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FEATURE

Nanobiotechnology

New Technologies Extended by Interdisciplinary Integration for a Healthy Society

Research Hot Line

UPDATE FROM THE CUTTING EDGE (April.-June. 2007)

In Brief

Nanobiotechnology

New Technologies Expanded by Interdisciplinary Integration for a Healthy Society

Collaboration Promotion Department
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Expectations for nanobiotechnology

We hope everyone can live long in a healthy state. This is thought to be one of the basic conditions to realize a safe and secure society. The importance of health is also shown in the New Health Frontier Strategy set up by the Japanese government, and the social interest in health has increased more than ever before.

In such a situation, various problems have arisen that cannot be solved in the conventional technical field alone. For example, for routine health care or predictive diagnosis to spread in society, a technology is needed that allows examinations to be done easily and quickly at hospital or home. This is the concept called POCT (point-of-care testing), which means easy and quick testing carried out easily and quickly at or near the site of patient care. An indicator to quantitatively show a fair or poor physical condition is called a biomarker. To realize POCT, it is necessary to search for a science-based biomarker and develop a small inexpensive chip device to measure it. For implementation of such a device, huge interest is being taken in nanobiotechnology, which is an integration of bioscience and nanotechnology. A wide range of applications of nanobiotechnology is also expected in various fields such as predictive diagnosis, medical care, drug discovery and support for it, and the environment.

In general, there are two approaches of nanobiotechnology: top-down and bottom-up. The top-down approach analyzes biological phenomena and biomolecules using nanotechnology such as microfabrication technology. The bottom-up approach builds a molecular assembly and enhances its functions making use of the properties of biomolecules. Technologies for observation, measurement and manipulation at the nanoscale are also important as fundamental technologies. Because biomolecules contain in themselves structures for self-assembling and/or recognizing other molecules, bottom-up nanobiotechnology can be said to be a sort of supramolecular chemistry using biomolecules. The top-down approach is artificial and hard technology, while the bottom-up approach is soft technology that uses principles of biology and supramolecular chemistry. Combination of these technologies opens up various possibilities, for example, to fabricate a diagnostic chip with higher selectivity.

Nanobiotechnology research at AIST

A feature and advantage of AIST is that researchers from life science and other various fields can work together to exercise their collective power. Another strength is that the environment is prepared to be favorable and appropriate for conducting interdisciplinary research such as nanobiotechnology. The research underway at AIST includes basic research to

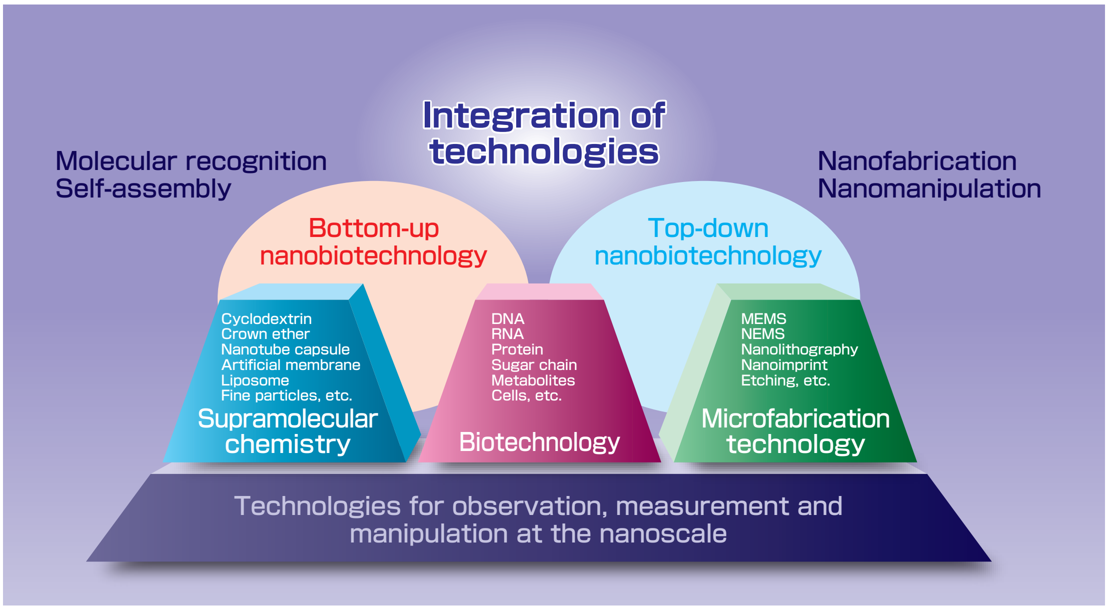

Figure: Creation of nanobiotechnology by interdisciplinary integration discover unknown phenomena or universal laws (Type 1 Basic Research), research to combine multiple pieces of scientific knowledge and technology (Type 2 Basic Research), and research to build up products (Product Realization Research). These are also conducted in a unified and concurrent manner (Full Research). Particularly, nanobiotechnology may be said to be representative of research centered on Type 2 Basic Research because the research evolves by integrating different disciplines. Research Institute for Cell Engineering, Institute for Biological Resources and Functions, and other research units are currently conducting research and development of cell and enzyme chips, disease marker sensors, stress measurement chips, predictive diagnosis chips, and other products, and are fostering personnel to lead the nanobiotechnology field in the future. Collaboration Promotion Department intends to promote cooperation with the industrial, governmental, academic, and other sectors through technological integration beyond interdisciplinary boundaries.

Fostering of Human Resources in the Nanobiotechnology Field

Research Institute for Cell Engineering
Noboru Yumoto

In the nanobiotechnology and other interdisciplinary fields, there is a serious shortage of personnel who can promote research and development. Thus, AIST established AIST Upbringing of Talent in Nanobiotechnology Course in FY 2003 (to FY 2007) by Promotion Budget for Science and Technology from Ministry of Education, Culture, Sports, Science and Technology (MEXT). This personnel fostering course consists of twelve full-time researchers belonging to AIST's five research units in the fields of life science, material and nanotechnology, and information technology and offers the curriculum as shown in the figure below. In addition to lectures and technical training, the trainees practice research under the common major theme of creating a nanobiomachine using motor protein to acquire hands-on skills and knowledge. Personnel training is given to professionals such as postdocs, graduate students, and engineers at companies, and a total of fifty-one persons were trained in the three years from 2003 to 2005. For personnel training, efforts have been made to keep track of corporate needs by questionnaire or other means, and the majority of those who completed in 2005 are already taking an active part at the companies.

For more information, please access http://unit.aist.go.jp/rice/link/nanobio/ (in Japanese).

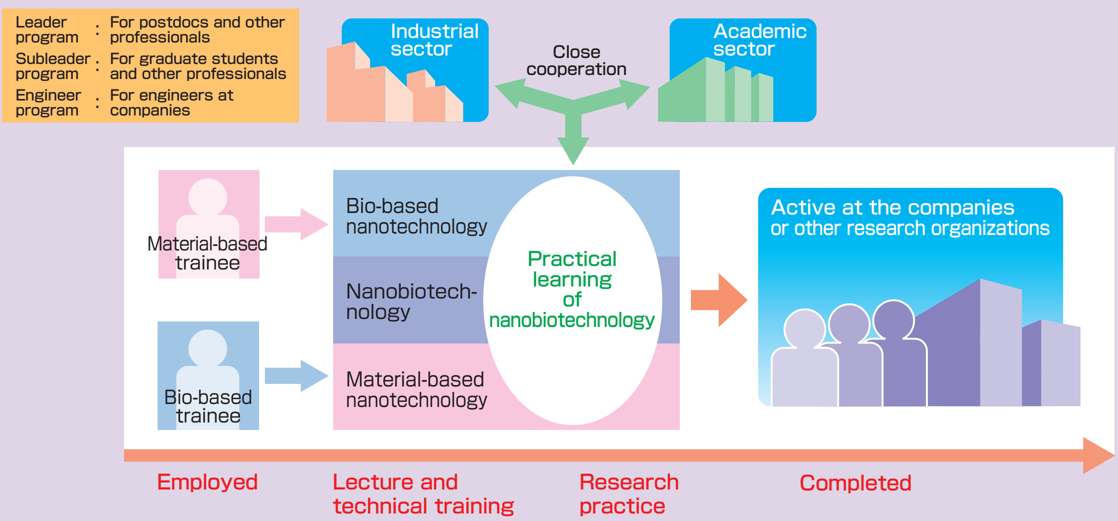

Figure: Curriculum of AIST Upbringing of Talent in Nanobiotechnology Course

Cell Chip Applicable to Compound Profiling

Research Institute for Cell Engineering
Masato Miyake

Importance of compound analysis

Today, we can find a wide variety of different types of chemical compounds such as pharmaceuticals, cosmetics, and food additives being used in all aspects of our everyday life. However, not all compounds have been thoroughly examined for their physiological action. If the biological effects of thalidomide, an antiepileptic drug notorious for its harmful effect, had been fully analyzed, the drug would not have caused severe malformations in infants born of mothers who had taken the drug during early pregnancy. It also might have been possible to predict at the first stage the usefulness of thalidomide in treating Hansen's disease and myeloma, which was found later.

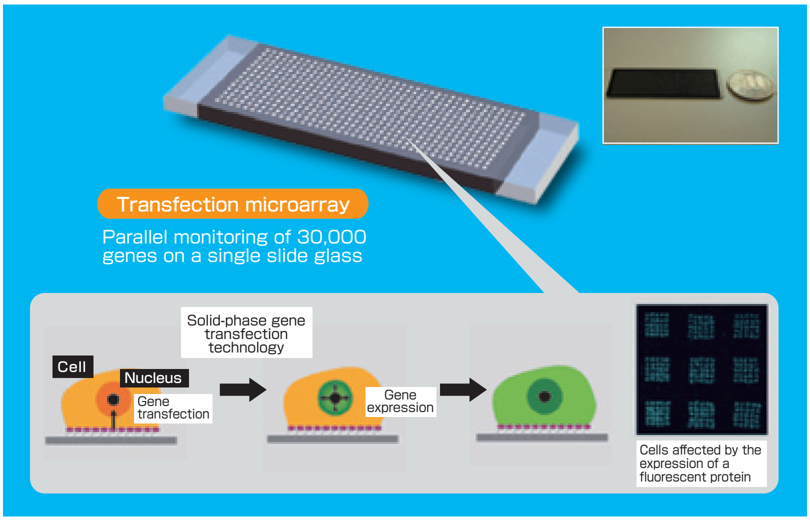

Figure 1: Appearance of transfection microarray and principle of gene transfection

Development of a profiling tool

The Cell Informatics Research Group developed some devices using cells of human origin designed for fast and detailed compound profiling (feature analysis) as a tool to support the search for new uses of compounds. One of these devices is a transfection microarray (Figure 1). In searching for a combination of RNA-interfering agents (for example, siRNA) that have similar action to, work together with, or interfere with a certain compound, this device can be used to search for such a combination fast among RNA-interfering agents targeting the entire human gene and thereby identify the target of that compound. Thus, it becomes possible to predict a compound that has similar or collaborative effects. In addition, an enzyme microarray (Figure 2) allows researchers to accelerate the search for a compound that specifically inhibits the combination of certain enzymes. The group is also conducting research and development of device and analysis technology to improve the accuracy of prediction of the biological action of compounds or their combination.

Compound profiling using the transfection microarray is commercialized by an AIST technology transfer venture, CytoPathfinder, Inc. (http://www.cytopathfinder.com/eng/), which serves mainly domestic and foreign pharmaceutical and chemical manufacturers.

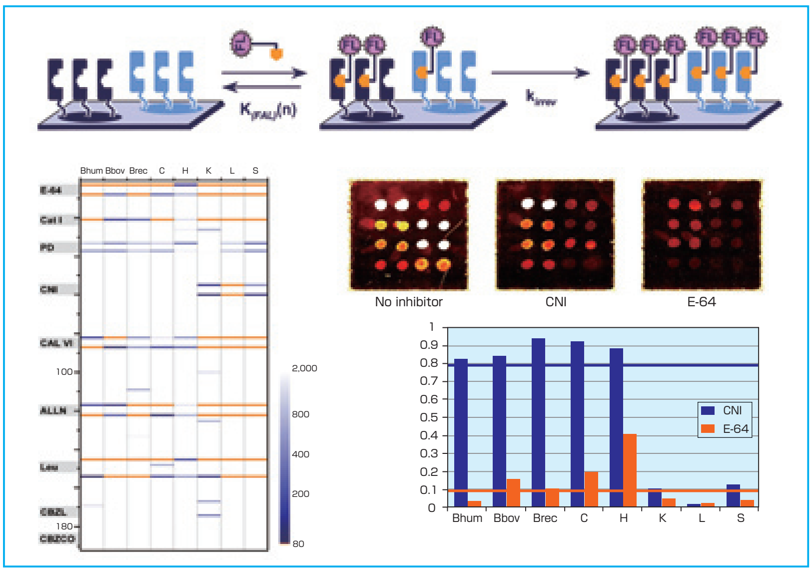

Figure 2: Parallel analysis of inhibitory effects of various compounds on the cathepsin family, using the enzyme microarray (Source: Nature Biotechnology, 23(5), 622–627 (2005))

Stress Measurement Chip: Aiming at Mental Disease Prevention

Human Stress Signal Research Center
Shin-ichi Wakida

Dilemma over stress marker measurement

Levels of catecholamines or other substances in the blood are known to serve as stress markers. For healthy people who are unaccustomed to blood drawing, however, blood drawing itself is a strong stress stimulus and causes stress responses such as a blood pressure rise. So, stress cannot be evaluated correctly, which is an intrinsic contradiction in stress measurement.

Aiming at a multicomponent measurement Lab-on-a-Chip

As shown in Figure 1, we are conducting basic research in an organized way, such as (1) development and demonstration research of Lab-on-a-Chip devices to measure stress-related substances in saliva, which can be taken as a noninvasive specimen, (2) research and development of Lab-on-a-Chip technology to measure stress-related substances in the blood in a minimally invasive manner, and (3) advanced fluid control technology to realize these techniques.

Development of a saliva stress measurement Lab-on-a-Chip device

We have chosen secretory immunoglobulin A (s-IgA), cortisol, and other substances in saliva, which are responsible for the biological defense function, as stress markers, and are developing a prototype of an electrophoretic Lab-on-a-Chip device and conducting basic research on a centrifugal Lab-on-a-Disk device.

Development of a saliva NO assay Lab-on-a-Chip device

We have chosen nitrogen monoxide (NO), which is responsible for the biological defense function, as an oxidative stress marker, and developed Lab-on-a-Chip technology for rapid assay of salivary NO metabolites. Existing NO assay kits use the Griess method and take more than 2 hours to measure the total content of nitrate and nitrite ions, which are metabolized rapidly.

Noting the fact that NO metabolites have absorption bands in the ultraviolet region, we have conducted further development following the strategy of separating on the basis of slight differences in physical properties by electrophoresis. As a result, we have achieved good quantitativity and reproducibility.

Demonstration research using saliva specimens

Saliva specimens were taken from subjects undergoing exercise stress approved by the Human Engineering Ethics Committee. By merely diluting the specimens 10 times, we realized separation and analysis of nitrate and nitrite ions for as short a time as 15 seconds, as shown in Figure 2. Furthermore, saliva specimens extracted from the high and low exercise intensity groups were used to analyze the relationships between the NO metabolite content and various exercise parameters. As a result, we obtained a preliminary result suggesting that the salivary NO metabolites would be an exercise stress indicator.

Clinical research on saliva NO measurement started

We are now conducting joint research with a circulatory system clinical laboratory and are working together to acquire fundamental clinical data not only of saliva measurement but also of blood measurement and breath measurement.

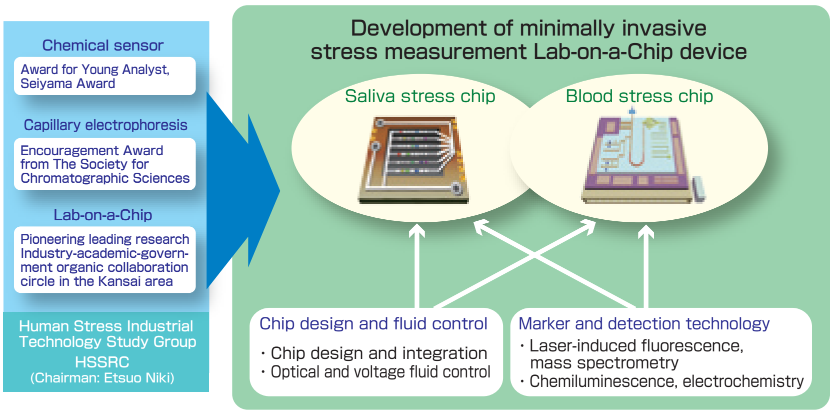

Figure 1: Schematic of R&D of a stress measurement Lab-on-a-Chip device and element technology and research structure for it

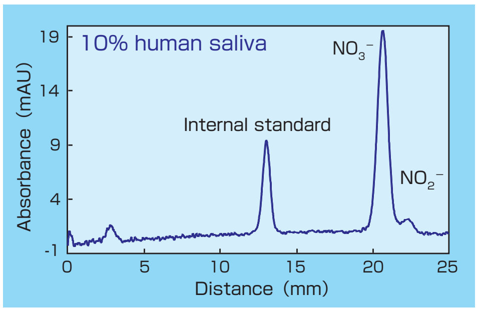

Figure 2: Example of 15-second separation and analysis of NO metabolites in 10% diluted human saliva

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New Fluorescence Detector Achieving Size Reduction of Biochip Devices

Health Technology Research Center
Mitsuru Ishikawa

Why light detection devices cannot be made more compact

Blood glucose and urine glucose meters have recently become commercially available for testing for diabetes at home. A urine glucose meter is about the same size as an electronic thermometer. Such measurements are made electrochemically and electrochemical devices are very compact. Why is it that light detection devices are not used for such purposes? A general feature of light detection is the ability to measure multiple wavelengths simultaneously with high sensitivity. We hear that developers of one company recognize this feature of light detection but ultimately choose electrochemical devices instead because it allows them to be made more compact. Using a light detection device involves an optical system made up of lenses and mirrors besides a light source. In the optical system, such optical elements must usually be placed taking a certain distance between them to keep a good S/N ratio. This ends up with a somewhat large optical system.

New fluorescence detection device that allows for compact implementation of light detection

Electrophoresis is a basic technique for analyzing biomolecules. If this technique could be combined with fluorescence measurement in microchip form, excellent performance would be realized in terms of reliability, speed, and detection sensitivity of analysis. A compact electrophoresis biochip that can be easily held between the fingertips (Figure 1) has now been successfully implemented in practical form by our research team. However, it seems that the measuring devices other than this chip cannot be made palm-sized because they include a microscope, laser, and a CCD camera. Therefore, it is very difficult to develop an electrophoresis-based diagnostic device that is as compact as the urine glucose meter.

The possibility to overcome this difficulty was provided by a new integrated fluorescence detection device (Figure 2) developed at the Nanoelectronics Research Institute (Toshihiro Kamei). A combination of this compact detector with microlenses and a compact light source for optical communication can dramatically reduce the optical system size. Joint development is now underway to develop an electrophoresis device for home diagnosis in a combination of these components with a biochip. This development is based on the interdisciplinary integration of biological measurement with device fabrication.

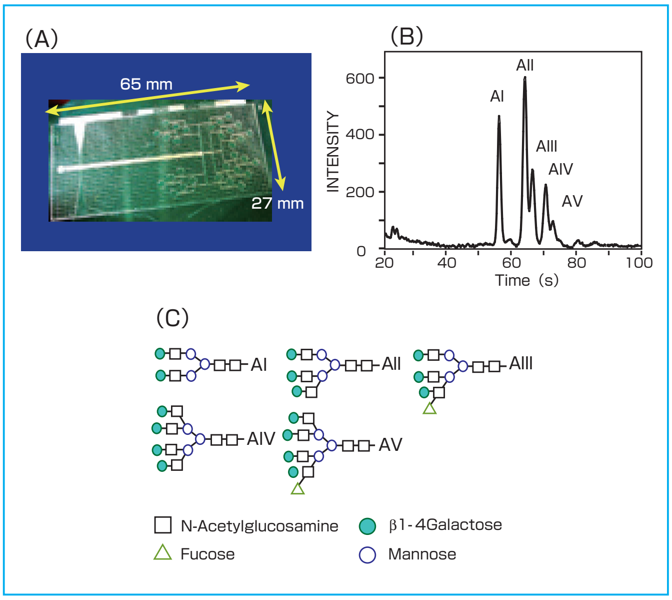


Figure 1 (A) Appearance of electrophoresis biochip, (B) Five different sugar chains analyzed using this chip, and (C) Structure of sugar chains used for analysis. ((B) and (C) are reproduced from Anal. Chem., 2006, 78, 1452-1458 with permission.)

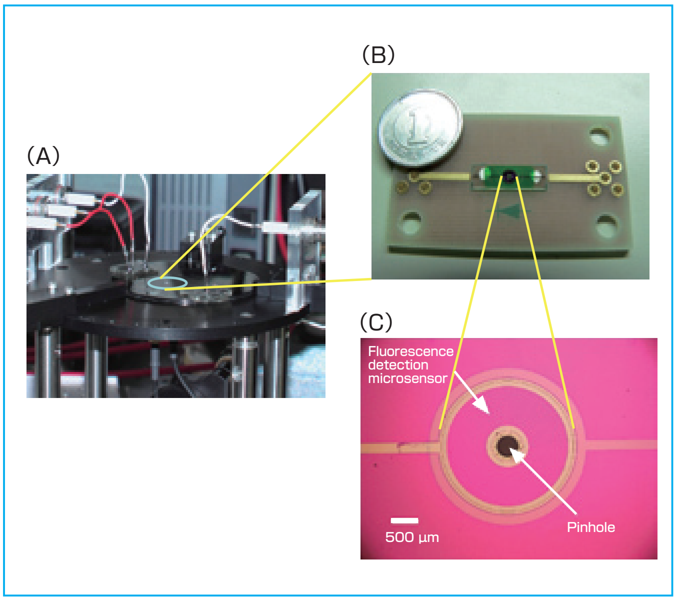


Figure 2 (A) Integrated fluorescence detection device in combination with an electrophoresis biochip, (B) Magnified view of the integrated fluorescence detection device, and (C) Magnified view of the photodiode of the device. ((C) is reproduced from Appl. Phys. Lett., 2006, 89, 114101 with permission.)

Fully-automatic Two-dimensional Electrophoresis for Proteomic Analysis

Research Center of Advanced Bionics
Kenji Yokoyama

Proteomic analysis tool

Proteome research analyzing proteins comprehensively is very important in understanding life phenomena that cannot be clarified by gene analysis alone. Proteomic analysis tools that have been used so far include two-dimensional electrophoresis. After separating proteins by two-dimensional electrophoresis, they are identified using a state-of-the-art mass spectrometer.

However, because the procedure of two-dimensional electrophoresis is not automated, reproducible results cannot be obtained unless the analysis is performed by a fully trained technician. The analysis takes 20 hours or more even if a small gel is used and almost three days for a large gel. Thus, the efficiency of analysis is very poor.

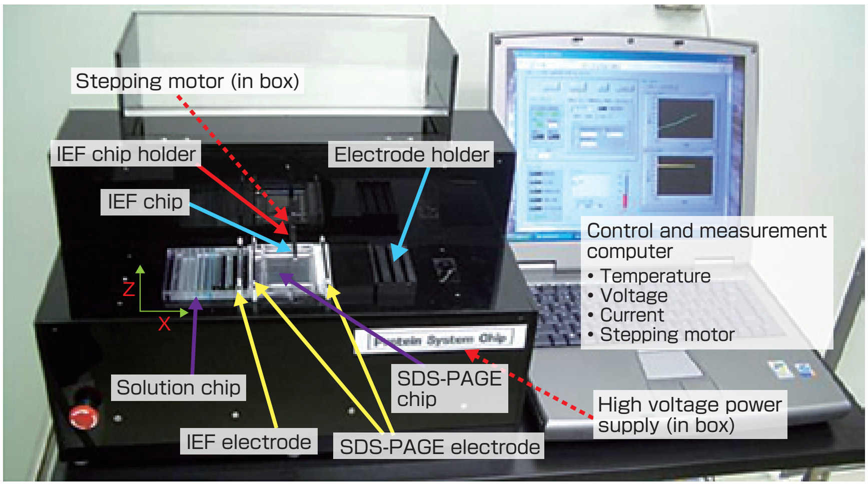


Figure 1: Fully-automatic two-dimensional electrophoresis system

Development of a new tool

We are developing a system that can perform two-dimensional electrophoresis in a fully-automatic fashion. It takes only one hour or so for the analysis and detection using the system. Figure 1 shows our prototype of such a fully-automatic two-dimensional electrophoresis system. In this mechanism, the isoelectric focusing (IEF) chips are placed on the holder for electrophoresis of the first dimension.

The chip holder holds a dry IEF chip (a support plate to which an IEF gel strip is fixed) and moves it into the protein sample bath. Then, the chip is moved into the swelling bath and then the IEF bath. There IEF takes place by applying a predetermined voltage. We employed an intermediate staining method in which the protein is stained between IEF and sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE). In this staining method, the chip is moved into the washing bath on completion of IEF and then transferred to the staining bath where the protein is stained with Cy5 or other fluorescent dye.

After washout of excessive dye, SDS equilibration treatment is carried out. The IEF chip is transferred to the SDS-PAGE gel start point of the second dimension, where the gels are brought into close contact with each other to start SDS-PAGE. This system has a CCD camera for detection, which allows real-time visualization of the separation during SDS-PAGE.

For practical implementation

We used this system to perform two-dimensional electrophoresis. It took 10 minutes for sample immersion and gel swelling, 20 to 30 minutes for IEF, 10 to 20 minutes for staining, washing, and SDS equilibration, and 20 to 30 minutes for SDS-PAGE and detection. That is, operations that previously took more than 20 hours could be performed in 60 to 90 minutes in our system. In the conventional system the gel is manually moved from the first dimension electrophoresis to the second dimension, while this system allows the fully-automatic two-dimensional electrophoresis.

We conducted an investigation using mouse liver lysates as a protein sample and succeeded in obtaining superior reproducibility and equal separation performance to a commercially available manual device (for small gels). This system is much better than conventional methods because results of two-dimensional electrophoresis can be obtained quickly and in a fully-automatic way.

Heart Disease Marker Sensor Using Self-assembled Monolayers

Institute for Biological Resources and Functions
Osamu Niwa

Disease diagnosis by heart hormone

A heart hormone called B-type natriuretic peptide (BNP), which is biosynthesized and secreted in cardiac muscle cells, is expected to have a significant beneficial effect on the diagnosis, prediction, and prognosis of heart disease.

However, because its concentration in blood is extremely low with about 10 pg/mL (3 pM) in healthy people, conventional immunochromatography is so low in sensitivity that radioimmunoassay or a large measuring apparatus such as a fluorescence detection system must be employed. A highly-sensitive sensing method is demanded that measures a sample with extremely low concentrations using a small, easy-to-use device in order to measure disease markers quickly on-site for diseases requiring urgent treatment such as heart disease.

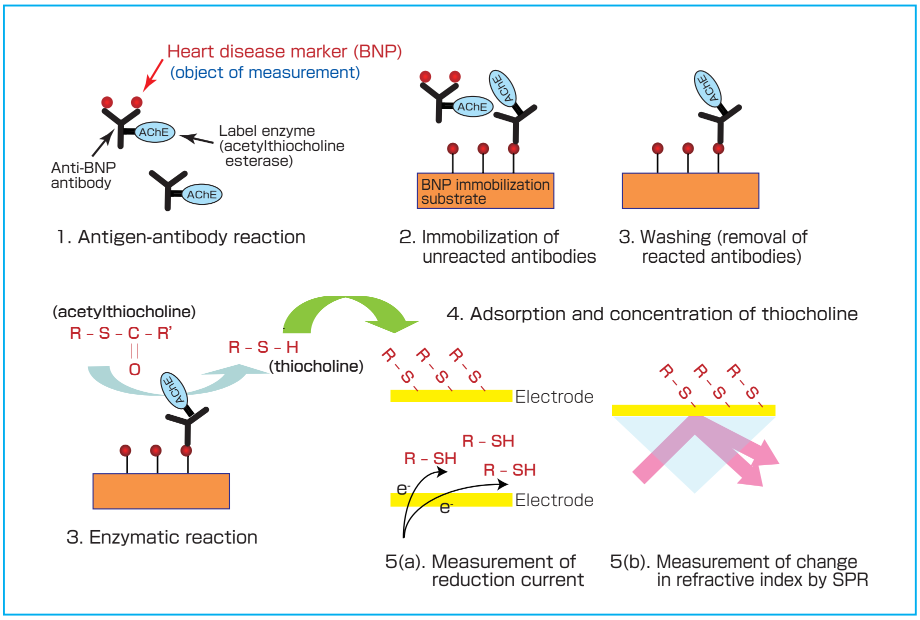
Development of new markers

Peptide disease markers such as BNP usually use antigen-antibody reaction for measurement. The key is to amplify the reaction of extremely low amounts of molecules as much as possible in the measurement process. In the field of surface science, thiol compounds having an SH group at the end of an organic molecule are known to form self-assembled monolayers of nanometer order on the surface of metals such as gold and silver. An anti-BNP antibody was therefore used, which was labeled with acetylthiocholine esterase (AChE), an enzyme that generates a thiol compound by enzymatic reaction. Unreacted labeled antibodies are captured on the substrate following antigen-antibody reaction with disease markers. When acetylthiocholine is introduced after the removal of reacted antibodies by washing, thiol compounds are generated as a result of decomposition by the enzyme from the captured unreacted antibodies. When introduced onto a noble metal film, thiocholine forms a monolayer, resulting in high concentration of the enzymatic reaction product. BNP can be measured with high sensitivity if electrical current is measured when the product is subjected to electrochemical reduction or if the change in surface refractive index is measured by the surface plasmon resonance (SPR) method (Figure).

Highly-functional system test using heart disease markers

To improve the detection limit through the measurement of extremely low quantities, the efficient capture of labeled antibodies and the concentration of the enzymatic reaction product (thiol compounds), a system has been developed which puts together a chip with siloxane polymer microchannels and a portable SPR instrument. This sensing chip enables immunoassay of heart disease markers to realize an extremely high sensitivity of 5 pg/mL within 30 minutes.

Relevant information
AIST TODAY (Japanese), Vol. 7, No. 2, 20–21 (2007)



Safer Gene Therapy with a Novel Gene Transfer Vector

Biotherapeutic Research Laboratory
Mahito Nakanishi

Obstacle to practical gene therapy

Causes of various diseases have been identified at the molecular level through advances in bioscience. However, there are diseases of known cause that are incurable with current treatment strategies, such as hereditary metabolic diseases, which cause the inability to maintain normal physical function due to inherent abnormal genes. Methods for treating such diseases are still very limited. Gene therapy is a state-of-the-art medical technique that involves the introduction of foreign therapeutic genes into cells in the human body to prevent, control or cure diseases. The therapy is expected to become practical as a radical treatment for such intractable diseases.

As surgical operation requires scalpels and surgical suture, gene therapy requires a nanoscale drug delivery system (DDS) to deliver a drug, i.e. gene. However, unlike the conventional DDS used to deliver low-molecular-weight drugs, a DDS (vector) for gene therapy must have the capability to carry a drug (gene) into cells. There are two major types of vectors that have been used in clinical studies for gene therapy. One is viral vectors engineered to carry therapeutic genes by recombinant DNA technology and the other is non-viral vectors carrying a combination of DNA molecules, produced in *E. coli*, and chemical substances. The delay in developing a vector with high gene transfer efficiency and safety has acted as a barrier against the practical application of gene therapy.

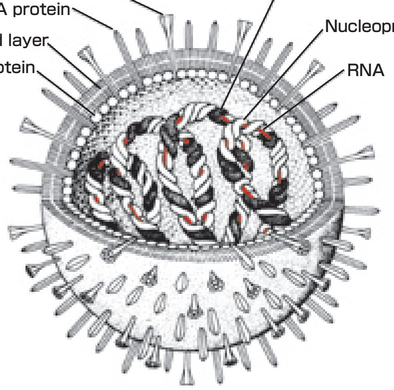


Figure 1: The structure of Sendai virus, which was used as material for the development of the RNA replicon by the Biotherapeutic Research Laboratory. It is a nanoparticle of about 240 nm in diameter having a lipid bilayer outside and genomic RNA inside.
(Reproduced with permission from Nikkei Science Inc.)

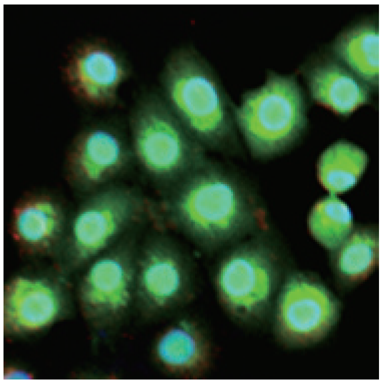


Figure 2: Simian cells emitting stable, green fluorescence for an extended period due to the expression of the enhanced green fluorescent protein (EGFP) gene carried on an independent RNA replicon (Photographed by Ken Nishimura)

Nanotechnology helps passage through barriers

To express a gene introduced into a cell, advanced technology is necessary that allows efficient passage of the gene through cellular barriers, such as cell and nuclear membranes, without injuring them. We have successfully laid the foundation for the development of highly functional non-viral vectors by developing a number of tools. One tool is a fusogenic liposome that can fuse directly with the cell membrane and transfer its content. The tools also include a nanoparticle that passes through cell membrane by the action of a peptide called PTD (protein transduction domain) (Eguchi, et al., 2001), and a nanoparticle that passes through the nuclear membrane actively by the action of a short peptide (nuclear localization signal) with which the nuclear protein is transported into the nucleus (Akuta, *et al*., 2002; Eguchi, *et al*., 2005).

Safer gene therapy using RNA vector

When long-term persistent expression of an introduced gene is required, as in hereditary metabolic diseases, a platform must be developed to carry and maintain genetic information stably in cells in addition to the development of a carrier for genes. In conventional DNA-based gene expression technology, foreign genes are stabilized by inserting them into chromosomes. However, random insertion of genes into chromosomes is inefficient and can cause safety problems including carcinogenesis. We thus tried to create a new platform for carrying genes and have successfully developed an independent RNA replicon that allows long-term stable gene expression even if the genes have not been inserted into chromosomes by using RNA instead of DNA as the genetic body.

AIST aims to contribute to the practical application of gene therapy through the development of high-performance vectors for gene therapy based on such results.

Smart Capsule with Highly-functional Nano Spaces

Nanotechnology Research Institute
Masahiro Fujiwara

Microcapsule

Hollow and porous fine particles in nanometer or micrometer size are like minute capsules (microcapsules) because they can contain and release various compounds as appropriate. In AIST, we conduct research into various nanobiotechnologies by incorporating various drugs or biomolecules into these minute capsule spaces composed of inorganic materials. For example, an inorganic spherical hollow particle has been successfully synthesized on a one-step method by making skillful use of water and oil interfaces.[1]

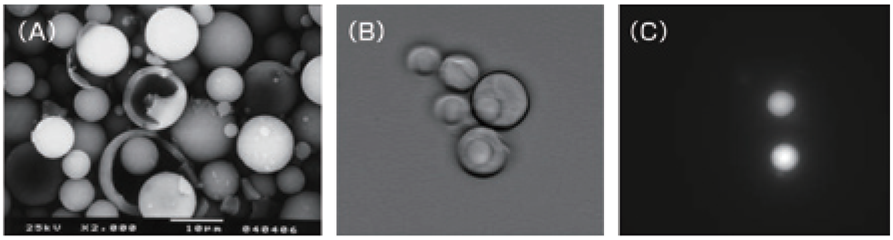


Figure 1: An electron microscope image (A) of a representative silica microcapsule. An optical microscope image (B) and fluorescence microscope image (C) at the same point of the silica microcapsule encapsulating BSA containing fluorescent dye. Glittering circular areas are observed in capsules.

Application to a drug delivery system

Figure 1-A, which presents an electron microscope image of silica microcapsules, indicates a large empty space inside each microcapsule. Protein and DNA molecules can be enclosed directly in the empty space if they are present together when synthesizing the microcapsule. Figures 1-B and -C present an optical microscope image (Figure 1-B) and a fluorescence microscope image (Figure 1-C) at almost the same point of a silica microcapsule encapsulating bovine serum albumin (BSA) containing fluorescent dye, respectively. These images indicate that there is fluorescent BSA in the microcapsule.[2] As the BSA contained is larger in size than the pore in the capsule shell, it will not be released outside unless the capsule is broken. Therefore, application to technologies, such as responsive drug delivery system or immobilized enzyme technologies, is expected.

New capsule technology

If a molecular gate that will open and close reversibly in response to external stimulation is installed at the outlet of a nanopore of silica that is uniform in size, storage in the pore and outward release of the enclosed compounds can be controlled by opening and closing the gate. For example, controlled releases are achieved by photoirradiation in a gate of a coumarin molecule that dimerizes reversibly by light[3] as well as by oxidation-reduction reaction in the disulfide moiety where the linkage is cleaved reversibly by oxidation and reduction[4] (Figure 2).

Thus, materials with a minute empty space are expected to be applied to various nanobiotechnologies as smart capsule materials that can control the transportation of molecules and biopolymers freely at the nano level.

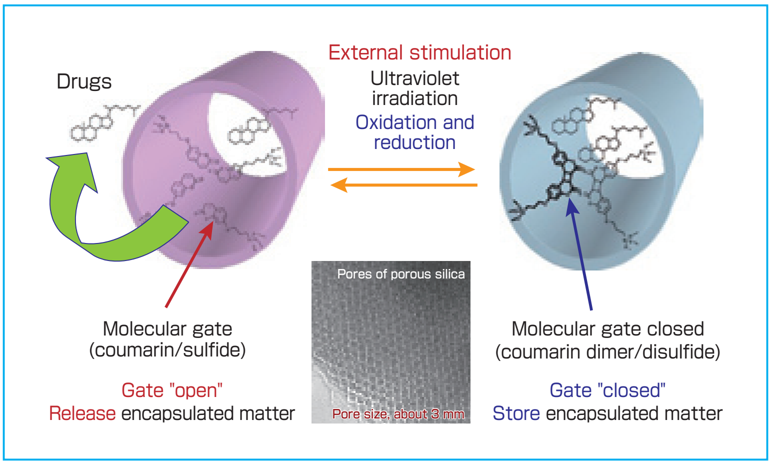


Figure 2: External stimulation-responsive drug delivery using porous silica

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Sensing and Manipulation of Cells

Research Center of Advanced Bionics
Toshiyuki Kanamori

From population to individual

Bioinformatics has established its usefulness in understanding the genome and the focus of its research is now shifting to the proteome. After that, the focus will shift further to the cellome.

Another important point is that the viewpoint of research is shifting from population mean to individual analysis as represented by single nucleotide polymorphism detection and single molecule measurement. This is an inevitable trend if biodiversity and biocomplexity are considered.

In response to this situation, we are developing techniques to sense and manipulate individual cells.

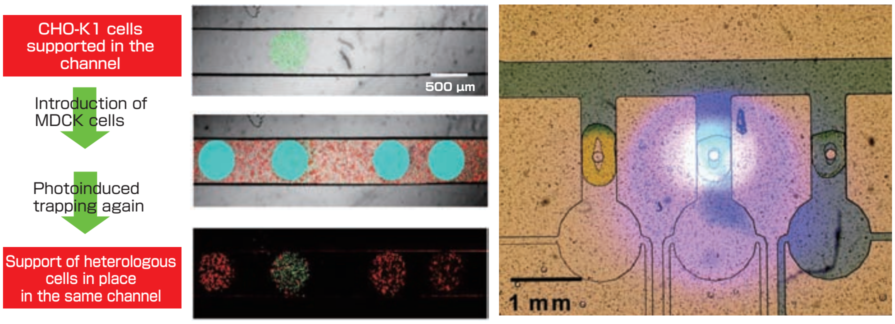

Figure 2: Cell spots (left) and optically-controlled microvalves (right) in a microchannel (1 mm wide)

On-demand two-dimensional cell manipulation techniques

Light is advantageous in manipulating a cell of several ten micrometers in size in a closed space because it can be radiated instantly and locally from a distance. We already developed a cell culture surface on which cell adhesion could be changed by light irradiation and reported that this technique can be applied to cell selection and precision pattern culture (Figure 1).

Furthermore, we developed an instrument that radiates light in an arbitrary pattern onto individual cells being observed through an optical microscope, and plan to set up a venture shortly to sell this instrument together with photoresponsive cell culture dishes and other products.

Figure 1: Pattern culture (top) and precision co-culture (bottom) of cells by on-demand two-dimensional cell manipulation techniques

A microchip handling cells

Considering that the cell size is several ten micrometers, microprocesses are advantageous in handling individual cells precisely. We aim at establishing techniques to integrate various elemental technologies, including the on-demand two-dimensional cell manipulation techniques described above, in a microchip and handle cells in it.

We have already succeeded in forming a particular cell spot (colony) in a channel in the microchip (Figure 2, left). Microvalves are needed to introduce cells into compartments in the microchip or inject a drug solution or other chemicals into compartments. Here again, we give attention to light and are developing an optically-controlled microvalve that can be operated by light from outside (Figure 2, right).

In the near future, it will become possible to inject a group of cells into individual compartments or culture cells in the form of a spot in the channel to give stimuli to these cell groups or cells with a particular drug solution or to perform cell assays for drugs in them.

Relevant information

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AIST TODAY (Japanese), Vol. 5, No. 10, 20–21 (2005)

Cell Surgery: Cell Manipulation with a Nanoscale Needle

Research Institute for Cell Engineering
Chikashi Nakamura

Nanoscale needle for cell manipulation

The human somatic cell is about 20 to 30 µm in diameter, so a very thin needle (nano-needle) about 200 nm in diameter is required for an insertion operation without killing the cell. The cell does not die even after an insertion operation for more than one hour, so it is expected that the cell can be analyzed or used after the insertion action. We named this cell manipulation technique using nano-needles "cell surgery" and are currently developing it.

Using an atomic force microscope (AFM) instrument, the nano-needle is manipulated and the very weak force acting between the needle and cell is observed. In this way, we can observe the inserted state of the needle. As shown in Figure 1, a typical pyramidal AFM probe is sharpened using a focused ion beam into a needle of 200 nm in diameter. As shown by the confocal fluorescence images, the typical AFM probe is forced into the cell involving the cell membrane at the probe tip while the nano-needle is inserted in the cell smoothly and reaches the inside of the cell nucleus without deforming the cell. With the typical probe, the repulsion simply increases when it is pushed against the cell. When the nano-needle was pushed against it, the phenomenon in which the repulsion was quickly relaxed was observed. This relaxation means that the needle got through the cell membrane successfully. The nano-needle insertion requires no particular cell modification and ensures that the success or failure of insertion action can be detected. Therefore, the cell can be used in a natural state after manipulations.

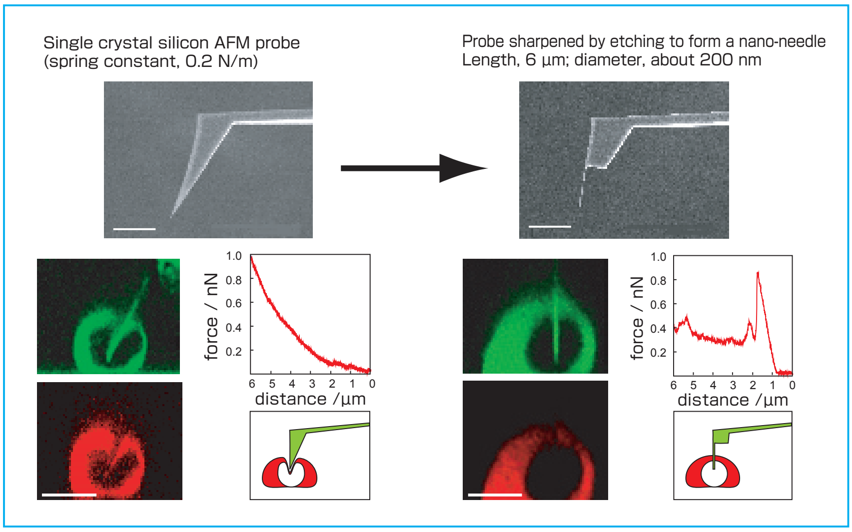

Figure 1: Insertion of a nano-needle into a cell and mechanical response (scale bar, 10 µm)

Efficient gene transfer technique using a nano-needle

The human bone marrow-derived mesenchymal stem cell is a flat cell of several micrometers in thickness in adhesion culture and has the problem of a very low gene transfer efficiency. We performed a transfer operation after modifying a nano-needle of 200 nm in diameter with polylysine and making it adsorb plasmid phrGFP. With the conventional microinjection technique using a glass capillary, the transfer efficiency was 10% or less. On the other hand, we succeeded in gene transfer with a high efficiency of 70% or more using the nano-needle. Gene transfer using the nano-needle ensures needle insertion not only into a cell but also into the cell nucleus. This is thought to have achieved the high gene transfer efficiency.

If further development of this technique makes it possible to recover the function of cells or make desired cells without changing the genetic characteristics of the cells, this will lead to regenerative medicine by safe autologous cell transplantation.

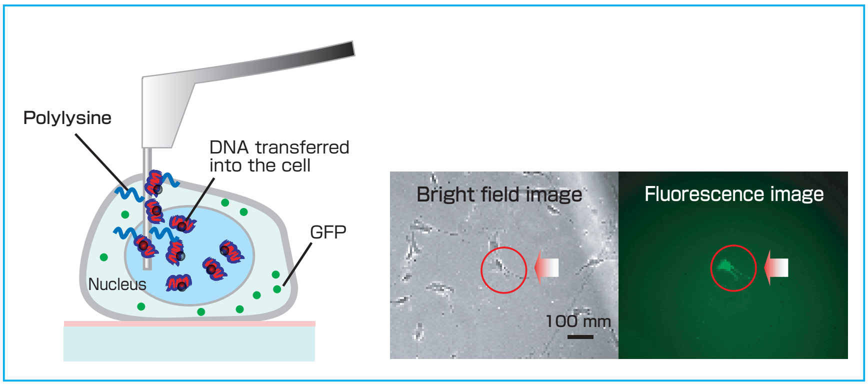

Figure 2: DNA transfer into a mesenchymal stem cell with a nano-needle

Aiming for the Development of Diagnostic Techniques for Cancer Metastasis

Institute for Biological Resources and Functions
Tomoko Okada

Cancer metastasis to bone marrow

It is not too much to say that the reason why people continue to die of cancer in spite of remarkable progress in the diagnostic and therapeutic techniques for cancer is that its metastasis cannot be prevented. Metastasis to bone (bone marrow), among others, occurs frequently in breast cancer, prostate cancer, and multiple myeloma. It causes severe pain or bone fracture in patients, resulting in a marked reduction in their quality of life. However, the mechanism of metastasis has not been fully elucidated.

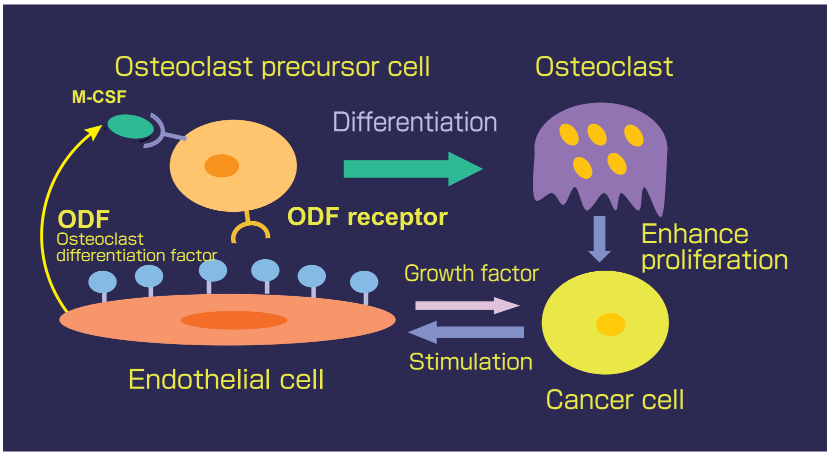

Figure: Hypothesis of the mechanism of osteoclast induction

Aiming at the clarification of the metastatic mechanism

We established a bone marrow metastasis model for murine myeloma cancer cells to study the mechanism of bone marrow metastasis. It was expected that cancer cells metastasized to bones, kind of special tissue, with the help of osteoclasts, cells destroying bones under physiological conditions. So, focusing on the interactions among cancer cells, bone marrow-derived endothelial cells, and osteoclasts, relationships among these cells in bone marrow metastasis were examined.

It was revealed that an osteoclast differentiation factor (ODF), which is essential for the differentiation and induction of osteoclasts from precursor cells, was found to be expressed on the surface of bone marrow-derived endothelial cells. It also became clear that when cancer, endothelial, and precursor cells were co-cultured, osteoclast induction was enhanced only in the presence of both cancer and endothelial cells. Co-culture of endothelial and cancer cells resulted in the increase in the expression of both mRNA and protein of ODF on the surface of endothelial cells. In other words, metastatic cancer cells were found to stimulate endothelial cells to express more ODF on their surface, leading to indirect promotion of osteoclast differentiation and induction[1].

To examine whether the same thing occurs *in vivo*, the cancer cells were injected to mice through the tail vein, and their femurs were analyzed. As a result, there was an increase in the number of osteoclasts in the murine femurs receiving the cancer cells, indicating enhanced induction of osteoclasts *in vivo* by these cancer cells[1], [2].

We are currently working at creating a highly bone marrow metastatic model of breast cancer, which has been increasing among Japanese women[3].

Use of nanobiotechnology for the diagnosis of metastasis

We are considering applying nanobiotechnology to develop a technology to diagnose such metastasis to other organs. In recent years various nanocarriers have been developed and are expected to be applied to cancer diagnosis and treatment. We are aiming to develop a nanocarrier that can be used to identify the site of metastasis as well as to localize (target) a drug to primary cancer site, in collaboration and cooperation with researchers in the field of material science.

References
[1] Tomoko Okada *et al.*: Bone marrow metastatic myeloma cells promote osteoclastogenesis through RANKL on endothelial cells, Clin. Exp. Metastasis, 20, 639-646 (2003)
[2] Tomoko Okada *et al.*: Osteoclast induction by bone marrow metastatic myeloma cells was mediated by M-CSF production from endothelial cells. Proc. 96th annual meeting of American Association for Cancer Research, 46, 1105 (2005)
[3] Tomoko Okada *et al.*: Establishment of highly metastatic murine breast cancer cell line to bone marrow, UICC World Cancer Congress 2006, 19, 476 (2006)

Motor Protein Used as a Nanoactuator

Research Institute for Cell Engineering
Taro Uyeda

Nanomotor in biological organisms

Organisms have a group of enzymes called motor proteins. For example, protein filaments called microtubules run through nerve axons, and the motor protein called kinesin transports membrane vesicles filled with neurotransmitters along the microtubules. Each molecule of the motor protein works as a motor, which is thus quite small. In addition, motor proteins have various features not found in artificial motors, such as the potential to form large structures by self-assembly, which are general properties of proteins. Applied research has been conducted all over the world to use those motor proteins as nanoactuators.

Manipulating motor proteins

To allow kinesin to move *in vitro* after taking it out of the cells, a system with a configuration reversed from the *in vivo* configuration has been used conventionally. In that system, kinesin is adsorbed onto a glass surface on which fluorescence-labeled microtubules move. However, the system does not allow the microtubules to do useful work to the outside because the microtubules move in random direction on the glass surface. We therefore created tracks on the glass surface by lithography as shown in Figure 1, and thereby succeeded in limiting the microtubule movement to one dimension. Moreover, moving almost all microtubules in one direction was realized by adding arrowhead-shaped "rectifier" patterns along the linear tracks. Microtubules moving in one direction along a track are expected to be used as a minute belt conveyor. To that end, various peripheral technologies must be developed, including a technology to control motor activity locally, a technology for external control of the traveling direction of microtubules at the junction of the track, a technology to bind a load to be carried to a moving microtubule and release the load at a destination, and a technology to sustain the movement for an extended period.

At AIST, specialists from various fields have established the Upbringing of Talent in Nanobiotechnology Course, led by Noboru Yumoto, Director, Research Institute for Cell Engineering, with the support of the Special Coordination Funds for Promoting Science and Technology to further technological development while training interdisciplinary personnel.

For example, Nomura and Tatsu (Biomolecular Engineering Research Group, Research Institute for Cell Engineering), who have skills in the technology for a "caged peptide," which is activated by ultraviolet irradiation, identified a peptide that inhibited the motor activity of kinesin reversibly, and have developed a system that stops microtubular movement reversibly by ultraviolet irradiation that "uncages" the peptide (Figure 2).

In addition, Konishi and Kubo (Molecular Neurophysiology Group, Neuroscience Research Institute), experts in protein engineering, have succeeded in the development of a chimeric kinesin molecule which is switched on by calcium ions.

Kato and Shibakami (Lipid Engineering Research Group, Institute for Biological Resources and Functions), who are skilled in organic synthesis, bound cyclodextrin chemically to microtubules. Moreover, they have succeeded in binding and dissociating azobenzene to and from cyclodextrin-conjugated, moving microtubules by reversible photo-modulation of the affinity between cyclodextrin and azobenzene. Taira and Kodaka (Molecular Recognition Research Group, Institute for Biological Resources and Functions) bound oligonucleotides to moving microtubules, and demonstrated that oligonucleotides with complementary sequences can be transported. Because even a single base-pair mismatch prevented this transport, this system may be helpful in the analysis of single nucleotide polymorphisms (SNPs), which will enable tailoring treatment regimens to individual patients. These and other novel technologies should be combined to realize micro-devices and systems in the future.

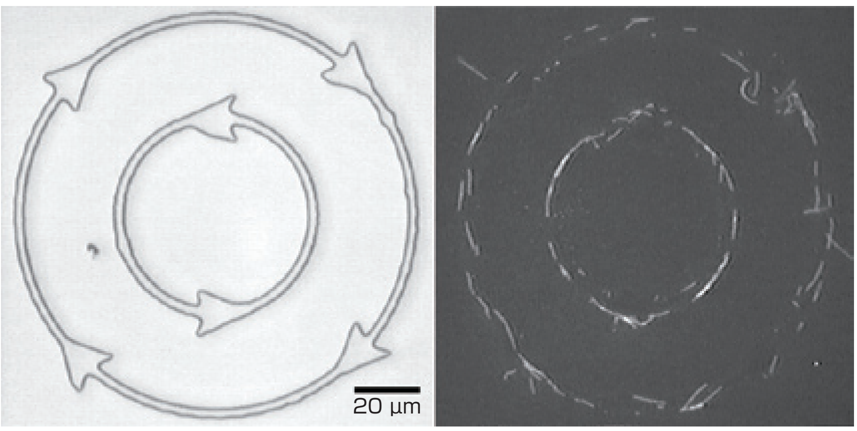

Figure 1: One-dimensional unidirectional movement system of microtubules
The resist applied on a glass surface was processed by lithography to form narrow groove-shaped tracks (transmission microscope image on the left). Selective adsorption of kinesin molecules onto the bottom surface of the track resulted in the successful confinement of microtubular movement within the track (the fluorescence microscope image on the right represents fluorescent microtubules). Unidirectional movement was achieved by adding arrowhead-shaped "rectifier" patterns. (Modified and reproduced from *Biophys. J.* 81:1555-1561 (2001))
Actual circling movement can be seen at http://staff.aist.go.jp/t-uyeda/motility/biomotors/.

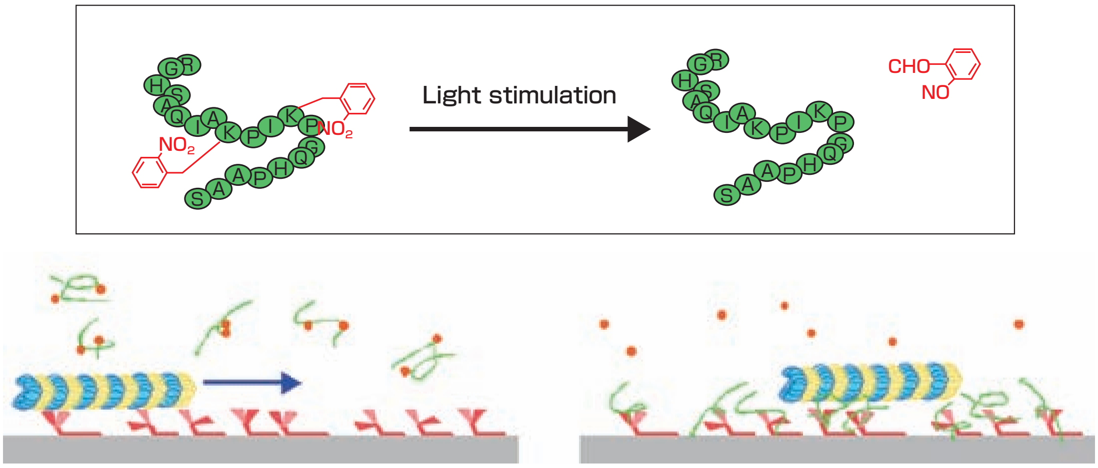

Figure 2: Microtubules can move normally in the presence of caged peptides (lower left). But the movement of microtubules is inhibited (lower right) when the caged peptide turns into a peptide with inhibitory activity (upper) due to light stimulation.
(By courtesy of Dr. Yoshiro Tatsu)

Use pre-assembled motile structures

Rather than using purified motor proteins as nano-components of micro devices, a more biological approach is to modify motile biological structures and use them as pre-assembled motile units in an artificial environment.

For example, Hiratsuka and Uyeda (Gene Function Research Center), with the cooperation of Miyata (Osaka City University) and Tada (Advanced Semiconductor Research Center), are working at the development to use the gliding bacteria *Mycoplasma mobile*, which moves at high speed (3 µm/s) continuously on a substrate, as a microactuator.

They developed a technology for unidirectional circling movement of *Mycoplasma* cells in a minute (20 µm in diameter) circular track, and bound a microrotor created using the MEMS technology to circling cells, resulting in the creation of a rotary micromotor driven by the bacteria (Figure 3). As we relied on cattle and horses for a long time before man-made vehicles such as cars are available, micro-cattle and horses may play an important role for some time in the field of nanobiotechnology.

(Positions cited are as of the time of publication).

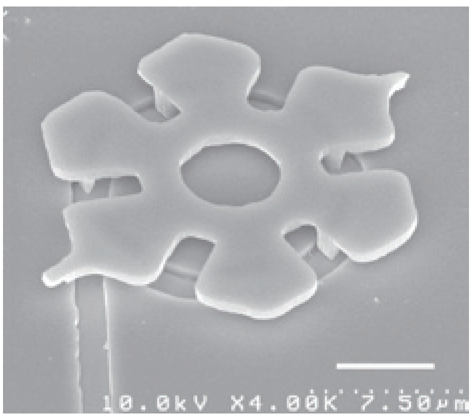

Figure 3: An electron micrograph (scale bar, 5 µm) of a rotary micromotor driven by *Mycoplasma mobile*. (Reproduced from Proc. Natl. Acad. Sci. USA 103: 13618-13623 (2006))
Actual rotational movement can be seen at http://www.pnas.org/cgi/content/full/0604122103/DC1#M1.

Research Hot Line

UPDATE FROM THE CUTTING EDGE

Apr.-Jun. 2007

The abstracts of the recent research information appearing in the Vol.7 No.4–6 of "AIST TODAY" are introduced, classified by research area. For inquiry about the full article, please contact the author via e-mail.

Life Science & Technology

Elucidation of mechanism of bone-conducted ultrasonic perception and development of a novel hearing aid

Human beings are normally unable to hear high-frequency sounds above 20 kHz (ultrasounds). However, bone-conducted ultrasound (BCU) can be experienced as sound, not only by people with normal hearing ability but also by severely hearing-impaired people. By measuring the magnetic field in the brain, BCU perception has been proven objectively. Furthermore, we have identified both the characteristics and the neurophysiological mechanism of BCU perception using psychological, neurophysiological and physical approaches, and developed a BCU hearing aid (BCUHA) for the profoundly deaf. Remarkable results have already been achieved; enabling 30 percent of the profoundly deaf trial subjects to hear simple words and half of them to perceive some sort of sound. The BCUHA is far easier to attach than a cochlear implant, which requires surgery, and thus substantially removes the mental and physical burden experienced by cochlear implant users.

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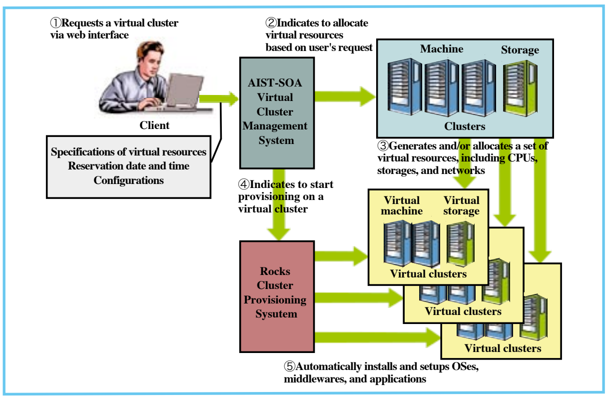
AIST TODAY Vol.7, No.5 p.16 (2007)

Bone-conducted ultrasonic hearing aid (BCUHA).

Development of "AIST-SOA Virtual Cluster Management System"

Since 2005, we have been developing “AIST-SOA Virtual Cluster Management System”, which fosters utility computing on commercial data centers by employing virtualization technology. The system allows clients to reserve and configure a virtual cluster through an easy-to-use web interface. For each reservation, the system automatically allocates a bunch of virtualized computing resources including Xen/VMware based virtual CPUs, iSCSI storages, and networks for a virtual cluster, and installs and configures operating systems and applications by using Rocks, a cluster provisioning system. A prototype system has already been running, and we are now conducting research to improve stability and extensibility of the system. We also plan to apply our system to actual data centers.



Scheme of AIST-SOA Virtual Cluster Management System.

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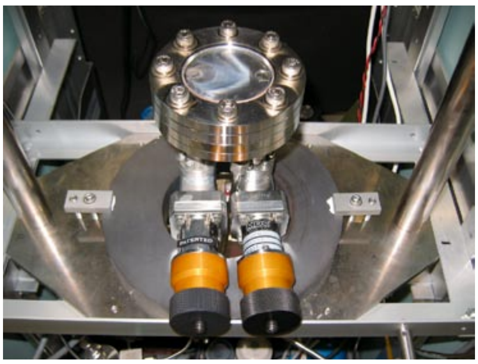
AIST TODAY Vol.7, No.5 p.17 (2007)

Device for highly-efficient generation of hyperpolarized xenon gas to improve MRI sensitivity

Our research group has succeeded in building a continuous-flow device that generates hyperpolarized xenon gas with a high efficiency and in developing the device into a commercialized, compact, automated high-performance system. The new device is a result of efforts to increase the level of sophistication of a continuous-flow system for the generation of hyperpolarized xenon gas in nuclear magnetic resonance (NMR) for medical use. In addition to being smaller in size, the device can be connected directly to an NMR apparatus by using simple capillaries. It is expected to be useful in the analysis of pore structures of nanoporous materials such as those used in fuel cells, and in medical diagnosis technology using sensitive magnetic resonance imaging (MRI) system.



Novel continuous-flow device for generating hyperpolarized xenon gas.

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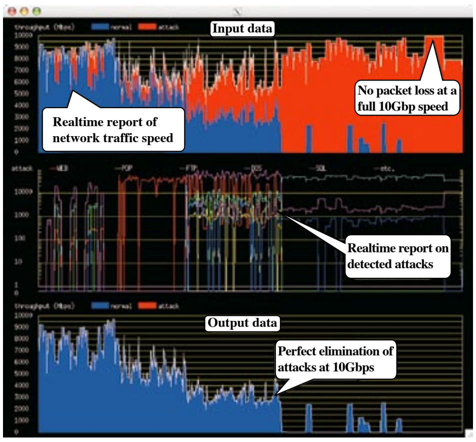
AIST TODAY Vol.7, No.6 p.32 (2007)

Intrusion protection system for large-scale networks

Network security is vital to the achievement of safety in modern society. Cyber attacks to the computer networks of companies, schools, and governments sometimes cause serious damage with service stoppage and /or information leak. “Snort” is commonly-used open software which accumulates rules to detect attacks, although processing speed is limited. We have developed high-speed hardware system where multiple pattern matching is performed in parallel by employing non-deterministic automaton, at the same time hardware compaction is achieved by sharing circuit elements all over the applied rules. Our system detects and eliminates attacks at the speed of 10 Gbps with 1,225 rules, setting a new world record. Since the circuit logic is automatically generated from the Snort rules by our developed program and is written to the FPGA (a logic programmable device) of the system, it is very easy to update the system against new kinds of attacks.



Report on cyber-attacks detected by the intrusion protection system.

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AIST TODAY Vol.7, No.6 p.33 (2007)

Development of a thin film for a mirror switchable between reflective and transparent states

The newly developed mirror with a Pd capped Mg-Ti alloy thin film can be switched between a metallic (mirror) state and a color-neutral transparent state. The switchable mirror window glass with a practical size of 60 cm × 70 cm coated by Pd/Mg-Ti thin film is successfully prepared and shows good optical switching using a gas containing hydrogen.

Large-size mirror switchable between reflective state (left) and transparent state (right).

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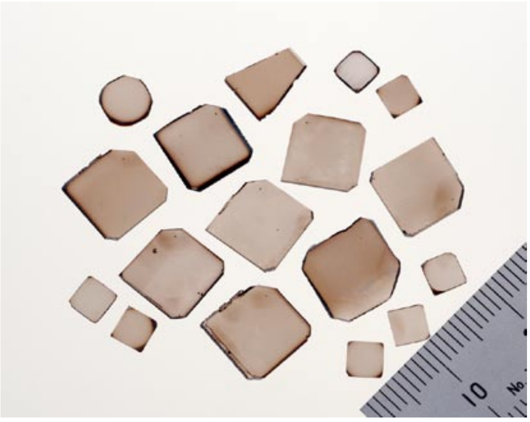
AIST TODAY Vol.7, No.4 p.28 (2007)

Development of production technology for large-area single crystalline diamond wafers

We have successfully developed a process which can fabricate a number of large diamond wafers from single seed crystal. This process, called "Direct Wafer-Making Technology", is a combination of high rate growth process using microwave plasma CVD and subsequent etching process of graphitized ion implanted layer in the seed. Using this process, 10 mm square, self standing, single crystalline CVD diamond wafers can be synthesized. These large diamond wafers will be essential for future electronic devices which utilize excellent properties of diamond as semiconducting material.



10 mm square single crystalline CVD diamond wafers

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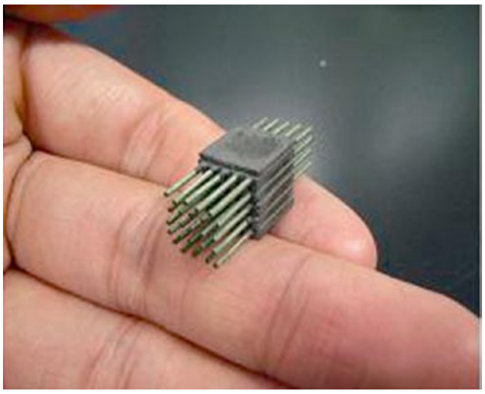
AIST TODAY Vol.7, No.6
p.34 (2007)

Micro SOFC with high output performance

A micro tubular SOFC (Solid Oxide Fuel Cell) bundle (cube) whose volume is 1 cm^3 was fabricated using a newly-developed advanced ceramic processing technology. The cube consists of micro tubular SOFCs and cathode matrices which act as a current collector and provide gas flow paths for air. The performance of the cube was shown to be over 2 W at 550 ^{o}C with H_2 fuel. Currently, a fabrication technology of micro SOFC stacks by integrating these cubes is under development, aimed for the output performance of several W to kW scale with quick start-up/shut-down performance. They are expected to be applied to portable power sources, APU units for automobiles.



Micro SOFC cube.

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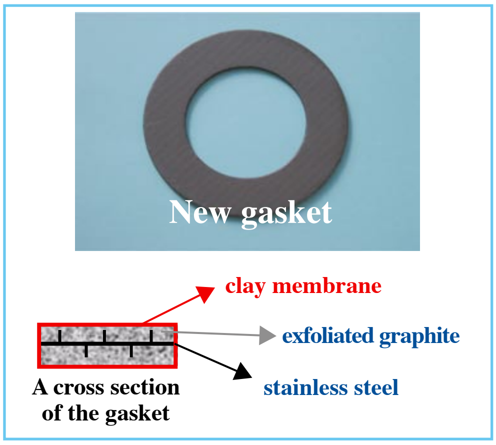
AIST TODAY Vol.7, No.6
p.35 (2007)

Development of a new gasket substituting for asbestos products

A heat-resistant clay membrane and exfoliated graphite - a conventional material of gaskets - are combined to develop a new gasket that is superior to existing nonasbestos products in terms of heat resistance, durability, and chemical resistance in addition to offering the same ease in handling as asbestos products. This gasket offers a wide range of applications in facilities such as chemical plants like oil refineries and heat power plants, taking advantage of its ease in handling and thermostability. Excellent results have already been obtained from the verification tests conducted in petrochemical plants.



New gasket and its structure.

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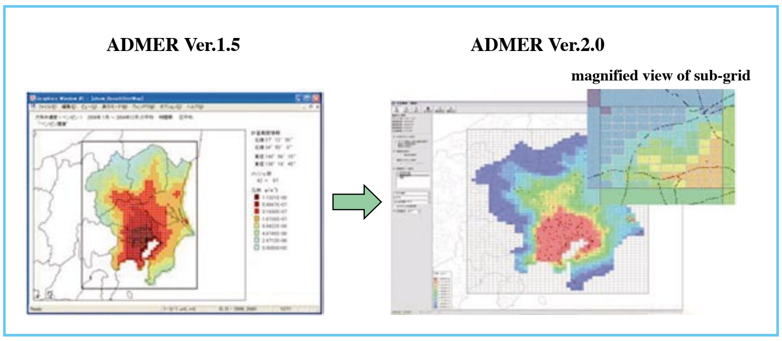
AIST TODAY Vol.7, No.4 p.29 (2007)

Environment & Energy

Functional enhancement of ADMER

The latest version (Ver. 2.0) of " the Atmospheric Dispersion Model for Exposure and Risk Management (ADMER) ", which is designed to estimate the distribution of regional atmospheric concentrations of chemical substances and the exposure to populations, has been developed. This version has a built-in function to analyze sub-grids that will assist users in their analysis of small areas such as cities, wards, towns, and villages. This function increased the surface imagery considerably from every 5 km to the maximum of every 100 m. In addition to this feature, the new version has been given the representational function and improved user-friendliness brought about by the geographical information system (GIS) with the various improvements to respond users' requests.



ADMER Ver.1.5 (left) and Ver.2.0 (right).

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AIST TODAY Vol.7, No.5 p.18 (2007)

Introduction of distributed energy networks to residential homes

The application of distributed energy network technology to the introduction of fuel cells in residential areas is described. The energy networks of electricity, heat, and hydrogen enable flexible operation of equipment and contribute to CO_2 emission mitigation, energy saving, and cost reduction.

Two concrete systems for a group of detached houses and an apartment building have been designed and proposed. The system for a group of detached houses reduces 6-8 % of CO_2 emission and 50 % of initial costs. The system for an apartment building provides flexibility on the supply of electricity and heat by combining CHP (Combined Heat and Power) systems which have different heat and electricity generation characteristics.

The demonstration in an apartment building has been started to evaluate the effect quantitatively and acquire know-how for practical application.

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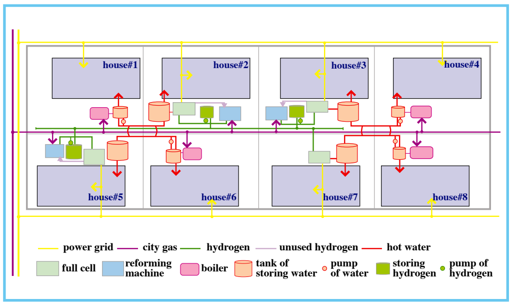
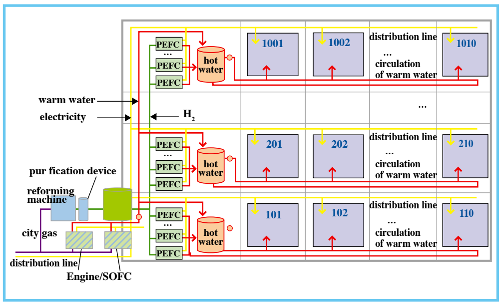
AIST TODAY Vol.7, No.6
p.36 (2007)



Systems for a group of detached houses.



Systems for an apartment building.

Development of a pulse-driven Josephson voltage standard

We have been developing a pulse-driven Josephson voltage standard in order to establish a quantized AC voltage standard at AIST. As the first step toward this goal, we have performed an experiment of operating an overdamped Josephson junction array by current pulse trains generated by triggering a photo detector located in a cryostat with an optical comb. Quantized voltage steps have been verified at a multiple of 10μV, which agrees with the repetition rate of the pulse laser and the number of Josephson junctions in the array.

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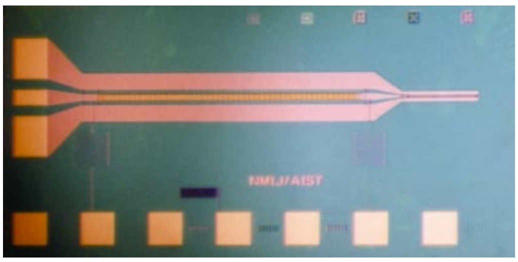
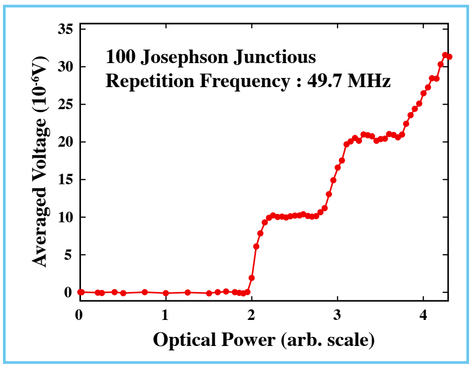
AIST TODAY Vol.7, No.4
p.30 (2007)



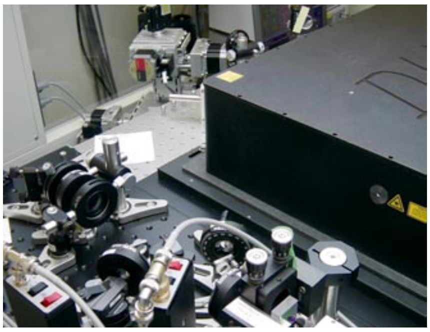
Josephson junction array used in the experiment (100 junctions).



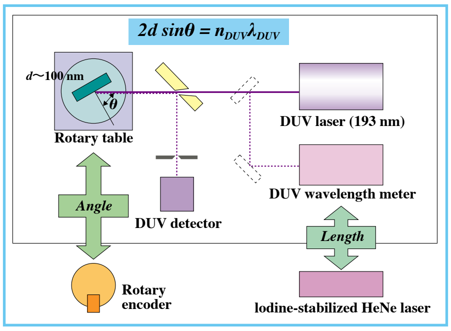
Optical power dependence of the output voltage of the Josephson Junction array.

Ultraprecision ruler in nanometer world

An ultraprecision pitch calibration system with a deep ultraviolet (DUV) laser diffractometer for rulers with the pitch of down to 97 nm has been newly constructed in collaboration with Japan Quality Assurance Organization (JQA). A built-in scanning interferometer-based DUV wavelengthmeter and a high-resolution optical diffractometer make every calibration of rulers traceable to the unit of length. Calibrated 100-nm rulers with an expanded uncertainty of 0.04 nm will be used as standards in the inspection of the size of next-generation nanodevices in advanced semiconductor production lines. With the extremely low uncertainty and pitch size comparable with the devices, the rulers will contribute to the improvement of the production yield.



Hardware overview of a pitch calibration system with a deep ultraviolet (DUV) laser diffractometer.



Schematic calibration principle of pitch standards using a DUV optical diffractometry.

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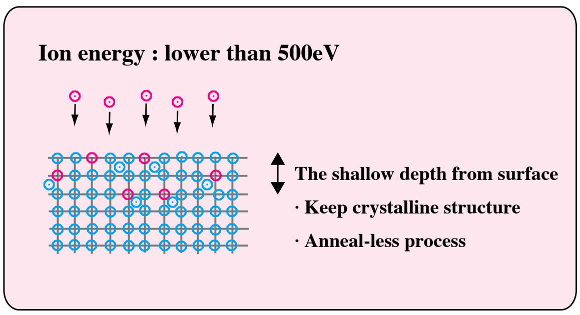
AIST TODAY Vol.7, No.5
p.19 (2007)

Ultra-low-energy ion implantation to decrease the resistance of silicon

In silicon technology it is thought that an electrically activated, ultra-shallow doping layer will be necessary, and it is predicted to reach 10nm in the year 2014. Ion implantation is a useful method, however, defects are also introduced. High-temperature annealing after ion implantation recovers the crystallization of silicon and activates the implanted dopant. However, it is difficult to keep the ultra-shallow dopant profile because of the diffusion of dopant in Si. In this study, ultra-low-energy ion implantation was examined to reduce the damage during implantation process. The lowest sheet resistance of 2.8 kΩ and the shallow dopant layers below 8 nm were achieved at the ion energy of 300 eV.



Ultra-low-energy ion implantation (● boron, ● silicon)

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AIST TODAY Vol.7, No.6
p.37 (2007)

Best Management Practice Seminar held with French National Center for Scientific Research (CNRS) and Environmental Catalysis (ECSAW) Cooperative Research Agreement Signed

On February 7, President Yoshikawa, Vice-President N. Kobayashi, Vice-President Yamazaki and other AIST executives visited the French National Center for Scientific Research (CNRS) where, together with President Brechignac and other executives of CNRS, the above seminar aimed at contributing to best laboratory management practices was held.

CNRS, with a total of 26,000 researchers and technologists, is France's largest public industrial technology research organization, possessing a large number of collaborative research laboratories with universities and stressing industry - academia - government collaboration and the development of innovation clusters. Since its entry into a comprehensive agreement with CNRS, AIST has promoted collaborative research such as the Joint Robotics Laboratory, but in addition, since both organizations have common issues regarding innovation and industrial technology management, this seminar came about because of the great benefit to be derived from an exchange of opinions and mutual instruction concerning laboratory management.

Best Management Practice Seminar

ECSAW Signing. President Yoshikawa (center), President Brechignac (left) & Director-General Migus (right)

The current situation of respective laboratories with regard to innovation, evaluation and venture strategy etc. was reported and opinions exchanged. It is planned that a similar seminar addressing other topics will be held at a future opportunity.

Also the signing of the "environmental catalysis for sustaining clean air and water (ECSAW)" cooperative research agreement was held. This agreement aims at innovations in catalysis technology which represents one of the core technologies in the field of environment/energy, with AIST and CNRS multiple research units cooperating over a period of 4 years. With this signing, it is expected that a stimulus will be provided to research cooperation in environmental research, including the development of European and Asian markets

Nanotechnology Symposium held at the Jawaharlal Nehru Research Center

On February 8 and 9, at Jawaharlal Nehru Research Center (Bangalore, India), a nanotechnology symposium entitled "Nano & Soft Matters" was held. From AIST, the Director of the Electronics Research Institute and the Director of the Nanotechnology Research Institute etc., all together 10 members, attended.

There were 4 themes: liquid crystals and nano-soft materials, nano/bio/molecular electronics, nano-oxides and green chemistry. All together, a total of 19 Japanese and Indian research projects were presented. In his speech, Chairman of the Scientific Advisory Committee to the Cabinet Dr. Rao explained the importance being placed on university education in India and India's nanotechnology policy and laid stress on the importance of short term personnel exchange between Japan and India.

In the summary session, there was a discussion of concrete methods of pursuing cooperative research, such as personnel exchange, joint workshops, joint research projects, external budgets, joint laboratories etc. There is to be an increase in the promotion of cooperative research in the field of nanotechnology, with the Jawaharlal Nehru Center taking a central role.

Participants of the Nanotechnology Symposium

Signing of the Comprehensive Cooperative Research Agreement based on the Japan - India Prime Ministerial Joint Declaration

On February 12, a comprehensive cooperative research agreement with the Council of Scientific and Industrial Research (CSIR) in New Delhi, India was signed. Also, on the same day, a comprehensive cooperative research agreement was signed with the Ministry of Science and Technology, Department of Biotechnology (DBT).

With regard to India, AIST has, since its establishment, effectively entered into 3 cooperative research agreements, with CSIR, Jawaharlal Nehru Center and others.

At the Japan - India summit meeting in April 2005, the governments decided to promote a Japan - India global partnership as part of which an increased focus would be placed on cooperation in science and industrial technology. The summit joint declaration given by Prime Minister Abe and Prime Minister Shin in December of last year expressed the intention of increasing the promotion of cooperation in the field of science and industrial technology, including collaboration/cooperation between AIST and CSIR and DBT.

Signing of Comprehensive Cooperative Research Agreement with CSIR

Signing of Comprehensive Cooperative Research Agreement with DBT

Before the AIST/CSIR signing, AIST and CSIR gave introductions to their respective research and exchanged opinions on methods of pursuing the cooperative research to come. In the case of DBT, before the signing, AIST's Director of the Research Center for Medical Glycoscience and Director of the Computational Biology Research Center gave introductions to their research and opinions were exchanged.

With the signing of the cooperative research agreement, the strengthening of exchanges of personnel using external funds and invited overseas personnel funds, and the promotion of cooperative research between the two countries has been confirmed.

Conclusion of Comprehensive Research Agreement with Australian Commonwealth Scientific and Research Organization (CSIRO) and Holding of Research Workshop

From March 6 to 7, a comprehensive research agreement was concluded in Newcastle, Australia between the Australian Commonwealth Scientific and Research Organization (CSIRO) and AIST, and in conjunction with this a research workshop was held. CSIRO is Australia's largest government general research organization, with 6600 employees and pursuing research in a wide range of areas such as environment, energy, resources, manufacturing, minerals and agricultural economics etc.

Research unit base collaboration with AIST has continued from its period as Industrial Research Institute, particularly in areas such as coal liquefaction, materials, resources and measurement standards etc. Recently, CSIRO Chief Executive Dr. Garrett, who was an AIST 2nd-term Advisory Board Meeting member, has been involved in detailed exchanges of opinion regarding research structure and management. Although Australia is not a signatory of the Kyoto Protocol, it held the AP6 (Japan, China, South Korea, Australia, America, India) Environment Ministerial Conference and is positively pursuing post-Kyoto Protocol measures against global warming. Australia, which has suffered the largest drought in history, is as this year's chair nation of APEC, positively pursuing "diplomacy for anti-global warming measures" such as the development of clean coal technology and carbon dioxide reduction technology etc.

Participants in the AIST/CSIRO Research Workshop

The research workshop was attended by 14 people from AIST including Senior Vice-President Kodama, Research Coordinator Tsukuda and others and there was an exchange of opinions on a diverse range of fields centered on environment, energy and nano-related such as clean coal, distributed energy production, solar power, geological remote sensing, methane hydrate, underground carbon dioxide storage and nanotechnology etc. After the workshop had finished, researchers separated according to research theme and visited research organizations in Newcastle, Brisbane, Clayton or Sydney etc, and there were further specialized exchanges of opinion in the respective research fields. It is planned that the two organizations will aim to strategically strengthen their collaboration, including information exchange, research personnel exchange and acquisition of outside funding, according to action plans in the respective research fields.

Exhibition at International Engineering & Technology Fair India

From February 13 to 16, the International Engineering & Technology Fair India (IETF 2007) was held in New Delhi. Japan, as a partner country (for the 2nd time, the 1st being in 1997), assisted in holding the fair, with the Japan External Trade Organization (JETRO) acting as representative and producing an exhibition including information on a large number of private enterprises. There were around 10,000 visitors to the Japanese pavilion on the first day and 3,000 to 4,000 daily on the remaining days.


AIST's Exhibition Booth

AIST presented posters regarding 12 items, describing summaries of laboratories, technology transfer and main research results (10 items). Various people from junior high school students to the elderly, both men and women visited and showed interest in the AIST booth. Amongst the visitors, there were people who made enquiries about postdoctoral positions, use of patents etc.

There were so many visitors that on the final day, the last of the posters prepared by AIST were all taken.

Vietnamese Minister of Science and Technology Visits Tsukuba Center

On March 9, the Vietnamese Science and Technology Minister Hoang Van Phong, together with Ministry of Science and Technology related personnel and Vietnamese Embassy related personnel resident in Tokyo etc., visited the Tsukuba Center.

In August of last year with the signing between the two governments of the Japan - Vietnam Science and Technology Cooperation Agreement, the 1st Japan - Vietnam Joint Committee on Science and Technology was held on March 7 in Tokyo, with around 20 people attending from Vietnam. This meeting was the first regarding science and technology to be held between the two governments and Minister Hoang Van Phong and Sanae Takaichi, minister responsible for science and technology, attended. There was also a report from AIST of the details of collaboration with the Vietnam Academy of Science and Technology.

AIST signed a comprehensive agreement with the Vietnam Academy of Science and Technology in December 2004, with the 1st workshop being held in Hanoi, the 2nd being held in October 2005 and the 3rd being held in November 2006, both at the Tsukuba Center. Various fields were promoted as areas for a strengthening of collaboration: environmental measures such as waste water processing, biomass related technology, marine/geological related research, GEO Grid and multi-language processing and open source software. The visit of the Vietnamese Science and Technology Minister to AIST, as a representative Japanese research organization, was arranged at the minister's request.

On the day of the visit, welcoming greetings were given by Senior Vice-President Kodama, an outline explanation of AIST was given by Vice-President Yamazaki, an introduction to the details of the collaboration between AIST and the Vietnamese Academy of Science and Technology was given by Research Coordinator Yamabe and an introduction to waste water processing technology, which is a particularly strong field of collaborative research with the Vietnamese Academy of Science and Technology, was given by Research Institute for Environmental Management Technology Vice-Director Tao. Then, a lively question and answer session was held regarding the details of establishment as an independent administrative institution, history and differences from universities and other research institutions. Following this, there was an inspection of the various facilities and of the research that they are pursuing: the Grid Technology Research Center, Research Center for Photovoltaics and the Nanotechnology Research Institute.


Senior Vice-President Kodama welcoming Minister Phong

At the Grid Technology Research Center, in particular, the GEO Grid was introduced as an area of cooperative research aiming at development in the ASEAN area. Also, regarding solar cells, Minister Phong showed strong interest in the promotion of cooperative research with AIST and showed interest in the utilization and value of nanotech processing facilities. At the end of the tour, Minister Phong stated that because AIST was pursuing extremely advanced research, he hoped that a large number of researchers could be accepted from Vietnam. With this visit to AIST, it is expected that collaboration between the two countries will be given a further boost.

GEO Grid Workshop (Several-Country Cross-Discipline International Meeting) held in Thailand

AIST and the Thailand National Science and Technology Development Agency (NSTDA) National Electronics and Computer Technology Center (NECTEC), with the support of the Coordinating Committee for Geoscience Programs in East and South East Asia (CCOP) and the American GEON (Geosciences Network), jointly held the GEO Grid Workshop on March 20 at the NSTDA Convention Center in the Bangkok Science Park (attended by from AIST Vice-President Kato, Research Coordinator Tsukuda, Grid Technology Research Center Director Sekiguchi, International Affairs Department Director Matsuo etc.).

This workshop was held as the first several-country international meeting to promote the merging of geoscience information systems with grid technology in order to achieve a solution that transcends national boundaries to the common issues faced by every country such as global environment, energy resource problems and natural disasters etc.

The workshop was attended by around 100 people from AIST's comprehensive MOU agreement contact organization the Thai NSDTA, the Vietnamese VAST and researchers in related areas from various South East Asian countries, with presentations of the GEO Grid, CCOP's activities (resources, environment, geological information etc.), the American GEON's activities and efforts relating to South East Asian GEO information, including usage of satellite data such as from ASTER etc.

Center Director Sekiguchi explaining the GEO Grid

In addition, the sharing of information and strengthening of collaboration across disciplines and national borders, the multi-country common issue of global environment and measures to cope with natural disasters such as earthquakes and tsunamis were discussed, with AIST Vice-President Kato giving an overall summary. The importance of promoting, from now on, concrete international collaborative projects was emphasized.

With the coming incentives such as the United Nation's GEOSS (Global Earth Observation System of Systems) implementation plan, and the UN designation of 2008 as "International Year of Planet Earth," promotion of concrete international collaborative research aimed at overcoming Asia's common global issues is expected and, together with the collaborative research organizations of the comprehensive MOU agreement, the two countries will pursue definite action in this direction.

Also with regard to Grid international collaboration, the 12th PRAGM Workshop (Pacific Rim Application and Grid Middleware Assembly) was simultaneously held in Bangkok.

For more detailed information on the GEO Grid, please see the special article in the previous issue of this publication (AIST TODAY 2007 - 4).

Participants in the workshop

Japanese - French (AIST - CNRS) Robotics Laboratory Management/ Assessment Committee Meeting

On April 16, a management meeting and research assessment committee meeting of the Joint Japanese - French Robotics Laboratory (JRL), which is jointly run by the AIST Intelligent Systems Research Institute and the French National Center for Scientific Research (CNRS: comprehensive MOU agreement) Department of Information and Engineering Sciences and Technologies, was held at the CNRS Laboratory of Analysis and Architecture of Systems (LAAS) in Toulouse, which houses the French research site (JRL - France). There was a demonstration using the humanoid robot HRP-2, introduced into the Toulouse laboratory last year from Japan, which received high praise from the members of the Research Assessment Committee, which comprises not only Japanese and French members, but also researchers from Germany and America. It is expected that with the further progress of JRL activities, the Intelligent Systems Research Institute's research collaboration will be further strengthened, of course with France but also with other EU robotics research organizations.

Demonstration of Humanoid Robot HRP-2

European Commission Member Reding Visits AIST Tsukuba Center

On April 5, European Commission Member Viviane Reding (EC Commissioner responsible for information and communications) and her staff visited AIST's Tsukuba Center. At the start, following welcoming greetings from Senior Vice-President Katsura, there was an outline explanation of AIST from Vice-President Yamazaki, and after an explanation of AIST's ICT related research activities by Research Coordinator Ohmaki, an explanation of Framework Program 7 (FP7), starting from this financial year, was given by the EC party. Following this, Commissioner Reding, Vice-President Yoshiumi and other AIST and EU members engaged in a lively exchange of opinions regarding research collaboration between Europe and AIST, centering on FP7.

After this, the group moved to the Tsukuba Open Space Laboratory (OSL) and Intelligent Systems Research Institute Director Hirai explained AIST's robotics research, following which the group saw the seal-shaped robot "Paro" and the Joint Japanese - French Robotics Laboratory (JRL) humanoid robot, with Commissioner Reding enthusiastically exchanging opinions with researchers particularly regarding collaboration in the field of robotics.

Senior Vice-President Katsura, showing around Commissioner Reding (right) and her group

Commissioner Reding exchanging opinions regarding collaboration in the field of robotics

In 1984, the European Commission started the first Framework Plan (FP) and from 2002, the 5 year plan FP6 was put into operation, with international joint research within the EU area (also including international cooperative research support from outside the EU) being pursued. 2007 sees the start of FP7, which apart from the stressing of infrastructure, will further strengthen cooperative research and networking and will run for 7 years with a planned total budget of 55 billion euros, with expectations of the strengthening of an open research network outside Europe also being expressed.

At the Intelligent Systems Research Institute, Joint Japanese - French Robotics Laboratory (JRL) formed with the French National Center for Scientific Research (CNRS), Department of Communication and Information Science and Technology, as an international laboratory, has participated in FP6 and with regard to future developments, at the CNRS/AIST Board Director Meeting held in Toulouse, France on April 16, further increases in the promotion of collaborative research, including FP7, were discussed. It is expected that with Commissioner Reding's visit, there will be a step up in the strength of research collaboration between the EU and AIST and, of course, the Intelligent Systems Research Institute.

Vietnamese Ministry of Planning and Investment Vice-Minister visits Tsukuba Center

On April 23, the Vietnamese Ministry of Planning and Investment Vice-Minister Truong Von Doan together with personal connected to the ministry's Small & Medium Sized Business Agency visited AIST's Tsukuba Center.

Vice-Minister Doan is the person with responsibility on the Vietnamese side for the Small and Medium Sized Business Support Center which is a joint project between JICA and Vietnam. This JICA project which aims to train leaders to develop small and medium sized businesses, started in the 2006 financial year and will run for a total period of 2 years.

Vice-Minister Truong Von Doan (center) and his party with Katsura Senior Vice-President and Executives of AIST

After welcoming greetings from Senior Vice-President Katsura, an outline explanation of AIST and an introduction to the details of the collaboration between AIST and the Vietnamese Academy of Science and Technology were given by Vice-President Yamazaki, and an introduction to AIST's industry - academia - government collaboration system was given by Collaboration Promotion Department Director Hama.

Vice-Minister Doan expressed his gratitude for the strengthening of collaboration between AIST and Vietnam and for cooperation given to the Vietnamese Small and Medium Sized Business Support Center and a lively question and answer session was held regarding reversion of patents and small/medium business support.

Exhibition at Hanover Messe 2007

For five days from April 16 to 20, the world industrial trade fair "Hanover Messe 2007," which gathers together various industrial fields, was held in the Hanover International Trade Fair Hall in Germany, with AIST presenting its 5th exhibition. 6400 companies from 62 countries exhibited at the event, with visitor numbers amounting to 230,000 (30% of which were from outside Germany), making Hanover Messe what can be called a true gateway to world markets.

At the Hanover Messe, which presents specialized trade fairs in 11 fields, AIST exhibited under the "Research, Development and Technology" field heading, exhibiting at the joint Japan booth, which had a floor space of around 200 m2 and was organized by the Japan External Trade Organization (JETRO) for Japanese corporate exhibitions. Here, together with JETRO, the Organization for Small and Medium Enterprises and Regional Innovation, and Sendai City, AIST presented its exhibitions, with introductions to imogolite, spinning processes, electrochemical reactors, heat resistant magnesium alloy, thermoelectric generating modules, clay membranes, the seal-shaped robot "Paro," organic nanotubes and the marine microbe Labyrinthula.

Visitors from various countries across the world, from businesses, universities and research organizations came to the AIST booth and engaged in lively discussions regarding technology and business discussions. In addition, since this year there was a special exhibition aimed at informing young people, a large number of students came to the exhibition hall in order to experience leading edge technology and this provided AIST with an opportunity to strongly impress its existence on visitors of various generations.

AIST's Exhibition Booth

Also, on the last day, under the auspices of the Economy, Trade and Industry Vice-Minister Hiromichi Watanabe, it was announced that the partner country for Hanover Messe 2008 (to be held April 21 to 25) would be Japan. This means that next year, as the partner country, a large number of Japanese businesses will produce exhibitions and Japanese technology will be shown off effectively at a global level. AIST hopes to use its experience of the previous 4 occasions as well as that of this year to utilize, to the greatest possible extent, Hanover Messe 2008 as a place for technology transfer, formation of high level group relationships, and international collaboration.

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