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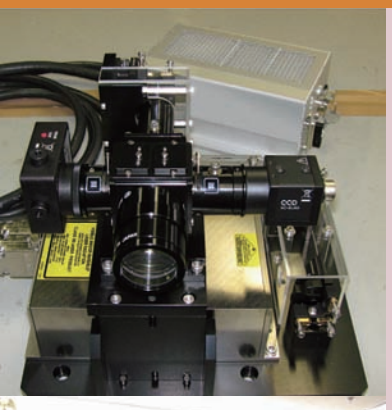

MESSAGE

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FEATURE

Biophotonics at AIST

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UPDATE FROM THE CUTTING EDGE（July–September 2009）

In Brief

President's Message: Open Innovation

Tamotsu Nomakuchi

President
National Institute of Advanced Industrial Science and Technology (AIST)

1. Introduction

The significance of open innovation and its importance are pointed out and discussed throughout the world these years. The concept of open innovation when its necessity was first stressed in the U.S. was that companies could not possibly cope with the competitions only with their original in-house technologies, but should best utilize external intellectual properties and technologies, such as of other companies or universities. Therefore, while serving in the industry I understood that open innovation is a concept for the management of R&D and technological strategies of the private sector.

However, once I moved as president to a public research institute, AIST, whose mission is to conduct research to respond to the social needs, open innovation began to appear as "the very concept to be applied to AIST." It is because our research results acquire their intended meanings only when companies in our society put them into actual use.

Also, for Japan, a small country with scarce resources, which had been trying to catch up with the Western countries and arrived at the leading edge of the world only these decades, it is quite evident that continuous innovations are essential. I think open innovation as means of continuous innovations has a special meaning for Japan.

2. Why Open Innovation?

Anyone would agree that the various innovations applied in the modernization process of Japan were introduced mostly from the then developed countries of Europe and America. It is the same with the technologies that supported Japan's modernization. Since the Meiji Era until the mid 1980's, our major and consistent national concern on technologies was how to catch up with Europe and America. Finally from the mid to late 1980's, Japan began to gain credible recognition at home and abroad

that it had caught up and joined in the world's leading group. Some even overestimated Japan's ability that there was nothing any more to learn from abroad, while at the same time Japanese industry had to experience harsh pressure through the tightened pro-patent policy and other measures of the U.S. As a member of a research institute of a company, I myself had to confront the Japan-U.S. semiconductor trade conflict, and keenly felt the severity in competing and surviving in the vanguard.

Soon after Japan reached the world's R&D forefront, China and Korea started to catch up with us. An example can be found in the transition of the number of patent applications of major countries surveyed by the Japanese Patent Agency. The number of applications of Japan which had been the top for more than 20 years was overtaken by the U.S. again in 2006. Japan's growth rate of the application numbers, in the last few years, has been far below those of China and Korea. Though the patents should be evaluated over the quality and not the quantity, this tendency is worrisome. More efforts than before might be required for Japan to maintain the leading status of the world.

In order to successively obtain achievements such as intellectual properties and products, solid results of basic and fundamental research are indispensable. However, the industry nowadays has pressing needs to focus on the business competition, and has less remaining power for research. Consequently, it is the universities and public research institutes, such as AIST, that could meet the extensive, compelling needs and expectation of the industry. Promotion of open innovation through substantial collaboration of industry, academia, and public sectors becomes increasingly significant.

3. AIST's Efforts for Open Innovation

Since the days of the former AIST, the Agency of Industrial Science and Technology, collaboration with universities and industry has been our great focus. The mission to maintain and enhance our industrial competence, I believe, has become even more crucial. I introduce here some of the cases I keep my eyes on, selected according to my own criteria and interest.

1) Digital human: child accident prevention

The Digital Human Research Center, AIST, aims to create a safe ergonomic environment for children to play as freely as they like. Here, accident surveillance systems collects accident information, whereas accident prevention contents service is provided based on our invention of "Bodygraphic Information System." This initiative could be defined as a new model of open innovation, and AIST functions as the hub of a network of variety of people and organizations, such as hospitals, nurseries, kindergartens, elementary schools, municipalities, universities, housewives, and businesses. Along with the development of research, valuable data have been fully accumulated, which in total serve to upgrade the quality of research.

The concept of "Digital Human" was invented and advocated by AIST. It means digitalization of data on human body and behavior, which enables mathematical and statistical approaches. Besides the above cases, it offers totally new guidelines for designing in wide areas that covers a variety of social services and products related to human behavior. It is gaining worldwide attention as an innovative concept born in Japan.

2) Photovoltaics (PV): for low cost and longer life

Japan is believed to have been leading the photovoltaic research. However, countries in Europe and America, China, Taiwan, and others are focusing on it lately, which results in fierce competitions. AIST, therefore, recently established "Consortium on fabrication and characterization of solar cell modules with long life and high reliability" in collaboration with 31 companies, both large and small. It is to strengthen Japanese competitive power in the PV fields for a great breakthrough. Extensive studies that are not feasible by one single company will be possible through cooperation among companies, or companies and AIST, on major module components, such as encapsulants, back

sheet, interconnectors, and sealing materials. By acquiring improved reliability and a longer life of PV modules, drastic reduction of electricity cost would be possible.

In cooperation with the Photovoltaic Power Generation Technology Research Association (PVTEC), the research achievements of PV module components themselves as well as evaluation and testing methods will be proposed as standards that would help secure the competence of the participating companies.

3) Upgrading of nanotechnology competence

In collaboration with the National Institute for Materials Science (NIMS), the University of Tsukuba and the industry, AIST is going to reinforce nanotechnology R&D. There used to be state-of-the-art R&D projects on semi-conductor technologies on the initiative of the private sector in cooperation with AIST, by using the AIST Super Clean Room. We need to overtake the U.S. and the EU countries in this field, in closer partnership with the industry, academia and public sectors. Nano-electronics, nano-MEMS (Micro-Electro-MechanicalSystems), carbon nanotubes, power-electronics, and safety evaluation of new materials would be the cores of researches. We aim to create technologies indispensable in realizing a low-carbon society, such as highly efficient power devices, though they may not be achieved all at one stroke. Thus, we are ready to persistently tackle the issues to improve our industrial competence and to address the global environmental issues.

Here, I would like to make my last remarks. AIST promotes *Full Research* that covers from the basic research through product realization research. In fact every AIST research unit has been very eager to collaborate with external organizations. We are proud to say that all of AIST functions as the hub of open innovation. If you are interested in the details, please visit our website at the URL below.

AIST website: http://www.aist.go.jp/index_en.html

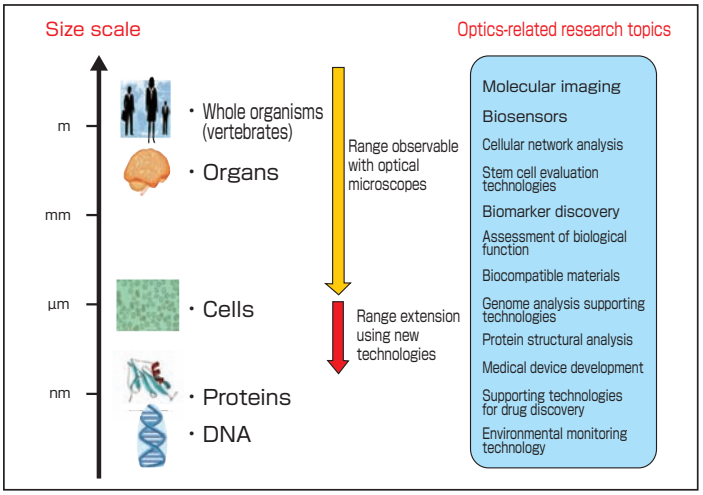
The "Visualization" Challenge: Development and Application of Bio-optical Technologies

The importance of "seeing"

The fundamental building block of living organisms is the cell, which is measured in microns. Invisible to the naked eye, cells were first rendered "visible" by the invention of the optical microscope. Closely packed inside the cell are the genes (DNA) and proteins, which are deeply involved in the maintenance of life. To understand the functioning of cells in both normal and abnormal disease states, "visualizing" the movements and workings of these molecules is essential. However, the size scale of genes and proteins is less than one hundredth of a micron, and due to limits imposed by the nature of light itself, these cannot be seen with an optical microscope.

Through scientists' hard efforts these past 20 years, various ingenious schemes have been devised, making it possible to harness light to reveal a single protein molecule's presence as well as capture the conformational changes a single molecule undergoes in the process of functioning. In this way we can see and grasp the "inner workings" of cells with our eyes and reliably diagnose cell abnormalities and their underlying causes. Comparing the cell to a theatrical stage, we've progressed from knowing only the names of the actors in a production to knowing the scenes in which they appear and whom they face when they speak their lines. Soon, the script in its entirety will become clear

Promotion of interdisciplinary research



Hierarchy of biological size scales (left side)
Light-related research themes within AIST laboratories in life science and biotechnology field (right side)

This sort of progress cannot be accomplished by biologists and medical scientists alone; cooperation among research experts from a variety of disciplines—optics, glass materials science, mechanical engineering, synthetic organic chemistry, image processing—is absolutely required. Fortunately, AIST houses many researchers not only in the life sciences, but also in electronics and materials science who are very active and cooperate routinely to advance their research. In this feature article we sift through some of our activities to introduce the very latest light-based technologies useful for biotechnology and medicine.

Each of these lies on the global technological forefront, and holds promise for groundbreaking applications in various fields of biotechnology and medicine. Uses aside from those that AIST researchers are currently contemplating will also likely emerge. Please let us know of any ideas you might have. This year's spread of H1N1 "swine" flu has been a major news topic, and the technologies discussed here are also said to be proving useful in the fight against it.

Trying to visualize the invisible

In this feature article, we introduce eight research achievements. At AIST, we have achieved many successes in using light for visualization, such as a microscope that is a hybrid of an optical and electron microscope, technologies to control and record the activity of neurons with light, and technologies for determining gene activity with light-emitting proteins. We are even holding training courses to actively spread these new technologies throughout society. By all means, contact us with your particular need if you find yourself saying, "If we could only see this thing, the project would move forward." Marshaling the strengths of AIST, we will show you a way to see it.

Research Coordinator
Takahisa Taguchi

For inquiries about this article：Takahisa Taguchi taguchi-takahisa@aist.go.jp

Development of Water Dispersible Indium Phosphide Nanocrystals for Use as Fluorescent Reagents

The promise of photoluminescent semiconductor nanocrystals

Semiconductor nanocrystals (NCs) emit light at wavelengths that can be tuned by particle size and composition, and are more stable to light than organic dyes, so hopes for their applied use are high. When coated with such agents as surfactants and a semiconductor with a wide band gap, these NCs show strong photoluminescence (PL), cadmium selenide (CdSe) and cadmium telluride (CdTe) being representative examples. Water dispersible NCs are well-suited to biotechnology applications, and furthermore are amenable to sol-gel processing, making it possible to produce highly photoluminescent glass beads incorporating multiple NCs.

In recent years, NCs have been sought that do not contain toxic cadmium, and we have succeeded in developing blue light emitting zinc selenide (ZnSe) family NCs followed by red~green light emitting indium phosphide (InP) family NCs.

The development of photoluminescent InP-containing NCs with water dispersibility

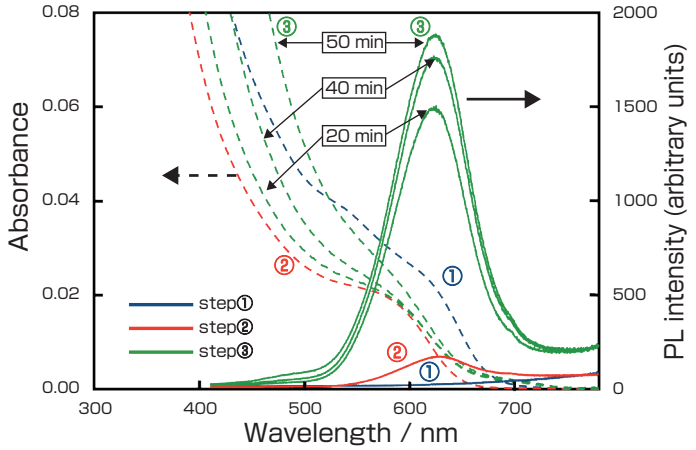
Initially, InP cores (particle diameter ~ 3 nm) are produced in an organic solution via a safe, inexpensive method, and we found a method to transfer these to an aqueous phase. Zinc sulfide (ZnS) shells were formed in a subsequent photochemical reaction using ultraviolet (UV) irradiation, and we produced water dispersible InP/ZnS core-shell type NCs exhibiting high PL efficiency in water.

Here the ZnS shell is formed by decomposition of a sulfur-containing surfactant, whereupon the generated S^{2-} reacts with Zn^{2+} in the aqueous solution. Previously, using thioglycolic acid (TGA) we obtained water-dispersible InP/ZnS NCs with a high PL efficiency (68 %) in water[1]. This time, using low-toxicity thioglycol (TG) we produced similar water-dispersible InP/ZnS NCs by the procedure below.

The InP NCs are dispersed in organic solvent, then brought into contact with an aqueous solution containing Zn^{2+} and TG. A surface reaction takes place with the NCs transferring into the aqueous phase. At this time, the NC surface dissolves, their light absorbance decreases, and simultaneously a thin ZnS shell is formed with weak PL appearing. (① → ② in the figure).

Next the NC suspension is irradiated with UV light, and the ZnS shells grow. Due to the electron confinement effect brought about by their thick shells (~1.5 nm), PL intensity of the InP/ZnS NCs increases (② → ③ in the figure), and a high PL efficiency (43 %) was obtained. Compared to using TGA, small scattering in longer wavelength region (③ in the figure) indicates that using TG, which lacks a charge, made the TG-coated NCs agglomerate somewhat easily than the TGA-coated NCs.

As described above, we prepared water-dispersible, photoluminescent InP/ZnS NCs using phase transfer and irradiation with light. The fact that we were able to use sulfur-containing surfactants with different



Changes in the absorbance (dotted lines) and PL spectra (solid lines) during the 3-step process of producing InP/ZnS NCs
Step ① : InP NC cores
Step ② : After transfer into the aqueous phase
Step ③ : After growth of the ZnS shell by UV irradiation (the duration of UV irradiation is indicated)

functional groups suggests the possibility of producing NCs coated with a wide variety of molecules. We plan to expand the range of fluorescent reagents this technology can provide.

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Photonics Research Institute
Masanori Ando
Chunliang Li
Norio Murase

For inquiries about this article：Photonics Research Institute photonics-sec@m.aist.go.jp

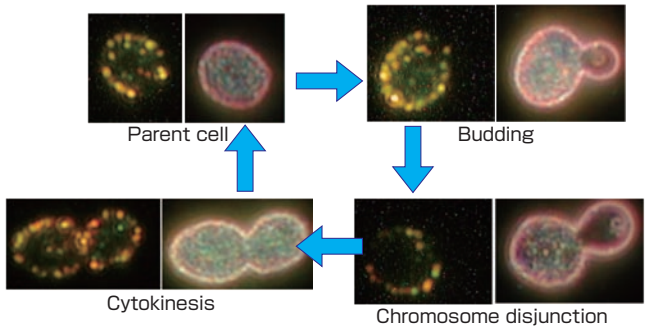
Observing the Cell Surface Using Surface Enhanced Raman Scattering (SERS) Spectroscopy

The importance of SERS-sensing of the cell surface

As cell surfaces are tasked with essential functions in cellular processes such as mass transfer and sensing the extracellular environment, development of methods for analyzing cell surfaces is important in terms of industrial applications such as drug discovery and cell function diagnostics. One such analysis method is to use antibodies combined with fluorescent tags that bind cell surface antigens, but this approach suffers problems due to the quenching of fluorescent pigments. As one possible alternative approach not subject to quenching, Raman scattering[term] spectroscopy might be used, but its low sensitivity has made it impractical. Therefore, to overcome this sensitivity problem, we developed a method[2][3] for *in situ* measurement of protein expression on living cell surfaces using spectroscopy based on the surface enhanced Raman scattering (SERS)[1]: a phenomenon whereby adsorption of a molecule to a metal nanoparticle can increase the molecule's Raman scattering intensity by up to a 10^{14}-fold.

In situ monitoring of protein expression on a cell surface

We carried out SERS imaging and spectroscopic measurements of the surfaces of budding yeast cells. On the left side of each of the four figure panels is a SERS-image obtained by laser-irradiation of silver nanoparticles (average diameter: 40 nm) adsorbed to living yeast cells. Many bright spots due to SERS light can be observed on the cells. Carrying out spectroscopic analysis of the bright points one-by-one, we found each to correspond to a mannoprotein abundantly present in the cell surface layer[2][3]. On the right of each panel are the light-scattering images of the adsorbed silver nanoparticles. Light-scattering spots on the cell showing up in colors such as blue and green correspond to plasma resonance of silver nanoparticles. Upon observation of these silver nanoparticles using an atomic force microscope, we found that most were made up of two particles joined together. Where the particles join, there is space for only about one molecule to fit in, but this is where SERS light is known to be most enhanced up to single molecule detection level[1]. Based on this fact, it can be strongly surmised that the measured SERS spectrum was scattered light from a single mannoprotein molecule adsorbed at the junction. Comparing the panels of the figure, we see that manifestation of SERS in the daughter cells (cell on the right in each panel) varies with cell cycle phase. During the period just after budding until just before cytokinesis, neither adsorption of silver nanoparticles nor manifestation of SERS occurs on the surface of the daughter cells. In contrast, following cytokinesis, silver nanoparticle adsorption and SERS are both manifested. Through comparison with previous studies, we find that the cell cycle



Silver nanoparticle adsorption status (right panels) and manifestation of SERS (left panels) at four stages of budding yeast's cell division cycle

phase at which SERS is observed coincides with mannoprotein expression.

Future plans

In order to increase the versatility of SERS spectroscopy for *in situ* measurement of protein expression on cell surfaces, we will pursue adaptation of this method for use with gold nanoparticles, which are less toxic than silver.

【Terminology】

Raman scattering: When monochromatic light of frequency ν, is irradiated to a molecule, the frequency of some of the scattered light is observed to differ slightly from ν. The structure and molecular species in a sample can be identified by the spectrum of the scattered light.

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Health Technology Research Center
Tamitake Itoh
Hiroko Abe
Biju Vasudevan Pillai
Mitsuru Ishikawa

For inquiries about this article：Health Technology Research Center webmasters-htrc@m.aist.go.jp

Highly-Sensitive Fluorescence-based Detection of Catecholamines as Stress Markers

Development background

Although mental healthcare is a crucial issue in stressful social environments, there is no established system for assessing stress objectively. One objective assessment approach is to measure the levels of stress-related substances. Catecholamines, present in the blood and urine, are closely related to stress, and constitute recognized stress markers. As a first step toward developing such a catecholamine-based stress assessment system, we have developed a system capable of convenient, rapid, and highly sensitive measurements.

Detection on a chip

Based on fluorescent detection of catecholamines selectively captured on a solid substrate, we have carried on development of a novel measurement system. We chemically modified the surface of the glass substrate with probe molecules [term1] that bond chemically with catecholamines to form a fluorescent complex. After exposing the detection chip to a solution containing catecholamines, we were able to observe fluorescence in 480 nm region upon irradiation of 375 nm light. This method allows fluorescence detection of catecholamine in ca. 5 minutes. However, because fluorescence on the chip surface is very weak, it is necessary to boost sensitivity. Therefore, we used an optical waveguide [term2] mode able to dramatically enhance the intensity of incident light at the waveguide surface. We fabricated an optical waveguide with aluminum and silica layers whose thicknesses were controlled at the nanometer scale, and used this as a detection chip. When fluorescent catecholamine complexes were present on the chip surface, strong fluorescence emission was confirmed by waveguide mode oscillation. In the case of adrenaline, we succeeded in detecting minute quantities of ca. 1.5×10^{-15} mol. Moreover, using the waveguide mode, it is possible simultaneously to detect both fluorescence and changes in reflectance brought about by changes in the thickness of the chip's surface layer. By acquiring both data simultaneously, we can increase detection accuracy.

Toward practical realization

In putting this system to use on actual samples, issues arise such as how to prepare samples and evaluate results. Going forward in cooperation with experts on clinical testing and stress evaluation, we would like to strive to improve the current system for practical measurements. In addition, we are giving careful consideration to construction of a system that would allow simultaneous detection of catecholamines together with other stress markers, and would like to proceed with development.

【Terminology】

Term1

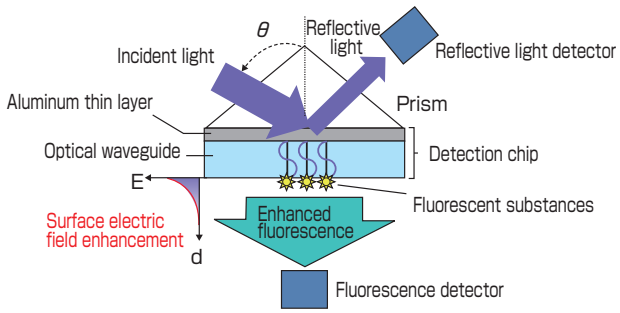
Probe molecule: To "probe" means to "examine". A probe molecule is a molecule used to detect the presence and distribution of certain chemical substances, and accomplishes this by selectively binding to the target molecule and emitting a signal such as fluorescence that can be monitored with a detector.

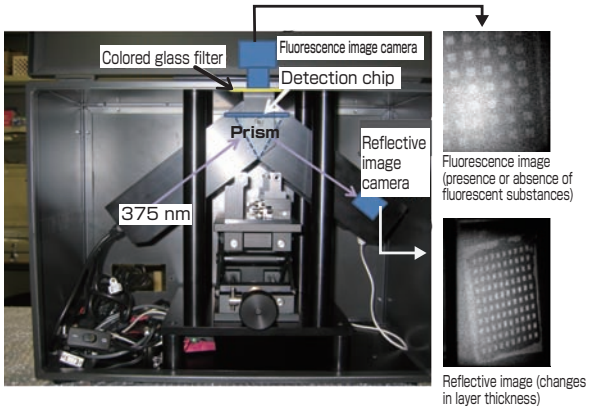
Term2

Optical waveguide: A circuit board for light that

is fabricated onto the substrate. By exploiting such things as differences in refractive index, an optical waveguide leads a light signal just as an electrical circuit provides a path for the flow of electrons. In principle it is the same as optical fiber, but whereas optical fiber is a filamentous conduit, an optical waveguide is a planar structure.

Photonics Research Institute
Nobuko Fukuda
Hirobumi Ushijima





When light hits the detection chip at the waveguide mode oscillation angle, incident light intensity is enhanced at the surface of the optical waveguide (left schematic). The photos to the right show a prototype measurement system.

For inquiries about this article：Photonics Research Institute photonics-sec@m.aist.go.jp

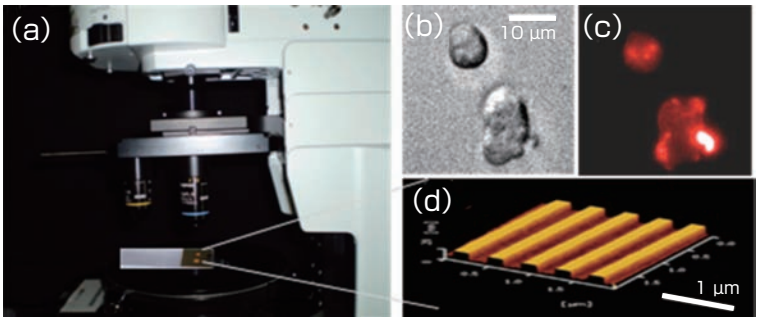
Fluorescence Microscopic Imaging Using a Substrate with a Sub-wavelength Grating

Surface plasmon resonance to date

About 20 years have passed since surface plasmon resonance [term1] (SPR) was commercialized for detecting minute amounts of biological molecules. As a result of numerous innovations made to improve sensitivity, even minute amounts undetectable by SPR can now be detected by surface plasmon field-enhanced fluorescence spectroscopy (SPFS: an SPR-based detection method to detect enhanced fluorescence of fluorescent molecules on the substrate surface selectively excited by an SPR-electrical field). Since in most instances biological substances must be detected in water (buffer solutions), a wider angle is required for resonance than in air. For instance, when using a prism and a substrate of refractive index 1.84 and light whose wavelength is 633 nm, the resonance angle [term2] should be ca. 60°. Thus, the wider angle severely restricts the optical setup as well as the available wavelength range.

High sensitivity fluorescence imaging

To overcome these problems of the conventional prism coupled-SPR design, we carried out enhanced fluorescence detection using grating-coupled (GC) – SPR. In GC-SPR, a thin metal coated grating substrate with a rectangular or trapezoidal surface profile (figure panel d), in which a periodic structure is shorter than the light wavelength (sub-wavelength), allows the resonance angle to be reduced. We fabricated this periodic structure using



(a) Photo of a fluorescence microscope using the grating substrate
(b) Bright-field image of fluorescently labeled cells on the grating substrate
(c) Fluorescence image of fluorescently labeled cells on the grating substrate
(d) Scanning probe microscope image of the grating

two-beam interference and dry etching, or uv-nanoimprint lithography. A periodical structure of 400 nm created on the substrate surface was covered with Ag and SiO_2 layers to be used as a biochip. Coupling this grating with a light wavelength of 633 nm, SPR was found at an incident angle of 8°. With this chip, we found a fluorescence enhancement of tens- to a hundred-fold compared with a glass slide. Applying this GC-SPR method, we are carrying out fluorescence microscopic imaging of fluorescently labeled cells (fig. panels (a) ~ (c)), and developing high sensitivity fluorescence imaging of a protein array chip that will specifically bind fluorescently labeled proteins to the substrate.

Future plans

The simple optical detection system promotes the combination with microfluidics and multi-arrays. We would like to develop this sub-wavelength grating chip for application to clinical diagnostics as a rapid and high-sensitivity chip to test multiple disease-related indicators simultaneously.

【Terminology】

Term1

Surface plasmon resonance (SPR): A phenomenon whereby polaritons (free electrons) on the surface of a metal film interact with incident light. When metal particles or needle-like pillars or holes of nanometer-scale dimensions are arrayed periodically, polaritons and photons are coupled, generating a very large electric field. This has been used as basic technology of DNA sensors and molecular sensors.

Term2

Resonance angle: In the propagated SPR, it is the angle coupled with polaritons and photons, which is determined by the dielectric constant of the interface and the wavelength of incident light. It is possible to detect immune reactions, etc., by monitoring the shift angle.

Research Institute for Cell Engineering
Keiko Tawa
Hironobu Hori
Yoshiro Tatsu
Photonics Research Institute
Junji Nishii
Kenji Kintaka
Neuroscience Research Institute
Kazuyuki Kiyosue

For inquiries about this article：Research Institute for Cell Engineering rice_webmaster@m.aist.go.jp

Revealing Amyloid Structure by Isotope-labeling Infrared Spectroscopy

The difficult structural elucidation of amyloids

In many neural degenerative diseases such as Alzheimer's dementia and bovine spongiform encephalopathy (BSE), protein aggregates (known generically as "amyloids" specific to each disease) are thought to be involved as causative factors. Amyloids exhibit granular or fibrous structures of about 10 nm thickness (Fig. 1). These amyloids lead to a disease and can be infectious in some cases; however, these same proteins normally exist as non-toxic individual protein molecules within humans and animals. The molecular level 3D structure of each amyloid is very important not only for "elucidation of the factors contributing to amyloid formation and pathogenic mechanisms" but also for "the development of methods for detection and medical treatment including drug design based on the structure of amyloids". However, in contrast to the 3D structural elucidation of numerous proteins by X-ray crystallography and multi-dimensional NMR, there are fundamental limits that create considerable difficulties for the structural analysis of amyloids. Even now, there are no more than a few structural models that have been estimated with limited information.

Extracting local structural information by isotope-labeling

Through experiments such as the characterization of engineered protein variants, we have explored the inter- and intramolecular interactions responsible for amyloid formation, and proposed a generalized structural model. Furthermore, in order to elucidate the structure of each individual amyloid, research is in progress using approaches such as isotope-labeling infrared spectroscopy (IR). Generally, spectroscopic structural analysis provides spectrum reflecting structural information for the entire molecule. However, by labeling only the position we want to learn about, obtaining information on the local structure can be realized. Especially in infrared spectroscopy, substitution of the usual ^{12}C with ^{13}C causes the stretching vibrations of related atomic bonds to shift towards lower

frequency, enabling the local structures of respectively labeled positions to be detected. In the case of proteins, the peptide bond linking amino acid residues contains a C=O bond, of which the IR signal appears at a characteristic wavenumber depending on the secondary structures (α-helix or β-structure). Thus, by analyzing the infrared spectrum of a protein with ^{13}C substitution at a specific position, it may be possible to determine the local secondary structure at that position. To date, although ^{13}C isotope-labeling infrared spectroscopy has been applied to certain instances, length has been limited to short polypeptides of about 10 residues. Furthermore, there has also been the problem that amyloids formed from the peptides corresponding to parts of a protein do not necessarily coincide with those formed from the whole protein. We have analyzed the infrared spectra obtained with a semi-comprehensive set of ^{13}C isotope-labeled proteins of the full-length 42 amino acid residue "amyloid-β" protein that causes Alzheimer's disease. Despite a weak signal derived from ^{13}C, we have succeeded in demonstrating with high reliability for each labeled position whether it is, or is not, β-like structure (Fig. 2). Integrating this with our other data, we are currently inferring that there are two specific regions in the molecule, each about 6 residues in length, and that they have high potential to interact with each other and predominantly form a nucleus of amyloid bearing β-structure. Taking advantage of our expertise in synthesis, we plan to close in on the structures of a variety of amyloids towards elucidation of the universal principles of their formation.

Institute for Biological Resources and Functions
Hisayuki Morii
Masahiro Koike

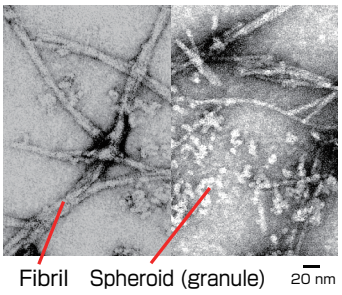


Fig.1 Electron microscopic images of amyloids consisting of amyloid-β protein

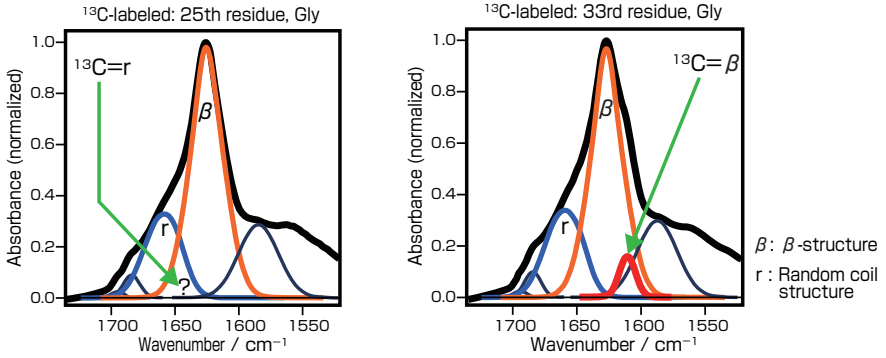


Fig.2 Infrared spectra of amyloids from isotope-labeled amyloid-β proteins

Co-researchers

Masayuki Nara (Tokyo Medical and Dental University) , Takeo Konakahara (Tokyo University of Science) , Tomoko Okada (AIST)

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For inquiries about this article：Institute for Biological Resources and Functions brf-webmaster@m.aist.go.jp

Capturing Tens-of-nanometers-scale Phenomena with a New Optical Microscope

Research background

Optical microscopes are widely used to observe phenomena on the order of micrometers (μm). In recent years, it has been found that, used ingeniously, an optical microscope can detect phenomena of the nanometer order such as fluorescence generated by a single molecule or light scattered by gold colloidal particles only a few nanometers (nm) in size. In order to understand the mechanisms by which neurons elongate, we have made prototypes of various types of high-precision optical microscopes and observed the motion of the neurons elongating. Our new polarizing microscope [term1], "Pol-Scope," has enabled the detection of a retardation (a unit for measuring the strength of birefringence) of ca. 0.2 nm and the visualization of the dynamism of actin filament bundles [term2] with a diameter of 20-60 nm inside a neuron

without staining (Fig. 1). Recently, we built a prototype apodized phase contrast microscope of high numerical aperture, and succeeded in direct observations of the actin filament mesh and movements within the cell nucleus. Here, we would like to describe our work, focusing on the apodized phase contrast microscope.

The apodized phase contrast method

The phase contrast microscope is widely used to observe cells at low magnification. However, this type of microscope suffers from decreased optical resolution due to a halo (a blur of light) around the circumference of a cell that conceals its fine structure. For this reason it is ill-suited to high-magnification, high-resolution observation. The apodized phase contrast method is a phase contrast technique that diminishes the halo by substituting an apodized phase ring (phase ring with a light-reduction film added to its circumference) for the phase ring within the objective lens (Fig. 2). The light-reduction film reduces the low-spatial-frequency component (corresponding to the information for large-size objects), thereby enhancing the high-frequency component (corresponding to the information for small-size objects) in relative terms (Fig. 3).

Application to biological samples

In 2000, Nikon Corporation developed an apodized phase contrast microscope with halo reduction and applied it to dry objective lenses for low magnification use. We thought that this method would be useful for immersion objective lenses with high aperture and high magnification, and launched a collaboration. Our resulting prototype apodized phase contrast immersion objective lens (NA1.3, 100-power) enabled the visualization of a mesh of actin filaments without staining, a task that is very difficult for a conventional phase contrast microscope (this achievement received the Optics Design "Merit" Prize of the Optical Society of Japan).

Furthermore, we have prototyped a pupil projection apodized phase contrast microscope, achieving phase contrast viewing with the world's highest numerical aperture (NA1.49). Using this microscope we have succeeded at the direct observation of fine structure inside the cell nucleus, fine structure that a conventional microscope cannot see. The thickness of the optical section was a few hundred nanometers. Going forward we plan to apply this technology for viewing samples from such fields as developmental engineering, medical science, as well as materials science. This microscope allows the detection of a shift in the wave front of light of less than 1 nm, 1/500~1/1000 of the wavelength of the illuminating light (546 nm). We are now looking to develop optical microscopes approaching the resolution of a low-magnification electron microscope.

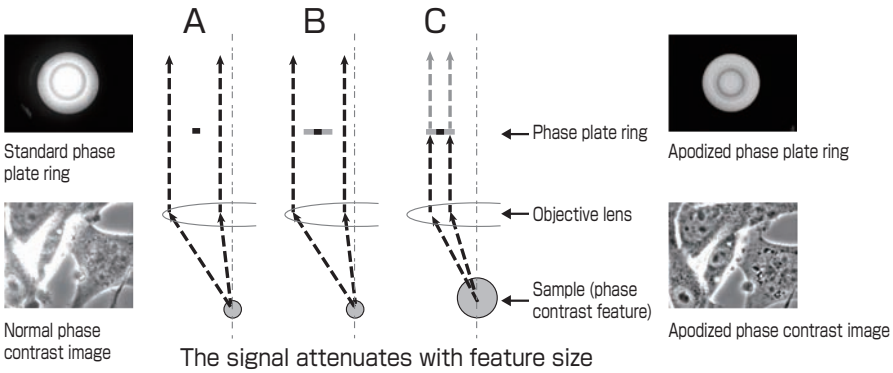


Fig. 2. The principle of apodized phase contrast microscopy (left: phase contrast microscopy, right: apodized phase contrast microscopy)

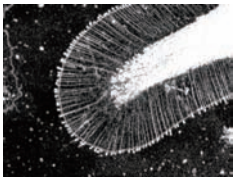


Fig.1 Actin filament bundles at the tip of a neuron (diameter: 20 – 60 nm) as viewed through the new polarizing microscope

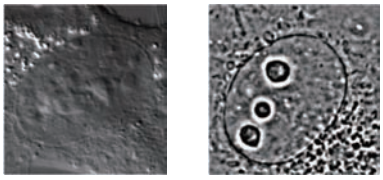


Fig.3 Images of a cell nucleus (left: phase contrast micrograph, right: apodized phase contrast micrograph)
Apodized phase contrast microscopy can discern the structure of intracellular particles.

【Terminology】

Term1

Polarizing microscope: A type of optical microscope. Illuminating a sample with polarized light enables observation of bifringence. Intracellular microcrystals are detected with high sensitivity, and so it has led to important discoveries such as proof for the existence of mitotic spindles, analysis of DNA structures, and the sliding filament theory of muscle contraction.

Term2

Actin filament bundles: Actin filaments, which are formed by polymerization of the protein actin, are an important constituent of the cellular skeleton, and play a variety

of roles. The actin fibers form higher-order structures such as bundles and meshes, and play important roles in cell division, extension and differentiation.

Neuroscience Research Institute
Kaoru Katoh
Ayako Kojima
Organ Development Research Laboratory
Akira Kurisaki
For inquiries about this article：Neuroscience Research Institute ns-office@m.aist.go.jp

Bio-mechanical Optical Imaging

Medical prosthetics and the measurement of bone stress

Bones are known to be heavily affected by their mechanical environment; examples of this include the growth of bone trabeculae in the direction of load and decrease in bone density under microgravity. Changes in a bone's mechanical environment also arise when a prosthetic device such as an artificial joint is implanted. Therefore, to achieve such prosthetics of long-lived usefulness after implantation, it is necessary to assess whether the stress to the bone is appropriate for bone maintenance.

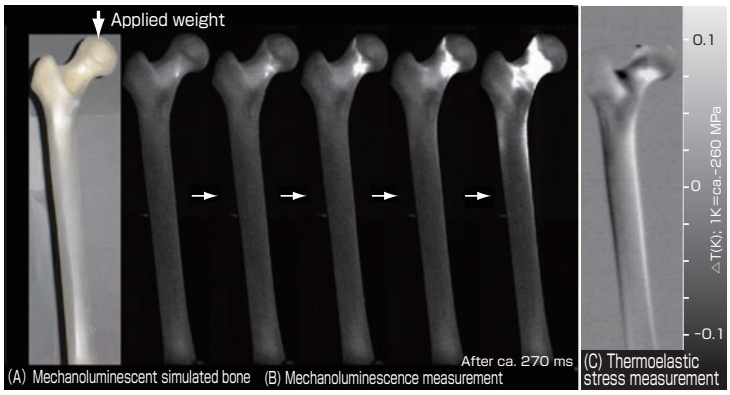
For experimental mechanical evaluation, the strain gauge method has become widely used. With the gauge pasted onto a sample, this method detects deformation of metal wires through changes in their electric resistance accompanying surface strain, allowing quick, quantitative measurements. However, the strain gauge method provides measurements only at the sites of the individual gauges, making it impossible to achieve full field monitoring.

The role bio-mechanical optical imaging plays

For this reason, we are promoting the application and development of thermoelastic (infrared) stress measurement and mechanoluminescence for imaging changes to bones' bio-mechanical environment *in vitro* [1].

Thermoelastic stress measurement is a method of visualizing the comprehensive distribution of principal stresses along a surface by using an infrared thermography to monitor temperature change that arise through adiabatic elastic deformations of an object (compression causing a temperature rise, and tensile deformation, a temperature fall). This has the advantage that a distribution measurement can be made without contact with the sample (Fig. panel C). Currently, standardization of this measurement procedure is underway for assessing the bio-mechanical compatibility of actual prosthetic devices.

For their part, the mechanoluminescent materials AIST has developed are novel inorganic materials ($SrAl_2O_4$:Eu, etc.) that can luminesce in response to applied mechanical energy[2]. A Bio-mechanical device in which these mechanoluminescent materials are applied to a simulated bone is a "mechanoluminescent simulated bone." (Fig. panel A) Since the region subjected to load emits high intensity light in the visible region, the device has allowed high-definition and high-speed visualization of the mechanical dynamic environment using conventional image sensors such as



Bio-mechanical optical imaging (using a simulated femur viewed from the posterior side)
(A): A mechanoluminescent simulated femur
(B): Kinetic imaging of (A)
An initial load of 100 N applied to the femoral head was increased to 1900 N at an increase rate of 7000 N/sec.
(C): Thermoelastic stress imaging of (A)
A sine wave-shaped compression load of 1000 ± 900 N (frequency = 5 Hz) was applied vertically to the femoral head.

CCDs (Fig. panel B). This simulated bone is fabricated to conform to the shape and mechanical characteristics of real bones. By comparing the luminescence distributions of variously designed prosthetic devices after attachment, the effect of each design on the bone's mechanical dynamic environment can be elucidated. This can be called a "smart screening tool" by which the bio-mechanical compatibility of a prosthetic device can be evaluated at the design stage.

We will continue exploiting the mutually complementary features of thermoelastic stress measurement and mechanoluminescence to carry on and expand our research and development, enabling us to contribute to a variety of bio-mechanical analyses and thus support the practical implementation of prosthetic devices.

Institute for Human Science and Biomedical Engineering

Koji Hyodo

Katsunobu Nonaka

Measurement Solution Research Center

Chao-Nan Xu

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[2] C.-N. Xu : *AIST TODAY*, 5(10), 8-9 (2005) (in Japanese).

For inquiries about this article：Institute for Human Science and Biomedical Engineering hsbe-webmaster@m.aist.go.jp

Measurement of Oxygen Saturation through the Eye

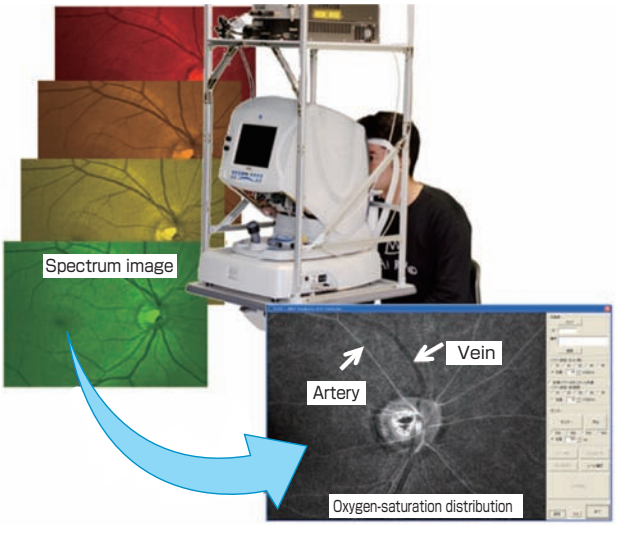
The goal of the research

The retina is a highly active tissue that consumes large quantities of oxygen. However, with a thickness of only 0.2-0.3 mm, it is a thin membrane with only a minimum of blood vessels. Thus, tiny cracks or disturbances in blood vessels caused by lifestyle-related diseases etc. affect circulation and lead to oxygen deprivation, directly damaging the tissue. Given this need, we have developed a fundus camera that photographs the back of the eye (fundus) to measure oxygen saturation, enabling metabolic disorders of the retina to be diagnosed at an early stage.

An instrument for measuring oxygen saturation

Exploiting faint changes in the color of hemoglobin that accompany changes in oxygen saturation, we use spectroscopy and regression analysis to measure oxygen saturation. Furthermore, since noninvasiveness and convenience are crucial for a routine screening procedure, we have developed a scanning laser ophthalmoscope with spectroscopic function, "Spectroscopic SLO," which allows high-speed measurement with low light that does not require the pupil to be dilated.

It was confirmed by validating on healthy volunteers that this new ophthalmoscope is able to measure the 2-dimensional distribution of oxygen saturation in the retina. The oxygen saturation is displayed as a brightness distribution: the blood vessel depicted in white corresponds to an artery with high oxygen saturation; the dark one, to a vein.



Spectroscopic SLO apparatus we developed, captured spectral images, and the resulting image indicating the pattern of oxygen saturation levels in a normal fundus
Scanning time: ca. 1 second

Validation on patients with eye pathologies

Collaborating with the Department of Ophthalmology and Visual Sciences, School of Medicine, Kyoto University, we tested the reliability of this instrument on patients with eye pathologies. Our results suggested that the fundus camera will be particularly effective for diagnosing diabetic retinopathy and vascular occlusions, and we were able to confirm that where it indicated low oxygen saturation of the retina, conventional fluorescein angiography [term] also saw abnormalities. The high invasiveness of fluorescein angiography precludes its use for routine screening, but since the new apparatus can take scans quickly and non-invasively, we think it would be a boon if it could enable discovery of asymptomatic, difficult-to-diagnose eye disorders and life style-related diseases in their early stages.

【Terminology】

Fluorescein angiography: A diagnostic method in which a fluorescent dye is injected intravenously to observe the blood vessels in the back of the eye (fundus).

Photonics Research Institute
Hiromitsu Furukawa
Hidenobu Arimoto
Tomohiro Shirai

Reference
· Hiromitsu Furukawa: *Optical and Electro-optical Engineering Contact*, 46, 640-645 (2008) (in Japanese).

For inquiries about this article：Photonics Research Institute photonics-sec@m.aist.go.jp

The Live Cell Imaging Workshop

Aim of the workshop

In recent years, the optical visualization of biological samples has made great strides, becoming one of the important pillars of biotechnology. It has even been possible to visualize such things as the rearrangement of neural circuits in living brain tissue and the motion of a transcriptase reading one base of DNA at a time.

As modern optical microscopes with their computer-controlled image-processing devices have become so complex, technical workshops on optical microscopy aimed at active researchers (from post-docs to professors) have become popular in the U.S. and Europe. The workshops there serve as focal points not only for technique dissemination but also for encounters between industry and academia and for technology evaluation. The first such workshop was the Analytical & Quantitative Light Microscopy course at the Marine Biological Laboratory (Woods Hole, U.S.A.) which is run regularly to this day, where Japanese companies also attend with new products for evaluation, and where they collect information.

Since 2005, in cooperation with the Hamamatsu University School of Medicine, optical instrument manufacturers and others, we have held an annual 5-day workshop that includes lectures and hands-on training using the latest equipment. Topnotch instructors are invited from academia and industry, and we carry out hands-on technical training with the latest instruments brought in by manufacturers as well as AIST's equipment. More than 160 attendees, made up of scientists from industry and academia, graduate students and the like, all gather each year at AIST with the latest equipment and reagents provided by more than 10 manufacturers of optical instrument and reagents. Both lecturers and attendees take "the spirit for learning" very seriously. The program is run by the Bioimaging Society and AIST in cooperation with universities and research institutes.

Summary of the 4th live cell imaging workshop (Oct. 2008)

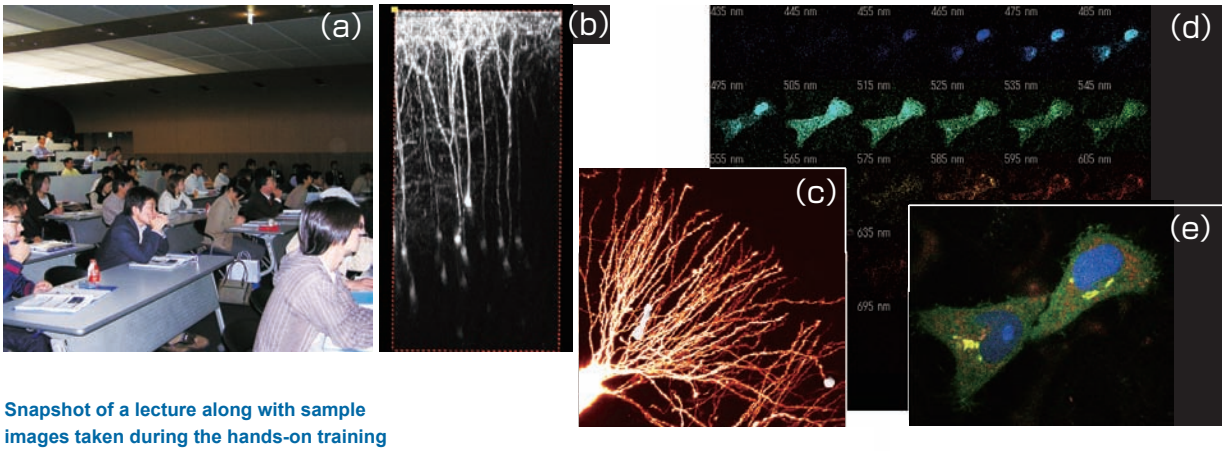
Companies in attendance: 12 (5 optical microscope makers, 2 camera makers, 2 makers of reagents, and 3 miscellaneous)

Attendees: 111 industry-related participants, 49 academicians, and 17 students

Equipment used: 4 confocal microscopes, 2 total internal reflection microscopes, 3 EMCCD cameras, etc. (The total list price value of equipment brought in by companies came to more than 150 million Japanese yen.)

Hand-on training syllabus (last year's course):

·Optical microscope basics (preparation of samples, Köhler illumination, phase contrast microscopy, differential interference microscopy and fluorescence-based methods)



Snapshot of a lecture along with sample images taken during the hands-on training
(a) Snapshot of a lecture
(b) Neurons within a mouse brain (observed by two-photon excitation microscopy)
(c) Hippocampal neurons (observed by two-photon excitation microscopy)
(d) Fluorescence image recorded simultaneously in 32-channels (observed by spectrum confocal microscopy)
(e) 4-color staining with CFP (nucleus), GFP (actin), YFP (Golgi), and DSRed (mitochondria) (observed by spectrum confocal microscopy)

·GFP imaging 1 (introduction of GFP into cultured cells, confocal imaging, FRAP, time-lapse observation, spectrum imaging, and observation of multiply tagged cells (CFP, GFP, YFP, etc.)
·GFP imaging 2 (time-lapse observation of a neuronal growth cone's cytoskeleton, evanescence microscopy [term], spectral microscopy, fluorescence spectrum observation and fluorescence-based single molecule observation)
·Calcium imaging (high-speed confocal microscopy, use of a high-speed CCD camera, and calcium imaging of cultured cells)
·Brain slice imaging (two-photon excitation microscopy, observation of a mouse brain synapse, and observation of a nematode synapse)
·Introduction of new technologies by the various microscope manufacturers

Summary of the 5th live cell imaging workshop

Date: Oct. 5-9, 2009

This year, we worked together with the National Institute for Material Science (NIMS) to organize the workshop. 15 % of the hands-on training was held at NIMS.

Companies in attendance: 13 (4 optical microscope makers, 4 camera makers, 2 makers of reagents, and 3 miscellaneous)

Attendees: 144 (75 industry-related participants, 55 academicians, and 14 students)

Equipment used: 5 confocal microscopes, 1 total internal reflection microscopes, 1 laser beam machining device, 5 EMCCD cameras, etc. (The total list price value of equipment brought in by companies came to more than 150 million Japanese yen.)

Due to the recession, there was a decrease of the number of attendees, but, on the other hand, there was an increase in the number of companies in attendance. Therefore, the workshop held was of the same size and content as the previous years.

【Terminology】

Evanescence microscopy: When total internal reflection of incident light occurs between two layers with different refractive indices such as glass and water, a very faint light called an evanescent wave arises that is restricted to within roughly one wavelength (a few hundred nm) of the surface. An evanescence microscope exploits this phenomenon, enabling imaging in which superfluous light is suppressed outside the miniscule sector that one wants to observe.

Neuroscience Research Institute
Kaoru Katoh
Ayako Kojima
Tatsuhiko Ebihara
Motomichi Doi
Kazuyuki Kiyosue
Kimihiko Kameyama
Tai Kubo
Research Institute for Cell Engineering
Akira Nagasaki
Institute for Biological Resources and Functions
Yoshikatsu Ogawa
Takafumi Mizuno
Research Coordinator
Takahisa Taguchi
For inquiries about this article：Neuroscience Research Institute ns-office@m.aist.go.jp

Research Hotline

UPDATE FROM THE CUTTING EDGE

Jul.-Sep. 2009

The abstracts of the recent research information appearing in Vol.9 No.7-9 of "AIST TODAY" are introduced here, classified by research area.
For inquiry about the full article, please contact the author via e-mail.

Life Science and Biotechnology

Development of a method for specific degradation of nuclear-localized RNAs with unknown functions

Road to new medical and pharmaceutical researches originated from the emerging RNA functions

We have developed a new experimental system to specifically degrade nuclear-localized RNAs in mammalian cultured cells. The noncoding RNAs (ncRNAs), whose functions have largely remained elusive, are expected to be playing various critical roles in the cell nucleus and to be related to various diseases. Since the available method to degrade the specific RNAs was limited in those targets for cytoplasmic mRNAs, we attempted and succeeded in developing a system that could target for nuclear RNAs by employing antisense DNA oligonucleotides (ASO) that were efficiently administered into the nucleus by electroporation. The introduced ASO forms DNA-RNA heteroduplex with the target RNA, which is recognized by a cellular enzyme called RNaseH that specifically degrades the target RNAs. We have confirmed that more than 50 different nuclear ncRNAs could be degraded by our method and the phenotypic alterations were also observed. Therefore, our system opened a new window in the research field of ncRNAs, and it would eventually link to a new approach of pharmaceutical application.

Tetsuro Hirose
Biomedicinal Information Research Center
tets-hirose@aist.go.jp

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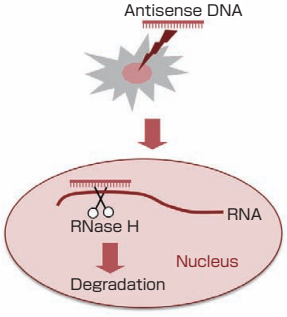
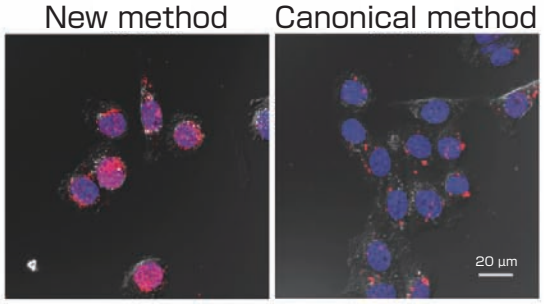


The method for specific degradation of nuclear RNAs



Introduction of antisense DNAs (red signal) into the nucleus (blue signal)

Development of thin-film electroluminescent device using inorganic oxides

Plane emission of red light with a starting voltage of ≈10 V

We have developed a perovskite thin-film electroluminescent device, opening up a new optical application of perovskite materials. Complete epitaxial growth of all of the layers and very flat interfaces with monoatomic steps have been obtained. With increasing driving voltage, the intensity of electroluminescence dramatically increases. The sharp electroluminescence peak at around 610 nm with 12 V becomes much stronger with increasing AC voltage. High-quality red light is emitted and the working voltage for whole-surface electroluminescence is as low as 10 V.

Hiroshi Takashima

Nanoelectronics Research Institute

h-takashima@aist.go.jp

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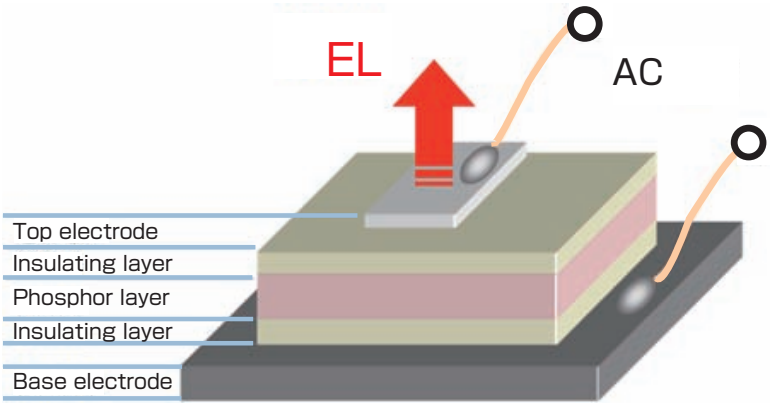

Schematic view of the developed inorganic electroluminescence(EL) device

New, simple method for separation of metallic and semiconducting carbon nanotubes

Freeze, thaw and squeeze method paves the way for mass production

We have developed an easy-to-use method to separate metallic and semiconducting single-wall carbon nanotubes (SWCNTs) using agarose gel. The most effective separation was realized by a simple procedure in which a piece of gel containing SWCNTs was frozen, thawed, and squeezed with the fingers (Figure). This process does not need any special equipment other than a domestic freezer and affords a solution containing metallic SWCNTs and leaves a gel containing semiconducting SWCNTs. The method is so simple that we can easily proceed to the automation and scaling up of the process. This high-yield, low-cost, and scalable method could be suited for the industrial production of metallic and semiconducting SWCNTs, facilitating basic and applied research on SWCNT electronics.

Takeshi Tanaka

Nanotechnology Research Institute

tanaka-t@aist.go.jp

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Separation of metallic and semiconducting SWCNTs by a freeze, thaw and squeeze method using SWCNTs-containing agarose gel

A solution containing metallic SWCNTs and gel debris containing semiconducting SWCNTs are simultaneously obtained by squeezing the SWCNTs-containing gel after freeze and thaw processes.

Development of a system capable of machining a metal tube of a human hair size into a complex shape

Highly functional microscopic medical instruments will be realized

Existing machining technologies have several problems: machining is sometimes impossible because the minute tube to be machined and the working tool come into contact with each other at a point other than the machining position; a tube of too small a diameter cannot be machined because it is easily bent by the tool contact force during machining; and finally, a general problem in any minute tube machining technology is that the tube cannot be precisely held.

The newly developed system adopts a non-contact laser machining technology in which the tube is not subjected to force during machining. As the same laser light source is used for both machining and measurement, no displacement appears between the measured and the machined positions, and the laser beam is irradiated on the precise position by means of an error-compensation even if the target tube has holding-position error. Through electrochemical finish machining, the heat-affected layer inherent to laser machining is removed to provide a smooth surface.

Tsuneo Kurita

Advanced Manufacturing Research Institute

t.kurita@aist.go.jp

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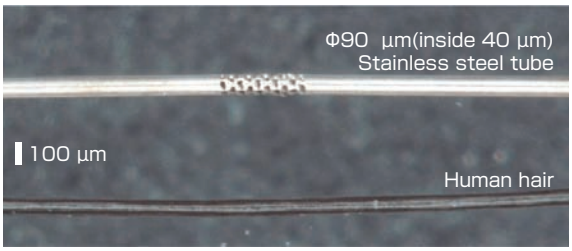


- Mesh holes
- Holes width 20 μm
- Holes penetrating to inside
- Total machining time 3 min.

Laser and electrochemical complex machining result

Development of low-cost photocatalyst responsive to visible light

Applicable to fiber, textile and plastic

We have developed a low-cost photocatalyst responsive to visible light and applicable to fiber, textile and plastics. The novel photocatalyst is composed of titanium dioxide, apatite and iron. It showed excellent activities of acetoaldehyde decomposition, NOx removal and anti-bacterial effect under visible light as well as UV light. The acetoaldehyde decomposition activity of the novel photocatalyst is 5.9 times higher than that of the conventional titanium dioxide photocatalyst under fluorescent lamp. Although photocatalysts responsive to visible light are usually yellow, the novel photocatalyst is almost white and it does not change color when it is coated on a white object. The novel photocatalyst helps to expand the market of photocatalytic products, because it makes possible its use for various indoor applications which were difficult to be realized by conventional photocatalysts.

Hiroshi Taoda

Materials Research Institute for Sustainable Development

h-taoda@aist.go.jp

AIST TODAY Vol.9 No.7 p.24 (2009)

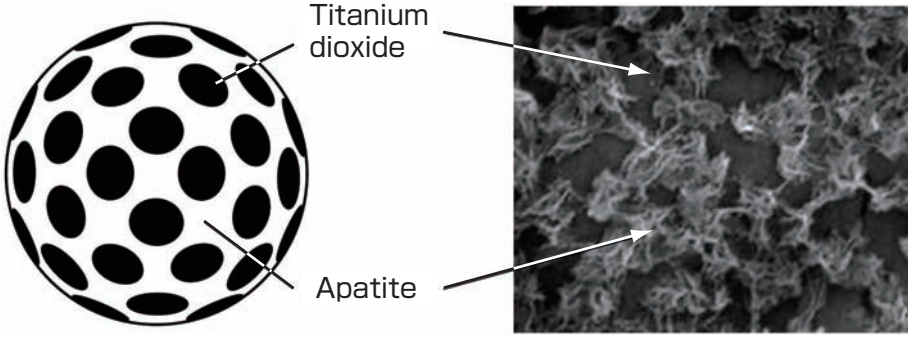


Diagram of the novel photocatalyst (left) and the SEM photograph of it (right)

Rapid production of bioactive substance, HMF, from saccharides

Realized by using high-pressure and high-temperature water in a microreaction system

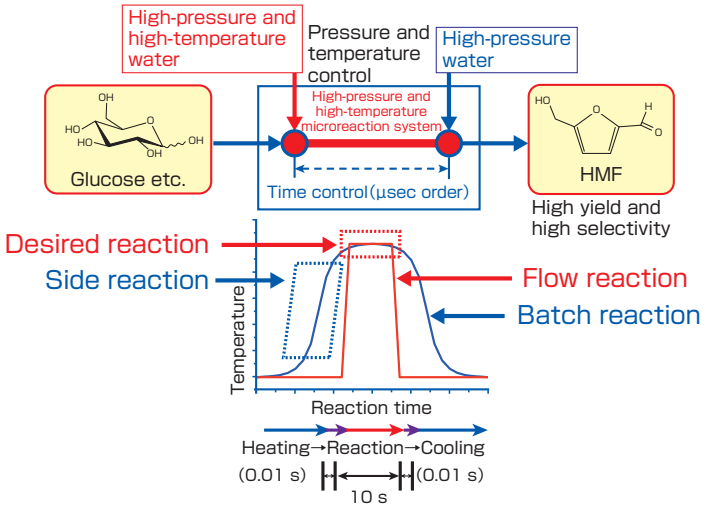
We have developed a new facile and continuous method for production of 5-hydroxymethylfurfural (HMF) which is expected to have beneficial effects on the prevention of life-style related diseases such as hypertension and diabetes. HMF is made from inexpensive saccharides such as glucose, in high-pressure and high-temperature water medium. The system enables rapid heating from room temperature to 400 °C within a very short time (less than 0.01 s) by mixing high-pressure and high-temperature water and an aqueous solution of saccharide in a microreactor (micromixer). The reaction method with rapid heating and cooling achieves the production of HMF in high yield (70 %) and high selectivity (80 %).

Hajime Kawanami

Research Center for Compact Chemical Process

h-kawanami@aist.go.jp

AIST TODAY Vol.9 No.8 p.16 (2009)



Schematic diagram and temperature profile of high-pressure and high-temperature microreaction system (blue box, size: 10 cm × 15 cm)

Development of an effective method of producing D-glyceric acid from glycerol

Materials for chemicals and pharmaceuticals to be produced from a by-product of biodiesel fuel productin

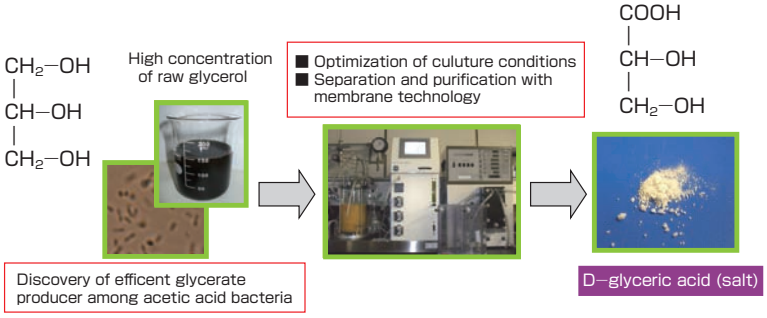
We have developed a new technique to effectively produce D-glyceric acid from glycerol, which is in abundant supply due to the proliferation of biodiesel fuel. The total amount of glycerol produced worldwide is estimated to be around a million tons a year, and therefore, an effective use for this surplus glycerol has been sought. In our new method for producing D-glyceric acid effectively, a highly oxidative microorganism belonging to acetic acid bacteria, and a membrane that selectively permeates ions for separation and concentration of the product were used. Although D-glyceric acid and its derivatives have excellent biological functions, including an action to accelerate alcohol metabolism, they are expensive because industrial methods have not been established for their production. If they can be produced at low cost, various uses will be expected, including raw materials for chemical products such as bioplastics, pharmaceuticals for alcohol metabolism acceleration or liver disease treatment, and cosmetics.

Hiroshi Habe

Research Institute for Innovation in Sustainable Chemistry

hiroshi.habe@aist.go.jp

AIST TODAY Vol.9 No.7 p.25 (2009)



Effective production of D-glyceric acid from concentrated crude glycerol produced as a by-product

Development of a new electric power device that enables the grid-connection of numerous distributed generators

Low-loss superconducting thin-film fault-current limiter elements that immediately suppress short-circuit currents

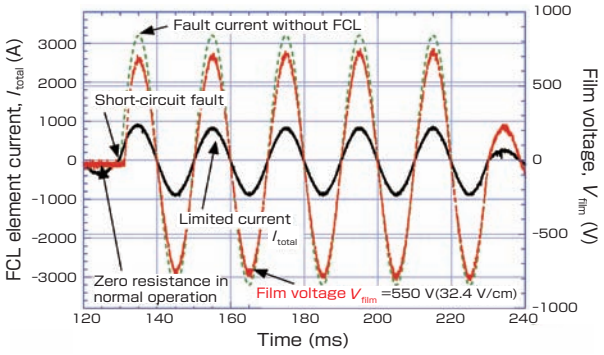
Recent awareness of global warming has prompted the connection of numerous distributed generators, such as cogeneration systems and wind turbine generators, to the existing power grid, sometimes causing significant increase in short-circuit currents. Introduction of a fault current limiter (FCL) is considered an attractive countermeasure to such increased short-circuit currents. We have developed 500 V/200 A superconducting FCL modules using large high-temperature superconducting (HTS) thin films with high-resistivity Au-Ag alloy shunt layers, which can withstand high electric fields (E > 30 V/cm). Two HTS thin films on sapphire substrates (2.7 cm × 20 cm), prepared with a metal organic decomposition method, were used to fabricate such FCL modules. Switching tests using a short-circuit generator confirmed good current limiting properties. The required length of expensive HTS thin films has become less than one-fourth of that for conventional thin-film FCL modules that use gold shunt layers. It is expected that compact and low-loss thin-film FCLs can be realized with much reduced costs.

Hirofumi Yamasaki

Energy Technology Research Institute

h.yamasaki@aist.go.jp

AIST TODAY Vol.9 No.8 p.17 (2009)



Switching test results using a short-circuit generator

Photon number discrimination with a superconducting transition edge sensor

New photon detection technique for realizing ultimate performances in quantum communication and metrology

I have developed a photon number resolving detector with superconducting transition edge sensors (TESs). The TES is a kind of calorimeters measuring the energy of incident photons as the increase of phonon temperature in a thin film absorber. The temperature rise also affects an electron temperature in the TES film resulting in the TES resistance change. The resistance change is proportional to the energy of incident photons. I have fabricated the TES devices with a thin film titanium superconductor embedded in an optical cavity to enhance the quantum efficiency. The titanium film has a relatively high transition temperature around 400 mK. With the illumination of weak coherent light pulses the fabricated device exhibited high quantum efficiency, fast response, and clear photon number discrimination up to 6 photons. TES-based photon number resolving detectors are quite promising for improving the performances of quantum communication and quantum optical radiometry.

Daiji Fukuda

Metrology Institute of Japan

d.fukuda@aist.go.jp

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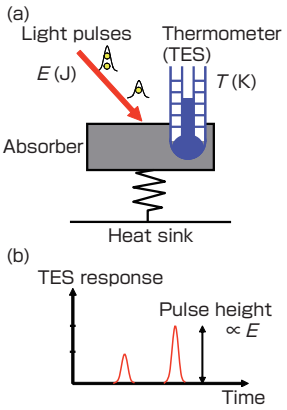

(a) Schematic diagram of the photon number resolving detector with the transition edge sensor (TES)
(b) Example of TES response signals to light pulses

A simple pretreatment technique for PCB analysis

A key to solving the PCB-waste issue: fast and accurate analysis

One of the persistent organic pollutants, polychlorinated biphenyl (PCB) was once widely used as dielectric fluids and other applications. Fast, simple and accurate determination of PCB concentration is essential to properly evaluate the risks of vast numbers of PCB-wastes.

We synthesized a sulfoxide residue and ammonium ion-bonded silica stationary phase for liquid chromatography, and investigated its ability to separate PCB from mineral oil matrices. After separation with the stationary phase, major PCB congeners in insulating oil samples containing Japanese legal regulation level of PCB (0.5 mg total PCB/kg) were determined with a gas chromatograph/quadrupole mass spectrometry system. The established method is much faster and requires less hazardous chemicals compared with the Japanese official method for PCB analysis. Because of the effectiveness, the stationary phase has been commercialized by a private company.

The potentials of the stationary phase for separation of other pollutants, such as polyaromatic hydrocarbons, dioxins, brominated frame retardants, and heavy metals are shown by other laboratories.

Masahiko Numata

Metrology Institute of Japan

mas-numata@aist.go.jp

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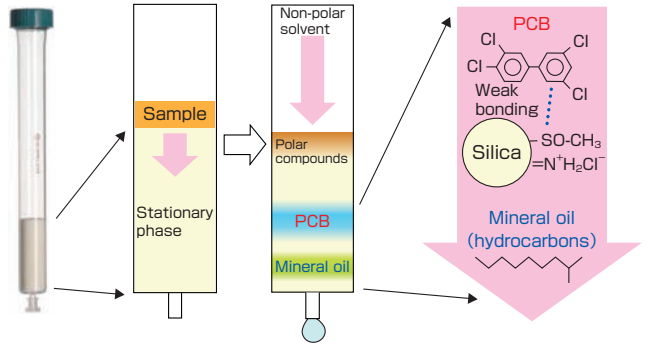

The novel stationary phase, and principle of separation

Beyond the limit of mass spectrometry

Kinetic-energy-sensitive mass spectrometry for separation of different ions with the same *m/z* value

The double-focusing mass spectrometer equipped with a superconducting-tunnel-junction (STJ) detector has been applied to measure relative ionization cross-sections for production of ions that are accompanied by different ionic species with the same mass-to-charge ratio (*m/z*). The STJ detector fabricated for this study enables kinetic energy (*E*) measurement of incoming individual ions at an energy resolution (*ΔE/E*) of 15 % with the assistance of an infrared-blocking filter which prevents detector-performance degradation due to infrared radiation illuminating the detector surface at 0.3 K. The high energy resolution is necessary to independently determine both *m* and *z* values. One of the limits of conventional mass spectrometry is that it measures the *m/z* values and thus different ions with the same *m/z* cannot be analyzed. The unconventional discrimination capability allows direct determination of relative ionization cross-section of the homonuclear diatomic ions $^{14}N_2^{2+}/^{14}N_2^{+}$ and $^{16}O_2^{2+}/^{16}O_2^{+}$, which are difficult to measure due to the strong interference by the signals of their dissociated atomic ions $^{14}N^{+}$ and $^{16}O^{+}$ with noticeably large ionization cross-sections. A kinetic-energy-sensitive mass spectrometer is useful for a wide range of analytical chemistry such as ionization processes of multiply ionized molecules and fragmentation of immunoglobulins.

Shigetomo Shiki

Research Institute of Instrumentation Frontier

s-shiki@aist.go.jp

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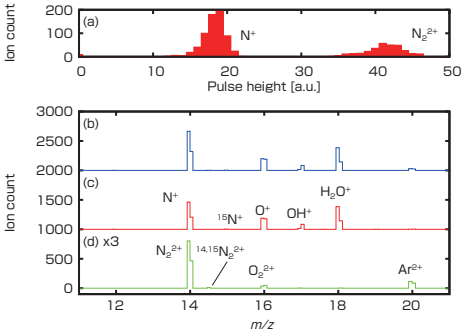

Mass spectra of the air ionized with electron impact at 70 eV
The superconducting tunnel junction detector enables us to distinguish different charge states and re-construct corresponding mass spectra; (a) pulse height spectrum for the ions with *m/z* of 14, (b) mass spectrum for all ions, (c) singly charged ions, (d) doubly charged ions.

Three-dimensional imaging of defect distributions using a positron microprobe

A practical technique for evaluating defect distributions in various materials

An intense positron microprobe has been developed for obtaining three-dimensional positron lifetime mappings in a sample to permit visual evaluation of defect distributions. The beam diameter of an intense positron beam injected into the sample was 30 micrometers. Two-dimensional images at arbitrary depth were demonstrated of positron lifetimes in a fused silica sample, which was irradiated with ion beams. The time taken to obtain a single image was about 1 hour.

Nagayasu Oshima

Research Institute of Instrumentation Frontier

nagayasu-oshima@aist.go.jp

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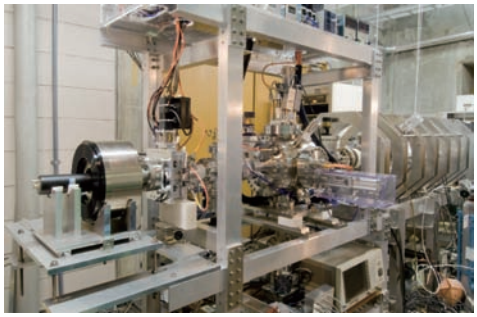
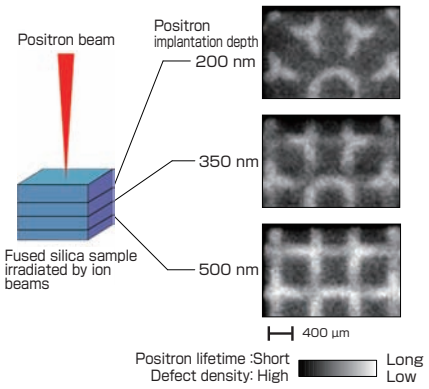


Positron probe microanalyzer



Positron lifetime images of a fused silica sample

In Brief

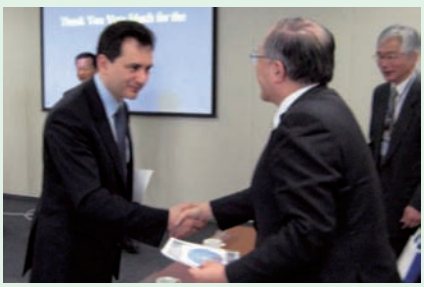
Deputy Prime Minister of the Republic of Serbia Visits Tokyo Akihabara Site

On April 17, H.E. Mr. Bozidar Djelic, Deputy Prime Minister and Minister for Science and Technological Development of the Republic of Serbia, and H.E. Mr. Ivan Mrkic, Serbian Ambassador to Japan, visited AIST Tokyo Akihabara Site.

Dr. Akira Ono, Senior Vice-President of AIST, gave a welcoming speech, which was followed by an overview of AIST by the International Affairs Department, and exchanges of views. Dr. Hideki Imai, Director of the Research Center for Information Security, presented an overview of the center, where Dr. Miodrag Mihaljevic from Serbia has been engaged in research since 2006 as an invited researcher.

The former Socialist Federal Republic of Yugoslavia and Japan signed an agreement on scientific and technological cooperation in 1981, and this has been passed on also to the present Republic of Serbia. The Deputy Prime Minister presented the scientific and technological activities of the Republic, and its participation in European programs and projects such as with FP7 and CERN. He expressed wishes for cooperation with Japan, particularly with AIST, based on the above agreement. The Deputy Prime Minister also stated his interest in revisiting AIST during his next visit to Japan in autumn.

This visit by the Deputy Prime Minister is a good occasion to reconsider future possibilities of research cooperation, including personnel exchange.



Deputy Prime Minister Djelic (left) and AIST Senior Vice-President Ono (right)

MOUs Concluded with 6 US National Laboratories in Energy and Environment Fields

On the occasion of the visit to the US of the then Minister Toshihiro Nikai, Ministry of Economy, Trade and Industry (METI) in early May, 2009, AIST, represented by President Tamotsu Nomakuchi, concluded MOUs with 5 research organizations of the Department of Energy (DOE), and with the National Institute of Standards and Technology (NIST) of the Department of Commerce (DOC). This was done in order to promote and strengthen research cooperation with the US in the fields of energy and environment, and to accelerate the technology development toward the realization of a low carbon society.

The research cooperation between AIST and the US research organizations gained impetus after the visit of the then Minister Nikai to the state of New Mexico in August, 2006, and a collaborative research in fuel cells and hydrogen began with Los Alamos National Laboratory (LANL) in December, 2007. The Obama administration which started in January, 2009, advocates the Green New Deal policy, and aims at the creation of new industry for the realization of sustainable development of society through promotion of R&D mainly in the fields of energy and environment. The Japanese government, in response, has confirmed to promote Japan-US research cooperation in the fields of energy and environment at the Japan-US summit meeting in February, 2009. There is a rapid increase in the momentum of cooperation between the two countries in these fields.

In this context, from the beginning of this year, experts on energy and environment of AIST, along with those of METI and others, have visited the US national laboratories several times for discussions which led to the conclusion of MOUs. The US laboratories which signed the MOUs, and the prospective fields of research cooperation are as follows.

1) Los Alamos National Laboratory (LANL): cooperation in the fields of fuel cells and hydrogen, computational science related to materials, and CCS (CO_2 capture and storage)

2) Sandia National Laboratories (SNL): cooperation in photovoltaics, nanoelectronics and nanomaterials, and computational science related to materials, as well as bilateral use of inter-lab facilities of nanotechnology

3) National Renewable Energy Laboratory (NREL): cooperation in the fields of photovoltaics, bio-fuels (of cellulose origin), and energy analysis

4) Laurence Livermore National Laboratory (LLNL): cooperation in bio-fuels (of cellulose origin), and fuel combustion technology

5) Laurence Berkeley National Laboratory (LBNL): cooperation in biofuels (of cellulose origin), nanomaterials for energy, and CCS

6) National Institute of Standards and Technology (NIST) of DOC: cooperation mainly in R&D for international standards

During this visit to the US, on May 1, AIST President Nomakuchi attended the ceremony for signing MOU between METI and the state of New Mexico, and met with H.E. Mr. Bill Richardson, Governor of New Mexico, and the two directors of Sandia National Laboratories and Los Alamos National Laboratory. On the morning of May 4, he visited NIST in Gaithersburg, Maryland, and concluded an MOU there. In the afternoon, he was present at talks between the then Minister Nikai and H.E. Dr. Steven Chu, Secretary of Energy in Washington, DC, and afterwards, concluded research cooperation MOUs with the 5 laboratories of DOE.

In research cooperation, around 20 AIST researchers will be sent to the US this fiscal year, and we intend to establish a collaborative research base for smooth cooperative activities such as joint research and exchange of researchers.

Signing of the memorandum between METI and the state of New Mexico

Dr. Gallagher, Deputy Director of NIST(left), and Dr. Nomakuchi, President of AIST(right)

Cover Photos
Above: Developed laser and electrochemical complex machining system (p. 19)
Below: Mr. Nikai, then Minister of METI, Dr. Chu, Secretary of Energy, Dr. Nomakuchi, President of AIST, and representatives of the 5 US national laboratories after signing the MOUs (p. 24)

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Publication Office, Public Relations Department
National Institute of Advanced Industrial Science and Technology (AIST)

AIST Tsukuba Central 2, 1-1-1 Umezono, Tsukuba, Ibaraki 305-8568, Japan
TEL: +81-29-862-6217 FAX: +81-29-862-6212 Email: prpub@m.aist.go.jp URL: http://www.aist.go.jp/