanese immigrants and Japanese American families"

Speaker: Dr. Keiko Ito, Stanford University  
Organizer: Dr. Gail Tripp, OIST

### 2008

#### January 7-8 HFSP International Workshop on Neural Control of Attention, Perception and Learning at the Seaside House

One of the Lecturers: Dr. Kenji Doya, OIST

#### January 10 Seminar at the Research Laboratory

"Yeast tropomyosin - crystallization and preliminary crystallographic analysis"

Speaker: Dr. Vladimir Meshcheryakov, RIKEN Harima Institute Spring-8 Center  
Organizer: Dr. Fadel Samatey, OIST

## HPC Workshop

A workshop on high-performance computing (HPC) for biological sciences, entitled "Hardware and Software for Large-Scale Biological Computing in the Next Decade," took place at the Seaside House in Onna Village on December 11-14, 2007. The goal of the workshop was to collect input from experts in the field for the development of scientific computing facilities at the OIST new campus, starting with the HPC center that is expected to open in 2009. Twelve speakers were invited, including researchers from Japan, the U.K. U.S.A., and the Blue Brain project in Switzerland. *OIST News* asked the participants about their impression of the HPC project and their advice for the new facility. The program of the workshop, organized by Drs. Kenji Doya, Klaus Stiefel and Erik De Schutter of OIST, and abstracts of presentations by the participants can be seen on our Website. <http://www.ird.oist.jp/hpc-workshop/abstracts.html>

### **"Experience is the best lesson"** Dr. Phil Andrews

Director, National Institute for Computational Sciences

Having worked on supercomputers for almost two decades, I can say that the OIST HPC facility is quite a big and exciting project. I suggest that OIST look into projects on supercomputers undertaken at other institutions, because some might offer a good lesson. A particular concern would be local power grids, because a lot of power supply is needed for the operation and cooling of HPC installations.

### **"Collaboration is the key"** Mr. John Shalf

Team Leader, National Energy Research Scientific Computing Center

The key thing is not having the biggest supercomputer in the world, but finding a Grand Challenge that will bring qualified people from home and abroad to run the facility. The environmental impact of installing and maintaining the facility is another key factor. Some supercomputers are not only fast, but they also consume considerably less electricity than others.

### **"Determine a purpose, and OIST will find its way"**

Dr. Tadashi Watanabe

Project Leader, RIKEN Next-Generation Supercomputer R&D Center

OIST should determine how it wants to use the HPC facility.

Given the emphasis of OIST on life sciences, which are becoming computation-based and data-driven, I believe it would add strength to OIST if you focused on analysis and modeling in collaboration with specialists in the fields of computer hardware, computer processing and neuroscience. Budgeting is another determining factor, and timing is also important, because computer technologies advance quickly.



Co-organizer, Dr. Erik De Schutter of the Computational Neuroscience Unit, delivers a welcome speech



Participants

At the end of the workshop, the participants agreed that large-scale computing will have a major impact on biological sciences in the next decade. As OIST develops its own world-class research program, the participants concluded, it will also need to deploy a top-ranking HPC facility with an unprecedented degree of integration with experimental systems, and it must formulate a long-term sustainable policy for expanding and improving the facilities according to the needs of the research.

#### **January 15 Seminar** at the Research Laboratory

"The positive feedback mechanisms that transduce short-live to long-lasting signals for cerebellar LTD"

Speaker: Dr. Keiko Tanaka of Duke University Medical Center

Organizer: Dr. Erik De Schutter, OIST

#### **January 28 Seminar** at the OITC

"Dissecting the neural machinery for face processing"

Speaker: Dr. Doris Tsao, University of Bremen

Organizer: OIST

#### **January 28- SBN Super-Hackathon Workshop**

**February 2** at the Seaside House

Co-organizer: Dr. Hiroaki Kitano, OIST

#### **February 1 Seminar** at the Research Laboratory

"Nitrite-dependent nitric oxide production mechanisms"

Speaker: Professor Hideo Yamasaki, the University of the Ryukyus

Organizer: Dr. Klaus Stiefel, OIST

#### **February 5 Seminar** at the OITC

"Taking apart the Neural Machinery of Face Processing"

Speaker: Dr. Winrich Freiwald, University of Bremen

Organizer: OIST

#### **February 5 Seminar** at the Research Laboratory

"Elementary Patterns of Resemblance"

Speaker: Dr. Gunnar Wilken, Westfaelische Wilhelms-Universitaet Muenster, Germany

Organizer: Dr. Robert Sinclair, OIST

#### **February 6 Seminar** at the Research Laboratory

"TRP channels and Magnesium homeostasis"

Speaker: Dr. Kouichi Iwasaki, Northwestern University

Organizer: Dr. Ichiro Maruyama, OIST

#### **February 18 Seminar** at the Seaside House

"Unraveling the 'Black Box' of the cerebellum"

Speaker: Dr. Marylka Uusisaari, RIKEN Brain Science Institute

Organizer: Dr. Erik De Schutter, OIST

#### **February 27 Seminar** at the OITC

"Integrating mass spectrometry and behavioral neuroscience in fruit fly models of courtship and aggression"

Speaker: Dr. Joanne Yew, Harvard Medical School

Organizer: Dr. Robert Sinclair, OIST

## Science Forum in Uruma City



BOG co-chair Dr. Akito Arima

The city of Uruma, where precursor research programs of OIST began in April 2004, held a science forum at Ishikawa Hall on February 16 to promote science to local residents. In the morning session, schoolchildren conducted a scientific experiment to experience firsthand the excitement of science. In the afternoon session, Dr. Akito Arima, a co-chair of the OIST Board of Governors, gave a keynote lecture discussing what science can do to save the Earth. Following the lecture, a panel of experts discussed ways in which Uruma City can become a "science city" in collaboration with OIST.



Children conduct a scientific experiment



Experts engage in a panel discussion

## Visit by Members of the Chamber of Commerce and Industry in the Northern Region of Okinawa

Twelve chairpersons and members of the Chamber of Commerce and Industry in Okinawa's northern city, villages and towns visited the Seaside House and the campus site on December 13, 2007. The members included those from Onna Village, where the Seaside House and the campus site are located. The visitors expressed hope that the launch of a world-class graduate university will enhance exchanges between the local community and the researchers and staff of OIST, and also bring economic benefits to the region.



CCI members from Okinawa's northern region were briefed by OIST staff on the main campus construction

## Main Campus Update

Construction of the main campus in Onna Village is under way, while construction of housing at the Seaside Center in the village has also begun. The extent of progress can be viewed on our Website, along with the latest activities at OIST. <http://www.oist.jp>



Housing at the Seaside Center (CG-image)

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